FIRST AID FOR THE
USMLE STEP 1
2015
25th ANNIVERSARY EDITION

- More than 1,250 frequently tested topics and mnemonics
- Hundreds of significant high-yield updates
- 250+ new photographs and diagrams
- Updated student ratings of review resources and apps
Dedication

To the contributors to this and past editions, who took time to share their knowledge, insight, and humor for the benefit of students.
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Twenty-Fifth Anniversary Foreword

Our exam experiences remain vivid in our minds to this day as we reflect on 25 years of First Aid. In 1989, our big idea was to cobble together a “quick and dirty” study guide so that we would never again have to deal with the USMLE Step 1. We passed, but in a Faustian twist, we now relive the exam yearly while preparing each new edition.

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

To pull it all together, we used a then–“state-of-the-art” computer database (Paradox/MS DOS 4) that fortuitously limited our entries to 256 characters. That single constraint mandated brevity, while the three-column layout created structure—and this was the blueprint upon which First Aid was founded.

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

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

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

We’re proud of the precedent that First Aid set for the many excellent student-to-student publications that followed. More importantly, First Aid itself owes its success to the global community of medical students and international medical graduates (IMGs) who each year contribute ideas, suggestions, and new content. In the early days, we
used book coupons and tear-out business reply mail forms. These days, we get more than 20,000 comments and suggestions each year via our blog FirstAidTeam.com and A nnnotate.

At the end of the day, we don’t take any of this for granted. There are big changes in store for the USMLE, and a bigger job ahead of us to try to keep First Aid indispensable to students and IMGs. We want and need your participation in the First Aid community. (See How to Contribute, p. xix.) With your help, we hope editing First Aid for the next 25 years will be just as fun and rewarding as the past 25 years have been.

Louisville
Tao Le
Los Angeles
Vikas Bhushan

First Aid for the USMLE Step 1 Through the Years
Preface

With the 25th anniversary 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:

- Dozens of entirely new facts and hundreds of major fact updates culled from more than 20,000 comments and suggestions.
- Extensive text revisions, new mnemonics, clarifications, and corrections curated by a team of 25 student authors who excelled on their Step 1 examinations and verified by a team of expert faculty and nationally recognized USMLE instructors.
- Updated with more than 250 new full-color images to help visualize various disorders, descriptive findings, and basic science concepts. Labeled and captioned photographs have been selected to aid retention by engaging visual memory in a manner complementary to mnemonics.
- Updated with dozens of new and revised diagrams. We continue to expand our collaboration with USMLE-Rx (MedIQ Learning, LLC) to develop and enhance illustrations with improved information design to help students integrate pathophysiology, therapeutics, and diseases into memorable frameworks for annotation and personalization.
- A revised exam preparation guide with updated data from the NBME and NRMP. The guide also features new high-yield techniques for efficient and effective test preparation.
- An updated summary guide to student-recommended USMLE Step 1 review resources, including mobile apps for iOS and Android. The full resource guide with detailed descriptions can be found at our blog, www.firstaidteam.com.
- Real-time Step 1 updates and corrections can also be found exclusively on our blog.

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

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Special Acknowledgments

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

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For help on the Web, thanks to Mark Ard, Edison Cano, Tim Durso, Ryan Nguyen, and Joe Savarese. For support and encouragement throughout the process, we are grateful to Thao Pham and Jonathan Kirsch, Esq. Thanks to Louise Petersen for organizing and supporting the project. Thanks to our publisher, McGraw-Hill, for the valuable assistance of its staff, including Midge Haramis and Jeffrey Herzich. Thanks to our editor, Catherine Johnson.

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

For exceptional editorial support, enormous thanks to our tireless senior editor, Emma D. Underdown, and her team of editors, Christine Diedrich, Linda Davoli, Janene Matragrano, Isabel Nogueira, and Rebecca Stigall. Many thanks to Tara Price for page design and all-around InDesign expertise. Special thanks to Jan Bednarczuk for a greatly improved index. We are also grateful to our medical illustrators, Andrea Charest, Justin Klein, Karina Metcalf, and Hans Neuhart, for their creative work on the new and updated illustrations. Lastly, tremendous thanks to Rainbow Graphics, especially David Hommel and Donna Campbell, for remarkable ongoing editorial and production support under time pressure.

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General Acknowledgments

This year, we were fortunate to receive the input of thousands of medical students and graduates who provided new material, clarifications, and potential corrections through our Web site 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 acknowledgements at our Web site, www.firstaidteam.com/. We will gladly make corrections if they are brought to our attention.

Special thanks to our mnemonics contest contributors: Dr. Cheryl Bernstein, Jonathan Berkman, Thomas Campi Jr., François-Xavier Crahay, Ryan Austin Denu, Rajkumar Doshi, Ethan Fram, Marcel T. Ghanim, Jessica Glatz, Alan Groves, Raven G. Harris, Ali Khan, Jacob T. Luty, Ryan Makipour, Alireza Mofid, Daniel Razzano, Paul T. Rutkowski, Kate Ryan, Yoni Samocha, Shan Siddiqi, Christopher Steele, James West, and Dane Yomtov.

How to Contribute

This version of *First Aid for the USMLE Step 1* incorporates hundreds of contributions and improvements suggested by student and faculty reviewers. 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 two current references:

- A dynamically updated Web resource such as Wikipedia, eMedicine, or UpToDate; and
- A link to an authoritative specialty textbook (search the “topic + Inkling” in Google and link to the courtesy pages available from a wide variety of major medical textbooks)

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.”

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

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

Alternatively, you can email us at: firstaidteam@yahoo.com.

Contributions submitted by May 15, 2015, receive priority consideration for the 2016 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.

Please include supporting hyperlinks on all content and errata suggestions. Check our Web site first to avoid duplicate submissions. In the event that similar or duplicate entries are received, only the first complete entry received with a valid, authoritative reference will be credited. Please follow the style, punctuation, and format of this edition as much as possible.

JOIN THE FIRST AID TEAM

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

For 2015, we are actively seeking passionate medical students and graduates with a specific interest in improving our medical illustrations, expanding our database of medical photographs, and developing the software that supports our crowdsourcing platform. We welcome people with prior experience and talent in these areas. Relevant skills include clinical imaging, digital photography, digital asset management, information design, medical illustration, graphic design, and software development.

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

Medical students who have used previous editions of this guide have given us feedback on how best to make use of the book.

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 reading Section IV: Top-Rated Review Resources.

LET FIRST AID BE YOUR GUIDE: Annotate material from other resources such as class notes or comprehensive textbooks into your copy of First Aid. Use it as a framework for distinguishing between high-yield and low-yield material. Note that First Aid is neither a textbook nor a comprehensive review book, and it is not a panacea for inadequate preparation during the first two years of medical school. We strongly recommend that you invest in the latest edition of at least one or two top-rated review resources on each subject to ensure that you learn the material thoroughly.

CONSOLIDATE THE MATERIAL: As you study new material, use the corresponding high-yield facts in First Aid for the USMLE Step 1 as a means of consolidating knowledge. Make high-yield connections between different organ systems and general principles and focus on material that is most likely to be tested.

INTEGRATE STUDY WITH CASES AND QUESTIONS: To broaden your learning strategy, consider integrating your First Aid study with case-based reviews (e.g., First Aid Cases for the USMLE Step 1) and practice questions (e.g., First Aid Q&A for the USMLE Step 1 or the USMLE-Rx Qmax Step 1 question bank). After reviewing a discipline or organ system chapter within First Aid, review cases on the same topics and test your knowledge with relevant practice questions. Maintain access to more comprehensive resources (e.g., First Aid for the Basic Sciences: General Principles and Organ Systems, First Aid Express and the Ultimate video courses) 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.
# Common USMLE Laboratory Values

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

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<th>SI Reference Intervals</th>
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<td><strong>Alanine aminotransferase (ALT, GPT at 30°C)</strong></td>
<td>8–20 U/L</td>
<td>8–20 U/L</td>
</tr>
<tr>
<td>Amylase, serum</td>
<td>25–125 U/L</td>
<td>25–125 U/L</td>
</tr>
<tr>
<td><strong>Aspartate aminotransferase (AST, GOT at 30°C)</strong></td>
<td>8–20 U/L</td>
<td>8–20 U/L</td>
</tr>
<tr>
<td>Bilirubin, serum (adult)</td>
<td>Total // Direct 0.1–1.0 mg/dL // 0.0–0.3 mg/dL</td>
<td>2–17 µmol/L // 0–5 µmol/L</td>
</tr>
<tr>
<td><strong>Calcium, serum (Total)</strong></td>
<td>8.4–10.2 mg/dL</td>
<td>2.1–2.8 mmol/L</td>
</tr>
<tr>
<td><strong>Cholesterol, serum (Total)</strong></td>
<td>140–200 mg/dL</td>
<td>3.6–6.5 mmol/L</td>
</tr>
<tr>
<td><strong>Creatinine, serum (Total)</strong></td>
<td>0.6–1.2 mg/dL</td>
<td>53–106 µmol/L</td>
</tr>
<tr>
<td>Electrolytes, serum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>135–147 mEq/L</td>
<td>135–147 mmol/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>95–105 mEq/L</td>
<td>95–105 mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.5–5.0 mEq/L</td>
<td>3.5–5.0 mmol/L</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>22–28 mEq/L</td>
<td>22–28 mmol/L</td>
</tr>
<tr>
<td>Gases, arterial blood (room air)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P_{O_2}$</td>
<td>75–105 mmHg</td>
<td>10.0–14.0 kPa</td>
</tr>
<tr>
<td>$P_{CO_2}$</td>
<td>35–44 mmHg</td>
<td>4.4–5.9 kPa</td>
</tr>
<tr>
<td>pH</td>
<td>7.35–7.45</td>
<td>$[H^+]$ 36–44 nmol/L</td>
</tr>
<tr>
<td><strong>Glucose, serum</strong></td>
<td>Fasting: 70–110 mg/dL</td>
<td>3.8–6.1 mmol/L</td>
</tr>
<tr>
<td></td>
<td>2-h postprandial: &lt; 120 mg/dL</td>
<td>&lt; 6.6 mmol/L</td>
</tr>
<tr>
<td>Growth hormone – arginine stimulation</td>
<td>Fasting: &lt; 5 ng/mL</td>
<td>&lt; 5 µg/L</td>
</tr>
<tr>
<td></td>
<td>provocative stimuli: &gt; 7 ng/mL</td>
<td>&gt; 7 µg/L</td>
</tr>
<tr>
<td>Osmolality, serum</td>
<td>275–295 mOsm/kg</td>
<td>275–295 mOsm/kg</td>
</tr>
<tr>
<td><strong>Phosphatase (alkaline), serum (p-NPP at 30°C)</strong></td>
<td>20–70 U/L</td>
<td>20–70 U/L</td>
</tr>
<tr>
<td><strong>Phosphorus (inorganic), serum</strong></td>
<td>3.0–4.5 mg/dL</td>
<td>1.0–1.5 mmol/L</td>
</tr>
<tr>
<td><strong>Proteins, serum</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (recumbent)</td>
<td>6.0–7.8 g/dL</td>
<td>60–78 g/L</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.5–5.5 g/dL</td>
<td>35–55 g/L</td>
</tr>
<tr>
<td>Globulins</td>
<td>2.3–3.5 g/dL</td>
<td>23–35 g/L</td>
</tr>
<tr>
<td><strong>Urea nitrogen, serum (BUN)</strong></td>
<td>7–18 mg/dL</td>
<td>1.2–3.0 mmol/L</td>
</tr>
<tr>
<td><strong>Uric acid, serum</strong></td>
<td>3.0–8.2 mg/dL</td>
<td>0.18–0.48 mmol/L</td>
</tr>
</tbody>
</table>

Cerebrospinal Fluid

| Glucose | 40–70 mg/dL | 2.2–3.9 mmol/L |

(continues)
## Hematologic

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal Ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erythrocyte count</strong></td>
<td>Male: 4.3–5.9 million/mm³</td>
</tr>
<tr>
<td></td>
<td>Female: 3.5–5.5 million/mm³</td>
</tr>
<tr>
<td></td>
<td>4.3–5.9 × 10¹²/L</td>
</tr>
<tr>
<td></td>
<td>3.5–5.5 × 10¹²/L</td>
</tr>
<tr>
<td><strong>Hematocrit</strong></td>
<td>Male: 41–53%</td>
</tr>
<tr>
<td></td>
<td>Female: 36–46%</td>
</tr>
<tr>
<td></td>
<td>0.41–0.53</td>
</tr>
<tr>
<td></td>
<td>0.36–0.46</td>
</tr>
<tr>
<td><strong>Hemoglobin, blood</strong></td>
<td>Male: 13.5–17.5 g/dL</td>
</tr>
<tr>
<td></td>
<td>Female: 12.0–16.0 g/dL</td>
</tr>
<tr>
<td></td>
<td>2.09–2.71 mmol/L</td>
</tr>
<tr>
<td></td>
<td>1.86–2.48 mmol/L</td>
</tr>
<tr>
<td><strong>Reticulocyte count</strong></td>
<td>0.5–1.5% of red cells</td>
</tr>
<tr>
<td></td>
<td>0.005–0.015</td>
</tr>
<tr>
<td><strong>Hemoglobin, plasma</strong></td>
<td>1–4 mg/dL</td>
</tr>
<tr>
<td></td>
<td>0.16–0.62 µmol/L</td>
</tr>
<tr>
<td><strong>Leukocyte count and differential</strong></td>
<td></td>
</tr>
<tr>
<td>Leukocyte count</td>
<td>4500–11,000/mm³</td>
</tr>
<tr>
<td></td>
<td>4.5–11.0 × 10⁹/L</td>
</tr>
<tr>
<td>Segmented neutrophils</td>
<td>54–62%</td>
</tr>
<tr>
<td></td>
<td>0.54–0.62</td>
</tr>
<tr>
<td>Band forms</td>
<td>3–5%</td>
</tr>
<tr>
<td></td>
<td>0.03–0.05</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>1–3%</td>
</tr>
<tr>
<td></td>
<td>0.01–0.03</td>
</tr>
<tr>
<td>Basophils</td>
<td>0–0.75%</td>
</tr>
<tr>
<td></td>
<td>0–0.0075</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>25–33%</td>
</tr>
<tr>
<td></td>
<td>0.25–0.33</td>
</tr>
<tr>
<td>Monocytes</td>
<td>3–7%</td>
</tr>
<tr>
<td></td>
<td>0.03–0.07</td>
</tr>
<tr>
<td><strong>Mean corpuscular hemoglobin</strong></td>
<td>25.4–34.6 pg/cell</td>
</tr>
<tr>
<td></td>
<td>0.39–0.54 fmol/cell</td>
</tr>
<tr>
<td><strong>Mean corpuscular volume</strong></td>
<td>80–100 µm³</td>
</tr>
<tr>
<td></td>
<td>80–100 fL</td>
</tr>
<tr>
<td><strong>Platelet count</strong></td>
<td>150,000–400,000/mm³</td>
</tr>
<tr>
<td></td>
<td>150–400 × 10⁹/L</td>
</tr>
<tr>
<td><strong>Prothrombin time</strong></td>
<td>11–15 seconds</td>
</tr>
<tr>
<td></td>
<td>11–15 seconds</td>
</tr>
<tr>
<td><strong>Activated partial thromboplastin time</strong></td>
<td>25–40 seconds</td>
</tr>
<tr>
<td></td>
<td>25–40 seconds</td>
</tr>
<tr>
<td><strong>Sedimentation rate, erythrocyte (Westergren)</strong></td>
<td>Male: 0–15 mm/h</td>
</tr>
<tr>
<td></td>
<td>Female: 0–20 mm/h</td>
</tr>
<tr>
<td></td>
<td>0–15 mm/h</td>
</tr>
<tr>
<td></td>
<td>0–20 mm/h</td>
</tr>
<tr>
<td><strong>Proteins in urine, total</strong></td>
<td>&lt; 150 mg/24 h</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.15 g/24 h</td>
</tr>
</tbody>
</table>
First Aid Checklist for the USMLE Step 1

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

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

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

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

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

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

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

**After the Exam**
- Celebrate, regardless.
- Send feedback to us on our Web site at [www.firstaidteam.com](http://www.firstaidteam.com).
SECTION I

Guide to Efficient Exam Preparation

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

“Finally, from so little sleeping and so much reading, his brain dried up and he went completely out of his mind.”
—Miguel de Cervantes Saavedra, Don Quixote
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:

- Not understanding how scoring is performed or what the score means
- 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 books or buying more books than you can ever use
- Buying only one publisher's review series for all subjects
- Not using practice examinations to maximum benefit
- 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 do it all alone

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

**USMLE STEP 1—THE BASICS**

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

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

- Anatomy
- Behavioral sciences
- Biochemistry
- Microbiology
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 46 questions each (see Figure 1) for a total of 322 questions, timed at 60 minutes per block. A short 11-question survey follows the last question block. The computer begins the survey with a prompt to proceed to the next block of questions.

Once an examinee finishes a particular question block on the CBT, he or she must click on a screen icon to continue to the next block. Examinees cannot go back and change their answers to questions from any previously completed block. However, changing answers is allowed within a block of questions as long as the block has not been ended and if time permits—unless the questions are part of a sequential item test set (see p. 4).

What Is the CBT Like?

Given the unique environment of the CBT, it’s important that you become familiar ahead of time with what your test-day conditions will be like. In fact, you can easily add 15 minutes to your break time! This is because the 15-minute tutorial offered on exam day may be skipped if you are already familiar with the exam procedures and the testing interface. The 15 minutes is then added to your allotted break time of 45 minutes for a total of 1 hour of potential break time. You can download the tutorial from the USMLE Web site and do it before test day. This tutorial is the exact same interface you will use in the exam; learn it now and you can skip taking it during the exam, giving you 15 extra minutes of break time. You can also gain experience with the CBT format by taking the 150 practice questions available online or by signing up for a practice session at a test center.


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

The typical question screen in the CBT consists of a question followed by a number of choices on which an examinee can click, together with several navigational buttons on the top of the screen. There is a countdown timer on the lower left corner of the screen as well. There is also a button that allows the examinee to mark a question for review. If a given question happens to be longer than the screen (which occurs very rarely), a scroll bar will appear on the right, allowing the examinee to see the rest of the question. Regardless of whether the examinee clicks on an answer choice or leaves it blank, he or she must click the “Next” button to advance to the next question.

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

The examinee can call up a window displaying normal laboratory values. In order to do so, he or she must click the “Lab” icon on the top part of the screen. Afterward, the examinee will have the option to choose between “Blood,” “Cerebrospinal,” “Hematologic,” or “Sweat and Urine.” The normal-values screen may obscure the question if it is expanded. The examinee may have to scroll down to search for the needed lab values. You might want to memorize some common lab values so you spend less time on questions that require you to analyze these.
The CBT interface provides a running list of questions on the left part of the screen at all times. The software also permits examinees to highlight or cross out information by using their mouse. Finally, there is a “Notes” icon on the top part of the screen that allows students to write notes to themselves for review at a later time. Being familiar with these features can save time and may help you better organize the information you need to answer a question.

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

The same USMLE Step 1 sample test items (150 questions) available on the USMLE Web site, www.usmle.org, are used at these sessions. No new items will be presented. The session is divided into a short tutorial and three 1-hour blocks of 50 test items each at a cost of about $75, if your testing region is in the United States or Canada. Students receive a printed percent-correct score after completing the session. No explanations of questions are provided.

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

How Do I Register to Take the Exam?

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

U.S. students can apply to take Step 1 at the NBME Web site. This application allows you to select one of 12 overlapping three-month blocks in which to be tested (e.g., 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. Prometric has no access to the codes. Do not lose your permit! You will not be allowed to take the exam unless you present this permit along with an unexpired, government-
issued photo ID that includes your signature (such as a driver’s license or passport). Make sure the name on your photo ID exactly matches the name that appears on your scheduling permit.

Once you receive your scheduling permit, you may access the Prometric Web site or call Prometric’s toll-free number to arrange a time to take the exam. You may contact Prometric two weeks before the test date if you want to confirm identification requirements. Although requests for taking the exam may be completed more than six months before the test date, examinees will not receive their scheduling permits earlier than six months before the eligibility period. The eligibility period is the three-month period you have chosen to take the exam. Most medical students choose the April–June or June–August period. Because exams are scheduled on a “first-come, first-served” basis, it is recommended that you contact Prometric as soon as you receive your permit. After you’ve scheduled your exam, it’s a good idea to confirm your exam appointment with Prometric at least one week before your test date. Prometric will provide appointment confirmation on a print-out and by email. Be sure to read the 2015 USMLE Bulletin of Information for further details.

What If I Need to Reschedule the Exam?

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

When Should I Register for the Exam?

Although there are no deadlines for registering for Step 1, you should plan to register at least six months ahead of your desired test date. This 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 U.S. medical students, the desired testing window is in June, since most medical school curricula for the second year end in May or June. Thus, U.S. 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 call for your test date (after you receive your scheduling permit). For a list of Prometric locations nearest you, visit www.prometric.com.

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

The USMLE reports scores in three to four weeks, unless there are delays in score processing. Examinees will be notified via email when their scores are available. By following the online instructions, examinees will be able to view, download, and print their score report. Additional information about score timetables and accessibility is available on the official USMLE Web site.

What About Time?

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

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

The computer will keep track of how much time has elapsed on the exam. However, the computer will show you only how much time you have remaining in a given block. Therefore, it is up to you to determine if you are pacing yourself properly (at a rate of approximately one question per 78 seconds).

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

Forty-five minutes is the minimum break time for the day, but you are not required to use all of it, nor are you required to use any of it. You can gain extra break time (but not time for the question blocks) by skipping the tutorial or by finishing a block ahead of the allotted time. Any time remaining on the clock when you finish a block gets added to your remaining break time. Once a new question block has been started, you may not take a break until you have reached the end of that block. If you do so, this will be recorded as an “unauthorized break” and will be reported on your final score report.
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 and pocket checks. Some students recommend pocketless clothing on exam day to streamline the process.

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

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

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

**What Types of Questions Are Asked?**

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

**How Is the Test Scored?**

Each Step 1 examinee receives an electronic score report that includes the examinee’s pass/fail status, a three-digit test score, and a graphic depiction of the examinee’s performance by discipline and organ system or subject area. The actual organ system profiles reported may depend on the statistical characteristics of a given administration of the examination.

The NBME provides a three-digit test score based on the total number of items answered correctly on the examination (see Figure 2). Since some questions may be experimental and are not counted, it is possible to get different scores for the same number of correct answers. The most recent mean score was 228 with a standard deviation of approximately 21.
A score of 192 or higher is required to pass Step 1. The NBME does not report the minimum number of correct responses needed to pass, but estimates that it is roughly 60-70%. The NBME may adjust the minimum passing score in the future, so please check the USMLE Web site or www.firstaidteam.com for updates.

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

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

**What Does My Score Mean?**

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

**TABLE 1. Passing Rates for the 2012-2013 USMLE Step 1.**

<table>
<thead>
<tr>
<th></th>
<th>2012</th>
<th>% Passing</th>
<th>2013</th>
<th>% Passing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopathic 1st takers</td>
<td>18,723</td>
<td>96%</td>
<td>19,108</td>
<td>97%</td>
</tr>
<tr>
<td>Repeaters</td>
<td>1,133</td>
<td>68%</td>
<td>915</td>
<td>72%</td>
</tr>
<tr>
<td>Allopathic total</td>
<td>19,856</td>
<td>94%</td>
<td>20,023</td>
<td>95%</td>
</tr>
<tr>
<td>Osteopathic 1st takers</td>
<td>2,496</td>
<td>92%</td>
<td>2,680</td>
<td>94%</td>
</tr>
<tr>
<td>Repeaters</td>
<td>68</td>
<td>68%</td>
<td>46</td>
<td>74%</td>
</tr>
<tr>
<td>Osteopathic total</td>
<td>2,564</td>
<td>91%</td>
<td>2,726</td>
<td>94%</td>
</tr>
<tr>
<td>Total U.S./Canadian</td>
<td>22,420</td>
<td>94%</td>
<td>22,749</td>
<td>95%</td>
</tr>
<tr>
<td>IMG 1st takers</td>
<td>14,201</td>
<td>76%</td>
<td>14,649</td>
<td>79%</td>
</tr>
<tr>
<td>Repeaters</td>
<td>4,261</td>
<td>40%</td>
<td>3,772</td>
<td>44%</td>
</tr>
<tr>
<td>IMG total</td>
<td>18,462</td>
<td>68%</td>
<td>18,421</td>
<td>72%</td>
</tr>
<tr>
<td>Total Step 1 examinees</td>
<td>40,882</td>
<td>82%</td>
<td>41,170</td>
<td>85%</td>
</tr>
</tbody>
</table>
Beyond that, the main point of having a quantitative score is to give you a sense of how well you’ve done on the exam and to help schools and residencies rank their students and applicants, respectively.

**Official NBME/USMLE Resources**

The NBME offers a Comprehensive Basic Science Examination (CBSE) for practice that is a shorter version of the Step 1. The CBSE contains four blocks of 50 questions each and covers material that is typically learned during the basic science years. Scores range from 45 to 95 and correlate with a Step 1 equivalent (see Table 2). The standard error of measurement is approximately 3 points, meaning a score of 80 would estimate the student’s proficiency is somewhere between 77 and 83. In other words, the actual Step 1 score could be predicted to be between 218 and 232. Of course, these values do not correlate exactly, and they do not reflect different test preparation methods. Many schools use this test to gauge whether a student is expected to pass Step 1. If this test is offered, it is usually conducted at the end of regular didactic time before any dedicated Step 1 preparation. Use the information to help set realistic goals and timetables for your success.

The NBME also offers the Comprehensive Basic Science Self-Assessment (CBSSA). Students who prepared for the exam using this Web-based tool reported that they found the format and content highly indicative of questions tested on the actual exam. In addition, the CBSSA is a fair predictor of USMLE performance (see Table 3).

The CBSSA exists in two forms: a standard-paced and a self-paced format, both of which consist of four sections of 50 questions each (for a total of 200 multiple choice items). The standard-paced format allows the user up to 65 minutes to complete each section, reflecting time limits similar to the actual exam. By contrast, the self-paced format places a 4:20 time limit on answering all multiple choice questions.

Keep in mind that this bank of questions is available only on the Web. The NBME requires that users log on, register, and start the test within 30 days of registration. Once the assessment has begun, users are required to complete the sections within 20 days. Following completion of the questions, the CBSSA provides a performance profile indicating the user’s relative strengths and weaknesses, much like the report profile for the USMLE Step 1 exam. The profile is scaled with an average score of 500 and a standard deviation of 100. Please note that the CBSSAs do not list the correct answers to the questions at the end of the session. However, some forms can be purchased with an extended feedback option; these tests show you which questions you answered incorrectly, but do not show you the correct answer or explain why your choice was wrong. Feedback from the self-assessment takes the form of a performance profile and nothing more. The NBME charges $50 for

---

**TABLE 2. CBSE to USMLE Score Prediction.**

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

*Practice questions may be easier than the actual exam.*
assessments without feedback and $60 for assessments with expanded feedback. The fees are payable by credit card or money order. For more information regarding the CBSE and the CBSSA, visit the NBME’s Web site at www.nbme.org.

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

Lastly, the International Foundations of Medicine (IFOM) offers a Basic Science Examination (BSE) practice exam at participating Prometric test centers for $200. Students may also take the self-assessment test online for $35 through the NBME’s Web site. 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/.

### TABLE 3. CBSSA to USMLE Score Prediction.

<table>
<thead>
<tr>
<th>CBSSA Score</th>
<th>Approximate USMLE Step 1 Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>164</td>
</tr>
<tr>
<td>250</td>
<td>175</td>
</tr>
<tr>
<td>300</td>
<td>185</td>
</tr>
<tr>
<td>350</td>
<td>196</td>
</tr>
<tr>
<td>400</td>
<td>207</td>
</tr>
<tr>
<td>450</td>
<td>217</td>
</tr>
<tr>
<td>500</td>
<td>228</td>
</tr>
<tr>
<td>550</td>
<td>239</td>
</tr>
<tr>
<td>600</td>
<td>249</td>
</tr>
<tr>
<td>650</td>
<td>260</td>
</tr>
<tr>
<td>700</td>
<td>271</td>
</tr>
<tr>
<td>750</td>
<td>281</td>
</tr>
<tr>
<td>800</td>
<td>292</td>
</tr>
</tbody>
</table>

---

**DEFINING YOUR GOAL**

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

Certain highly competitive residency programs, such as those in plastic surgery and orthopedic surgery, have acknowledged their use of Step 1 scores in the selection process. In such residency programs, greater emphasis may be placed on attaining a high score, so students who seek to enter these programs may wish to consider aiming for a very high score on the Step 1 exam (see Figure 3). At the same time, your Step 1 score is only one of a number of factors that are assessed when you apply for residency. In fact, many residency programs value other criteria such as letters of recommendation, third-year clerkship grades, honors, and research experience more than a high score on Step 1. Fourth-year medical students who have recently completed the residency application process can be a valuable resource in this regard.
*EXCELling in the preclinical years*

Many students feel overwhelmed during the first few weeks of medical school and struggle to find a workable system. Strategies that worked during your undergraduate years may or may not work as you prepare for the USMLE Step 1. Below are three study methods to use during the preclinical years and their effectiveness for Step 1 preparation. Regardless of your choice, the foundation of knowledge you build during your basic science years is the most important resource for success on the USMLE Step 1.

**Highlight, Read, and Reread**

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

**Flash cards**

There is no shortage of flash card applications, from make-your-own cards to purchasable premade decks. Self-made flash cards, if done correctly, offer the ability to objectively test necessary facts. Written in an open-ended format and coupled with spaced repetition, they train both recognition and recall. Apps exist for various smartphones and tablets, so the flash cards are always accessible. However, the speed of creating digital cards and sharing can lead to flash card overload (it is unsustainable to make 50 flash cards per lecture!). Even at a modest pace, the thousands upon thousands of cards are too many for Step 1 preparation. Unless you have specified high-yield cards...
(and checked the content with high-yield resources), stick to premade cards by reputable sources that curate the vast amount of knowledge for you.

**Differential Tables and Summaries**

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

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**TIMELINE FOR STUDY**

**Before Starting**

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

**Make a Schedule**

After you have defined your goals, map out a study schedule that is consistent with your objectives, your vacation time, the difficulty of your ongoing coursework, and your family and social commitments (see Figure 4). Determine whether you want to spread out your study time or concentrate it into 14-hour study days in the final weeks. Then factor in your own history in preparing for standardized examinations (e.g., SAT, MCAT). Talk to students at your school who have recently taken Step 1. Ask them for their study schedules, especially those who have study habits and goals similar to yours.

Typically, U.S. medical students allot between five and seven weeks for dedicated preparation for Step 1. 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.

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

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

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

Year(s) Prior

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

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 First Aid for the Student with a Disability, p. 41).

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 school work strong, take a day off, and then get to work. Start by simulating a full-length USMLE Step 1 if you haven’t yet done so. Consider doing one NBME CBSSA and the 150 free questions from the NBME Web site. Alternatively, you could choose 7 blocks of randomized questions from a commercial question bank. Make sure you get feedback on your strengths and weaknesses and adjust your studying accordingly. Many students study from review sources or comprehensive programs for part of the day, then do question blocks. Also, keep in mind that reviewing 46 questions can take upward of two hours. Feedback from CBSSA exams and question banks will help you focus on your weaknesses.

One Week Prior

Make sure you have your CIN (found on your scheduling permit) as well as other items necessary for the day of the examination, including a current driver’s license or another form of photo ID with your signature (make sure the name on your ID exactly matches that on your scheduling permit). Confirm the Prometric testing center location and test time. Work out how you will get to the testing center and what parking and traffic problems you might encounter. Drive separately from other students taking the test on the same day, and exchange cell phone numbers in case of emergencies. If possible, visit the testing site to get a better idea of the testing conditions you will face. Determine what you will do for lunch. Make sure you have everything you need to ensure that you will be comfortable and alert at the test site. It may be beneficial to adjust your schedule to start waking up at the same time that you will on your test day. And of course, make sure to maintain a healthy lifestyle and get enough sleep.
One 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 (e.g., massage, exercise, warm milk, no back-lit screens at night). Do not change your daily routine prior to the exam. Exam day is not the day for a caffeine-withdrawal headache.

Morning of the Exam

On the morning of the Step 1 exam, wake up at your regular time and eat a normal breakfast. If you think it will help you, have a close friend or family member check to make sure you get out of bed. Make sure you have your scheduling permit admission ticket, test-taking materials, and comfort measures as discussed earlier. Wear loose, comfortable clothing. Plan for a variable temperature in the testing center. Arrive at the test site 30 minutes before the time designated on the admission ticket; however, do not come too early, as doing so may intensify your anxiety. When you arrive at the test site, the proctor should give you a USMLE information sheet that will explain critical factors such as the proper use of break time. Seating may be assigned, but ask to be reseated if necessary; you need to be seated in an area that will allow you to remain comfortable and to concentrate. Get to know your testing station, especially if you have never been in a Prometric testing center before. Listen to your proctors regarding any changes in instructions or testing procedures that may apply to your test site.

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

After the Test

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

### STUDY MATERIALS

#### Quality and Cost Considerations

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

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

#### Review Books

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

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

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

#### Practice Tests

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

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.

Clinical Review Books

Keep your eye out for more clinically oriented review books; purchase them early and begin to use them. A number of students are turning to Step 2 CK books, pathophysiology books, and case-based reviews to prepare for the clinical vignettes. Examples of such books include:

- First Aid Cases for the USMLE Step 1 (McGraw-Hill)
- First Aid for the Wards (McGraw-Hill)
- First Aid Clerkship series (McGraw-Hill)
- Blueprints clinical series (Lippincott Williams & Wilkins)
- PreTest Physical Diagnosis (McGraw-Hill)
- Washington Manual (Lippincott Williams & Wilkins)

Texts, Syllabi, and Notes

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 (e.g., drug dosages, complex chemical structures). Syllabi, although familiar, are inconsistent across medical schools and frequently reflect the emphasis of individual faculty, which often does not correspond to that of the USMLE Step 1. Syllabi also tend to be less organized than top-rated books and generally contain fewer diagrams and study questions.

Test-taking Strategies

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

- Most practice exams are shorter and less clinical than the real thing.
- Use practice tests to identify concepts and areas of weakness, not just facts that you missed.
- Practice! Develop your test-taking skills and strategies well before the test date.
Pacing

You have seven hours to complete 322 questions. Note that each one-hour block contains 46 questions. This works out to about 78 seconds per question. If you find yourself spending too much time on a question, mark the question, make an educated guess, and move on. If time permits, come back to the question later. Remember that some questions may be experimental and do not count for points (and reassure yourself that these experimental questions are the ones that are stumping you). In the past, pacing errors have been detrimental to the performance of even highly prepared examinees. The bottom line is to keep one eye on the clock at all times!

Dealing with Each Question

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

Guessing

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

Changing Your Answer

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

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.

Strategy

Remember that Step 1 vignettes usually describe diseases or disorders in their most classic presentation. So look for cardinal signs (e.g., 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.
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.\(^5\) You may take Step 1 no more than three times within a 12-month period. Your fourth and subsequent attempts must be at least 12 months after your first attempt at that exam and at least six months after your most recent attempt at that exam.

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

### IF YOU FAILED

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

### TESTING AGENCIES

- **National Board of Medical Examiners (NBME)**
  Department of Licensing Examination Services
  3750 Market Street
  Philadelphia, PA 19104-3102
  (215) 590-9500
  Fax: (215) 590-9457
  Email: webmail@nbme.org
  www.nbme.org

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

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¬ First Aid for the Student with a Disability 41
“International medical graduate” (IMG) is the accepted term now used to describe any student or graduate of a non-U.S., non-Canadian, non–Puerto Rican medical school, regardless of whether he or she is a U.S. citizen or resident. Technically the term IMG encompasses FMGs (foreign medical graduates; i.e., medical graduates from medical schools outside the United States who are not residents of the United States—that is, U.S. citizens or green-card holders), although the terms IMG and FMG are often used interchangeably.

**IMG’s Steps to Licensure in the United States**

To be eligible to take the USMLE Steps, you (the applicant) must be officially enrolled in a medical school located outside the United States and Canada that is listed in the International Medical Education Directory (IMED; http://www.faimer.org/resources/imed.html), both at the time you apply for examination and on your test day. In addition, your “Graduation Year” must be listed as “Current” at the time you apply and on your test day. If you are an IMG, you must go through the following steps (not necessarily in this order) to apply for residency programs and become licensed to practice in the United States. You must complete these steps even if you are already a practicing physician and have completed a residency program in your own country.

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

Section I

Certification (i.e., Step 1, Step 2 CK, and Step 2 CS) by the rank order list deadline (usually in late February before the Match). If you do not pass these exams by the deadline, you will be withdrawn from the Match.

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

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

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

The USMLE and the IMG

The USMLE is a series of standardized exams that give IMGs and U.S. medical graduates a level playing field. The passing marks for IMGs for Step 1, Step 2 CK, and Step 2 CS are determined by a statistical distribution that is based on the scores of U.S. medical school students. For example, to pass Step 1, you will probably have to score higher than the bottom 8–10% of U.S. and Canadian graduates.
Under USMLE program rules, a maximum of six attempts will be permitted to pass any USMLE Step or component exam. There is a limit of three attempts within a 12-month period for any of the USMLE Steps.

**Timing of the USMLE**

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

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

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

**USMLE Step 1 and the IMG**

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

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

**Fee.** The fee for Step 1 is $850 plus an international test delivery surcharge (if you choose a testing region other than the United States or Canada).

**Statistics.** In 2013–2014, 79% of IMG examinees passed Step 1 on their first attempt, compared with 97% of MD degree examinees from the United States and Canada.

**Tips.** Although few if any students feel totally prepared to take Step 1, IMGs in particular require serious study and preparation in order to reach their full potential on this exam. It is also imperative that IMGs do their best on Step 1, as a poor score on Step 1 is a distinct disadvantage in applying for most residencies. Remember that if you pass Step 1, you cannot retake it in an attempt to improve your score. Your goal should thus be to beat the mean, because you can then assert with confidence that you have done better.
than average for U.S. students (see Table 4). Higher Step 1 scores will also lend credibility to your residency application and help you get into highly competitive specialties such as radiology, orthopedics, and dermatology.

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

**USMLE Step 2 CK and the IMG**

**What Is the Step 2 CK?** It is a computerized test of the clinical sciences consisting of up to 355 multiple-choice questions divided into eight blocks. It can be taken at Prometric centers in the United States and several other countries.

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

- Internal medicine
- Obstetrics and gynecology-

<table>
<thead>
<tr>
<th>Specialty</th>
<th>U.S. Graduates</th>
<th>U.S. IMGs</th>
<th>Non-U.S. IMGs</th>
</tr>
</thead>
<tbody>
<tr>
<td>All specialties</td>
<td>230</td>
<td>217</td>
<td>227</td>
</tr>
<tr>
<td>Anesthesiology</td>
<td>230</td>
<td>234</td>
<td>226</td>
</tr>
<tr>
<td>Dermatology(^a)</td>
<td>247</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Emergency medicine</td>
<td>230</td>
<td>225</td>
<td>226</td>
</tr>
<tr>
<td>Family medicine</td>
<td>218</td>
<td>206</td>
<td>213</td>
</tr>
<tr>
<td>Internal medicine</td>
<td>231</td>
<td>221</td>
<td>231</td>
</tr>
<tr>
<td>Neurology</td>
<td>230</td>
<td>216</td>
<td>230</td>
</tr>
<tr>
<td>Obstetrics and gynecology</td>
<td>226</td>
<td>221</td>
<td>226</td>
</tr>
<tr>
<td>Pathology</td>
<td>231</td>
<td>224</td>
<td>226</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>226</td>
<td>216</td>
<td>223</td>
</tr>
<tr>
<td>Physical medicine and rehabilitation</td>
<td>220</td>
<td>223</td>
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<td>Psychiatry</td>
<td>220</td>
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<tr>
<td>Diagnostic radiology</td>
<td>241</td>
<td>237</td>
<td>232</td>
</tr>
<tr>
<td>General surgery</td>
<td>232</td>
<td>227</td>
<td>233</td>
</tr>
</tbody>
</table>

\(^a\)No PGY-1 positions were filled by IMGs. Fourteen PGY-2 positions were filled by IMGs. Source: www.nrmp.org.
Special Situations

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

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

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

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

**Fee.** The fee for the Step 2 CK is $850 plus an international test delivery surcharge (if you choose a testing region other than the United States or Canada).

**Statistics.** In 2012–2013, 84% of ECFMG candidates passed the Step 2 CK on their first attempt, compared with 98% of MD degree examinees from U.S. and Canadian schools.

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

**USMLE Step 2 CS and the IMG**

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

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

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

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

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

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

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

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

**Fee.** The fee for the Step 2 CS is $1480.

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

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

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

For more information about the Step 2 CS exam, please refer to First Aid for the Step 2 CS.
**USMLE Step 3 and the IMG**

**What Is the USMLE Step 3?** It is a two-day computerized test in clinical medicine consisting of 454 multiple-choice questions and 13 computer-based case simulations (CCS). The exam aims to test your knowledge and its application to patient care and clinical decision making (i.e., this exam tests if you can safely practice medicine independently and without supervision). Please go to the USMLE Web site to learn more about recent changes to the exam.

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

**Fee.** The fee for Step 3 is $815.

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

- Have completed an MD or DO degree from an LCME- or AOA-accredited U.S. or Canadian medical school, or from a medical school outside the U.S. and Canada listed in the International Medical Education Directory.
- Have taken and passed the Step 1, Step 2 CK, and Step 2 CS exams.
- If an IMG: be certified by the ECFMG or have completed a Fifth Pathway program.

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

**Statistics.** In 2013–2014, 87% of IMG candidates passed the Step 3 on their first attempt, compared with 96% of MD degree examinees from U.S. and Canadian schools.

**Residencies and the IMG**

In the Match, the number of U.S.-citizen IMG applications has grown over the past few years, while the percentage accepted has remained constant (see Table 5). More information about residency programs can be obtained at www.ama-assn.org.

**The Match and the IMG**

Given the growing number of IMG candidates with strong applications, you should bear in mind that good USMLE scores are not the only way to gain a competitive edge. However, USMLE Step 1 and Step 2 CK scores continue to be used as the initial screening mechanism when candidates are being considered for interviews.
Based on accumulated IMG Match experiences over recent years, here are a few pointers to help IMGs maximize their chances for a residency interview:

- **Apply early.** Programs offer a limited number of interviews and often select candidates on a first-come, first-served basis. Because of this, you should aim to complete the entire process of applying for the ERAS token, registering with the Association of American Medical Colleges (AAMC), mailing necessary documents to ERAS, and completing the ERAS application by mid-September (see Figure 5). Community programs usually send out interview offers earlier than do university and university-affiliated programs.

- **U.S. clinical experience helps.** Externships and observerships in a U.S. hospital setting have emerged as an important credential on an IMG application. Externships are like short-term medical school internships and offer hands-on clinical experience. Observerships, also called “shadowing,” involve following a physician and observing how he or she manages patients. Some programs require students to have participated in an externship or observership before applying. It is best to gain such an experience before or at the time you apply to various programs so that you can mention it on your ERAS application. If such an experience or opportunity comes up after you apply, be sure to inform the programs accordingly.

- **Clinical research helps.** University programs are attracted to candidates who show a strong interest in clinical research and academics. They may even relax their application criteria for individuals with unique backgrounds and strong research experience. Publications in well-known journals are an added bonus.

- **Time the Step 2 CS well.** ECFMG has published the new Step 2 CS score-reporting schedule for 2014–2015 at http://www.ecfmg.org. Most program directors would like to see a passing score on the Step 1, Step 2 CK, and Step 2 CS exams before they rank an IMG on their rank order list in mid-February. There have been many instances in which candidates have lost a potential Match—either because of delayed CS results or because they have been unable to retake the exam on time.

Most U.S. hospitals allow externship only when the applicant is actively enrolled in a medical school, so plan ahead.
following a failure. It is difficult to predict a result on the Step 2 CS, since the grading process is not very transparent. Therefore, it is advisable to take the Step 2 CS as early as possible in the application year.

- **U.S. letters of recommendation** help. Letters of recommendation from clinicians practicing in the United States carry more weight than recommendations from home countries.

- **Step up the Step 3.** If H1B visa sponsorship is desired, aim to have Step 3 results by January of the Match year. In addition to the visa advantage you will gain, an early and good Step 3 score may benefit IMGs who have been away from clinical medicine for a while as well as those who have low scores on Step 1 and the Step 2 CK.

- **Verify medical credentials in a timely manner.** Do not overlook the medical school credential verification process. The ECFMG certificate arrives only after credentials have been verified and after you have passed

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**FIGURE 5. IMG Timeline for Application.**

<table>
<thead>
<tr>
<th>Month</th>
<th>Tasks</th>
</tr>
</thead>
<tbody>
<tr>
<td>June</td>
<td>Obtain ERAS token and obtain AAMC ID</td>
</tr>
<tr>
<td></td>
<td>If USMLE Steps 1, 2 CS, and 2 CK completed: request ECFMG certification</td>
</tr>
<tr>
<td>July</td>
<td>Send documents to ERAS</td>
</tr>
<tr>
<td></td>
<td>Request letters of recommendation be uploaded</td>
</tr>
<tr>
<td></td>
<td>Complete CAF and personal statement on MyERAS</td>
</tr>
<tr>
<td>August</td>
<td></td>
</tr>
<tr>
<td>September</td>
<td>Select and apply to programs through MyERAS</td>
</tr>
<tr>
<td>October</td>
<td>Schedule and attend interviews</td>
</tr>
<tr>
<td></td>
<td>Complete any pending USMLE Step exams</td>
</tr>
<tr>
<td>November</td>
<td></td>
</tr>
<tr>
<td>December</td>
<td></td>
</tr>
<tr>
<td>January</td>
<td>Obtain ECFMG certification (if not done earlier)</td>
</tr>
<tr>
<td>February</td>
<td>Submit rank order list</td>
</tr>
<tr>
<td></td>
<td>Complete USMLE Step 3 (if interested in H1B)</td>
</tr>
<tr>
<td>March</td>
<td>Match results (day 1)</td>
</tr>
<tr>
<td></td>
<td>SOAP (days 3–5)</td>
</tr>
<tr>
<td></td>
<td>Matched program results (day 5)</td>
</tr>
</tbody>
</table>

* A good score on the Step 3 may help offset poorer scores on the Step 1 or 2 CK exams.
Step 1, the Step 2 CK, and the Step 2 CS, so you should keep track of the process and check with the ECFMG from time to time about your status.

- Don’t count on a pre-Match. Programs participating in NRMP Match can no longer offer a pre-Match.

What if You Do Not Match?

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

Resources for the IMG

- ECFMG
  3624 Market Street
  Philadelphia, PA 19104-2685
  (215) 386-5900
  Fax: (215) 386-9196
  www.ecfmg.org

  The ECFMG telephone number is answered only between 9:00 a.m.–5:00 p.m. Monday through Friday EST. The ECFMG often takes a long time to answer the phone, which is frequently busy at peak times of the year, and then gives you a long voice-mail message—so it is better to write or fax early than to rely on a last-minute phone call. Do not contact the NBME, as all IMG exam matters are conducted by the ECFMG. The ECFMG also publishes an information booklet on ECFMG certification and the USMLE program, which gives details on the dates and locations of forthcoming Step tests for IMGs together with application forms. It is free of charge and is also available from the public affairs offices of U.S. embassies and consulates worldwide as well as from Overseas Educational Advisory Centers. You may order single copies of the handbook by calling (215) 386-5900, preferably on weekends or between 6 P.M. and 6 A.M. Eastern time, or by faxing to (215) 386-9196. Requests for multiple copies must be made by fax or mail on organizational letterhead. The full text of the booklet is also available on the ECFMG’s Web site at www.ecfmg.org.
The FSMB has a number of publications available, including free policy documents. To obtain these publications, print and mail the order form on the Web site listed above. Alternatively, write to Federation Publications at the above address. All orders must be prepaid with a personal check drawn on a U.S. bank, a cashier’s check, or a money order payable to the FSMB. Foreign orders must be accompanied by an international money order or the equivalent, payable in U.S. dollars through a U.S. bank or a U.S. affiliate of a foreign bank. For Step 3 inquiries, the telephone number is (817) 868-4041.

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

Other resources that may be useful and of interest to IMGs include the following:


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

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

The COMLEX-USA series assesses osteopathic medical knowledge and clinical skills using clinical presentations and physician tasks. A description of the COMLEX-USA Written Examination Blueprints for each level, which outline the various clinical presentations and physician tasks that examinees will encounter, is given on the NBOME Web site. Another stated goal of the COMLEX-USA Level 1 is to create a more primary care–oriented exam that integrates osteopathic principles into clinical situations.
To be eligible to take the COMLEX-USA Level 1, you must have satisfactorily completed your first year in an American Osteopathic Association (AOA)–approved medical school. The office of the dean at each school informs the NBOME that a student has completed his or her first year of school and is in good standing. At this point, the NBOME sends out an email with detailed instructions on how to register for the exam.

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

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

Note that effective July 1, 2016, candidates taking COMLEX-USA examinations will be limited to a total of six attempts for each examination.

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

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

Questions are grouped into eight sections of 50 questions each in a manner similar to the USMLE. Reviewing and changing answers may be done only in the current section. A “review page” is presented for each block in order to advise test takers of questions completed, questions marked for further review, and incomplete questions for which no answer has been given.

Breaks are even more structured with COMLEX-USA than they are with the USMLE. Students are allowed to take a 10-minute break at the end of the second and sixth sections. Students who do not take these 10-minute breaks can apply the time toward their test time. After section 4, students are given a 40-minute lunch break. These are the only times a student is permitted a break. More information about the computer-based COMLEX-USA examinations can be obtained from www.nbome.org.
What Is the Difference Between the USMLE and the COMLEX-USA?

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

- Health promotion and disease prevention
- The history and physical
- Diagnostic technologies
- Management
- Scientific understanding of mechanisms
- Health care delivery

Although the COMLEX-USA and the USMLE are similar in scope, content, and emphasis, some differences are worth noting. For example, the interface is different; you cannot search for lab values. The expectation is that you can make a diagnosis without having performed testing. Fewer details are given about a patient’s condition, so a savvy student needs to know how to differentiate between similar pathologies. Also, age, gender, and race are key factors for diagnosis on the COMLEX-USA. Images are embedded in the question stem and the examinee has to click an attachment button to see the image. If you don’t read the question carefully, the attachment buttons are very easy to miss.

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

COMLEX-USA test takers can expect to have only a few questions on biochemistry, molecular biology, or lab technique. On the other hand, microbiology is very heavily tested by clinical presentation and by lab identification. Another main difference is that the COMLEX-USA exam stresses osteopathic manipulative medicine. Therefore, question banks specific to the USMLE will not be adequate, and supplementation with a question bank specific to the COMLEX-USA is highly recommended.

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

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

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

- **If you are applying to allopathic residencies.** Although there is growing acceptance of COMLEX-USA certification on the part of allopathic residencies, some allopathic programs prefer or even require passage of the USMLE Step 1. These include many academic programs, programs in competitive specialties (e.g., orthopedics, ophthalmology, or dermatology), and programs in competitive geographic areas (e.g., Vermont, Utah, and California). Fourth-year doctor of osteopathy (DO) students who have already Matched may be a good source of information about which programs and specialties look for USMLE scores. It is also a good idea to contact program directors at the institutions you are interested in to ask about their policy regarding the COMLEX-USA versus the USMLE.

- **If you are unsure about your postgraduate training plans.** Successful passage of both the COMLEX-USA Level 1 and the USMLE Step 1 is certain to provide you with the greatest possible range of options when you are applying for internship and residency training.

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

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

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

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

**NBOME**
8765 W. Higgins Road, Suite 200
Chicago, IL 60631-4174
(773) 714-0622
Fax: (773) 714-0631
www.nbome.org

The NBOME developed the Comprehensive Osteopathic Medical Self-Assessment Examination (COMSAE) series to fill the need for self-assessment on the part of osteopathic medical students. Many students take the COMSAE exam before the COMLEX-USA in addition to using test-bank questions and board review books. Students can purchase a copy of this exam at www.nbome.org/comsae.asp.

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

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

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

Since topics that were repeatedly tested appeared in all four booklets, students found it useful to review them in between the two test days. It is important to understand that the topics emphasized on the current exam may not be stressed on future exams. However, some topics are heavily tested each year, so it may be beneficial to have a solid foundation in the above-mentioned topics.
The National Board of Podiatric Medical Examiners (NBPMEx) offers the American Podiatric Medical Licensing Examinations (APMLE), which are designed to assess whether a candidate possesses the knowledge required to practice as a minimally competent entry-level podiatric surgeon. The APMLE is used as part of the licensing process governing the practice of podiatric medicine and surgery. The APMLE is recognized by all 50 states and the District of Columbia, the U.S. Army, the U.S. Navy, and the Canadian provinces of Alberta, British Columbia, and Ontario. Individual states use the examination scores differently; therefore, doctor of podiatric medicine (DPM) candidates should refer to the APMLE Bulletin of Information: 2014 Examinations.

The APMLE Part I is generally taken after the completion of the second year of podiatric medical education. Unlike the USMLE Step 1, there is no behavioral science section, nor is biomechanics tested. The exam samples seven basic science disciplines: general anatomy (13%); lower extremity anatomy (25%); biochemistry (7%); physiology (15%); microbiology and immunology (15%); pathology (12%); and pharmacology (15%). A detailed outline of topics and subtopics covered on the exam can be found in the APMLE Bulletin of Information, available at www.apmle.org.

Your APMLE Appointment

In early spring, your college registrar will have you fill out an application for the APMLE Part I. New this year, applicants can register for the exam online at www.prometric.com/NBPME. The exam will be offered at an independent Prometric testing facility in each city with a podiatric medical school (New York, Philadelphia, Miami, Cleveland, Chicago, Des Moines, Phoenix, Pomona, and San Francisco), along with any other city Prometric deems necessary. Please contact Prometric for a full list of testing sites. You may take the exam at any of these locations regardless of which school you attend. However, you must designate on your application which testing location you desire. Specific instructions about exam dates and registration deadlines can be found in the APMLE Bulletin.

Exam Format

The APMLE Part I is a written exam consisting of 205 questions. The test consists of multiple choice questions that have one best answer or multiple “select all that apply” answers, as well as a drag-and-drop section. Examinees have four hours in which to complete the exam and are given scratch paper and a calculator, both of which must be turned in at the end of the exam. Some questions on the exam will be “trial questions.” These questions are evaluated as future board questions but are not counted in your score.
Interpreting Your Score

Three to four weeks following the exam date, the dean’s office at the student’s respective school will receive scores. APMLE scores are reported as pass/fail, with a scaled score of at least 75 needed to pass. Historically, 85% of first-time test takers pass the APMLE Part I. Failing candidates receive a report with a score between 55 and 74 in addition to diagnostic messages intended to help identify strengths or weaknesses in specific content areas. If you fail the APMLE Part I, you must retake the entire examination at a later date. There is no limit to the number of times you can retake the exam.

Preparation for the APMLE Part I

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

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

The APMLE, like the USMLE, requires that you apply and integrate knowledge over several areas of basic science in order to answer exam questions. Students report that many questions emphasize clinical presentations; however, the facts in this book are very useful in helping students recall the various diseases and organisms. DPM candidates should expand on the high-yield pharmacology section and study antifungal drugs and treatments for *Pseudomonas*, methicillin-resistant *S. aureus*, candidiasis, and erythrasma. The high-yield section focusing on pathology is very useful; however, additional emphasis on diabetes mellitus and all its secondary manifestations, particularly peripheral neuropathy, should not be overlooked. Students should also focus on renal physiology and drug elimination, the biochemistry of gout, and neurophysiology, all of which have been noted to be important topics on the APMLE Part I exam.
A sample set of questions is found on the APMLE website www.apmle.org. These samples are somewhat similar in difficulty to actual board questions. If you have any questions regarding registration, fees, test centers, authorization forms, or score reports, please contact your college registrar or:

Prometric  
Phone: 877-302-8952  
Fax: 800-813-6670  
Email: nbpmeinquiry@prometric.com  
www.prometric.com

**FIRST AID FOR THE STUDENT WITH A DISABILITY**

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

To provide appropriate support, the administrators of the USMLE must be informed of both the nature and the severity of an examinee’s disability. Such documentation is required for an examinee to receive testing accommodations. Accommodations include extra time on tests, low-stimulation environments, extra or extended breaks, and zoom text.

**Who Can Apply for Accommodations?**

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

**Who Is Not Eligible for Accommodations?**

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

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

Getting the Information

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

Disability Services
National Board of Medical Examiners
3750 Market Street
Philadelphia, PA 19104-3102
(215) 590-9509
Fax: (215) 590-9457
Email: disabilityservices@nbme.org
www.usmle.org/test-accommodations

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

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

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

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

High-Yield General Principles

“There comes a time when for every addition of knowledge you forget something that you knew before. It is of the highest importance, therefore, not to have useless facts elbowing out the useful ones.”
—Sir Arthur Conan Doyle, A Study in Scarlet

“Never regard study as a duty, but as the enviable opportunity to learn.”
—Albert Einstein

“Live as if you were to die tomorrow. Learn as if you were to live forever.”
—Gandhi
HOW TO USE THE DATABASE

The 2015 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 pathology and the foundational principles of behavioral science, biochemistry, microbiology, immunology, and pharmacology. Section III focuses on organ systems, with subsections covering the embryology, anatomy and histology, physiology, pathology, and pharmacology relevant to each. Each subsection is then divided into smaller topic areas containing related facts. Individual facts are generally presented in a three-column format, with the **Title** of the fact in the first column, the **Description** of the fact in the second column, and the **Mnemonic** or **Special Note** in the third column. Some facts do not have a mnemonic and are presented in a two-column format. Others are presented in list or tabular form in order to emphasize key associations.

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

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

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

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

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Disclaimer

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

Behavioral Science

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

“It’s psychosomatic. You need a lobotomy. I’ll get a saw.”
—Calvin, “Calvin & Hobbes”

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

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

A heterogeneous mix of epidemiology, biostatistics, ethics, psychology, sociology, and more falls under the heading of behavioral science. Many medical students do not diligently study this discipline because the material is felt to be easy or a matter of common sense. In our opinion, this is a missed opportunity.

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

<table>
<thead>
<tr>
<th>STUDY TYPE</th>
<th>DESIGN</th>
<th>MEASURES/EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-sectional study</td>
<td>Collects data from a group of people to assess disease frequency (and related risk factors) at a particular point in time. Asks, “What is happening?”</td>
<td>Disease prevalence. Can show risk factor association with disease, but does not establish causality.</td>
</tr>
<tr>
<td>Case-control study</td>
<td>Compares a group of people with disease to a group without disease. Looks for prior exposure or risk factor. Asks, “What happened?”</td>
<td>Odds ratio (OR). “Patients with COPD had higher odds of a history of smoking than those without COPD.”</td>
</tr>
<tr>
<td>Cohort study</td>
<td>Compares a group with a given exposure or risk factor to a group without such exposure. Looks to see if exposure ↑ the likelihood of disease. Can be prospective (asks, “Who will develop disease?”) or retrospective (asks, “Who developed the disease [exposed vs. nonexposed]?”).</td>
<td>Relative risk (RR). “Smokers had a higher risk of developing COPD than nonsmokers.”</td>
</tr>
<tr>
<td>Twin concordance study</td>
<td>Compares the frequency with which both monozygotic twins or both dizygotic twins develop the same disease.</td>
<td>Measures heritability and influence of environmental factors (&quot;nature vs. nurture&quot;).</td>
</tr>
<tr>
<td>Adoption study</td>
<td>Compares siblings raised by biological vs. adoptive parents.</td>
<td>Measures heritability and influence of environmental factors.</td>
</tr>
</tbody>
</table>

### Clinical trial

Experimental study involving humans. Compares therapeutic benefits of 2 or more treatments, or of treatment and placebo. Study quality improves when study is randomized, controlled, and double-blinded (i.e., neither patient nor doctor knows whether the patient is in the treatment or control group). Triple-blind refers to the additional blinding of the researchers analyzing the data.

<table>
<thead>
<tr>
<th>DRUG TRIALS</th>
<th>TYPICAL STUDY SAMPLE</th>
<th>PURPOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>Small number of healthy volunteers.</td>
<td>“Is it safe?” Assesses safety, toxicity, pharmacokinetics, and pharmacodynamics.</td>
</tr>
<tr>
<td>Phase II</td>
<td>Small number of patients with disease of interest.</td>
<td>“Does it work?” Assesses treatment efficacy, optimal dosing, and adverse effects.</td>
</tr>
<tr>
<td>Phase III</td>
<td>Large number of patients randomly assigned either to the treatment under investigation or to the best available treatment (or placebo).</td>
<td>“Is it as good or better?” Compares the new treatment to the current standard of care.</td>
</tr>
<tr>
<td>Phase IV</td>
<td>Postmarketing surveillance of patients after treatment is approved.</td>
<td>“Can it stay?” Detects rare or long-term adverse effects. Can result in treatment being withdrawn from market.</td>
</tr>
</tbody>
</table>
Evaluation of diagnostic tests

Uses 2 × 2 table comparing test results with the actual presence of disease. TP = true positive; FP = false positive; TN = true negative; FN = false negative. Sensitivity and specificity are fixed properties of a test. PPV and NPV vary depending on disease prevalence.

Sensitivity (true-positive rate)

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

\[ \text{Sensitivity} = \frac{\text{TP}}{\text{TP} + \text{FN}} = 1 - \text{false-negative rate} \]

SN-N-OUT = highly Sensitive test, when Negative, rules OUT disease

If sensitivity is 100%, \( \frac{\text{TP}}{\text{TP} + \text{FN}} = 1 \), \( \text{FN} = 0 \), and all negatives must be TNs

Specificity (true-negative rate)

Proportion of all people without disease who test negative, or the probability that a test indicates no disease when disease is absent. Value approaching 100% is desirable for ruling in disease and indicates a low false-positive rate. High specificity test used for confirmation after a positive screening test.

\[ \text{Specificity} = \frac{\text{TN}}{\text{TN} + \text{FP}} = 1 - \text{false-positive rate} \]

SP-P-IN = highly Specific test, when Positive, rules IN disease

If specificity is 100%, \( \frac{\text{TN}}{\text{TN} + \text{FP}} = 1 \), \( \text{FP} = 0 \), and all positives must be TPs

Positive predictive value (PPV)

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

\[ \text{Positive predictive value} = \frac{\text{TP}}{\text{TP} + \text{FP}} \]

PPV varies directly with prevalence or pretest probability: high pretest probability → high PPV

Negative predictive value (NPV)

Proportion of negative test results that are true negative. Probability that person actually is disease free given a negative test result.

\[ \text{Negative predictive value} = \frac{\text{TN}}{\text{TN} + \text{FN}} \]

NPV varies inversely with prevalence or pretest probability: high pretest probability → low NPV

Incidence vs. prevalence

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

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

Prevalence = incidence for short duration disease (e.g., common cold).

Incidence looks at new cases (incidents).

Prevalence looks at all current cases.
Quantifying risk

Definitions and formulas are based on the classic 2x2 or contingency table.

<table>
<thead>
<tr>
<th>Risk factor or intervention</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

**Odds ratio (OR)**

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

\[
\text{OR} = \frac{a/c}{b/d} = \frac{ad}{bc}
\]

**Relative risk (RR)**

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

\[
\text{RR} = \frac{a/(a + b)}{c/(c + d)}
\]

**Attributable risk (AR)**

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

\[
\text{AR} = \frac{a}{a + b} - \frac{c}{c + d}
\]

**Relative risk reduction (RRR)**

The proportion of risk reduction attributable to the intervention as compared to a control (e.g., 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).

\[
\text{RRR} = 1 - \text{RR}
\]

**Absolute risk reduction (ARR)**

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

\[
\text{ARR} = \frac{c}{c + d} - \frac{a}{a + b}
\]

**Number needed to treat (NNT)**

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

\[
\text{NNT} = 1/\text{ARR}
\]

**Number needed to harm (NNH)**

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

\[
\text{NNH} = 1/\text{AR}
\]
## Precision vs. accuracy

<table>
<thead>
<tr>
<th></th>
<th>Precision</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>The consistency and reproducibility of a test (reliability). The absence of random variation in a test.</td>
<td>The trueness of test measurements (validity). The absence of systematic error or bias in a test.</td>
</tr>
<tr>
<td><strong>Random error</strong></td>
<td>↓ precision in a test. ↓ precision → ↓ standard deviation. ↓ precision → ↑ statistical power ($1 - \beta$).</td>
<td>Systematic error ↓ accuracy in a test.</td>
</tr>
</tbody>
</table>

### Diagrams:

- Accurate, not precise
- Precise, not accurate
- Accurate and precise
- Not accurate, not precise

---

**Note:**
- Precision = $\text{Accuracy} + \text{Random error}$
- Accuracy = $\text{Precision} - \text{Random error}$

---

**Table:**

<table>
<thead>
<tr>
<th>Precision</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not accurate, not precise</td>
<td>Not accurate, not precise</td>
</tr>
<tr>
<td>Accurate and precise</td>
<td>Accurate and precise</td>
</tr>
<tr>
<td>Precise, not accurate</td>
<td>Precise, not accurate</td>
</tr>
<tr>
<td>Accurate, not precise</td>
<td>Accurate, not precise</td>
</tr>
</tbody>
</table>
## Bias and study errors

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
<th>Examples</th>
<th>Strategy to reduce bias</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recruiting participants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Selection bias           | Error in assigning subjects to a study group resulting in an unrepresentative sample. Most commonly a sampling bias. | Berkson bias—study population selected from hospital is less healthy than general population  
Healthy worker effect—study population is healthier than the general population  
Non-response bias—participating subjects differ from nonrespondents in meaningful ways | Randomization  
Ensure the choice of the right comparison/reference group |
| **Performing study**     |                                                                                               |                                                                          |                         |
| Recall bias              | Awareness of disorder alters recall by subjects; common in retrospective studies.            | Patients with disease recall exposure after learning of similar cases     | Decrease time from exposure to follow-up |
| Measurement bias         | Information is gathered in a way that distorts it.                                            | Miscalibrated scale consistently overstates weights of subjects          | Use standardized method of data collection |
| Procedure bias           | Subjects in different groups are not treated the same.                                        | Patients in treatment group spend more time in highly specialized hospital units | Blinding and use of placebo reduce influence of participants and researchers on procedures and interpretation of outcomes as neither are aware of group allocation |
| Observer-expectancy bias | Researcher’s belief in the efficacy of a treatment changes the outcome of that treatment (aka Pygmalion effect; self-fulfilling prophecy). | If observer expects treatment group to show signs of recovery, then he is more likely to document positive outcomes |                         |
| **Interpreting results** |                                                                                               |                                                                          |                         |
| Confounding bias         | When a factor is related to both the exposure and outcome, but not on the causal pathway → factor distorts or confuses effect of exposure on outcome. | Pulmonary disease is more common in coal workers than the general population; however, people who work in coal mines also smoke more frequently than the general population | Multiple/repeated studies  
Crossover studies (subjects act as their own controls)  
Matching (patients with similar characteristics in both treatment and control groups) |
| Lead-time bias           | Early detection is confused with † survival.                                                  | Early detection makes it seem as though survival has increased, but the natural history of the disease has not changed | Measure “back-end” survival (adjust survival according to the severity of disease at the time of diagnosis) |
### Statistical distribution

<table>
<thead>
<tr>
<th>Measures of central tendency</th>
<th>Mean = ( \frac{\text{sum of values}}{\text{total number of values}} ).</th>
<th>Most affected by outliers (extreme values).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median = middle value of a list of data sorted from least to greatest.</td>
<td>If there is an even number of values, the median will be the average of the middle two values.</td>
<td></td>
</tr>
<tr>
<td>Mode = most common value.</td>
<td>Least affected by outliers.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Measures of dispersion</th>
<th>Standard deviation = how much variability exists from the mean in a set of values.</th>
<th>( \sigma = \text{SD}; n = \text{sample size} ).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard error of the mean = an estimate of how much variability exists between the sample mean and the true population mean.</td>
<td>( \text{SEM} = \frac{\sigma}{\sqrt{n}} ). SEM ↓ as n ↑.</td>
</tr>
</tbody>
</table>

### Normal distribution

Gaussian, also called bell-shaped. 
Mean = median = mode.

### Nonnormal distributions

<table>
<thead>
<tr>
<th>Bimodal</th>
<th>Suggests two different populations (e.g., metabolic polymorphism such as fast vs. slow acetylators; age at onset of Hodgkin lymphoma; suicide rate by age).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive skew</td>
<td>Typically, mean &gt; median &gt; mode. Asymmetry with longer tail on right.</td>
</tr>
<tr>
<td>Negative skew</td>
<td>Typically, mean &lt; median &lt; mode. Asymmetry with longer tail on left.</td>
</tr>
</tbody>
</table>

### Statistical hypotheses

<table>
<thead>
<tr>
<th>Null (H₀)</th>
<th>Hypothesis of no difference or relationship (e.g., there is no association between the disease and the risk factor in the population).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative (H₁)</td>
<td>Hypothesis of some difference or relationship (e.g., there is some association between the disease and the risk factor in the population).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study results</th>
<th>Reality</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₀</td>
<td>( \beta ) Type II error</td>
</tr>
<tr>
<td>H₁</td>
<td>( \alpha ) Type I error</td>
</tr>
</tbody>
</table>

#### Normal Distribution

68%  95%  99.7%

\(-\sigma\)  \(+\sigma\)  \(-2\sigma\)  \(+2\sigma\)  \(-3\sigma\)  \(+3\sigma\)
### Outcomes of statistical hypothesis testing

#### Correct result

- Stating that there is an effect or difference when one exists (null hypothesis rejected in favor of alternative hypothesis).
- Stating that there is not an effect or difference when none exists (null hypothesis not rejected).

#### Incorrect result

**Type I error (α)**
- Stating that there is an effect or difference when none exists (null hypothesis incorrectly rejected in favor of alternative hypothesis).
- $\alpha$ is the probability of making a type I error. $\alpha$ is judged against a preset $\alpha$ level of significance (usually $< .05$). If $p < 0.05$, then there is less than a 5% chance that the data will show something that is not really there.
- Also known as false-positive error.
- $\alpha = \text{you saw a difference that did not exist (e.g., convicting an innocent man)}$.

**Type II error (β)**
- Stating that there is not an effect or difference when one exists (null hypothesis is not rejected when it is in fact false).
- $\beta$ is the probability of making a type II error. $\beta$ is related to statistical power ($1 - \beta$), which is the probability of rejecting the null hypothesis when it is false.
- $\beta = \text{you were blind to the truth (e.g., setting a guilty man free)}$.
- If you $\uparrow$ sample size, you $\uparrow$ power. There is power in numbers.

<table>
<thead>
<tr>
<th>$\uparrow$ power and $\uparrow$ $\beta$ by:</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\uparrow$ sample size</td>
</tr>
<tr>
<td>$\uparrow$ expected effect size</td>
</tr>
<tr>
<td>$\uparrow$ precision of measurement</td>
</tr>
</tbody>
</table>

### Confidence interval

- Range of values in which a specified probability of the means of repeated samples would be expected to fall.
- CI = mean $\pm Z($SEM$)$.
- The 95% CI (corresponding to $p = .05$) is often used.
- For the 95% CI, $Z = 1.96$.
- For the 99% CI, $Z = 2.58$.
- If the 95% CI for a mean difference between 2 variables includes 0, then there is no significant difference and $H_0$ is not rejected.
- If the 95% CI for odds ratio or relative risk includes 1, $H_0$ is not rejected.
- If the CIs between 2 groups do not overlap $\Rightarrow$ statistically significant difference exists.
- If the CIs between 2 groups overlap $\Rightarrow$ usually no significant difference exists.
Common statistical tests

**t-test**
Checks differences between means of 2 groups. Tea is meant for 2. Example: comparing the mean blood pressure between men and women.

**ANOVA**
Checks differences between means of 3 or more groups.

**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 percentage of members of 3 different ethnic groups who have essential hypertension.

**Pearson correlation coefficient ($r$)**
$r$ 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. 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 $= r^2$ (value that is usually reported).

Disease prevention

**Primary**
Prevent disease occurrence (e.g., HPV vaccination)

**Secondary**
Screening early for disease (e.g., Pap smear)

**Tertiary**
Treatment to reduce disability from disease (e.g., chemotherapy)

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

Medicare and Medicaid
Medicare and Medicaid—federal programs that originated from amendments to the Social Security Act. Medicare is available to patients ≥ 65 years old, < 65 with certain disabilities, and those with end-stage renal disease. Medicaid is joint federal and state health assistance for people with very low income. Medicare is for Elderly. Medicaid is for Destitute.

The 4 parts of Medicare:
- Part A: Hospital insurance
- Part B: Basic medical bills (e.g., doctor’s fees, diagnostic testing)
- Part C: (Parts A+B) delivered by approved private companies
- Part D: Prescription drugs
### 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 (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 (e.g., triage). |

### Informed consent

A process (not just a document/signature) that requires:
- Disclosure: discussion of pertinent information
- Understanding: ability to comprehend
- Capacity: ability to reason and make one’s own decisions (distinct from competence, a legal determination)
- Voluntariness: freedom from coercion and manipulation

Patients must have an intelligent understanding of their diagnosis and the risks/benefits of proposed treatment and alternative options, including no treatment. Patient must be informed that he or she can revoke written consent at any time, even orally.

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

### Consent for minors

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

### Situations in which parental consent is usually not required:
- **Sex** (contraception, STIs, pregnancy)
- **Drugs** (addiction)
- **Rock and roll** (emergency/trauma)

Physicians should always encourage healthy minor-guardian communication.
## Decision-making capacity

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

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

## Advance directives

Instructions given by a patient in anticipation of the need for a medical decision. Details vary per state law.

### Oral advance directive

Incapacitated patient’s prior oral statements commonly used as guide. Problems arise from variance in interpretation. If patient was informed, directive was specific, patient made a choice, and decision was repeated over time to multiple people, then the oral directive is more valid.

### Living will (written advance directive)

Describes treatments the patient wishes to receive or not receive if he/she loses decision-making capacity. Usually, patient directs physician to withhold or withdraw life-sustaining treatment if he/she develops a terminal disease or enters a persistent vegetative state.

### Medical power of attorney

Patient designates an agent to make medical decisions in the event that he/she loses decision-making capacity. Patient may also specify decisions in clinical situations. Can be revoked anytime patient wishes (regardless of competence). More flexible than a living will.

## Surrogate decision-maker

If a patient loses decision-making capacity and has not prepared an advance directive, individuals (surrogates) who know the patient must determine what the patient would have done. Priority of surrogates: spouse > adult children > parents > adult siblings > other relatives.

## Confidentiality

Confidentiality respects patient privacy and autonomy. If patient is not present or is incapacitated, disclosing information to family and friends should be guided by professional judgment of patient’s best interest. The patient may voluntarily waive the right to confidentiality (e.g., insurance company request).

### General principles for exceptions to confidentiality:
- Potential physical harm to others is serious and imminent
- Likelihood of harm to self is great
- No alternative means exists to warn or to protect those at risk
- Physicians can take steps to prevent harm

### Examples of exceptions to patient confidentiality (many are state-specific) include:
- Reportable diseases (e.g., STIs, TB, hepatitis, food poisoning)—physicians may have a duty to warn public officials, who will then notify people at risk
- The Tarasoff decision—California Supreme Court decision requiring physician to directly inform and protect potential victim from harm
- Child and/or elder abuse
- Impaired automobile drivers (e.g., epileptics)
- Suicidal/homicidal patients
### Ethical situations

<table>
<thead>
<tr>
<th>SITUATION</th>
<th>APPROPRIATE RESPONSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient is not adherent.</td>
<td>Attempt to identify the reason for nonadherence and determine his/her willingness to change; do not coerce the patient into adhering or refer him/her to another physician.</td>
</tr>
<tr>
<td>Patient desires an unnecessary procedure.</td>
<td>Attempt to understand why the patient wants the procedure and address underlying concerns. Do not refuse to see the patient or refer him/her to another physician. Avoid performing unnecessary procedures.</td>
</tr>
<tr>
<td>Patient has difficulty taking medications.</td>
<td>Provide written instructions; attempt to simplify treatment regimens; use teach-back method (ask patient to repeat medication regimen back to physician) to ensure patient comprehension.</td>
</tr>
<tr>
<td>Family members ask for information about patient’s prognosis.</td>
<td>Avoid discussing issues with relatives without the patient’s permission.</td>
</tr>
<tr>
<td>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.”</td>
<td>Attempt to identify why the family member believes such information would be detrimental to the patient’s condition. Explain that as long as the patient has decision-making capacity and does not indicate otherwise, communication of information concerning his/her care will not be withheld.</td>
</tr>
<tr>
<td>A child wishes to know more about his/her illness.</td>
<td>Ask what the parents have told the child about his/her illness. Parents of a child decide what information can be relayed about the illness.</td>
</tr>
<tr>
<td>A 17-year-old girl is pregnant and requests an abortion.</td>
<td>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 attempt to sway the decision of the patient to have an elective abortion (regardless of maternal age or fetal condition).</td>
</tr>
<tr>
<td>A 15-year-old girl is pregnant and wants to keep the child. Her parents want you to tell her to give the child up for adoption.</td>
<td>The patient retains the right to make decisions regarding her child, even if her parents disagree. Provide information to the teenager about the practical issues of caring for a baby. Discuss the options, if requested. Encourage discussion between the teenager and her parents to reach the best decision.</td>
</tr>
<tr>
<td>A terminally ill patient requests physician assistance in ending his/her own life.</td>
<td>In the overwhelming majority of states, refuse involvement in any form of physician-assisted suicide. Physicians may, however, prescribe medically appropriate analgesics that coincidentally shorten the patient’s life.</td>
</tr>
<tr>
<td>Patient is suicidal.</td>
<td>Assess the seriousness of the threat. If it is serious, suggest that the patient remain in the hospital voluntarily; patient can be hospitalized involuntarily if he/she refuses.</td>
</tr>
<tr>
<td>Patient states that he/she finds attractive.</td>
<td>Ask direct, closed-ended questions and use a chaperone if necessary. Romantic relationships with patients are never appropriate. Never say, “There can be no relationship while you are a patient,” because this implies that a relationship may be possible if the individual is no longer a patient.</td>
</tr>
<tr>
<td>A woman who had a mastectomy says she now feels “ugly.”</td>
<td>Find out why the patient feels this way. Do not offer falsely reassuring statements (e.g., “You still look good”).</td>
</tr>
<tr>
<td>Patient is angry about the amount of time he/she spent in the waiting room.</td>
<td>Acknowledge the patient’s anger, but do not take a patient’s anger personally. Apologize for any inconvenience. Stay away from efforts to explain the delay.</td>
</tr>
<tr>
<td>Patient is upset with the way he/she was treated by another doctor.</td>
<td>Suggest that the patient speak directly to that physician regarding his/her concerns. If the problem is with a member of the office staff, tell the patient you will speak to that person.</td>
</tr>
<tr>
<td>An invasive test is performed on the wrong patient.</td>
<td>Regardless of the outcome, a physician is ethically obligated to inform a patient that a mistake has been made.</td>
</tr>
<tr>
<td>A patient requires a treatment not covered by his/her insurance.</td>
<td>Never limit or deny care because of the expense in time or money. Discuss all treatment options with patients, even if some are not covered by their insurance companies.</td>
</tr>
</tbody>
</table>
Apgar score
Assessment of newborn vital signs following labor via a 10-point scale evaluated at 1 minute and
5 minutes. Apgar score is based on Appearance, Pulse, Grimace, Activity, and Respiration
(≥ 7 = good; 4–6 = assist and stimulate; < 4 = resuscitate). If Apgar score remains < 4 at later time
points, there is 1 risk that 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 1 risk of sudden infant death syndrome (SIDS) and with 1 overall mortality. Other problems
include impaired thermoregulation and immune function, hypoglycemia, polycythemia, and
impaired neurocognitive/emotional development. Complications include infections, respiratory
distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, and persistent fetal
circulation.

Early developmental milestones
Milestone dates are ranges that have been approximated and vary by source. Children not meeting
milestones may need assessment for potential developmental delay.

<table>
<thead>
<tr>
<th>AGE</th>
<th>MOTOR</th>
<th>SOCIAL</th>
<th>VERBAL/COGNITIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant</td>
<td>Parents</td>
<td>Start</td>
<td>Observing</td>
</tr>
<tr>
<td>0–12 mo</td>
<td>Primitive reflexes disappear—Moro (by 3 mo), rooting (by 4 mo), palmar (by 6 mo), Babinski (by 12 mo)</td>
<td>Social smile (by 2 mo)</td>
<td>Orients—first to voice (by 4 mo), then to name and gestures (by 9 mo)</td>
</tr>
<tr>
<td></td>
<td>Posture—lifts head up prone (by 1 mo), rolls and sits (by 6 mo), crawls (by 8 mo), stands (by 10 mo), walks (by 12–18 mo)</td>
<td>Stranger anxiety (by 6 mo)</td>
<td>Object permanence (by 9 mo)</td>
</tr>
<tr>
<td></td>
<td>Picks—passes toys hand to hand (by 6 mo), Pincer grasp (by 10 mo)</td>
<td>Separation anxiety (by 9 mo)</td>
<td>Oratory—says “mama” and “dada” (by 10 mo)</td>
</tr>
<tr>
<td></td>
<td>Points to objects (by 12 mo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant</td>
<td>Toddler</td>
<td>Rearing</td>
<td>Working</td>
</tr>
<tr>
<td>12–36 mo</td>
<td>Cruises, takes first steps (by 12 mo)</td>
<td>Recreation—parallel play (by 24–36 mo)</td>
<td>Words—200 words by age 2 (2 zeros), 2-word sentences</td>
</tr>
<tr>
<td></td>
<td>Climbs stairs (by 18 mo)</td>
<td>Rapprochement—moves away from and returns to mother (by 24 mo)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cubes stacked—number = age (yr) × 3</td>
<td>Realization—core gender identity formed (by 36 mo)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cultured—feeds self with fork and spoon (by 20 mo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kicks ball (by 24 mo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant</td>
<td>Preschool</td>
<td>Don’t</td>
<td>Forget, they’re still</td>
</tr>
<tr>
<td>3–5 yr</td>
<td>Drive—tricycle (3 wheels at 3 yr)</td>
<td>Freedom—comfortably spends part of day away from mother (by 3 yr)</td>
<td>Language—1000 words by age 3 (3 zeros), uses complete sentences and prepositions (by 4 yr)</td>
</tr>
<tr>
<td></td>
<td>Drawings—copies line or circle, stick figure (by 4 yr)</td>
<td>Friends—cooperative play, has imaginary friends (by 4 yr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dexterity—hops on one foot (by 4 yr), uses buttons or zippers, grooms self (by 5 yr)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Changes in the elderly

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

Sleep patterns:
- ↓ REM and slow-wave sleep;
- ↑ sleep onset latency and ↑ early awakenings
- ↑ suicide rate
- ↓ vision, hearing, immune response, bladder control
- ↓ renal, pulmonary, GI function
- ↓ muscle mass, ↑ fat

Sexual interest does not decrease.
Intelligence does not decrease.

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

<table>
<thead>
<tr>
<th>Common causes of death (U.S.) by age</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1YR</td>
</tr>
<tr>
<td>#1</td>
</tr>
<tr>
<td>#2</td>
</tr>
<tr>
<td>#3</td>
</tr>
</tbody>
</table>
"Biochemistry is the study of carbon compounds that crawl."  
— Mike Adams

“We think we have found the basic mechanism by which life comes from life.”  
— Francis H. C. Crick

This high-yield material includes molecular biology, genetics, cell biology, and principles of metabolism (especially vitamins, cofactors, minerals, and single-enzyme-deficiency diseases). When studying metabolic pathways, emphasize important regulatory steps and enzyme deficiencies that result in disease, as well as reactions targeted by pharmacologic interventions. For example, understanding the defect in Lesch-Nyhan syndrome and its clinical consequences is higher yield than memorizing every intermediate in the purine salvage pathway. Do not spend time on hard-core organic chemistry, mechanisms, or physical chemistry. Detailed chemical structures are infrequently tested; however, many structures have been included here to help students learn reactions and the important enzymes involved. Familiarity with the biochemical techniques that have medical relevance—such as ELISA, immunoelectrophoresis, Southern blotting, and PCR—is useful. Review the related biochemistry when studying pharmacology or genetic diseases as a way to reinforce and integrate the material.
**Chromatin structure**

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

<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterochromatin</td>
<td>Condensed, appears darker on EM. Transcriptionally inactive, sterically inaccessible.</td>
</tr>
<tr>
<td>Euchromatin</td>
<td>Less condensed, appears lighter on EM. Transcriptionally active, sterically accessible.</td>
</tr>
<tr>
<td>DNA methylation</td>
<td>Template strand cytosine and adenine are methylated in DNA replication, which allows mismatch repair enzymes to distinguish between old and new strands in prokaryotes. DNA methylation at CpG islands represses transcription.</td>
</tr>
<tr>
<td>Histone methylation</td>
<td>Usually reversibly represses DNA transcription, but can activate it in some cases depending on methylation location.</td>
</tr>
<tr>
<td>Histone acetylation</td>
<td>Relaxes DNA coiling, allowing for transcription.</td>
</tr>
</tbody>
</table>

**Heterochromatin = Highly Condensed.** Barr bodies (inactive X chromosomes) are heterochromatin.

**Eu = true, “truly transcribed.”**

**CpG Methylation Makes DNA Mute.**

**Histone Methylation Mostly Makes DNA Mute.**

**Histone Acetylation makes DNA Active.**
Nucleotides

**PURines (A, G)**—2 rings.
**PYrimidines (C, T, U)**—1 ring.
Thymine has a methyl.
Deamination of cytosine makes uracil.
Uracil found in RNA; thymine in DNA.
G-C bond (3 H bonds) stronger than A-T bond (2 H bonds). ↑ G-C content → ↑ melting temperature of DNA.

---

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

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

---

**De novo pyrimidine and purine synthesis**

**Purines**
- Make temporary base (orotic acid)
- Start with sugar + phosphate (PRPP)
- Add base
- Modify base

**Pyrimidines**
- Add sugar + phosphate (PRPP)
- Purine base production or reuse from salvage pathway (de novo requires aspartate, glycine, glutamine, and THF)
- Carboxyl phosphate is involved in 2 metabolic pathways: de novo pyrimidine synthesis and the urea cycle.
- Various immunosuppressive, antineoplastic, and antibiotic drugs function by interfering with nucleotide synthesis:
  - Leflunomide inhibits dihydroorotate dehydrogenase
  - Mycophenolate and ribavirin inhibit IMP dehydrogenase
  - Hydroxyurea inhibits ribonucleotide reductase
  - 6-mercaptopurine (6-MP) and its prodrug azathioprine inhibit de novo purine synthesis
  - 5-fluorouracil (5-FU) inhibits thymidylate synthase (4 deoxothyridine monophosphate [dTMP])
  - Methotrexate (MTX), trimethoprim (TMP), and pyrimethamine inhibit dihydrofolate reductase (4 dTMP) in humans, bacteria, and protozoa, respectively

---

**Pyrimidine base production (requires aspartate)**
- Glutamine + CO₂
- 2 ATP
- 2 ADP + P + Glutamate
- Carbamoyl phosphate synthetase II
- Leflunomide
- Impaired in orotic aciduria
- Hydroxyurea

**Purine base production or reuse from salvage pathway (de novo requires aspartate, glycine, glutamine, and THF)**
- Ribose 5-P
- PRPP (phosphoribosyl pyrophosphate) synthetase
- 6-MP
- Mycophenolate, ribavirin
- AMP
- CMP
- UMP
- UDP
- dUDP
- dCTP
- dUTP
- 5-FU
Purine salvage deficiencies

![Diagram of purine metabolism]

**Adenosine deaminase deficiency**
Excess ATP and dATP imbalances nucleotide pool via feedback inhibition of ribonucleotide reductase → prevents DNA synthesis and thus ↓ lymphocyte count.

**Lesch-Nyhan syndrome**
Defective purine salvage due to absent HGPRT, which converts hypoxanthine to IMP and guanine to GMP. Results in excess uric acid production and de novo purine synthesis. X-linked recessive.
Findings: intellectual disability, self-mutilation, aggression, hyperuricemia, gout, dystonia.
Treatment: allopurinol or febuxostat (2nd line).

### Genetic code features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unambiguous</strong></td>
<td>Each codon specifies only 1 amino acid.</td>
</tr>
<tr>
<td><strong>Degenerate/redundant</strong></td>
<td>Most amino acids are coded by multiple codons. Exceptions: methionine and tryptophan encoded by only 1 codon (AUG and UGG, respectively).</td>
</tr>
<tr>
<td><strong>Commaless, nonoverlapping</strong></td>
<td>Read from a fixed starting point as a continuous sequence of bases. Exceptions: some viruses.</td>
</tr>
<tr>
<td><strong>Universal</strong></td>
<td>Genetic code is conserved throughout evolution.</td>
</tr>
<tr>
<td></td>
<td>Exception in humans: mitochondria.</td>
</tr>
</tbody>
</table>
**DNA replication**

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

<table>
<thead>
<tr>
<th><strong>Origin of replication</strong></th>
<th>Particular consensus sequence of base pairs in genome where DNA replication begins. May be single (prokaryotes) or multiple (eukaryotes).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Replication fork</strong></td>
<td>Y-shaped region along DNA template where leading and lagging strands are synthesized.</td>
</tr>
<tr>
<td><strong>Helicase</strong></td>
<td>Unwinds DNA template at replication fork.</td>
</tr>
<tr>
<td><strong>Single-stranded binding proteins</strong></td>
<td>Prevent strands from reannealing.</td>
</tr>
<tr>
<td><strong>DNA topoisomerases</strong></td>
<td>Create a single- or double-stranded break in the helix to add or remove supercoils. Fluoroquinolones—inhibit prokaryotic enzymes topoisomerase II (DNA gyrase) and topoisomerase IV.</td>
</tr>
<tr>
<td><strong>Primase</strong></td>
<td>Makes an RNA primer on which DNA polymerase III can initiate replication.</td>
</tr>
<tr>
<td><strong>DNA polymerase III</strong></td>
<td>Prokaryotic only. Elongates leading strand by adding deoxynucleotides to the 3′ end. Elongates lagging strand until it reaches primer of preceding fragment. 3′ → 5′ exonuclease activity &quot;proofreads&quot; each added nucleotide. DNA polymerase III has 5′ → 3′ synthesis and proofreads with 3′ → 5′ exonuclease.</td>
</tr>
<tr>
<td><strong>DNA polymerase I</strong></td>
<td>Prokaryotic only. Degrades RNA primer; replaces it with DNA. Has same functions as DNA polymerase III but also excises RNA primer with 5′ → 3′ exonuclease.</td>
</tr>
<tr>
<td><strong>DNA ligase</strong></td>
<td>Catalyzes the formation of a phosphodiester bond within a strand of double-stranded DNA (i.e., joins Okazaki fragments). Seals.</td>
</tr>
</tbody>
</table>

**Telomerase**

An RNA-dependent DNA polymerase that adds DNA to 3′ ends of chromosomes to avoid loss of genetic material with every duplication. Eukaryotes only.
Mutations in DNA

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

For point (silent, missense, and nonsense) mutations:
- **Transition**—purine to purine (e.g., A to G) or pyrimidine to pyrimidine (e.g., C to T).
- **Transversion**—purine to pyrimidine (e.g., A to T) or pyrimidine to purine (e.g., C to G).

<table>
<thead>
<tr>
<th>Silent</th>
<th>Missense</th>
<th>Nonsense</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleotide substitution but codes for same (synonymous) amino acid; often base change in 3rd position of codon (tRNA wobble).</td>
<td>Nucleotide substitution resulting in changed amino acid (called conservative if new amino acid is similar in chemical structure).</td>
<td>Sickle cell disease (substitution of glutamic acid with valine).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-sense</th>
<th>Frameshift</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleotide substitution resulting in early stop codon.</td>
<td>Deletion or insertion of a number of nucleotides not divisible by 3, resulting in misreading of all nucleotides downstream, usually resulting in a truncated, nonfunctional protein.</td>
</tr>
</tbody>
</table>

**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** → ↑ adenyl cyclase activity → ↑ generation of cAMP from ATP → activation of catabolite activator protein (CAP) → ↑ transcription.
- **High lactose** → unbinds repressor protein from repressor/operator site → ↑ transcription.
### DNA repair

**Single strand**

| **Nucleotide excision repair** | Specific endonucleases release the oligonucleotides containing damaged bases; DNA polymerase and ligase fill and reseal the gap, respectively. Repairs bulky helix-distorting lesions. Occurs in G1 phase of cell cycle. | Defective in xeroderma pigmentosum, which prevents repair of pyrimidine dimers because of ultraviolet light exposure. |
| **Base excision repair** | Base-specific glycosylase removes altered base and creates AP site (apurinic/apyrimidinic). One or more nucleotides are removed by AP-endonuclease, which cleaves the 5′ end. Lyase cleaves the 3′ end. DNA polymerase-β fills the gap and DNA ligase seals it. Occurs throughout cell cycle. | Important in repair of spontaneous/toxic deamination. |
| **Mismatch repair** | Newly synthesized strand is recognized, mismatched nucleotides are removed, and the gap is filled and resealed. Occurs predominantly in G2 phase of cell cycle. | Defective in hereditary nonpolyposis colorectal cancer (HNPCC). |

**Double strand**

| **Nonhomologous end joining** | Brings together 2 ends of DNA fragments to repair double-stranded breaks. No requirement for homology. Some DNA may be lost. | Mutated in ataxia telangiectasia; Fanconi anemia. |

### DNA/RNA/protein synthesis direction

DNA and RNA are both synthesized 5′ → 3′. The 5′ end of the incoming nucleotide bears the triphosphate (energy source for bond). Protein synthesis is N-terminus to C-terminus.

mRNA is read 5′ to 3′. The triphosphate bond is the target of the 3′ hydroxyl attack. Drugs blocking DNA replication often have modified 3′ OH, preventing addition of the next nucleotide ("chain termination").

### Start and stop codons

| **mRNA start codons** | AUG (or rarely GUG). | AUG in AUGurates 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 Gone. |
**Functional organization of a eukaryotic gene**

- **Sense/coding strand**
- **Template strand**
- **Transcribed region**
- **Termination signals**
- **Promoter**
- **TATA box**
- **Intron**
- **Exon**
- **Enhancer**
- **5’**
- **3’**

**Regulation of gene expression**

**Promoter**
- Site where RNA polymerase II and multiple other transcription factors bind to DNA upstream from gene locus (AT-rich upstream sequence with TATA and CAAT boxes).
- Promoter mutation commonly results in dramatic \( \downarrow \) in level of gene transcription.

**Enhancer**
- Stretch of DNA that alters gene expression by binding transcription factors.
- Enhancers and silencers may be located close to, far from, or even within (in an intron) the gene whose expression it regulates.

**Silencer**
- Site where negative regulators (repressors) bind.

**RNA polymerases**

**Eukaryotes**
- RNA polymerase I makes rRNA (most numerous RNA, rampant).
- RNA polymerase II makes mRNA (largest RNA, massive).
- RNA polymerase III makes tRNA (smallest RNA, tiny).
- No proofreading function, but can initiate chains. RNA polymerase II opens DNA at promoter site.
- I, II, and III are numbered as their products are used in protein synthesis.
- \( \alpha \)-amanitin, found in *Amanita phalloides* (death cap mushrooms), inhibits RNA polymerase II. Causes severe hepatotoxicity if ingested.
- Rifampin inhibits RNA polymerase in prokaryotes. Actinomycin D inhibits RNA polymerase in both prokaryotes and eukaryotes.

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

**RNA processing (eukaryotes)**

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

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

Capped, tailed, and spliced transcript is called mRNA.

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

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

Poly-A polymerase does not require a template. AAUAAA = polyadenylation signal.
Splicing of pre-mRNA

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

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

Introns vs. exons

Exons contain the actual genetic information coding for protein. Introns are intervening noncoding segments of DNA. Different exons are frequently combined by alternative splicing to produce a larger number of unique proteins.

Introns are intervening sequences and stay in the nucleus, whereas exons exit and are expressed. Abnormal splicing variants are implicated in oncogenesis and many genetic disorders (e.g., β-thalassemia).
tRNA

**Structure**

75–90 nucleotides, 2º 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 (thymine, pseudouracil, cytosine) sequence necessary for tRNA-ribosome binding.

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

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

**Charging**

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

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

**Wobble**

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

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

**Eukaryotes**: 40S + 60S \(\rightarrow\) 80S (Even).
**Prokaryotes**: 30S + 50S \(\rightarrow\) 70S (Odd).

ATP–tRNA Activation (charging).
GTP–tRNA Gipping and Going places (translocation).

Think of “going APE”:
- A site = incoming Aminoacyl-tRNA.
- P site = accommodates growing Peptide.
- E site = holds Empty tRNA as it Exits.

**Elongation**
1. Aminoacyl-tRNA binds to A site (except for initiator methionine)
2. tRNA (“ribozyme”) catalyzes peptide bond formation, transfers growing polypeptide to amino acid in A site
3. Ribosome advances 3 nucleotides toward 3’ end of mRNA, moving peptidyl tRNA to P site (translocation)

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

Posttranslational modifications

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

**Covalent alterations**
Phosphorylation, glycosylation, hydroxylation, methylation, acetylation, and ubiquitination.

**Chaperone protein**
Intracellular protein involved in facilitating and/or maintaining protein folding. For example, in yeast, heat shock proteins (e.g., Hsp60) are expressed at high temperatures to prevent protein denaturing/misfolding.
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). G₁ and G₀ are of variable duration.

REGULATION OF CELL CYCLE

<table>
<thead>
<tr>
<th>CDKs</th>
<th>Constitutive and inactive.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclins</td>
<td>Regulatory proteins that control cell cycle events; phase specific; activate CDKs.</td>
</tr>
<tr>
<td>Cyclin-CDK complexes</td>
<td>Phosphorylate other proteins to coordinate cell cycle progression; must be activated and inactivated at appropriate times for cell cycle to progress.</td>
</tr>
<tr>
<td>Tumor suppressors</td>
<td>p53 and hypophosphorylated Rb normally inhibit G₁-to-S progression; mutations in these genes result in unrestrained cell division (e.g., Li-Fraumeni syndrome).</td>
</tr>
</tbody>
</table>

CELL TYPES

| Permanent | Remain in G₀, regenerate from stem cells. | Neurons, skeletal and cardiac muscle, RBCs. |
| Stable (quiescent) | Enter G₁ from G₀ when stimulated. | Hepatocytes, lymphocytes. |
| Labile | Never go to G₀, divide rapidly with a short G₁. Most affected by chemotherapy. | Bone marrow, gut epithelium, skin, hair follicles, germ cells. |

Rough endoplasmic reticulum

Site of synthesis of secretory (exported) proteins and of N-linked oligosaccharide addition to many proteins. Nissl bodies (RER in neurons)—synthesize peptide neurotransmitters for secretion. Free ribosomes—unattached to any membrane; site of synthesis of cytosolic and organellar proteins. Mucus-secreting goblet cells of the small intestine and antibody-secreting plasma cells are rich in RER.

Smooth endoplasmic reticulum

Site of steroid synthesis and detoxification of drugs and poisons. Lacks surface ribosomes. Liver hepatocytes and steroid hormone—producing cells of the adrenal cortex and gonads are rich in SER.
**Cell trafficking**

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

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

**Signal recognition particle (SRP)**

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

**Vesicular trafficking proteins**

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

COPII: ER → cis-Golgi (anterograde).

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

---

**Peroxisome**

Membrane-enclosed organelle involved in catabolism of very-long-chain fatty acids, branched-chain fatty acids, and amino acids.

**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.

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

Immunohistochemical stains for intermediate filaments

<table>
<thead>
<tr>
<th>STAIN</th>
<th>CELL TYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vimentin</td>
<td>Connective tissue</td>
</tr>
<tr>
<td>DesMin</td>
<td>Muscle</td>
</tr>
<tr>
<td>Cytokeratin</td>
<td>Epithelial cells</td>
</tr>
<tr>
<td>GFAP</td>
<td>NeuroGlia</td>
</tr>
<tr>
<td>Neurofilaments</td>
<td>Neurons</td>
</tr>
</tbody>
</table>

Microtubule

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

Molecular motor proteins—transport cellular cargo toward opposite ends of microtubule tracks.
- Dynein—retrograde to microtubule (+ → −).
- Kinesin—anterograde to microtubule (− → +).

Drugs that act on microtubules (Microtubules Get Constructed Very Poorly):
- Mebendazole (anthelmintic)
- Griseofulvin (antifungal)
- Colchicine (antigout)
- Vincristine/Vinblastine (anticancer)
- Paclitaxel (anticancer)

Kartagener syndrome (1° ciliary dyskinesia)—immotile cilia due to a dynein arm defect. Results in male and female infertility due to immotile sperm and dysfunctional fallopian tube cilia, respectively; ↑ risk of ectopic pregnancy. Can cause bronchiectasis, recurrent sinusitis, and situs inversus (e.g., dextrocardia on CXR).

Cilia structure

9 + 2 arrangement of microtubule doublets (arrows in A).

Axonemal dynein—ATPase that links peripheral 9 doublets and causes bending of cilium by differential sliding of doublets.
Plasma membrane composition
Asymmetric lipid bilayer. Contains cholesterol, phospholipids, sphingolipids, glycolipids, and proteins. Fungal membranes contain ergosterol.

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

Ouabain inhibits by binding to K\(^+\) site. Cardiac glycosides (digoxin and digitoxin) directly inhibit the Na\(^+\)-K\(^+\) ATPase, which leads to indirect inhibition of Na\(^+\)/Ca\(^{2+}\) exchange → ↑[Ca\(^{2+}\)] → ↓ cardiac contractility.

Collagen

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

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

- **Type II**: Cartilage (including hyaline), vitreous body, nucleus pulposus.

  Type II: cartilage.

- **Type III**: Reticulin—skin, blood vessels, uterus, fetal tissue, granulation tissue.

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

- **Type IV**: Basement membrane, basal lamina, lens.

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

**Inside fibroblasts**

1. **Synthesis (RER)**
   Translation of collagen α chains (procollagen)—usually Gly-X-Y (X and Y are proline or lysine). Glycine content best reflects collagen synthesis (collagen is 1/3 glycine).

2. **Hydroxylation (RER)**
   Hydroxylation of specific proline and lysine residues (requires vitamin C; deficiency → scurvy).

3. **Glycosylation (RER)**

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

**Outside fibroblasts**

5. **Proteolytic processing**
   Cleavage of disulfide-rich terminal regions of procollagen, transforming it into insoluble tropocollagen.

6. **Cross-linking**
   Reinforcement of many staggered tropocollagen molecules by covalent lysine-hydroxylysine cross-linkage (by copper-containing lysyl oxidase) to make collagen fibrils. Problems with cross-linking → Ehlers-Danlos syndrome, Menkes disease.

**Osteogenesis imperfecta**

- Genetic bone disorder (brittle bone disease) caused by a variety of gene defects.
- Most common form is autosomal dominant with production of otherwise normal type I collagen. Manifestations can include:
  - Multiple fractures with minimal trauma; may occur during the birth process
  - Blue sclerae due to the translucency of the connective tissue over the choroidal veins
  - Hearing loss (abnormal ossicles)
  - Dental imperfections due to lack of dentin

May be confused with child abuse.
**Ehlers-Danlos syndrome**

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

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

**Menkes disease**

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

**Elastin**

Stretchy protein within skin, lungs, large arteries, elastic ligaments, vocal cords, ligamenta flava (connect vertebrae → relaxed and stretched conformations). Rich in nonhydroxylated proline, glycine, and lysine residues. Tropoelastin with fibrillin scaffolding. Cross-linking takes place extracellularly and gives elastin its elastic properties. Broken down by elastase, which is normally inhibited by α1-antitrypsin.

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

**Emphysema**—can be caused by α1-antitrypsin deficiency, resulting in excess elastase activity. Wrinkles of aging are due to collagen and elastin production.

**Polymerase chain reaction**

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

Steps:
1. Denaturation—DNA is denatured by heating to generate 2 separate strands.
2. Annealing—during cooling, excess premade DNA primers anneal to a specific sequence on each strand to be amplified.
3. Elongation—heat-stable DNA polymerase replicates the DNA sequence following each primer.

These steps are repeated multiple times for DNA sequence amplification. Agarose gel electrophoresis—used for size separation of PCR products (smaller molecules travel further); compared against DNA ladder.
Blotting procedures

**Southern blot**
A DNA sample is enzymatically cleaved into smaller pieces, electrophoresed on a gel, and then transferred to a filter. The filter is then soaked in a denaturant and subsequently exposed to a radiolabeled DNA probe that recognizes and anneals to its complementary strand. The resulting double-stranded, labeled piece of DNA is visualized when the 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 filter. Labeled antibody is used to bind to relevant protein. Confirmatory test for HIV after ELISA.

**Southwestern blot**
Identifies DNA-binding proteins (e.g., transcription factors) using labeled oligonucleotide probes.

---

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

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**Enzyme-linked immunosorbent assay**
Used to detect the presence of either a specific antigen or a specific antibody in a patient’s blood sample. Patient’s blood sample is probed with either:
- Direct ELISA: uses a test antibody to see if a specific antigen is present. The antibody is directly coupled to a color-generating enzyme to detect the antigen.
- Indirect ELISA: uses either a test antigen or antibody to see if a specific antibody or antigen, respectively, is present. A secondary antibody coupled to a color-generating enzyme is added to detect the antibody-antigen complex.
  Target antigen or antibody present $\rightarrow$ color/fluorescence.

Used in many laboratories to determine whether a particular antibody (e.g., anti-HIV) is present in a patient’s blood sample. Both the sensitivity and specificity of ELISA approach 100%, but both false-positive and false-negative results occur.
### Karyotyping
A process in which metaphase chromosomes are stained, ordered, and numbered according to morphology, size, arm-length ratio, and banding pattern. Can be performed on a sample of blood, bone marrow, amniotic fluid, or placental tissue. Used to diagnose chromosomal imbalances (e.g., autosomal trisomies, sex chromosome disorders).

### Fluorescence in situ hybridization
Fluorescent DNA or RNA probe binds to specific gene site of interest on chromosomes. Used for specific localization of genes and direct visualization of anomalies (e.g., microdeletions) at molecular level (when deletion is too small to be visualized by karyotype). Fluorescence = gene is present; no fluorescence = gene is absent/deleted.

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

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

### Gene expression modifications
Transgenic strategies in mice involve:
- Random insertion of gene into mouse genome
- Targeted insertion or deletion of gene through homologous recombination with mouse gene

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

### Cre-lox system
Can inducibly manipulate genes at specific developmental points (e.g., to study a gene whose deletion causes embryonic death).

### RNA interference
dsRNA is synthesized that is complementary to the mRNA sequence of interest. When transfected into human cells, dsRNA separates and promotes degradation of target mRNA, "knocking down" gene expression.
Genetic terms

<table>
<thead>
<tr>
<th>TERM</th>
<th>DEFINITION</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Codominance</strong></td>
<td>Both alleles contribute to the phenotype of the heterozygote.</td>
<td>Blood groups A, B, AB; α1-antitrypsin deficiency.</td>
</tr>
<tr>
<td><strong>Variable expressivity</strong></td>
<td>Phenotype varies among individuals with same genotype.</td>
<td>2 patients with neurofibromatosis type 1 (NF1) may have varying disease severity.</td>
</tr>
<tr>
<td><strong>Incomplete penetrance</strong></td>
<td>Not all individuals with a mutant genotype show the mutant phenotype.</td>
<td>BRCA1 gene mutations do not always result in breast or ovarian cancer.</td>
</tr>
<tr>
<td><strong>Pleiotropy</strong></td>
<td>One gene contributes to multiple phenotypic effects.</td>
<td>Untreated phenylketonuria (PKU) manifests with light skin, intellectual disability, and musty body odor.</td>
</tr>
<tr>
<td><strong>Anticipation</strong></td>
<td>Increased severity or earlier onset of disease in succeeding generations.</td>
<td>Trinucleotide repeat diseases (e.g., Huntington disease).</td>
</tr>
<tr>
<td><strong>Loss of heterozygosity</strong></td>
<td>If a patient inherits or develops a mutation in a tumor suppressor gene, the complementary allele must be deleted/mutated before cancer develops. This is not true of oncogenes.</td>
<td>Retinoblastoma and the “two-hit hypothesis.”</td>
</tr>
<tr>
<td><strong>Dominant negative mutation</strong></td>
<td>Exerts a dominant effect. A heterozygote produces a nonfunctional altered protein that also prevents the normal gene product from functioning.</td>
<td>Mutation of a transcription factor in its allosteric site. Nonfunctioning mutant can still bind DNA, preventing wild-type transcription factor from binding.</td>
</tr>
<tr>
<td><strong>Linkage disequilibrium</strong></td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td><strong>Mosaicism</strong></td>
<td>Presence of genetically distinct cell lines in the same individual.</td>
<td>McCune-Albright syndrome—due to mutation affecting G-protein signaling. Presents with unilateral café-au-lait spots, polyostotic fibrous dysplasia, precocious puberty, multiple endocrine abnormalities. Lethal if mutation occurs before fertilization (affecting all cells), but survivable in patients with mosaicism.</td>
</tr>
<tr>
<td><strong>Locus heterogeneity</strong></td>
<td>Mutations at different loci can produce a similar phenotype.</td>
<td>Albinism.</td>
</tr>
<tr>
<td><strong>Allelic heterogeneity</strong></td>
<td>Different mutations in the same locus produce the same phenotype.</td>
<td>β-thalassemia.</td>
</tr>
<tr>
<td><strong>Heteroplasmy</strong></td>
<td>Presence of both normal and mutated mtDNA, resulting in variable expression in mitochondrially inherited disease.</td>
<td></td>
</tr>
</tbody>
</table>
Genetic terms (continued)

<table>
<thead>
<tr>
<th>TERM</th>
<th>DEFINITION</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uniparental disomy</strong></td>
<td>Offspring receives 2 copies of a chromosome from 1 parent and no copies from the other parent. Heterodisomy (heterozygous) indicates a meiosis I error. Isodisomy (homozygous) indicates a meiosis II error or postzygotic chromosomal duplication of one of a pair of chromosomes, and loss of the other of the original pair.</td>
<td>Uniparental is eUpload (correct number of chromosomes), not aneuploid. Most occurrences of UPD → normal phenotype. Consider UPD in an individual manifesting a recessive disorder when only one parent is a carrier.</td>
</tr>
</tbody>
</table>

**Hardy-Weinberg population genetics**

If a population is in Hardy-Weinberg equilibrium and if $p$ and $q$ are the frequencies of separate alleles, then: $p^2 + 2pq + q^2 = 1$ and $p + q = 1$, which implies that:

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

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

Hardy-Weinberg law assumptions include:

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

**Imprinting**

At some loci, only one allele is active; the other is inactive (imprinted/inactivated by methylation). With one allele inactivated, deletion of the active allele → disease.

Both Prader-Willi and Angelman syndromes are due to mutation or deletion of genes on chromosome 15.

**Prader-Willi syndrome**

Maternal imprinting: gene from mom is normally silent and Paternal gene is deleted/mutated. Results in hyperphagia, obesity, intellectual disability, hypogonadism, and hypotonia.

25% of cases due to maternal uniparental disomy (two maternally imprinted genes are received; no paternal gene received).

**Angelman syndrome**

Paternal imprinting: gene from dad is normally silent and Maternal gene is deleted/mutated. Results in inappropriate laughter ("happy puppet"), seizures, ataxia, and severe intellectual disability.

5% of cases due to paternal uniparental disomy (two paternally imprinted genes are received; no maternal gene received).
**Modes of inheritance**

**Autosomal dominant**
- Often due to defects in structural genes. Many generations, both male and female, affected.
- Often pleiotropic (multiple apparently unrelated effects) and variably expressive (different between individuals). Family history crucial to diagnosis. With one affected (heterozygous) parent, on average, 1/2 of children affected.

**Autosomal recessive**
- Often due to enzyme deficiencies. Usually seen in only 1 generation.
- Commonly more severe than dominant disorders; patients often present in childhood. ↑ risk in consanguineous families. With 2 carrier (heterozygous) parents, on average: ¼ of children will be affected (homozygous), ½ of children will be carriers, and ¼ of children will be neither affected nor carriers.

**X-linked recessive**
- Sons of heterozygous mothers have a 50% chance of being affected. No male-to-male transmission. Skips generations.
- Commonly more severe in males. Females usually must be homozygous to be affected.

**X-linked dominant**
- Transmitted through both parents. Mothers transmit to 50% of daughters and sons; fathers transmit to all daughters but no sons.
- Hypophosphatemic rickets—formerly known as vitamin D–resistant rickets. Inherited disorder resulting in ↑ phosphate wasting at proximal tubule. Results in rickets-like presentation.

**Mitochondrial inheritance**
- Transmitted only through the mother. All offspring of affected females may show signs of disease. Variable expression in a population or even within a family due to heteroplasmy. **Mitochondrial myopathies**—rare disorders; often present with myopathy, lactic acidosis and CNS disease. 2° to failure in oxidative phosphorylation. Muscle biopsy often shows “ragged red fibers.”

= unaffected male; ■ = affected male; ○ = unaffected female; ● = affected female.
Autosomal dominant diseases

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal dominant polycystic kidney disease (ADPKD)</td>
<td>Bilateral, massive enlargement of kidneys due to multiple large cysts. 85% of cases are due to mutation in PKD1 (chromosome 16); remainder due to mutation in PKD2 (chromosome 4).</td>
<td>PKD1, PKD2</td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>Colon becomes covered with adenomatous polyps after puberty. Progresses to colon cancer unless colon is resected. Mutations on chromosome 5q (APC gene); 5 letters in “polyp.”</td>
<td>APC</td>
</tr>
<tr>
<td>Familial hypercholesterolemia</td>
<td>Elevated LDL due to defective or absent LDL receptor. Leads to severe atherosclerotic disease early in life, corneal arcus, tendon xanthomas (classically in the Achilles tendon).</td>
<td></td>
</tr>
<tr>
<td>Hereditary hemorrhagic telangiectasia</td>
<td>Inherited disorder of blood vessels. Findings: branching skin lesions (telangiectasias), recurrent epistaxis, skin discolorations, arteriovenous malformations (AVMs), GI bleeding, hematuria. Also known as Osler-Weber-Rendu syndrome.</td>
<td></td>
</tr>
<tr>
<td>Hereditary spherocytosis</td>
<td>Spheroid erythrocytes due to spectrin or ankyrin defect; hemolytic anemia; ↑ MCHC, ↑ RDW. Treatment: splenectomy.</td>
<td></td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>Abnormalities in TP53 → multiple malignancies at an early age. Also known as SBLA cancer syndrome (sarcoma, breast, leukemia, adrenal gland).</td>
<td>TP53</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>FBN1 gene mutation on chromosome 15 → defective fibrin (scaffold for elastin) → connective tissue disorder affecting skeleton, heart, and eyes. Findings: tall with long extremities, pectus excavatum, hypermobile joints, and long, tapering fingers and toes (arachnodactyly); cystic medial necrosis of aorta → aortic incompetence and dissecting aortic aneurysms; floppy mitral valve. Subluxation of lenses, typically upward and temporally.</td>
<td>FBN1</td>
</tr>
<tr>
<td>Multiple endocrine neoplasias (MEN)</td>
<td>Several distinct syndromes (1, 2A, 2B) characterized by familial tumors of endocrine glands, including those of the pancreas, parathyroid, pituitary, thyroid, and adrenal medulla. MEN 1 is associated with MEN1 gene, MEN 2A and 2B are associated with RET gene.</td>
<td>MEN1, MEN2A, MEN2B</td>
</tr>
<tr>
<td>Neurofibromatosis type 1 (von Recklinghausen disease)</td>
<td>Neurocutaneous disorder characterized by café-au-lait spots, cutaneous neurofibromas, optic gliomas, pheochromocytomas, Lisch nodules (pigmented iris hamartomas). Autosomal dominant, 100% penetrance, variable expression. Caused by mutations in the NF1 gene on chromosome 17; 17 letters in “von Recklinghausen.”</td>
<td>NF1</td>
</tr>
<tr>
<td>Neurofibromatosis type 2</td>
<td>Findings: bilateral acoustic schwannomas, juvenile cataracts, meningiomas, and ependymomas. NF2 gene on chromosome 22; type 2 = 22.</td>
<td>NF2</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>Neurocutaneous disorder with multi-organ system involvement, characterized by numerous benign hamartomas. Incomplete penetrance, variable expression.</td>
<td></td>
</tr>
<tr>
<td>von Hippel-Lindau disease</td>
<td>Disorder characterized by development of numerous tumors, both benign and malignant. Associated with deletion of VHL gene (tumor suppressor) on chromosome 3 (3p). Von Hippel-Lindau = 3 words for chromosome 3.</td>
<td>VHL</td>
</tr>
</tbody>
</table>
Autosomal recessive diseases

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

Cystic fibrosis

**GENETICS**

Autosomal recessive; defect in CFTR gene on chromosome 7; commonly a deletion of Phe508. Most common lethal genetic disease in Caucasian population.

**PATHOPHYSIOLOGY**

CFTR encodes an ATP-gated Cl− channel that secretes Cl− in lungs and GI tract, and reabsorbs Cl− in sweat glands. Most common mutation → misfolded protein → protein retained in RER and not transported to cell membrane, causing ↓ Cl− (and H2O) secretion; ↑ intracellular Cl− results in compensatory ↓ Na+ reabsorption via epithelial Na+ channels → ↑ H2O reabsorption → abnormally thick mucus secreted into lungs and GI tract. ↓ Na+ reabsorption also causes more negative transepithelial potential difference.

**DIAGNOSIS**

↑ Cl− concentration (> 60 mEq/L) in sweat is diagnostic. Can present with contraction alkalosis and hypokalemia (ECF effects analogous to a patient taking a loop diuretic) because of ECF H2O/Na+ losses and concomitant renal K+/H+ wasting. ↑ immunoreactive trypsinogen (newborn screening).

**COMPLICATIONS**

Recurrent pulmonary infections (e.g., Pseudomonas), chronic bronchitis and bronchiectasis → reticulonodular pattern on CXR, pancreatic insufficiency, malabsorption with steatorrhea, and nasal polyps. Meconium ileus in newborns. Infertility in males (absence of vas deferens), and subfertility in females (amenorrhea, abnormally thick cervical mucus). Fat-soluble vitamin deficiencies (A, D, E, K).

**TREATMENT**

N-acetylcysteine to loosen mucus plugs (cleaves disulfide bonds within mucus glycoproteins), dornase alfa (DNAse) to clear leukocytic debris.

X-linked recessive disorders

Bruton agammaglobulinemia, Wiskott-Aldrich syndrome, Fabry disease, G6PD deficiency, Ocular albinism, Lesch-Nyhan syndrome, Duchenne (and Becker) muscular dystrophy, Hunter Syndrome, Hemophilia A and B, Ornithine transcarbamylase deficiency. Female carriers can be variably affected depending on the percentage inactivation of the X chromosome carrying the mutant vs. normal gene.

Be Wise, Fool’s GOLD Heeds Silly HOpe.
Muscular dystrophies

Duchenne

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

Becker

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

Myotonic type 1

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

Fragile X syndrome

X-linked defect affecting the methylation and expression of the FMR1 gene. The 2nd most common cause of genetic intellectual disability (after Down syndrome). Findings: post-pubertal macroorchidism (enlarged testes), long face with a large jaw, large everted ears, autism, mitral valve prolapse.

Trinucleotide repeat expansion diseases


Try (trinucleotide) hunting for my fried eggs (X). X-Girlfriend’s First Aid Helped Ace My Test. May show genetic anticipation (disease severity ↑ and age of onset ↓ in successive generations).
Autosomal trisomies

**Down syndrome** (trisomy 21), 1:700
Findings: intellectual disability, flat facies, prominent epicanthal folds, single palmar crease, gap between 1st 2 toes, duodenal atresia, Hirschsprung disease, congenital heart disease (atrial septal defect [ASD]), Brushfield spots. Associated with early-onset Alzheimer disease (chromosome 21 codes for amyloid precursor protein) and ↑ risk of ALL and AML. 95% of cases due to meiotic nondisjunction (associated with advanced maternal age; from 1:1500 in women < 20 to 1:25 in women > 45 years old). 4% of cases due to Robertsonian translocation. 1% of cases due to mosaicism (no maternal association; post-fertilization mitotic error).

**Edwards syndrome** (trisomy 18), 1:8000
Findings: severe intellectual disability, rocker-bottom feet, micrognathia (small jaw), low-set Ears, clenched hands with overlapping fingers, prominent occiput, congenital heart disease. Death usually occurs within 1 year of birth.

**Patau syndrome** (trisomy 13), 1:15,000
Findings: severe intellectual disability, rocker-bottom feet, microphthalmia, microcephaly, cleft li/]/]Palate, holoprosencephaly, Polydactyly, congenital heart disease, cutis aplasia. Death usually occurs within 1 year of birth.

**Drinking age** (21).
Most common viable chromosomal disorder and most common cause of genetic intellectual disability.
First-trimester ultrasound commonly shows ↑ nuchal translucency and hypoplastic nasal bone; serum PAPP-A is ↓, free β-hCG is ↑. Second-trimester quad screen shows ↓ α-fetoprotein, ↑ β-hCG, ↓ estriol, ↑ inhibin A.

**Election age** (18).
2nd most common trisomy resulting in live birth (most common is Down syndrome). PAPP-A and free β-hCG are ↓ in first trimester. Quad screen shows ↓ α-fetoprotein, ↓ β-hCG, ↓ estriol, ↓ or normal inhibin A.

**Puberty** (13).
First-trimester pregnancy screen shows ↓ free β-hCG, ↓ PAPP-A, and ↑ nuchal translucency.

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Meiotic nondisjunction

<table>
<thead>
<tr>
<th>Meiosis I</th>
<th>Meiosis II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gametes</td>
<td>Gametes</td>
</tr>
<tr>
<td>n+1</td>
<td>n+1</td>
</tr>
<tr>
<td>n+1</td>
<td>n+1</td>
</tr>
<tr>
<td>n-1</td>
<td>n-1</td>
</tr>
<tr>
<td>n-1</td>
<td>n-1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nondisjunction in meiosis I</th>
<th>Nondisjunction in meiosis II</th>
</tr>
</thead>
<tbody>
<tr>
<td>trisomy</td>
<td></td>
<td>normal</td>
</tr>
<tr>
<td>monosomy</td>
<td></td>
<td>trisomy</td>
</tr>
</tbody>
</table>

Meiotic nondisjunction diagram:

- Meiosis I
  - Gametes: n+1, n+1, n-1, n-1
  - Outcome: trisomy, monosomy, trisomy, normal

- Meiosis II
  - Gametes: n+1, n+1, n, n
### Chromosomal disorders

<table>
<thead>
<tr>
<th>CHROMOSOME</th>
<th>SELECTED EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>von Hippel-Lindau disease, renal cell carcinoma</td>
</tr>
<tr>
<td>4</td>
<td>ADPKD with PKD2 defect, Huntington disease</td>
</tr>
<tr>
<td>5</td>
<td>Cri-du-chat syndrome, familial adenomatous polyposis</td>
</tr>
<tr>
<td>7</td>
<td>Williams syndrome, cystic fibrosis</td>
</tr>
<tr>
<td>9</td>
<td>Friedreich ataxia</td>
</tr>
<tr>
<td>11</td>
<td>Wilms tumor</td>
</tr>
<tr>
<td>13</td>
<td>Patau syndrome, Wilson disease</td>
</tr>
<tr>
<td>15</td>
<td>Prader-Willi syndrome, Angelman syndrome</td>
</tr>
<tr>
<td>16</td>
<td>ADPKD with PKD1 defect</td>
</tr>
<tr>
<td>17</td>
<td>Neurofibromatosis type 1</td>
</tr>
<tr>
<td>18</td>
<td>Edwards syndrome</td>
</tr>
<tr>
<td>21</td>
<td>Down syndrome</td>
</tr>
<tr>
<td>22</td>
<td>Neurofibromatosis type 2, DiGeorge syndrome (22q11)</td>
</tr>
<tr>
<td>X</td>
<td>Fragile X syndrome, X-linked agammaglobulinemia, Klinefelter syndrome (XXY)</td>
</tr>
</tbody>
</table>

### Robertsonian translocation

Chromosomal translocation that commonly involves chromosome pairs 13, 14, 15, 21, and 22. One of the most common types of translocation. Occurs when the long arms of 2 acrocentric chromosomes (chromosomes with centromeres near their ends) fuse at the centromere and the 2 short arms are lost. Balanced translocations normally do not cause any abnormal phenotype. Unbalanced translocations can result in miscarriage, stillbirth, and chromosomal imbalance (e.g., Down syndrome, Patau syndrome).

### Cri-du-chat syndrome

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

*Cri du chat = cry of the cat.*

### Williams syndrome

Congenital microdeletion of long arm of chromosome 7 (deleted region includes elastin gene). Findings: distinctive "elfin" facies, intellectual disability, hypercalcemia (1 sensitivity to vitamin D), well-developed verbal skills, extreme friendliness with strangers, cardiovascular problems.
22q11 deletion syndromes

Microdeletion at chromosome 22q11 → variable presentations including Cleft palate, Abnormal facies, Thymic aplasia → T-cell deficiency, Cardiac defects, and Hypocalcemia 2° to parathyroid aplasia.

DiGeorge syndrome—thymic, parathyroid, and cardiac defects.

Velocardiofacial syndrome—palate, facial, and cardiac defects.

CATCH-22.
Due to aberrant development of 3rd and 4th branchial pouches.

Vitamins: fat soluble

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

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

Vitamins: water soluble

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

All wash out easily from body except B₁₂ and folate (stored in liver).
B-complex deficiencies often result in dermatitis, glossitis, and diarrhea.
### Vitamin A (retinol)

**FUNCTION**
Antioxidant; constituent of visual pigments (retinal); essential for normal differentiation of epithelial cells into specialized tissue (pancreatic cells, mucus-secreting cells); prevents squamous metaplasia. Used to treat measles and AML subtype M3.

**DEFICIENCY**
Night blindness (nyctalopia); dry, scaly skin (xerosis cutis); corneal degeneration (keratomalacia); Bitot spots on conjunctiva; immunosuppression.

**EXCESS**
Acute toxicity—nausea, vomiting, vertigo, and blurred vision. Chronic toxicity—alopecia, dry skin (e.g., scaliness), hepatic toxicity and enlargement, arthralgias, and pseudotumor cerebri. Teratogenic (cleft palate, cardiac abnormalities), therefore a ⊗ pregnancy test and reliable contraception are required before isotretinoin (vitamin A derivative) is prescribed for severe acne.

Retinol is vitamin A, so think retin-A (used topically for wrinkles and acne). Found in liver and leafy vegetables.

### Vitamin B₁ (thiamine)

**FUNCTION**
In thiamine pyrophosphate (TPP), a cofactor for several dehydrogenase enzyme reactions:  
- Pyruvate dehydrogenase (links glycolysis to TCA cycle)  
- α-ketoglutarate dehydrogenase (TCA cycle)  
- Transketolase (HMP shunt)  
- Branched-chain ketoacid dehydrogenase

Think ATP: α-ketoglutarate dehydrogenase, Transketolase, and Pyruvate dehydrogenase. Spell beriberi as Ber1Ber1 to remember vitamin B₁. 

Wernicke-Korsakoff syndrome—confusion, ophthalmoplegia, ataxia (classic triad) + confabulation, personality change, memory loss (permanent). Damage to medial dorsal nucleus of thalamus, mammillary bodies. 

Dry beriberi—polyneuritis, symmetrical muscle wasting. 

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

**DEFICIENCY**
Impaired glucose breakdown → ATP depletion worsened by glucose infusion; highly aerobic tissues (e.g., brain, heart) are affected first. Wernicke-Korsakoff syndrome and beriberi. Seen in malnutrition and alcoholism (2° to malnutrition and malabsorption). Diagnosis made by ⊕ in RBC transketolase activity following vitamin B₁ administration.

### Vitamin B₂ (riboflavin)

**FUNCTION**
Component of flavins FAD and FMN, used as cofactors in redox reactions, e.g., the succinate dehydrogenase reaction in the TCA cycle.

FAD and FMN are derived from riboFlavin ($B₂ = 2$ ATP).

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

The 2 C’s of B₂.
### Vitamin B₃ (niacin)

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

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

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

**NAD derived from Niacin (B₃ ≈ 3 ATP).**

**The 3 Ds of B₃**

### Vitamin B₅ (pantothenic acid)

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

**DEFICIENCY**
Dermatitis, enteritis, alopecia, adrenal insufficiency.

**B₅ is “pento”thenic acid.**

### Vitamin B₆ (pyridoxine)

**FUNCTION**
Converted to pyridoxal phosphate (PLP), a cofactor used in transamination (e.g., ALT and AST), decarboxylation reactions, glycogen phosphorylase. Synthesis of cystathionine, heme, niacin, histamine, and neurotransmitters including serotonin, epinephrine, norepinephrine (NE), dopamine, and GABA.

**DEFICIENCY**
Convulsions, hyperirritability, peripheral neuropathy (deficiency inducible by isoniazid and oral contraceptives), sideroblastic anemias due to impaired hemoglobin synthesis and iron excess.
### Vitamin B7 (biotin)

**FUNCTION**
Cofactor for carboxylation enzymes (which add a 1-carbon group):
- Pyruvate carboxylase: pyruvate (3C) → oxaloacetate (4C)
- Acetyl-CoA carboxylase: acetyl-CoA (2C) → malonyl-CoA (3C)
- Propionyl-CoA carboxylase: propionyl-CoA (3C) → methylmalonyl-CoA (4C)

“Avid in egg whites avidly binds biotin.”

**DEFICIENCY**
Relatively rare. Dermatitis, alopecia, enteritis. Caused by antibiotic use or excessive ingestion of raw egg whites.

### Vitamin B9 (folate)

**FUNCTION**
Converted to tetrahydrofolic acid (THF), a coenzyme for 1-carbon transfer/methylation reactions. Important for the synthesis of nitrogenous bases in DNA and RNA.

Found in leafy green vegetables. Absorbed in jejunum. Folate from foliage. Small reserve pool stored primarily in the liver.

**DEFICIENCY**
Macrocytic, megaloblastic anemia; hypersegmented polymorphonuclear cells (PMNs); glossitis; no neurologic symptoms (as opposed to vitamin B12 deficiency). Labs: ↑ homocysteine, normal methylmalonic acid levels. Most common vitamin deficiency in the United States. Seen in alcoholism and pregnancy.

Deficiency can be caused by several drugs (e.g., phenytoin, sulfonamides, methotrexate). Supplemental maternal folic acid in early pregnancy decreases risk of neural tube defects.
**Vitamin B<sub>12</sub> (cobalamin)**

**FUNCTION**

Cofactor for homocysteine methyltransferase (transfers CH₃ groups as methylcobalamin) and methylmalonyl-CoA mutase.

**DEFICIENCY**

Macrocytic, megaloblastic anemia; hypersegmented PMNs; paresthesias and subacute combined degeneration (degeneration of dorsal columns, lateral corticospinal tracts, and spinocerebellar tracts) due to abnormal myelin. Associated with ↑ serum homocysteine and methylmalonic acid levels. Prolonged deficiency → irreversible nerve damage.

Found in animal products. Synthesized only by microorganisms. Very large reserve pool (several years) stored primarily in the liver. Deficiency is usually caused by insufficient intake (e.g., veganism), malabsorption (e.g., sprue, enteritis, *Diphyllobothrium latum*), lack of intrinsic factor (pernicious anemia, gastric bypass surgery), or absence of terminal ileum (Crohn disease).

Anti-intrinsic factor antibodies diagnostic for pernicious anemia.

Macrocytic, megaloblastic anemia; hypersegmented PMNs; paresthesias and subacute combined degeneration (degeneration of dorsal columns, lateral corticospinal tracts, and spinocerebellar tracts) due to abnormal myelin. Associated with ↑ serum homocysteine and methylmalonic acid levels. Prolonged deficiency → irreversible nerve damage.

Fatty acids with odd number of carbons, branched-chain amino acids

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**Diagram**

- **Homocysteine**
  - Cofactor for homocysteine methyltransferase (transfers CH₃ groups as methylcobalamin) and methylmalonyl-CoA mutase.

- **Deficiency**
  - Macrocytic, megaloblastic anemia; hypersegmented PMNs; paresthesias and subacute combined degeneration (degeneration of dorsal columns, lateral corticospinal tracts, and spinocerebellar tracts) due to abnormal myelin. Associated with ↑ serum homocysteine and methylmalonic acid levels. Prolonged deficiency → irreversible nerve damage.

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- **Anti-intrinsic factor antibodies diagnostic for pernicious anemia.**
**Vitamin C (ascorbic acid)**

**FUNCTION**
- Antioxidant; also facilitates iron absorption by reducing it to Fe^{2+} state. Necessary for hydroxylation of proline and lysine in collagen synthesis. Necessary for dopamine β-hydroxylase, which converts dopamine to NE.
- Found in fruits and vegetables.
- Pronounce “absorbic” acid.
- Ancillary treatment for methemoglobinemia by reducing Fe^{3+} to Fe^{2+}.

**DEFICIENCY**
- Scurvy—swollen gums, bruising, petechiae, hemorrhosis, anemia, poor wound healing, perifollicular and subperiosteal hemorrhages, “corkscrew” hair.
- Weakened immune response.
- Vitamin C deficiency causes scurvy due to a collagen synthesis defect.

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

**Vitamin D**

**D_2** = ergocalciferol—ingested from plants.
**D_3** = cholecalciferol—consumed in milk, formed in sun-exposed skin (stratum basale).
25-OH D_3 = storage form.
1,25-(OH)_2 D_3 (calcitriol) = active form.

**FUNCTION**
- ↑ intestinal absorption of calcium and phosphate.
- ↑ bone mineralization.
- Drinking milk (fortified with vitamin D) is good for bones.

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

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

**Vitamin E (tocopherol/tocotrienol)**

**FUNCTION**
- Antioxidant (protects RBCs and membranes from free radical damage).
- Can enhance anticoagulant effects of warfarin.

**DEFICIENCY**
- Hemolytic anemia, acanthocytosis, muscle weakness, posterior column and spinocerebellar tract demyelination.
- Neurologic presentation may appear similar to vitamin B_{12} deficiency, but without megaloblastic anemia, hypersegmented neutrophils, or ↑ serum methylmalonic acid levels.
**Vitamin K (phytomenadione, phylloquinone, phytonadione)**

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


**DEFICIENCY**
Neonatal hemorrhage with ↑ PT and ↑ aPTT but normal bleeding time (neonates have sterile intestines and are unable to synthesize vitamin K). Can also occur after prolonged use of broad-spectrum antibiotics.

Not in breast milk; neonates are given vitamin K injection at birth to prevent hemorrhagic disease of the newborn.

---

**Zinc**

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

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

---

**Malnutrition**

**Kwashiorkor**
Protein malnutrition resulting in skin lesions, edema due to ↓ plasma oncotic pressure, liver malfunction (fatty change due to ↓ apolipoprotein synthesis). Clinical picture is small child with swollen abdomen A.

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

**Marasmus**
Total calorie malnutrition resulting in tissue and muscle wasting, loss of subcutaneous fat, and variable edema.

Marasmus results in Muscle wasting.
Ethanol metabolism

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

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

NAD⁺ is the limiting reagent.

Alcohol dehydrogenase operates via zero-order kinetics.

Ethanol metabolism ↑ NADH/NAD⁺ ratio in liver, causing:
- Pyruvate → lactate (lactic acidosis).
- Oxaloacetate → malate (prevents gluconeogenesis → fasting hypoglycemia)
- Dihydroxyacetone phosphate → glycerol-3-phosphate (combines with fatty acids to make triglycerides → hepatosteatosis)

End result is clinical picture seen in chronic alcoholism.

Additionally, ↑ NADH/NAD⁺ ratio disfavors TCA production of NADH → ↑ utilization of acetyl-CoA for ketogenesis (→ ketoacidosis) and lipogenesis (→ hepatosteatosis).

▶ BIOCHEMISTRY—METABOLISM

Metabolism sites

**Mitochondria**
- Fatty acid oxidation (β-oxidation), acetyl-CoA production, TCA cycle, oxidative phosphorylation, ketogenesis.

**Cytoplasm**
- Glycolysis, fatty acid synthesis, HMP shunt, protein synthesis (RER), steroid synthesis (SER), cholesterol synthesis.

**Both**
- Heme synthesis, Urea cycle, Gluconeogenesis. **HUGs take two** (i.e., both).
### Enzyme terminology
An enzyme’s name often describes its function. For example, glucokinase is an enzyme that catalyzes the phosphorylation of glucose using a molecule of ATP. The following are commonly used enzyme descriptors.

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinase</td>
<td>Uses ATP to add high-energy phosphate group onto substrate (e.g., phosphofructokinase).</td>
<td>Phosphofructokinase</td>
</tr>
<tr>
<td>Phosphorylase</td>
<td>Adds inorganic phosphate onto substrate without using ATP (e.g., glycogen phosphorylase).</td>
<td>Glycogen phosphorylase</td>
</tr>
<tr>
<td>Phosphatase</td>
<td>Removes phosphate group from substrate (e.g., fructose-1,6-bisphosphatase).</td>
<td>Fructose-1,6-bisphosphatase</td>
</tr>
<tr>
<td>Dehydrogenase</td>
<td>Catalyzes oxidation-reduction reactions (e.g., pyruvate dehydrogenase).</td>
<td>Pyruvate dehydrogenase</td>
</tr>
<tr>
<td>Hydroxylase</td>
<td>Adds hydroxyl group (−OH) onto substrate (e.g., tyrosine hydroxylase).</td>
<td>Tyrosine hydroxylase</td>
</tr>
<tr>
<td>Carboxylase</td>
<td>Transfers CO₂ groups with the help of biotin (e.g., pyruvate carboxylase).</td>
<td>Pyruvate carboxylase</td>
</tr>
<tr>
<td>Mutase</td>
<td>Relocates a functional group within a molecule (e.g., vitamin B₁₂-dependent methylmalonyl-CoA mutase).</td>
<td>Vitamin B₁₂-dependent methylmalonyl-CoA mutase.</td>
</tr>
</tbody>
</table>

### Rate-determining enzymes of metabolic processes

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

1. Galactokinase (mild galactosemia)
2. Galactose-1-phosphate uridylytransferase (severe galactosemia)
3. Hexokinase/glucokinase
4. Glucose-6-phosphatase (von Gierke’s)
5. Glucose-6-phosphate dehydrogenase (G6PD)
6. Transketolase
7. Phosphofructokinase-1
8. Fructose-1,6-bisphosphatase
9. Fructose bisphosphate aldolase (essential fructosuria)
10. Aldolase B (fructose intolerance)
11. Fructose bisphosphate aldolase (liver), A (muscle)
12. Pyruvate kinase
13. Pyruvate dehydrogenase
14. HMG-CoA reductase
15. Pyruvate carboxylase
16. PEP carboxykinase
17. Citrate synthase
18. Isocitrate dehydrogenase
19. α-ketoglutarate dehydrogenase
20. Ornithine transcarbamylase
21. Propionyl-CoA carboxylase
ATP production

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

Arsenic causes glycolysis to produce zero net ATP.

Activated carriers

<table>
<thead>
<tr>
<th>CARRIER MOLECULE</th>
<th>CARRIED IN ACTIVATED FORM</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP</td>
<td>Phosphoryl groups</td>
</tr>
<tr>
<td>NADH, NADPH, FADH₂</td>
<td>Electrons</td>
</tr>
<tr>
<td>CoA, lipoamide</td>
<td>Acyl groups</td>
</tr>
<tr>
<td>Biotin</td>
<td>CO₂</td>
</tr>
<tr>
<td>Tetrahydrofolates</td>
<td>1-carbon units</td>
</tr>
<tr>
<td>S-adenosylmethionine (SAM)</td>
<td>CH₃ groups</td>
</tr>
<tr>
<td>TPP</td>
<td>Aldehydes</td>
</tr>
</tbody>
</table>

Universal electron acceptors

Nicotinamides (NAD⁺ from vitamin B₃, NADP⁺) and flavin nucleotides (FAD⁺ from vitamin B₂). NAD⁺ is generally used in catabolic processes to carry reducing equivalents away as NADH. NADPH is used in anabolic processes (steroid and fatty acid synthesis) as a supply of reducing equivalents.

NADPH is a product of the HMP shunt. NADPH is used in:
- Anabolic processes
- Respiratory burst
- Cytochrome P-450 system
- Glutathione reductase

Hexokinase vs. glucokinase

Phosphorylation of glucose to yield glucose-6-phosphate serves as the 1st step of glycolysis (also serves as the 1st step of glycogen synthesis in the liver). Reaction is catalyzed by either hexokinase or glucokinase, depending on the tissue. At low glucose concentrations, hexokinase sequesters glucose in the tissue. At high glucose concentrations, excess glucose is stored in the liver.

<table>
<thead>
<tr>
<th>Hexokinase</th>
<th>Glucokinase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Most tissues, except liver and pancreatic β cells</td>
</tr>
<tr>
<td></td>
<td>Liver, β cells of pancreas</td>
</tr>
<tr>
<td>Kₘ</td>
<td>Lower († affinity)</td>
</tr>
<tr>
<td>Vₘₐₓ</td>
<td>Higher (‡ affinity)</td>
</tr>
<tr>
<td>Induced by insulin</td>
<td>No</td>
</tr>
<tr>
<td>Feedback-inhibited by glucose-6-phosphate</td>
<td>Yes</td>
</tr>
<tr>
<td>Gene mutation associated with maturity-onset diabetes of the young (MODY)</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>
Glycolysis regulation, key enzymes

Net glycolysis (cytoplasm):
Glucose + 2 P, + 2 ADP + 2 NAD⁺ → 2 pyruvate + 2 ATP + 2 NADH + 2 H⁺ + 2 H₂O.

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

**REQUIRE ATP**

<table>
<thead>
<tr>
<th>Glucose</th>
<th>Glucose-6-P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexokinase/glucokinase&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Fructose-6-P</td>
</tr>
<tr>
<td>Phosphofructokinase-1 (rate-limiting step)</td>
<td>Fructose-1,6-BP</td>
</tr>
</tbody>
</table>

<sup>a</sup>Gluokinase in liver and β cells of pancreas; hexokinase in all other tissues.

**PRODUCE ATP**

<table>
<thead>
<tr>
<th>1,3-BPG</th>
<th>3-PG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphoglycerate kinase</td>
<td>Pyruvate</td>
</tr>
<tr>
<td>Pyruvate kinase</td>
<td></td>
</tr>
</tbody>
</table>

Fructose-1,6-bisphosphate ⊕. ATP ⊕, alanine ⊕.

Regulation by fructose-2,6-bisphosphate

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

**Fasting state:** → glucagon → ↑ cAMP → ↑ protein kinase A → ↑ FBPase-2, ↓ PFK-2, less glycolysis, more gluconeogenesis.

**Fed state:** → insulin → ↓ cAMP → ↓ protein kinase A → ↓ FBPase-2, ↑ PFK-2, more glycolysis, less gluconeogenesis.

Pyruvate dehydrogenase complex

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

Reaction: pyruvate + NAD⁺ + CoA → acetyl-CoA + CO₂ + NADH.

The complex contains 3 enzymes that require 5 cofactors:
1. Pyrophosphate (B₁, thiamine; TPP)
2. FAD (B₂, riboflavin)
3. NAD (B₃, niacin)
4. CoA (B₅, pantothenic acid)
5. Lipoic acid

Activated by exercise, which:
1. ↑ NAD⁺/NADH ratio
2. ↑ ADP
3. ↑ Ca²⁺

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

Arsenic inhibits lipoic acid. Findings: vomiting, rice-water stools, garlic breath.
Pyruvate dehydrogenase complex deficiency

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

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

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

Lysine and Leucine—the only purely ketogenic amino acids.

Pyruvate metabolism

Functions of different pyruvate metabolic pathways (and their associated cofactors):
1. Alanine aminotransferase (B6): alanine carries amino groups to the liver from muscle
2. Pyruvate carboxylase (biotin): oxaloacetate can replenish TCA cycle or be used in gluconeogenesis
3. Pyruvate dehydrogenase (B1, B2, B3, B5, lipoic acid): transition from glycolysis to the TCA cycle
4. Lactic acid dehydrogenase (B3): end of anaerobic glycolysis (major pathway in RBCs, WBCs, kidney medulla, lens, testes, and cornea)

TCA cycle (Krebs cycle)
Pyruvate → acetyl-CoA produces 1 NADH, 1 CO₂.

The TCA cycle produces 3 NADH, 1 FADH₂, 2 CO₂, 1 GTP per acetyl-CoA = 10 ATP/ acetyl-CoA (2× everything per glucose). TCA cycle reactions occur in the mitochondria. α-ketoglutarate dehydrogenase complex requires the same cofactors as the pyruvate dehydrogenase complex (B1, B2, B3, B5, lipoic acid).

Citrate is Kreb's Starting Substrate for Making Oxaloacetate.
Electron transport chain and oxidative phosphorylation

NADH electrons from glycolysis enter mitochondria via the malate-aspartate or glycerol-3-phosphate shuttle. FADH₂ electrons are transferred to complex II (at a lower energy level than NADH). The passage of electrons results in the formation of a proton gradient that, coupled to oxidative phosphorylation, drives the production of ATP.

\[
\begin{align*}
&\text{NADH} \rightarrow \text{FADH}_2 \rightarrow \text{H}_2\text{O} \\
&\text{ADP} + \text{P}_i \rightarrow \text{ATP}
\end{align*}
\]

**Gluconeogenesis, irreversible enzymes**

Pathway Produces Fresh Glucose.

- **Pyruvate carboxylase**
  - In mitochondria. Pyruvate $\rightarrow$ oxaloacetate.
  - Requires biotin, ATP. Activated by acetyl-CoA.

- **Phosphoenolpyruvate carboxykinase**
  - In cytosol. Oxaloacetate $\rightarrow$ phosphoenolpyruvate.
  - Requires GTP.

- **Fructose-1,6-bisphosphatase**
  - In cytosol. Fructose-1,6-bisphosphate $\rightarrow$ fructose-6-phosphate.
  - Citrate $\oplus$, fructose 2,6-bisphosphate $\ominus$.

- **Glucose-6-phosphatase**
  - In ER. Glucose-6-phosphate $\rightarrow$ glucose.

Occurs primarily in liver; serves to maintain euglycemia during fasting. Enzymes also found in kidney, intestinal epithelium. Deficiency of the key gluconeogenic enzymes causes hypoglycemia. (Muscle cannot participate in gluconeogenesis because it lacks glucose-6-phosphatase.) Odd-chain fatty acids yield 1 propionyl-CoA during metabolism, which can enter the TCA cycle (as succinyl-CoA), undergo gluconeogenesis, and serve as a glucose source. Even-chain fatty acids cannot produce new glucose, since they yield only acetyl-CoA equivalents.
HMP shunt (pentose phosphate pathway) Provides a source of NADPH from abundantly available glucose-6-P (NADPH is required for reductive reactions, e.g., glutathione reduction inside RBCs, fatty acid and cholesterol biosynthesis). Additionally, this pathway yields ribose for nucleotide synthesis and glycolytic intermediates. 2 distinct phases (oxidative and nonoxidative), both of which occur in the cytoplasm. No ATP is used or produced.

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

<table>
<thead>
<tr>
<th>REACTIONS</th>
<th>KEY ENZYMES</th>
<th>PRODUCTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oxidative</strong></td>
<td>Glucose-6-P dehydrogenase</td>
<td>NADPH, CO2</td>
</tr>
<tr>
<td>(irreversible)</td>
<td></td>
<td>2 NADPH, Ribulose-5-Pi</td>
</tr>
<tr>
<td></td>
<td>Rate-limiting step</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nonoxidative</strong></td>
<td>Phosphopentose isomerase,</td>
<td>Ribose-5-Pi, Glucose-3-phosphate,</td>
</tr>
<tr>
<td>(reversible)</td>
<td>transketolases</td>
<td>Fructose-6-P</td>
</tr>
<tr>
<td></td>
<td>Requires B1</td>
<td></td>
</tr>
</tbody>
</table>

Glucose-6-phosphate dehydrogenase deficiency NADPH is necessary to keep glutathione reduced, which in turn detoxifies free radicals and peroxides. 4 NADPH in RBCs leads to hemolytic anemia due to poor RBC defense against oxidizing agents (e.g., fava beans, sulfonamides, primaquine, antituberculosis drugs). Infection can also precipitate hemolysis (free radicals generated via inflammatory response can diffuse into RBCs and cause oxidative damage).

\[ \text{NADP}^+ \rightarrow \text{NADPH} \]

X-linked recessive disorder; most common human enzyme deficiency; more prevalent among blacks. 4 malarial resistance. Heinz bodies—denatured Hemoglobin precipitates 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, since fructose is not trapped in cells.
Symptoms: fructose appears in blood and urine.
Disorders of fructose metabolism cause milder symptoms than analogous disorders of galactose metabolism.

**Fructose intolerance**
Hereditary deficiency of aldolase B. Autosomal recessive. Fructose-1-phosphate accumulates, causing a \( \downarrow \) in available phosphate, which results in inhibition of glycogenolysis and gluconeogenesis. Symptoms present following consumption of fruit, juice, or honey. Urine dipstick will be \( \Theta \) (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: \( \downarrow \) intake of both fructose and sucrose (glucose + fructose).

Disorders of galactose metabolism

**Galactokinase deficiency**
Hereditary deficiency of galactokinase. Galactitol accumulates if galactose is present in diet.
Relatively mild condition. Autosomal recessive.
Symptoms: galactose appears in blood and urine, infantile cataracts. May present as failure to track objects or to develop a social smile.

**Classic galactosemia**
Absence of galactose-1-phosphate uridylyltransferase. Autosomal recessive. Damage is caused by accumulation of toxic substances (including galactitol, which accumulates in the lens of the eye).
Symptoms: failure to thrive, jaundice, hepatomegaly, infantile cataracts, intellectual disability. Can lead to E. coli sepsis in neonates.
Treatment: exclude galactose and lactose (galactose + glucose) from diet.

**Fructose is to Aldolase B as Galactose is to UridylTransferase (FAB GUT).**
The more serious defects lead to \( PO_4^{3-} \) depletion.
Sorbitol

An alternative method of trapping glucose in the cell is to convert it to its alcohol counterpart, called sorbitol, via aldose reductase. Some tissues then convert sorbitol to fructose using sorbitol dehydrogenase; tissues with an insufficient amount of this enzyme are at risk for intracellular sorbitol accumulation, causing osmotic damage (e.g., 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.

Lactase deficiency

Insufficient lactase enzyme → dietary lactose intolerance. Lactase functions on the brush border to digest lactose (in human and cow milk) into glucose and galactose.

Primary: age-dependent decline after childhood (absence of lactase-persistent allele), common in people of Asian, African, or Native American descent.

Secondary: loss of brush border due to gastroenteritis (e.g., rotavirus), autoimmune disease, etc.

Congenital lactase deficiency: rare, due to defective gene.

Stool demonstrates pH and breath shows hydrogen content with lactose tolerance test. Intestinal biopsy reveals normal mucosa in patients with hereditary lactose intolerance.

FINDINGS

Bloating, cramps, flatulence, osmotic diarrhea.

TREATMENT

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

Amino acids

Only L-amino acids are found in proteins.

Essential

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

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

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

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

Acidic

Aspartic acid (Asp) and glutamic acid (Glu).

Negatively charged at body pH.

Basic

Arginine (Arg), lysine (Lys), histidine (His).

Arg is most basic.

His has no charge at body pH.

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

Amino acid catabolism results in the formation of common metabolites (e.g., pyruvate, acetyl-CoA), which serve as metabolic fuels. Excess nitrogen (NH₃) generated by this process is converted to urea and excreted by the kidneys.

Ordinarily, Careless Crappers Are Also Frivolous About Urination.
Hyperammonemia

Can be acquired (e.g., liver disease) or hereditary (e.g., urea cycle enzyme deficiencies). Results in excess NH$_4^+$, which depletes $\alpha$-ketoglutarate, leading to inhibition of TCA cycle.

Treatment: limit protein in diet. Lactulose to acidify the GI tract and trap NH$_4^+$ for excretion. Rifaximin to ↓ colonic ammoniagenic bacteria. Benzoate or phenylbutyrate (both of which bind amino acid and lead to excretion) may be given to ↓ ammonia levels.

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

$N$-acetylglutamate synthase deficiency

Required cofactor for carbamoyl phosphate synthetase I. Absence of $N$-acetylglutamate → hyperammonemia. Presents in neonates as poorly regulated respiration and body temperature, poor feeding, developmental delay, intellectual disability (identical to presentation of carbamoyl phosphate synthetase I deficiency).

Ornithine transcarbamylase deficiency

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

Findings: ↑ orotic acid in blood and urine, ↓ BUN, symptoms of hyperammonemia. No megaloblastic anemia (vs. orotic aciduria).

Amino acid derivatives

- Phenylalanine → Tyrosine → Dopamine → NE → Epi
- Tryptophan → Niacin → NAD$^+$/NADP$^+$
- Histidine → Serotonin → Melatonin
- Glycine → Porphyrin → Heme
- Glutamate → GABA
- Arginine → Urea
- BH$_4$, BH$_4$, B$_6$, B$_6$, B$_6$, B$_6$, B$_6$, B$_6$
**Catecholamine synthesis/tyrosine catabolism**

- **Phenylalanine**
  - BH₄
  - Phenylalanine hydroxylase
  - PKU

- **Tyrosine**
  - BH₄
  - Tyrosine hydroxylase
  - Albinism
  - Tyrosinase

- **DOPA (Dihydroxyphenylalanine)**
  - DOPA decarboxylase
  - Carbidopa

- **Vitamin C**

- **TCA cycle**

- **Dopamine**
  - Tyrosine hydroxylase
  - DOPA-decarboxylase

- **Norepinephrine**
  - Phenylethanolamine-N-methyltransferase

- **Epinephrine**
  - Cortisol
  - Normetanephrine

- **Metanephrine**
  - Vanillylmandelic acid
  - Homovanillic acid

---

**Phenylketonuria**

Due to ↓ phenylalanine hydroxylase or ↓ tetrahydrobiopterin cofactor (malignant PKU). Tyrosine becomes essential.

↑ phenylalanine ⇒ excess phenylketones in urine.

Findings: intellectual disability, growth retardation, seizures, fair skin, eczema, musty body odor.

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

**Maternal PKU**—lack of proper dietary therapy during pregnancy. Findings in infant: microcephaly, intellectual disability, growth retardation, congenital heart defects.

---

**Maple syrup urine disease**

Blocked degradation of branched amino acids (Isoleucine, Leucine, Valine) due to ↓ α-ketoacid dehydrogenase (B₁). Causes ↑ α-ketoacids in the blood, especially those of leucine.

Causes severe CNS defects, intellectual disability, and death.

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

Autosomal recessive. Incidence ≈ 1:10,000.

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

Phenylketones—phenylacetate, phenyllactate, and phenylpyruvate.

Disorder of aromatic amino acid metabolism ⇒ musty body odor.

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

---

*Maple syrup urine disease* Blocked degradation of branched amino acids (Isoleucine, Leucine, Valine) due to ↓ α-ketoacid dehydrogenase (B₁). Causes ↑ α-ketoacids in the blood, especially those of leucine.

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---

[Maple syrup disease image from Biochemistry](image_url)
**Alkaptonuria (ochronosis)**

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

Findings: dark connective tissue, brown pigmented sclerae, urine turns black on prolonged exposure to air. May have debilitating arthralgias (homogentisic acid toxic to cartilage).

**Homocystinuria**

Types (all autosomal recessive):
- Cystathionine synthase deficiency (treatment: ↓ methionine, ↑ cysteine, ↑ B₁₂ and folate in diet)
- ↓ affinity of cystathionine synthase for pyridoxal phosphate (treatment: ↑ B₆ and ↑ cysteine in diet)
- Homocysteine methyltransferase (methionine synthase) deficiency (treatment: ↑ methionine in diet)

All forms result in excess homocysteine.

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

**Cystinuria**

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

Excess cystine in the urine can lead to recurrent precipitation of hexagonal cystine stones A. Treatment: urinary alkalinization (e.g., potassium citrate, acetazolamide) and chelating agents (e.g., penicillamine) ↑ solubility of cystine stones; good hydration.

Autosomal recessive. Common (1:7000).

Urinary cyanide-nitroprusside test is diagnostic.

Cystine is made of 2 cysteines connected by a disulfide bond.
Glycogen regulation by insulin and glucagon/epinephrine

**Glycogen**
Branches have \( \alpha-(1,6) \) bonds; linkages have \( \alpha-(1,4) \) bonds.

**Skeletal muscle**
Glycogen undergoes glycogenolysis \( \rightarrow \) glucose-1-phosphate \( \rightarrow \) glucose-6-phosphate, which is rapidly metabolized during exercise.

**Hepatocytes**
Glycogen is stored and undergoes glycogenolysis to maintain blood sugar at appropriate levels. Glycogen phosphorylase liberates glucose-1-phosphate residues off branched glycogen until 4 glucose units remain on a branch. Then 4-\( \alpha \)-D-glucanotransferase (debranching enzyme 5) moves 3 molecules of glucose-1-phosphate from the branch to the linkage. Then \( \alpha \)-1,6-glucosidase (debranching enzyme 6) cleaves off the last residue, liberating glucose. “Limit dextrin” refers to the one to four residues remaining on a branch after glycogen phosphorylase has already shortened it.

Note: A small amount of glycogen is degraded in lysosomes by \( \alpha \)-1,4-glucosidase (acid maltase).
### Glycogen storage diseases

12 types, all resulting in abnormal glycogen metabolism and an accumulation of glycogen within cells. **Very Poor Carbohydrate Metabolism.**

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>FINDINGS</th>
<th>DEFICIENT ENZYME</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Von Gierke disease</strong> (type I)</td>
<td>Severe fasting hypoglycemia, ↑↑ glycogen in liver, ↑ blood lactate, ↑ triglycerides, ↑ uric acid, and hepatomegaly</td>
<td>Glucose-6-phosphatase</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment: frequent oral glucose/cornstarch; avoidance of fructose and galactose</td>
</tr>
<tr>
<td><strong>Pompe disease</strong> (type II)</td>
<td>Cardiomegaly, hypertrophic cardiomyopathy, exercise intolerance, and systemic findings leading to early death</td>
<td>Lysosomal α-1,4-glucosidase (acid maltase)</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pompe trashes the Pump (heart, liver, and muscle)</td>
</tr>
<tr>
<td><strong>Cori disease</strong> (type III)</td>
<td>Milder form of type I with normal blood lactate levels</td>
<td>Debranching enzyme (α-1,6-glucosidase)</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gluconeogenesis is intact</td>
</tr>
<tr>
<td><strong>McArdle disease</strong> (type V)</td>
<td>↑ glycogen in muscle, but muscle cannot break it down → painful muscle cramps, myoglobinuria (red urine) with strenuous exercise, and arrhythmia from electrolyte abnormalities</td>
<td>Skeletal muscle glycogen phosphorylase (myophosphorylase)</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Blood glucose levels typically unaffected</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>McArdle = Muscle</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treat with vitamin B₆ (cofactor)</td>
</tr>
</tbody>
</table>
## Lysosomal storage diseases

Each is caused by a deficiency in one of the many lysosomal enzymes. Results in an accumulation of abnormal metabolic products.

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>FINDINGS</th>
<th>DEFICIENT ENZYME</th>
<th>ACCUMULATED SUBSTRATE</th>
<th>INHERITANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sphingolipidoses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fabry disease</td>
<td>Peripheral neuropathy of hands/feet, angiokeratomas, cardiovascular/renal disease.</td>
<td>α-galactosidase A</td>
<td>Ceramide trihexoside</td>
<td>XR</td>
</tr>
<tr>
<td>Gaucher disease</td>
<td>Most common. Hepatosplenomegaly, pancytopenia, osteoporosis, aseptic necrosis of femur, bone crises, Gaucher cells (lipid-laden macrophages resembling crumpled tissue paper); treatment is recombinant glucocerebrosidase.</td>
<td>Glucocerebrosidase (β-glucosidase)</td>
<td>Glucocerebroside</td>
<td>AR</td>
</tr>
<tr>
<td>Niemann-Pick disease</td>
<td>Progressive neurodegeneration, hepatosplenomegaly, foam cells (lipid-laden macrophages), “cherry-red” spot on macula.</td>
<td>Sphingomyelinase</td>
<td>Sphingomyelin</td>
<td>AR</td>
</tr>
<tr>
<td>Tay-Sachs disease</td>
<td>Progressive neurodegeneration, developmental delay, “cherry-red” spot on macula, lysosomes with onion skin, no hepatosplenomegaly (vs. Niemann-Pick).</td>
<td>Hexosaminidase A</td>
<td>GM₂ ganglioside</td>
<td>AR</td>
</tr>
<tr>
<td>Krabbe disease</td>
<td>Peripheral neuropathy, developmental delay, optic atrophy, globoid cells.</td>
<td>Galactocerebrosidase</td>
<td>Galactocerebroside, psychosine</td>
<td>AR</td>
</tr>
<tr>
<td>Metachromatic leukodystrophy</td>
<td>Central and peripheral demyelination with ataxia, dementia.</td>
<td>Arylsulfatase A</td>
<td>Cerebroside sulfate</td>
<td>AR</td>
</tr>
</tbody>
</table>

| **Mucopolysaccharidoses** |                                                                          |                  |                       |             |
| Hurler syndrome      | Developmental delay, gargoilsm, airway obstruction, corneal clouding, hepatosplenomegaly. | α-L-iduronidase | Heparan sulfate, dermatan sulfate | AR          |
| Hunter syndrome      | Mild Hurler + aggressive behavior, no corneal clouding.                  | Iduronate sulfatase | Heparan sulfate, dermatan sulfate | XR          |

No man picks (Niemann-Pick) his nose with his sphinger (sphingomyelinase). Tay-SaX lacks heXosaminidase. **Hunters** see clearly (no corneal clouding) and aggressively aim for the X (X-linked recessive). † incidence of Tay-Sachs, Niemann-Pick, and some forms of Gaucher disease in Ashkenazi Jews.
Fatty acid metabolism

**Synthesis**

- Fatty acid synthesis (palmitate, a 16C FA)
  - Malonyl-CoA
  - CO$_2$ (biotin)
  - Acetyl-CoA
  - ATP citrate lyase

**Degradation**

- Fatty acid + CoA
  - Fatty acid CoA synthase
  - Fatty Acyl-CoA

**Carnitine shuttle**

- Fatty Acyl-CoA
  - Acyl CoA dehydrogenases (β-oxidation)
  - Ketone bodies
  - TCA cycle

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.

“SYnthesis” = SYntesis.

CARnitate = CARnage of fatty acids.

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

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

**Medium-chain acyl-CoA dehydrogenase deficiency**

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

**Ketone bodies**

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

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

Breath smells like acetone (fruity odor). Urine test for ketones does not detect β-hydroxybutyrate.
Metabolic fuel use

**Exercise**

<table>
<thead>
<tr>
<th>Time</th>
<th>Stored ATP</th>
<th>Creatine phosphate</th>
<th>Anaerobic metabolism</th>
<th>Aerobic metabolism</th>
<th>Overall performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 sec</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 sec</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 hrs</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

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

**Fasting and starvation**

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

**Fed state (after a meal)**
Glycolysis and aerobic respiration.
Insulin stimulates storage of lipids, proteins, and glycogen.

**Fasting (between meals)**
Hepatic glycogenolysis (major); hepatic gluconeogenesis, adipose release of FFA (minor).
Glucagon and epinephrine stimulate use of fuel reserves.

**Starvation days 1–3**
Blood glucose levels maintained by:
- Hepatic glycogenolysis
- Adipose release of FFA
- Muscle and liver, which shift fuel use from glucose to FFA
- Hepatic gluconeogenesis from peripheral tissue lactate and alanine, and from adipose tissue glycerol and propionyl-CoA (from odd-chain FFA—the only triacylglycerol components that contribute to gluconeogenesis)
Glycogen reserves depleted after day 1.
RBCs lack mitochondria and therefore cannot use ketones.

**Starvation after day 3**
Adipose stores (ketone bodies become the main source of energy for the brain). After these are depleted, vital protein degradation accelerates, leading to organ failure and death.
Amount of excess stores determines survival time.
**Cholesterol synthesis**

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

Rate-limiting step catalyzed by HMG-CoA reductase (induced by insulin), which converts HMG-CoA to mevalonate. 3% of plasma cholesterol esterified by lecithin-cholesterol acyltransferase (LCAT).

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

**Lipid transport, key enzymes**

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

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

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

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

LCAT—catalyzes esterification of cholesterol.

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

<table>
<thead>
<tr>
<th>Apolipoprotein</th>
<th>Function</th>
<th>Chylomicron</th>
<th>Chylomicron remnant</th>
<th>VLDL</th>
<th>IDL</th>
<th>LDL</th>
<th>HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>Mediates remnant uptake</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>A-I</td>
<td>Activates LCAT</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-II</td>
<td>Lipoprotein lipase cofactor</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-48</td>
<td>Mediates chylomicron secretion</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-100</td>
<td>Binds LDL receptor</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

Lipoprotein functions

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

LDL transports cholesterol from liver to tissues. HDL transports cholesterol from periphery to liver.

LDL is **Lousy.** HDL is **Healthy.**

**Chylomicron**

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

**VLDL**

Delivers hepatic TGs to peripheral tissue. Secreted by liver.

**IDL**

Formed in the degradation of VLDL. Delivers TGs and cholesterol to liver.

**LDL**

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

**HDL**

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

Familial dyslipidemias

<table>
<thead>
<tr>
<th>TYPE</th>
<th>INCREASED BLOOD LEVEL</th>
<th>PATHOPHYSIOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>I—hyper-chylomicronemia</td>
<td>Chylomicrons, TG, cholesterol</td>
<td>Autosomal recessive. Lipoprotein lipase deficiency or altered apolipoprotein C-II. Causes pancreatitis, hepatosplenomegaly, and eruptive/pruritic xanthomas (no ↑ risk for atherosclerosis). Creamy layer in supernatant.</td>
</tr>
<tr>
<td>Ila—familial hypercholesterolemia</td>
<td>LDL, cholesterol</td>
<td>Autosomal dominant. Absent or defective LDL receptors. Heterozygotes (1:500) have cholesterol ≈ 300 mg/dL; homozygotes (very rare) have cholesterol = 700+ mg/dL. Causes accelerated atherosclerosis (may have MI before age 20), tendon (Achilles) xanthomas, and corneal arcus.</td>
</tr>
<tr>
<td>IV—hyper-triglyceridemia</td>
<td>VLDL, TG</td>
<td>Autosomal dominant. Hepatic overproduction of VLDL. Hypertriglyceridemia (&gt; 1000 mg/ dL) can cause acute pancreatitis.</td>
</tr>
</tbody>
</table>
“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

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

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

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

#### Bacterial structures

<table>
<thead>
<tr>
<th>Structure</th>
<th>Function</th>
<th>Chemical Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptidoglycan</td>
<td>Gives rigid support, protects against osmotic pressure.</td>
<td>Sugar backbone with peptide side chains cross-linked by transpeptidase.</td>
</tr>
<tr>
<td>Cell wall</td>
<td>Major surface antigen.</td>
<td>Peptidoglycan for support. Lipoteichoic acid induces TNF and IL-1.</td>
</tr>
<tr>
<td>Outer membrane</td>
<td>Site of endotoxin (lipopolysaccharide [LPS]); major surface antigen.</td>
<td>Lipid A induces TNF and IL-1; O polysaccharide is the antigen.</td>
</tr>
<tr>
<td>(gram negatives)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma membrane</td>
<td>Site of oxidative and transport enzymes.</td>
<td>Phospholipid bilayer.</td>
</tr>
<tr>
<td>Ribosome</td>
<td>Protein synthesis.</td>
<td>50S and 30S subunits.</td>
</tr>
<tr>
<td>Periplasm</td>
<td>Space between the cytoplasmic membrane and outer membrane in gram-negative bacteria.</td>
<td>Contains many hydrolytic enzymes, including β-lactamases.</td>
</tr>
<tr>
<td>Pilus/fimbria</td>
<td>Mediate adherence of bacteria to cell surface; sex pilus forms attachment between 2 bacteria during conjugation.</td>
<td>Glycoprotein.</td>
</tr>
<tr>
<td>Flagellum</td>
<td>Motility.</td>
<td>Protein.</td>
</tr>
<tr>
<td>Spore</td>
<td>Resistant to dehydration, heat, and chemicals.</td>
<td>Keratin-like coat; dipicolinic acid; peptidoglycan.</td>
</tr>
<tr>
<td>Plasmid</td>
<td>Contains a variety of genes for antibiotic resistance, enzymes, and toxins.</td>
<td>DNA.</td>
</tr>
<tr>
<td>Capsule</td>
<td>Protects against phagocytosis.</td>
<td>Organized, discrete polysaccharide layer (except <em>Bacillus anthracis</em>, which contains d-glutamate).</td>
</tr>
<tr>
<td>Glycocalyx</td>
<td>Mediates adherence to surfaces, especially foreign surfaces (e.g., indwelling catheters).</td>
<td>Loose network of polysaccharides.</td>
</tr>
</tbody>
</table>

#### Cell walls

<table>
<thead>
<tr>
<th>Unique to gram-positive</th>
<th>Common to both</th>
<th>Unique to gram-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipoteichoic acid</td>
<td>Flagellum</td>
<td>Porin</td>
</tr>
<tr>
<td></td>
<td>Pili</td>
<td>Endotoxin/LPS (outer membrane)</td>
</tr>
<tr>
<td></td>
<td>Capsule</td>
<td>Periplasmic space (β-lactamase location)</td>
</tr>
</tbody>
</table>

Gram-positive: Lipoteichoic acid, Flagellum, Capsule, Peptidoglycan, Cytoplasmic membrane.

Gram-negative: Periplasmic space (β-lactamase location), Endotoxin/LPS (outer membrane).
### Bacterial taxonomy

<table>
<thead>
<tr>
<th>MORPHOLOGY</th>
<th>Gram-positive examples</th>
<th>Gram-negative examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spherical (coccus)</td>
<td>Staphylococcus</td>
<td>Monaxella catarrhalis</td>
</tr>
<tr>
<td></td>
<td>Streptococcus</td>
<td>Neisseria</td>
</tr>
<tr>
<td>Rod (bacillus)</td>
<td>Bacillus</td>
<td>Enterics:</td>
</tr>
<tr>
<td></td>
<td>Clostridium</td>
<td>• Bacteroides</td>
</tr>
<tr>
<td></td>
<td>Corynebacterium</td>
<td>• Campylobacter</td>
</tr>
<tr>
<td></td>
<td>Gardnerella (gram variable)</td>
<td>• E. coli</td>
</tr>
<tr>
<td></td>
<td>Lactobacillus</td>
<td>• Enterobacter</td>
</tr>
<tr>
<td></td>
<td>Listeria</td>
<td>• Helicobacter</td>
</tr>
<tr>
<td></td>
<td>Mycobacterium (acid fast)</td>
<td>• Klebsiella</td>
</tr>
<tr>
<td></td>
<td>Propionibacterium</td>
<td>• Proteus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pseudomonas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Salmonella</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Serratia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Shigella</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Vibrio</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Yersinia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Respiratory:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Bordetella</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Haemophilus (pleomorphic)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Legionella (silver stain)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zoonotic:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Bartonella</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Brucella</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Francisella</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pasteurella</td>
</tr>
<tr>
<td>Branching filamentous</td>
<td>Actinomyces</td>
<td>Chlamydiaceae (Giemsa)</td>
</tr>
<tr>
<td></td>
<td>Nocardia (weakly acid fast)</td>
<td>Rickettsiaceae (Giemsa)</td>
</tr>
<tr>
<td>Pleomorphic</td>
<td></td>
<td>Spirochetes:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Borrelia (Giemsa)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Leptospira</td>
</tr>
<tr>
<td>Spiral</td>
<td></td>
<td>• Treponema</td>
</tr>
<tr>
<td>No cell wall</td>
<td>Mycoplasma, Ureaplasma (contain sterols, which do not Gram stain)</td>
<td></td>
</tr>
</tbody>
</table>
**Gram stain limitations**

These bugs do not Gram stain well:
- *Treponema* (too thin to be visualized).
- *Mycobacteria* (high lipid content; mycolic acids in cell wall detected by carbol fuchsin in acid-fast stain).
- *Mycoplasma* (no cell wall).
- *Legionella pneumophila* (primarily intracellular).
- *Rickettsia* (intracellular parasite).
- *Chlamydia* (intracellular parasite; lacks classic peptidoglycan because of low muramic acid).

These microbes may lack real color.
- Treponemes—dark-field microscopy and fluorescent antibody staining.
- *Legionella*—silver stain.

**Stains**

<table>
<thead>
<tr>
<th>Stains</th>
<th>Giemsa</th>
<th>PAS (periodic acid–Schiff)</th>
<th>Ziehl-Neelsen (carbol fuchsin)</th>
<th>India ink</th>
<th>Silver stain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>Chlamydia, Borrelia, Rickettsia, Trypanosomes, Plasmodium.</em></td>
<td>Stains glycogen, mucopolysaccharides; used to diagnose Whipple disease (<em>Tropheryma whippelii</em>).</td>
<td>Acid-fast bacteria (<em>Nocardia, Mycobacteria</em>), protozoa (<em>Cryptosporidium oocysts</em>).</td>
<td><em>Cryptococcus neoformans</em> (mucicarmine can also be used to stain thick polysaccharide capsule red).</td>
<td>Fungi (e.g., <em>Pneumocystis, Legionella, Helicobacter pylori</em>).</td>
</tr>
</tbody>
</table>
### Special culture requirements

<table>
<thead>
<tr>
<th>Bug</th>
<th>Media used for isolation</th>
<th>Media contents/other</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. influenzae</td>
<td>Chocolate agar</td>
<td>Factors V (NAD+) and X (hematin)</td>
</tr>
<tr>
<td>N. gonorrhoeae, N. meningitidis</td>
<td>Thayer-Martin agar</td>
<td>Vancomycin (inhibits gram-positive organisms), Trimethoprim, Colistin (inhibits gram-negative organisms except Neisseria), and Nystatin (inhibits fungi)</td>
</tr>
<tr>
<td>B. pertussis</td>
<td>Bordet-Gengou agar (Bordet for Bordetella)</td>
<td>Potato Charcoal, blood, and antibiotic</td>
</tr>
<tr>
<td>C. diphtheriae</td>
<td>Tellurite agar, Löffler medium</td>
<td></td>
</tr>
<tr>
<td>M. tuberculosis</td>
<td>Löwenstein-Jensen agar</td>
<td></td>
</tr>
<tr>
<td>M. pneumoniae</td>
<td>Eaton agar</td>
<td>Requires cholesterol</td>
</tr>
<tr>
<td>Lactose-fermenting enterics</td>
<td>MacConkey agar</td>
<td>Fermentation produces acid, causing colonies to turn pink</td>
</tr>
<tr>
<td>E. coli</td>
<td>Eosin–methylene blue (EMB) agar</td>
<td>Colonies with green metallic sheen</td>
</tr>
<tr>
<td>Legionella</td>
<td>Charcoal yeast extract agar buffered with cysteine and iron</td>
<td></td>
</tr>
<tr>
<td>Fungi</td>
<td>Sabouraud agar</td>
<td>“Sab’s a fun guy!”</td>
</tr>
</tbody>
</table>

### Aerobes

Aerobes are aerobic bacteria that require oxygen to function. Key examples include:

- **Nocardiia**, **Pseudomonas aeruginosa**, and **Mycobacterium tuberculosis**.

Reactivation of M. tuberculosis (e.g., after immunocompromise or TNF-α inhibitor use) has a predilection for the apices of the lung, which have the highest PO₂.

**Nagging Pests Must Breathe.**

### Anaerobes

Anaerobes are bacteria that cannot utilize oxygen. Important examples include:

- **Fusobacterium**, **Clostridium**, **Bacteroides**, and **Actinomyces**.

Anaerobes are normal flora in GI tract, typically pathogenic elsewhere. AminO₂glycosides are ineffective against anaerobes because these antibiotics require O₂ to enter into bacterial cell.

Anaerobes Frankly Can’t Breathe Air.
Intracellular bugs

**Obligate intracellular**
- *Rickettsia*, *CHlamydia*, *COxiella*. Rely on host ATP. Stay inside (cells) when it is Really CHilly and COld.

**Facultative intracellular**

Encapsulated bacteria

Examples are *Streptococcus pneumoniae*, *Haemophilus influenzae* type B, *Neisseria meningitidis*, *Escherichia coli*, *Salmonella*, *Klebsiella pneumoniae*, and group B Strep. Their capsules serve as an antiphagocytic virulence factor. Capsule + protein conjugate serves as an antigen in vaccines.

Encapsulated bacteria vaccines

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

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

Urease-positive organisms

- *Cryptococcus*, *H. pylori*, *Proteus*, *Ureaplasma*, *Nocardia*, *Klebsiella*, *S. epidermidis*, *S. saprophyticus*. CHuck Norris hates PUNKSS.

Catalase-positive organisms

Catalase degrades H$_2$O$_2$ into H$_2$O and bubbles of O$_2$ before it can be converted to microbicidal products by the enzyme myeloperoxidase. People with chronic granulomatous disease (NADPH oxidase deficiency) have recurrent infections with certain catalase ⊕ organisms. Examples: *Nocardia*, *Pseudomonas*, *Listeria*, *Aspergillus*, *Candida*, *E. coli*, *Staphylococci*, *Serratia*. Cats Need PLACESS to hide.

Pigment-producing bacteria

- *Actinomyces israelii*—yellow “sulfur” granules, which are composed of filaments of bacteria. Israel has yellow sand.
- *S. aureus*—yellow pigment. *Aureus* (Latin) = gold.
- *Pseudomonas aeruginosa*—blue-green pigment. *Aerugula* is green.
- *Serratia marcescens*—red pigment. *Serratia marcescens*—think red maraschino cherries.
**Bacterial virulence factors**

These promote evasion of host immune response.

- **Protein A**
  Binds Fc region of IgG. Prevents opsonization and phagocytosis. Expressed by *S. aureus*.

- **IgA protease**
  Enzyme that cleaves IgA. Secreted by *S. pneumoniae*, *H. influenzae* type B, and *Neisseria* (SHiN) in order to colonize respiratory mucosa.

- **M protein**
  Helps prevent phagocytosis. Expressed by group A streptococci. Shares similar epitopes to human cellular proteins (molecular mimicry); possibly underlies the autoimmune response seen in acute rheumatic fever.

**Type III secretion system**

Also known as “injectisome.” Needle-like protein appendage facilitating direct delivery of toxins from certain gram-negative bacteria (e.g., *Pseudomonas*, *Salmonella*, *Shigella*, *E. coli*) to eukaryotic host cell.

**Main features of exotoxins and endotoxins**

<table>
<thead>
<tr>
<th>PROPERTY</th>
<th>Exotoxin</th>
<th>Endotoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOURCE</td>
<td>Certain species of gram-positive and gram-negative bacteria</td>
<td>Outer cell membrane of most gram-negative bacteria</td>
</tr>
<tr>
<td>SECRETED FROM CELL</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>CHEMISTRY</td>
<td>Polypeptide</td>
<td>Lipopolysaccharide (structural part of bacteria; released when lysed)</td>
</tr>
<tr>
<td>LOCATION OF GENES</td>
<td>Plasmid or bacteriophage</td>
<td>Bacterial chromosome</td>
</tr>
<tr>
<td>TOXICITY</td>
<td>High (fatal dose on the order of 1 µg)</td>
<td>Low (fatal dose on the order of hundreds of micrograms)</td>
</tr>
<tr>
<td>CLINICAL EFFECTS</td>
<td>Various effects (see following pages)</td>
<td>Fever, shock (hypotension), DIC</td>
</tr>
<tr>
<td>MODE OF ACTION</td>
<td>Various modes (see following pages)</td>
<td>Induces TNF, IL-1, and IL-6</td>
</tr>
<tr>
<td>ANTIGENICITY</td>
<td>Induces high-titer antibodies called antitoxins</td>
<td>Poorly antigenic</td>
</tr>
<tr>
<td>VACCINES</td>
<td>Toxoids used as vaccines</td>
<td>No toxoids formed and no vaccine available</td>
</tr>
<tr>
<td>HEAT STABILITY</td>
<td>Destroyed rapidly at 60°C (except staphylococcal enterotoxin)</td>
<td>Stable at 100°C for 1 hr</td>
</tr>
<tr>
<td>TYPICAL DISEASES</td>
<td>Tetanus, botulism, diphtheria</td>
<td>Meningococcemia; sepsis by gram-negative rods</td>
</tr>
</tbody>
</table>
### Bugs with exotoxins

<table>
<thead>
<tr>
<th>BACTERIA</th>
<th>TOXIN</th>
<th>MECHANISM</th>
<th>MANIFESTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhibit protein synthesis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Corynebacterium diphtheriae</em></td>
<td>Diphtheria toxin*</td>
<td>Inactivate elongation factor (EF-2)</td>
<td>Pharyngitis with pseudomembranes in throat and severe lymphadenopathy (bull neck)</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Exotoxin A*</td>
<td></td>
<td>Host cell death</td>
</tr>
<tr>
<td><em>Shigella</em> spp.</td>
<td>Shiga toxin (ST)*</td>
<td>Inactivate 60S ribosome by removing adenine from rRNA</td>
<td>GI mucosal damage → dysentry; ST also enhances cytokine release, causing hemolytic-uremic syndrome (HUS)</td>
</tr>
<tr>
<td>Enterohemorrhagic <em>E. coli</em> (EHEC)</td>
<td>Shiga-like toxin (SLT)*</td>
<td></td>
<td>SLT enhances cytokine release, causing HUS (prototypically in EHEC serotype O157:H7). Unlike <em>Shigella</em>, EHEC does not invade host cells</td>
</tr>
<tr>
<td><strong>Increase fluid secretion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterotoxigenic <em>E. coli</em> (ETEC)</td>
<td>Heat-labile toxin (LT)*</td>
<td>Overactivates adenylate cyclase (cAMP) → Cl− secretion in gut and H2O efflux</td>
<td>Watery diarrhea: “labile in the Air (Adenylate cyclase), stable on the Ground (Guanylate cyclase)”</td>
</tr>
<tr>
<td></td>
<td>Heat-stable toxin (ST)*</td>
<td>Overactivates guanylate cyclase (cGMP) → resorption of NaCl and H2O in gut</td>
<td></td>
</tr>
<tr>
<td><em>Bacillus anthracis</em></td>
<td>Edema toxin*</td>
<td>Mimics the adenylate cyclase enzyme (cAMP)</td>
<td>Likely responsible for characteristic edematous borders of black eschar in cutaneous anthrax</td>
</tr>
<tr>
<td><em>Vibrio cholerae</em></td>
<td>Cholera toxin*</td>
<td>Overactivates adenylate cyclase (cAMP) by permanently activating Gi, → Cl− secretion in gut and H2O efflux</td>
<td>Voluminous “rice-water” diarrhea</td>
</tr>
<tr>
<td><strong>Inhibit phagocytic ability</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Bordetella pertussis</em></td>
<td>Pertussis toxin*</td>
<td>Overactivates adenylate cyclase (cAMP) by disabling Gi, impairing phagocytosis to permit survival of microbe</td>
<td>Whooping cough—child coughs on expiration and “whoops” on inspiration (toxin may not actually be a cause of cough; can cause “100-day cough” in adults)</td>
</tr>
<tr>
<td><strong>Inhibit release of neurotransmitter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Clostridium tetani</em></td>
<td>Tetanospasmin*</td>
<td>Both are proteases that cleave SNARE (soluble NSF attachment protein receptor), a set of proteins required for neurotransmitter release via vesicular fusion</td>
<td>Spasticity, risus sardonius, and “lockjaw”; toxin prevents release of inhibitory (GABA and glycine) neurotransmitters from Renshaw cells in spinal cord</td>
</tr>
<tr>
<td><em>Clostridium botulinum</em></td>
<td>Botulinum toxin*</td>
<td></td>
<td>Flaccid paralysis, floppy baby; toxin prevents release of stimulatory (ACh) signals at neuromuscular junctions → flaccid paralysis</td>
</tr>
</tbody>
</table>

*a*Toxin is an ADP ribosylating A-B toxin: B (binding) component binds to host cell surface receptor, enabling endocytosis; A (active) component attaches ADP-ribosyl to disrupt host cell proteins.
**Bugs with exotoxins (continued)**

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

**Endotoxin**

LPS found in outer membrane of gram-negative bacteria (both cocci and rods).

**ENDOTOXIN:**
- Edema
- Nitric oxide
- DIC/Death
- Outer membrane
- TNF-α
- O-antigen
eXXtremely heat stable
- IL-1
- Neutrophil chemotaxis
### Bacterial genetics

#### Transformation

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

#### Conjugation

- **F⁺ × 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 (also known as the “mating bridge”). No transfer of chromosomal DNA.

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

#### Transposition

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

#### Transduction

- **Generalized**
  - A “packaging” event. Lytic phage infects bacterium, leading to cleavage of bacterial DNA. Parts of bacterial chromosomal DNA may become packaged in viral 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 viral capsid and can infect another bacterium.

  Genes for the following 5 bacterial toxins are encoded in a lysogenic phage (**ABCDE**):
  - ShigA-like toxin
  - Botulinum toxin (certain strains)
  - Cholera toxin
  - Diphtheria toxin
  - Erythrogenic toxin of *Streptococcus pyogenes*
Gram-positive lab algorithm

Identification of gram-positive cocci

**Staphylococci**
- Novobiocin—*Saprophyticus* is **Resistant**; *Epidermidis* is **Sensitive**.

**Streptococci**
- Optochin—*Viridans* is **Resistant**; *Pneumoniae* is **Sensitive**.
- Bacitracin—group **B** strep are **Resistant**; group **A** strep are **Sensitive**.

On the office’s “*staph*” retreat, there was **NO StRESs**.

OVRPS (overpass).

B-**BRAS**.
**α-hemolytic bacteria**

Form green ring around colonies on blood agar. Include the following organisms:

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

**β-hemolytic bacteria**

Form clear area of hemolysis on blood agar. Include the following organisms:

- *Staphylococcus aureus* (catalase and coagulase)
- *Streptococcus pyogenes*—group A strep (catalase and bacitracin sensitive)
- *Streptococcus agalactiae*—group B strep (catalase and bacitracin resistant)
- *Listeria monocytogenes* (tumbling motility, meningitis in newborns, unpasteurized milk)

**Staphylococcus aureus**

Gram-positive cocc in clusters. Protein A (virulence factor) binds Fe-IgG, inhibiting complement activation and phagocytosis. Commonly colonizes the nares. Causes:

- Inflammatory disease—skin infections, organ abscesses, pneumonia (often after influenza virus infection), endocarditis, septic arthritis, and osteomyelitis.
- Toxin-mediated disease—toxic shock syndrome (TSST-1), scalded skin syndrome (exfoliative toxin), rapid-onset food poisoning (enterotoxins).
- MRSA (methicillin-resistant *S. aureus*) infection—important cause of serious nosocomial and community-acquired infections; resistant to methicillin and nafcillin because of altered penicillin-binding protein.

TSST is a superantigen that binds to MHC II and T-cell receptor, resulting in polyclonal T-cell activation. Staphylococcal toxic shock syndrome (TSS) presents as fever, vomiting, rash, desquamation, shock, end-organ failure. Associated with prolonged use of vaginal tampons or nasal packing. Compare with *Streptococcus pyogenes* TSS (a toxic shock–like syndrome associated with painful skin infection).

*S. aureus* food poisoning due to ingestion of preformed toxin → short incubation period (2–6 hr) followed by nonbloody diarrhea and emesis. Enterotoxin is heat stable → not destroyed by cooking.

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

**Staphylococcus epidermidis**

Infests prosthetic devices (e.g., hip implant, heart valve) and intravenous catheters by producing adherent biofilms. Component of normal skin flora; contaminates blood cultures. Novobiocin sensitive.

**Staphylococcus saprophyticus**

Second most common cause of uncomplicated UTI in young women (first is *E. coli*). Novobiocin resistant.
Streptococcus pneumoniae

Most common cause of:
- Meningitis
- Otitis media (in children)
- Pneumonia
- Sinusitis


S. pneumoniae MOPS are Most Optochin Sensitive.

Pneumococcus is associated with “rusty” sputum, sepsis in sickle cell disease and splenectomy.

No virulence without capsule.

Viridans group streptococci

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

Sanguinis = blood. Think, “there is lots of blood in the heart” (endocarditis). S. sanguinis makes dextrans, which bind to fibrin-platelet aggregates on damaged heart valves.

Viridans group strep live in the mouth because they are not afraid of-the-chin (op-to-chin resistant).

Streptococcus pyogenes (group A streptococci)

Group A strep cause:
- Pyogenic—pharyngitis, cellulitis, impetigo, erysipelas
- Toxigenic—scarlet fever, toxic shock-like syndrome, necrotizing fasciitis
- Immunologic—rheumatic fever, acute glomerulonephritis

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

ASO titer detects recent S. pyogenes infection.

J♥NES (major criteria for acute rheumatic fever):
- Joints—polyarthritis
- ♥—carditis
- Nodules (subcutaneous)
- Erythema marginatum
- Sydenham chorea

Pharyngitis can result in rheumatic “Ph”ever” and glomerulonephritis.

Impetigo more commonly precedes glomerulonephritis than pharyngitis.

Scarlet fever—scarlet rash with sandpaper-like texture, strawberry tongue, circumoral pallor, subsequent desquamation.

Streptococcus agalactiae (group B streptococci)

Bacitracin resistant, β-hemolytic, colonizes vagina; causes pneumonia, meningitis, and sepsis, mainly in babies.

Produces CAMP factor, which enlarges the area of hemolysis formed by S. aureus. (Note: CAMP stands for the authors of the test, not cyclic AMP) Hippurate test °.

Screen pregnant women at 35–37 weeks of gestation. Patients with ° culture receive intrapartum penicillin prophylaxis.

Group B for Babies!
**Enterococci (group D streptococci)**

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). Lancefield group D includes the enterococci and the nonenterococcal group D streptococci. Lancefield grouping is based on differences in the C carbohydrate on the bacterial cell wall. Variable hemolysis.

VRE (vancomycin-resistant enterococci) are an important cause of nosocomial infection.

Enterococci, harder than nonenterococcal group D, can grow in 6.5% NaCl and bile (lab test). *Entero* = intestine, *faecalis* = feces, *strepto* = twisted (chains), *coccus* = berry.

---

**Streptococcus bovis (group D streptococci)**

Colonizes the gut. S. galolyticus (S. bovis biotype 1) can cause bacteremia and subacute endocarditis and is associated with colon cancer.

Bovis in the blood = cancer in the colon.

---

**Corynebacterium diphtheriae**


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

Lab diagnosis based on gram-positive rods with metachromatic (blue and red) granules and Elek test for toxin. Toxoid vaccine prevents diphtheria.

**Spores: bacterial**

Some bacteria can form spores at the end of the stationary phase when nutrients are limited. Spores are highly resistant to heat and chemicals. Have dipicolinic acid in their core. Have no metabolic activity. Must autoclave to potentially kill spores (as is done to surgical equipment) by steaming at 121°C for 15 minutes.

**Species**

- *Bacillus anthracis*
- *Bacillus cereus*
- *Clostridium botulinum*
- *Clostridium difficile*
- *Clostridium perfringens*
- *Clostridium tetani*
- *Coxiella burnetii*

**Disease**

- Anthrax
- Food poisoning
- Botulism
- Antibiotic-associated colitis
- Gas gangrene
- Tetanus
- Q fever

---

**ABCDEF**

- ADP-ribosylation
- β-prophage
- *Corynebacterium*
- *Diphtheriae*
- Elongation Factor 2
- Granules
Clostridia (with exotoxins)

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

| **C. botulinum** | Produces a preformed, heat-labile toxin that inhibits ACh release at the neuromuscular junction, causing botulism. In adults, disease is caused by ingestion of preformed toxin. In babies, ingestion of spores in honey causes disease (floppy baby syndrome). Treat with antitoxin. |
| **Botulinum** is from bad bottles of food and honey (causes a flaccid paralysis). |

| **C. perfringens** | Produces α toxin (lecithinase, a phospholipase) that can cause myonecrosis (gas gangrene A) and hemolysis. |
| **Perfringens** perforates a gangrenous leg. |

| **C. difficile** | Produces 2 toxins. Toxin A, enterotoxin, binds to the brush border of the gut. Toxin B, cytotoxin, causes cytoskeletal disruption via actin depolymerization → pseudomembranous colitis  → diarrhea. Often 2° to antibiotic use, especially clindamycin or ampicillin. Diagnosed by detection one or both toxins in stool by PCR. |
| **Difficile** causes diarrhea. Treatment: metronidazole or oral vancomycin. For recurrent cases, consider repeating prior regimen, fidaxomicin, or fecal microbiota transplant. |

---

**Gas gangrene due to Clostridium perfringens infection.**

**Pseudomembranous colitis.** Yellow pseudomembranes (arrow) on endoscopy.
Anthrax

Caused by *Bacillus anthracis*, a gram-positive, spore-forming rod (A, left) that produces anthrax toxin. The only bacterium with a polypeptide capsule (contains d-glutamate).

Cutaneous anthrax

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

Pulmonary anthrax

Inhalation of spores → flu-like symptoms that rapidly progress to fever, pulmonary hemorrhage, mediastinitis, and shock.

**Bacillus cereus**

Causes food poisoning. Spores survive cooking rice. Keeping rice warm results in germination of spores and enterotoxin formation.

Emetic type usually seen with rice and pasta.

Nausea and vomiting within 1–5 hr. Caused by cereulide, a preformed toxin.

Diarrheal type causes watery, nonbloody diarrhea and GI pain within 8–18 hr.

Reheated rice syndrome.

**Listeria monocytogenes**

Facultative intracellular microbe; acquired by ingestion of unpasteurized dairy products and cold deli meats, via transplacental transmission, or by vaginal transmission during birth. Forms “rocket tails” (via actin polymerization) that allow intracellular movement and cell-to-cell spread across cell membranes, thereby avoiding antibody. Characteristic tumbling motility; is only gram-positive organism to produce endotoxin.

Can cause amnionitis, septicemia, and spontaneous abortion in pregnant women; granulomatosis infantiseptica; neonatal meningitis; meningitis in immunocompromised patients; mild gastroenteritis in healthy individuals.

Treatment: gastroenteritis is usually self-limited; ampicillin in infants, immunocompromised, and the elderly as empirical treatment of meningitis.
**Actinomyces vs. Nocardia**

Both form long, branching filaments resembling fungi.

<table>
<thead>
<tr>
<th>Actinomyces</th>
<th>Nocardia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive anaerobe</td>
<td>Gram-positive aerobe</td>
</tr>
<tr>
<td>Not acid fast</td>
<td>Acid fast (weak)</td>
</tr>
<tr>
<td>Normal oral flora</td>
<td>Found in soil</td>
</tr>
<tr>
<td>Causes oral/facial abscesses that drain through sinus tracts, forms yellow “sulfur granules”</td>
<td>Causes pulmonary infections in immunocompromised and cutaneous infections after trauma in immunocompetent</td>
</tr>
<tr>
<td>Treat with penicillin</td>
<td>Treat with sulfonamides</td>
</tr>
<tr>
<td>Treatment is a SNAP: Sulfonamides—Nocardia; Actinomyces—Penicillin</td>
<td></td>
</tr>
</tbody>
</table>

---

**1° and 2° tuberculosis**

PPD ⊕ if current infection or past exposure. False positives with BCG vaccination (further workup required).

PPD ⊖ if no infection or anergic (steroids, malnutrition, immunocompromise) and in sarcoidosis.

Interferon-γ release assay (IGRA) has fewer false positives from BCG vaccination.

---

**Caseating granuloma.** Central necrosis (pinkish region in upper left) with multinucleated Langhans giant cell (arrow).
**Mycobacteria**

*Mycobacterium tuberculosis* (TB, often resistant to multiple drugs).
*M. avium–intracellulare* (causes disseminated, non-TB disease in AIDS; often resistant to multiple drugs). Prophylaxis with azithromycin when CD4+ count < 50 cells/mm³.
*M. scrofulaceum* (cervical lymphadenitis in children).
*M. marinum* (hand infection in aquarium handlers).

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

**TB symptoms** include fever, night sweats, weight loss, cough (nonproductive or productive), hemoptysis.

Cord factor in virulent strains inhibits macrophage maturation and induces release of TNF-α. Sulfatides (surface glycolipids) inhibit phagolysosomal fusion.

---

**Leprosy (Hansen disease)**

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

Hansen disease has 2 forms:

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

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

Lepromatous can be lethal.

---
Gram-negative lab algorithm

**Lactose-fermenting enteric bacteria**

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

Lactose is key:
Test with MacConKEE’S agar, EMB agar—lactose fermenters grow as purple/black colonies. *E. coli* grows colonies with a green sheen.
### Neisseria

**Gram-negative diplococci. Both ferment glucose and produce IgA proteases.** *N. gonorrhoeae* is often intracellular (within neutrophils) \( A \).

### Gonococci

- No polysaccharide capsule
- No maltose fermentation
- No vaccine due to antigenic variation of pilus proteins
- Sexually or perinatally transmitted
- Causes gonorrhea, septic arthritis, neonatal conjunctivitis, pelvic inflammatory disease (PID), and Fitz-Hugh–Curtis syndrome
- Condoms \( \downarrow \) sexual transmission. Erythromycin ointment prevents neonatal transmission
- Treatment: ceftriaxone + (azithromycin or doxycycline) for possible chlamydial coinfection

### Meningococci

- Polysaccharide capsule
- Maltose fermentation
- Vaccine (type B vaccine not widely available)
- Transmitted via respiratory and oral secretions
- Causes meningococcemia \( B \) and meningitis, Waterhouse-Friderichsen syndrome
- Rifampin, ciprofloxacin, or ceftriaxone prophylaxis in close contacts
- Treatment: ceftriaxone or penicillin G

### Haemophilus influenzae

**Small gram-negative (coccobacillary) rod.** Aerosol transmission. Nontypeable strains are the most common cause of mucosal infections (otitis media, conjunctivitis, bronchitis) as well as invasive infections since the vaccine for capsular type b was introduced. Produces IgA protease. Culture on chocolate agar, which contains factors V (NAD\(^+\)) and X (hematin) for growth; can also be grown with *S. aureus*, which provides factor V through the hemolysis of RBCs. *HaEMOPhilus* causes *Epiglottitis* \( A B \) (“cherry red” in children), Meningitis, Otitis media, and Pneumonia.
- Treat mucosal infections with amoxicillin +\/- clavulanate.
- Treat meningitis with ceftriaxone. Rifampin prophylaxis for close contacts.

**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).**
Legionella pneumophila

Gram-negative rod. Gram stains poorly—use silver stain. Grow on charcoal yeast extract culture with iron and cysteine. Detected by presence of antigen in urine. Labs may show hyponatremia. Aerosol transmission from environmental water source habitat (e.g., air conditioning systems, hot water tanks). No person-to-person transmission. Treatment: macrolide or quinolone.

Legionnaires’ disease—severe pneumonia (often unilateral and lobar), fever, GI and CNS symptoms.

Pontiac fever—mild flu-like syndrome.

Pseudomonas aeruginosa

Aerobic, motile, gram-negative rod. Non-lactose fermenting, oxidase. Produces pyocyanin (blue-green pigment), has a grape-like odor. Produces endotoxin (fever, shock) and exotoxin (inactivates EF-2).

PSEUDOMonas is associated with:
- Pneumonia
- Sepsis
- Otitis Externa (swimmer’s ear)
- UTIs
- Drug use
- Diabetes
- Osteomyelitis (e.g., puncture wounds)

Depending on source and severity, treatment may include:
- Extended-spectrum β-lactams (e.g., piperacillin, ticarcillin, ceferpine)
- Carbapenems (e.g., imipenem, meropenem)
- Monobactams (e.g., aztreonam)
- Fluoroquinolones (e.g., ciprofloxacin)
- Aminoglycosides (e.g., gentamicin, tobramycin)
- For multidrug-resistant strains: colistin, polymyxin B

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

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

Aeruginosa—acrobic.

Think Pseudomonas in burn victims. Mucoid polysaccharide capsule may contribute to chronic pneumonia in cystic fibrosis patients due to biofilm formation. Can cause wound infection in burn victims. Frequently found in water → hot tub folliculitis.
**E. coli**

*E. coli* virulence factors: fimbriae—cystitis and pyelonephritis; K capsule—pneumonia, neonatal meningitis; LPS endotoxin—septic shock.

<table>
<thead>
<tr>
<th>STRAIN</th>
<th>TOXIN AND MECHANISM</th>
<th>PRESENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>EIEC</td>
<td>Microbe invades intestinal mucosa and causes necrosis and inflammation. Clinical manifestations similar to <em>Shigella</em>.</td>
<td>Invasive; dysentery.</td>
</tr>
<tr>
<td>ETEC</td>
<td>Produces heat-labile and heat-stable enterotoxins. No inflammation or invasion.</td>
<td>Travelers’ diarrhea (watery).</td>
</tr>
<tr>
<td>EHEC</td>
<td>Also called STEC (Shiga toxin–producing <em>E. coli</em>). O157:H7 is most common serotype in U.S. Shiga-like toxin causes <strong>hemolytic-uremic syndrome</strong>: triad of anemia, thrombocytopenia, and acute renal failure due to microthrombi forming on damaged endothelium → mechanical hemolysis (with schistocytes on peripheral blood smear), platelet consumption, and renal blood flow.</td>
<td>Dysentery (toxin alone causes necrosis and inflammation). Does not ferment sorbitol (distinguishes EHEC from other <em>E. coli</em>).</td>
</tr>
</tbody>
</table>

**Klebsiella**

An intestinal flora that causes lobar pneumonia in alcoholics and diabetics when aspirated. Very mucoid colonies caused by abundant polysaccharide capsules. Dark red “currant jelly” sputum (blood/mucus). Also cause of nosocomial UTIs.

4 A’s of KlebsiellA:
- Aspiration pneumonia
- Abscess in lungs and liver
- Alcoholics
- di-A-betics

**Campylobacter jejuni**

Major cause of bloody diarrhea, especially in children. Fecal-oral transmission through person-to-person contact or via ingestion of poultry, meat, unpasteurized milk. Contact with infected animals (dogs, cats, pigs) is also a risk factor. Comma- or S-shaped, oxidase ⊕, grows at 42°C (“Campylobacter likes the hot campfire”). Common antecedent to Guillain-Barré syndrome and reactive arthritis.
**Salmonella vs. Shigella** Both *Salmonella* and *Shigella* are gram-negative bacilli that are non-lactose fermenters and oxidase ⊕.

<table>
<thead>
<tr>
<th></th>
<th><em>Salmonella typhi</em></th>
<th><em>Salmonella</em> spp. (except <em>S. typhi</em>)</th>
<th><em>Shigella</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reservoirs</strong></td>
<td>Humans only</td>
<td>Humans and animals</td>
<td>Humans only</td>
</tr>
<tr>
<td><strong>Spread</strong></td>
<td>Can disseminate hemogenously</td>
<td>Can disseminate hemogenously</td>
<td>Cell to cell; no hematogenous spread</td>
</tr>
<tr>
<td><strong>H₂S production</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Flagella</strong></td>
<td>Yes (salmon swim)</td>
<td>Yes (salmon swim)</td>
<td>No</td>
</tr>
<tr>
<td><strong>Virulence Factors</strong></td>
<td>Endotoxin; Vi capsule</td>
<td>Endotoxin</td>
<td>Endotoxin; Shiga toxin (enterotoxin)</td>
</tr>
<tr>
<td><strong>Infectious dose (ID₅₀)</strong></td>
<td>High—large inoculum required because organism inactivated by gastric acids</td>
<td>High</td>
<td>Low—very small inoculum required; resistant to gastric acids</td>
</tr>
<tr>
<td><strong>Effect of Antibiotics on Fecal Excretion</strong></td>
<td>Prolongs duration</td>
<td>Prolongs duration</td>
<td>Shortens duration</td>
</tr>
<tr>
<td><strong>Immune Response</strong></td>
<td>Primarily monocytes</td>
<td>PMNs in disseminated disease</td>
<td>Primarily PMN infiltration</td>
</tr>
<tr>
<td><strong>GI Manifestations</strong></td>
<td>Constipation, followed by diarrhea</td>
<td>Bloody diarrhea</td>
<td>Bloody diarrhea (bacillary dysentery)</td>
</tr>
<tr>
<td><strong>Vaccine</strong></td>
<td>Oral vaccine contains live attenuated <em>S. typhi</em></td>
<td>No vaccine</td>
<td>No vaccine</td>
</tr>
<tr>
<td><strong>Unique Properties</strong></td>
<td>Poultry, eggs, pets, and turtles are common sources</td>
<td>Gastroenteritis is usually caused by non-typhoidal <em>Salmonella</em></td>
<td>Four F’s: Fingers, Flies, Food, Feces</td>
</tr>
<tr>
<td></td>
<td>Invasion is the key to pathogenicity; organisms that produce little toxin can cause disease due to invasion</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Vibrio cholerae** Produces profuse rice-water diarrhea via enterotoxin that permanently activates Gₛ, ‡ cAMP. Comma shaped, oxidase ⊕, grows in alkaline media. Endemic to developing countries. Prompt oral rehydration is necessary.

**Yersinia enterocolitica** Usually transmitted from pet feces (e.g., puppies), contaminated milk, or pork. Causes acute diarrhea or pseudoappendicitis (right lower abdominal pain due to mesenteric adenitis and/or terminal ileitis).
**Helicobacter pylori**

Causes gastritis and peptic ulcers (especially duodenal). Risk factor for peptic ulcer, gastric adenocarcinoma, and MALT lymphoma. Curved gram-negative rod that is catalase, oxidase, and urease (can use urea breath test or fecal antigen test for diagnosis). Creates alkaline environment.

Most common initial treatment is triple therapy: proton pump inhibitor + clarithromycin + amoxicillin (or metronidazole if penicillin allergy).

---

**Spirochetes**

Spiral-shaped bacteria with axial filaments. Includes *Borrelia* (big size), *Leptospira*, and *Treponema*. Only *Borrelia* can be visualized using aniline dyes (Wright or Giemsa stain) in light microscopy due to size. *Treponema* is visualized by dark-field microscopy.

**Leptospira interrogans**

Found in water contaminated with animal urine, causes leptospirosis—flu-like symptoms, myalgias (classically of calves), jaundice, photophobia with conjunctival suffusion (erythema without exudate). Prevalent among surfers and in tropics (i.e., Hawaii).

*Weil disease* (icterohemorrhagic leptospirosis)—severe form with jaundice and azotemia from liver and kidney dysfunction, fever, hemorrhage, and anemia.

**Lyme disease**

Caused by *Borrelia burgdorferi*, which is transmitted by the *Ixodes* deer tick (also vector for *Anaplasma* spp. and protozoa *Babesia*). Natural reservoir is the mouse. Mice are important to tick life cycle.

Common in northeastern United States.

- Initial symptoms—erythema chronicum migrans, flu-like symptoms, +/- facial nerve palsy.
- Later symptoms—monoarthritis (large joints) and migratory polyarthritis, cardiac (AV nodal block), neurologic (meningitis, facial nerve palsy, polyneuropathy).

Treatment: doxycycline, ceftriaxone.

A Key Lyme pie to the FACE:

- Facial nerve palsy (typically bilateral)
- Arthritis
- Cardiac block
- Erythema chronicum migrans
**Syphilis**

Caused by spirochete *Treponema pallidum*.

1° syphilis

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

2° syphilis

Disseminated disease with constitutional symptoms, maculopapular rash (including palms and soles), condylomata lata (smooth, moist, painless, wart-like white lesions on genitals); also confirmable with dark-field microscopy. Serologic testing: VDRL/RPR (nonspecific), confirm diagnosis with specific test (e.g., FTA-ABS). Secondary syphilis = Systemic. Latent syphilis ($\oplus$ serology without symptoms) follows.

3° syphilis

Gummas (chronic granulomas), aortitis (vasa vasaorum destruction), neurosyphilis (tabes dorsalis, "general paresis"), Argyll Robertson pupil (constricts with accommodation but is not reactive to light; also called "prostitute's pupil" since it accommodates but does not react). Signs: broad-based ataxia, $\oplus$ Romberg, Charcot joint, stroke without hypertension. For neurosyphillis: test spinal fluid with VDRL and PCR.

**Congenital syphilis**

Presents with facial abnormalities such as rhyhades (linear scars at angle of mouth, black arrow in G), snuffles (nasal discharge, red arrow in G), saddle nose, notched (Hutchinson) teeth, mulberry molars, and short maxilla; saber shins; CN VIII deafness. To prevent, treat mother early in pregnancy, as placental transmission typically occurs after first trimester.

---

**VDRL false positives**

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

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

**Jarisch-Herxheimer reaction**

Flu-like syndrome (fever, chills, headache, myalga) after antibiotics are started; due to killed bacteria (usually spirochetes) releasing endotoxins.
**Zoonotic bacteria**

Zoonosis: infectious disease transmitted between animals and humans.

<table>
<thead>
<tr>
<th>SPECIES</th>
<th>DISEASE</th>
<th>TRANSMISSION AND SOURCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Anaplasma spp.</em></td>
<td>Anaplasmosis</td>
<td>Ixodes ticks (live on deer and mice)</td>
</tr>
<tr>
<td><em>Bartonella spp.</em></td>
<td>Cat scratch disease, bacillary angiomatosis</td>
<td>Cat scratch</td>
</tr>
<tr>
<td><em>Borrelia burgdorferi</em></td>
<td>Lyme disease</td>
<td>Ixodes ticks (live on deer and mice)</td>
</tr>
<tr>
<td><em>Borrelia recurrentis</em></td>
<td>Relapsing fever</td>
<td>Louse (recurrent due to variable surface antigens)</td>
</tr>
<tr>
<td><em>Brucella spp.</em></td>
<td>Brucellosis/undulant fever</td>
<td>Unpasteurized dairy</td>
</tr>
<tr>
<td><em>Campylobacter</em></td>
<td>Bloody diarrhea</td>
<td>Puppies, livestock (fecal-oral, ingestion of undercooked meat)</td>
</tr>
<tr>
<td><em>Chlamyphila psittaci</em></td>
<td>Psittacosis</td>
<td>Parrots, other birds</td>
</tr>
<tr>
<td><em>Coxiella burnetii</em></td>
<td>Q fever</td>
<td>Aerosols of cattle/sheep amniotic fluid</td>
</tr>
<tr>
<td><em>Ehrlichia chaffeensis</em></td>
<td>Ehrlichiosis</td>
<td><em>Ambylomma</em> (Lone Star tick)</td>
</tr>
<tr>
<td><em>Francisella tularensis</em></td>
<td>Tularemia</td>
<td>Ticks, rabbits, deer fly</td>
</tr>
<tr>
<td><em>Leptospira spp.</em></td>
<td>Leptospirosis</td>
<td>Animal urine</td>
</tr>
<tr>
<td><em>Mycobacterium leprae</em></td>
<td>Leprosy</td>
<td>Humans with lepromatous leprosy; armadillo (rare)</td>
</tr>
<tr>
<td><em>Pasteurella multocida</em></td>
<td>Cellulitis, osteomyelitis</td>
<td>Animal bite, cats, dogs</td>
</tr>
<tr>
<td><em>Rickettsia prowazekii</em></td>
<td>Epidemic typhus</td>
<td>Louse</td>
</tr>
<tr>
<td><em>Rickettsia rickettsii</em></td>
<td>Rocky Mountain spotted fever</td>
<td><em>Dermacentor</em> (dog tick)</td>
</tr>
<tr>
<td><em>Rickettsia typhi</em></td>
<td>Endemic typhus</td>
<td>Fleas</td>
</tr>
<tr>
<td><em>Salmonella</em></td>
<td>Diarrhea (which may be bloody), vomiting, fever, abdominal cramps</td>
<td>Reptiles and poultry</td>
</tr>
<tr>
<td><em>Yersinia pestis</em></td>
<td>Plague</td>
<td>Fleas (rats and prairie dogs are reservoirs)</td>
</tr>
</tbody>
</table>

**Gardnerella vaginalis**

A pleomorphic, gram-variable rod involved in bacterial vaginosis. Presents as a gray vaginal discharge with a *fishy* smell; nonpainful (vs. vaginitis). Associated with sexual activity, but not sexually transmitted. Bacterial vaginosis is also characterized by overgrowth of certain anaerobic bacteria in vagina. **Clue** cells, or vaginal epithelial cells covered with *Gardnerella* bacteria (“stippled” appearance along outer margins), are visible under the microscope (arrow in ![A](image)). Treatment: metronidazole or clindamycin.

I don’t have a **clue** why I smell **fish** in the **vagina garden**! Amine whiff test—mixing discharge with 10% KOH enhances fishy odor.
Rickettsial diseases and vector-borne illness

<table>
<thead>
<tr>
<th>Disease</th>
<th>Description</th>
<th>Rash Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rocky Mountain spotted fever</td>
<td><em>Rickettsia rickettsii</em>, vector is tick. Despite its name, disease occurs primarily in the South Atlantic states, especially North Carolina. Rash typically starts at wrists and ankles and then spreads to trunk, palms, and soles.</td>
<td>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).</td>
</tr>
</tbody>
</table>

RASH COMMON

**Ehrlichiosis**  *Ehrlichia*, vector is tick. Monocytes with morulae (berry-like inclusions) in cytoplasm.

**Anaplasmosis**  *Anaplasma*, vector is tick. Granulocytes with morulae in cytoplasm.

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

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

Chlamydiae cannot make their own ATP. They are obligate intracellular organisms that cause mucosal infections. 2 forms:
- Elementary body (small, dense) is “Infectious” and Enter cell via Endocytosis; transforms into reticulate body.
- Reticulate body Replicates in cell by fission; Reorganizes into elementary bodies.

*Chlamydia trachomatis* causes reactive arthritis (Reiter syndrome), follicular conjunctivitis, nongonococcal urethritis, and PID.
*C. pneumoniae* and *C. psittaci* cause atypical pneumonia; transmitted by aerosol.
Treatment: azithromycin (favored because one-time treatment) or doxycycline.

Chlamydia trachomatis serotypes

<table>
<thead>
<tr>
<th>Types A, B, and C</th>
<th>Chronic infection, cause blindness due to follicular conjunctivitis in Africa.</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>ABC</em> = Africa, Blindness, Chronic infection.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Types D–K</th>
<th>Urethritis/PID, ectopic pregnancy, neonatal pneumonia (staccato cough) with cosinophilia, neonatal conjunctivitis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>D–K = everything else.</td>
<td>Neonatal disease can be acquired during passage through infected birth canal.</td>
</tr>
</tbody>
</table>

| Types L1, L2, and L3 | Lymphogranuloma venereum—small, painless ulcers on genitals → swollen, painful inguinal lymph nodes that ulcerate (buboes). Treat with doxycycline. |

Mycoplasma pneumoniae

Classic cause of atypical “walking” pneumonia (insidious onset, headache, nonproductive cough, patchy or diffuse interstitial infiltrate). X-ray looks worse than patient. High titer of cold agglutinins (IgM), which can agglutinate or lyse RBCs. Grown on Eaton agar.
Treatment: macrolides, doxycycline, or fluoroquinolone (penicillin ineffective since *Mycoplasma* have no cell wall).

No cell wall. Not seen on Gram stain.
Pleomorphic
Bacterial membrane contains sterols for stability.
Mycoplasmal pneumonia is more common in patients < 30 years old.
Frequent outbreaks in military recruits and prisons.
**Microbiology—Mycology**

**Systemic mycoses**

All of the following can cause pneumonia and can disseminate. All are caused by dimorphic fungi: cold (20°C) = mold; heat (37°C) = yeast. The only exception is coccidioidomycosis, which is a spherule (not yeast) in tissue. Treatment: fluconazole or itraconazole for local infection; amphotericin B for systemic infection. Systemic mycoses can mimic TB (granuloma formation), except, unlike TB, have no person-person transmission.

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

Tinea (dermatophytes)
Tinea is the clinical name given to dermatophyte (cutaneous fungal) infections. Dermatophytes include Microsporum, Trichophyton, and Epidermophyton. Branching septate hyphae visible on KOH preparation with blue fungal stain A.

Tinea capitis
Occurs on head, scalp. Associated with lymphadenopathy, alopecia, scaling B.

Tinea corporis
Occurs on body. Characterized by erythematous scaling rings (“ringworm”) and central clearing C. Can be acquired from contact with an infected cat or dog.

Tinea cruris
Occurs in inguinal area D. Often does not show the central clearing seen in tinea corporis.

Tinea pedis
Three varieties:
- Interdigital E; most common
- Moccasin distribution F
- Vesicular type

Tinea unguium
Onychomycosis; occurs on nails.

Tinea versicolor
Caused by Malassezia spp. (Pityrosporum spp.), a yeast-like fungus (not a dermatophyte despite being called tinea). Degradation of lipids produces acids that damage melanocytes and cause hypopigmented G and/or pink patches. Can occur any time of year but common in summer (hot, humid weather). “Spaghetti and meatballs” appearance on microscopy H. Treatment: topical and/or oral antifungal medications, selenium sulfide.
Opportunistic fungal infections

Candida albicans

*alba* = white.
Systemic or superficial fungal infection.
Oral and esophageal thrush in immunocompromised (neonates, steroids, diabetes, AIDS), vulvovaginitis (diabetes, use of antibiotics), diaper rash, endocarditis in IV drug users, disseminated candidiasis (to any organ), chronic mucocutaneous candidiasis.
Treatment: topical azole for vaginal; nystatin, fluconazole, or caspofungin for oral/esophageal; fluconazole, caspofungin, or amphotericin B for systemic.

Aspergillus fumigatus

Invasive aspergillosis, especially in immunocompromised and those with chronic granulomatous disease.
Allergic bronchopulmonary aspergillosis (ABPA): associated with asthma and cystic fibrosis; may cause bronchiectasis and eosinophilia.
Aspergillomas in lung cavities, especially after TB infection.
Some species of *Aspergillus* produce aflatoxins, which are associated with hepatocellular carcinoma.
Think “A” for Acute Angles in *Aspergillus*. Not dimorphic.

Cryptococcus neoformans

Cryptococcal meningitis, cryptococcosis.
Heavily encapsulated yeast. Not dimorphic.
Found in soil, pigeon droppings. Acquired through inhalation with hematogenous dissemination to meninges. Culture on Sabouraud agar. Stains with India ink and mucicarmine. Latex agglutination test detects polysaccharide capsular antigen and is more specific. “Soap bubble” lesions in brain.

Mucor *E* and Rhizopus spp.

Mucormycosis. Disease mostly in ketoacidotic diabetic and/or neutropenic patients (e.g., leukemia). Fungi proliferate in blood vessel walls, penetrate cribriform plate, and enter brain. Rhinocerebral, frontal lobe abscess; cavernous sinus thrombosis. Headache, facial pain, black necrotic eschar on face; may have cranial nerve involvement.
Treatment: surgical debridement, amphotericin B.
**Pneumocystis jirovecii**

Causes *Pneumocystis* pneumonia (PCP), a diffuse interstitial pneumonia. Yeast-like fungus (originally classified as protozoan). Inhaled. Most infections are asymptomatic. Immunosuppression (e.g., AIDS) predisposes to disease. Diffuse, bilateral ground-glass opacities on CXR/CT. Diagnosed by lung biopsy or lavage. Disc-shaped yeast forms on methenamine silver stain of lung tissue. Treatment/prophylaxis: TMP-SMX, pentamidine, dapsone (prophylaxis only), atovaquone (prophylaxis only). Start prophylaxis when CD4+ count drops to < 200 cells/mm³ in HIV patients.

![Pneumocystis jirovecii pneumonia.](image1)

![Pneumocystis jirovecii on methenamine silver stain.](image2)

---

**Sporothrix schenckii**

Sporotrichosis. Dimorphic, cigar-shaped budding yeast that 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). Disseminated disease possible in immunocompromised host. Treatment: itraconazole or potassium iodide. “Plant a rose in the pot.”

![Sporotrichosis.](image3)

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## Protozoa—GI infections

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

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

<table>
<thead>
<tr>
<th>ORGANISM</th>
<th>DISEASE</th>
<th>TRANSMISSION</th>
<th>DIAGNOSIS</th>
<th>TREATMENT</th>
</tr>
</thead>
</table>
| *Plasmodium*  
  *P. vivax/ovale*  
  *P. falciparum*  
  *P. malariae*        | **Malaria**—fever, headache, anemia, splenomegaly  
                      *P. vivax/ovale*—48-hr cycle (tertian; includes fever on first day and third day, thus fevers are actually 48 hr apart); dormant form (hypnozoite) in liver  
                      *P. falciparum*—severe; irregular fever patterns; parasitized RBCs occlude capillaries in brain (cerebral malaria), kidneys, lungs  
                      *P. malariae*—72-hr cycle (quartan)  
                      Anopheles mosquito             | Blood smear: trophozoite ring form within RBC; schizont containing merozoites red granules (Schüffner stippling) throughout RBC cytoplasm seen with *P. vivax/ovale*  | Chloroquine (for sensitive species), which blocks *Plasmodium* heme polymerase; if resistant, use mefloquine or atovaquone/proguanil  
                      If life-threatening, use intravenous quinidine or artesunate (test for G6PD deficiency)  
                      For *P. vivax/ovale*, add primaquine for hypnozoite (test for G6PD deficiency)  |
| **Babesia**  
  *Babesia*  
                      *Babesiosis*—fever and hemolytic anemia; predominantly in northeastern United States; asplenia ↑ risk of severe disease  
                      *Ixodes* tick (same as *Borrelia burgdorferi* of Lyme disease; may often coinfect humans) | Blood smear: ring form  
                      *Ixodes* tick (same as *Borrelia burgdorferi* of Lyme disease; may often coinfect humans)  
                      “Maltese cross”  
                      PCR  | Atovaquone + azithromycin  |

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*11/6/14   1:10 PM*
Protozoa—Others

<table>
<thead>
<tr>
<th>ORGANISM</th>
<th>DISEASE</th>
<th>TRANSMISSION</th>
<th>DIAGNOSIS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trypanosoma</td>
<td>Chagas disease—dilated</td>
<td>Reduviid bug (&quot;kissing bug&quot;) feces, deposited in a painless bite (much like a kiss)</td>
<td>Blood smear</td>
<td>Benznidazole or nifurtimox</td>
</tr>
<tr>
<td>cruzi</td>
<td>cardiomopathy with apical atrophy, megacolon, megaesophagus; predominantly in South America</td>
<td></td>
<td>Blood smear</td>
<td>Benznidazole or nifurtimox</td>
</tr>
<tr>
<td></td>
<td>Unilateral periorbital swelling (Romaña sign) characteristic of acute stage</td>
<td></td>
<td>Blood smear</td>
<td>Benznidazole or nifurtimox</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Blood smear</td>
<td>Benznidazole or nifurtimox</td>
</tr>
<tr>
<td>Leishmania</td>
<td>Visceral leishmaniasis</td>
<td>Sandfly</td>
<td>Macrophages containing amastigotes</td>
<td>Amphotericin B, sodium stibogluconate</td>
</tr>
<tr>
<td>donovani</td>
<td>(kala-azar)—spiking fevers, hepatosplenomegaly, pancytopenia</td>
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</tr>
<tr>
<td>Trichomonas</td>
<td>Vaginitis—foul-smelling, greenish discharge; itching and burning; do not confuse with Gardnerella vaginalis, a gram-variable bacterium associated with bacterial vaginosis</td>
<td>Sexual (cannot exist outside human because it cannot form cysts)</td>
<td>Trophozoites (motile) on wet mount; &quot;strawberry cervix&quot;</td>
<td>Metronidazole for patient and partner (prophylaxis)</td>
</tr>
<tr>
<td>vaginalis</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
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</tr>
</tbody>
</table>
## Nematodes (roundworms)

<table>
<thead>
<tr>
<th>ORGANISM</th>
<th>TRANSMISSION</th>
<th>DISEASE</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intestinal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Enterobius vermicularis</em></td>
<td>Fecal-oral</td>
<td>Intestinal infection causing anal pruritus (diagnosed by seeing egg via the tape test)</td>
<td><strong>Bendazoles</strong> (because worms are <strong>bendy</strong>*)</td>
</tr>
<tr>
<td>(pinworm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Ascaris lumbricoides</em></td>
<td>Fecal-oral; eggs visible in feces under microscope</td>
<td>Intestinal infection with possible obstruction at ileocecal valve</td>
<td><strong>Bendazoles</strong></td>
</tr>
<tr>
<td>(giant roundworm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Strongyloides stercoralis</em></td>
<td>Larvae in soil penetrate the skin</td>
<td>Intestinal infection causing vomiting, diarrhea, epigastric pain (may feel like peptic ulcer)</td>
<td><strong>Ivermectin or bendazoles</strong></td>
</tr>
<tr>
<td><em>Ancylostoma duodenale,</em> <em>Necator americanus</em> (hookworms)</td>
<td>Larvae penetrate skin</td>
<td>Intestinal infection causing anemia by sucking blood from intestinal walls</td>
<td><strong>Bendazoles or pyrantel pamoate</strong></td>
</tr>
<tr>
<td><em>Trichinella spiralis</em></td>
<td>Fecal-oral; undercooked meat (esp. pork)</td>
<td>Intestinal infection; larvae enter bloodstream and encyst in striated muscle cells → inflammation of muscle. <strong>Trichinosis</strong>—fever, vomiting, nausea, periorbital edema, myalgia</td>
<td><strong>Bendazoles</strong></td>
</tr>
<tr>
<td><strong>Tissue</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Onchocerca volvulus</em></td>
<td>Female blackfly bite</td>
<td>Hyperpigmented skin and river blindness (black flies, black skin nodules, “black sight”); allergic reaction to microfilaria possible</td>
<td><strong>Ivermectin</strong> (<strong>ivermectin for river blindness</strong>)</td>
</tr>
<tr>
<td><em>Loa loa</em></td>
<td>Deer fly, horse fly, mango fly</td>
<td>Swelling in skin, worm in conjunctiva</td>
<td><strong>Diethylcarbamazine</strong></td>
</tr>
<tr>
<td><em>Wuchereria bancrofti</em></td>
<td>Female mosquito</td>
<td><strong>Elephantiasis</strong>—worms block lymphatic vessels, takes 9 mo–1 yr after bite to become symptomatic</td>
<td><strong>Diethylcarbamazine</strong></td>
</tr>
<tr>
<td><em>Toxocara canis</em></td>
<td>Fecal-oral</td>
<td>Visceral larva migrans</td>
<td><strong>Bendazoles</strong></td>
</tr>
</tbody>
</table>
### Nematode routes of infection

Ingested—*Enterobius, Ascaris, Toxocara, Trichinella*
Cutaneous—*Strongyloides, Ancylostoma, Necator*
Bites—*Loa loa, Onchocerca volvulus, Wuchereria bancrofti*

You’ll get sick if you **EATT** these!

These get into your feet from the **SANd**.

Lay **LOW** to avoid getting bitten.

#### Cestodes (tapeworms)

<table>
<thead>
<tr>
<th>ORGANISM</th>
<th>TRANSMISSION</th>
<th>DISEASE</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Taenia solium</em></td>
<td>Ingestion of larvae encysted in undercooked pork</td>
<td>Intestinal infection</td>
<td>Praziquantel</td>
</tr>
<tr>
<td></td>
<td>Ingestion of eggs</td>
<td>Cysticercosis, neurocysticercosis</td>
<td>Praziquantel; albendazole for neurocysticercosis</td>
</tr>
<tr>
<td><em>Diphyllobothrium latum</em></td>
<td>Ingestion of larvae from raw freshwater fish</td>
<td>Vitamin B₁₂ deficiency</td>
<td>Praziquantel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(tapeworm competes for B₁₂ in intestine)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>→ megaloblastic anemia</td>
<td></td>
</tr>
<tr>
<td><em>Echinococcus granulosus</em></td>
<td>Ingestion of eggs from dog feces</td>
<td>Hydatid cysts</td>
<td>Albendazole</td>
</tr>
<tr>
<td></td>
<td>Sheep are an intermediate host</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>D</strong> in liver <strong>E</strong>, causing anaphylaxis if</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>antigens released (hydatid cyst injected with</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ethanol or hypertonic saline to kill daughter</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>cysts before removal)</td>
<td></td>
</tr>
</tbody>
</table>

![Image of tapeworm structures]
### Trematodes (flukes)

<table>
<thead>
<tr>
<th>ORGANISM</th>
<th>TRANSMISSION</th>
<th>DISEASE</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schistosoma</td>
<td>Snails are host; cercariae</td>
<td>Liver and spleen enlargement (S. mansoni, egg with lateral spine A), fibrosis, and inflammation</td>
<td>Praziquantel</td>
</tr>
<tr>
<td></td>
<td>penetrate skin of humans</td>
<td>Chronic infection with S. haematobium (egg with terminal spine B) can lead to squamous cell carcinoma of the bladder (painless hematuria) and pulmonary hypertension</td>
<td></td>
</tr>
<tr>
<td>Clonorchis</td>
<td>Undercooked fish</td>
<td>Biliary tract inflammation → pigmented gallstones Associated with cholangiocarcinoma</td>
<td>Praziquantel</td>
</tr>
<tr>
<td>sinensis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Parasite hints

<table>
<thead>
<tr>
<th>ASSOCIATIONS</th>
<th>ORGANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary tract disease, cholangiocarcinoma</td>
<td>Clonorchis sinensis</td>
</tr>
<tr>
<td>Brain cysts, seizures</td>
<td>Taenia solium (cysticercosis)</td>
</tr>
<tr>
<td>Hematuria, squamous cell bladder cancer</td>
<td>Schistosoma haematobium</td>
</tr>
<tr>
<td>Liver (hydatid) cysts</td>
<td>Echinococcus granulosus</td>
</tr>
<tr>
<td>Microcytic anemia</td>
<td>Ancylostoma, Necator</td>
</tr>
<tr>
<td>Myalgias, periorbital edema</td>
<td>Trichinella spiralis</td>
</tr>
<tr>
<td>Perianal pruritus</td>
<td>Enterobius</td>
</tr>
<tr>
<td>Portal hypertension</td>
<td>Schistosoma mansoni, Schistosoma japonicum</td>
</tr>
<tr>
<td>Vitamin B₁₂ deficiency</td>
<td>Diphyllobothrium latum</td>
</tr>
</tbody>
</table>
**Viral structure—general features**

- **Naked virus with icosahedral capsid**
  - Capsid
  - Nucleic acid

- **Enveloped virus with icosahedral capsid**
  - Surface protein
  - Lipid bilayer
  - Capsid
  - Nucleic acid

- **Enveloped virus with helical capsid**
  - Surface protein
  - Lipid bilayer
  - Helical capsid with nucleic acid inside

---

**Viral genetics**

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recombination</strong></td>
<td>Exchange of genes between 2 chromosomes by crossing over within regions of significant base sequence homology.</td>
</tr>
<tr>
<td><strong>Reassortment</strong></td>
<td>When viruses with segmented genomes (e.g., 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.</td>
</tr>
<tr>
<td><strong>Complementation</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Phenotypic mixing</strong></td>
<td>Occurs with simultaneous infection of a cell with 2 viruses. Genome of virus A can be partially or completely coated (forming pseudovirion) with the surface proteins of virus B. Type B protein coat determines the tropism (infectivity) of the hybrid virus. However, the progeny from this infection have a type A coat that is encoded by its type A genetic material.</td>
</tr>
</tbody>
</table>

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**Viral vaccines**

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Live attenuated vaccines</strong></td>
<td>Induce humoral and cell-mediated immunity but have reverted to virulence on rare occasions. Killed/inactivated vaccines induce only humoral immunity but are stable. <strong>Live</strong> attenuated: smallpox, yellow fever, rotavirus, chickenpox (VZV), Sabin polio virus, MMR, Influenza (intranasal). No booster needed for live attenuated vaccines. Dangerous to give live vaccines to immunocompromised patients or their close contacts. “Live! One night only! See small yellow rotating chickens get vaccinated with Sabin and MMR! It’s incredible!” MMR = measles, mumps, rubella; live attenuated vaccine that can be given to HIV-positive patients who do not show signs of immunodeficiency.</td>
</tr>
<tr>
<td><strong>Killed</strong></td>
<td>Rabies, Influenza (injected), Salk Polio, and HAV vaccines. SalK = Killed. RIP Always.</td>
</tr>
<tr>
<td><strong>Subunit</strong></td>
<td>HBV (antigen = HBsAg), HPV (types 6, 11, 16, and 18).</td>
</tr>
</tbody>
</table>
DNA viral genomes

All DNA viruses except the Parvoviridae are dsDNA.
All are linear except papilloma-, polyoma-, and hepadnaviruses (circular).

RNA viral genomes

All RNA viruses except Reoviridae are ssRNA.
Positive-stranded RNA viruses: I went to a retro (retrovirus) toga (togavirus) party,
where I drank flavored (flavivirus) Corona (coronavirus) and ate hippy (hepevirus)
California (calcivirus) pickles (picornavirus).

Naked viral genome infectivity

Purified nucleic acids of most dsDNA (except poxviruses and HBV) and ⊕ strand ssRNA
(≈ mRNA) viruses are infectious. Naked nucleic acids of ⊗ strand ssRNA and dsRNA viruses are
not infectious. They require polymerases contained in the complete virion.

Viral replication

DNA viruses

All replicate in the nucleus (except poxvirus).

RNA viruses

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

Viral envelopes

Naked (nonenveloped) viruses include Papillomavirus, Adenovirus, Parvovirus,
Polyomavirus, Calicivirus, Picornavirus, Reovirus, and Hepevirus.
Generally, enveloped viruses acquire their envelopes from plasma membrane when
they exit from cell. Exceptions include herpesviruses, which acquire envelopes from
nuclear membrane.

DNA virus characteristics

Some general rules—all DNA viruses:

<table>
<thead>
<tr>
<th>General Rule</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are HHAPPPy viruses</td>
<td>Hepadna, Herpes, Adeno, Pox, Parvo, Papilloma, Polyoma.</td>
</tr>
<tr>
<td>Are double stranded</td>
<td>Except parvo (single stranded).</td>
</tr>
<tr>
<td>Are linear</td>
<td>Except papilloma and polyoma (circular, supercoiled) and hepadna (circular, incomplete).</td>
</tr>
<tr>
<td>Are icosahedral</td>
<td>Except pox (complex).</td>
</tr>
<tr>
<td>Replicate in the nucleus</td>
<td>Except pox (carries own DNA-dependent RNA polymerase).</td>
</tr>
</tbody>
</table>
### DNA viruses

<table>
<thead>
<tr>
<th>VIRAL FAMILY</th>
<th>ENVELOPE</th>
<th>DNA STRUCTURE</th>
<th>MEDICAL IMPORTANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Herpesviruses</strong></td>
<td>Yes</td>
<td>DS and linear</td>
<td>HSV-1—oral (and some genital) lesions, spontaneous temporal lobe encephalitis, keratoconjunctivitis HSV-2—genital (and some oral) lesions VZV (HHV-3)—chickenpox, zoster (shingles) EBV (HHV-4)—mononucleosis, Burkitt lymphoma, Hodgkin lymphoma, nasopharyngeal carcinoma CMV (HHV-5)—infection in immunosuppressed patients (AIDS retinitis [&quot;sightomegalovirus&quot;]), especially transplant recipients; congenital defects HHV-6—roseola (exanthem subitum) HHV-7—less common cause of roseola HHV-8—Kaposi sarcoma</td>
</tr>
<tr>
<td><strong>Hepadnavirus</strong></td>
<td>Yes</td>
<td>Partially DS and circular</td>
<td>HBV: * Acute or chronic hepatitis * Not a retrovirus but has reverse transcriptase</td>
</tr>
<tr>
<td><strong>Adenovirus</strong></td>
<td>No</td>
<td>DS and linear</td>
<td>Febrile pharyngitis — sore throat Acute hemorrhagic cystitis Pneumonia Conjunctivitis — &quot;pink eye&quot;</td>
</tr>
<tr>
<td><strong>Parvovirus</strong></td>
<td>No</td>
<td>SS and linear (smallest DNA virus)</td>
<td>B19 virus—aplastic crises in sickle cell disease, &quot;slapped cheeks&quot; rash in children (erythema infectiosum, or fifth disease) RBC destruction in fetus leads to hydrops fetalis and death, in adults leads to pure RBC aplasia and rheumatoid arthritis—like symptoms</td>
</tr>
<tr>
<td><strong>Papillomavirus</strong></td>
<td>No</td>
<td>DS and circular</td>
<td>HPV—warts (serotypes 1, 2, 6, 11), CIN, cervical cancer (most commonly 16, 18)</td>
</tr>
<tr>
<td><strong>Polyomavirus</strong></td>
<td>No</td>
<td>DS and circular</td>
<td>JC virus—progressive multifocal leukoencephalopathy (PML) in HIV BK virus—transplant patients, commonly targets kidney JC: Junky Cerebrum, BK: Bad Kidney</td>
</tr>
<tr>
<td><strong>Poxvirus</strong></td>
<td>Yes</td>
<td>DS and linear (largest DNA virus)</td>
<td>Smallpox eradicated by use of live attenuated vaccine. Eradication was achieved by world-wide use of the live attenuated vaccine Cowpox (&quot;milkmaid blisters&quot;) Molluscum contagiosum — flesh-colored papule with central umbilication</td>
</tr>
</tbody>
</table>
### Herpesviruses

<table>
<thead>
<tr>
<th>Virus</th>
<th>Description</th>
<th>Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV-1</td>
<td>Gingivostomatitis, keratoconjunctivitis, herpes labialis, temporal lobe encephalitis (most common cause of sporadic encephalitis, can present with altered mental status, seizures, and/or aphasia). Transmitted by respiratory secretions, saliva.</td>
<td></td>
</tr>
<tr>
<td>HSV-2</td>
<td>Herpes genitalis, neonatal herpes. Latent in sacral ganglia. Transmitted by sexual contact, perinatally.</td>
<td></td>
</tr>
<tr>
<td>VZV</td>
<td>Varicella-zoster (chickenpox, shingles), encephalitis, pneumonia. Latent in dorsal root or trigeminal ganglia. Most common complication of shingles is post-herpetic neuralgia. Transmitted by respiratory secretions.</td>
<td></td>
</tr>
<tr>
<td>EBV</td>
<td>Mononucleosis. Characterized by fever, hepatosplenomegaly, pharyngitis, and lymphadenopathy (especially posterior cervical nodes). Transmitted by respiratory secretions and saliva; also called “kissing disease” since commonly seen in teens, young adults. Infects B cells through CD21. Atypical lymphocytes seen on peripheral blood smear are not infected B cells but rather reactive cytotoxic T cells. Detect by Monospot test—heterophile antibodies detected by agglutination of sheep or horse RBCs. Associated with lymphomas (e.g., endemic Burkitt lymphoma), nasopharyngeal carcinoma.</td>
<td></td>
</tr>
<tr>
<td>CMV</td>
<td>Congenital infection, mononucleosis (Monospot), pneumonia, retinitis. Infected cells have characteristic “owl eye” inclusions. Latent in mononuclear cells. Transmitted congenitally and by transfusion, sexual contact, saliva, urine, transplant.</td>
<td></td>
</tr>
<tr>
<td>HHV-6/HHV-7</td>
<td>Roseola: high fevers for several days that can cause seizures, followed by a diffuse macular rash. Transmitted by saliva.</td>
<td></td>
</tr>
<tr>
<td>HHV-8</td>
<td>Kaposi sarcoma, a neoplasm of endothelial cells. Seen in HIV/AIDS and transplant patients. Dark/violaceous plaques or nodules representing vascular proliferations. Can also affect GI tract and lungs. Transmitted by sexual contact.</td>
<td></td>
</tr>
</tbody>
</table>
HSV identification

Viral culture for skin/genitalia.
CSF PCR for herpes encephalitis.
Tzanck test—a smear of an opened skin vesicle
to detect multinucleated giant cells commonly
seen in HSV-1, HSV-2, and VZV infection.
Intranuclear inclusions also seen with HSV-1,
HSV-2, VZV.

Tzanck heavens I do not have herpes.

Positive Tzanck smear in genital herpes (HSV-2). Note
multinucleated giant cells (arrows).
### RNA viruses

<table>
<thead>
<tr>
<th>Viral Family</th>
<th>Envelope</th>
<th>RNA Structure</th>
<th>Capsid Symmetry</th>
<th>Medical Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reoviruses</strong></td>
<td>No</td>
<td>DS linear 10–12 segments</td>
<td>Icosahedral (double)</td>
<td>Coltivirus—a—Colorado tick fever Rotavirus—#1 cause of fatal diarrhea in children</td>
</tr>
<tr>
<td><strong>Picornaviruses</strong></td>
<td>No</td>
<td>SS ⊕ linear</td>
<td>Icosahedral</td>
<td>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</td>
</tr>
<tr>
<td><strong>Hepevirus</strong></td>
<td>No</td>
<td>SS ⊕ linear</td>
<td>Icosahedral</td>
<td>HEV</td>
</tr>
<tr>
<td><strong>Caliciviruses</strong></td>
<td>No</td>
<td>SS ⊕ linear</td>
<td>Icosahedral</td>
<td>Norovirus—viral gastroenteritis</td>
</tr>
<tr>
<td><strong>Flaviviruses</strong></td>
<td>Yes</td>
<td>SS ⊕ linear</td>
<td>Icosahedral</td>
<td>HCV Yellow fever&lt;sup&gt;a&lt;/sup&gt; Dengue&lt;sup&gt;a&lt;/sup&gt; St. Louis encephalitis&lt;sup&gt;a&lt;/sup&gt; West Nile virus&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Togaviruses</strong></td>
<td>Yes</td>
<td>SS ⊕ linear</td>
<td>Icosahedral</td>
<td>Rubella Eastern equine encephalitis&lt;sup&gt;a&lt;/sup&gt; Western equine encephalitis&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Retroviruses</strong></td>
<td>Yes</td>
<td>SS ⊕ linear 2 copies</td>
<td>Icosahedral (HTLV), complex and conical (HIV)</td>
<td>Have reverse transcriptase HTLV—T-cell leukemia HIV—AIDS</td>
</tr>
<tr>
<td><strong>Coronaviruses</strong></td>
<td>Yes</td>
<td>SS ⊕ linear</td>
<td>Helical</td>
<td>Coronavirus—“common cold” and SARS</td>
</tr>
<tr>
<td><strong>Orthomyxoviruses</strong></td>
<td>Yes</td>
<td>SS ⊕ linear 8 segments</td>
<td>Helical</td>
<td>Influenza virus</td>
</tr>
<tr>
<td><strong>Paramyxoviruses</strong></td>
<td>Yes</td>
<td>SS ⊕ linear Nonsegmented</td>
<td>Helical</td>
<td>Parainfluenza—influenza RSV—bronchiolitis in babies; Rx—ribavirin Measles, Mumps</td>
</tr>
<tr>
<td><strong>Rhabdoviruses</strong></td>
<td>Yes</td>
<td>SS ⊕ linear</td>
<td>Helical</td>
<td>Rabies</td>
</tr>
<tr>
<td><strong>Filoviruses</strong></td>
<td>Yes</td>
<td>SS ⊕ linear</td>
<td>Helical</td>
<td>Ebola/Marburg hemorrhagic fever—often fatal!</td>
</tr>
<tr>
<td><strong>Arenaviruses</strong></td>
<td>Yes</td>
<td>SS ⊕ circular 2 segments</td>
<td>Helical</td>
<td>LCMV—lymphocytic choriomeningitis virus Lassa fever encephalitis—spread by rodents</td>
</tr>
<tr>
<td><strong>Bunyaviruses</strong></td>
<td>Yes</td>
<td>SS ⊕ circular 3 segments</td>
<td>Helical</td>
<td>California encephalitis&lt;sup&gt;a&lt;/sup&gt; Sandfly/Rift Valley fevers&lt;sup&gt;a&lt;/sup&gt; Crimean-Congo hemorrhagic fever&lt;sup&gt;a&lt;/sup&gt; Hantavirus—hemorrhagic fever, pneumonia</td>
</tr>
<tr>
<td><strong>Delta virus</strong></td>
<td>Yes</td>
<td>SS ⊕ circular Uncertain</td>
<td></td>
<td>HDV is a “defective” virus that requires the presence of HBV to replicate</td>
</tr>
</tbody>
</table>

SS, single-stranded; DS, double-stranded; ⊕, positive sense; ⊖, 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, Orthomyxoviruses (influenza viruses), Arenaviruses, and Reoviruses.

BOAR.

Picornavirus
Includes Poliovirus, Echovirus, Rhinovirus, Coxackievirus, and HAV. RNA is translated into 1 large polypeptide that is cleaved by proteases into functional viral proteins. Can cause aseptic (viral) meningitis (except rhinovirus and HAV). All are enteroviruses (fecal-oral spread) except rhinovirus.

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).

Rhin has a runny nose.

Yellow fever virus
A flavivirus (also an arbovirus) transmitted by Aedes mosquitoes. Virus has a monkey or human reservoir. Symptoms: high fever, black vomitus, and jaundice. May see Councilman bodies (eosinophilic apoptotic globules) on liver biopsy.

Flavi = yellow, jaundice.

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

ROTA = Right Out The Ants. CDC recommends routine vaccination of all infants.
**Influenza viruses**

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

<table>
<thead>
<tr>
<th>Genetic shift/antigenic shift</th>
<th>Causes pandemics. Reassortment of viral genome segments, such as when segments of human flu A virus reassort with swine flu A virus.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden shift</td>
<td>more deadly than gradual drift.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genetic drift/antigenic drift</th>
<th>Causes epidemics. Minor (antigenic drift) changes based on random mutation in hemagglutinin or neuraminidase genes.</th>
</tr>
</thead>
</table>

**Rubella virus**

A togavirus. Causes rubella, once known as German (3-day) measles. Fever, postauricular and other lymphadenopathy, arthralgias, and fine rash. Causes mild disease in children but serious congenital disease (a ToRCHes infection). Congenital rubella findings include “blueberry muffin” appearance, indicative of extramedullary hematopoiesis.

<table>
<thead>
<tr>
<th>A Rubella rash</th>
<th>Fine, confluent macules that start on the face and spread centrifugally to involve the trunk and extremities.</th>
</tr>
</thead>
<tbody>
<tr>
<td>B Congenital rubella virus infection</td>
<td>“Blueberry muffin” appearance.</td>
</tr>
</tbody>
</table>

**Paramyxoviruses**

Paramyxoviruses cause disease in children. They include those that cause parainfluenza (croup: seal-like barking cough), mumps, and measles as well as RSV, which causes respiratory tract infection (bronchiolitis, pneumonia) in infants. All contain surface F (fusion) protein, which causes respiratory epithelial cells to fuse and form multinucleated cells. Palivizumab (monoclonal antibody against F protein) prevents pneumonia caused by RSV infection in premature infants.
**Croup (acute laryngotracheobronchitis)**

Caused by parainfluenza viruses (paramyxovirus). Results in a “seal-like” barking cough and inspiratory stridor. Narrowing of upper trachea and subglottis leads to characteristic steeple sign on X-ray A. Severe croup can result in pulsus paradoxus due to upper airway obstruction.

**Measles (rubeola) virus**

A paramyxovirus that causes measles. Usual presentation involves prodromal fever with cough, coryza, and conjunctivitis, then eventually Koplik spots A, followed by a maculopapular rash B that starts at the head/neck and spreads downward. Lymphadenitis with Warthin-Finkeldey giant cells (fused lymphocytes) in a background of paracortical hyperplasia. SSPE (subacute sclerosing panencephalitis, occurring years later), encephalitis (1:2000), and giant cell pneumonia (rarely, in immunosuppressed) are possible sequelae.

3 C's of measles:
- Cough
- Coryza
- Conjunctivitis

Vitamin A supplementation can reduce measles mortality in malnourished or vitamin-deficient children.

**Koplik spots.** Note bright red spots with blue-white center on buccal mucosa (arrows) that precede the measles rash by 1–2 days.

**Rash of measles.** Confluent erythematous macules and papules, presents late, and includes limbs as it spreads downward.
**Mumps virus**

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

Symptoms: Parotitis, Orchitis (inflammation of testes), and aseptic Meningitis. Can cause sterility (especially after puberty).

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

---

**Rabies virus**

Bullet-shaped virus. Negri bodies commonly found in Purkinje cells of cerebellum and in hippocampal neurons.

Rabies has long incubation period (weeks to months) before symptom onset. Postexposure prophylaxis is wound cleaning plus immunization with killed vaccine and rabies immunoglobulin. Example of passive-active immunity.

Travels to the CNS by migrating in a retrograde fashion up nerve axons after binding to ACh receptors.

Progression of disease: fever, malaise → agitation, photophobia, hydrophobia, hypersalivation → paralysis, coma → death.

More commonly from bat, raccoon, and skunk bites than from dog bites in the United States.

---

**Ebola virus**


Transmission requires direct contact with bodily fluids or fomites (including dead bodies); high incidence of nosocomial infection.
### Hepatitis viruses

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>TRANSMISSION</th>
<th>CARRIER</th>
<th>INCUBATION</th>
<th>HCC RISK</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAV&lt;sup&gt;a&lt;/sup&gt;</td>
<td>RNA picornavirus</td>
<td>Fecal-oral</td>
<td>No</td>
<td>Short (weeks)</td>
<td>No</td>
</tr>
<tr>
<td>HBV&lt;sup&gt;b&lt;/sup&gt;</td>
<td>DNA hepadnavirus</td>
<td>Parenteral, sexual, perinatal</td>
<td>Yes</td>
<td>Long (months)</td>
<td>Yes</td>
</tr>
<tr>
<td>HCV</td>
<td>RNA flavivirus</td>
<td>Primarily blood (IVDU, post-transfusion)</td>
<td>Yes</td>
<td>Long</td>
<td>Yes</td>
</tr>
<tr>
<td>HDV</td>
<td>RNA delta virus</td>
<td>Parenteral, sexual, perinatal</td>
<td>Yes</td>
<td>Superinfection (HDV after HBV)—short Coinfection (HDV with HBV)—long</td>
<td>Yes</td>
</tr>
<tr>
<td>HEV&lt;sup&gt;a&lt;/sup&gt;</td>
<td>RNA hepevirus</td>
<td>Fecal-oral, especially waterborne</td>
<td>No</td>
<td>Short</td>
<td>No</td>
</tr>
</tbody>
</table>

Signs and symptoms of all hepatitis viruses: episodes of fever, jaundice, ↑ ALT and AST. May see Councilman bodies (eosinophilic apoptotic globules) on liver biopsy.

<sup>a</sup>HAV and HEV are fecal-oral: The **vowels** hit your **bowels**. Naked viruses do not rely on an envelope, so they are not destroyed by the gut.

<sup>b</sup>In HBV, the DNA polymerase has both DNA- and RNA-dependent activities. Upon entry into the nucleus, the polymerase functions to complete the partial dsDNA. The 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.
### Hepatitis serologic markers

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HAV (IgM)</td>
<td>IgM antibody to HAV; best test to detect acute hepatitis A.</td>
</tr>
<tr>
<td>Anti-HAV (IgG)</td>
<td>IgG antibody indicates prior HAV infection and/or prior vaccination; protects against reinfection.</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Antigen found on surface of HBV; indicates hepatitis B infection.</td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>Antibody to HBsAg; indicates immunity to hepatitis B.</td>
</tr>
<tr>
<td>HBeAg</td>
<td>A second, different antigenic determinant in the HBV core. HBeAg indicates active viral replication and therefore high transmissibility.</td>
</tr>
<tr>
<td>Anti-HBe</td>
<td>Antibody to HBeAg; indicates low transmissibility.</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>Antibody to HBcAg; IgM = acute/recent infection; IgG = prior exposure or chronic infection. IgM anti-HBc may be the sole positive marker of infection during window period.</td>
</tr>
</tbody>
</table>

**Diagram:**
- **Virus particle:**
  - Coat protein (HBsAg)
  - Core (HBcAg)
  - DNA genome
  - DNA polymerase

**In viral hepatitis, ALT > AST.**
**In alcoholic hepatitis, AST > ALT.**

<table>
<thead>
<tr>
<th>Disease Stage</th>
<th>HBsAg</th>
<th>Anti-HBs</th>
<th>HBeAg</th>
<th>Anti-HBe</th>
<th>Anti-HBc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute HBV</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>IgM</td>
</tr>
<tr>
<td>Window</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>IgM</td>
</tr>
<tr>
<td>Chronic HBV (high infectivity)</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td>IgG</td>
</tr>
<tr>
<td>Chronic HBV (low infectivity)</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td>IgG</td>
</tr>
<tr>
<td>Recovery</td>
<td></td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>IgG</td>
</tr>
<tr>
<td>Immunized</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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)—capsid protein.
- **pol**—reverse transcriptase, aspartate protease, integrase.

Reverse transcriptase synthesizes dsDNA from genomic RNA; dsDNA integrates into host genome.

Virus binds CD4 as well as a coreceptor, either CCR5 on macrophages (early infection) or CXCR4 on T cells (late infection).

Homozygous CCR5 mutation = immunity.

Heterozygous CCR5 mutation = slower course.

---

**HIV diagnosis**

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

Viral load tests determine the amount of viral RNA in the plasma. High viral load associated with poor prognosis. Also use viral load to monitor effect of drug therapy.

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

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

Four stages of untreated infection:
1. **Flu-like (acute)**
2. **Feeling fine (latent)**
3. **Falling count**
4. **Final crisis**

During latent phase, virus replicates in lymph nodes.

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

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

As CD4+ count ↓, risks of reactivation of past infections (e.g., TB, HSV, shingles), dissemination of bacterial infections and fungal infections (e.g., coccidioidomycosis), and non-Hodgkin lymphomas ↑.

<table>
<thead>
<tr>
<th>PATHOGEN</th>
<th>PRESENTATION</th>
<th>FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 500 cells/mm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Candida albicans</em></td>
<td>Oral thrush</td>
<td>Scrapable white plaque, pseudohyphae on microscopy</td>
</tr>
<tr>
<td><em>EBV</em></td>
<td>Oral hairy leukoplakia</td>
<td>Unscrapable white plaque on lateral tongue</td>
</tr>
<tr>
<td><em>Bartonella henselae</em></td>
<td>Bacillary angiomatosis</td>
<td>Biopsy with neutrophilic inflammation</td>
</tr>
<tr>
<td><em>HHV-8</em></td>
<td>Kaposi sarcoma</td>
<td>Biopsy with lymphocytic inflammation</td>
</tr>
<tr>
<td><em>Cryptosporidium spp.</em></td>
<td>Chronic, watery diarrhea</td>
<td>Acid-fast oocysts in stool</td>
</tr>
<tr>
<td><em>HPV</em></td>
<td>Squamous cell carcinoma, commonly of anus (men who have sex with) or cervix (women)</td>
<td></td>
</tr>
</tbody>
</table>

| < 200 cells/mm³           |                                                   |                                        |
| *Toxoplasma gondii*       | Brain abscesses                                   | Multiple ring-enhancing lesions on MRI |
| *HIV*                     | Dementia                                          |                                        |
| *JC virus (reactivation)* | Progressive multifocal leukoencephalopathy        | Nonenhancing areas of demyelination on MRI |
| *Pneumocystis jirovecii*  | *Pneumocystis pneumonia*                          | “Ground-glass” opacities on CXR        |

| < 100 cells/mm³           |                                                   |                                        |
| *Aspergillus fumigatus*   | Hemoptysis, pleuritic pain                        | Cavitation or infiltrates on chest imaging |
| *Cryptococcus neoformans* | Meningitis                                        |                                        |
| *Candida albicans*        | Esophagitis                                       | White plaques on endoscopy; yeast and pseudohyphae on biopsy |
| *CMV*                     | Retinitis, esophagitis, colitis, pneumonitis, encephalitis | Linear ulcers on endoscopy, cotton-wool spots on fundoscopy Biopsy reveals cells with intranuclear (owl eye) inclusion bodies |
| *EBV*                     | B-cell lymphoma (e.g., non-Hodgkin lymphoma, CNS lymphoma) | CNS lymphoma—ring enhancing, may be solitary (vs. *Toxoplasma*) |
| *Histoplasma capsulatum*  | Fever, weight loss, fatigue, cough, dyspnea, nausea, vomiting, diarrhea | Oval yeast cells within macrophages |
| *Mycobacterium avium—intracellulare, Mycobacterium avium complex* | Non-specific systemic symptoms (fever, night sweats, weight loss) or focal lymphadenitis |                                        |
Prions

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

Creutzfeldt-Jakob disease—rapidly progressive dementia, typically sporadic (some familial forms). Bovine spongiform encephalopathy (BSE)—also known as “mad cow disease.” Kuru—acquired prion disease noted in tribal populations practicing human cannibalism.

Normal flora:

<table>
<thead>
<tr>
<th>LOCATION</th>
<th>MICROORGANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>S. epidermidis</td>
</tr>
<tr>
<td>Nose</td>
<td>S. epidermidis; colonized by S. aureus</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>Viridans group streptococci</td>
</tr>
<tr>
<td>Dental plaque</td>
<td>S. mutans</td>
</tr>
<tr>
<td>Colon</td>
<td>B. fragilis &gt; E. coli</td>
</tr>
<tr>
<td>Vagina</td>
<td>Lactobacillus, colonized by E. coli and group B strep</td>
</tr>
</tbody>
</table>

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

Bugs causing food poisoning

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

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

*V. vulnificus can also cause wound infections from contact with contaminated water or shellfish.
## Bugs causing diarrhea

<table>
<thead>
<tr>
<th>Category</th>
<th>Organism</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bloody diarrhea</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Campylobacter</td>
<td>Comm- or S-shaped organisms; growth at 42°C</td>
<td></td>
</tr>
<tr>
<td>E. histolytica</td>
<td>Protozoan; amebic dysentery; liver abscess</td>
<td></td>
</tr>
<tr>
<td>Enterohemorrhagic E. coli</td>
<td>O157:H7; can cause HUS; makes Shiga-like toxin</td>
<td></td>
</tr>
<tr>
<td>Enteroinvasive E. coli</td>
<td>Invades colonic mucosa</td>
<td></td>
</tr>
<tr>
<td>Salmonella</td>
<td>Lactose (coli); flagellar motility; has animal reservoir, especially poultry and eggs</td>
<td></td>
</tr>
<tr>
<td>Shigella</td>
<td>Lactose (coli); very low ID₅₀; produces Shiga toxin (human reservoir only); bacillary dysentery</td>
<td></td>
</tr>
<tr>
<td>Y. enterocolitica</td>
<td>Day care outbreaks, pseudoappendicitis</td>
<td></td>
</tr>
<tr>
<td><strong>Watery diarrhea</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. difficile</td>
<td>Pseudomembranous colitis; caused by antibiotics; occasionally bloody diarrhea</td>
<td></td>
</tr>
<tr>
<td>C. perfringens</td>
<td>Also causes gas gangrene</td>
<td></td>
</tr>
<tr>
<td>Enterotoxigenic E. coli</td>
<td>Travelers’ diarrhea; produces heat-labile (LT) and heat-stable (ST) toxins</td>
<td></td>
</tr>
<tr>
<td>Protozoa</td>
<td>Giardia, Cryptosporidium</td>
<td></td>
</tr>
<tr>
<td>V. cholera</td>
<td>Comma-shaped organisms; rice-water diarrhea; often from infected seafood</td>
<td></td>
</tr>
<tr>
<td>Viruses</td>
<td>Rotavirus, norovirus, adenovirus</td>
<td></td>
</tr>
</tbody>
</table>

## Common causes of pneumonia

<table>
<thead>
<tr>
<th>Category</th>
<th>Neonates (&lt; 4 wk)</th>
<th>Children (4 wk–18 yr)</th>
<th>Adults (18–40 yr)</th>
<th>Adults (40–65 yr)</th>
<th>Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group B streptococci E. coli</td>
<td>Viruses (RSV)</td>
<td>Mycoplasma</td>
<td>S. pneumoniae</td>
<td>S. pneumoniae</td>
<td>S. pneumoniae</td>
</tr>
<tr>
<td>C. trachomatis</td>
<td>(infants–3 yr)</td>
<td>C. pneumoniae</td>
<td>H. influenzae</td>
<td>Anaerobes</td>
<td>Anaerobes</td>
</tr>
<tr>
<td>C. pneumoniae</td>
<td>(school-aged children)</td>
<td>S. pneumoniae</td>
<td>Virus</td>
<td>Mycoplasma</td>
<td>H. influenzae</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>Runts May Cough</td>
<td>Chunky Sputum</td>
<td>Gram-negative rods</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Special groups

<table>
<thead>
<tr>
<th>Category</th>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholic/IV drug user</td>
<td>S. pneumoniae, Klebsiella, S. aureus</td>
</tr>
<tr>
<td>Aspiration</td>
<td>Anaerobes (e.g., Peptostreptococcus, Fusobacterium, Prevotella, Bacteroides)</td>
</tr>
<tr>
<td>Atypical</td>
<td>Mycoplasma, Legionella, Chlamydia</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Pseudomonas, S. aureus, S. pneumoniae</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>S. aureus, enteric gram-negative rods, fungi, viruses, P. jirovecii (with HIV)</td>
</tr>
<tr>
<td>Nosocomial (hospital acquired)</td>
<td>S. aureus, Pseudomonas, other enteric gram-negative rods</td>
</tr>
<tr>
<td>Postviral</td>
<td>S. aureus, H. influenzae, S. pneumoniae</td>
</tr>
</tbody>
</table>
Common causes of meningitis

<table>
<thead>
<tr>
<th>NEWBORN (0–6 MO)</th>
<th>CHILDREN (6 MO–6 YR)</th>
<th>6–60 YR</th>
<th>60 YR +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group B streptococci</td>
<td>S. pneumoniae</td>
<td>S. pneumoniae</td>
<td>S. pneumoniae</td>
</tr>
<tr>
<td>E. coli</td>
<td>N. meningitidis</td>
<td>N. meningitidis (#1 in teens)</td>
<td>Gram-negative rods</td>
</tr>
<tr>
<td>Listeria</td>
<td>H. influenzae type B</td>
<td>Enteroviruses</td>
<td>Enteroviruses</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Listeria</td>
</tr>
</tbody>
</table>

Give ceftriaxone and vancomycin empirically (add ampicillin if Listeria is suspected).

Viral causes of meningitis: enteroviruses (especially coxsackievirus), HSV-2 (HSV-1 = encephalitis), HIV, West Nile virus (also causes encephalitis), VZV.

In HIV: Cryptococcus spp.

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

CSF findings in meningitis

<table>
<thead>
<tr>
<th></th>
<th>OPENING PRESSURE</th>
<th>CELL TYPE</th>
<th>PROTEIN</th>
<th>SUGAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial</td>
<td>↑</td>
<td>↑ PMNs</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Fungal/TB</td>
<td>↑</td>
<td>↑ lymphocytes</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Viral</td>
<td>Normal/↑</td>
<td>↑ lymphocytes</td>
<td>Normal/↑</td>
<td>Normal</td>
</tr>
</tbody>
</table>

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

Assume if no other information is available

- Sexually active: Neisseria gonorrhoeae (rare), septic arthritis more common
- Sickle cell disease: Salmonella and S. aureus
- Prosthetic joint replacement: S. aureus and S. epidermidis
- Vertebral involvement: S. aureus, Mycobacterium tuberculosis (Pott disease)
- Cat and dog bites: Pasteurella multocida
- IV drug abuse: Pseudomonas, Candida, S. aureus are most common

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

Cystitis presents with dysuria, frequency, urgency, suprapubic pain, and WBCs (but not WBC casts) in urine. Primarily caused by ascension of microbes from urethra to bladder. Males—infants with congenital defects, vesicoureteral reflux. Elderly—enlarged prostate. Ascension to kidney results in pyelonephritis, which presents with fever, chills, flank pain, costovertebral angle tenderness, hematuria, and WBC casts.


### UTI bugs

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

### Common vaginal infections

#### Bacterial vaginosis
No inflammation  
Thin, white discharge with fishy odor

#### Trichomoniasis
Inflammation (“strawberry cervix”)  
Frothy, grey-green, foul-smelling discharge

#### Candida vulvovaginitis
Inflammation  
Thick, white, “cottage cheese” discharge

<table>
<thead>
<tr>
<th>SIGNS AND SYMPTOMS</th>
<th>BACTERIAL VAGINOSIS</th>
<th>TRICHOMEONIASIS</th>
<th>CANDIDA VULVOVAGINITIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lab Findings</td>
<td>Clue cells pH &gt; 4.5</td>
<td>Motile trichomonads pH &gt; 4.5</td>
<td>Pseudohyphae pH normal (4.0–4.5)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Metronidazole</td>
<td>Metronidazole</td>
<td>-azoles</td>
</tr>
</tbody>
</table>

- Metronidazole
- -azoles
**ToRCH** infections

Microbes that may pass from mother to fetus. Transmission is transplacental in most cases, or via delivery (especially HSV-2). Nonspecific signs common to many ToRCH infections include hepatosplenomegaly, jaundice, thrombocytopenia, and growth retardation. Other important infectious agents include *Streptococcus agalactiae* (group B streptococci), *E. coli*, and *Listeria monocytogenes*—all causes of meningitis in neonates. Parvovirus B19 causes hydrops fetalis.

<table>
<thead>
<tr>
<th>AGENT</th>
<th>MODE OF TRANSMISSION</th>
<th>MATERNAL MANIFESTATIONS</th>
<th>NEONATAL MANIFESTATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Toxoplasma gondii</em></td>
<td>Cat feces or ingestion of undercooked meat</td>
<td>Usually asymptomatic; lymphadenopathy (rarely)</td>
<td>Classic triad: chorioretinitis, hydrocephalus, and intracranial calcifications, +/- “blueberry muffin” rash</td>
</tr>
<tr>
<td>Rubella</td>
<td>Respiratory droplets</td>
<td>Rash, lymphadenopathy, arthritis</td>
<td>Classic triad: PDA (or pulmonary artery hypoplasia), cataracts, and deafness, +/- “blueberry muffin” rash</td>
</tr>
<tr>
<td>CMV</td>
<td>Sexual contact, organ transplants</td>
<td>Usually asymptomatic; mononucleosis-like illness</td>
<td>Hearing loss, seizures, petechial rash, “blueberry muffin” rash, periventricular calcifications</td>
</tr>
<tr>
<td>HIV</td>
<td>Sexual contact, needlestick</td>
<td>Variable presentation depending on CD4+ count</td>
<td>Recurrent infections, chronic diarrhea</td>
</tr>
<tr>
<td>Herpes simplex virus-2</td>
<td>Skin or mucous membrane contact</td>
<td>Usually asymptomatic; herpetic (vesicular) lesions</td>
<td>Encephalitis, herpetic (vesicular) lesions</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Sexual contact</td>
<td>Chancre (1°) and disseminated rash (2°) are the two stages likely to result in fetal infection</td>
<td>Often results in stillbirth, hydrops fetalis; if child survives, presents with facial abnormalities (e.g., notched teeth, saddle nose, short maxilla), saber shins, CN VIII deafness</td>
</tr>
</tbody>
</table>

*PDA: persistent ductus arteriosus*
## Red rashes of childhood

<table>
<thead>
<tr>
<th>AGENT</th>
<th>ASSOCIATED SYNDROME/DISEASE</th>
<th>CLINICAL PRESENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coxsackievirus type A</td>
<td>Hand-foot-mouth disease</td>
<td>Oval-shaped vesicles on palms and soles, vesicles and ulcers in oral mucosa</td>
</tr>
<tr>
<td>HHV-6</td>
<td>Roseola (exanthem subitum)</td>
<td>Asymptomatic rose-colored macules appear on body after several days of high fever; can present with febrile seizures; usually affects infants</td>
</tr>
<tr>
<td>Measles virus</td>
<td>Measles (rubeola)</td>
<td>Beginning at head and moving down; rash is preceded by cough, coryza, conjunctivitis, and blue-white (Koplik) spots on buccal mucosa</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>Erythema infectiosum (fifth disease)</td>
<td>“Slapped cheek” rash on face (can cause hydrops fetalis in pregnant women)</td>
</tr>
<tr>
<td>Rubella virus</td>
<td>Rubella (German measles)</td>
<td>Pink coalescing macules begin at head and move down; fine desquamating truncal rash; postauricular lymphadenopathy</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>Scarlet fever</td>
<td>Erythematous, sandpaper-like rash with fever and sore throat</td>
</tr>
<tr>
<td>VZV</td>
<td>Chickenpox</td>
<td>Vesicular rash begins on trunk; spreads to face and extremities with lesions of different ages</td>
</tr>
</tbody>
</table>

![Hand-foot-mouth disease](imageA)  
![Erythema infectiosum](imageB)
### Sexually transmitted infections

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>CLINICAL FEATURES</th>
<th>ORGANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>Opportunistic infections, Kaposi sarcoma, lymphoma</td>
<td>HIV</td>
</tr>
<tr>
<td>Chancroid</td>
<td>Painful genital ulcer with exudate, inguinal adenopathy</td>
<td><em>Haemophilus ducreyi</em> (it’s so painful, you “do cry”)</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>Urethritis, cervicitis, conjunctivitis, reactive arthritis, PID</td>
<td><em>Chlamydia trachomatis</em> (D–K)</td>
</tr>
<tr>
<td>Condylomata acuminata</td>
<td>Genital warts, koilocytes</td>
<td>HPV-6 and -11</td>
</tr>
<tr>
<td>Genital herpes</td>
<td>Painful penile, vulvar, or cervical vesicles and ulcers; can cause systemic symptoms such as fever, headache, myalgia</td>
<td>HSV-2, less commonly HSV-1</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>Urethritis, cervicitis, PID, prostatitis, epididymitis, arthritis, creamy purulent discharge</td>
<td><em>Neisseria gonorrhoeae</em></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Jaundice</td>
<td>HBV</td>
</tr>
<tr>
<td>Lymphogranuloma venereum</td>
<td>Infection of lymphatics; painless genital ulcers, painful lymphadenopathy (i.e., buboes)</td>
<td><em>C. trachomatis</em> (L1–L3)</td>
</tr>
<tr>
<td>1° syphilis</td>
<td>Painless chancre</td>
<td><em>Treponema pallidum</em></td>
</tr>
<tr>
<td>2° syphilis</td>
<td>Fever, lymphadenopathy, skin rashes, condylomata lata</td>
<td></td>
</tr>
<tr>
<td>3° syphilis</td>
<td>Gummas, tabes dorsalis, general paresis, aortitis, Argyll Robertson pupil</td>
<td></td>
</tr>
<tr>
<td>Trichomoniasis</td>
<td>Vaginitis, strawberry cervix, motile in wet prep</td>
<td><em>Trichomonas vaginalis</em></td>
</tr>
</tbody>
</table>
Pelvic inflammatory disease

Top bugs—Chlamydia trachomatis (subacute, often undiagnosed), Neisseria gonorrhoeae (acute). C. trachomatis—most common bacterial STI in the United States. Cervical motion tenderness (chandelier sign), purulent cervical discharge. PID may include salpingitis, endometritis, hydrosalpinx, and tubo-ovarian abscess.

Salpingitis is a risk factor for ectopic pregnancy, infertility, chronic pelvic pain, and adhesions. Can lead to Fitz-Hugh–Curtis syndrome—infestation of the liver capsule and “violin string” adhesions of peritoneum to liver.

Nosocomial infections

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Pathogen</th>
<th>Unique Signs/Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered mental status, old age, aspiration</td>
<td>Polymicrobial, gram-negative bacteria, often anaerobes</td>
<td>Right lower lobe infiltrate or right upper/middle lobe (patient recumbent); purulent malodorous sputum</td>
</tr>
<tr>
<td>Antibiotic use</td>
<td>Clostridium difficile</td>
<td>Watery diarrhea, leukocytosis</td>
</tr>
<tr>
<td>Decubitus ulcers, surgical wounds, drains</td>
<td>S. aureus (including MRSA), gram-negative anaerobes</td>
<td>Erythema, tenderness, induration, drainage from surgical wound sites</td>
</tr>
<tr>
<td>Intravascular catheters</td>
<td>S. aureus (including MRSA), S. epidermidis (long term), Enterobacter</td>
<td>Erythema, induration, tenderness, drainage from access sites</td>
</tr>
<tr>
<td>Mechanical ventilation, endotracheal intubation</td>
<td>Late onset: P. aeruginosa, Klebsiella, Acinetobacter, S. aureus</td>
<td>New infiltrate on CXR, ↑ sputum production; sweet odor (Pseudomonas)</td>
</tr>
<tr>
<td>Renal dialysis unit, needlestick</td>
<td>HBV</td>
<td></td>
</tr>
<tr>
<td>Urinary catheterization</td>
<td>E. coli, Klebsiella, Proteus spp.</td>
<td>Dysuria, leukocytosis, flank pain or costovertebral angle tenderness</td>
</tr>
<tr>
<td>Water aerosols</td>
<td>Legionella</td>
<td>Signs of pneumonia, GI symptoms (nausea, vomiting)</td>
</tr>
</tbody>
</table>
## Bugs affecting unimmunized children

<table>
<thead>
<tr>
<th>Dermatologic</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rash</strong></td>
<td>Beginning at head and moving down with postauricular lymphadenopathy</td>
<td><strong>Rubella virus</strong></td>
</tr>
<tr>
<td></td>
<td>Beginning at head and moving down; rash preceded by cough, coryza, conjunctivitis, and blue-white (Koplik) spots on buccal mucosa</td>
<td><strong>Measles virus</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurologic</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Meningitis</strong></td>
<td>Microbe colonizes nasopharynx</td>
<td><strong>H. influenzae</strong> type B</td>
</tr>
<tr>
<td></td>
<td>Can also lead to myalgia and paralysis</td>
<td><strong>Poliovirus</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epiglottitis</strong></td>
<td>Fever with dysphagia, drooling, and difficulty breathing due to edematous &quot;cherry red&quot; epiglottis; “thumbprint sign” on X-ray</td>
<td><strong>H. influenzae</strong> type B (also capable of causing epiglottitis in fully immunized children)</td>
</tr>
<tr>
<td><strong>Pharyngitis</strong></td>
<td>Grayish oropharyngeal exudate (&quot;pseudomembranes&quot; may obstruct airway); painful throat</td>
<td><strong>Corynebacterium diphtheriae</strong> (elaborates toxin that causes necrosis in pharynx, cardiac, and CNS tissue)</td>
</tr>
</tbody>
</table>

### Bug hints (if all else fails)

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

**Penicillin G, V**

Penicillin G (IV and IM form), penicillin V (oral). Prototype β-lactam antibiotics.

**Mechanism**

Bind penicillin-binding proteins (transpeptidases).
Block transpeptidase cross-linking of peptidoglycan in cell wall.
Activate autolytic enzymes.

**Clinical Use**

Mostly used for gram-positive organisms (*S. pneumoniae, S. pyogenes, Actinomyces*). Also used for gram-negative cocci (mainly *N. meningitidis*) and spirochetes (namely *T. pallidum*). Bactericidal for gram-positive cocci, gram-positive rods, gram-negative cocci, and spirochetes. Penicillinase sensitive.

**Toxicity**

Hypersensitivity reactions, hemolytic anemia.

**Resistance**

Penicillinase in bacteria (a type of β-lactamase) cleaves β-lactam ring.
### Amoxicillin, ampicillin (aminopenicillins, penicillinase-sensitive penicillins)

| MECHANISM | Same as penicillin. Wider spectrum; penicillinase sensitive. Also combine with clavulanic acid to protect against destruction by β-lactamase. | AMinoPenicillins are AMPed-up penicillin. AmOxicillin has greater Oral bioavailability than ampicillin. |
| TOXICITY | Hypersensitivity reactions; rash; pseudomembranous colitis. |
| MECHANISM OF RESISTANCE | Penicillinase in bacteria (a type of β-lactamase) cleaves β-lactam ring. |

### Dicloxacillin, nafcillin, oxacillin (penicillinase-resistant penicillins)

| MECHANISM | Same as penicillin. Narrow spectrum; penicillinase resistant because bulky R group blocks access of β-lactamase to β-lactam ring. |
| CLINICAL USE | *S. aureus* (except MRSA; resistant because of altered penicillin-binding protein target site). | “Use naf (nafcillin) for staph.” |
| TOXICITY | Hypersensitivity reactions, interstitial nephritis. |

### Piperacillin, ticarcillin (antipseudomonals)

| MECHANISM | Same as penicillin. Extended spectrum. |
| CLINICAL USE | *Pseudomonas* spp. and gram-negative rods; susceptible to penicillinase; use with β-lactamase inhibitors. |
| TOXICITY | Hypersensitivity reactions. |

### β-lactamase inhibitors

| Include Clavulanic Acid, Sulbactam, Tazobactam. Often added to penicillin antibiotics to protect the antibiotic from destruction by β-lactamase (penicillinase). | CAST. |
### Cephalosporins (generations I–V)

| Mechanism | \( \beta \)-lactam drugs that inhibit cell wall synthesis but are less susceptible to penicillinases. Bactericidal. |
| Organisms typically not covered by cephalosporins are LAME: *Listeria*, Atypicals (*Chlamydia*, *Mycoplasma*), MRSA, and Enterococci. Exception: ceftaroline covers MRSA. |

| Clinical Use | 1st generation (cefaclor, cephalexin)—gram-positive cocci, *Proteus mirabilis*, *E. coli*, *Klebsiella pneumoniae*. Cefazolin used prior to surgery to prevent *S. aureus* wound infections. |
| 3rd generation (ceftriaxone, cefotaxime, ceftazidime)—serious gram-negative infections resistant to other \( \beta \)-lactams. |
| 4th generation (cefeprime)—gram-negative organisms, with \( \uparrow \) activity against *Pseudomonas* and gram-positive organisms. |
| 5th generation (cefaroline)—broad gram-positive and gram-negative organism coverage, including MRSA; does not cover *Pseudomonas*. |

| Toxicity | Hypersensitivity reactions, autoimmune hemolytic anemia, disulfiram-like reaction, vitamin K deficiency. Exhibit cross-reactivity with penicillins. \( \uparrow \) nephrotoxicity of aminoglycosides. |

| Mechanism of Resistance | Structural change in penicillin-binding proteins (transpeptidases). |
## Carbapenems

**MECHANISM**
Imipenem is a broad-spectrum, β-lactamase-resistant carbapenem. Always administered with cilastatin (inhibitor of renal dehydropeptidase I) to inactivation of drug in renal tubules. With imipenem, “the kill is lastin’ with cilastatin.”

Newer carbapenems include ertapenem (limited Pseudomonas coverage) and doripenem.

**CLINICAL USE**
Gram-positive cocci, gram-negative rods, and anaerobes. Wide spectrum, but significant side effects limit use to life-threatening infections or after other drugs have failed. Meropenem has a risk of seizures and is stable to dehydropeptidase I.

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

## Monobactams

**MECHANISM**

**CLINICAL USE**
Gram-negative rods only—no activity against gram-positives or anaerobes. For penicillin-allergic patients and those with renal insufficiency who cannot tolerate aminoglycosides.

**TOXICITY**
Usually nontoxic; occasional GI upset.

## Vancomycin

**MECHANISM**
Inhibits cell wall peptidoglycan formation by binding D-ala D-ala portion of cell wall precursors. Bactericidal. Not susceptible to β-lactamases.

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

**TOXICITY**
Well tolerated in general—but NOT trouble free. Nephrotoxicity, Ototoxicity, Thrombophlebitis, diffuse flushing—red man syndrome (can largely prevent by pretreatment with antihistamines and slow infusion rate).

**MECHANISM OF RESISTANCE**
Occurs in bacteria via amino acid modification of D-ala D-ala to D-ala D-lac. “Pay back 2 D-alas dollars for vandalizing (vancomycin).”
Specifically target smaller bacterial ribosome (70S, made of 30S and 50S subunits), leaving human ribosome (80S) unaffected.

**30S inhibitors**

<table>
<thead>
<tr>
<th>A</th>
<th>Aminoglycosides [bactericidal]</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>Tetracyclines [bacteriostatic]</td>
</tr>
</tbody>
</table>

**50S inhibitors**

<table>
<thead>
<tr>
<th>C</th>
<th>Chloramphenicol, Clindamycin [bacteriostatic]</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>Erythromycin (macrolides) [bacteriostatic]</td>
</tr>
<tr>
<td>L</td>
<td>Linezolid [variable]</td>
</tr>
</tbody>
</table>

“Buy AT 30, CCEL (sell) at 50.”

### Aminoglycosides

- Gentamicin, Neomycin, Amikacin, Tobramycin, Streptomycin.

#### MECHANISM

Bactericidal; irreversible inhibition of initiation complex through binding of the 30S subunit. Can cause misreading of mRNA. Also block translocation. Require O₂ for uptake; therefore ineffective against anaerobes.

#### CLINICAL USE


#### TOXICITY

Nephrotoxicity, Neuromuscular blockade, Otoxicity (especially when used with loop diuretics). Teratogen.

#### MECHANISM OF RESISTANCE

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

“Mean” (aminoglycoside) GNATS caNNOT kill anaerobes.
### Tetracyclines

**Mechanism**
Bacteriostatic; bind to 30S and prevent attachment of aminoacyl-tRNA; limited CNS penetration. Doxycycline is fecally eliminated and can be used in patients with renal failure. Do not take tetracyclines with milk (Ca²⁺), antacids (Ca²⁺ or Mg²⁺), or iron-containing preparations because divalent cations inhibit drugs’ absorption in the gut.

**Clinical Use**
*Borrelia burgdorferi, M. pneumoniae*. Drugs’ ability to accumulate intracellularly makes them very effective against *Rickettsia* and *Chlamydia*. Also used to treat acne.

**Toxicity**

**Mechanism of Resistance**
↓ uptake or ↑ efflux out of bacterial cells by plasmid-encoded transport pumps.

### Chloramphenicol

**Mechanism**
Blocks peptidyltransferase at 50S ribosomal subunit. Bacteriostatic.

**Clinical Use**
Meningitis (*Haemophilus influenzae, Neisseria meningitidis, Streptococcus pneumoniae*) and Rocky Mountain spotted fever (*Rickettsia rickettsii*). Limited use owing to toxicities but often still used in developing countries because of low cost.

**Toxicity**
Anemia (dose dependent), aplastic anemia (dose independent), gray baby syndrome (in premature infants because they lack liver UDP-glucuronyl transferase).

**Mechanism of Resistance**
Plasmid-encoded acetyltransferase inactivates the drug.

### Clindamycin

**Mechanism**
Blocks peptide transfer (translocation) at 50S ribosomal subunit. Bacteriostatic.

**Clinical Use**
Anaerobic infections (e.g., *Bacteroides* spp., *Clostridium perfringens*) 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).

**Toxicity**
Pseudomembranous colitis (*C. difficile* overgrowth), fever, diarrhea.

### Oxazolidinones

**Linezolid**

**Mechanism**
Inhibit protein synthesis by binding to 50S subunit and preventing formation of the initiation complex.

**Clinical Use**
Gram-positive species including MRSA and VRE.

**Toxicity**
Bone marrow suppression (especially thrombocytopenia), peripheral neuropathy, serotonin syndrome.

**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 (Mycoplasma, Chlamydia, Legionella), STIs (Chlamydia), gram-positive cocci (streptococcal infections in patients allergic to penicillin), and B. pertussis. |
| MECHANISM OF RESISTANCE | Methylation of 23S rRNA-binding site prevents binding of drug. |

**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, Shigella, Salmonella, Pneumocystis jirovecii pneumonia treatment and prophylaxis, toxoplasmosis prophylaxis. |
| TOXICITY | Megaloblastic anemia, leukopenia, granulocytopenia. (May alleviate with supplemental folic acid). TMP Treats Marrow Poorly. |

**Sulfonamides**

| MECHANISM | Inhibit folate synthesis. Para-aminobenzoic acid (PABA) antimetabolites inhibit dihydropteroate synthase. Bacteriostatic (bactericidal when combined with trimethoprim). (Dapsone, used to treat lepromatous leprosy, is a closely related drug that also inhibits folate synthesis.) |
| CLINICAL USE | Gram-positives, gram-negatives, Nocardia, Chlamydia. Triple sulfas or SMX for simple UTI. |
| TOXICITY | Hypersensitivity reactions, hemolysis if G6PD deficient, nephrotoxicity (tubulointerstitial nephritis), photosensitivity, kernicterus in infants, displace other drugs from albumin (e.g., warfarin). |
| MECHANISM OF RESISTANCE | Altered enzyme (bacterial dihydropteroate synthase), ↓ uptake, or ↑ PABA synthesis. |
### Fluoroquinolones

**MECHANISM**

Inhibit prokaryotic enzymes topoisomerase II (DNA gyrase) and topoisomerase IV. Bactericidal. Must not be taken with antacids.

**CLINICAL USE**

Gram-negative rods of urinary and GI tracts (including *Pseudomonas*, *Neisseria*, some gram-positive organisms).

**TOXICITY**

GI upset, superinfections, skin rashes, headache, dizziness. Less commonly, can cause leg cramps and myalgias. Contraindicated in pregnant women, nursing mothers, and children < 18 years old due to possible damage to cartilage. Some may prolong QT interval. May cause tendonitis or tendon rupture in people > 60 years old and in patients taking prednisone.

**MECHANISM OF RESISTANCE**

Chromosome-encoded mutation in DNA gyrase, plasmid-mediated resistance, efflux pumps.

**Fluoroquinolones hurt attachments to your bones.**

### Daptomycin

**MECHANISM**

Lipopeptide that disrupts cell membrane of gram-positive cocci.

**CLINICAL USE**

*S. aureus* skin infections (especially MRSA), bacteremia, endocarditis, VRE. Not used for pneumonia (avidly binds to and is inactivated by surfactant).

**TOXICITY**

Myopathy, rhabdomyolysis.

### Metronidazole

**MECHANISM**

Forms toxic free radical metabolites in the bacterial cell that damage DNA. Bactericidal, antiprotozoal.

**CLINICAL USE**

Treats *Giardia*, *Entamoeba*, *Trichomonas*, *Gardnerella vaginalis*, Anaerobes (*Bacteroides*, *C. difficile*). Used with a proton pump inhibitor and clarithromycin for “triple therapy” against *H. Pylori*.

**TOXICITY**

Disulfiram-like reaction (severe flushing, tachycardia, hypotension) with alcohol; headache, metallic taste.

**GET GAP on the Metro with metronidazole!**

Treats anaerobic infection below the diaphragm vs. clindamycin (anaerobic infections above diaphragm).
### Antimycobacterial drugs

<table>
<thead>
<tr>
<th>BACTERIUM</th>
<th>PROPHYLAXIS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. tuberculosis</em></td>
<td>Isoniazid</td>
<td>Rifampin, Isoniazid, Pyrazinamide, Ethambutol (RIPE for treatment)</td>
</tr>
<tr>
<td><em>M. avium–intracellulare</em></td>
<td>Azithromycin, rifabutin</td>
<td>More drug resistant than <em>M. tuberculosis</em>. Azithromycin or clarithromycin + ethambutol. Can add rifabutin or ciprofloxacin.</td>
</tr>
<tr>
<td><em>M. leprae</em></td>
<td>N/A</td>
<td>Long-term treatment with dapsone and rifampin for tuberculoid form. Add clofazimine for lepromatous form.</td>
</tr>
</tbody>
</table>

### Rifamycins

**MECHANISM**
Inhibit DNA-dependent RNA polymerase.

**CLINICAL USE**
*Mycobacterium tuberculosis*; delay resistance to dapsone when used for leprosy. Used for meningococcal prophylaxis and chemoprophylaxis in contacts of children with *Haemophilus influenzae* type B.

**TOXICITY**
Minor hepatotoxicity and drug interactions († cytochrome P-450); orange body fluids (nonhazardous side effect). Rifabutin favored over rifampin in patients with HIV infection due to less cytochrome P-450 stimulation.

**MECHANISM OF RESISTANCE**
Mutations reduce drug binding to RNA polymerase. Monotherapy rapidly leads to resistance.

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**
- *Mycobacterium tuberculosis*. The only agent used as solo prophylaxis against TB.

**TOXICITY**
- Neurotoxicity, hepatotoxicity. Pyridoxine (vitamin B₆) can prevent neurotoxicity. INH Injures Neurons and Hepatocytes.

**MECHANISM OF RESISTANCE**
- Mutations leading to underexpression of KatG.

### Pyrazinamide

**MECHANISM**
- Mechanism uncertain. Pyrazinamide is a prodrug that is converted to the active compound pyrazinoic acid.

**CLINICAL USE**
- *Mycobacterium tuberculosis*.

**TOXICITY**
- Hyperuricemia, hepatotoxicity.

### Ethambutol

**MECHANISM**
- ↓ carbohydrate polymerization of mycobacterium cell wall by blocking arabinosyltransferase.

**CLINICAL USE**
- *Mycobacterium tuberculosis*.

**TOXICITY**
- Optic neuropathy (red-green color blindness). Pronounce “eyethambutol.”

### Antimicrobial prophylaxis

<table>
<thead>
<tr>
<th>CLINICAL SCENARIO</th>
<th>MEDICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk for endocarditis and undergoing surgical or dental procedures</td>
<td>Amoxicillin</td>
</tr>
<tr>
<td>Exposure to gonorrhea</td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td>History of recurrent UTIs</td>
<td>TMP-SMX</td>
</tr>
<tr>
<td>Exposure to meningococcal infection</td>
<td>Ceftriaxone, ciprofloxacin, or rifampin</td>
</tr>
<tr>
<td>Pregnant woman carrying group B strep</td>
<td>Penicillin G</td>
</tr>
<tr>
<td>Prevention of gonococcal conjunctivitis in newborn</td>
<td>Erythromycin ointment</td>
</tr>
<tr>
<td>Prevention of postsurgical infection due to <em>S. aureus</em></td>
<td>Cefazolin</td>
</tr>
<tr>
<td>Prophylaxis of strep pharyngitis in child with prior rheumatic fever</td>
<td>Benzathine penicillin G or oral penicillin V</td>
</tr>
<tr>
<td>Exposure to syphilis</td>
<td>Benzathine penicillin G</td>
</tr>
</tbody>
</table>
Prophylaxis in HIV patients

<table>
<thead>
<tr>
<th>CELL COUNT</th>
<th>PROPHYLAXIS</th>
<th>INFECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 &lt; 200 cells/mm³</td>
<td>TMP-SMX</td>
<td>Pneumocystis pneumonia</td>
</tr>
<tr>
<td>CD4 &lt; 100 cells/mm³</td>
<td>TMP-SMX</td>
<td>Pneumocystis pneumonia and toxoplasmosis</td>
</tr>
<tr>
<td>CD4 &lt; 50 cells/mm³</td>
<td>Azithromycin or clarithromycin</td>
<td>Mycobacterium avium complex</td>
</tr>
</tbody>
</table>

Treatment of highly resistant bacteria

MRSA: vancomycin, daptomycin, linezolid, tigecycline, ceftaroline.

VRE: linezolid and streptogramins (quinupristin, dalfopristin).

Multidrug-resistant *P. aeruginosa*, multidrug-resistant *Acinetobacter baumannii*: polymyxins B and E (colistin).

Antifungal therapy

**LANOSTEROL SYNTHESIS**
- Terbinafine

**ERGOSTEROL SYNTHESIS**
- Azoles (Clotrimazole, Fluconazole, Itraconazole, Ketoconazole, Miconazole, Voriconazole)

**CELL WALL SYNTHESIS**
- Echinocandins (Anidulafungin, Caspofungin, Micafungin)

**FUNGAL CELL**
- Squalene epoxidase
- Squalene
- 14α-demethylase
- Ergosterol
- Cell wall

**CELL WALL SYNTHESIS**
- Polymyxins B and E (colistin)
- Polyenes (Amphotericin B, Nystatin)

**NUCLEIC ACID SYNTHESIS**
- Flucytosine

**Amphotericin B**

**MECHANISM**
Binds ergosterol (unique to fungi); forms membrane pores that allow leakage of electrolytes.

**CLINICAL USE**

**TOXICITY**
Fever/chills (“shake and bake”), hypotension, nephrotoxicity, arrhythmias, anemia, IV phlebitis (“*amphoterrible*”). Hydration ↓ nephrotoxicity. Liposomal amphotericin ↓ toxicity.
<table>
<thead>
<tr>
<th><strong>Nystatin</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECHANISM</strong></td>
<td>Same as amphotericin B. Topical use only as too toxic for systemic use.</td>
</tr>
<tr>
<td><strong>CLINICAL USE</strong></td>
<td>“Swish and swallow” for oral candidiasis (thrush); topical for diaper rash or vaginal candidiasis.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Flucytosine</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECHANISM</strong></td>
<td>Inhibits DNA and RNA biosynthesis by conversion to 5-fluorouracil by cytosine deaminase.</td>
</tr>
<tr>
<td><strong>CLINICAL USE</strong></td>
<td>Systemic fungal infections (especially meningitis caused by Cryptococcus) in combination with amphotericin B.</td>
</tr>
<tr>
<td><strong>TOXICITY</strong></td>
<td>Bone marrow suppression.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th><strong>Terbinafine</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECHANISM</strong></td>
<td>Inhibits the fungal enzyme squalene epoxidase.</td>
</tr>
<tr>
<td><strong>CLINICAL USE</strong></td>
<td>Dermatophytoses (especially onychomycosis—fungal infection of finger or toe nails).</td>
</tr>
<tr>
<td><strong>TOXICITY</strong></td>
<td>GI upset, headaches, hepatotoxicity, taste disturbance.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Echinocandins</strong></th>
<th>Anidulafungin, caspofungin, micafungin.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECHANISM</strong></td>
<td>Inhibit cell wall synthesis by inhibiting synthesis of β-glucan.</td>
</tr>
<tr>
<td><strong>CLINICAL USE</strong></td>
<td>Invasive aspergillosis, Candida.</td>
</tr>
<tr>
<td><strong>TOXICITY</strong></td>
<td>GI upset, flushing (by histamine release).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Griseofulvin</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECHANISM</strong></td>
<td>Interferes with microtubule function; disrupts mitosis. Deposits in keratin-containing tissues (e.g., nails).</td>
</tr>
<tr>
<td><strong>CLINICAL USE</strong></td>
<td>Oral treatment of superficial infections; inhibits growth of dermatophytes (tinea, ringworm).</td>
</tr>
<tr>
<td><strong>TOXICITY</strong></td>
<td>Teratogenic, carcinogenic, confusion, headaches, ↑ cytochrome P-450 and warfarin metabolism.</td>
</tr>
</tbody>
</table>

| **Antiprotozoan therapy** | Pyrimethamine (toxoplasmosis), suramin and melarsoprol (Trypanosoma brucei), nifurtimox (T. cruzi), sodium stibogluconate (leishmaniasis). |
**Anti-mite/louse therapy**

Permethrin (blocks Na⁺ channels → neurotoxicity), malathion (acetylcholinesterase inhibitor), lindane (blocks GABA channels → neurotoxicity). 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 U.S. (quinine elsewhere) or artesunate.

**TOXICITY**
Retinopathy; pruritus (especially in dark-skinned individuals).

**Antihelminthic therapy**

Mebendazole, pyrantel pamoate, ivermectin, diethylcarbamazine, praziquantel.

**Antiviral therapy**
**Oseltamivir, zanamivir**

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

**Acyclovir, famciclovir, valacyclovir**

| MECHANISM | Guanosine analogs. Monophosphorylated by HSV/VZV thymidine kinase and not phosphorylated in uninfected cells → few adverse effects. Triphosphate formed by cellular enzymes. Preferentially inhibit viral DNA polymerase by chain termination. |
| CLINICAL USE | HSV and VZV. Weak activity against EBV. No activity against CMV. Used for HSV-induced mucocutaneous and genital lesions as well as for encephalitis. Prophylaxis in immunocompromised patients. No effect on latent forms of HSV and VZV. Valacyclovir, a prodrug of acyclovir, has better oral bioavailability. For herpes zoster, use famciclovir. |
| TOXICITY | Obstructive crystalline nephropathy and acute renal failure if not adequately hydrated. |
| MECHANISM OF RESISTANCE | Mutated viral thymidine kinase. |

**Ganciclovir**

| MECHANISM | 5′-monophosphate formed by a CMV viral kinase. Guanosine analog. Triphosphate formed by cellular kinases. Preferentially inhibits viral DNA polymerase. Preferentially inhibit viral DNA polymerase by chain termination. |
| CLINICAL USE | CMV, especially in immunocompromised patients. Valganciclovir, a prodrug of ganciclovir, has better oral bioavailability. |
| TOXICITY | 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 activation by viral kinase. |
| CLINICAL USE | CMV retinitis in immunocompromised patients when ganciclovir fails; acyclovir-resistant HSV. |
| TOXICITY | Nephrotoxicity, electrolyte abnormalities (hypo- or hypercalcemia, hypo- or hyperphosphatemia, hypokalemia, hypomagnesemia) can lead to seizures. |
| MECHANISM OF RESISTANCE | Mutated DNA polymerase. |

**Foscarnet** = pyrophosphate analog.
**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.

**TOXICITY**
Nephrotoxicity (coadminister with probenecid and IV saline to ↓ toxicity).

---

**HIV therapy**
Highly active antiretroviral therapy (HAART): often initiated at the time of HIV diagnosis. Strongest indication for patients presenting with AIDS-defining illness, low CD4+ cell counts (< 500 cells/mm³), or high viral load. Regimen consists of 3 drugs to prevent resistance: 2 NRTIs and 1 of the following: NNRTI or protease inhibitor or integrase inhibitor.

**DRUG**
- Abacavir (ABC)
- Didanosine (ddI)
- Emtricitabine ( FTC)
- Lamivudine (3TC)
- Stavudine (d4T)
- Tenofovir (TDF)
- Zidovudine (ZDV, formerly AZT)

**NRTIs**
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 and need to be phosphorylated to be active.

- Abacavir (ABC)
- Didanosine (ddI)
- Emtricitabine (FTC)
- Lamivudine (3TC)
- Stavudine (d4T)
- Tenofovir (TDF)
- Zidovudine (ZDV, formerly AZT)

- Have you dined (vudine) with my nuclear (nucleosides) family?

**NNRTIs**
Bind to reverse transcriptase at site different from NRTIs. Do not require phosphorylation to be active or compete with nucleotides.

- Delavirdine
- Efavirenz
- Nevirapine

Rash and hepatotoxicity are common to all NNRTIs. Vivid dreams and CNS symptoms are common with efavirenz. Delavirdine and efavirenz are contraindicated in pregnancy.

**Integrase inhibitors**
Inhibits HIV genome integration into host cell chromosome by reversibly inhibiting HIV integrase.

- Raltegravir

↑ creatine kinase.

**Fusion inhibitors**
Binds gp41, inhibiting viral entry.

- Enfuvirtide
- Maraviroc

Skin reaction at injection sites.
Interferons

**MECHANISM**
Glycoproteins normally synthesized by virus-infected cells, exhibiting a wide range of antiviral and antitumoral properties.

**CLINICAL USE**
- IFN-β: multiple sclerosis.
- IFN-γ: chronic granulomatous disease.

**TOXICITY**
Neutropenia, myopathy.

---

**Hepatitis C therapy**

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

---

**Infection control techniques**
Goals include the reduction of pathogenic organism counts to safe levels (disinfection) and the inactivation of self-propagating biological entities (sterilization).

- **Autoclave**
  Pressurized steam at > 120°C. May be sporicidal.

- **Alcohols**
  Denature proteins and disrupt cell membranes. Not sporicidal.

- **Chlorhexidine**
  Denatures proteins and disrupts cell membranes. Not sporicidal.

- **Hydrogen peroxide**
  Free radical oxidation. Sporicidal.

- **Iodine and iodophors**
  Halogenation of DNA, RNA, and proteins. May be sporicidal.

---

**Antibiotics to avoid in pregnancy**

<table>
<thead>
<tr>
<th>ANTIBiotic</th>
<th>ADVERSE EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonamides</td>
<td>Kernicterus</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Otoxicity</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Cartilage damage</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Embryotoxic</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Discolored teeth, inhibition of bone growth</td>
</tr>
<tr>
<td>Ribavirin (antiviral)</td>
<td>Teratogenic</td>
</tr>
<tr>
<td>Griseofulvin (antifungal)</td>
<td>Teratogenic</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Gray baby syndrome</td>
</tr>
<tr>
<td><strong>SAFE Children Take Really Good Care.</strong></td>
<td></td>
</tr>
</tbody>
</table>
HIGH-YIELD PRINCIPLES IN

Immunology

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

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

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

**Lymph node**
A 2° lymphoid organ that has many afferents, 1 or more efferents. Encapsulated, with trabeculae. Functions are nonspecific filtration by macrophages, storage of B and T cells, and immune response activation.

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

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

**Paracortex**
Houses T cells. Region of cortex between follicles and medulla. Contains high endothelial venules through which T and B cells enter from blood. Not well developed in patients with DiGeorge syndrome.

**Lymph Drainage**

<table>
<thead>
<tr>
<th>Lymph Node Cluster</th>
<th>Area of Body Drained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>Head and neck</td>
</tr>
<tr>
<td>Hilar</td>
<td>Lungs</td>
</tr>
<tr>
<td>Mediastinal</td>
<td>Trachea and esophagus</td>
</tr>
<tr>
<td>Axillary</td>
<td>Upper limb, breast, skin above umbilicus</td>
</tr>
<tr>
<td>Celiac</td>
<td>Liver, stomach, spleen, pancreas, upper duodenum</td>
</tr>
<tr>
<td>Superior mesenteric</td>
<td>Lower duodenum, jejunum, ileum, colon to splenic flexure</td>
</tr>
<tr>
<td>Inferior mesenteric</td>
<td>Colon from splenic flexure to upper rectum</td>
</tr>
<tr>
<td>Internal iliac</td>
<td>Lower rectum to anal canal (above pectinate line), bladder, vagina (middle third), prostate</td>
</tr>
<tr>
<td>Para-aortic</td>
<td>Testes, ovaries, kidneys, uterus</td>
</tr>
<tr>
<td>Superficial inguinal</td>
<td>Anal canal (below pectinate line), skin below umbilicus (except popliteal territory), scrotum</td>
</tr>
<tr>
<td>Popliteal</td>
<td>Dorsolateral foot, posterior calf</td>
</tr>
</tbody>
</table>

Paracortex enlarges in an extreme cellular immune response (e.g., viral infection).
Sinusoids of spleen

Long, vascular channels in red pulp with fenestrated “barrel hoop” basement membrane.

- T cells are found in the periarteriolar lymphatic sheath (PALS) within the white pulp of the spleen.
- B cells are found in follicles within the white pulp of the spleen.
- The marginal zone, in between the red pulp and white pulp, contains APCs and specialized B cells, and is where APCs capture blood-borne antigens for recognition by lymphocytes.

Macrophages found nearby in spleen remove encapsulated bacteria.

Splenic dysfunction (e.g., postsplenectomy, sickle cell disease): ↓ IgM → ↓ complement activation → ↓ C3b opsonization → ↑ susceptibility to encapsulated organisms (SHiNE SKS):

- Streptococcus pneumoniae
- Haemophilus influenzae type b
- Neisseria meningitidis
- Escherichia coli
- Salmonella spp.
- Klebsiella pneumoniae
- Group B Streptococci

Postsplenectomy:

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

Thymus

Site of T-cell differentiation and maturation. Encapsulated. Thymus is derived from the Third pharyngeal pouch. Lymphocytes of mesenchymal origin. Cortex is dense with immature T cells; medulla is pale with mature T cells and Hassall corpuscles containing epithelial reticular cells.

T cells = Thymus
B cells = Bone marrow
### Innate vs. Adaptive Immunity

<table>
<thead>
<tr>
<th></th>
<th>Innate Immunity</th>
<th>Adaptive Immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Components</strong></td>
<td>Neutrophils, macrophages, monocytes, dendritic cells, natural killer (NK) cells (lymphoid origin), complement</td>
<td>T cells, B cells, circulating antibodies</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Germline encoded</td>
<td>Variation through V(D)J recombination during lymphocyte development</td>
</tr>
<tr>
<td><strong>Resistance</strong></td>
<td>Resistance persists through generations; does not change within an organism's lifetime</td>
<td>Microbial resistance not heritable</td>
</tr>
<tr>
<td><strong>Response to Pathogens</strong></td>
<td>Nonspecific</td>
<td>Highly specific, refined over time</td>
</tr>
<tr>
<td></td>
<td>Occurs rapidly (minutes to hours)</td>
<td>Develops over long periods; memory response is faster and more robust</td>
</tr>
<tr>
<td><strong>Physical Barriers</strong></td>
<td>Epithelial tight junctions, mucus</td>
<td>—</td>
</tr>
<tr>
<td><strong>Secreted Proteins</strong></td>
<td>Lysozyme, complement, C-reactive protein (CRP), defensins</td>
<td>Immunoglobulins</td>
</tr>
<tr>
<td><strong>Key Features in Pathogen Recognition</strong></td>
<td>Toll-like receptors (TLRs): pattern recognition receptors that recognize pathogen-associated molecular patterns (PAMPs). Examples of PAMPs include LPS (gram-negative bacteria), flagellin (bacteria), ssRNA (viruses)</td>
<td>Memory cells: activated B and T cells; subsequent exposure to a previously encountered antigen → stronger, quicker immune response</td>
</tr>
</tbody>
</table>

### MHC I and II

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

<table>
<thead>
<tr>
<th></th>
<th>MHC I</th>
<th>MHC II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loc</strong></td>
<td>HLA-A, HLA-B, HLA-C</td>
<td>HLA-DR, HLA- DP, HLA-DQ</td>
</tr>
<tr>
<td><strong>Binding</strong></td>
<td>TCR and CD8</td>
<td>TCR and CD4</td>
</tr>
<tr>
<td><strong>Expression</strong></td>
<td>Expressed on all nucleated cells</td>
<td>Expressed on APCs</td>
</tr>
<tr>
<td><strong>Function</strong></td>
<td>Present endogenously synthesized antigens (e.g., viral or cytosolic proteins) to CD8+ cytotoxic T cells</td>
<td>Present exogenously synthesized antigens (e.g., bacterial proteins) to CD4+ helper T cells</td>
</tr>
<tr>
<td><strong>Antigen Loading</strong></td>
<td>Antigen peptides loaded onto MHC I in RER after delivery via TAP (transporter associated with antigen processing)</td>
<td>Antigen loaded following release of invariant chain in an acidified endosome</td>
</tr>
<tr>
<td><strong>Associated Proteins</strong></td>
<td>$\beta_2$-microglobulin</td>
<td>Invariant chain</td>
</tr>
</tbody>
</table>

[Diagram of MHC class I and II]
HLA subtypes associated with diseases

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>A3</td>
<td>Hemochromatosis.</td>
</tr>
<tr>
<td>B27</td>
<td>Psoriatic arthritis, Ankylosing spondylitis, arthritis of inflammatory bowel disease, Reactive arthritis (formerly Reiter syndrome).</td>
</tr>
<tr>
<td>DQ2/DQ8</td>
<td>Celiac disease.</td>
</tr>
<tr>
<td>DR2</td>
<td>Multiple sclerosis, hay fever, SLE, Goodpasture syndrome.</td>
</tr>
<tr>
<td>DR3</td>
<td>Diabetes mellitus type 1, SLE, Graves disease, Hashimoto thyroiditis.</td>
</tr>
<tr>
<td>DR4</td>
<td>Rheumatoid arthritis, diabetes mellitus type 1. There are 4 walls in a “rheum” (room).</td>
</tr>
<tr>
<td>DR5</td>
<td>Pernicious anemia → vitamin B₁₂ deficiency, Hashimoto thyroiditis.</td>
</tr>
</tbody>
</table>

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

Major functions of B and T cells

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

T-cell functions
CD4+ T cells help B cells make antibodies and produce cytokines to recruit phagocytes and activate other leukocytes.
CD8+ T cells directly kill virus-infected cells.
Delayed cell-mediated hypersensitivity (type IV).
Acute and chronic cellular organ rejection.
Rule of 8: MHC II × CD4 = 8; MHC I × CD8 = 8.
**Differentiation of T cells**

- **Bone marrow** → **Thymus** → **Lymph node**
- **T-cell precursor**
- **CD4+CD8+ T cell**
- **CD4+ T cell**
- **CD8+ T cell**
- **Helper T cell**
- **Cytotoxic T cell**

**Positive selection**
- Thymic cortex. T cells expressing TCRs capable of binding surface self-MHC molecules survive.

**Negative selection**
- Medulla. T cells expressing TCRs with high affinity for self antigens undergo apoptosis.

**Helper T cells**

<table>
<thead>
<tr>
<th><strong>Th1 cell</strong></th>
<th><strong>Th2 cell</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Secretes IFN-γ</td>
<td>Secretes IL-4, IL-5, IL-10, IL-13</td>
</tr>
<tr>
<td>Activates macrophages and cytotoxic T cells</td>
<td>Recruits eosinophils for parasite defense and promotes IgE production by B cells</td>
</tr>
<tr>
<td>Activated by INF-γ and IL-12</td>
<td>Activated by IL-4</td>
</tr>
<tr>
<td>Inhibited by IL-4 and IL-10 (from Th2 cell)</td>
<td>Inhibited by IFN-γ (from Th1 cell)</td>
</tr>
</tbody>
</table>

Macrophage-lymphocyte interaction—macrophages release IL-12, which stimulates T cells to differentiate into Th1 cells. Th1 cells release IFN-γ to stimulate macrophages. Helper T cells have CD4, which binds to MHC II on APCs.

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

**Regulatory T cells**
- Help maintain specific immune tolerance by suppressing CD4 and CD8 T-cell effector functions.
- Identified by expression of CD3, CD4, CD25, and FOXP3.
- Activated regulatory T cells produce anti-inflammatory cytokines (e.g., IL-10, TGF-β).
**T- and B-cell activation**  
Antigen-presenting cells (APCs): B cells, macrophages, dendritic cells.  
Two signals are required for T-cell activation, B-cell activation, and class switching.

**Naive T-cell activation**  
1. Dendritic cell (specialized APC) samples and processes antigen.  
2. Dendritic cell migrates to the draining lymph node.  
3. Foreign antigen is presented on MHC II and recognized by TCR on Th (CD4+) cell. Antigen is presented on MHC I to Tc (CD8+) cell.  
4. “Costimulatory signal” is given by interaction of B7 and CD28 (signal 2).  
5. Th cell activates and produces cytokines. Tc cell activates and is able to recognize and kill virus-infected cell.

**B-cell activation and class switching**  
1. Th-cell activation as above.  
2. B-cell receptor–mediated endocytosis; foreign antigen is presented on MHC II and recognized by TCR on Th cell (signal 1).  
3. CD40 receptor on B cell binds CD40 ligand (CD40L) on Th cell (signal 2).  
4. Th cell secretes cytokines that determine Ig class switching of B cell. B cell activates and undergoes class switching, affinity maturation, and antibody production.
**Antibody structure and function**

Fab (variable) region 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 idiootype: unique antigen-binding pocket; only 1 antigenic specificity expressed per B cell

**Fc:**
- Constant
- Carboxy terminal
- Complement binding
- Carbohydrate side chains
- Determines isotype (IgM, IgD, etc.)

Antibody diversity is generated by:
- Random recombination of VJ (light-chain) or V(D)J (heavy-chain) genes
- Random combination of heavy chains with light chains
- Somatic hypermutation (following antigen stimulation)
- Addition of nucleotides to DNA during recombination by terminal deoxynucleotidyl transferase
### Immunoglobulin isotypes

Mature B cells express IgM and IgD on their surfaces. They may differentiate in germinal centers of lymph nodes by isotype switching (gene rearrangement; mediated by cytokines and CD40L) into plasma cells that secrete IgA, IgE, or IgG.

<table>
<thead>
<tr>
<th>Immunoglobulin isotypes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IgG</strong></td>
<td>Main antibody in 2° (delayed) response to an antigen. Most abundant isotype in serum. Fixes complement, crosses the placenta (provides infants with passive immunity), opsonizes bacteria, neutralizes bacterial toxins and viruses.</td>
</tr>
<tr>
<td><strong>IgA</strong></td>
<td>Prevents attachment of bacteria and viruses to mucous membranes; does not fix complement. Monomer (in circulation) or dimer (when secreted). Crosses epithelial cells by transcytosis. Produced in GI tract (e.g., by Peyer patches) and protects against gut infections (e.g., <em>Giardia</em>). 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 before secretion.</td>
</tr>
<tr>
<td><strong>IgM</strong></td>
<td>Produced in the 1° (immediate) response to an antigen. Fixes complement but does not cross the placenta. Antigen receptor on the surface of B cells. Monomer on B cell, pentamer when secreted. Pentamer enables avid binding to antigen while humoral response evolves.</td>
</tr>
<tr>
<td><strong>IgD</strong></td>
<td>Unclear function. Found on surface of many B cells and in serum.</td>
</tr>
<tr>
<td><strong>IgE</strong></td>
<td>Binds mast cells and basophils; cross-links when exposed to allergen, mediating immediate (type I) hypersensitivity through release of inflammatory mediators such as histamine. Mediates immunity to worms by activating eosinophils. Lowest concentration in serum.</td>
</tr>
</tbody>
</table>

### Antigen type and memory

<table>
<thead>
<tr>
<th>Antigen type and memory</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thymus-independent antigens</strong></td>
<td>Antigens lacking a peptide component (e.g., lipopolysaccharides from gram-negative bacteria); cannot be presented by MHC to T cells. Weakly or nonimmunogenic; vaccines often require boosters and adjuvants (e.g., pneumococcal polysaccharide vaccine).</td>
</tr>
<tr>
<td><strong>Thymus-dependent antigens</strong></td>
<td>Antigens containing a protein component (e.g., diphtheria vaccine). Class switching and immunologic memory occur as a result of direct contact of B cells with Th cells (CD40–CD40L interaction).</td>
</tr>
</tbody>
</table>

### Acute-phase reactants

Factors whose serum concentrations change significantly in response to inflammation; produced by the liver in both acute and chronic inflammatory states. Notably induced by IL-6.

#### POSITIVE (UPREGULATED)

<table>
<thead>
<tr>
<th>Acute-phase reactant</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactive protein</td>
<td>Opsonin; fixes complement and facilitates phagocytosis. Measured clinically as a sign of ongoing inflammation.</td>
</tr>
<tr>
<td>Ferritin</td>
<td>Binds and sequesters iron to inhibit microbial iron scavenging.</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Coagulation factor; promotes endothelial repair; correlates with ESR.</td>
</tr>
<tr>
<td>Hepcidin</td>
<td>Prevents release of iron bound by ferritin → anemia of chronic disease.</td>
</tr>
<tr>
<td>Serum amyloid A</td>
<td>Prolonged elevation can lead to amyloidosis.</td>
</tr>
</tbody>
</table>

#### NEGATIVE (DOWNREGULATED)

<table>
<thead>
<tr>
<th>Acute-phase reactant</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>Reduction conserves amino acids for positive reactants.</td>
</tr>
<tr>
<td>Transferrin</td>
<td>Internalized by macrophages to sequester iron.</td>
</tr>
</tbody>
</table>
Complement

System of hepatically synthesized plasma proteins that play a role in innate immunity and inflammation. Membrane attack complex (MAC) defends against gram-negative bacteria.

**ACTIVATION**
- **Classic** pathway—IgG or IgM mediated.
- **Alternative** pathway—microbe surface molecules.
- **Lectin** pathway—mannose or other sugars on microbe surface.
- **GM** makes **classic** cars.

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

**Opsonins**—C3b and IgG are the two 1° opsonins in bacterial defense; enhance phagocytosis. C3b also helps clear immune complexes.

**Inhibitors**—decay-accelerating factor (DAF, aka CD55) and C1 esterase inhibitor help prevent complement activation on self cells (e.g., RBCs).

**Complement disorders**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C1 esterase inhibitor deficiency</strong></td>
<td>Causes hereditary angioedema. ACE inhibitors are contraindicated.</td>
</tr>
<tr>
<td><strong>C3 deficiency</strong></td>
<td>Increases risk of severe, recurrent pyogenic sinus and respiratory tract infections; ↑ susceptibility to type III hypersensitivity reactions.</td>
</tr>
<tr>
<td><strong>C5–C9 deficiencies</strong></td>
<td>Terminal complement deficiency increases susceptibility to recurrent Neisseria bacteremia.</td>
</tr>
<tr>
<td><strong>DAF (GPI-anchored enzyme) deficiency</strong></td>
<td>Causes complement-mediated lysis of RBCs and paroxysmal nocturnal hemoglobinuria.</td>
</tr>
</tbody>
</table>
**Important cytokines**

**SECRETED BY MACROPHAGES**

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IL-1</strong></td>
<td>Also called osteoclast-activating factor. Causes fever, acute inflammation. Activates endothelium to express adhesion molecules. Induces chemokine secretion to recruit WBCs.</td>
</tr>
<tr>
<td><strong>IL-6</strong></td>
<td>Causes fever and stimulates production of acute-phase proteins.</td>
</tr>
<tr>
<td><strong>IL-8</strong></td>
<td>Major chemotactic factor for neutrophils.</td>
</tr>
<tr>
<td><strong>IL-12</strong></td>
<td>Induces differentiation of T cells into Th1 cells. Activates NK cells.</td>
</tr>
<tr>
<td><strong>TNF-α</strong></td>
<td>Mediates septic shock. Activates endothelium. Causes WBC recruitment, vascular leak.</td>
</tr>
</tbody>
</table>

**SECRETED BY ALL T CELLS**

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IL-2</strong></td>
<td>Stimulation of growth of helper, cytotoxic, and regulatory T cells, and NK cells.</td>
</tr>
<tr>
<td><strong>IL-3</strong></td>
<td>Supports growth and differentiation of bone marrow stem cells. Functions like GM-CSF.</td>
</tr>
</tbody>
</table>

**FROM TH1 CELLS**

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interferon-γ</strong></td>
<td>Secreted by NK cells in response to IL-12 from macrophages; stimulates macrophages to kill phagocytosed pathogens. Also activates NK cells to kill virus-infected cells. Increases MHC expression and antigen presentation by all cells.</td>
</tr>
</tbody>
</table>

**FROM TH2 CELLS**

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IL-4</strong></td>
<td>Induces differentiation into Th2 cells. Promotes growth of B cells. Enhances class switching to IgE and IgG.</td>
</tr>
<tr>
<td><strong>IL-5</strong></td>
<td>Promotes differentiation of B cells. Enhances class switching to IgA. Stimulates growth and differentiation of eosinophils.</td>
</tr>
<tr>
<td><strong>IL-10</strong></td>
<td>Modulates inflammatory response. Decreases expression of MHC class II and Th1 cytokines. Inhibits activated macrophages and dendritic cells. Also secreted by regulatory T cells. TGF-β and IL-10 both attenuate the immune response.</td>
</tr>
</tbody>
</table>
**Respiratory burst (oxidative burst)**

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

![Diagram of Respiratory Burst](image)

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 (e.g., *S. aureus*, *Aspergillus*) capable of neutralizing their own $H_2O_2$, leaving phagocytes without ROS for fighting infections. Pyocyanin of *P. aeruginosa* functions to generate ROS to kill competing microbes. Lactoferrin is a protein found in secretory fluids and neutrophils that inhibits microbial growth via iron chelation.

**Interferon α and β**

A part of innate host defense against both RNA and DNA viruses. Interferons are glycoproteins synthesized by virus-infected cells that act locally on uninfected cells, “priming them” for viral defense by helping to selectively degrade viral nucleic acid and protein. Essentially results in apoptosis, thereby disrupting viral amplification.
### Cell surface proteins

MHC I present on all nucleated cells (i.e., not mature RBCs).

<table>
<thead>
<tr>
<th><strong>T cells</strong></th>
<th>TCR (binds antigen-MHC complex)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CD3 (associated with TCR for signal transduction)</td>
</tr>
<tr>
<td></td>
<td>CD28 (binds B7 on APC)</td>
</tr>
<tr>
<td><strong>Helper T cells</strong></td>
<td>CD4, CD40L</td>
</tr>
<tr>
<td><strong>Cytotoxic T cells</strong></td>
<td>CD8</td>
</tr>
<tr>
<td><strong>Regulatory T cells</strong></td>
<td>CD4, CD25</td>
</tr>
<tr>
<td><strong>B cells</strong></td>
<td>Ig (binds antigen)</td>
</tr>
<tr>
<td></td>
<td>CD19, CD20, CD21 (receptor for EBV), CD40 MHC II, B7</td>
</tr>
<tr>
<td><strong>Macrophages</strong></td>
<td>CD14, CD40 MHC II, B7</td>
</tr>
<tr>
<td></td>
<td>Fc and C3b receptors (enhanced phagocytosis)</td>
</tr>
<tr>
<td><strong>NK cells</strong></td>
<td>CD16 (binds Fc of IgG), CD56 (unique marker for NK)</td>
</tr>
<tr>
<td><strong>Hematopoietic stem cells</strong></td>
<td>CD34</td>
</tr>
</tbody>
</table>

### Anergy

State during which a cell cannot become activated by exposure to its antigen. T and B cells become anergic when exposed to their antigen without costimulatory signal (signal 2). Another mechanism of self-tolerance.

### Effects of bacterial toxins

Superantigens (S. pyogenes and S. aureus)—cross-link the β region of the T-cell receptor to the MHC class II on APCs. Can activate any CD4+ T cell → massive release of cytokines. Endotoxins/lipopolysaccharide (gram-negative bacteria)—directly stimulate macrophages by binding to endotoxin receptor TLR4/CD14; Th cells are not involved.

### Antigenic variation

Classic examples:
- Bacteria—Salmonella (2 flagellar variants), Borrelia recurrentis (relapsing fever), N. gonorrhoeae (pilus protein)
- Viruses—influenza, HIV, HCV
- Parasites—trypanosomes

Some mechanisms for variation include DNA rearrangement and RNA segment reassortment (e.g., influenza major shift). You can drink Beer at the Bar when you're 21: B cells, Epstein-Barr virus, CD21.
# Passive vs. active immunity

<table>
<thead>
<tr>
<th>Passive</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Means of acquisition</strong></td>
<td>Receiving preformed antibodies</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Rapid</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Short span of antibodies (half-life = 3 weeks)</td>
</tr>
<tr>
<td><strong>Examples</strong></td>
<td>IgA in breast milk, maternal IgG crossing placenta, antitoxin, humanized monoclonal antibody</td>
</tr>
</tbody>
</table>

**Notes**: After exposure to 
- Tetanus toxin, 
- Botulinum toxin, 
- HBV, Varicella, or 
- Rabies virus, 
unvaccinated patients are given preformed antibodies (passive)—“To Be Healed Very Rapidly”

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.

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Description</th>
<th>Pros/Cons</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Live attenuated vaccine</strong></td>
<td>Microorganism loses its pathogenicity but retains capacity for transient growth within inoculated host. Induces cellular and humoral responses. MMR is the only live attenuated vaccine given to persons with HIV.</td>
<td>Pro: induces strong, often lifelong immunity. Con: may revert to virulent form. Often contraindicated in pregnancy and immunodeficiency.</td>
<td>Measles, mumps, rubella, polio (Sabin), influenza (intranasal), varicella, yellow fever.</td>
</tr>
<tr>
<td><strong>Inactivated or killed vaccine</strong></td>
<td>Pathogen is inactivated by heat or chemicals. Maintaining epitope structure on surface antigens is important for immune response. Mainly induces a humoral response.</td>
<td>Pro: safer than live vaccines. Con: weaker immune response; booster shots usually required.</td>
<td>Rabies, Influenza (injection), Polio (Salk), hepatitis A (“R.I.P. Always”).</td>
</tr>
</tbody>
</table>
Hypersensitivity types

**Type I**

Anaphylactic and atopic—free antigen cross-links IgE on presensitized mast cells and basophils, triggering immediate release of vasoactive amines that act at postcapillary venules (i.e., histamine). Reaction develops rapidly after antigen exposure because of preformed antibody. Delayed response follows due to production of arachidonic acid metabolites (e.g., leukotrienes).

*First (type) and Fast (anaphylaxis). Types I, II, and III are all antibody mediated. Test: skin test for specific IgE.*

**Type II**

Cytotoxic (antibody mediated)—IgM, IgG bind to fixed antigen on “enemy” cell → cellular destruction.

3 mechanisms:
- Opsonization and phagocytosis
- Complement- and Fc receptor–mediated inflammation
- Antibody-mediated cellular dysfunction

*Type II is cy-2-toxic. Antibody and complement lead to MAC. Direct and indirect Coombs’ tests: Direct—detects antibodies that have adhered to patient’s RBCs (e.g., test an Rh⊕ infant of an Rh⊖ mother). Indirect—detects serum antibodies that can adhere to other RBCs (e.g., test an Rh⊖ woman for Rh⊕ antibodies).*

**Type III**

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

*Serum sickness*—an immune complex disease in which antibodies to foreign proteins are produced (takes 5 days). Immune complexes form and are deposited in membranes, where they fix complement (leads to tissue damage). More common than Arthus reaction.

*Arthus reaction*—a local subacute antibody-mediated hypersensitivity reaction. Intradermal injection of antigen induces antibodies, which form antigen-antibody complexes in the skin. Characterized by edema, necrosis, and activation of complement.

**Type IV**

Delayed (T-cell–mediated) type—sensitized T cells encounter antigen and then release cytokines (leads to macrophage activation; no antibody involved).

*4th and last—delayed. Cell mediated; therefore, it is not transferable by serum. 4 T’s = T cells, Transplant rejections, T skin tests, Touching (contact dermatitis). Test: patch test, PPD.*

**ACID:**
- Anaphylactic and Atopic (type I)
- Cytotoxic (antibody mediated) (type II)
- Immune complex (type III)
- Delayed (cell mediated) (type IV)
## Hypersensitivity disorders

<table>
<thead>
<tr>
<th>REACTION</th>
<th>EXAMPLES</th>
<th>PRESENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type I</strong></td>
<td>Allergic and atopic disorders (e.g., rhinitis, hay fever, eczema, hives, asthma) Anaphylaxis (e.g., bee sting, some food/drug allergies)</td>
<td>Immediate, anaphylactic, atopic</td>
</tr>
<tr>
<td><strong>Type II</strong></td>
<td>Acute hemolytic transfusion reactions Autoimmune hemolytic anemia Bullous pemphigoid Erythroblastosis fetalis Goodpasture syndrome Graves disease Guillain-Barré syndrome Idiopathic thromocytopenic purpura Myasthenia gravis Pemphigus vulgaris Pernicious anemia Rheumatic fever</td>
<td>Disease tends to be specific to tissue or site where antigen is found</td>
</tr>
<tr>
<td><strong>Type III</strong></td>
<td>Arthus reaction (e.g., swelling and inflammation following tetanus vaccine) SLE Polyarteritis nodosa Poststreptococcal glomerulonephritis Serum sickness</td>
<td>Can be associated with vasculitis and systemic manifestations</td>
</tr>
<tr>
<td><strong>Type IV</strong></td>
<td>Contact dermatitis (e.g., poison ivy, nickel allergy) Graft-versus-host disease Multiple sclerosis PPD (test for <em>M. tuberculosis</em>)</td>
<td>Response is delayed and does not involve antibodies (vs. types I, II, and III)</td>
</tr>
</tbody>
</table>

## Blood transfusion reactions

<table>
<thead>
<tr>
<th>TYPE</th>
<th>PATHOGENESIS</th>
<th>CLINICAL PRESENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allergic reaction</strong></td>
<td>Type I hypersensitivity reaction against plasma proteins in transfused blood.</td>
<td>Urticaria, pruritus, wheezing, fever. Treat with antihistamines.</td>
</tr>
<tr>
<td><strong>Anaphylactic reaction</strong></td>
<td>Severe allergic reaction. IgA-deficient individuals must receive blood products without IgA.</td>
<td>Dyspnea, bronchospasm, hypotension, respiratory arrest, shock. Treat with epinephrine.</td>
</tr>
<tr>
<td><strong>Febrile nonhemolytic transfusion reaction</strong></td>
<td>Type II hypersensitivity reaction. Host antibodies against donor HLA antigens and WBCs.</td>
<td>Fever, headaches, chills, flushing.</td>
</tr>
<tr>
<td><strong>Acute hemolytic transfusion reaction</strong></td>
<td>Type II hypersensitivity reaction. Intravascular hemolysis (ABO blood group incompatibility) or extravascular hemolysis (host antibody reaction against foreign antigen on donor RBCs).</td>
<td>Fever, hypotension, tachypnea, tachycardia, flank pain, hemoglobinuria (intravascular hemolysis), jaundice (extravascular).</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>Associated Disorder</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>----------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Anti-ACh receptor</td>
<td>Myasthenia gravis</td>
<td></td>
</tr>
<tr>
<td>Anti-basement membrane</td>
<td>Goodpasture syndrome</td>
<td></td>
</tr>
<tr>
<td>Anti-cardiolipin, lupus anticoagulant</td>
<td>SLE, antiphospholipid syndrome</td>
<td></td>
</tr>
<tr>
<td>Anticentromere</td>
<td>Limited scleroderma (CREST syndrome)</td>
<td></td>
</tr>
<tr>
<td>Anti-desmosome (anti-desmoglein)</td>
<td>Pemphigus vulgaris</td>
<td></td>
</tr>
<tr>
<td>Anti-dsDNA, anti-Smith</td>
<td>SLE</td>
<td></td>
</tr>
<tr>
<td>Anti-glutamic acid decarboxylase (GAD-65)</td>
<td>Type 1 diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>Antihemidesmosome</td>
<td>Bullous pemphigoid</td>
<td></td>
</tr>
<tr>
<td>Anti-histone</td>
<td>Drug-induced lupus</td>
<td></td>
</tr>
<tr>
<td>Anti-Jo-1, anti-SRP, anti-Mi-2</td>
<td>Polymyositis, dermatomyositis</td>
<td></td>
</tr>
<tr>
<td>Antimicrosomal, antithyroglobulin</td>
<td>Hashimoto thyroiditis</td>
<td></td>
</tr>
<tr>
<td>Antimitochondrial</td>
<td>1° biliary cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Antinuclear antibodies</td>
<td>SLE, nonspecific</td>
<td></td>
</tr>
<tr>
<td>Antiparietal cell</td>
<td>Pernicious anemia</td>
<td></td>
</tr>
<tr>
<td>Anti-Scl-70 (anti-DNA topoisomerase I)</td>
<td>Scleroderma (diffuse)</td>
<td></td>
</tr>
<tr>
<td>Anti-smooth muscle</td>
<td>Autoimmune hepatitis</td>
<td></td>
</tr>
<tr>
<td>Anti-SSA, anti-SSB (anti-Ro, anti-La)</td>
<td>Sjögren syndrome</td>
<td></td>
</tr>
<tr>
<td>Anti-TSH receptor</td>
<td>Graves disease</td>
<td></td>
</tr>
<tr>
<td>Anti-U1 RNP (ribonucleoprotein)</td>
<td>Mixed connective tissue disease</td>
<td></td>
</tr>
<tr>
<td>IgA anti-endomysial, IgA anti-tissue</td>
<td>Celiac disease</td>
<td></td>
</tr>
<tr>
<td>transglutaminase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPO-ANCA/p-ANCA</td>
<td>Microscopic polyangiitis, eosinophilic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>granulomatosis with polyangiitis (Churg-Strauss syndrome)</td>
<td></td>
</tr>
<tr>
<td>PR3-ANCA/c-ANCA</td>
<td>Granulomatosis with polyangiitis (Wegener)</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid factor (IgM antibody that targets IgG Fc region), anti-CCP (more specific)</td>
<td>Rheumatoid arthritis</td>
<td></td>
</tr>
<tr>
<td><strong>Immunodeficiencies</strong></td>
<td><strong>DEFECT</strong></td>
<td><strong>PRESENTATION</strong></td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------</td>
<td>-----------------</td>
</tr>
<tr>
<td><strong>B-cell disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>X-linked (Bruton) agammaglobulinemia</strong></td>
<td>Defect in BTK, a tyrosine kinase gene → no B-cell maturation. X-linked recessive († in Boys).</td>
<td>Recurrent bacterial and enteroviral infections after 6 months († maternal IgG).</td>
</tr>
<tr>
<td><strong>Selective IgA deficiency</strong></td>
<td>Unknown. Most common 1° immunodeficiency.</td>
<td>Majority Asymptomatic. Can see Airway and GI infections, Autoimmune disease, Atopy, Anaphylaxis to IgA-containing products.</td>
</tr>
<tr>
<td><strong>Common variable immunodeficiency</strong></td>
<td>Defect in B-cell differentiation. Many causes.</td>
<td>Can be acquired in 20s–30s; † risk of autoimmune disease, bronchiectasis, lymphoma, sinopulmonary infections.</td>
</tr>
<tr>
<td><strong>T-cell disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Thymic aplasia (DiGeorge syndrome)</strong></td>
<td>22q11 deletion; failure to develop 3rd and 4th pharyngeal pouches → absent thymus and parathyroids.</td>
<td>Tetany (hypocalcemia), recurrent viral/fungal infections (T-cell deficiency), conotruncal abnormalities (e.g., tetralogy of Fallot, truncus arteriosus).</td>
</tr>
<tr>
<td><strong>IL-12 receptor deficiency</strong></td>
<td>† Th1 response. Autosomal recessive.</td>
<td>Disseminated mycobacterial and fungal infections; may present after administration of BCG vaccine.</td>
</tr>
<tr>
<td><strong>Autosomal dominant hyper-IgE syndrome (Job syndrome)</strong></td>
<td>Deficiency of Th17 cells due to STAT3 mutation → impaired recruitment of neutrophils to sites of infection.</td>
<td>FATED: coarse Facies, cold (noninflamed) staphylococcal Abscesses, retained primary Tc teeth, † IgE, Dermatologic problems (eczema).</td>
</tr>
</tbody>
</table>
### Immunodeficiencies (continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Defect</th>
<th>Presentation</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B- and T-cell disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Severe combined immunodeficiency (SCID)</strong></td>
<td>Several types including defective IL-2R gamma chain (most common, X-linked), adenosine deaminase deficiency (autosomal recessive).</td>
<td>Failure to thrive, chronic diarrhea, thrush. Recurrent viral, bacterial, fungal, and protozoal infections. Treatment: bone marrow transplant (no concern for rejection).</td>
<td>† T-cell receptor excision circles (TRECs). Absence of thymic shadow (CXR), germinal centers (lymph node biopsy), and T cells (flow cytometry).</td>
</tr>
<tr>
<td><strong>Ataxia-telangiectasia</strong></td>
<td>Defects in ATM gene → failure to repair DNA double strand breaks → cell cycle arrest.</td>
<td>Triad: cerebellar defects (Ataxia), spider Angiomas (telangiectasia), IgA deficiency.</td>
<td>† AFP.</td>
</tr>
<tr>
<td><strong>Hyper-IgM syndrome</strong></td>
<td>Most commonly due to defective CD40L on Th cells → class switching defect; X-linked recessive.</td>
<td>Severe pyogenic infections early in life; opportunistic infection with <em>Pneumocystis</em>, <em>Cryptosporidium</em>, CMV.</td>
<td>† IgG.</td>
</tr>
<tr>
<td><strong>Wiskott-Aldrich syndrome</strong></td>
<td>Mutation in WAS gene (X-linked recessive); T cells unable to reorganize actin cytoskeleton.</td>
<td><strong>WATER</strong>: Wiskott-Aldrich: Thrombocytopenic purpura, Eczema, Recurrent infections.</td>
<td>† to normal IgG, IgM.</td>
</tr>
<tr>
<td><strong>Phagocyte dysfunction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Leukocyte adhesion deficiency (type 1)</strong></td>
<td>Defect in LFA-1 integrin (CD18) protein on phagocytes; impaired migration and chemotaxis; autosomal recessive.</td>
<td>Recurrent bacterial skin and mucosal infections, absent pus formation, impaired wound healing, delayed separation of umbilical cord (&gt; 30 days).</td>
<td>† neutrophils. Absence of neutrophils at infection sites.</td>
</tr>
<tr>
<td><strong>Chronic granulomatous disease</strong></td>
<td>Defect of NADPH oxidase → reactive oxygen species (e.g., superoxide) and respiratory burst in neutrophils; X-linked recessive most common.</td>
<td>† susceptibility to catalase organisms (Need PLACESS): <em>Nocardia</em>, <em>Pseudomonas</em>, <em>Listeria</em>, <em>Aspergillus</em>, <em>Candida</em>, <em>E. coli</em>, <em>S. aureus</em>, <em>Serratia</em>.</td>
<td>Abnormal dihydrorhodamine (flow cytometry) test. Nitroblue tetrazolium dye reduction test is ⊗.</td>
</tr>
</tbody>
</table>
### Infections in immunodeficiency

<table>
<thead>
<tr>
<th>PATHOGEN</th>
<th>↓ T CELLS</th>
<th>↓ B CELLS</th>
<th>↓ GRANULOCYTES</th>
<th>↓ COMPLEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria</strong></td>
<td>Sepsis</td>
<td>Encapsulated: Staphylococcus <em>pneumoniae</em>, <em>Haemophilus influenzae</em> type B, <em>Neisseria meningitidis</em>, <em>Escherichia coli</em>, <em>Salmonella</em>, <em>Klebsiella pneumoniae</em>, group B <em>Strep</em> (HiNE SKiS)</td>
<td>Staphylococcus, <em>Burkholderia cepacia</em>, <em>Pseudomonas aeruginosa</em>, <em>Serratia</em>, <em>Nocardia</em></td>
<td>Encapsulated species with early component deficiencies <em>Neisseria</em> with late component (MAC) deficiencies</td>
</tr>
<tr>
<td><strong>Viruses</strong></td>
<td>CMV, EBV, JCV, VZV, chronic infection with respiratory/GI viruses</td>
<td>Enteroviral encephalitis, poliovirus (live vaccine contraindicated)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Fungi/parasites</strong></td>
<td><em>Candida</em> (local), PCP GI giardiasis (no IgA)</td>
<td><em>Candida</em> (systemic), <em>Aspergillus</em></td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autograft</td>
<td>From self.</td>
</tr>
<tr>
<td>Syngeneic graft (isograft)</td>
<td>From identical twin or clone.</td>
</tr>
<tr>
<td>Allograft</td>
<td>From nonidentical individual of same species.</td>
</tr>
<tr>
<td>Xenograft</td>
<td>From different species.</td>
</tr>
</tbody>
</table>

## Transplant rejection

<table>
<thead>
<tr>
<th>Type of Rejection</th>
<th>Onset</th>
<th>Pathogenesis</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute</td>
<td>Within minutes</td>
<td>Pre-existing recipient antibodies react to donor antigen (type II hypersensitivity reaction), activate complement.</td>
<td>Widespread thrombosis of graft vessels → ischemia/necrosis. Graft must be removed.</td>
</tr>
<tr>
<td>Acute</td>
<td>Weeks to months</td>
<td>Cellular: CD8+ T cells activated against donor MHCs. Humoral: similar to hyperacute, except antibodies develop after transplant.</td>
<td>Vasculitis of graft vessels with dense interstitial lymphocytic infiltrate. Prevent/reverse with immunosuppressants.</td>
</tr>
<tr>
<td>Chronic</td>
<td>Months to years</td>
<td>CD4+ T cells respond to recipient APCs presenting donor peptides, including allogeneic MHC. Both cellular and humoral components.</td>
<td>Recipient T cells react and secrete cytokines → proliferation of vascular smooth muscle and parenchymal fibrosis. Dominated by arteriosclerosis.</td>
</tr>
</tbody>
</table>
### Immunosuppressants

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Use</th>
<th>Toxicity</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine</td>
<td>Calcineurin inhibitor; binds cyclophilin. Blocks T-cell activation by preventing IL-2 transcription.</td>
<td>Transplant rejection prophylaxis, psoriasis, rheumatoid arthritis.</td>
<td>Nephrotoxicity, hypertension, hyperlipidemia, neurotoxicity, gingival hyperplasia, hirsutism.</td>
<td>Both calcineurin inhibitors are highly nephrotoxic.</td>
</tr>
<tr>
<td>Tacrolimus (FK506)</td>
<td>Calcineurin inhibitor; binds FK506 binding protein (FKBP). Blocks T-cell activation by preventing IL-2 transcription.</td>
<td>Transplant rejection prophylaxis.</td>
<td>Similar to cyclosporine, ↑ risk of diabetes and neurotoxicity; no gingival hyperplasia or hirsutism.</td>
<td></td>
</tr>
<tr>
<td>Sirolimus (Rapamycin)</td>
<td>mTOR inhibitor; binds FKBP. Blocks T-cell activation and B-cell differentiation by preventing response to IL-2.</td>
<td>Kidney transplant rejection prophylaxis.</td>
<td>Anemia, thrombocytopenia, leukopenia, insulin resistance, hyperlipidemia; not nephrotoxic.</td>
<td>Kidney “sir-vides.” Synergistic with cyclosporine. Also used in drug-eluting stents.</td>
</tr>
<tr>
<td>Daclizumab, basiliximab</td>
<td>Monoclonal antibodies; block IL-2R.</td>
<td>Kidney transplant rejection prophylaxis.</td>
<td>Edema, hypertension, tremor.</td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Antimetabolite precursor of 6-mercaptopurine. Inhibits lymphocyte proliferation by blocking nucleotide synthesis.</td>
<td>Transplant rejection prophylaxis, rheumatoid arthritis, Crohn disease, glomerulonephritis, other autoimmune conditions.</td>
<td>Leukopenia, anemia, thrombocytopenia.</td>
<td>6-MP degraded by xanthine oxidase; toxicity ↑ by allopurinol. Pronounce “azathiopurine.”</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Inhibit NF-κB. Suppress both B- and T-cell function by ↓ transcription of many cytokines.</td>
<td>Transplant rejection prophylaxis (immunosuppression), many autoimmune disorders, inflammation.</td>
<td>Hyperglycemia, osteoporosis, central obesity, muscle breakdown, psychosis, acne, hypertension, cataracts, avascular necrosis.</td>
<td>Can cause iatrogenic Cushing syndrome.</td>
</tr>
</tbody>
</table>
Immunosuppression targets

Recombinant cytokines and clinical uses

<table>
<thead>
<tr>
<th>AGENT</th>
<th>CLINICAL USES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldesleukin (IL-2)</td>
<td>Renal cell carcinoma, metastatic melanoma</td>
</tr>
<tr>
<td>Epoetin alfa (erythropoietin)</td>
<td>Anemias (especially in renal failure)</td>
</tr>
<tr>
<td>Filgrastim (G-CSF)</td>
<td>Recovery of bone marrow</td>
</tr>
<tr>
<td>Sargramostim (GM-CSF)</td>
<td>Recovery of bone marrow</td>
</tr>
<tr>
<td>IFN-α</td>
<td>Chronic hepatitis B and C, Kaposi sarcoma, malignant melanoma</td>
</tr>
<tr>
<td>IFN-β</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>Chronic granulomatous disease</td>
</tr>
<tr>
<td>Romiplostim, eltrombopag</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Oprelvekin (IL-11)</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Therapeutic antibodies</td>
<td>TARGET</td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------</td>
</tr>
<tr>
<td><strong>Cancer therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>CD52</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>VEGF</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>EGFR</td>
</tr>
<tr>
<td>Rituximab</td>
<td>CD20</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>HER2/neu</td>
</tr>
<tr>
<td><strong>Autoimmune disease therapy</strong></td>
<td>Soluble TNF-α</td>
</tr>
<tr>
<td>Eculizumab</td>
<td>Complement protein C5</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>α4-integrin</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td>Abciximab</td>
<td>Platelet glycoproteins IIb/IIIa</td>
</tr>
<tr>
<td>Denosumab</td>
<td>RANKL</td>
</tr>
<tr>
<td>Digoxin immune Fab</td>
<td>Digoxin</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>IgE</td>
</tr>
<tr>
<td>Palivizumab</td>
<td>RSV F protein</td>
</tr>
<tr>
<td>Ranibizumab, bevacizumab</td>
<td>VEGF</td>
</tr>
</tbody>
</table>
“Digressions, objections, delight in mockery, carefree mistrust are signs of health; everything unconditional belongs in pathology.”
—Friedrich Nietzsche

The fundamental principles of pathology are key to understanding diseases in all organ systems. Major topics such as inflammation and neoplasia appear frequently in questions across different organ systems, and such topics are definitely high yield. For example, the concepts of cell injury and inflammation are key to understanding the inflammatory response that follows myocardial infarction, a very common subject of board questions. Similarly, a familiarity with the early cellular changes that culminate in the development of neoplasias—for example, esophageal or colon cancer—is critical. Finally, make sure you recognize the major tumor-associated genes and are comfortable with key cancer concepts such as tumor staging and metastasis.
Apoptosis

Programmed cell death; ATP required. Intrinsic or extrinsic pathway; both pathways → activation of cytosolic caspases that mediate cellular breakdown. No significant inflammation (unlike necrosis).

Characterized by deeply eosinophilic cytoplasm, cell shrinkage, nuclear shrinkage (pyknosis) and basophilia, membrane blebbing, nuclear fragmentation (karyorrhexis), and formation of apoptotic bodies, which are then phagocytosed.

DNA laddering is a sensitive indicator of apoptosis; during karyorrhexis, endonucleases cleave at internucleosomal regions, yielding fragments in multiples of 180 bp. Radiation therapy causes apoptosis of tumors and surrounding tissue via free radical formation and dsDNA breakage. Rapidly dividing cells (e.g., skin, GI mucosa) are very susceptible to radiation therapy–induced apoptosis.

Intrinsic pathway

Involved in tissue remodeling in embryogenesis. Occurs when a regulating factor is withdrawn from a proliferating cell population (e.g., IL-2 after a completed immunologic reaction → apoptosis of proliferating effector cells). Also occurs after exposure to injurious stimuli (e.g., radiation, toxins, hypoxia).

Changes in proportions of anti- and pro-apoptotic factors → mitochondrial permeability and cytochrome c release. BAX and BAK are proapoptotic proteins; Bcl-2 is antiapoptotic.

Bcl-2 prevents cytochrome c release by binding to and inhibiting Apaf-1. Apaf-1 normally induces the activation of caspases. If Bcl-2 is overexpressed (e.g., follicular lymphoma), then Apaf-1 is overly inhibited, → caspase activation and tumorigenesis.

Extrinsic pathway

2 pathways:

- Ligand receptor interactions (FasL binding to Fas [CD95])
- Immune cell (cytotoxic T-cell release of perforin and granzyme B)

Fas-FasL interaction is necessary in thymic medullary negative selection. Mutations in Fas → numbers of circulating self-reacting lymphocytes due to failure of clonal deletion. After Fas crosslinks with FasL, multiple Fas molecules coalesce, forming a binding site for a death domain–containing adapter protein, FADD. FADD binds inactive caspases, activating them.

Defective Fas-FasL interactions contribute to autoimmune disorders.
## Necrosis

Enzymatic degradation and protein denaturation of cell due to exogenous injury → intracellular components leak. Inflammatory process (unlike apoptosis).

<table>
<thead>
<tr>
<th>TYPE</th>
<th>SEEN IN</th>
<th>DUE TO</th>
<th>HISTOLOGY</th>
</tr>
</thead>
</table>
| Coagulative | Ischemia/infarcts in most tissues (except brain) | Ischemia or infarction; proteins denature, then enzymatic degradation | Cell outlines preserved; ↑ cytoplasmic binding of acidophilic dyes
| Liquefactive | Bacterial abscesses, brain infarcts (due to ↑ fat content) | Neutrophils releasing lysosomal enzymes that digest the tissue; enzymatic degradation first, then proteins denature | Early: cellular debris and macrophages
|            |                                              |                                             | Late: cystic spaces and cavitation (brain)
|            |                                              |                                             | Neutrophils and cell debris seen with bacterial infection
| Caseous    | TB, systemic fungi (e.g., *Histoplasma capsulatum*), *Nocardia* | Macrophages wall off the infecting microorganism → granular debris | Fragmented cells and debris surrounded by lymphocytes and macrophages
| Fat        | Enzymatic: acute pancreatitis (saponification) Nonenzymatic: breast trauma | Damaged cells release lipase, which breaks down fatty acids in cell membranes | Outlines of dead fat cells without peripheral nuclei; saponification of fat (combined with Ca²⁺) appears dark blue on H&E stain
| Fibrinoid  | Immune reactions in vessels | Immune complexes combine with fibrin → vessel wall damage | Vessel walls are thick and pink
| Gangrenous | Distal extremity, after chronic ischemia | Dry: ischemia | Coagulative
|            | Wet: superinfection | Liquefactive |
### Cell injury

<table>
<thead>
<tr>
<th>Reversible with O₂</th>
<th>Irreversible</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP depletion</td>
<td>Nuclear pyknosis, karyorrhexis, karyolysis</td>
</tr>
<tr>
<td>Cellular/mitochondrial swelling (↓ ATP)</td>
<td>Plasma membrane damage (degradation of membrane phospholipid)</td>
</tr>
<tr>
<td>↓ → ↓ activity of Na⁺/K⁺ pumps</td>
<td>Lysosomal rupture</td>
</tr>
<tr>
<td>Nuclear chromatin clumping</td>
<td>Mitochondrial permeability/vacuolization; phospholipid-containing amorphous densities within mitochondria (swelling alone is reversible)</td>
</tr>
<tr>
<td>↓ glycogen</td>
<td></td>
</tr>
<tr>
<td>Fatty change</td>
<td></td>
</tr>
<tr>
<td>Ribosomal/polysomal detachment (↓ protein synthesis)</td>
<td></td>
</tr>
<tr>
<td>Membrane blebbing</td>
<td></td>
</tr>
</tbody>
</table>

### Ischemia: susceptible areas

Areas susceptible to hypoxia/ischemia and infarction:

<table>
<thead>
<tr>
<th>Organ</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>ACA/MCA/PCA boundary areas&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Heart</td>
<td>Subendocardium (LV)</td>
</tr>
<tr>
<td>Kidney</td>
<td>Straight segment of proximal tubule (medulla)</td>
</tr>
<tr>
<td></td>
<td>Thick ascending limb (medulla)</td>
</tr>
<tr>
<td>Liver</td>
<td>Area around central vein (zone III)</td>
</tr>
<tr>
<td>Colon</td>
<td>Splenic flexure&lt;sup&gt;a&lt;/sup&gt;, rectum&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Watershed areas (border zones) receive dual blood supply from most distal branches of 2 arteries, which protects these areas from single-vessel focal blockage. However, these areas are susceptible to ischemia from systemic hypoperfusion.

<sup>b</sup>Hypoxic ischemic encephalopathy (HIE) affects pyramidal cells of hippocampus and Purkinje cells of cerebellum.

### Infarcts: red vs. pale

#### Red

Red (hemorrhagic) infarcts (left in A) occur in venous occlusion and tissues with multiple blood supplies, such as liver, lung, and intestine; reperfusion (e.g., after angioplasty). Reperfusion injury is due to damage by free radicals. **Red** = reperfusion.

#### Pale

Pale (anemic) infarcts (right in A) occur in solid organs with a single (end-arterial) blood supply, such as heart, kidney, and spleen.
**Atrophy**  
Reduction in the size and/or number of cells. Causes include:  
- ↓ endogenous hormones (e.g., post-menopausal ovaries)  
- ↑ exogenous hormones (e.g., factitious thyrotoxicosis, steroid use)  
- ↓ innervation (e.g., motor neuron damage)  
- ↓ blood flow/nutrients  
- ↓ metabolic demand (e.g., prolonged hospitalization, paralysis)  
- ↑ pressure (e.g., nephrolithiasis)  
- Occlusion of secretory ducts (e.g., cystic fibrosis, calculus/stone)

**Inflammation**  
Characterized by *rubor* (redness), *dolor* (pain), *calor* (heat), *tumor* (swelling), and *functio laesa* (loss of function).  

<table>
<thead>
<tr>
<th>Vascular component</th>
<th>↑ vascular permeability, vasodilation, endothelial injury.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellular component</td>
<td>Neutrophils extravasate from circulation to injured tissue to participate in inflammation through phagocytosis, degranulation, and inflammatory mediator release.</td>
</tr>
<tr>
<td>Acute</td>
<td>Neutrophil, eosinophil, and antibody mediated. Acute inflammation is rapid onset (seconds to minutes) and of short duration (minutes to days). Outcomes include complete resolution, abscess formation, or progression to chronic inflammation.</td>
</tr>
<tr>
<td>Chronic</td>
<td>Mononuclear cell and fibroblast mediated. Characterized by persistent destruction and repair. Associated with blood vessel proliferation, fibrosis. Granuloma: nodular collections of epithelioid macrophages and giant cells. Outcomes include scarring and amyloidosis.</td>
</tr>
</tbody>
</table>

**Chromatolysis**  
Process involving the neuronal cell body following axonal injury. Changes reflect ↑ protein synthesis in effort to repair the damaged axon. Characterized by:  
- Round cellular swelling  
- Displacement of the nucleus to the periphery  
- Dispersion of Nissl substance throughout cytoplasm
Types of calcification

**Dystrophic calcification**

Ca$^{2+}$ deposition in abnormal tissues due to injury or necrosis. Tends to be localized (e.g., calcific aortic stenosis). Seen in TB (lungs and pericardium), liquefactive necrosis of chronic abscesses, fat necrosis, infarcts, thrombi, schistosomiasis, Mönckeberg arteriolosclerosis, congenital CMV + toxoplasmosis, psammoma bodies. Is not directly associated with serum Ca$^{2+}$ levels (patients are usually normocalcemic).

**Metastatic calcification**

Widespread (i.e., diffuse, metastatic) deposition of Ca$^{2+}$ in normal tissue due to hypercalcemia (e.g., 1° hyperparathyroidism, sarcoidosis, hypervitaminosis D) or high calcium-phosphate product levels (e.g., chronic renal failure with 2° hyperparathyroidism, long-term dialysis, calciphylaxis, warfarin). Ca$^{2+}$ deposits predominantly in interstitial tissues of kidney, lung, and gastric mucosa (these tissues lose acid quickly; pH favors deposition). Patients are usually not normocalcemic.
Extravasation predominantly occurs at postcapillary venules. WBCs exit from blood vessels at sites of tissue injury and inflammation in 4 steps:

<table>
<thead>
<tr>
<th>STEP</th>
<th>VASCULATURE/STROMA</th>
<th>LEUKOCYTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Margination and rolling—defective in leukocyte adhesion deficiency type 2 (4 Sialyl-LewisX)</td>
<td>E-selectin</td>
<td>Sialyl-LewisX</td>
</tr>
<tr>
<td></td>
<td>P-selectin</td>
<td>Sialyl-LewisX</td>
</tr>
<tr>
<td></td>
<td>GlyCAM-1, CD34</td>
<td>L-selectin</td>
</tr>
<tr>
<td>2 Tight-binding—defective in leukocyte adhesion deficiency type 1 (4 CD18 integrin subunit)</td>
<td>ICAM-1 (CD54)</td>
<td>CD11/18 integrins (LFA-1, Mac-1)</td>
</tr>
<tr>
<td></td>
<td>VCAM-1 (CD106)</td>
<td>VLA-4 integrin</td>
</tr>
<tr>
<td>3 Diapedesis—WBC travels between endothelial cells and exits blood vessel</td>
<td>PECAM-1 (CD31)</td>
<td>PECAM-1 (CD31)</td>
</tr>
<tr>
<td>4 Migration—WBC travels through interstitium to site of injury or infection guided by chemotactic signals</td>
<td>Chemotactic products released in response to bacteria: C5a, IL-8, LTB4, kallikrein, platelet-activating factor</td>
<td>Various</td>
</tr>
</tbody>
</table>

![Diagram of leukocyte extravasation](image)
Free radical injury

Free radicals damage cells via membrane lipid peroxidation, protein modification, and DNA breakage. Initiated via radiation exposure (e.g., cancer therapy), metabolism of drugs (phase I), redox reactions, nitric oxide, transition metals, WBC (e.g., neutrophils, macrophages) oxidative burst. Free radicals can be eliminated by scavenging enzymes (e.g., catalase, superoxide dismutase, glutathione peroxidase), spontaneous decay, antioxidants (e.g., vitamins A, C, E), and certain metal carrier proteins (e.g., transferrin, ceruloplasmin).

Pathologies include:
- Retinopathy of prematurity (abnormal vascularization)
- Bronchopulmonary dysplasia
- Carbon tetrachloride, leading to liver necrosis (fatty change)
- Acetaminophen overdose (fulminant hepatitis, renal papillary necrosis)
- Iron overload (hemochromatosis)
- Reperfusion injury (e.g., superoxide), especially after thrombolytic therapy

Inhalational injury and sequelae

Pulmonary complication associated with smoke and fire. Caused by heat, particulates (< 1 μm diameter), or irritants (e.g., NH₃) → chemical tracheobronchitis, edema, pneumonia, ARDS. Many patients present 2° to burns, CO inhalation, or arsenic poisoning.
Scar formation

70–80% of tensile strength regained at 3 months; little additional tensile strength will be regained afterward.

<table>
<thead>
<tr>
<th>Scar type</th>
<th>Hypertrophic scars</th>
<th>Keloid scars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collagen synthesis</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Collagen arrangement</td>
<td>Parallel</td>
<td>Disorganized</td>
</tr>
<tr>
<td>Extent</td>
<td>Confined to borders of original wound</td>
<td>Extend beyond borders of original wound</td>
</tr>
<tr>
<td>Recurrence</td>
<td>Infrequently recur following resection</td>
<td>Frequently recur following resection</td>
</tr>
<tr>
<td>Notes</td>
<td>Higher incidence in African Americans</td>
<td></td>
</tr>
</tbody>
</table>

Wound healing

<table>
<thead>
<tr>
<th>Tissue mediators</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDGF</td>
<td>Secreted by activated platelets and macrophages</td>
</tr>
<tr>
<td></td>
<td>Induces vascular remodeling and smooth muscle cell migration</td>
</tr>
<tr>
<td>FGF</td>
<td>Stimulates fibroblast growth for collagen synthesis</td>
</tr>
<tr>
<td>EGF</td>
<td>Stimulates angiogenesis</td>
</tr>
<tr>
<td>TGF-β</td>
<td>Angiogenesis, fibrosis, cell cycle arrest</td>
</tr>
<tr>
<td>Metalloproteinases</td>
<td>Tissue remodeling</td>
</tr>
<tr>
<td>VEGF</td>
<td>Stimulates angiogenesis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase of wound healing</th>
<th>Mediators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory (up to 3 days after wound)</td>
<td>Platelets, neutrophils, macrophages</td>
</tr>
<tr>
<td></td>
<td>Clot formation, vessel permeability and neutrophil migration into tissue; macrophages clear debris 2 days later</td>
</tr>
<tr>
<td>Proliferative (day 3–weeks after wound)</td>
<td>Fibroblasts, myofibroblasts, endothelial cells, keratinocytes, macrophages</td>
</tr>
<tr>
<td></td>
<td>Deposition of granulation tissue and collagen, angiogenesis, epithelial cell proliferation, dissolution of clot, and wound contraction (mediated by myofibroblasts)</td>
</tr>
<tr>
<td>Remodeling (1 week–6+ months after wound)</td>
<td>Fibroblasts</td>
</tr>
<tr>
<td></td>
<td>Type III collagen replaced by type I collagen, tensile strength of tissue</td>
</tr>
</tbody>
</table>
**Granulomatous diseases**

- *Bartonella henselae* (cat scratch disease)
- Berylliosis
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
- Crohn disease (noncaseating granuloma)
- Foreign bodies
- *Francisella tularensis*
- Fungal infections (caseous necrosis)
- Granulomatosis with polyangiitis (Wegener)
- *Listeria monocytogenes* (granulomatosis infantiseptica)
- *M. leprae* (leprosy; Hansen disease)
- *M. tuberculosis* (caseous necrosis)
- *Treponema pallidum* (3° syphilis)
- Sarcoidosis \( \text{(noncaseating granuloma)} \)
- Schistosomiasis

**Th1 cells secrete IFN-\( \gamma \), activating macrophages. TNF-\( \alpha \) from macrophages induces and maintains granula formation. Anti-TNF drugs can, as a side effect, cause sequestering granulomas to break down, leading to disseminated disease. Always test for latent TB before starting anti-TNF therapy.**

<table>
<thead>
<tr>
<th>Exudate vs. transudate</th>
<th>Exudate (“Thick…”)</th>
<th>Transudate (“and thin”)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cellular</strong></td>
<td>Hypocellular</td>
<td></td>
</tr>
<tr>
<td><strong>Protein-rich</strong></td>
<td>Protein-poor</td>
<td></td>
</tr>
</tbody>
</table>
| **Specific gravity > 1.020** | Specific gravity < 1.012 | Due to:
- Lymphatic obstruction
- Inflammation/infection
- Malignancy
- ↑ hydrostatic pressure (e.g., HF)
- ↓ oncotic pressure (e.g., cirrhosis, nephrotic syndrome)
- Na\(^+\) retention

**Erythrocyte sedimentation rate**

Products of inflammation (e.g., fibrinogen) coat RBCs and cause aggregation. The denser RBC aggregates fall at a faster rate within a pipette tube. Often co-tested with CRP levels.

<table>
<thead>
<tr>
<th>↑ ESR</th>
<th>↓ ESR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most anemias</td>
<td>Sickle cell anemia (altered shape)</td>
</tr>
<tr>
<td>Infections</td>
<td>Polycythemia (↑ RBCs “dilute” aggregation factors)</td>
</tr>
<tr>
<td>Inflammation (e.g., temporal arteritis)</td>
<td>HF</td>
</tr>
<tr>
<td>Cancer (e.g., multiple myeloma)</td>
<td>Microcytosis</td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
</tr>
<tr>
<td>Autoimmune disorders (e.g., SLE)</td>
<td>Hypofibrinogenemia</td>
</tr>
</tbody>
</table>
**Amyloidosis**

Abnormal aggregation of proteins \( \text{A} \beta \text{B} \) (or their fragments) into \( \beta \)-pleated sheets → damage and apoptosis.

<table>
<thead>
<tr>
<th>COMMON TYPES</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AL (primary)</strong></td>
<td>Due to deposition of proteins from Ig Light chains. Can occur as a plasma cell disorder or associated with multiple myeloma. Often affects multiple organ systems, including renal (nephrotic syndrome), cardiac (restrictive cardiomyopathy, arrhythmia), hematologic (easy bruising, splenomegaly), GI (hepatomegaly), and neurologic (neuropathy).</td>
</tr>
<tr>
<td><strong>AA (secondary)</strong></td>
<td>Seen with chronic inflammatory conditions such as rheumatoid arthritis, IBD, spondyloarthropathy, protracted infection. Fibrils composed of serum ( \text{A} )myloid ( \text{A} ). Often multisystem like AL amyloidosis.</td>
</tr>
<tr>
<td><strong>Dialysis-related</strong></td>
<td>Fibrils composed of ( \beta_2 )-microglobulin in patients with ESRD and/or on long-term dialysis. May present as carpal tunnel syndrome.</td>
</tr>
<tr>
<td><strong>Heritable</strong></td>
<td>Heterogeneous group of disorders, including familial amyloid polyneuropathies due to transthyretin gene mutation.</td>
</tr>
<tr>
<td><strong>Age-related (senile)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>systemic</strong></td>
<td>Due to deposition of normal (wild-type) transthyretin in myocardium and other sites. Slower progression of cardiac dysfunction relative to AL amyloidosis.</td>
</tr>
<tr>
<td><strong>Organ-specific</strong></td>
<td>Amyloid deposition localized to a single organ. Most important form is amyloidosis in Alzheimer disease due to deposition of ( \beta )-amyloid protein cleaved from amyloid precursor protein (APP). Islet amyloid polypeptide (IAPP) is commonly seen in diabetes mellitus type 2 and is caused by deposition of amylin in pancreatic islets.</td>
</tr>
</tbody>
</table>

**Lipofuscin**

A yellow-brown “wear and tear” pigment \( \text{A} \) associated with normal aging. Formed by oxidation and polymerization of autophagocytosed organellar membranes. Autopsy of elderly person will reveal deposits in heart, colon, liver, kidney, eye, and other organs.
Neoplastic progression  

Normal cells
Normal cells with basal (A, red arrow) → apical (A, blue arrow) differentiation.

Hyperplasia
Hyperplasia—cells ↑ in number B.
Dysplasia—abnormal proliferation of cells with loss of size, shape, and orientation.

Carcinoma in situ/preinvasive
Neoplastic cells have not invaded intact basement membrane C.
↑ nuclear/cytoplasmic (N/C) ratio and clumped chromatin.
Neoplastic cells encompass entire thickness.

Invasive carcinoma
Cells have invaded basement membrane using collagenases and hydrolases (metalloproteinases) D.
Cell-cell contacts lost by inactivation of E-cadherin.

Metastasis
Metastasis—spread to distant organ, e.g., metastatic cells (E, blue arrow) in liver parenchyma (E, red arrow).
“Seed and soil” theory of metastasis:
- Seed = tumor embolus
- Soil = target organ is often the first-encountered capillary bed (e.g., liver, lungs, bone, brain, etc.)
**P-glycoprotein**

Also known as multidrug resistance protein 1 (MDR1). Classically seen in adrenal cell carcinoma but also expressed by other cancer cells (e.g., colon, liver). Used to pump out toxins, including chemotherapeutic agents (one mechanism of 
† responsiveness or resistance to chemotherapy over time).

---

**neoplasia definitions**

**REVERSIBLE**

Hyperplasia

† in number of cells. Distinct from hypertrophy († in size of cells).

Metaplasia

One adult cell type is replaced by another. Often 2º to irritation (e.g., Barrett esophagus) and/or environmental exposure (e.g., smoking-induced tracheal/bronchial squamous metaplasia). Also occurs where two different epithelia meet (e.g., squamocolumnar junction of the uterine cervix).

Dysplasia

Abnormal growth with loss of cellular orientation, shape, and size in comparison to normal tissue maturation; commonly preneoplastic.

**IRREVERSIBLE**

Anaplasia

Loss of structural differentiation and function of cells, resembling primitive cells of same tissue; often equated with undifferentiated malignant neoplasms. May see “giant cells” with single large nucleus or several nuclei.

Neoplasia

An uncontrolled and excessive clonal proliferation of cells. Neoplasia may be benign or malignant.

Desmoplasia

Fibrous tissue formation in response to neoplasm (e.g., linitis plastica in diffuse stomach cancer).

---

**Tumor grade vs. stage**

**Grade**

Degree of cellular differentiation and mitotic activity on histology. Usually graded 1–4; 1 = low grade, well differentiated; 4 = high grade, poorly differentiated, anaplastic.

Stage almost always has more prognostic value than grade.

**Stage**

Degree of localization/spread based on site and size of 1º lesion, spread to regional lymph nodes, presence of metastases. Based on clinical (c) or pathology (p) findings. Example: ct3N1M0

TNM staging system (Stage = Spread):

T = Tumor size
N = Node involvement
M = Metastases

Each TNM factor has independent prognostic value.
**Tumor nomenclature**

Carcinoma implies epithelial origin, whereas sarcoma denotes mesenchymal origin. Both terms imply malignancy. Most carcinomas spread via lymphatics; most sarcomas spread hematogenously. Terms for non-neoplastic malformations include hamartoma (disorganized overgrowth of tissues in their native location, e.g., Peutz-Jeghers polyps) and choristoma (normal tissue in a foreign location, e.g., gastric tissue located in small bowel in Meckel diverticulum).

<table>
<thead>
<tr>
<th>CELL TYPE</th>
<th>BENIGN</th>
<th>MALIGNANT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelium</td>
<td>Adenoma, papilloma</td>
<td>Adenocarcinoma, papillary carcinoma</td>
</tr>
<tr>
<td>Mesenchyme</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood vessels</td>
<td>Hemangioma</td>
<td>Angiosarcoma</td>
</tr>
<tr>
<td>Smooth muscle</td>
<td>Leiomyoma</td>
<td>Leiomyosarcoma</td>
</tr>
<tr>
<td>Striated muscle</td>
<td>Rhabdomyoma</td>
<td>Rhabdomyosarcoma</td>
</tr>
<tr>
<td>Connective tissue</td>
<td>Fibroma</td>
<td>Fibrosarcoma</td>
</tr>
<tr>
<td>Bone</td>
<td>Osteoma</td>
<td>Osteosarcoma</td>
</tr>
<tr>
<td>Fat</td>
<td>Lipoma</td>
<td>Liposarcoma</td>
</tr>
</tbody>
</table>

**Tumor classifications**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>Usually well differentiated, well demarcated, low mitotic activity, no metastasis, no necrosis.</td>
</tr>
<tr>
<td>Malignant</td>
<td>May show poor differentiation, erratic growth, local invasion, metastasis, and apoptosis. Upregulation of telomerase prevents chromosome shortening and cell death.</td>
</tr>
</tbody>
</table>

**Cachexia**

Weight loss, muscle atrophy, and fatigue that occur in chronic disease (e.g., cancer, AIDS, heart failure, TB). Mediated by TNF-α (nicknamed cachectin), IFN-γ, IL-1, and IL-6.
### Disease conditions associated with neoplasms

<table>
<thead>
<tr>
<th>Gastrointestinal</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acanthosis nigricans</td>
<td>Rare paraneoplastic indicator of visceral malignancy (more commonly associated with insulin resistance)</td>
</tr>
<tr>
<td>Barrett esophagus</td>
<td>Precursor to esophageal adenocarcinoma</td>
</tr>
<tr>
<td>Chronic atrophic gastritis, postsurgical gastric remnants</td>
<td>Predispose to gastric adenocarcinoma</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Predisposes to hepatocellular carcinoma</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>Predisposes to colon adenocarcinoma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Musculoskeletal and skin</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinic keratosis</td>
<td>Precursor to squamous cell carcinoma of the skin</td>
</tr>
<tr>
<td>Dermato- and polymyositis</td>
<td>Predispose to visceral malignances, particularly genitourinary</td>
</tr>
<tr>
<td>Dysplastic nevus</td>
<td>Precursor to malignant melanoma</td>
</tr>
<tr>
<td>Multiple seborrheic keratoses</td>
<td>GI, breast, lung, and lymphoid malignancies</td>
</tr>
<tr>
<td>Paget disease of bone</td>
<td>Predisposes to 2° osteosarcoma and fibrosarcoma</td>
</tr>
<tr>
<td>Plummer-Vinson syndrome</td>
<td>Predisposes to squamous cell carcinoma of the esophagus</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>Often manifests with multiple hamartomatous (benign) tumors including giant cell astrocytomas, renal angiomyolipomas, cardiac rhabdomyomas; tumors may become malignant</td>
</tr>
<tr>
<td>Xeroderma pigmentosum, albinism</td>
<td>Predispose to squamous cell carcinoma, basal cell carcinoma, melanoma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hematologic</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>Predisposes to aggressive lymphoma (non-Hodgkin) and Kaposi sarcoma</td>
</tr>
<tr>
<td>Autoimmune diseases (e.g., Hashimoto thyroiditis, SLE)</td>
<td>Predispose to lymphoma</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>Predisposes to acute lymphocytic leukemia</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>Predisposes to lymphoma, melanoma, renal cell carcinoma</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>$p53$ mutation predisposes to various cancer types at a young age (e.g., sarcoma, breast, leukemia, adrenal gland)</td>
</tr>
<tr>
<td>Radiation exposure</td>
<td>High risk of developing leukemia, sarcoma, papillary thyroid cancer, breast cancer</td>
</tr>
</tbody>
</table>
### Oncogenes

Gain of function → ↑ cancer risk. Need damage to only 1 allele.

<table>
<thead>
<tr>
<th>GENE</th>
<th>GENE PRODUCT</th>
<th>ASSOCIATED TUMOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCR-ABL</td>
<td>Tyrosine kinase</td>
<td>CML, ALL</td>
</tr>
<tr>
<td>BCL-2</td>
<td>Antiapoptotic molecule (inhibits apoptosis)</td>
<td>Follicular and undifferentiated lymphomas</td>
</tr>
<tr>
<td>B Raf</td>
<td>Serine/threonine kinase</td>
<td>Melanoma, non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>c-kit</td>
<td>Cytokine receptor</td>
<td>Gastrointestinal stromal tumor (GIST)</td>
</tr>
<tr>
<td>c-myc</td>
<td>Transcription factor</td>
<td>Burkitt lymphoma</td>
</tr>
<tr>
<td>HER2/neu (c-erbB2)</td>
<td>Tyrosine kinase</td>
<td>Breast, ovarian, and gastric carcinomas</td>
</tr>
<tr>
<td>L-myc</td>
<td>Transcription factor</td>
<td>Lung tumor</td>
</tr>
<tr>
<td>N-myc</td>
<td>Transcription factor</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>RAS</td>
<td>GTPase</td>
<td>Colon cancer, lung cancer, pancreatic cancer</td>
</tr>
<tr>
<td>RET</td>
<td>Tyrosine kinase</td>
<td>MEN 2A and 2B, medullary thyroid cancer</td>
</tr>
</tbody>
</table>

### Tumor suppressor genes

Loss of function → ↑ cancer risk; both alleles must be lost for expression of disease.

<table>
<thead>
<tr>
<th>GENE</th>
<th>ASSOCIATED TUMOR</th>
<th>GENE PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>Colorectal cancer (associated with FAP)</td>
<td></td>
</tr>
<tr>
<td>BRCA1/BRCA2</td>
<td>Breast and ovarian cancer</td>
<td>DNA repair protein</td>
</tr>
<tr>
<td>DCC</td>
<td>Colon cancer</td>
<td>DCC—Deleted in Colon Cancer</td>
</tr>
<tr>
<td>DPC4/SMAD4</td>
<td>Pancreatic cancer</td>
<td>DPC—Deleted in Pancreatic Cancer</td>
</tr>
<tr>
<td>MEN1</td>
<td>MEN 1</td>
<td>Menin</td>
</tr>
<tr>
<td>NF1</td>
<td>Neurofibromatosis type 1</td>
<td>Ras GTPase activating protein (neurofibromin)</td>
</tr>
<tr>
<td>NF2</td>
<td>Neurofibromatosis type 2</td>
<td>Merlin (schwannomin) protein</td>
</tr>
<tr>
<td>p16</td>
<td>Melanoma</td>
<td>Cyclin-dependent kinase inhibitor 2A</td>
</tr>
<tr>
<td>p53</td>
<td>Most human cancers, Li-Fraumeni syndrome</td>
<td>Transcription factor for p21, blocks G1 → S phase</td>
</tr>
<tr>
<td>PTEN</td>
<td>Breast cancer, prostate cancer, endometrial cancer</td>
<td></td>
</tr>
<tr>
<td>Rb</td>
<td>Retinoblastoma, osteosarcoma</td>
<td>Inhibits E2F; blocks G1 → S phase</td>
</tr>
<tr>
<td>TSC1</td>
<td>Tuberous sclerosis</td>
<td>Hamartin protein</td>
</tr>
<tr>
<td>TSC2</td>
<td>Tuberous sclerosis</td>
<td>Tuberin protein</td>
</tr>
<tr>
<td>VHL</td>
<td>von Hippel-Lindau disease, renal cell carcinoma</td>
<td>Inhibits hypoxia inducible factor 1a</td>
</tr>
<tr>
<td>WT1/WT2</td>
<td>Wilms Tumor (nephroblastoma)</td>
<td></td>
</tr>
</tbody>
</table>
### Tumor markers

Tumor markers should not be used as the 1° tool for cancer diagnosis or screening. They may be used to monitor tumor recurrence and response to therapy, but definitive diagnosis is usually made via biopsy.

<table>
<thead>
<tr>
<th>Tumor marker</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline phosphatase</td>
<td>Metastases to bone or liver, Paget disease of bone, seminoma (placental ALP).</td>
</tr>
<tr>
<td>α-fetoprotein</td>
<td>Hepatocellular carcinoma, hepatoblastoma, yolk sac (endodermal sinus) tumor, mixed germ cell tumor.</td>
</tr>
<tr>
<td>β-hCG</td>
<td>Hydatidiform moles and Choriocarcinomas (Gestational trophoblastic disease), testicular cancer, mixed germ cell tumor.</td>
</tr>
<tr>
<td>CA 15-3/CA 27-29</td>
<td>Breast cancer.</td>
</tr>
<tr>
<td>CA 19-9</td>
<td>Pancreatic adenocarcinoma.</td>
</tr>
<tr>
<td>CA 125</td>
<td>Ovarian cancer.</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Medullary thyroid carcinoma.</td>
</tr>
<tr>
<td>CEA</td>
<td>CarcinoEmbryonic Antigen. Very nonspecific but produced by ~ 70% of colorectal and pancreatic cancers; also produced by gastric, breast, and medullary thyroid carcinomas.</td>
</tr>
<tr>
<td>Chromogranin</td>
<td>Neuroendocrine tumors/carcinoid.</td>
</tr>
<tr>
<td>PSA</td>
<td>Prostate-specific antigen. Prostate cancer. Can also be elevated in BPH and prostatitis. Questionable risk/benefit for screening.</td>
</tr>
</tbody>
</table>

### Oncogenic microbes

<table>
<thead>
<tr>
<th>Microbe</th>
<th>Associated cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBV</td>
<td>Burkitt lymphoma, Hodgkin lymphoma, nasopharyngeal carcinoma, 1° CNS lymphoma (in immunocompromised patients)</td>
</tr>
<tr>
<td>HBV, HCV</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>HHV-8</td>
<td>Kaposi sarcoma</td>
</tr>
<tr>
<td>HPV</td>
<td>Cervical and penile/anal carcinoma (types 16, 18), head and neck cancer</td>
</tr>
<tr>
<td>H. pylori</td>
<td>Gastric adenocarcinoma and MALT lymphoma</td>
</tr>
<tr>
<td>HTLV-1</td>
<td>Adult T-cell leukemia/lymphoma</td>
</tr>
<tr>
<td>Liver fluke (<em>Clonorchis sinensis</em>)</td>
<td>Bladder cancer (squamous cell)</td>
</tr>
<tr>
<td>Schistosoma haematobium</td>
<td></td>
</tr>
</tbody>
</table>
### Carcinogens

<table>
<thead>
<tr>
<th>TOXIN</th>
<th>ORGAN</th>
<th>IMPACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflatoxins (Aspergillus)</td>
<td>Liver</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td>Blood</td>
<td>Leukemia/lymphoma</td>
</tr>
<tr>
<td>Aromatic amines (e.g., benzidine, 2-naphthylamine)</td>
<td>Bladder</td>
<td>Transitional cell carcinoma</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Liver</td>
<td>Angiosarcoma</td>
</tr>
<tr>
<td></td>
<td>Lung</td>
<td>Lung cancer</td>
</tr>
<tr>
<td></td>
<td>Skin</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>Asbestos</td>
<td>Lung</td>
<td>Bronchogenic carcinoma &gt; mesothelioma</td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td>Liver</td>
<td>Centrilobular necrosis, fatty change</td>
</tr>
<tr>
<td>Cigarette smoke</td>
<td>Bladder</td>
<td>Transitional cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Cervix</td>
<td>Cervical carcinoma</td>
</tr>
<tr>
<td></td>
<td>Esophagus</td>
<td>Squamous cell carcinoma/adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td>Kidney</td>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Larynx</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Lung</td>
<td>Squamous cell and small cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Pancreas</td>
<td>Pancreatic adenocarcinoma</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Esophagus</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Liver</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Ionizing radiation</td>
<td>Thyroid</td>
<td>Papillary thyroid carcinoma</td>
</tr>
<tr>
<td>Nitrosamines (smoked foods)</td>
<td>Stomach</td>
<td>Gastric cancer</td>
</tr>
<tr>
<td>Radon</td>
<td>Lung</td>
<td>Lung cancer (2nd leading cause after cigarette smoke)</td>
</tr>
<tr>
<td>Vinyl chloride</td>
<td>Liver</td>
<td>Angiosarcoma</td>
</tr>
</tbody>
</table>

### Paraneoplastic syndromes

<table>
<thead>
<tr>
<th>HORMONE/AGENT</th>
<th>EFFECT</th>
<th>NEOPLASMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,25-(OH)₂ D₃ (calcitriol)</td>
<td>Hypercalcemia</td>
<td>Hodgkin lymphoma, non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>ACTH</td>
<td>Cushing syndrome</td>
<td>Small cell lung carcinoma, renal cell carcinoma</td>
</tr>
<tr>
<td>ADH</td>
<td>SIADH</td>
<td>Small cell lung carcinoma, intracranial neoplasms</td>
</tr>
<tr>
<td>Antibodies against presynaptic Ca²⁺ channels at NMJ</td>
<td>Lambert-Eaton myasthenic syndrome (muscle weakness)</td>
<td>Small cell lung carcinoma</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>Polycythemia</td>
<td>Renal cell carcinoma, hemangioblastoma, hepatocellular carcinoma, leiomyoma, pheochromocytoma</td>
</tr>
<tr>
<td>PTHrP</td>
<td>Hypercalcemia</td>
<td>Squamous cell lung carcinoma, renal cell carcinoma, breast cancer</td>
</tr>
</tbody>
</table>
Psammoma bodies

Laminated, concentric spherules with dystrophic calcification. Psammoma bodies are seen in:
- Papillary carcinoma of thyroid
- Serous papillary cystadenocarcinoma of ovary
- Meningioma
- Malignant mesothelioma

Psammoma bodies.

Cancer epidemiology

<table>
<thead>
<tr>
<th>Incidence</th>
<th>MALE</th>
<th>FEMALE</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Prostate</td>
<td>1. Breast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Lung</td>
<td>2. Lung</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Colon/rectum</td>
<td>3. Colon/rectum</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Lung cancer incidence has dropped in men, but has not changed significantly in women.

<table>
<thead>
<tr>
<th>Mortality</th>
<th>MALE</th>
<th>FEMALE</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lung</td>
<td>1. Lung</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Prostate</td>
<td>2. Breast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Colon/rectum</td>
<td>3. Colon/rectum</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cancer is the 2nd leading cause of death in the United States (heart disease is 1st).
### Common metastases

<table>
<thead>
<tr>
<th>SITE OF METASTASIS</th>
<th>1st TUMOR</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Lung &gt; breast &gt; prostate &gt; melanoma &gt; GI.</td>
<td>50% of brain tumors are from metastases. Commonly seen as multiple well-circumscribed tumors at gray/white matter junction.</td>
</tr>
<tr>
<td>Liver</td>
<td>Colon &gt;&gt; stomach &gt; pancreas.</td>
<td>Liver and lung are the most common sites of metastasis after the regional lymph nodes.</td>
</tr>
<tr>
<td>Bone</td>
<td>Prostate, breast &gt; lung, thyroid, kidney.</td>
<td>Bone metastasis &gt;&gt; 1st bone tumors (e.g., multiple myeloma, lytic). Common mets to bone: breast (mixed), lung (mixed), thyroid (lytic), kidney (lytic), prostate (blastic). Predilection for axial skeleton.</td>
</tr>
</tbody>
</table>

---

![Image A](image1.png)

![Image B](image2.png)

![Image C](image3.png)

![Image D](image4.png)

![Image E](image5.png)

![Image F](image6.png)

![Image G](image7.png)
HIGH-YIELD PRINCIPLES IN

Pharmacology

“Take me, I am the drug; take me, I am hallucinogenic.”
—Salvador Dali

“I was under medication when I made the decision not to burn the tapes.”
—Richard Nixon

“I wonder why ye can always read a doctor’s bill an’ ye niver can read his purscription.”
—Finley Peter Dunne

“Once you get locked into a serious drug collection, the tendency is to push it as far as you can.”
—Hunter S. Thompson

Preparation for questions on pharmacology is straightforward. Memorizing all the key drugs and their characteristics (e.g., mechanisms, clinical use, and important side effects) is high yield. Focus on understanding the prototype drugs in each class. Avoid memorizing obscure derivatives. Learn the “classic” and distinguishing toxicities of the major drugs. Specific drug dosages or trade names are generally not testable. Reviewing associated biochemistry, physiology, and microbiology can be useful while studying pharmacology. There is a strong emphasis on ANS, CNS, antimicrobial, and cardiovascular agents as well as on NSAIDs. Much of the material is clinically relevant. We occasionally mention drugs that are no longer available in the U.S., but help illustrate high-yield pharmacologic or disease mechanisms. They are highlighted as being of historical significance and should not appear on the USMLE. However, recently approved drugs are fair game for the exam.
Enzyme kinetics

**Michaelis-Menten kinetics**

\[ [S] = \text{concentration of substrate}; \ V = \text{velocity}. \]

\[ K_m \text{ is inversely related to the affinity of the enzyme for its substrate.} \]

\[ V_{\text{max}} \text{ is directly proportional to the enzyme concentration.} \]

Most enzymatic reactions follow a hyperbolic curve (i.e., Michaelis-Menten kinetics); however, enzymatic reactions that exhibit a sigmoid curve usually indicate cooperative kinetics (i.e., hemoglobin).

**Lineweaver-Burk plot**

\[ \text{slope} = \frac{K_m}{V_{\text{max}}} \]

The further to the right the x-intercept (i.e., closer to zero), the greater the \( K_m \) and the lower the affinity.

**Enzyme inhibition**

Reversible competitive inhibitors cross each other competitively, whereas noncompetitive inhibitors do not.

<table>
<thead>
<tr>
<th>Competitive inhibitors, reversible</th>
<th>Competitive inhibitors, irreversible</th>
<th>Noncompetitive inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resemble substrate</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Overcome by ( [S] )</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Bind active site</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Effect on ( V_{\text{max}} )</td>
<td>Unchanged</td>
<td>↓</td>
</tr>
<tr>
<td>Effect on ( K_m )</td>
<td>↑</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Pharmacodynamics</td>
<td>↓ potency</td>
<td>↓ efficacy</td>
</tr>
</tbody>
</table>

**Noncompetitive inhibitor**

Yes

Yes

No
Pharmacokinetics

**Bioavailability (F)**
Fraction of administered drug reaching systemic circulation unchanged. For an IV dose, F = 100%. Orally: F typically < 100% due to incomplete absorption and first-pass metabolism.

**Volume of distribution (V<sub>d</sub>)**
Theoretical volume occupied by the total amount of drug in the body relative to its plasma concentration. Apparent V<sub>d</sub> of plasma protein–bound drugs can be altered by liver and kidney disease (protein binding, ↑ V<sub>d</sub>). Drugs may distribute in more than one compartment.

\[
V_d = \frac{\text{amount of drug in the body}}{\text{plasma drug concentration}}
\]

<table>
<thead>
<tr>
<th>V&lt;sub&gt;d&lt;/sub&gt;</th>
<th>COMPARTMENT</th>
<th>DRUG TYPES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Blood</td>
<td>Large/charged molecules; plasma protein bound</td>
</tr>
<tr>
<td>Medium</td>
<td>ECF</td>
<td>Small hydrophilic molecules</td>
</tr>
<tr>
<td>High</td>
<td>All tissues including fat</td>
<td>Small lipophilic molecules, especially if bound to tissue protein</td>
</tr>
</tbody>
</table>

**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<sub>1/2</sub>)**
The time required to change the amount of drug in the body by 1⁄2 during elimination (or constant infusion). Property of first-order elimination. A drug infused at a constant rate takes 4–5 half-lives to reach steady state. It takes 3.3 half-lives to reach 90% of the steady-state level.

\[
t_{1/2} = \frac{0.693 \times V_d}{CL}
\]

<table>
<thead>
<tr>
<th># of half-lives</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>% remaining</td>
<td>50%</td>
<td>25%</td>
<td>12.5%</td>
<td>6.25%</td>
</tr>
</tbody>
</table>

**Dosage calculations**

- Loading dose = \( \frac{C_p \times V_d}{F} \)
- Maintenance dose = \( \frac{C_p \times CL \times \tau}{F} \)

\(C_p\) = target plasma concentration at steady state
\(\tau\) = dosage interval (time between doses), if not administered continuously

In renal or liver disease, maintenance dose ↓ and loading dose is usually unchanged.
Time to steady state depends primarily on \(t_{1/2}\) and is independent of dose and dosing frequency.
Elimination of drugs

**Zero-order elimination**  
Rate of elimination is constant regardless of $C_p$ (i.e., constant amount of drug eliminated per unit time). $C_p \downarrow$ linearly with time. Examples of drugs—Phenytoin, Ethanol, and Aspirin (at high or toxic concentrations).

**Capacity-limited elimination.**  
PEA. (A pea is round, shaped like the “0” in zero-order.)

**First-order elimination**  
Rate of elimination is directly proportional to the drug concentration (i.e., constant fraction of drug eliminated per unit time). $C_p \downarrow$ exponentially with time.

Flow-dependent elimination.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Plasma concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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, TCAs. Trapped in basic environments. Treat overdose with bicarbonate.

\[
\text{RCOOH} \rightleftharpoons \text{RCOO}^- + \text{H}^+ \\
\text{(lipid soluble)} \quad \text{(trapped)}
\]

**Weak bases**  
Example: amphetamines. Trapped in acidic environments. Treat overdose with ammonium chloride.

\[
\text{RNH}_3^+ \rightleftharpoons \text{RNH}_2 + \text{H}^+ \\
\text{(trapped)} \quad \text{(lipid soluble)}
\]

Drug metabolism

**Phase I**  
Reduction, oxidation, hydrolysis with cytochrome P-450 usually yield slightly polar, water-soluble metabolites (often still active).

Geriatric patients lose phase I first.

**Phase II**  
Conjugation (Glucuronidation, Acetylation, Sulfation) usually yields very polar, inactive metabolites (renally excreted).

Geriatric patients have GAS (phase II). Patients who are slow acetylators have 1 side effects from certain drugs because of ↓ rate of metabolism.
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 (i.e., 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. $\uparrow$ potency ($EC_{50}$) = $\downarrow$ drug needed. Represented by the x-value ($EC_{50}$). Left-shifting = $\downarrow$ $EC_{50}$ = $\uparrow$ potency. Unrelated to efficacy (i.e., potent drugs can have high or low efficacy).
### Receptor Binding

<table>
<thead>
<tr>
<th>Agonist Alone</th>
<th>Agonist Plus Competitive Antagonist</th>
<th>Agonist Plus Noncompetitive Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>60%</td>
<td>50%</td>
</tr>
<tr>
<td>10%</td>
<td>50%</td>
<td>40%</td>
</tr>
<tr>
<td>50%</td>
<td>30%</td>
<td>20%</td>
</tr>
<tr>
<td>100%</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Effect</strong></td>
<td><strong>Effect of</strong></td>
<td><strong>Partial agonist</strong></td>
</tr>
<tr>
<td></td>
<td>competitive antagonist</td>
<td>alone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Therapeutic Index

**Measurement of drug safety.**

\[
\text{Therapeutic index} = \frac{\text{TD}_{50}}{\text{ED}_{50}}
\]

Safer drugs have higher TI values. Drugs with lower TI values include digoxin, lithium, theophylline, and warfarin.

**LD_{50}** (lethal median dose) often replaces **TD_{50}** in animal studies.

---

### Examples

1. **Competitive antagonist**
   - Shifts curve right (↓ potency), no change in efficacy. Can be overcome by ↑ the concentration of agonist substrate.
   - **Example:** Diazepam (agonist) + flumazenil (competitive antagonist) on GABA receptor.

2. **Noncompetitive antagonist**
   - Shifts curve down (↓ efficacy). Cannot be overcome by ↑ agonist substrate concentration.
   - **Example:** Norepinephrine (agonist) + phenoxybenzamine (noncompetitive antagonist) on α-receptors.

3. **Partial agonist (alone)**
   - Acts at same site as full agonist, but with lower maximal effect (↓ efficacy). Potency is an independent variable.
   - **Example:** Morphine (full agonist) vs. buprenorphine (partial agonist) at opioid μ-receptors.

---

**Therapeutic Window**

- Measure of clinical drug effectiveness for a patient.
- **Efficacy** vs. **Toxicity**
- **ED_{50}** vs. **TD_{50}**
- **% of patients responding** vs. **Log (drug concentration)**
Central and peripheral nervous system

Note that the adrenal medulla and sweat glands are part of the sympathetic nervous system but are innervated by cholinergic fibers. Botulinum toxin prevents release of acetylcholine at cholinergic terminals.

**ACh receptors**

Nicotinic ACh receptors are ligand-gated Na⁺/K⁺ channels; N₅ (found in autonomic ganglia) and N₇M (found in neuromuscular junction) subtypes.

Muscarinic ACh receptors are G-protein–coupled receptors that usually act through 2nd messengers; 5 subtypes: M₁, M₂, M₃, M₄, and M₅.
### G-protein–linked 2nd messengers

<table>
<thead>
<tr>
<th>Receptor</th>
<th>G-Protein Class</th>
<th>Major Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sympathetic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\alpha_1)</td>
<td>q</td>
<td>↑ vascular smooth muscle contraction, ↑ pupillary dilator muscle contraction (mydriasis), ↑ intestinal and bladder sphincter muscle contraction</td>
</tr>
<tr>
<td>(\alpha_2)</td>
<td>i</td>
<td>↓ sympathetic outflow, ↓ insulin release, ↓ lipolysis, ↑ platelet aggregation, ↓ aqueous humor production</td>
</tr>
<tr>
<td>(\beta_1)</td>
<td>s</td>
<td>↑ heart rate, ↑ contractility, ↑ renin release, ↓ lipolysis</td>
</tr>
<tr>
<td>(\beta_2)</td>
<td>s</td>
<td>Vasodilation, bronchodilation, ↑ lipolysis, ↑ insulin release, ↓ uterine tone (tocolysis), ciliary muscle relaxation, ↓ aqueous humor production</td>
</tr>
<tr>
<td><strong>Parasympathetic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(M_1)</td>
<td>q</td>
<td>CNS, enteric nervous system</td>
</tr>
<tr>
<td>(M_2)</td>
<td>i</td>
<td>↓ heart rate and contractility of atria</td>
</tr>
<tr>
<td>(M_3)</td>
<td>q</td>
<td>↑ exocrine gland secretions (e.g., lacrimal, salivary, gastric acid), ↑ gut peristalsis, ↑ bladder contraction, bronchoconstriction, ↑ pupillary sphincter muscle contraction (miosis), ciliary muscle contraction (accommodation)</td>
</tr>
<tr>
<td><strong>Dopamine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(D_1)</td>
<td>s</td>
<td>Relaxes renal vascular smooth muscle</td>
</tr>
<tr>
<td>(D_2)</td>
<td>i</td>
<td>Modulates transmitter release, especially in brain</td>
</tr>
<tr>
<td><strong>Histamine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(H_1)</td>
<td>q</td>
<td>↑ nasal and bronchial mucus production, ↑ vascular permeability, contraction of bronchioles, pruritus, pain</td>
</tr>
<tr>
<td>(H_2)</td>
<td>s</td>
<td>↑ gastric acid secretion</td>
</tr>
<tr>
<td><strong>Vasopressin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(V_1)</td>
<td>q</td>
<td>↑ vascular smooth muscle contraction</td>
</tr>
<tr>
<td>(V_2)</td>
<td>s</td>
<td>↑ H2O permeability and reabsorption in collecting tubules of kidney ((V_2) is found in the 2 kidneys)</td>
</tr>
</tbody>
</table>

“Qiss (kiss) and qiq (kick) till you’re sqs (sick) of sqs (super qinky sex).”

**Diagram**

- **H1, α1, V1, M1, M3**
  - Receptor → G\(_i\) → Phospholipase C → DAG → Protein kinase C → [Ca\(^{2+}\)]\(_i\) → Smooth muscle contraction
  - Lipids → PIP\(_2\) → IP\(_3\) → [Ca\(^{2+}\)]\(_i\) (heart)

- **β1, β2, D1, H2, V2**
  - Receptor → G\(_i\) → Adenyl cyclase → ATP → cAMP → Protein kinase A → [Ca\(^{2+}\)]\(_i\) (heart)
  - Myosin light-chain kinase (smooth muscle)

**MAD 2’s.**
Autonomic drugs

**CHOLINERGIC**
- Choline
- Hemicholinium
- Vesamicol
- Ca²⁺
- Botulinum
- ACh receptor
- AChE
- AChE inhibitors

**NORADRENERGIC**
- Tyrosine
- Metyrosine
- Dopamine
- Reserpine
- Ca²⁺
- NE
- Adrenoreceptors α or β
- Release-modulating receptors
- Diffusion, metabolism
- Negative feedback

Circles with rotating arrows represent transporters. Drugs in italics are of historical significance.

*Release of norepinephrine from a sympathetic nerve ending is modulated by norepinephrine itself, acting on presynaptic α₂-autoreceptors.*
### Cholinomimetic agents

<table>
<thead>
<tr>
<th>DRUG</th>
<th>CLINICAL APPLICATIONS</th>
<th>ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direct agonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bethanechol</td>
<td>Postoperative ileus, neurogenic ileus, urinary retention</td>
<td>Activates bowel and bladder smooth muscle; resistant to AChE. “Bethany, call (bethanechol) me to activate your bowels and bladder.”</td>
</tr>
<tr>
<td>Carbachol</td>
<td>Constricts pupil and relieves intraocular pressure in glaucoma</td>
<td>Carbon copy of acetylcholine.</td>
</tr>
<tr>
<td>Methacholine</td>
<td>Challenge test for diagnosis of asthma</td>
<td>Stimulates muscarinic receptors in airway when inhaled.</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>Potent stimulator of sweat, tears, and saliva</td>
<td>Contracts ciliary muscle of eye (open-angle glaucoma), pupillary sphincter (closed-angle glaucoma); resistant to AChE. “You cry, drool, and sweat on your ‘pilo.’”</td>
</tr>
</tbody>
</table>

**Indirect agonists (anticholinesterases)**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>CLINICAL APPLICATIONS</th>
<th>ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil, galantamine, rivastigmine</td>
<td>Alzheimer disease.</td>
<td>↑ ACh.</td>
</tr>
<tr>
<td>Edrophonium</td>
<td>Historically, diagnosis of myasthenia gravis (extremely short acting). Myasthenia now diagnosed by anti-AChR Ab (anti-acetylcholine receptor antibody) test.</td>
<td>↑ ACh.</td>
</tr>
<tr>
<td>Neostigmine</td>
<td>Postoperative and neurogenic ileus and urinary retention, myasthenia gravis, reversal of neuromuscular junction blockade (postoperative).</td>
<td>↑ ACh.</td>
</tr>
<tr>
<td>Physostigmine</td>
<td>Anticholinergic toxicity; crosses blood-brain barrier → CNS.</td>
<td>↑ ACh.</td>
</tr>
<tr>
<td>Pyridostigmine</td>
<td>Myasthenia gravis (long acting); does not penetrate CNS.</td>
<td>↑ ACh; ↑ muscle strength. Pyridostigmine gets rid of myasthenia gravis.</td>
</tr>
</tbody>
</table>

**Note:** With all cholinomimetic agents, watch for exacerbation of COPD, asthma, and peptic ulcers when giving to susceptible patients.

### Cholinesterase inhibitor poisoning

Often due to organophosphates, such as parathion, that **irreversibly** inhibit AChE. Causes **Diarrhea, Urination, Miosis, Bronchospsasm, Bradycardia, Excitation** of skeletal muscle and CNS, **Lacrimation, Sweating, and Salivation.**

**DUMBBELSS.**

Organophosphates are often components of insecticides; poisoning usually seen in farmers. Antidote—atropine (competitive inhibitor) + pralidoxime (regenerates AChE if given early).
**Muscarinic antagonists**

<table>
<thead>
<tr>
<th>DRUGS</th>
<th>ORGAN SYSTEMS</th>
<th>APPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine, homatropine, tropicamide</td>
<td>Eye</td>
<td>Produce mydriasis and cycloplegia.</td>
</tr>
<tr>
<td>Benztrapine</td>
<td>CNS</td>
<td>Parkinson disease (“park my Benz”). Acute dystonia.</td>
</tr>
<tr>
<td>Hyoscyamine, dicyclomine</td>
<td>GI</td>
<td>Antispasmodics for irritable bowel syndrome.</td>
</tr>
<tr>
<td>Ipratropium, tiotropium</td>
<td>Respiratory</td>
<td>COPD, asthma (“I pray I can breathe soon!”).</td>
</tr>
<tr>
<td>Oxybutynin, solifenacin, tolterodine</td>
<td>Genitourinary</td>
<td>Reduce bladder spasms and urge urinary incontinence (overactive bladder).</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>CNS</td>
<td>Motion sickness.</td>
</tr>
</tbody>
</table>

**Atropine**

Muscarinic antagonist. Used to treat bradycardia and for ophthalmic applications.

<table>
<thead>
<tr>
<th>ORGAN SYSTEM</th>
<th>ACTION</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye</td>
<td>† pupil dilation, cycloplegia</td>
<td>Blocks DUMBBLeSS. Skeletal muscle and CNS excitation mediated by nicotinic receptors. See previous page.</td>
</tr>
<tr>
<td>Airway</td>
<td>† secretions</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>† acid secretion</td>
<td></td>
</tr>
<tr>
<td>Gut</td>
<td>† motility</td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>† urgency in cystitis</td>
<td></td>
</tr>
</tbody>
</table>

**TOXICITY**

† body temperature (due to ‡ sweating); rapid pulse; dry mouth; dry, flushed skin; cycloplegia; constipation; disorientation

Can cause acute angle-closure glaucoma in elderly (due to mydriasis), urinary retention in men with prostatic hyperplasia, and hyperthermia in infants

Side effects:
Hot as a hare
Dry as a bone
Red as a beet
Blind as a bat
Mad as a hatter
Jimson weed (*Datura*) → gardener’s pupil (mydriasis due to plant alkaloids)
Tetrodotoxin

Highly potent toxin that binds fast voltage-gated Na⁺ channels in cardiac and nerve tissue, preventing depolarization (blocks action potential without changing resting potential). Causes nausea, diarrhea, paresthesias, weakness, dizziness, loss of reflexes. Treatment is primarily supportive.

Poisoning can result from ingestion of poorly prepared pufferfish (fugu), a delicacy in Japan.

Ciguatoxin

Causes ciguatera fish poisoning. Opens Na⁺ channels causing depolarization. Symptoms easily confused with cholinergic poisoning. Temperature-related dysesthesia (e.g., “cold feels hot; hot feels cold”) is regarded as a specific finding of ciguatera. Treatment is primarily supportive.

Caused by consumption of reef fish (e.g., barracuda, snapper, moray eel).

Scombroid poisoning

Acute-onset burning sensation of the mouth, flushing of face, erythema, urticaria, pruritus, headache. May cause anaphylaxis-like presentation (i.e., bronchospasm, angioedema, hypotension). Treat supportively with antihistamines; if needed, antianaphylactics (e.g., bronchodilators, epinephrine).

Caused by consumption of dark-meat fish (e.g., bonito, mackerel, mahi-mahi, tuna) improperly stored at warm temperature. Bacterial histidine decarboxylase converts histidine → histamine. Histamine is not degraded by cooking. Frequently misdiagnosed as allergy to fish.
<table>
<thead>
<tr>
<th><strong>Sympathomimetics</strong></th>
<th><strong>APPLICATIONS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direct sympathomimetics</strong></td>
<td></td>
</tr>
<tr>
<td>Albuterol, salmeterol</td>
<td>Albuterol for acute asthma; salmeterol for long-term asthma or COPD control.</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>Heart failure (HF) (inotropic &gt; chronotropic), cardiac stress testing.</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Unstable bradycardia, HF, shock; inotropic and chronotropic ( \alpha ) effects predominate at high doses.</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Anaphylaxis, asthma, open-angle glaucoma; ( \alpha ) effects predominate at high doses. Significantly stronger effect at ( \beta_2 )-receptor than norepinephrine.</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>Electrophysiologic evaluation of tachyarrhythmias. Can worsen ischemia.</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Hypotension (but ↓ renal perfusion). Significantly weaker effect at ( \beta_2 )-receptor than epinephrine.</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>Hypotension (vasoconstrictor), ocular procedures (mydriatic), rhinitis (decongestant).</td>
</tr>
<tr>
<td><strong>Indirect sympathomimetics</strong></td>
<td></td>
</tr>
<tr>
<td>Amphetamine</td>
<td>Narcolepsy, obesity, ADHD.</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Causes vasoconstriction and local anesthesia. Never give ( \beta )-blockers if cocaine intoxication is suspected (can lead to unopposed ( \alpha_1 ) activation and extreme hypertension).</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>Nasal decongestion, urinary incontinence, hypotension.</td>
</tr>
</tbody>
</table>
Norepinephrine vs. isoproterenol

Norepinephrine ↑ systolic and diastolic pressures as a result of α₁-mediated vasoconstriction → ↑ mean arterial pressure → reflex bradycardia. However, isoproterenol (no longer commonly used) has little α effect but causes β₂-mediated vasodilation, resulting in ↓ mean arterial pressure and ↑ heart rate through β₁ and reflex activity.

<table>
<thead>
<tr>
<th>Sympatholytics (α₂-agonists)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DRUG</strong></td>
</tr>
<tr>
<td>Clonidine</td>
</tr>
<tr>
<td>α-methyldopa</td>
</tr>
</tbody>
</table>
**α-blockers**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>APPLICATIONS</th>
<th>SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonselective</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenoxybenzamine (irreversible)</td>
<td>Pheochromocytoma (used preoperatively) to prevent catecholamine (hypertensive) crisis</td>
<td>Orthostatic hypotension, reflex tachycardia</td>
</tr>
<tr>
<td>Phentolamine (reversible)</td>
<td>Give to patients on MAO inhibitors who eat tyramine-containing foods</td>
<td></td>
</tr>
<tr>
<td><strong>α₁ selective (-osin ending)</strong></td>
<td>Urinary symptoms of BPH, PTSD (prazosin); hypertension (except tamsulosin)</td>
<td>1st-dose orthostatic hypotension, dizziness, headache</td>
</tr>
<tr>
<td>Prazosin, terazosin, doxazosin, tamsulosin</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>α₂ selective</strong></td>
<td>Depression</td>
<td>Sedation, ↑ serum cholesterol, ↑ appetite</td>
</tr>
</tbody>
</table>

**α-blockade of epinephrine vs. phenylephrine**

![Diagram showing the effects of an α-blocker (e.g., phentolamine) on blood pressure responses to epinephrine and phenylephrine. The epinephrine response exhibits reversal of the mean blood pressure change, from a net increase (the α response) to a net decrease (the β₂ response). The response to phenylephrine is suppressed but not reversed because phenylephrine is a “pure” α-agonist without β action.](image)

Shown above are the effects of an α-blocker (e.g., phentolamine) on blood pressure responses to epinephrine and phenylephrine. The epinephrine response exhibits reversal of the mean blood pressure change, from a net increase (the α response) to a net decrease (the β₂ response). The response to phenylephrine is suppressed but not reversed because phenylephrine is a “pure” α-agonist without β action.
### β-blockers

<table>
<thead>
<tr>
<th>APPLICATION</th>
<th>EFFECTS</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina pectoris</td>
<td>↓ heart rate and contractility, resulting in ↓ O&lt;sub&gt;2&lt;/sub&gt; consumption</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>β-blockers (metoprolol, carvedilol, and bisoprolol) ↓ mortality</td>
<td></td>
</tr>
<tr>
<td>SVT (metoprolol, esmolol)</td>
<td>↑ AV conduction velocity (class II antiarrhythmic)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>↓ cardiac output, ↓ renin secretion (due to β&lt;sub&gt;1&lt;/sub&gt;-receptor blockade on JGA cells)</td>
<td></td>
</tr>
<tr>
<td>HF</td>
<td>↓ mortality in chronic HF</td>
<td></td>
</tr>
<tr>
<td>Glaucoma (timolol)</td>
<td>↓ secretion of aqueous humor</td>
<td></td>
</tr>
</tbody>
</table>

### TOXICITY

Impotence, cardiovascular adverse effects (bradycardia, AV block, HF), CNS adverse effects (seizures, sedation, sleep alterations), dyslipidemia (metoprolol), and asthma/COPD exacerbations

Avoid in cocaine users due to risk of unopposed α-adrenergic receptor agonist activity

Despite theoretical concern of masking hypoglycemia in diabetics, benefits likely outweigh risks; not contraindicated

### SELECTIVITY

#### β<sub>1</sub>-selective antagonists (β<sub>1</sub> > β<sub>2</sub>)—acebutolol (partial agonist), atenolol, betaxolol, esmolol, metoprolol

Selective antagonists mostly go from A to M (β<sub>1</sub> with 1st half of alphabet)

#### Nonselective antagonists (β<sub>1</sub> = β<sub>2</sub>)—nadolol, pindolol (partial agonist), propranolol, timolol

Nonselective antagonists mostly go from N to Z (β<sub>2</sub> with 2nd half of alphabet)

#### Nonselective α- and β-antagonists—carvedilol, labetalol

Nonselective α- and β-antagonists have modified suffixes (instead of “-olol”)

#### Nebivolol combines cardiac-selective β<sub>1</sub>-adrenergic blockade with stimulation of β<sub>3</sub>-receptors, which activate nitric oxide synthase in the vasculature
### Specific Antidotes

<table>
<thead>
<tr>
<th>TOXIN</th>
<th>ANTIDOTE/TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>N-acetylcysteine (replenishes glutathione)</td>
</tr>
<tr>
<td>AChE inhibitors, organophosphates</td>
<td>Atropine &gt; pralidoxime</td>
</tr>
<tr>
<td>Amphetamines (basic)</td>
<td>N\textsubscript{2}Cl (acidify urine)</td>
</tr>
<tr>
<td>Antimuscarinic, anticholinergic agents</td>
<td>Physostigmine salicylate, control hyperthermia</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Flumazenil</td>
</tr>
<tr>
<td>(\beta)-blockers</td>
<td>Glucagon</td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>100% O\textsubscript{2}, hyperbaric O\textsubscript{2}</td>
</tr>
<tr>
<td>Copper, arsenic, gold</td>
<td>Penicillamine</td>
</tr>
<tr>
<td>Cyanide</td>
<td>Nitrite + thiosulfate, hydroxocobalamin</td>
</tr>
<tr>
<td>Digitalis (digoxin)</td>
<td>Anti-dig Fab fragments</td>
</tr>
<tr>
<td>Heparin</td>
<td>Protamine sulfate</td>
</tr>
</tbody>
</table>

### Drug Reactions—Cardiovascular

<table>
<thead>
<tr>
<th>DRUG REACTION</th>
<th>CAUSAL AGENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary vasospasm</td>
<td>Cocaine, sumatriptan, ergot alkaloids</td>
</tr>
<tr>
<td>Cutaneous flushing</td>
<td>Vancomycin, Adenosine, Niacin, Ca\textsuperscript{2+} channel blockers (VANC)</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>Anthracyclines (e.g., doxorubicin, daunorubicin); prevent with dextrazoxane</td>
</tr>
<tr>
<td>Torsades de pointes</td>
<td>Class III (e.g., sotalol) and class IA (e.g., quinidine) antiarrhythmics, macrolide antibiotics, antipsychotics, TCAs</td>
</tr>
</tbody>
</table>
# Drug reactions—endocrine/reproductive

<table>
<thead>
<tr>
<th>Drug Reaction</th>
<th>Causal Agents</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenocortical insufficiency</td>
<td>HPA suppression 2° to glucocorticoid withdrawal</td>
<td></td>
</tr>
<tr>
<td>Hot flashes</td>
<td>Tamoxifen, clomiphene</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>Tacrolimus, Protease inhibitors, Niacin, HCTZ, Corticosteroids</td>
<td>Taking Pills Necessitates Having blood Checked</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Lithium, amiodarone, sulfonamides</td>
<td></td>
</tr>
</tbody>
</table>

# Drug reactions—GI

<table>
<thead>
<tr>
<th>Drug Reaction</th>
<th>Causal Agents</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute cholestatic hepatitis, jaundice</td>
<td>Erythromycin</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Metformin, Erythromycin, Colchicine, Orlistat, Acarbose</td>
<td>Might Excite Colon On Accident</td>
</tr>
<tr>
<td>Focal to massive hepatic necrosis</td>
<td>Halothane, Amanita phalloides (death cap mushroom), Valproic acid, Acetaminophen</td>
<td>Liver “HAVAc”</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Rifampin, isoniazid, pyrazinamide, statins, fibrates</td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Didanosine, Corticosteroids, Alcohol, Valproic acid, Azathioprine, Diuretics (furosemide, HCTZ)</td>
<td>Drugs Causing A Violent Abdominal Distress</td>
</tr>
<tr>
<td>Pseudomembranous colitis</td>
<td>Clindamycin, ampicillin, cephalosporins</td>
<td>Antibiotics predispose to superinfection by resistant C. difficile</td>
</tr>
</tbody>
</table>

# Drug reactions—hematologic

<table>
<thead>
<tr>
<th>Drug Reaction</th>
<th>Causal Agents</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agranulocytosis</td>
<td>Ganciclovir, Clozapine, Carbamazepine, Colchicine, Methimazole, Propylthiouracil</td>
<td>Gangs CCCrush Myeloblasts and Promyelocytes</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>Carbamazepine, Methimazole, NSAIDs, Benzene, Chloramphenicol, Propylthiouracil</td>
<td>Can’t Make New Blood Cells Properly</td>
</tr>
<tr>
<td>Direct Coombs-positive hemolytic anemia</td>
<td>Methyldopa, penicillin</td>
<td></td>
</tr>
<tr>
<td>Gray baby syndrome</td>
<td>Chloramphenicol</td>
<td></td>
</tr>
<tr>
<td>Hemolysis in G6PD deficiency</td>
<td>Isoniazid, Sulfonamides, Dapsone, Primaquine, Aspirin, Ibuprofen, Nitrofurantoin</td>
<td>Hemolysis IS D PAIN</td>
</tr>
<tr>
<td>Megaloblastic anemia</td>
<td>Phenyltoin, Methotrexate, Sulfquinone</td>
<td>Having a blast with PMS</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Heparin</td>
<td></td>
</tr>
<tr>
<td>Thrombotic complications</td>
<td>OCPs, hormone replacement therapy</td>
<td></td>
</tr>
</tbody>
</table>
### Drug reactions—musculoskeletal/skin/connective tissue

<table>
<thead>
<tr>
<th>Drug Reaction</th>
<th>Causal Agents</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat redistribution</td>
<td>Protease inhibitors, Glucocorticoids</td>
<td>Fat PiG</td>
</tr>
<tr>
<td>Gingival hyperplasia</td>
<td>Phenytoin, Ca^{2+} channel blockers, cyclosporine</td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia (gout)</td>
<td>Pyrazinamide, Thiazides, Furosemide, Niacin, Cyclosporine</td>
<td>Painful Tophi and Feet Need Care</td>
</tr>
<tr>
<td>Myopathy</td>
<td>Fibrates, niacin, colchicine, hydroxychloroquine, interferon-α, penicillamine, statins, glucocorticoids</td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Corticosteroids, heparin</td>
<td></td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>Sulfonamides, Amiodarone, Tetracyclines, 5-FU</td>
<td>SAT For Photo</td>
</tr>
<tr>
<td>Rash (Stevens-Johnson syndrome)</td>
<td>Anti-epileptic drugs (especially lamotrigine), allopurinol, sulfa drugs, penicillin</td>
<td>Steven Johnson has epileptic allergy to sulfa drugs and penicillin</td>
</tr>
<tr>
<td>SLE-like syndrome</td>
<td>Sulfonamide, Hydralazine, Isoniazid, Procainamide, Phenytoin, Etanercept</td>
<td>Having lupus is “SHIPP-E”</td>
</tr>
<tr>
<td>Teeth discoloration</td>
<td>Tetracyclines</td>
<td></td>
</tr>
<tr>
<td>Tendonitis, tendon rupture, and cartilage damage</td>
<td>Fluoroquinolones</td>
<td></td>
</tr>
</tbody>
</table>

### Drug reactions—neurologic

<table>
<thead>
<tr>
<th>Drug Reaction</th>
<th>Causal Agents</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cinchonism</td>
<td>Quinidine, quinine</td>
<td></td>
</tr>
<tr>
<td>Parkinson-like syndrome</td>
<td>Antipsychotics, Reserpine, Metoclopramide</td>
<td>Cogwheel rigidity of ARM</td>
</tr>
<tr>
<td>Seizures</td>
<td>Isoniazid (vitamin B_6 deficiency), Bupropion, Imipenem/cilastatin, Enflurane</td>
<td>With seizures, I Breathe my tongue</td>
</tr>
<tr>
<td>Tardive dyskinesia</td>
<td>Antipsychotics, metoclopramide</td>
<td></td>
</tr>
</tbody>
</table>

### Drug reactions—renal/genitourinary

<table>
<thead>
<tr>
<th>Drug Reaction</th>
<th>Causal Agents</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes insipidus</td>
<td>Lithium, demeclocycline</td>
<td></td>
</tr>
<tr>
<td>Fanconi syndrome</td>
<td>Expired tetracycline</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic cystis</td>
<td>Cyclophosphamide, ifosfamide</td>
<td>Prevent by coadministering with mesna</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>Methicillin, NSAIDs, furosemide</td>
<td></td>
</tr>
<tr>
<td>SIADH</td>
<td>Carbamazepine, Cyclophosphamide, SSRIs</td>
<td>Can’t Concentrate Serum Sodium</td>
</tr>
</tbody>
</table>
Drug reactions—respiratory

<table>
<thead>
<tr>
<th>Drug reaction</th>
<th>Causal agents</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry cough</td>
<td>ACE inhibitors</td>
<td></td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>Bleomycin, Amiodarone, Busulfan, Methotrexate</td>
<td>Breathing Air Badly from Medications</td>
</tr>
</tbody>
</table>

Drug reactions—multiorgan

<table>
<thead>
<tr>
<th>Drug reaction</th>
<th>Causal agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimuscarinic</td>
<td>Atropine, TCAs, H₁-blockers, antipsychotics</td>
</tr>
<tr>
<td>Disulfiram-like reaction</td>
<td>Metronidazole, certain cephalosporins, griseofulvin, procarbazine, 1st-generation sulfonylureas</td>
</tr>
<tr>
<td>Nephrotoxicity/ ototoxicity</td>
<td>Aminoglycosides, vancomycin, loop diuretics, cisplatin. Cisplatin toxicity may respond to amifostine.</td>
</tr>
</tbody>
</table>

Cytochrome P-450 interactions (selected)

<table>
<thead>
<tr>
<th>Inducers (+)</th>
<th>Substrates</th>
<th>Inhibitors (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic alcohol</td>
<td>Anti-epileptics</td>
<td>Acute alcohol abuse</td>
</tr>
<tr>
<td>St. John's wort</td>
<td>Theophylline</td>
<td>Ritonavir</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Warfarin</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>OCPs</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Nevirapine</td>
<td></td>
<td>Ketoconazole</td>
</tr>
<tr>
<td>Rifampin</td>
<td></td>
<td>Sulfonamides</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td></td>
<td>Isoniazid (INH)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
<td>Grapefruit juice</td>
</tr>
<tr>
<td>Chronic alcoholics</td>
<td>Steal</td>
<td>Quinidine</td>
</tr>
<tr>
<td>Phen-Phen and Never</td>
<td>Always Think When Outdoors</td>
<td>Macrolides (except azithromycin)</td>
</tr>
<tr>
<td>Refuse Greasy Carbs</td>
<td>AAA RACKS IN GQ</td>
<td>Magazine</td>
</tr>
</tbody>
</table>

Sulfa drugs

| Probenecid, Furosemide, Acetzolamide, Celecoxib, Thiazides, Sulfonamide antibiotics, Sulfasalazine, Sulfonyleureas. Patients with sulfa allergies may develop fever, urinary tract infection, Stevens-Johnson syndrome, hemolytic anemia, thrombocytopenia, agranulocytosis, and urticaria (hives). Symptoms range from mild to life threatening. | Popular FACTSSS |

<p>| Public |</p>
<table>
<thead>
<tr>
<th>ENDING</th>
<th>CATEGORY</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>-azole</td>
<td>Ergosterol synthesis inhibitor</td>
<td>Ketoconazole</td>
</tr>
<tr>
<td>-bendazole</td>
<td>Antiparasitic/anthelmintic</td>
<td>Mebendazole</td>
</tr>
<tr>
<td>-cillin</td>
<td>Peptidoglycan synthesis inhibitor</td>
<td>Ampicillin</td>
</tr>
<tr>
<td>-cycline</td>
<td>Protein synthesis inhibitor</td>
<td>Tetracycline</td>
</tr>
<tr>
<td>-ivir</td>
<td>Neuraminidase inhibitor</td>
<td>Oseltamivir</td>
</tr>
<tr>
<td>-navir</td>
<td>Protease inhibitor</td>
<td>Ritonavir</td>
</tr>
<tr>
<td>-ovir</td>
<td>DNA polymerase inhibitor</td>
<td>Acyclovir</td>
</tr>
<tr>
<td>-thromycin</td>
<td>Macrolide antibiotic</td>
<td>Azithromycin</td>
</tr>
<tr>
<td>-ane</td>
<td>Inhalational general anesthetic</td>
<td>Halothane</td>
</tr>
<tr>
<td>-azine</td>
<td>Typical antipsychotic</td>
<td>Thioridazine</td>
</tr>
<tr>
<td>-barbital</td>
<td>Barbiturate</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>-caine</td>
<td>Local anesthetic</td>
<td>Lidocaine</td>
</tr>
<tr>
<td>-etine</td>
<td>SSRI</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>-ipramine, -triptyline</td>
<td>TCA</td>
<td>Imipramine, amitriptyline</td>
</tr>
<tr>
<td>-triptan</td>
<td>5-HT\textsubscript{1B/1D} agonists</td>
<td>Sumatriptan</td>
</tr>
<tr>
<td>-zepam, -zolam</td>
<td>Benzodiazepine</td>
<td>Diazepam, alprazolam</td>
</tr>
<tr>
<td>-chol</td>
<td>Cholinergic agonist</td>
<td>Bethanechol/carbachol</td>
</tr>
<tr>
<td>-curium, -curonium</td>
<td>Nondepolarizing paralytic</td>
<td>Atracurium, vecuronium</td>
</tr>
<tr>
<td>-olol</td>
<td>β-blocker</td>
<td>Propranolol</td>
</tr>
<tr>
<td>-stigmine</td>
<td>AChE inhibitor</td>
<td>Neostigmine</td>
</tr>
<tr>
<td>-terol</td>
<td>β\textsubscript{2}-agonist</td>
<td>Albuterol</td>
</tr>
<tr>
<td>-zosin</td>
<td>α\textsubscript{1}-antagonist</td>
<td>Prazosin</td>
</tr>
<tr>
<td>-afil</td>
<td>PDE-5 inhibitor</td>
<td>Sildenafil</td>
</tr>
<tr>
<td>-dipine</td>
<td>Dihydropyridine CCB</td>
<td>Amlodipine</td>
</tr>
<tr>
<td>-pril</td>
<td>ACE inhibitor</td>
<td>Captopril</td>
</tr>
<tr>
<td>-sartan</td>
<td>Angiotensin-II receptor blocker</td>
<td>Losartan</td>
</tr>
<tr>
<td>-statin</td>
<td>HMG-CoA reductase inhibitor</td>
<td>Atorvastatin</td>
</tr>
<tr>
<td>-dronate</td>
<td>Bisphosphonate</td>
<td>Alendronate</td>
</tr>
<tr>
<td>-glitazone</td>
<td>PPAR-γ activator</td>
<td>Rosiglitazone</td>
</tr>
<tr>
<td>-prazole</td>
<td>Proton pump inhibitor</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>-prost</td>
<td>Prostaglandin analog</td>
<td>Latanoprost</td>
</tr>
<tr>
<td>-tidine</td>
<td>H\textsubscript{2}-antagonist</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>-tropin</td>
<td>Pituitary hormone</td>
<td>Somatotropin</td>
</tr>
<tr>
<td>-ximab</td>
<td>Chimeric monoclonal Ab</td>
<td>Basiliximab</td>
</tr>
<tr>
<td>-zumab</td>
<td>Humanized monoclonal Ab</td>
<td>Daclizumab</td>
</tr>
</tbody>
</table>
High-Yield Organ Systems

“Symptoms, then, are in reality nothing but the cry from suffering organs.”
—Jean-Martin Charcot

“Man is an intelligence in servitude to his organs.”
—Aldous Huxley

“Learn that you are a machine, your heart an engine, your lungs a fanning machine and a sieve, your brain with its two lobes an electric battery.”
—Andrew T. Still

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- Reproductive 557
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APPROACHING THE ORGAN SYSTEMS

In this section, we have divided the High-Yield Facts into the major Organ Systems. Within each Organ System are several subsections, including Embryology, Anatomy, Physiology, Pathology, and Pharmacology. As you progress through each Organ System, refer back to information in the previous subsections to organize these basic science subsections into a “vertically integrated” framework for learning. Below is some general advice for studying the organ systems by these subsections.

Embryology

Relevant embryology is included in each organ system subsection. Embryology tends to correspond well with the relevant anatomy, especially with regard to congenital malformations.

Anatomy

Several topics fall under this heading, including gross anatomy, histology, and neuroanatomy. Do not memorize all the small details; however, do not ignore anatomy altogether. Review what you have already learned and what you wish you had learned. Many questions require two or more steps. The first step is to identify a structure on anatomic cross section, electron micrograph, or photomicrograph. The second step may require an understanding of the clinical significance of the structure.

When studying, stress clinically important material. For example, be familiar with gross anatomy and radiologic anatomy related to specific diseases (e.g., Pancoast tumor, Horner syndrome), traumatic injuries (e.g., fractures, sensory and motor nerve deficits), procedures (e.g., lumbar puncture), and common surgeries (e.g., 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 (e.g., 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 (e.g., the Fick equation, clearance equations). You are seldom asked to perform complex
calculations. Hormones are the focus of many questions, so learn their sites of production and action as well as their regulatory mechanisms.

A large portion of the physiology tested on the USMLE Step 1 is clinically relevant and involves understanding physiologic changes associated with pathologic processes (e.g., 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 (e.g., 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 (e.g., café-au-lait macules and neurofibromatosis); you must also know the clinical descriptions of these findings.

Given the clinical slant of the USMLE Step 1, it is also important to review the classic presenting signs and symptoms of diseases as well as their associated laboratory findings. Delve into the signs, symptoms, and pathophysiology of major diseases that have a high prevalence in the United States (e.g., alcoholism, diabetes, hypertension, heart failure, ischemic heart disease, infectious disease). Be prepared to think one step beyond the simple diagnosis to treatment or complications.

The examination includes a number of color photomicrographs and photographs of gross specimens that are presented in the setting of a brief clinical history. However, read the question and the choices carefully before looking at the illustration, because the history will help you identify the pathologic process. Flip through an illustrated pathology textbook, color atlases, and appropriate Web sites in order to look at the pictures in the days before the exam. Pay attention to potential clues such as age, sex, ethnicity, occupation, recent activities and exposures, and specialized lab tests.

**Pharmacology**

Preparation for questions on pharmacology is straightforward. Memorizing all the key drugs and their characteristics (e.g., mechanisms, clinical use, and important side effects) is high yield. Focus on understanding the prototype drugs in each class. Avoid memorizing obscure derivatives. Learn the “classic” and distinguishing toxicities of the major drugs. Do not bother with drug dosages or trade names. Reviewing associated biochemistry, physiology, and microbiology can be useful while studying pharmacology. There is a strong emphasis on ANS, CNS, antimicrobial, and cardiovascular agents as well as NSAIDs. Much of the material is clinically relevant. Newer drugs on the market are also fair game.
HIGH-YIELD SYSTEMS

Cardiovascular

“As for me, except for an occasional heart attack, I feel as young as I ever did.”
—Robert Benchley

“Hearts will never be practical until they are made unbreakable.”
—The Wizard of Oz

“As the arteries grow hard, the heart grows soft.”
—H. L. Mencken

“Nobody has ever measured, not even poets, how much the heart can hold.”
—Zelda Fitzgerald

“Only from the heart can you touch the sky.”
—Rumi

“It is not the size of the man but the size of his heart that matters.”
—Evander Holyfield
Heart embryology

<table>
<thead>
<tr>
<th>Embryonic Structure</th>
<th>Gives Rise To</th>
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</thead>
<tbody>
<tr>
<td>Truncus arteriosus</td>
<td>Ascending aorta and pulmonary trunk</td>
</tr>
<tr>
<td>Bulbus cordis</td>
<td>Smooth parts (outflow tract) of left and right ventricles</td>
</tr>
<tr>
<td>Primitive atrium</td>
<td>Trabeculated part of left and right atria</td>
</tr>
<tr>
<td>Primitive ventricle</td>
<td>Trabeculated part of left and right ventricles</td>
</tr>
<tr>
<td>Primitive pulmonary vein</td>
<td>Smooth part of left atrium</td>
</tr>
<tr>
<td>Left horn of sinus venosus</td>
<td>Coronary sinus</td>
</tr>
<tr>
<td>Right horn of sinus venosus</td>
<td>Smooth part of right atrium (sinus venarum)</td>
</tr>
<tr>
<td>Right common cardinal vein</td>
<td>Superior vena cava (SVC)</td>
</tr>
</tbody>
</table>

Heart morphogenesis
First functional organ in vertebrate embryos; beats spontaneously by week 4 of development.

Cardiac looping
Primary heart tube loops to establish left-right polarity; begins in week 4 of gestation.
Defect in left-right dynein (involved in L/R asymmetry) can lead to dextrocardia, as seen in Kartagener syndrome (primary ciliary dyskinesia).

Septation of the chambers

**Atria**

1. Septum primum grows toward endocardial cushions, narrowing foramen primum.
2. Foramen secundum forms in septum primum (foramen primum disappears).
3. Septum secundum develops as foramen secundum maintains right-to-left shunt.
4. Septum secundum expands and covers most of the foramen secundum. The residual foramen is the foramen ovale.
5. Remaining portion of septum primum forms valve of foramen ovale.
6. (Not shown) Septum secundum and septum primum fuse to form the atrial septum.
7. (Not shown) Foramen ovale usually closes soon after birth because of LA pressure.

**Patent foramen ovale**—caused by failure of septum primum and septum secundum to fuse after birth; most are left untreated. Can lead to paradoxical emboli (venous thromboemboli that enter systemic arterial circulation), similar to those resulting from an ASD.
Heart morphogenesis (continued)

Ventricles

1. Muscular ventricular septum forms. Opening is called interventricular foramen.
2. Aorticopulmonary septum rotates and fuses with muscular ventricular septum to form membranous interventricular septum, closing interventricular foramen.
3. Growth of endocardial cushions separates atria from ventricles and contributes to both atrial septation and membranous portion of the interventricular septum.

Ventricular septal defect (VSD)—most commonly occurs in the membranous septum.

Outflow tract formation

- Truncus arteriosus rotates; neural crest and endocardial cell migrations → truncal and bulbar ridges that spiral and fuse to form aorticopulmonary septum → ascending aorta and pulmonary trunk.

Conotruncal abnormalities:
- Transposition of great vessels.
- Tetralogy of Fallot.
- Persistent truncus arteriosus.

Valve development

- Aortic/pulmonary: derived from endocardial cushions of outflow tract.
- Mitral/tricuspid: derived from fused endocardial cushions of the AV canal.

Valvular anomalies may be stenotic, regurgitant, atretic (e.g., tricuspid atresia), or displaced (e.g., Ebstein anomaly).
Fetal erythropoiesis occurs in:
- Yolk sac (3–8 weeks)
- Liver (6 weeks–birth)
- Spleen (10–28 weeks)
- Bone marrow (18 weeks to adult)

Young Liver Synthesizes Blood.

Hemoglobin development
Embryonic globins: ζ and ε.
Fetal hemoglobin (HbF) = α2γ2.
Adult hemoglobin (HbA1) = α2β2.
HbF has higher affinity for O2 due to less avid binding of 2,3-BPG, allowing HbF to extract O2 from maternal hemoglobin (HbA1 and HbA2) across the placenta.

From fetal to adult hemoglobin:
Alpha Always; Gamma Goes, Becomes Beta.

Site of erythropoiesis
% of total globin synthesis

Weeks: 6 12 18 24 30 36 6 12 18 24 30 36 42 >>

FETUS (weeks) POSTNATAL (months) ADULT >>
Fetal circulation

Blood in umbilical vein has a $P_O_2$ of $\approx 30$ mmHg and is $\approx 80\%$ saturated with $O_2$. Umbilical arteries have low $O_2$ saturation.

3 important shunts:

1. Blood entering fetus through the umbilical vein is conducted via the ductus venosus into the IVC, bypassing hepatic circulation.
2. Most of the highly oxygenated blood reaching the heart via the IVC is directed through the foramen ovale and pumped into the aorta to supply the head and body.
3. Deoxygenated blood from the SVC passes through the RA $\rightarrow$ RV $\rightarrow$ main pulmonary artery $\rightarrow$ patent ductus arteriosus $\rightarrow$ descending aorta; shunt is due to high fetal pulmonary artery resistance (due partly to low $O_2$ tension).

At birth, infant takes a breath; 1. resistance in pulmonary vasculature $\rightarrow$ ↑ left atrial pressure vs. right atrial pressure; foramen ovale closes (now called fossa ovalis); ↑ in $O_2$ (from respiration) and ↓ in prostaglandins (from placental separation) $\rightarrow$ closure of ductus arteriosus.

Indomethacin helps close PDA $\rightarrow$ ligamentum arteriosum (remnant of ductus arteriosus).

Prostaglandins $E_1$ and $E_2$ keep PDA open.

### Fetal-postnatal derivatives

<table>
<thead>
<tr>
<th>AllenTois $\rightarrow$ urachus</th>
<th>MediaN umbilical ligament</th>
<th>Urachus is part of allantoic duct between bladder and umbilicus.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductus arteriosus</td>
<td>Ligamentum arteriosum</td>
<td></td>
</tr>
<tr>
<td>Ductus venosus</td>
<td>Ligamentum venosum</td>
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<tr>
<td>Foramen ovale</td>
<td>Fossa ovalis</td>
<td></td>
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<tr>
<td>Notochord</td>
<td>Nucleus pulposus</td>
<td></td>
</tr>
<tr>
<td>Umbilical arteries</td>
<td>MediaL umbilical ligaments</td>
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</tr>
<tr>
<td>Umbilical vein</td>
<td>Ligamentum teres hepatis</td>
<td>Contained in falciform ligament.</td>
</tr>
</tbody>
</table>
Coronary artery anatomy

SA and AV nodes are usually supplied by RCA. Infarct may cause nodal dysfunction (bradycardia or heart block).

Right-dominant circulation = 85% = PDA arises from RCA.

Left-dominant circulation = 8% = PDA arises from LCX.

Codominant circulation = 7% = PDA arises from both LCX and RCA.

Coronary artery occlusion most commonly occurs in the LAD.

Coronary blood flow peaks in early diastole.

The most posterior part of the heart is the left atrium; enlargement can cause dysphagia (due to compression of the esophagus) or hoarseness (due to compression of the left recurrent laryngeal nerve, a branch of the vagus).

Cardiac output

CO = stroke volume (SV) × heart rate (HR).

Fick principle:

\[
CO = \frac{\text{rate of } O_2 \text{ consumption}}{\text{arterial } O_2 \text{ content} - \text{venous } O_2 \text{ content}}
\]

Mean arterial pressure (MAP) = CO × total peripheral resistance (TPR).

MAP = \(\frac{2}{3}\) diastolic pressure + \(\frac{1}{3}\) systolic pressure.

Pulse pressure = systolic pressure – diastolic pressure.

Pulse pressure is proportional to SV, inversely proportional to arterial compliance.

SV = end-diastolic volume (EDV) – end-systolic volume (ESV).

During the early stages of exercise, CO is maintained by ↑ HR and ↑ SV. During the late stages of exercise, CO is maintained by ↑ HR only (SV plateaus).

Diastole is preferentially shortened with ↑ HR; less filling time → ↓ CO (e.g., ventricular tachycardia).

↑ pulse pressure in hyperthyroidism, aortic regurgitation, aortic stiffening (isolated systolic hypertension in elderly), obstructive sleep apnea (↑ sympathetic tone), exercise (transient).

↑ pulse pressure in aortic stenosis, cardiogenic shock, cardiac tamponade, advanced heart failure (HF).
### Cardiac output variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke volume</strong></td>
<td>Stroke volume affected by <strong>Contractility</strong>, <strong>Afterload</strong>, and <strong>Preload</strong>.</td>
</tr>
<tr>
<td></td>
<td><strong>SV</strong> with:</td>
</tr>
<tr>
<td></td>
<td>† <strong>Contractility</strong> (e.g., anxiety, exercise, pregnancy)</td>
</tr>
<tr>
<td></td>
<td>† <strong>Preload</strong></td>
</tr>
<tr>
<td></td>
<td>† <strong>Afterload</strong></td>
</tr>
<tr>
<td><strong>Contractility</strong></td>
<td>Contractility (and <strong>SV</strong>) with:</td>
</tr>
<tr>
<td></td>
<td>† Catecholamines († activity of Ca(^{2+}) pump in sarcoplasmic reticulum)</td>
</tr>
<tr>
<td></td>
<td>† intracellular Ca(^{2+})</td>
</tr>
<tr>
<td></td>
<td>† extracellular Na(^{+}) (‡ activity of Na(^{+})/Ca(^{2+}) exchanger)</td>
</tr>
<tr>
<td></td>
<td>Digitalis (blocks Na(^{+})/K(^{+}) pump)</td>
</tr>
<tr>
<td></td>
<td>† intracellular Na(^{+}) → ‡ Na(^{+})/Ca(^{2+}) exchanger activity → † intracellular Ca(^{2+})</td>
</tr>
<tr>
<td><strong>Myocardial oxygen demand</strong></td>
<td>† Myocardial O(_2) demand is † by:</td>
</tr>
<tr>
<td></td>
<td>† <strong>Contractility</strong></td>
</tr>
<tr>
<td></td>
<td>† <strong>Afterload</strong> (proportional to arterial pressure)</td>
</tr>
<tr>
<td></td>
<td>† <strong>heart Rate</strong></td>
</tr>
<tr>
<td></td>
<td>† <strong>Diameter</strong> of ventricle (<strong>wall tension</strong>)</td>
</tr>
<tr>
<td><strong>Preload</strong></td>
<td>Preload approximated by ventricular EDV; depends on venous tone and circulating blood volume.</td>
</tr>
<tr>
<td></td>
<td>VEndilators (e.g., nitroglycerin) ⇑ prEload.</td>
</tr>
<tr>
<td><strong>Afterload</strong></td>
<td>Afterload approximated by MAP.</td>
</tr>
<tr>
<td></td>
<td>† afterload → † pressure → † wall tension per Laplace’s law.</td>
</tr>
<tr>
<td></td>
<td>LV compensates for † afterload by thickening (hypertrophy) in order to ‡ wall tension.</td>
</tr>
<tr>
<td></td>
<td>VAsodilators (e.g., hydralazine) ⇑ Afterload (Arterial).</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitors and ARBs ⇑ both preload and afterload.</td>
</tr>
<tr>
<td></td>
<td>Chronic hypertension († MAP) → LV hypertrophy.</td>
</tr>
<tr>
<td><strong>Ejection fraction</strong></td>
<td>EF = (\frac{SV}{EDV} = \frac{EDV - ESV}{EDV})</td>
</tr>
<tr>
<td></td>
<td>Left ventricular EF is an index of ventricular contractility; normal EF is ≥ 55%.</td>
</tr>
<tr>
<td></td>
<td>EF ‡ in systolic HF.</td>
</tr>
<tr>
<td></td>
<td>EF normal in diastolic HF.</td>
</tr>
</tbody>
</table>
**Starling curve**

![Starling curve diagram]

Force of contraction is proportional to end-diastolic length of cardiac muscle fiber (preload).

- ↑ contractility with catecholamines, positive inotropes (e.g., digoxin).
- ↓ contractility with loss of myocardium (e.g., MI), β-blockers (acutely), non-dihydropyridine Ca^{2+} channel blockers, dilated cardiomyopathy.

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**Resistance, pressure, flow**

\[
\Delta P = Q \times R
\]

Similar to Ohm’s law: \( \Delta V = IR \)

Volumetric flow rate \( Q \) = flow velocity \( v \) \times cross-sectional area \( A \)

Resistance

\[
R = \frac{\text{driving pressure} (\Delta P)}{\text{flow} (Q)} = \frac{8\eta \text{ (viscosity)} \times \text{length}}{\pi r^4}
\]

Total resistance of vessels in series:

\[
TR = R_1 + R_2 + R_3 + \ldots
\]

Total resistance of vessels in parallel:

\[
\frac{1}{TR} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} + \ldots
\]

Viscosity depends mostly on hematocrit

- Viscosity ↑ in hyperproteinic states (e.g., multiple myeloma), polycythemia
- Viscosity ↓ in anemia

Capillaries have highest total cross-sectional area and lowest flow velocity.

Organ removal (e.g., nephrectomy) → ↑ TPR and ↓ CO.

Pressure gradient drives flow from high pressure to low pressure.

Arterioles account for most of TPR. Veins provide most of blood storage capacity.
**Cardiac and vascular function curves**

Intersection of curves = operating point of heart (i.e., venous return and CO are equal).

<table>
<thead>
<tr>
<th>CURVE</th>
<th>EFFECT</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong> Inotropy</td>
<td>Changes in contractility → altered CO for a given RA pressure (preload).</td>
<td>1 Catecholamines, digoxin ⊕ 2 Uncompensated HF, narcotic overdose ⊝</td>
</tr>
<tr>
<td><strong>B</strong> Venous return</td>
<td>Changes in circulating volume or venous tone → altered RA pressure for a given CO. Mean systemic pressure (x-intercept) changes with volume/venous tone.</td>
<td>3 Fluid infusion, sympathetic activity ⊕ 4 Acute hemorrhage, spinal anesthesia ⊝</td>
</tr>
<tr>
<td><strong>C</strong> Total peripheral resistance</td>
<td>Changes in TPR → altered CO at a given RA pressure; however, mean systemic pressure (x-intercept) is unchanged.</td>
<td>5 Vasopressors ⊕ 6 Exercise, AV shunt ⊝</td>
</tr>
</tbody>
</table>

Changes often occur in tandem, and may be reinforcing (e.g., exercise ↑ inotropy and ↓ TPR to maximize CO) or compensatory (e.g., HF ↓ inotropy → fluid retention to ↑ preload to maintain CO).
Pressure-volume loops and cardiac cycle

The black loop represents normal cardiac physiology.

Phases—left ventricle:
1. Isovolumetric contraction—period between mitral valve closing and aortic valve opening; period of highest O₂ consumption
2. Systolic ejection—period between aortic valve opening and closing
3. Isovolumetric relaxation—period between aortic valve closing and mitral valve opening
4. Rapid filling—period just after mitral valve opening
5. Reduced filling—period just before mitral valve closing

Sounds:
S1—mitral and tricuspid valve closure. Loudest at mitral area.
S2—aortic and pulmonary valve closure. Loudest at left upper sternal border.
S3—in early diastole during rapid ventricular filling phase. Associated with ↑ filling pressures (e.g., mitral regurgitation, HF) and more common in dilated ventricles (but normal in children and pregnant women).
S4—in late diastole (“atrial kick”). Best heard at apex with patient in left lateral decubitus position. High atrial pressure. Associated with ventricular hypertrophy. Left atrium must push against stiff LV wall.

Jugular venous pulse (JVP):
a wave—atrial contraction. Absent in atrial fibrillation.
c wave—RV contraction (closed tricuspid valve bulging into atrium).
x descent—atrial relaxation and downward displacement of closed tricuspid valve during ventricular contraction. Absent in tricuspid regurgitation.
v wave—↑ right atrial pressure due to filling (“villing”) against closed tricuspid valve.
y descent—RA emptying into RV.
<table>
<thead>
<tr>
<th>Splitting</th>
<th>Inspiration</th>
<th>Expiration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal splitting</strong></td>
<td>Inspiration → drop in intrathoracic pressure → ↑ venous return → ↑ RV filling → ↑ RV stroke volume → ↑ RV ejection time → delayed closure of pulmonic valve.</td>
<td>Expiration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inspiration</td>
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<tr>
<td><strong>Wide splitting</strong></td>
<td>Seen in conditions that delay RV emptying (e.g., pulmonic stenosis, right bundle branch block). Delay in RV emptying causes delayed pulmonic sound (regardless of breath). An exaggeration of normal splitting.</td>
<td>Expiration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inspiration</td>
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<tr>
<td><strong>Fixed splitting</strong></td>
<td>Seen in ASD. ASD → left-to-right shunt → ↑ RA and RV volumes → ↑ flow through pulmonic valve such that, regardless of breath, pulmonic closure is greatly delayed.</td>
<td>Expiration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inspiration</td>
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<tr>
<td><strong>Paradoxical splitting</strong></td>
<td>Seen in conditions that delay aortic valve closure (e.g., aortic stenosis, left bundle branch block). Normal order of valve closure is reversed so that P2 sound occurs before delayed A2 sound. Therefore on inspiration, P2 closes later and moves closer to A2, thereby “paradoxically” eliminating the split.</td>
<td>Expiration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inspiration</td>
</tr>
<tr>
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</tbody>
</table>
Auscultation of the heart

Where to listen: APT M

**Aortic area:**
- Systolic murmur
- Aortic stenosis
- Flow murmur
- Aortic valve sclerosis

**Pulmonic area:**
- Systolic ejection murmur
- Pulmonic stenosis
- Flow murmur (e.g., physiologic murmur)

**Tricuspid area:**
- Pansystolic murmur
- Tricuspid regurgitation
- Ventricular septal defect
- Diastolic murmur
- Tricuspid stenosis
- Atrial septal defect

**Mitral area:**
- Systolic murmur
- Mitral regurgitation
- Diastolic murmur
- Mitral stenosis

**Left sternal border:**
- Diastolic murmur
- Aortic regurgitation
- Pulmonic regurgitation
- Systolic murmur
- Hypertrophic cardiomyopathy

**Left infraclavicular region:**
- Continuous murmur
- Patent ductus arteriosus

**Bedside maneuver** | **Effect**
--- | ---
Inspiration (↑ venous return to right atrium) | ↑ intensity of right heart sounds
Hand grip (↑ afterload) | ↑ intensity of MR, AR, VSD murmurs ↓ hypertrophic cardiomyopathy murmurs MVP: later onset of click/murmur
Valsalva (phase II), standing up (↓ preload) | ↓ intensity of most murmurs (including AS) ↑ intensity of hypertrophic cardiomyopathy murmur MVP: earlier onset of click/murmur
Rapid squatting (↑ venous return, ↑ preload) | ↓ intensity of hypertrophic cardiomyopathy murmur ↑ intensity of AS murmur MVP: later onset of click/murmur

Systolic heart sounds include aortic/pulmonic stenosis, mitral/tricuspid regurgitation, VSD, MVP. Diastolic heart sounds include aortic/pulmonic regurgitation, mitral/tricuspid stenosis.

*ASD commonly presents with a pulmonary flow murmur (↑ flow through pulmonary valve) and a diastolic rumble (↑ flow across tricuspid); blood flow across the actual ASD does not cause a murmur because there is no significant pressure gradient. The murmur later progresses to a louder diastolic murmur of pulmonic regurgitation from dilatation of the pulmonary artery.*
### Heart murmurs

#### Systolic

<table>
<thead>
<tr>
<th>Aortic stenosis (AS)</th>
<th>Crescendo-decrescendo systolic ejection murmur. LV &gt;&gt; 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). Often due to age-related calcification or early-onset calcification of bicuspid aortic valve.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral/tricuspid regurgitation (MR/TR)</td>
<td>Holosystolic, high-pitched “blowing murmur.” Mitral—loudest at apex and radiates toward axilla. MR is often due to ischemic heart disease (post-MI), MVP, LV dilatation. Tricuspid—loudest at tricuspid area and radiates to right sternal border. TR commonly caused by RV dilatation. Rheumatic fever and infective endocarditis can cause either MR or TR.</td>
</tr>
<tr>
<td>Mitral valve prolapse (MVP)</td>
<td>Late systolic crescendo murmur with midsystolic click (MC; due to sudden tensing of chordae tendineae). Most frequent valvular lesion. Best heard over apex. Loudest just before S2. Usually benign. Can predispose to infective endocarditis. Can be caused by myxomatous degeneration (1° or 2° to connective tissue disease such as Marfan or Ehlers-Danlos syndrome), rheumatic fever, chordae rupture.</td>
</tr>
<tr>
<td>VSD</td>
<td>Holosystolic, harsh-sounding murmur. Loudest at tricuspid area.</td>
</tr>
</tbody>
</table>

#### Diastolic

<table>
<thead>
<tr>
<th>Aortic regurgitation (AR)</th>
<th>High-pitched “blowing” early diastolic decrescendo murmur. Long diastolic murmur and signs of hyperdynamic pulse when severe and chronic. Often due to aortic root dilation, bicuspid aortic valve, endocarditis, rheumatic fever. Progresses to left HF.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral stenosis (MS)</td>
<td>Follows opening snap (OS; due to abrupt halt in leaflet motion in diastole, after rapid opening due to fusion at leaflet tips). Delayed rumbling late diastolic murmur (4 interval between S2 and OS correlates with severity). LA &gt;&gt; LV pressure during diastole. Often occurs 2° to rheumatic fever. Chronic MS can result in LA dilatation.</td>
</tr>
</tbody>
</table>

#### Continuous

| PDA | Continuous machine-like murmur. Loudest at S2. Often due to congenital rubella or prematurity. Best heard at left infraclavicular area. |
Myocardial action potential

Also occurs in bundle of His and Purkinje fibers.

**Phase 0** = rapid upstroke and depolarization—voltage-gated Na⁺ channels open.

**Phase 1** = initial repolarization—inactivation of voltage-gated Na⁺ channels. Voltage-gated K⁺ channels begin to open.

**Phase 2** = plateau—Ca²⁺ influx through voltage-gated Ca²⁺ channels balances K⁺ efflux. Ca²⁺ influx triggers Ca²⁺ release from sarcoplasmic reticulum and myocyte contraction.

**Phase 3** = rapid repolarization—massive K⁺ efflux due to opening of voltage-gated slow K⁺ channels and closure of voltage-gated Ca²⁺ channels.

**Phase 4** = resting potential—high K⁺ permeability through K⁺ channels.

In contrast to skeletal muscle:

- Cardiac muscle action potential has a plateau, which is due to Ca²⁺ influx and K⁺ efflux; myocyte contraction occurs due to Ca²⁺-induced Ca²⁺ release from the sarcoplasmic reticulum.
- Cardiac nodal cells spontaneously depolarize during diastole, resulting in automaticity due to Iₖ channels (“funny current” channels responsible for a slow, mixed Na⁺/K⁻ inward current).
- Cardiac myocytes are electrically coupled to each other by gap junctions.
Pacemaker action potential

Occurs in the SA and AV nodes. Key differences from the ventricular action potential include:

**Phase 0** = upstroke—opening of voltage-gated Ca²⁺ channels. Fast voltage-gated Na⁺ channels are permanently inactivated because of the less negative resting voltage of these cells. Results in a slow conduction velocity that is used by the AV node to prolong transmission from the atria to ventricles. Phases 1 and 2 are absent.

**Phase 3** = inactivation of the Ca²⁺ channels and activation of K⁺ channels → K⁺ efflux.

**Phase 4** = slow spontaneous diastolic depolarization as Na⁺ conductance (If different from INa 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 If channels are open and thus ↑ HR.
Electrocardiogram

- **P wave**—atrial depolarization. Atrial repolarization is masked by QRS complex.
- **PR interval**—time from start of atrial depolarization to start of ventricular depolarization (normally < 200 msec).
- **QRS complex**—ventricular depolarization (normally < 120 msec).
- **QT interval**—ventricular depolarization, mechanical contraction of the ventricles, ventricular repolarization.
- **T wave**—ventricular repolarization. T-wave inversion may indicate recent MI.
- **J point**—junction between end of QRS complex and start of ST segment.
- **ST segment**—isoelectric, ventricles depolarized. U wave—caused by hypokalemia, bradycardia.

**Speed of conduction**
- Purkinje > atria > ventricles > AV node.
- Pacemakers: SA > AV > bundle of His/Purkinje/ventricles.
- Conduction pathway: SA node → atria → AV node → common bundle → bundle branches → fascicles → Purkinje fibers → ventricles.
- SA node “pacemaker” inherent dominance with slow phase of upstroke.
- AV node—located in posteroinferior part of interatrial septum. Blood supply usually from RCA. 100-msec delay allows time for ventricular filling.
### 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⁺, ↓ Mg²⁺, other abnormalities. Treatment includes magnesium sulfate.

### Congenital long QT syndrome

Inherited disorder of myocardial repolarization, typically due to ion channel defects; ↑ risk of sudden cardiac death (SCD) due to torsades de pointes. Includes:
- Romano-Ward syndrome—autosomal dominant, pure cardiac phenotype (no deafness).
- Jervell and Lange-Nielsen syndrome—autosomal recessive, sensorineural deafness.

### Brugada syndrome

Autosomal dominant disorder most common in Asian males. ECG pattern of pseudo-right bundle branch block and ST elevations in V1-V3. ↑ risk of ventricular tachyarrhythmias and SCD. Prevent SCD with implantable cardioverter-defibrillator (ICD).

### Wolff-Parkinson-White syndrome

Most common type of ventricular preexcitation syndrome. Abnormal fast accessory conduction pathway from atria to ventricle (bundle of Kent) bypasses the rate-slowing AV node → ventricles begin to partially depolarize earlier → characteristic delta wave with widened QRS complex and shortened PR interval on ECG. May result in reentry circuit → supraventricular tachycardia.

---

Drug-induced long QT (ABCDE):
- AntiArrhythmics (class IA, III)
- AntiBiotics (e.g., macrolides)
- AntiC’ychotics (e.g., haloperidol)
- AntiDepressants (e.g., TCAs)
- AntiEmetics (e.g., ondansetron)
ECG tracings

Atrial fibrillation
Chaotic and erratic baseline (irregularly irregular) with no discrete P waves in between irregularly spaced QRS complexes. Associated with hypertension, coronary artery disease (CAD), rheumatic heart disease, binge drinking (“holiday heart”), HF, valvular disease, hyperthyroidism. Can result in atrial stasis and lead to cardioembolic events. Treatment includes antithrombotic therapy (e.g., warfarin), rate control (β-blocker, non-dihydropyridine Ca²⁺ channel blocker, digoxin), rhythm control (class IC or III antiarrhythmics), and/or cardioversion (pharmacological or electrical).

Atrial flutter
A rapid succession of identical, back-to-back atrial depolarization waves. The identical appearance accounts for the “sawtooth” appearance of the flutter waves. Management similar to atrial fibrillation (rate control, anticoagulation, cardioversion). Definitive treatment is catheter ablation.

Ventricular fibrillation
A completely erratic rhythm with no identifiable waves. Fatal arrhythmia without immediate CPR and defibrillation.

AV block
1st degree
The PR interval is prolonged (> 200 msec). Benign and asymptomatic. No treatment required.

2nd degree
Mobitz type I (Wenckebach)
Progressive lengthening of PR interval until a beat is “dropped” (a P wave not followed by a QRS complex). Usually asymptomatic. Variable RR interval with a pattern (regularly irregular).
ECG tracings (continued)

**Mobitz type II**
Dropped beats that are not preceded by a change in the length of the PR interval (as in type I). May progress to 3rd-degree block. Often treated with pacemaker.

![ECG tracing](image)

**3rd degree (complete)**
The atria and ventricles beat independently of each other. Both P waves and QRS complexes are present, although the P waves bear no relation to the QRS complexes. Atrial rate is faster than ventricular rate. Usually treated with pacemaker. Lyme disease can result in 3rd-degree heart block.

![ECG tracing](image)

**Atrial natriuretic peptide**
Released from atrial myocytes in response to ↑ blood volume and atrial pressure. Acts via cGMP. Causes vasodilation and ↓ 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 ↓ and ↑ in BP).
- Carotid sinus (dilated region at carotid bifurcation) transmits via glossopharyngeal nerve to solitary nucleus of medulla (responds to ↓ and ↑ in BP).

Baroreceptors:
- Hypotension—↓ arterial pressure → ↓ stretch → ↓ afferent baroreceptor firing → ↑ efferent sympathetic firing and ↓ efferent parasympathetic stimulation → vasoconstriction, ↑ HR, ↑ contractility, ↓ BP. Important in the response to severe hemorrhage.
- Carotid massage—↑ pressure on carotid sinus → ↑ stretch → ↑ afferent baroreceptor firing → ↑ AV node refractory period → ↓ HR.
- Contributes to Cushing reaction (triad of hypertension, bradycardia, and respiratory depression)—↑ intracranial pressure constricts arterioles → cerebral ischemia → ↑ pCO₂ and ↓ pH → central reflex sympathetic ↑ in perfusion pressure (hypertension) → ↑ stretch → peripheral reflex baroreceptor induced—bradycardia.

Chemoreceptors:
- Peripheral—carotid and aortic bodies are stimulated by ↓ Po₂ (< 60 mmHg), ↑ Pco₂, and ↓ pH of blood.
- Central—are stimulated by changes in pH and Pco₂ of brain interstitial fluid, which in turn are influenced by arterial CO₂. Do not directly respond to Po₂.

Normal pressures

PCWP—pulmonary capillary wedge pressure (in mmHg) is a good approximation of left atrial pressure. In mitral stenosis, PCWP > LV diastolic pressure. Measured with pulmonary artery catheter (Swan-Ganz catheter).
## Autoregulation
How blood flow to an organ remains constant over a wide range of perfusion pressures.

<table>
<thead>
<tr>
<th>ORGAN</th>
<th>FACTORS DETERMINING AUTOREGULATION</th>
<th>Note: the pulmonary vasculature is unique in that hypoxia causes vasoconstriction so that only well-ventilated areas are perfused. In other organs, hypoxia causes vasodilation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>Local metabolites (vasodilatory): adenosine, NO, CO₂, O₂</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>Local metabolites (vasodilatory): CO₂ (pH)</td>
<td></td>
</tr>
<tr>
<td>Kidneys</td>
<td>Myogenic and tubuloglomerular feedback</td>
<td></td>
</tr>
<tr>
<td>Lungs</td>
<td>Hypoxia causes vasoconstriction</td>
<td></td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>Local metabolites during exercise: lactate, adenosine, K⁺, H⁺, CO₂</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>Sympathetic stimulation most important mechanism: temperature control</td>
<td></td>
</tr>
</tbody>
</table>

### Capillary fluid exchange
Starling forces determine fluid movement through capillary membranes:

\[
\begin{align*}
\text{Capillary pressure} &= \text{pushes fluid out of capillary} \\
\text{Interstitial fluid pressure} &= \text{pushes fluid into capillary} \\
\text{Plasma colloid osmotic pressure} &= \text{pulls fluid into capillary} \\
\text{Interstitial fluid colloid osmotic pressure} &= \text{pulls fluid out of capillary} \\
J &= \text{net fluid flow} = K_f [(P_c - P_i) - \zeta(\pi_c - \pi_i)] \\
K_f &= \text{permeability of capillary to fluid} \\
\zeta &= \text{permeability of capillary to protein} \\
\end{align*}
\]

Edema—excess fluid outflow into interstitium commonly caused by:

\[
\begin{align*}
\text{↑ capillary pressure (↑ P_c; e.g., HF)} & \\
\text{↓ plasma proteins (↓ \pi_c; e.g., nephrotic syndrome, liver failure)} & \\
\text{↑ capillary permeability (↑ K_f; e.g., toxins, infections, burns)} & \\
\text{↑ interstitial fluid colloid osmotic pressure (↑ \pi_i; e.g., lymphatic blockage)} & \\
\end{align*}
\]
### Congenital heart diseases

**RIGHT-TO-LEFT SHUNTS**

Early cyanosis—“blue babies.” Often diagnosed prenatally or become evident immediately after birth. Usually require urgent surgical correction and/or maintenance of a PDA.

**The 5 Ts:**

1. Truncus arteriosus (1 vessel)
2. Transposition (2 switched vessels)
3. Tricuspid atresia (3 = Tri)
4. Tetralogy of Fallot (4 = Tetra)
5. TAPVR (5 letters in the name)

**Persistent truncus arteriosus**

Truncus arteriosus fails to divide into pulmonary trunk and aorta due to lack of aorticopulmonary septum formation; most patients have accompanying VSD.

**D-transposition of great vessels**

Aorta leaves RV (anterior) and pulmonary trunk leaves LV (posterior) → separation of systemic and pulmonary circulations. Not compatible with life unless a shunt is present to allow mixing of blood (e.g., VSD, PDA, or patent foramen ovale).

Due to failure of the aorticopulmonary septum to spiral.

Without surgical intervention, most infants die within the first few months of life.

**Tricuspid atresia**

Absence of tricuspid valve and hypoplastic RV; requires both ASD and VSD for viability.

**Tetralogy of Fallot**

Caused by anterosuperior displacement of the infundibular septum. Most common cause of early childhood cyanosis.

1. Pulmonary infundibular stenosis (most important determinant for prognosis)
2. Right ventricular hypertrophy (RVH)—boot-shaped heart on CXR
3. Overriding aorta
4. VSD

Pulmonary stenosis forces right-to-left flow across VSD → early cyanotic “tet spells,” RVH.

**PROVe.**

Squatting: ↓ SVR, ↓ right-to-left shunt, improves cyanosis.

Treatment: early surgical correction.

**Total anomalous pulmonary venous return (TAPVR)**

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.
### Congenital heart diseases (continued)

<table>
<thead>
<tr>
<th>LEFT-TO-RIGHT SHUNTS</th>
<th>Right-to-Left shunts: caRLy cyanosis.</th>
<th>Left-to-Right shunts: “LateR” cyanosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ventricular septal defect</strong></td>
<td>Most common congenital cardiac defect. Asymptomatic at birth, may manifest weeks later or remain asymptomatic throughout life. Most self resolve; larger lesions may lead to LV overload and HF.</td>
<td><strong>Atrial septal defect</strong></td>
</tr>
<tr>
<td><strong>Patent ductus arteriosus</strong></td>
<td>In fetal period, shunt is right to left (normal). In neonatal period, lung resistance → shunt becomes left to right → progressive RVH and/or LVH and HF. Associated with a continuous, “machine-like” murmur. Patency is maintained by PGE synthesis and low O₂ tension. Uncorrected PDA can eventually result in late cyanosis in the lower extremities (differential cyanosis).</td>
<td><strong>Eisenmenger syndrome</strong></td>
</tr>
<tr>
<td><strong>Coarctation of the aorta</strong></td>
<td>Aortic narrowing near insertion of ductus arteriosus (“juxtaductal”). Associated with bicuspid aortic valve, other heart defects, and Turner syndrome. Hypertension in upper extremities and weak, delayed pulse in lower extremities (brachial-femoral delay). With age, collateral arteries erode ribs (notched appearance on CXR).</td>
<td></td>
</tr>
</tbody>
</table>
### Congenital cardiac defect associations

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>DEFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol exposure in utero (fetal alcohol syndrome)</td>
<td>VSD, PDA, ASD, tetralogy of Fallot</td>
</tr>
<tr>
<td>Congenital rubella</td>
<td>Septal defects, PDA, pulmonary artery stenosis</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>AV septal defect (endocardial cushion defect), VSD, ASD</td>
</tr>
<tr>
<td>Infant of diabetic mother</td>
<td>Transposition of great vessels</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>MVP, thoracic aortic aneurysm and dissection, aortic regurgitation</td>
</tr>
<tr>
<td>Prenatal lithium exposure</td>
<td>Ebstein anomaly</td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>Bicuspid aortic valve, coarctation of aorta</td>
</tr>
<tr>
<td>Williams syndrome</td>
<td>Supravalvular aortic stenosis</td>
</tr>
<tr>
<td>22q11 syndromes</td>
<td>Truncus arteriosus, tetralogy of Fallot</td>
</tr>
</tbody>
</table>

### Hypertension

**Defined as persistent systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg**

**RISK FACTORS**
- Age, obesity, diabetes, physical inactivity, excess salt intake, excess alcohol intake, family history; black > white > Asian.

**FEATURES**
- 90% of hypertension is 1° (essential) and related to ↑ CO or ↑ TPR; remaining 10% mostly 2° to renal/renovascular disease (e.g., fibromuscular dysplasia, usually found in younger women) and 1° hyperaldosteronism.

- **Hypertensive urgency**—severe (≥ 180/≥ 120 mmHg) hypertension without acute end-organ damage.

- **Hypertensive emergency**—severe hypertension with evidence of acute end-organ damage (e.g., 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; chronic kidney disease (hypertensive nephropathy); retinopathy.
### Hyperlipidemia signs

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Xanthomas</strong></td>
<td>Plaques or nodules composed of lipid-laden histiocytes in skin A, especially the eyelids (xanthelasma B).</td>
</tr>
<tr>
<td><strong>Tendinous xanthoma</strong></td>
<td>Lipid deposit in tendon C, especially Achilles.</td>
</tr>
<tr>
<td><strong>Corneal arcus</strong></td>
<td>Lipid deposit in cornea. Common in elderly (arcus senilis D), but appears earlier in life in hypercholesterolemia.</td>
</tr>
</tbody>
</table>

### Arteriosclerosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arteriosclerosis</strong></td>
<td>Hardening of arteries, with arterial wall thickening and loss of elasticity.</td>
</tr>
<tr>
<td><strong>Arteriolosclerosis</strong></td>
<td>Common. Affects small arteries and arterioles. Two types: hyaline (thickening of vessel walls in essential hypertension or diabetes mellitus A) and hyperplastic (“onion skinning” in severe hypertension B with proliferation of smooth muscle cells).</td>
</tr>
</tbody>
</table>
Atherosclerosis
Very common. Disease of elastic arteries and large- and medium-sized muscular arteries; a form of arteriosclerosis caused by buildup of cholesterol plaques.

RISK FACTORS
Modifiable: smoking, hypertension, hyperlipidemia, diabetes.
Nonmodifiable: age, sex (↑ in men and postmenopausal women), family history.

PROGRESSION
Inflammation important in pathogenesis:
- endothelial cell dysfunction → macrophage and LDL accumulation → foam cell formation → fatty streaks → smooth muscle cell migration (involves PDGF and FGF), proliferation, and extracellular matrix deposition → fibrous plaque → complex atheromas A.

COMPLICATIONS
Aneurysms, ischemia, infarcts, peripheral vascular disease, thrombus, emboli.

LOCATION
Abdominal aorta > coronary artery > popliteal artery > carotid artery B.

SYMPTOMS
Angina, claudication, but can be asymptomatic.

Aortic aneurysm
Localized pathologic dilatation of the aorta. May cause abdominal and/or back pain, which is a sign of leaking, dissection, or imminent rupture.

Abdominal aortic aneurysm
Associated with atherosclerosis. Risk factors include history of tobacco use, ↑ age, male sex, family history. May present as palpable pulsatile abdominal mass A.

Thoracic aortic aneurysm
Associated with cystic medial degeneration. Risk factors include hypertension, bicuspid aortic valve, connective tissue disease (e.g., Marfan syndrome). Also historically associated with 3° syphilis (obliterative endarteritis of the vasa vasorum).
Aortic dissection

Longitudinal intimal tear forming a false lumen. Associated with hypertension, bicuspid aortic valve, inherited connective tissue disorders (e.g., Marfan syndrome). Can present with tearing chest pain, of sudden onset, radiating to the back +/- markedly unequal BP in arms. CXR shows mediastinal widening. Can result in rupture, pericardial tamponade, death. Two types:

- Stanford type A (proximal): involves ascending aorta. May extend to aortic arch or descending aorta. Treatment is surgery.
- Stanford type B (distal): involves descending aorta and/or aortic arch. No ascending aorta involvement. Treat medically with β-blockers, then vasodilators.

Ischemic heart disease manifestations

Angina

Chest pain due to ischemic myocardium 2° to coronary artery narrowing or spasm; no myocyte necrosis.

- Stable—usually 2° to atherosclerosis; exertional chest pain in classic distribution (usually with ST depression on ECG), resolving with rest or nitroglycerin.
- Variant (Prinzmetal)—occurs at rest 2° to coronary artery spasm; transient ST elevation on ECG. Known triggers include tobacco, cocaine, and triptans, but trigger is often unknown. Treat with Ca²⁺ channel blockers, nitrates, and smoking cessation (if applicable).
- Unstable—thrombosis with incomplete coronary artery occlusion; +/- ST depression and/or T-wave inversion on ECG but no cardiac biomarker elevation (unlike NSTEMI); ↑ in frequency or intensity of chest pain or any chest pain at rest.

Coronary steal syndrome

Distal to coronary stenosis, vessels are maximally dilated at baseline. Administration of vasodilators (e.g., dipyridamole, regadenoson) dilates normal vessels and shunts blood toward well-perfused areas → ↓ flow and ischemia in poststenotic region. Principle behind pharmacologic stress tests.

Myocardial infarction

Most often acute thrombosis due to rupture of coronary artery atherosclerotic plaque. If transmural, ECG may show ST elevations (STEMI); if subendocardial, ECG may show ST depressions (NSTEMI). Cardiac biomarkers are diagnostic.

Sudden cardiac death

Death from cardiac causes within 1 hour of onset of symptoms, most commonly due to a lethal arrhythmia (e.g., ventricular fibrillation). Associated with CAD (up to 70% of cases), cardiomyopathy (hypertrophic, dilated), and hereditary ion channelopathies (e.g., long QT syndrome, Brugada syndrome).

Chronic ischemic heart disease

Progressive onset of HF over many years due to chronic ischemic myocardial damage.
**Evolution of MI**

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.

<table>
<thead>
<tr>
<th>TIME</th>
<th>GROSS</th>
<th>LIGHT MICROSCOPE</th>
<th>COMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4 hr</td>
<td>None</td>
<td>None</td>
<td>Arrhythmia, HF, cardiogenic shock.</td>
</tr>
<tr>
<td>4–24 hr</td>
<td></td>
<td>Early coagulative necrosis, release of necrotic cell contents into blood; edema, hemorrhage, wavy fibers. Neutrophils appear. Reperfusion injury may cause contraction bands (due to free radical damage).</td>
<td>Arrhythmia, HF, cardiogenic shock.</td>
</tr>
<tr>
<td>1–3 days</td>
<td></td>
<td>Extensive coagulative necrosis. Tissue surrounding infarct shows acute inflammation with neutrophils.</td>
<td>Postinfarction fibrinous pericarditis.</td>
</tr>
<tr>
<td>3–14 days</td>
<td></td>
<td>Macrophages, then granulation tissue at margins.</td>
<td>Free wall rupture → tamponade; papillary muscle rupture → mitral regurgitation; interventricular septal rupture due to macrophage-mediated structural degradation. LV pseudoaneurysm (risk of rupture).</td>
</tr>
<tr>
<td>2 weeks to several months</td>
<td></td>
<td>Contracted scar complete.</td>
<td>Dressler syndrome, HF, arrhythmias, true ventricular aneurysm (risk of mural thrombus).</td>
</tr>
</tbody>
</table>
Diagnosis of MI

In the first 6 hours, ECG is the gold standard. Cardiac troponin I rises after 4 hours and is ↑ for 7–10 days; more specific than other protein markers. CK-MB rises after 6–12 hours 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. 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).

Types of infarcts

<table>
<thead>
<tr>
<th>Transmural infarcts</th>
<th>Subendocardial infarcts</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ necrosis</td>
<td>Due to ischemic necrosis of &lt; 50% of ventricle wall</td>
</tr>
<tr>
<td>Affects entire wall</td>
<td>Subendocardium especially vulnerable to ischemia</td>
</tr>
<tr>
<td>ST elevation on ECG, Q waves</td>
<td>ST depression on ECG</td>
</tr>
</tbody>
</table>

ECG localization of STEMI

<table>
<thead>
<tr>
<th>INFARCT LOCATION</th>
<th>LEADS WITH ST ELEVATIONS OR Q WAVES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anteroseptal (LAD)</td>
<td>V1–V2</td>
</tr>
<tr>
<td>Anteroapical (distal LAD)</td>
<td>V3–V4</td>
</tr>
<tr>
<td>Anterolateral (LAD or LCX)</td>
<td>V5–V6</td>
</tr>
<tr>
<td>Lateral (LCX)</td>
<td>I, aVL</td>
</tr>
<tr>
<td>InPerior (RCA)</td>
<td>II, III, aVF</td>
</tr>
</tbody>
</table>

MI complications

Cardiac arrhythmia—important cause of death before reaching hospital; common in first few days. LV failure and pulmonary edema. Cardiogenic shock (large infarct → high risk of mortality). Ventricular free wall rupture → cardiac tamponade; papillary muscle rupture → severe mitral regurgitation; and interventricular septum rupture → VSD. Greatest risk 3–14 days post-MI. Ventricular pseudoaneurysm formation (contained free wall rupture) → ↓ CO, risk of arrhythmia, embolus from mural thrombus; greatest risk approximately 3–14 days post-MI (as with rupture). True ventricular aneurysm—outward bulge during contraction (“dyskinesia”), associated with fibrosis; arises 2 weeks to several months after MI. Postinfarction fibrinous pericarditis—friction rub (1–3 days post-MI). Dressler syndrome—autoimmune phenomenon resulting in fibrinous pericarditis (several weeks post-MI).

Acute coronary syndrome treatments

Unstable angina/NSTEMI—Anticoagulation (e.g., heparin), antiplatelet therapy (e.g., aspirin + clopidogrel), β-blockers, ACE inhibitors, statins. Symptom control with nitrroglycerin and morphine. STEMI—In addition to above, reperfusion therapy most important (percutaneous coronary intervention preferred over fibrinolysis).
### Cardiomyopathies

#### Dilated cardiomyopathy

Most common cardiomyopathy (90% of cases). Often idiopathic or familial. Other etiologies include chronic alcohol abuse, wet Beriberi, Coxsackie B virus myocarditis, chronic Cocaine use, Chagas disease, Doxorubicin toxicity, hemochromatosis, sarcoidosis, peripartum cardiomyopathy.

**Findings:** HF, S3, systolic regurgitant murmur, dilated heart on echocardiogram, balloon appearance of heart on CXR.

**Treatment:** Na+ restriction, ACE inhibitors, β-blockers, diuretics, digoxin, ICD, heart transplant.

Systolic dysfunction ensues. Eccentric hypertrophy (sarcomeres added in series).

ABCCCD.

#### Hypertrophic cardiomyopathy

60–70% of cases are familial, autosomal dominant (commonly a β-myosin heavy-chain mutation). Can be associated with Friedreich ataxia. Causes syncope during exercise and may lead to sudden death in young athletes due to ventricular arrhythmia.

**Findings:** S4, systolic murmur. May see mitral regurgitation due to impaired mitral valve closure.

**Treatment:** cessation of high-intensity athletics, use of β-blocker or non-dihydropyridine Ca²⁺ channel blockers (e.g., verapamil). ICD if patient is high risk.

Diastolic dysfunction ensues. Marked ventricular hypertrophy, often septal predominance. Myofibrillar disarray and fibrosis. Obstructive hypertrophic cardiomyopathy (subset)—asymmetric septal hypertrophy → outflow obstruction → dyspnea, possible syncope.

#### Restrictive/infiltrative cardiomyopathy

Major causes include sarcoidosis, amyloidosis, postradiation fibrosis, endocardial fibroelastosis (thick fibroelastic tissue in endocardium of young children), Löffler syndrome (endomyocardial fibrosis with a prominent eosinophilic infiltrate), and hemochromatosis (dilated cardiomyopathy can also occur).

Diastolic dysfunction ensues. Can have low-voltage ECG despite thick myocardium (especially amyloid).
Heart failure

Clinical syndrome of cardiac pump dysfunction → congestion and low perfusion. Symptoms include dyspnea, orthopnea, fatigue; signs include rales, JVD, pitting edema. Systolic dysfunction—reduced EF, ↑ EDV; ↓ contractility often 2° to ischemia/MI or dilated cardiomyopathy. Diastolic dysfunction—preserved EF, normal EDV; ↓ compliance often 2° to myocardial hypertrophy. Right HF most often results from left HF. Isolated right HF is usually due to cor pulmonale. ACE inhibitors or angiotensin II receptor blockers, β-blockers (except in acute decompensated HF), and spironolactone ↓ mortality. Thiazide or loop diuretics are used mainly for symptomatic relief. Hydralazine with nitrates 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 edema, etc.

Pulmonary edema

↑ pulmonary venous pressure → pulmonary venous distention and transudation of fluid. Presence of hemosiderin-laden macrophages (“HF” cells) in lungs.

Right heart failure

Hepatomegaly (nutmeg liver)

↑ central venous pressure → ↑ resistance to portal flow. Rarely, leads to “cardiac cirrhosis.”

Jugular venous distention

↑ venous pressure.

Peripheral edema

↑ venous pressure → fluid transudation.

Shock

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>SKIN</th>
<th>CVP (PRELOAD)</th>
<th>CO</th>
<th>SVR (AFTERLOAD)</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemic</td>
<td>Hemorrhage, dehydration, burns</td>
<td>Cold, clammy</td>
<td>↓↓</td>
<td>↑ ↑</td>
<td>↑</td>
</tr>
<tr>
<td>Cardiogenic</td>
<td>Acute MI, HF, valvular dysfunction, arrhythmia</td>
<td>Cold, clammy</td>
<td>↑</td>
<td>↓↓</td>
<td>↑</td>
</tr>
<tr>
<td>Obstructive</td>
<td>Cardiac tamponade, PE</td>
<td>Cold, clammy</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Distributive</td>
<td>Sepsis, CNS injury, anaphylaxis</td>
<td>Warm, dry</td>
<td>↓</td>
<td>↑</td>
<td>↓↓</td>
</tr>
</tbody>
</table>

↓↓ = primary insult.
Systemic inflammatory response syndrome (≥ 2: fever/hypothermia, tachycardia, tachypnea, leukocytosis/leukopenia). First sign of shock is tachycardia. Multiple organ dysfunction syndrome (MODS) is the end result of shock.
**Bacterial endocarditis**

Fever (most common symptom), new murmur, Roth spots (round white spots on retina surrounded by hemorrhage), Osler nodes (tender raised lesions on finger or toe pads), Janeway lesions (small, painless, erythematous lesions on palm or sole), glomerulonephritis, septic arterial or pulmonary emboli, splinter hemorrhages on nail bed. Multiple blood cultures necessary for diagnosis.

- **Acute**—*S. aureus* (high virulence). Large vegetations on previously normal valves. Rapid onset.
- **Subacute**—viridans streptococci (low virulence). Smaller vegetations on congenitally abnormal or diseased valves. Sequel of dental procedures. Gradual onset.

*S. bovis* (*galloyticus*) is present in colon cancer, *S. epidermidis* on prosthetic valves. Endocarditis may also be nonbacterial (marantic/thrombotic) secondary to malignancy, hypercoagulable state, or lupus.

Mitral valve is most frequently involved. Tricuspid valve endocarditis is associated with IV drug abuse (don’t “tri” drugs). Associated with *S. aureus, Pseudomonas*, and *Candida*. Culture—most likely *Coxiella burnetii, Bartonella* spp., HACEK (*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella*).

♥ Bacteria FROM JANE ♥:

- Fever
- Roth spots
- Osler nodes
- Murmur
- Janeway lesions
- Anemia
- Nail-bed hemorrhage
- Emboli

*Mitral valve is most frequently involved.*
Rheumatic fever

A consequence of pharyngeal infection with group A β-hemolytic streptococci. Late sequelae include rheumatic heart disease, which affects heart valves—mitral > aortic >> tricuspid (high-pressure valves affected most). Early lesion is mitral valve regurgitation; late lesion is mitral stenosis. Associated with Aschoff bodies (granuloma with giant cells [blue arrows in A]), Anitschkow cells (enlarged macrophages with ovoid, wavy, rod-like nucleus [red arrow in A]), t anti-streptolysin O (ASO) titers. Immune mediated (type II hypersensitivity); not a direct effect of bacteria. Antibodies to M protein cross-react with self antigens (molecular mimicry). Treatment/prophylaxis: penicillin.

Acute pericarditis

Commonly presents with sharp pain, aggravated by inspiration, and relieved by sitting up and leaning forward. Presents with friction rub. ECG changes include widespread ST-segment elevation and/or PR depression. Causes include idiopathic (most common; presumed viral), confirmed infection (e.g., Coxsackievirus), neoplasia, autoimmune (e.g., SLE, rheumatoid arthritis), uremia, cardiovascular (acute STEMI or Dressler syndrome), radiation therapy.

Cardiac tamponade

Compression of heart by fluid (e.g., blood, effusions) in pericardial space A → ↓ CO. Equilibration of diastolic pressures in all 4 chambers. Findings: Beck triad (hypotension, distended neck veins, distant heart sounds), ↑ HR, pulsus paradoxus. ECG shows low-voltage QRS and electrical alternans (due to “swinging” movement of heart in large effusion).

Pulsus paradoxus → ↓ in amplitude of systolic BP by > 10 mmHg during inspiration. Seen in cardiac tamponade, asthma, obstructive sleep apnea, pericarditis, croup.

Syphilitic heart disease

3° syphilis disrupts the vasa vasorum of the aorta with consequent atrophy of vessel wall and dilatation of aorta and valve ring. May see calcification of aortic root and ascending aortic arch. Leads to “tree bark” appearance of aorta.

J♥NES (major criteria):
Joint (migratory polyarthritis)
♥ (carditis)
Nodules in skin (subcutaneous)
Erythema marginatum
Sydenham chorea

Can result in aneurysm of ascending aorta or aortic arch, aortic insufficiency.
### Cardiac tumors

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myxomas</strong></td>
<td>Most common primary cardiac tumor in adults. 90% occur in the atria (mostly left atrium). Myxomas are usually described as a “ball valve” obstruction in the left atrium (associated with multiple syncopal episodes). May hear early diastolic “tumor plop” sound.</td>
</tr>
<tr>
<td><strong>Rhabdomyomas</strong></td>
<td>Most frequent primary cardiac tumor in children (associated with tuberous sclerosis).</td>
</tr>
</tbody>
</table>

![Myxoma MRI](image)

### Kussmaul sign

Kussmaul sign is seen in JVP on inspiration instead of a normal ↓. Inspiration → negative intrathoracic pressure not transmitted to heart → impaired filling of right ventricle → blood backs up into venae cavae → JVD. May be seen with constrictive pericarditis, restrictive cardiomyopathies, right atrial or ventricular tumors.
Vascular tumors

**Angiosarcoma**
Rare blood vessel malignancy typically occurring in the head, neck, and breast areas. Usually in elderly, on sun-exposed areas. Associated with radiation therapy and chronic postmastectomy lymphedema. Hepatic angiosarcoma associated with vinyl chloride and arsenic exposures. Very aggressive and difficult to resect due to delay in diagnosis.

**Bacillary angiomatosis**
Benign capillary skin papules found in AIDS patients. Caused by *Bartonella henselae* infections. Frequently mistaken for Kaposi sarcoma, but has neutrophilic infiltrate.

**Cherry hemangioma**
Benign capillary hemangioma of the elderly. Does not regress. Frequency ↑ with age.

**Cystic hygroma**
Cavernous lymphangioma of the neck. Associated with Turner syndrome.

**Glomus tumor**
Benign, painful, red-blue tumor under fingernails. Arises from modified smooth muscle cells of the thermoregulatory glomus body.

**Kaposi sarcoma**
Endothelial malignancy most commonly of the skin, but also mouth, GI tract, and respiratory tract. Associated with HHV-8 and HIV. Frequently mistaken for bacillary angiomatosis, but has lymphocytic infiltrate.

**Pyogenic granuloma**
Polypoid capillary hemangioma that can ulcerate and bleed. Associated with trauma and pregnancy.

**Strawberry hemangioma**
Benign capillary hemangioma of infancy. Appears in first few weeks of life (1/200 births); grows rapidly and regresses spontaneously by 5–8 years old.

---

**Raynaud phenomenon**
↓ blood flow to the skin due to arteriolar (small vessel) vasospasm in response to cold or stress: color change from white (ischemia) to blue (hypoxia) to red (reperfusion). Most often in the fingers and toes. Called Raynaud disease when 1° (idiopathic), Raynaud syndrome when 2° to a disease process such as mixed connective tissue disease, SLE, or CREST (limited form of systemic sclerosis) syndrome. Treat with Ca²⁺ channel blockers.
## Vasculitides

<table>
<thead>
<tr>
<th>Large-vessel vasculitis</th>
<th>Epidemiology/Presentation</th>
<th>Pathology/Labs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Temporal (giant cell) arteritis</strong></td>
<td>Usually elderly females. Unilateral headache (temporal artery), jaw claudication. May lead to irreversible blindness due to ophthalmic artery occlusion. Associated with polymyalgia rheumatica.</td>
<td>Most commonly affects branches of carotid artery. Focal granulomatous inflammation. ESR. Treat with high-dose corticosteroids prior to temporal artery biopsy to prevent blindness.</td>
</tr>
</tbody>
</table>

| Takayasu arteritis | Usually Asian females < 40 years old. “Pulseless disease” (weak upper extremity pulses), fever, night sweats, arthritis, myalgias, skin nodules, ocular disturbances. | Granulomatous thickening and narrowing of aortic arch and proximal great vessels. ESR. Treat with corticosteroids. |

<table>
<thead>
<tr>
<th>Medium-vessel vasculitis</th>
<th>Epidemiology/Presentation</th>
<th>Pathology/Labs</th>
</tr>
</thead>
</table>

| Kawasaki disease | Asian children < 4 years old. Mucocutaneous lymph node syndrome: Conjunctival injection, rash (polymorphous desquamating), adenopathy (cervical), strawberry tongue (oral mucositis), hand-foot changes (edema, erythema), fever. | CRASH and burn. May develop coronary artery aneurysms; thrombosis or rupture can cause death. Treat with IV immunoglobulin and aspirin. |

| Buerger disease (thromboangiitis obliterans) | Heavy smokers, males < 40 years old. Intermittent claudication may lead to gangrene, autoamputation of digits, superficial nodular phlebitis. Raynaud phenomenon is often present. | Segmental thrombosing vasculitis. Treat with smoking cessation. |

<table>
<thead>
<tr>
<th>Small-vessel vasculitis</th>
<th>Epidemiology/Presentation</th>
<th>Pathology/Labs</th>
</tr>
</thead>
</table>

| Microscopic polyangiitis | Necrotizing vasculitis commonly involving lung, kidneys, and skin with pauci-immune glomerulonephritis and palpable purpura. Presentation similar to granulomatosis with polyangiitis but without nasopharyngeal involvement. | No granulomas. MPO-ANCA/p-ANCA (anti-myeloperoxidase). Treat with cyclophosphamide, corticosteroids. |
Vasculitides (continued)

<table>
<thead>
<tr>
<th>Small-vessel vasculitis (continued)</th>
<th>Epidemiology/Presentation</th>
<th>Pathology/Labs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)</strong></td>
<td>Asthma, sinusitis, skin nodules or purpura, peripheral neuropathy (e.g., wrist/foot drop). Can also involve heart, GI, kidneys (pauci-immune glomerulonephritis).</td>
<td>Granulomatous, necrotizing vasculitis with eosinophilia. MPO-ANCA/p-ANCA, ↑ IgE level.</td>
</tr>
<tr>
<td><strong>Henoch-Schönlein purpura</strong></td>
<td>Most common childhood systemic vasculitis. Often follows URI. Classic triad: * Skin: palpable purpura on buttocks/legs * Arthralgias * GI: abdominal pain</td>
<td>Vasculitis 2° to IgA immune complex deposition. Associated with IgA nephropathy (Berger disease).</td>
</tr>
</tbody>
</table>
# Cardiovascular—Pharmacology

## Antihypertensive therapy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Therapies</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary (essential) hypertension</strong></td>
<td>Thiazide diuretics, ACE inhibitors, angiotensin II receptor blockers (ARBs), dihydropyridine Ca²⁺ channel blockers.</td>
<td>See the Renal chapter for more details about diuretics and ACE inhibitors/ARBs.</td>
</tr>
<tr>
<td><strong>Hypertension with heart failure</strong></td>
<td>Diuretics, ACE inhibitors/ARBs, β-blockers (compensated HF), aldosterone antagonists.</td>
<td>β-blockers must be used cautiously in decompensated HF and are contraindicated in cardiogenic shock.</td>
</tr>
<tr>
<td><strong>Hypertension with diabetes mellitus</strong></td>
<td>ACE inhibitors/ARBs, Ca²⁺ channel blockers, thiazide diuretics, β-blockers.</td>
<td>ACE inhibitors/ARBs are protective against diabetic nephropathy.</td>
</tr>
<tr>
<td><strong>Hypertension in pregnancy</strong></td>
<td>Hydralazine, labetalol, methyldopa, nifedipine.</td>
<td></td>
</tr>
</tbody>
</table>

## Calcium channel blockers

- Amlodipine, clevidipine, nicardipine, nifedipine, nimodipine (dihydropyridines, act on vascular smooth muscle); diltiazem, verapamil (non-dihydropyridines, act on heart).

**Mechanism**

Block voltage-dependent L-type calcium channels of cardiac and smooth muscle → ↓ muscle contractility.

Vascular smooth muscle—amlodipine = nifedipine > diltiazem > verapamil.

Heart—verapamil > diltiazem > amlodipine = nifedipine (verapamil = ventricle).

**Clinical Use**

- Dihydropyridines (except nimodipine): hypertension, angina (including Prinzmetal), Raynaud phenomenon.
- Nimodipine: subarachnoid hemorrhage (prevents cerebral vasospasm).
- Clevidipine: hypertensive urgency or emergency.
- Non-dihydropyridines: hypertension, angina, atrial fibrillation/flutter.

**Toxicity**

- Cardiac depression, AV block (non-dihydropyridines), peripheral edema, flushing, dizziness, hyperprolactinemia (verapamil), constipation, gingival hyperplasia.

## Hydralazine

**Mechanism**

↑ cGMP → smooth muscle relaxation. Vasodilates arterioles > veins; afterload reduction.

**Clinical Use**

- Severe hypertension (particularly acute), HF (with organic nitrate). Safe to use during pregnancy. Frequently coadministered with a β-blocker to prevent reflex tachycardia.

**Toxicity**

- Compensatory tachycardia (contraindicated in angina/CAD), fluid retention, headache, angina. Lupus-like syndrome.

## Hypertensive emergency

- Drugs include clevidipine, fenoldopam, labetalol, nicardipine, nitroprusside.

### Nitroprusside

- Short acting; ↑ cGMP via direct release of NO. Can cause cyanide toxicity (releases cyanide).

### Fenoldopam

- Dopamine D₁ receptor agonist—coronary, peripheral, renal, and splanchnic vasodilation. ↓ BP, ↓ natriuresis.
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.

TOXICITY
Reflex tachycardia (treat with β-blockers), hypotension, flushing, headache, “Monday disease” in industrial exposure: development of tolerance for the vasodilating action during the work week and loss of tolerance over the weekend → tachycardia, dizziness, headache upon reexposure.

Antianginal therapy
Goal is reduction of myocardial O₂ consumption (MVO₂) by ↓1 or more of the determinants of MVO₂: end-diastolic volume, BP, HR, contractility.

<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>NITRATES</th>
<th>β-BLOCKERS</th>
<th>NITRATES + β-BLOCKERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-diastolic volume</td>
<td>↓</td>
<td>No effect or ↓</td>
<td>No effect or ↓</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Contractility</td>
<td>No effect</td>
<td>↓</td>
<td>Little/no effect</td>
</tr>
<tr>
<td>Heart rate</td>
<td>↑ (reflex response)</td>
<td>↓</td>
<td>No effect or ↓</td>
</tr>
<tr>
<td>Ejection time</td>
<td>↓</td>
<td>↑</td>
<td>Little/no effect</td>
</tr>
<tr>
<td>MVO₂</td>
<td>↓</td>
<td>↓</td>
<td>↓↓</td>
</tr>
</tbody>
</table>

Verapamil is similar to β-blockers in effect.
Pindolol and acebutolol—partial β-agonists contraindicated in angina.
### Lipid-lowering agents

<table>
<thead>
<tr>
<th>DRUG</th>
<th>LDL Δ</th>
<th>HDL Δ</th>
<th>TRIGLYCERIDES Δ</th>
<th>MECHANISMS OF ACTION</th>
<th>SIDE EFFECTS/PROBLEMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG-CoA reductase inhibitors (lovastatin, pravastatin, simvastatin, atorvastatin, rosuvastatin)</td>
<td>↓↓↓</td>
<td>↑</td>
<td>↓</td>
<td>Inhibit conversion of HMG-CoA to mevalonate, a cholesterol precursor; ↓ mortality in CAD patients</td>
<td>Hepatotoxicity (↑ LFTs), myopathy (esp. when used with fibrates or niacin)</td>
</tr>
<tr>
<td>Bile acid resins (cholestyramine, colestipol, colesvelam)</td>
<td>↓</td>
<td>Slightly ↑</td>
<td>Slightly ↑</td>
<td>Prevent intestinal reabsorption of bile acids; liver must use cholesterol to make more</td>
<td>GI upset, ↓ absorption of other drugs and fat-soluble vitamins</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>↓</td>
<td>—</td>
<td>—</td>
<td>Prevent cholesterol absorption at small intestine brush border</td>
<td>Rare ↑ LFTs, diarrhea</td>
</tr>
<tr>
<td>Fibrates (gemfibrozil, clofibrate, bezafibrate, fenofibrate)</td>
<td>↓</td>
<td>↑</td>
<td>↓↓↓</td>
<td>Upregulate LPL → ↑ TG clearance Activates PPAR-α to induce HDL synthesis</td>
<td>Myopathy (↑ risk with statins), cholesterol gallstones</td>
</tr>
<tr>
<td>Niacin (vitamin B₃)</td>
<td>↓</td>
<td>↑↑</td>
<td>↓</td>
<td>Inhibits lipolysis (hormone-sensitive lipase) in adipose tissue; reduces hepatic VLDL synthesis</td>
<td>Red, flushed face, which is ↓ by NSAIDs or long-term use Hyperglycemia Hypuricemia</td>
</tr>
</tbody>
</table>

![Lipid metabolism diagram](image)
**Cardiac glycosides**

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Direct inhibition of Na⁺/K⁺ ATPase → indirect inhibition of Na⁺/Ca²⁺ exchanger. ↑ [Ca²⁺]ᵢ → positive inotropy. Stimulates vagus nerve → ↓ HR.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>HF (↑ contractility); atrial fibrillation (↓ conduction at AV node and depression of SA node).</td>
</tr>
<tr>
<td>TOXICITY</td>
<td>Cholinergic—nausea, vomiting, diarrhea, blurry yellow vision (think van Gogh), arrhythmias, AV block. Can lead to hyperkalemia, which indicates poor prognosis. Factors predisposing to toxicity: renal failure (↓ excretion), hypokalemia (permissive for digoxin binding at K⁺-binding site on Na⁺/K⁺ ATPase), verapamil, amiodarone, quinidine (↓ digoxin clearance; displaces digoxin from tissue-binding sites).</td>
</tr>
<tr>
<td>ANTIDOTE</td>
<td>Slowly normalize K⁺, cardiac pacer, anti-digoxin Fab fragments, Mg²⁺.</td>
</tr>
</tbody>
</table>
# Antiarrhythmics—sodium channel blockers (class I)

## Class IA

**MECHANISM**

- ↑ AP duration, ↑ effective refractory period (ERP) in ventricular action potential, ↑ QT interval.

**CLINICAL USE**

Both atrial and ventricular arrhythmias, especially re-entrant and ectopic SVT and VT.

**TOXICITY**

Cinchanism (headache, tinnitus with quinidine), reversible SLE-like syndrome (procainamide), heart failure (disopyramide), thrombocytopenia, torsades de pointes due to ↑ QT interval.

### Examples

- **Quinidine**, Procainamide, Disopyramide. “The Queen Proclaims Diso’s pyramid.”

## Class IB

**MECHANISM**

- ↑ AP duration. Preferentially affect ischemic or depolarized Purkinje and ventricular tissue. Phenytoin can also fall into the IB category.

**CLINICAL USE**

Acute ventricular arrhythmias (especially post-MI), digitalis-induced arrhythmias. IB is Best post-MI.

**TOXICITY**

CNS stimulation/depression, cardiovascular depression.

### Examples


## Class IC

**MECHANISM**

- Significantly prolongs ERP in AV node and accessory bypass tracts. No effect on ERP in Purkinje and ventricular tissue. Minimal effect on AP duration.

**CLINICAL USE**

SVTs, including atrial fibrillation. Only as a last resort in refractory VT.

**TOXICITY**

Proarrhythmic, especially post-MI (contraindicated). IC is Contraindicated in structural and ischemic heart disease.

### Examples

- **Flecainide**, Propafenone. “Can I have Fries, Please.”
**Antiarrhythmics—β-blockers (class II)**

Metoprolol, propranolol, esmolol, atenolol, timolol, carvedilol.

**MECHANISM**
Decrease SA and AV nodal activity by ↑ cAMP, ↑ Ca²⁺ currents. Suppress abnormal pacemakers by ↑ slope of phase 4. AV node particularly sensitive—↑ PR interval. Esmolol very short acting.

**CLINICAL USE**
SVT, ventricular rate control for atrial fibrillation and atrial flutter.

**TOXICITY**
Impotence, exacerbation of COPD and asthma, cardiovascular effects (bradycardia, AV block, HF), CNS effects (sedation, sleep alterations). May mask the signs of hypoglycemia. Metoprolol can cause dyslipidemia. Propranolol can exacerbate vasospasm in Prinzmetal angina. β-blockers cause unopposed α₁-agonism if given alone for pheochromocytoma or cocaine toxicity. Treat β-blocker overdose with saline, atropine, glucagon.

---

**Antiarrhythmics—potassium channel blockers (class III)**

Amiodarone, Ibutilide, Dofetilide, Sotalol. AIDS.

**MECHANISM**
↑ AP duration, ↑ ERP, ↑ QT interval.

**CLINICAL USE**
Atrial fibrillation, atrial flutter; ventricular tachycardia (amiodarone, sotalol).

**TOXICITY**
Sotalol—torsades de pointes, excessive β blockade. Ibutilide—torsades de pointes. Amiodarone—pulmonary fibrosis, hepatotoxicity, hypothyroidism/hyperthyroidism (amiodarone is 40% iodine by weight), acts as hapten (corneal deposits, blue/grey skin deposits resulting in photodermatitis), neurologic effects, constipation, cardiovascular effects (bradycardia, heart block, HF). Remember to check PFTs, LFTs, and TFTs when using amiodarone. Amiodarone is lipophilic and has class I, II, III, and IV effects.
Antiarrhythmics—calcium channel blockers (class IV)

Verapamil, diltiazem.

**MECHANISM**  
↓ conduction velocity, ↑ ERP, ↑ PR interval.

**CLINICAL USE**  
Prevention of nodal arrhythmias (e.g., SVT), rate control in atrial fibrillation.

**TOXICITY**  
Constipation, flushing, edema, cardiovascular effects (HF, AV block, sinus node depression).

Other antiarrhythmics

**Adenosine**  
↑ K+ out of cells → hyperpolarizing the cell and ↓ \( I_{Ca} \). Drug of choice in diagnosing/abolishing supraventricular tachycardia. Very short acting (~15 sec). Effects blunted by theophylline and caffeine (both are adenosine receptor antagonists). Adverse effects include flushing, hypotension, chest pain, sense of impending doom, bronchospasm.

**Mg\(^{2+}\)**  
Effective in torsades de pointes and digoxin toxicity.
“We have learned that there is an endocrinology of elation and despair, a chemistry of mystical insight, and, in relation to the autonomic nervous system, a meteorology and even . . . an astro-physics of changing moods.”
—Aldous (Leonard) Huxley

“Chocolate causes certain endocrine glands to secrete hormones that affect your feelings and behavior by making you happy.”
—Elaine Sherman, Book of Divine Indulgences
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 pyramidal lobe of thyroid. Foramen cecum is normal remnant of thyroglossal duct. Most common ectopic thyroid tissue site is the tongue.

Thyroglossal duct cyst presents as an anterior midline neck mass that moves with swallowing or protrusion of the tongue (vs. persistent cervical sinus leading to branchial cleft cyst in lateral neck).

Adrenal cortex and medulla

Adrenal cortex (derived from mesoderm) and medulla (derived from neural crest).

<table>
<thead>
<tr>
<th>ANATOMY</th>
<th>PRIMARY REGULATORY CONTROL</th>
<th>SECRETORY PRODUCTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zona Glomerulosa</td>
<td>Renin-angiotensin</td>
<td>Aldosterone</td>
</tr>
<tr>
<td>Zona Fasciculata</td>
<td>ACTH, CRH</td>
<td>Cortisol, sex hormones</td>
</tr>
<tr>
<td>Zona Reticularis</td>
<td>ACTH, CRH</td>
<td>Sex hormones (e.g., androgens)</td>
</tr>
<tr>
<td>Chromaffin cells</td>
<td>Preganglionic sympathetic fibers</td>
<td>Catecholamines (epinephrine, norepinephrine)</td>
</tr>
</tbody>
</table>

"GFR corresponds with Salt (Na⁺), Sugar (glucocorticoids), and Sex (androgens)."

"The deeper you go, the sweeter it gets."

Pheochromocytoma—most common tumor of the adrenal medulla in adults.
Episodic hypertension.

Neuroblastoma—most common tumor of the adrenal medulla in children.
Rarely causes hypertension.
### Pituitary gland

#### Anterior pituitary (adenohypophysis)
Secretes FSH, LH, ACTH, TSH, prolactin, GH. Melanotropin (MSH) secreted from intermediate lobe of pituitary. Derived from oral ectoderm (Rathke pouch).

- \( \alpha \) subunit—hormone subunit common to TSH, LH, FSH, and hCG.
- \( \beta \) subunit—determines hormone specificity.

#### Posterior pituitary (neurohypophysis)
Secretes vasopressin (antidiuretic hormone, or ADH) and oxytocin, made in the hypothalamus (supraoptic and paraventricular nuclei, respectively) and transported to posterior pituitary via neurophysins (carrier proteins). Derived from neuroectoderm.

### 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)

Insulin (\( \beta \) cells) inside.
Insulin

**SYNTHESIS**
Preproinsulin (synthesized in RER) $\rightarrow$ 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.

**SOURCE**
Released from pancreatic $\beta$ cells.

**FUNCTION**
Binds insulin receptors (tyrosine kinase activity $\uparrow$), inducing glucose uptake (carrier-mediated transport) into insulin-dependent tissue $\uparrow$ and gene transcription. Anabolic effects of insulin:
- $\uparrow$ glucose transport in skeletal muscle and adipose tissue
- $\uparrow$ glycogen synthesis and storage
- $\uparrow$ triglyceride synthesis
- $\uparrow$ Na$^+$ retention (kidneys)
- $\uparrow$ protein synthesis (muscles)
- $\uparrow$ cellular uptake of K$^+$ and amino acids
- $\uparrow$ glucagon release

Unlike glucose, insulin does not cross placenta.

**REGULATION**
Glucose is a major regulator of insulin release. GH (causes insulin resistance $\rightarrow$ $\uparrow$ insulin release) and $\beta_2$-agonists $\rightarrow$ $\uparrow$ insulin.

Glucose enters $\beta$ cells $\rightarrow$ $\uparrow$ ATP generated from glucose metabolism $\rightarrow$ closes K$^+$ channels (target of sulfonylureas) and depolarizes $\beta$ cell membrane $\rightarrow$ Voltage-gated Ca$^{2+}$ channels open $\rightarrow$ Ca$^{2+}$ influx $\rightarrow$ stimulation of insulin exocytosis $\rightarrow$ Insulin secretion by pancreatic $\beta$ cells.
**Glucagon**

**SOURCE**
Made by α cells of pancreas.

**FUNCTION**
Catabolic effects of glucagon:
* Glycogenolysis, gluconeogenesis
* Lipolysis and ketone production

**REGULATION**
Secreted in response to hypoglycemia. Inhibited by insulin, hyperglycemia, and somatostatin.

---

**Hypothalamic-pituitary hormones**

<table>
<thead>
<tr>
<th>HORMONE</th>
<th>FUNCTION</th>
<th>CLINICAL NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRH</td>
<td>↑ ACTH, MSH, β-endorphin</td>
<td>↓ in chronic exogenous steroid use</td>
</tr>
<tr>
<td>Dopamine</td>
<td>↓ prolactin</td>
<td>Dopamine antagonists (e.g., antipsychotics) can cause galactorrhea due to hyperprolactinemia</td>
</tr>
<tr>
<td>GHRH</td>
<td>↑ GH</td>
<td>Analog (tesamorelin) used to treat HIV-associated lipodystrophy</td>
</tr>
<tr>
<td>GnRH</td>
<td>↑ FSH, LH</td>
<td>Regulated by prolactin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tonic GnRH suppresses HPA axis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulsatile GnRH leads to puberty, fertility</td>
</tr>
<tr>
<td>Prolactin</td>
<td>↓ GnRH</td>
<td>Pituitary prolactinoma → amenorrhea, osteoporosis, hypogonadism, galactorrhea</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>↓ GH, TSH</td>
<td>Analogs used to treat acromegaly</td>
</tr>
<tr>
<td>TRH</td>
<td>↑ TSH, prolactin</td>
<td></td>
</tr>
</tbody>
</table>
### Prolactin

<table>
<thead>
<tr>
<th><strong>SOURCE</strong></th>
<th>Secreted mainly by anterior pituitary.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FUNCTION</strong></td>
<td>Stimulates milk production in breast; inhibits ovulation in females and spermatogenesis in males by inhibiting GnRH synthesis and release.</td>
</tr>
<tr>
<td><strong>REGULATION</strong></td>
<td>Prolactin secretion from anterior pituitary is tonically inhibited by dopamine from hypothalamus. Prolactin in turn inhibits its own secretion by ↑ dopamine synthesis and secretion from hypothalamus. TRH ↑ prolactin secretion (e.g., in 1° or 2° hypothyroidism).</td>
</tr>
</tbody>
</table>

![Diagram](https://via.placeholder.com/150)
### Growth hormone (somatotropin)

<table>
<thead>
<tr>
<th><strong>SOURCE</strong></th>
<th>Secreted by anterior pituitary.</th>
</tr>
</thead>
</table>
| **FUNCTION** | Stimulates linear growth and muscle mass through IGF-1 (somatomedin C) secretion.  
† insulin resistance (diabetogenic). |
| **REGULATION** | Released in pulses in response to growth hormone–releasing hormone (GHRH).  
† during exercise and sleep.  
Secretion inhibited by glucose and somatostatin release via negative feedback by somatomedin.  
Excess secretion of GH (e.g., pituitary adenoma) may cause acromegaly (adults) or gigantism (children). |

### Appetite regulation

| **Ghrelin** | Stimulates hunger (orexigenic effect) and GH release (via GH secretagog receptor). Produced by stomach.  
† with sleep loss and Prader-Willi syndrome.  
Ghrelin make you hunghre. |
|-------------|---------------------------------|
| **Leptin** | Satiety hormone. Produced by adipose tissue.  
† during starvation. Mutation of leptin gene → congenital obesity. Sleep deprivation → ↓ leptin production.  
Leptin keeps you thin. |
| **Endocannabinoids** | Stimulate cortical reward centers → ↑ desire for high-fat foods.  
The munchies. |

### Antidiuretic hormone

<table>
<thead>
<tr>
<th><strong>SOURCE</strong></th>
<th>Synthesized in hypothalamus (supraoptic nuclei), released by posterior pituitary.</th>
</tr>
</thead>
</table>
| **FUNCTION** | Regulates serum osmolarity (V₂-receptors) and blood pressure (V₁-receptors). Primary function is serum osmolarity regulation (ADH ↑ serum osmolarity, ↑ urine osmolarity) via regulation of aquaporin channel insertion in principal cells of renal collecting duct.  
ADH level is ↓ in central diabetes insipidus (DI), normal or ↑ in nephrogenic DI.  
Nephrogenic DI can be caused by mutation in V₂-receptor.  
Desmopressin acetate (ADH analog) is a treatment for central DI. |
| **REGULATION** | Osmoreceptors in hypothalamus (1°); hypovolemia (2°). |
Adrenal steroids and congenital adrenal hyperplasias

**Enzyme Deficiency** | Mineralocorticoids | Cortisol | Sex Hormones | BP | [K+] | Labs | Presentation
--- | --- | --- | --- | --- | --- | --- | ---
**A 17α-hydroxylase** | ↑ | ↓ | ↓ | ↑ | ↓ | ↓ androstenedione | XY: pseudohermaphroditism (ambiguous genitalia, undescended testes) XX: lack secondary sexual development

**B 21-hydroxylase** | ↓ | ↓ | ↑ | ↓ | ↑ | ↑ renin activity ↑ 17-hydroxyprogesterone | Most common Presents in infancy (salt wasting) or childhood (precocious puberty) XX: virilization

**C 11β-hydroxylase** | ↓ aldosterone | ↓ | ↑ | ↓ | ↓ | ↑ renin activity | XX: virilization

*All congenital adrenal enzyme deficiencies are characterized by an enlargement of both adrenal glands due to ↑ ACTH stimulation (due to ↓ cortisol).*
Cortisol

**SOURCE**

Adrenal zona fasciculata.

**FUNCTION**

† Blood pressure:
  * Upregulates α₁-receptors on arterioles → † sensitivity to norepinephrine and epinephrine
  * At high concentrations, can bind to mineralocorticoid (aldosterone) receptors
  † Insulin resistance (diabetogenic)
  † Gluconeogenesis, lipolysis, and proteolysis
  † Fibroblast activity (causes striae)
  † Inflammatory and Immune responses:
    * Inhibits production of leukotrienes and prostaglandins
    * Inhibits WBC adhesion → neutrophilia
    * Blocks histamine release from mast cells
    * Reduces eosinophils
    * Blocks IL-2 production
  † Bone formation († osteoblast activity)

**REGULATION**

CRH (hypothalamus) stimulates ACTH release (pituitary) → cortisol production in adrenal zona fasciculata. Excess cortisol † CRH, ACTH, and cortisol secretion.

Cortisol is a **BIG FIB**.

Exogenous corticosteroids can cause reactivation of TB and candidiasis (blocks IL-2 production).

Calcium homeostasis

Plasma Ca²⁺ exists in three forms:

* Ionized (~ 45%)
* Bound to albumin (~ 40%)
* Bound to anions (~ 15%)

† in pH → † affinity of albumin († negative charge) to bind Ca²⁺ → hypocalcemia (cramps, pain, paresthesias, carpopedal spasm).

Vitamin D (cholecalciferol)

**SOURCE**

D₁ from sun exposure in skin. D₂ ingested from plants. Both converted to 25-OH in liver and to 1,25-(OH)₂ (active form) in kidney.

**FUNCTION**

† absorption of dietary Ca²⁺ and PO₄³⁻.
† bone resorption → † Ca²⁺ and PO₄³⁻.

**REGULATION**

† PTH, † [Ca²⁺], † PO₄³⁻ → † 1,25-(OH)₂ production.
1,25-(OH)₂ feedback inhibits its own production.


24,25-(OH)₂ D₃ is an inactive form of vitamin D. PTH leads to † Ca²⁺ reabsorption and † PO₄³⁻ reabsorption in the kidney, whereas 1,25-(OH)₂ D₃ leads to † absorption of both Ca²⁺ and PO₄³⁻ in the gut.
**Parathyroid hormone**

**SOURCE**

Chief cells of parathyroid.

**FUNCTION**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ bone resorption of Ca(^{2+}) and PO(_{4})(^{3–}).</td>
<td></td>
</tr>
<tr>
<td>↑ kidney reabsorption of Ca(^{2+}) in distal convoluted tubule.</td>
<td></td>
</tr>
<tr>
<td>↓ reabsorption of PO(_{4})(^{3–}) in proximal convoluted tubule.</td>
<td></td>
</tr>
<tr>
<td>↑ 1,25-(OH)(<em>{2})D(</em>{3}) (calcitriol) production by stimulating kidney 1α-hydroxylase in proximal convoluted tubule.</td>
<td></td>
</tr>
</tbody>
</table>

**Regulation**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ serum Ca(^{2+}), ↓ serum (PO(<em>{4})(^{3–})), ↓ urine (PO(</em>{4})(^{3–})).</td>
<td></td>
</tr>
<tr>
<td>↑ production of macrophage colony-stimulating factor and RANK-L (receptor activator of NF-κB ligand). RANK-L (ligand) secreted by osteoblasts and osteocytes binds RANK (receptor) on osteoclasts and their precursors to stimulate osteoclasts and ↑ Ca(^{2+}).</td>
<td></td>
</tr>
<tr>
<td>Intermittent PTH release can stimulate bone formation.</td>
<td></td>
</tr>
</tbody>
</table>

**PTH = Phosphate Trashing Hormone.**

PTH-related peptide (PTHrP) functions like PTH and is commonly increased in malignancies.

**Regulation**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ serum Ca(^{2+}) → ↑ PTH secretion.</td>
<td></td>
</tr>
<tr>
<td>↑ serum PO(_{4})(^{3–}) → ↑ PTH secretion.</td>
<td></td>
</tr>
<tr>
<td>↓ serum Mg(^{2+}) → ↑ PTH secretion.</td>
<td></td>
</tr>
<tr>
<td>↓↓ serum Mg(^{2+}) → ↓↓ PTH secretion.</td>
<td></td>
</tr>
</tbody>
</table>

Common causes of ↓ Mg\(^{2+}\) include diarrhea, aminoglycosides, diuretics, alcohol abuse.

---

**Calcium homeostasis**

- Low ionized calcium
- Four parathyroid glands
- PTH (1-84) released into circulation
- Renal tubular cells
- Bone
- Bone stimulates calcium release from bone mineral compartment
- Bone stimulates osteoblastic cells
- Bone stimulates bone resorption via indirect effect on osteoclasts
- Bone enhances bone matrix degradation
- Increases serum calcium
- Increases intestinal calcium absorption

**Phosphate homeostasis**

- Low serum phosphorus
- ↑ Conversion 25-(OH)D\(_{3}\) → 1,25-(OH)\(_{2}\)D\(_{3}\)
- Bone releases phosphate from matrix
- Bone stimulates osteoclastic cells
- Bone stimulates bone resorption via indirect effect on osteoclasts
- Bone enhances bone matrix degradation
- Bone increases intestinal phosphate reabsorption
Calcitonin

SOURCE
Parafollicular cells (C cells) of thyroid.

FUNCTION
↓ bone resorption of Ca^{2+}.

REGULATION
↑ serum Ca^{2+} → calcitonin secretion.

Calcitonin opposes actions of PTH. Not important in normal Ca^{2+} homeostasis. Calcitonin tones down Ca^{2+} levels.

### Signaling pathways of endocrine hormones

<table>
<thead>
<tr>
<th>cAMP</th>
<th>FSH, LH, ACTH, TSH, CRH, hCG, ADH (V2-receptor), MSH, PTH, calcitonin, GHRH, glucagon</th>
</tr>
</thead>
<tbody>
<tr>
<td>cGMP</td>
<td>ANP, BNP, NO (EDRF)</td>
</tr>
<tr>
<td>IP3</td>
<td>GnRH, Oxytocin, ADH (V1-receptor), TRH, Histamine (H1-receptor), Angiotensin II, Gastrin</td>
</tr>
<tr>
<td>Intracellular receptor</td>
<td>Vitamin D, Estrogen, Testosterone, T3/T4, Cortisol, Aldosterone, Progesterone</td>
</tr>
<tr>
<td>Intrinsic tyrosine kinase</td>
<td>Insulin, IGF-1, FGF, PDGF, EGF</td>
</tr>
<tr>
<td>Receptor-associated tyrosine kinase</td>
<td>Prolactin, Immunomodulators (e.g., cytokines IL-2, IL-6, IFN), GH, G-CSF, Erythropoietin, Thrombopoietin</td>
</tr>
</tbody>
</table>

### Signaling pathway of steroid hormones

Steroid hormones are lipophilic and therefore must circulate bound to specific binding globulins, which ↑ their solubility. In men, ↑ sex hormone–binding globulin (SHBG) lowers free testosterone → gynecomastia. In women, ↓ SHBG raises free testosterone → hirsutism. OCPs, pregnancy ↑ SHBG (free estrogen levels remain unchanged).
Thyroid hormones (T₃/T₄)

Iodine-containing hormones that control the body’s metabolic rate.

**SOURCE**
- Follicles of thyroid. Most T₃ formed in target tissues.

**FUNCTION**
- Bone growth (synergism with GH)
- CNS maturation
- β receptors in heart = ↑ CO, HR, SV, contractility
- ↑ basal metabolic rate via ↑ Na⁺/K⁺-ATPase activity → ↑ O₂ consumption, RR, body temperature
- ↑ glycogenolysis, gluconeogenesis, lipolysis

**REGULATION**
- TRH (hypothalamus) stimulates TSH (pituitary), which stimulates follicular cells. Negative feedback by free T₃, T₄ to anterior pituitary ↓ sensitivity to TRH. Thyroid-stimulating immunoglobulins (e.g., TSH) stimulate follicular cells (e.g., Graves disease). Wolff-Chaikoff effect—excess iodine temporarily inhibits thyroid peroxidase → ↓ iodine organification → ↓ T₃/T₄ production.

T₃ functions—4 B’s:
- Brain maturation
- Bone growth
- β-adrenergic effects
- Basal metabolic rate ↑

Thyroïd-binding globulin (TBG) binds most T₃/T₄ in blood; only free hormone is active. ↓ TBG in hepatic failure, steroids; ↑ TBG in pregnancy or OCP use (estrogen ↑ TBG).

T₄ is major thyroid product; converted to T₃ in peripheral tissue by 5'-deiodinase.

T₃ binds nuclear receptor with greater affinity than T₄.

Peroxidase is the enzyme responsible for oxidation and organification of iodide as well as coupling of monoiodotyrosine (MIT) and di-iodotyrosine (DIT).

Propylthiouracil inhibits both peroxidase and 5'-deiodinase. Methimazole inhibits peroxidase only.
Cushing syndrome

**Etiology**

- ↑ cortisol due to a variety of causes:
  - Exogenous corticosteroids—result in ↓ ACTH, bilateral adrenal atrophy. Most common cause.
  - Primary adrenal adenoma, hyperplasia, or carcinoma—result in ↓ ACTH, atrophy of uninvolved adrenal gland. Can also present with pseudohyperaldosteronism.
  - ACTH-secreting pituitary adenoma (Cushing disease); paraneoplastic ACTH secretion (e.g., small cell lung cancer, bronchial carcinoids)—result in ↑ ACTH, bilateral adrenal hyperplasia. Cushing disease is responsible for the majority of endogenous cases of Cushing syndrome.

**Findings**

Hypertension, weight gain, moon facies, truncal obesity, buffalo hump, skin changes (thinning, striae), osteoporosis, hyperglycemia (insulin resistance), amenorrhea, immunosuppression.

**Diagnosis**

Screening tests include:
- ↑ free cortisol on 24-hr urinalysis,
- ↑ midnight salivary cortisol, and no suppression with overnight low-dose dexamethasone test. Measure serum ACTH. If ↓, suspect adrenal tumor. If ↑, distinguish between Cushing disease and ectopic ACTH secretion with a high-dose (8 mg) dexamethasone suppression test and CRH stimulation test. Ectopic secretion will not decrease with dexamethasone because the source is resistant to negative feedback; ectopic secretion will not increase with CRH because pituitary ACTH is suppressed.

![Image of Cushing syndrome with symptoms and diagnostic flowchart]

<table>
<thead>
<tr>
<th>ACTH-independent Cushing syndrome</th>
<th>ACTH-dependent Cushing syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suppressed (&lt;5 pg/mL)</td>
<td>Elevated (&gt;20 pg/mL)</td>
</tr>
<tr>
<td>Measure ACTH</td>
<td></td>
</tr>
<tr>
<td>MRI to confirm adrenal tumor</td>
<td>High-dose dexamethasone suppression test</td>
</tr>
<tr>
<td>Adequate suppression = Cushing disease</td>
<td>No suppression = ectopic ACTH secretion</td>
</tr>
<tr>
<td></td>
<td>1 ACTH, cortisol = Cushing disease</td>
</tr>
<tr>
<td></td>
<td>No 1 ACTH, cortisol = ectopic ACTH secretion</td>
</tr>
<tr>
<td></td>
<td>CRH stimulation test</td>
</tr>
</tbody>
</table>
**Adrenal insufficiency**

Inability of adrenal glands to generate enough glucocorticoids +/- mineralocorticoids for the body’s needs. Symptoms include weakness, fatigue, orthostatic hypotension, muscle aches, weight loss, GI disturbances, sugar and/or salt cravings.

Diagnosis involves measurement of serum electrolytes, morning/random serum cortisol and ACTH, and response to ACTH stimulation test.

Alternatively, can use metyrapone stimulation test: metyrapone blocks last step of cortisol synthesis (11-deoxycortisol → cortisol). Normal response is ↑ cortisol and compensatory ↑ ACTH. In adrenal insufficiency, ACTH remains ↓ after test.

---

**Primary**

Deficiency of aldosterone and cortisol production due to loss of gland function → hypotension (hyponatremic volume contraction), hyperkalemia, metabolic acidosis, skin and mucosal hyperpigmentation (due to MSH, a byproduct of ↑ ACTH production from pro-opiomelanocortin).

- **Acute**—sudden onset (e.g., due to massive hemorrhage). May present with shock in acute adrenal crisis.
- **Chronic**—aka *Addison disease*. Due to adrenal atrophy or destruction by disease (e.g., autoimmune, TB, metastasis).

---

**Secondary**

Seen with ↓ pituitary ACTH production. No skin/mucosal hyperpigmentation, no hyperkalemia (aldosterone synthesis preserved).

---

**Tertiary**

Seen in patients with chronic exogenous steroid use, precipitated by abrupt withdrawal. Aldosterone synthesis unaffected.

---

**Waterhouse-Friderichsen syndrome**—acute 1° adrenal insufficiency due to adrenal hemorrhage associated with septicemia (usually *Neisseria meningitidis*), DIC, endotoxic shock.
Neuroblastoma

Most common tumor of the adrenal medulla in children, usually < 4 years old. Originates from neural crest cells; Homer-Wright rosettes characteristic. 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). Can also present with opsoclonus-myoclonus syndrome (“dancing eyes-dancing feet”). Homovanillic acid (HVA; a breakdown product of dopamine) and vanillylmandelic acid (VMA; a breakdown product of norepinephrine) in urine. Bombesin and neuron-specific enolase. Less likely to develop hypertension. Associated with overexpression of N-myc oncogene.
### Pheochromocytoma

| **ETIOLOGY** | **Most common tumor of the adrenal medulla in adults.** Derived from chromaffin cells (arise from neural crest). |
| **Rule of 10’s:** | 10% malignant  
10% bilateral  
10% extra-adrenal  
10% calcify  
10% kids |
| **SYMPTOMS** | Most tumors secrete epinephrine, norepinephrine, and dopamine, which can cause episodic hypertension. 
Associated with neurofibromatosis type 1, von Hippel-Lindau disease, MEN 2A and 2B. 
Symptoms occur in “spells”—relapse and remit. |
| **Episodic hyperadrenergic symptoms (5 P’s):** | Pressure (↑ BP)  
Pain (headache)  
Perspiration  
Palpitations (tachycardia)  
Pallor |
| **FINDINGS** | ↑ catecholamines and metanephrines in urine and plasma. |
| **TREATMENT** | Irreversible α-antagonists (e.g., phenoxybenzamine) followed by β-blockers prior to tumor resection. α-blockade must be achieved before giving β-blockers to avoid a hypertensive crisis. |

---

#### A
Pheochromocytoma involving adrenal medulla. 

#### B
Chromaffin cells in pheochromocytoma. Note enlarged pleomorphic nuclei (arrows) typical of malignancy.
### Hypothyroidism vs. Hyperthyroidism

<table>
<thead>
<tr>
<th>Signs/Symptoms</th>
<th>Hypothyroidism</th>
<th>Hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold intolerance (↓ heat production)</td>
<td>Heat intolerance (↑ heat production)</td>
<td></td>
</tr>
<tr>
<td>Weight gain, ↓ appetite</td>
<td>Weight loss, ↑ appetite</td>
<td></td>
</tr>
<tr>
<td>Hypoactivity, lethargy, fatigue, weakness</td>
<td>Hyperactivity</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td>↓ reflexes</td>
<td>↑ reflexes</td>
<td></td>
</tr>
<tr>
<td>Myxedema (facial/peri orbital)</td>
<td>Pretibial myxedema (Graves disease), peri orbital edema</td>
<td></td>
</tr>
<tr>
<td>Dry, cool skin; coarse, brittle hair</td>
<td>Warm, moist skin; fine hair</td>
<td></td>
</tr>
<tr>
<td>Bradycardia, dyspnea on exertion</td>
<td>Chest pain, palpitations, arrhythmias, ↑ number and sensitivity of β-adrenergic receptors</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lab Findings</th>
<th>Hypothyroidism</th>
<th>Hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ TSH (sensitive test for 1° hypothyroidism)</td>
<td>↓ TSH (if 1°)</td>
<td></td>
</tr>
<tr>
<td>↓ free $T_3$ and $T_4$</td>
<td>↑ free or total $T_3$ and $T_4$</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia (due to ↓ LDL receptor expression)</td>
<td>Hypcholesterolemia (due to ↑ LDL receptor expression)</td>
<td></td>
</tr>
</tbody>
</table>
Hypothyroidism

**Hashimoto thyroiditis**  Most common cause of hypothyroidism in iodine-sufficient regions; an autoimmune disorder (anti-thyroid peroxidase, antimicrosomal and anti-thyroglobulin antibodies). Associated with HLA-DR5. ↑ risk of non-Hodgkin lymphoma.

May be hyperthyroid early in course due to thyrotoxicosis during follicular rupture.

Histologic findings: Hürthle cells, lymphoid aggregate with germinal centers.

Findings: moderately enlarged, non-tender thyroid.

**Congenital hypothyroidism (cretinism)**  Severe fetal hypothyroidism due to maternal hypothyroidism, thyroid agenesis, thyroid dysgenesis (most common cause in U.S.), iodine deficiency, dyshormonogenetic goiter.


**Subacute thyroiditis (de Quervain)**  Self-limited disease often following a flu-like illness.

May be hyperthyroid early in course, followed by hypothyroidism.

Histology: granulomatous inflammation.

Findings: ↑ ESR, jaw pain, early inflammation, very tender thyroid. (de Quervain is associated with pain.)

**Riedel thyroiditis**  Thyroid replaced by fibrous tissue (hypothyroid). Fibrosis may extend to local structures (e.g., airway), mimicking anaplastic carcinoma.

Considered a manifestation of IgG4-related systemic disease (e.g., autoimmune pancreatitis, retroperitoneal fibrosis, noninfectious aortitis).

Findings: fixed, hard (rock-like), painless goiter.

**Other causes**  Iodine deficiency, goitrogens, Wolff-Chaikoff effect (thyroid gland downregulation in response to ↑ iodide).
Hyperthyroidism

Graves disease
Most common cause of hyperthyroidism. Autoantibodies (IgG) stimulate TSH receptors on thyroid (hyperthyroidism, diffuse goiter), retro-orbital fibroblasts (exophthalmos: proptosis, extraocular muscle swelling), and dermal fibroblasts (pretibial myxedema). Often presents during stress (e.g., childbirth).

Toxic multinodular goiter
Focal patches of hyperfunctioning follicular cells working independently of TSH due to mutation in TSH receptor. Release of T3 and T4. Hot nodules are rarely malignant.

Thyroid storm
Stress-induced catecholamine surge seen as a serious complication of thyrotoxicosis due to disease and other hyperthyroid disorders. Presents with agitation, delirium, fever, diarrhea, coma, and tachyarrhythmia (cause of death). May see increased ALP due to bone turnover. Treat with the 3 P's: β-blockers (e.g., Propranolol), Propylthiouracil, corticosteroids (e.g., Prednisolone).

Jod-Basedow phenomenon
Thyrotoxicosis if a patient with iodine deficiency goiter is made iodine replete.

Graves disease (exophthalmos). Patient with bilateral proptosis and eyelid retraction. Visible sclera causes appearance of a "stare."
Thyroid cancer
Thyroidectomy is an option for thyroid cancers and hyperthyroidism. Complications of surgery include hoarseness (due to recurrent laryngeal nerve damage), hypocalcemia (due to removal of parathyroid glands), and transection of recurrent and superior laryngeal nerves (during ligation of inferior thyroid artery and superior laryngeal artery, respectively).

Papillary carcinoma
Most common, excellent prognosis. Empty-appearing nuclei with central clearing (“Orphan Annie” eyes), psammoma bodies, nuclear grooves. Lymphatic invasion common. ↑ risk with RET and BRAF mutations, childhood irradiation.

Follicular carcinoma
Good prognosis, invades thyroid capsule (unlike follicular adenoma), uniform follicles.

Medullary carcinoma
From parafollicular “C cells”; produces calcitonin, sheets of cells in an amyloid stroma, hematogenous spread common. Associated with MEN 2A and 2B (RET mutations).

Undifferentiated/anaplastic carcinoma
Older patients; invades local structures, very poor prognosis.

Lymphoma
Associated with Hashimoto thyroiditis.

A Thyroid papillary carcinoma. Note classic empty-appearing nucleus (“Orphan Annie” eye, arrow).
B Medullary carcinoma. Solid sheets of cells with amyloid deposition (arrow).
Hypoparathyroidism

Due to accidental surgical excision of parathyroid glands, autoimmune destruction, or DiGeorge syndrome. Findings: hypocalcemia, tetany.

Chvostek sign—tapping of facial nerve (tap the Check) → contraction of facial muscles.

Trousseau sign—occlusion of brachial artery with BP cuff (cuff the Triceps) → carpal spasm.

Pseudohypoparathyroidism (Albright hereditary osteodystrophy)—unresponsiveness of kidney to PTH. Hypocalcemia, shortened 4th/5th digits, short stature. Autosomal dominant.

Familial hypocalciuric hypercalcemia

Defective Ca^{2+}-sensing receptor on parathyroid cells. PTH cannot be suppressed by an increase in Ca^{2+} level → mild hypercalcemia with normal to ↑ PTH levels.
**Hyperparathyroidism**

**Primary**

Usually due to parathyroid adenoma or hyperplasia. **Hypercalcemia**, hypercalciuria (renal stones), hypophosphatemia, ↑PTH, ↑ALP, ↑cAMP in urine. Most often asymptomatic. May present with weakness and constipation ("groans"), abdominal/flank pain (kidney stones, acute pancreatitis), depression ("psychiatric overtones").

**Osteitis fibrosa cystica**—cystic bone spaces filled with brown fibrous tissue ("brown tumor" consisting of deposited hemosiderin from hemorrhages; causes bone pain). "Stones, bones, groans, and psychiatric overtones."

**Secondary**

2° hyperplasia due to ↓Ca²⁺ absorption and/or ↑PO₄³⁻, most often in chronic renal disease (causes hypovitaminosis D → ↓Ca²⁺ absorption). **Hypocalcemia**, hyperphosphatemia in chronic renal failure (vs. hypophosphatemia with most other causes), ↑ALP, ↑PTH.

**Renal osteodystrophy**—bone lesions due to 2° or 3° hyperparathyroidism due in turn to renal disease.

**Tertiary**

Refractory (autonomous) hyperparathyroidism resulting from chronic renal disease. ↑↑PTH, ↑Ca²⁺.

**Pituitary adenoma**

Most commonly prolactinoma (benign). Adenoma may be functional (hormone producing) or nonfunctional (silent). Nonfunctional tumors present with mass effect (bitemporal hemianopia, hypopituitarism, headache). Functional tumor presentation is based on the hormone produced (e.g., prolactinoma: amenorrhea, galactorrhea, low libido, infertility; somatotropic adenoma: acromegaly).

Treatment for prolactinoma: dopamine agonists (bromocriptine or cabergoline), transsphenoidal resection.

**Pituitary adenoma.** Coronal (left) and sagittal (right) MRI shows large lobulated mass (arrow).
Acromegaly
Excess GH in adults. Typically caused by pituitary adenoma.

**Findings**
- Large tongue with deep furrows, deep voice, large hands and feet, coarse facial features, impaired glucose tolerance (insulin resistance).
- Risk of colorectal polyps and cancer.

**Diagnosis**
- ↑ serum IGF-1; failure to suppress serum GH following oral glucose tolerance test; pituitary mass seen on brain MRI.

**Treatment**
- Pituitary adenoma resection. If not cured, treat with octreotide (somatostatin analog) or pegvisomant (growth hormone receptor antagonist).

Diabetes insipidus
Characterized by intense thirst and polyuria with inability to concentrate urine due to lack of ADH (central) or failure of response to circulating ADH (nephogenic).

<table>
<thead>
<tr>
<th>Central DI</th>
<th>Nephrogenic DI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology</td>
<td>Pituitary tumor, autoimmune, trauma, surgery, ischemic encephalopathy, idiopathic</td>
</tr>
<tr>
<td>Findings</td>
<td>↓ ADH</td>
</tr>
<tr>
<td></td>
<td>Urine specific gravity &lt; 1.006</td>
</tr>
<tr>
<td></td>
<td>Serum osmolality &gt; 290 mOsm/kg</td>
</tr>
<tr>
<td></td>
<td>Hyperosmotic volume contraction</td>
</tr>
<tr>
<td>Water Deprivation Test</td>
<td>&gt; 50% ↑ in urine osmolality only after administration of ADH analog</td>
</tr>
<tr>
<td>Treatment</td>
<td>Intranasal desmopressin acetate</td>
</tr>
<tr>
<td></td>
<td>Hydration</td>
</tr>
</tbody>
</table>

*No water intake for 2–3 hr followed by hourly measurements of urine volume and osmolality and plasma Na⁺ concentration and osmolality. ADH analog (desmopressin acetate) is administered if normal values are not clearly reached.

SIADH
Syndrome of inappropriate antidiuretic hormone secretion:
- Excessive free water retention
- Euvolemic hyponatremia with continued urinary Na⁺ excretion
- Urine osmolality > serum osmolality
- Body responds to water retention with ↓ aldosterone (hyponatremia) to maintain near-normal volume status. Very low serum Na⁺ levels can lead to cerebral edema, seizures. Correct slowly to prevent osmotic demyelination syndrome (formerly known as central pontine myelinolysis).

Causes include:
- Ectopic ADH (e.g., small cell lung cancer)
- CNS disorders/head trauma
- Pulmonary disease
- Drugs (e.g., cyclophosphamide)

Treatment: fluid restriction, IV hypertonic saline, conivaptan, tolvaptan, demeclocycline.
**Hypopituitarism**

Undersecretion of pituitary hormones due to:
- Nonsecreting pituitary adenoma, craniopharyngioma
- **Sheehan syndrome** — ischemic infarct of pituitary following postpartum bleeding; usually presents with failure to lactate, absent menstruation, cold intolerance
- **Empty sella syndrome** — atrophy or compression of pituitary, often idiopathic, common in obese women
- **Pituitary apoplexy** — sudden hemorrhage of pituitary gland, often in the presence of an existing pituitary adenoma
- Brain injury
- Radiation

Treatment: hormone replacement therapy (corticosteroids, thyroxine, sex steroids, human growth hormone).

**Diabetes mellitus**

**ACUTE MANIFESTATIONS**

Insulin deficiency or insensitivity (and glucagon excess)

- Decreased serum glucose uptake
- Increased protein catabolism
- Increased lipolysis (insulin deficiency only)
- Hyperglycemia, glycosuria, osmotic diuresis, electrolyte depletion
- Increased plasma amino acids, nitrogen loss in urine
- Increased plasma FFAs, ketogenesis, ketonuria, ketonemia
- Dehydration +/- acidosis

Coma, death

**CHRONIC COMPLICATIONS**

Nonenzymatic glycation:
- Small vessel disease (diffuse thickening of basement membrane) → retinopathy (hemorrhage, exudates, microaneurysms, vessel proliferation), glaucoma, neuropathy, nephropathy (nodular glomerulosclerosis, aka Kimmelstiel-Wilson nodules → progressive proteinuria and arteriolosclerosis → hypertension; both lead to chronic renal failure).
- Large vessel atherosclerosis, CAD, peripheral vascular occlusive disease, gangrene → limb loss, cerebrovascular disease. MI most common cause of death.

Osmotic damage (sorbitol accumulation in organs with aldose reductase and/or absent sorbitol dehydrogenase):
- Neuropathy (motor, sensory, and autonomic degeneration)
- Cataracts

**DIAGNOSIS**

Fasting serum glucose, oral glucose tolerance test, HbA1c (reflects average blood glucose over prior 3 months). Polydipsia, polyuria, polyphagia, weight loss, DKA (type 1), hyperosmolar coma (type 2). Rarely, can be caused by unopposed secretion of GH and epinephrine. Also seen in patients on glucocorticoid therapy (steroid diabetes).
### Type 1 vs. type 2 diabetes mellitus

<table>
<thead>
<tr>
<th>Variable</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1° DEFECT</strong></td>
<td>Autoimmune destruction of β cells</td>
<td>↑ resistance to insulin, progressive pancreatic β-cell failure</td>
</tr>
<tr>
<td>INSULIN NECESSARY IN TREATMENT</td>
<td>Always</td>
<td>Sometimes</td>
</tr>
<tr>
<td>AGE (EXCEPTIONS COMMONLY OCCUR)</td>
<td>&lt; 30 yr</td>
<td>&gt; 40 yr</td>
</tr>
<tr>
<td>ASSOCIATION WITH OBESITY</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>GENETIC PREDISPOSITION</td>
<td>Relatively weak (50% concordance in identical twins), polygenic</td>
<td>Relatively strong (90% concordance in identical twins), polygenic</td>
</tr>
<tr>
<td>ASSOCIATION WITH HLA SYSTEM</td>
<td>Yes (HLA-DR3 and -DR4)</td>
<td>No</td>
</tr>
<tr>
<td>GLUCOSE INTOLERANCE</td>
<td>Severe</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>INSULIN SENSITIVITY</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>KETOACIDOSIS</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>β-CELL NUMBERS IN THE ISLETS</td>
<td>↑</td>
<td>Variable (with amyloid deposits)</td>
</tr>
<tr>
<td>SERUM INSULIN LEVEL</td>
<td>↓</td>
<td>Variable</td>
</tr>
<tr>
<td>CLASSIC SYMPTOMS OF POLYURIA,</td>
<td>Common</td>
<td>Sometimes</td>
</tr>
<tr>
<td>POLYDIPSIA, POLYPHAGIA, WEIGHT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOSS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HISTOLOGY</td>
<td>Islet leukocytic infiltrate</td>
<td>Islet amyloid polypeptide (IAPP) deposits</td>
</tr>
</tbody>
</table>

#### Diabetic ketoacidosis

One of the most feared complications of diabetes. Usually due to ↑ insulin requirements from ↑ stress (e.g., infection). Excess fat breakdown and ↑ ketogenesis from ↑ free fatty acids, which are then made into ketone bodies (β-hydroxybutyrate > acetooacetate). Usually occurs in type 1 diabetes, as endogenous insulin in type 2 diabetes usually prevents lipolysis.

**Signs/Symptoms**
- Kussmaul respirations (rapid/deep breathing), nausea/vomiting, abdominal pain, psychosis/delirium, dehydration. Fruity breath odor (due to exhaled acetone).

**Labs**
- Hyperglycemia, ↑ H⁺, ↓ HCO₃⁻ (↑ anion gap metabolic acidosis), ↑ blood ketone levels, leukocytosis. Hyperkalemia, but depleted intracellular K⁺ due to transcellular shift from ↓ insulin (therefore total body K⁺ is depleted).

**Complications**
- Life-threatening mucormycosis (usually caused by *Rhizopus* infection), cerebral edema, cardiac arrhythmias, heart failure.

**Treatment**
- IV fluids, IV insulin, and K⁺ (to replete intracellular stores); glucose if necessary to prevent hypoglycemia.

#### Glucagonoma

Tumor of pancreatic α cells → overproduction of glucagon. Presents with dermatitis (necrotic migratory erythema), diabetes (hyperglycemia), DVT, and depression.
Insulinoma

Tumor of pancreatic β cells → overproduction of insulin → hypoglycemia. May see Whipple triad: low blood glucose, symptoms of hypoglycemia (e.g., lethargy, syncope, diplopia), and resolution of symptoms after normalization of glucose levels. Symptomatic patients have ↓ blood glucose and ↑ C-peptide levels (vs. exogenous insulin use). Treatment: surgical resection.

Carcinoid syndrome

Rare syndrome caused by carcinoid tumors (neuroendocrine cells), especially metastatic small bowel tumors, which secrete high levels of serotonin (5-HT). Not seen if tumor is limited to GI tract (5-HT undergoes first-pass metabolism in liver). Results in recurrent diarrhea, cutaneous flushing, asthmatic wheezing, right-sided valvular disease. ↑ 5-hydroxyindoleacetic acid (5-HIAA) in urine, niacin deficiency (pellagra). Treatment: surgical resection, somatostatin analog (e.g., octreotide).

Zollinger-Ellison syndrome

Gastrin-secreting tumor (gastrinoma) of pancreas or duodenum. Acid hypersecretion causes recurrent ulcers in duodenum and jejunum. Presents with abdominal pain (peptic ulcer disease, distal ulcers), diarrhea (malabsorption). Positive secretin stimulation test: gastrin levels remain elevated after administration of secretin, which normally inhibits gastrin release. May be associated with MEN 1.
### Multiple endocrine neoplasias

All MEN syndromes have autosomal dominant inheritance. "All MEN are dominant" (or so they think).

<table>
<thead>
<tr>
<th>SUBTYPE</th>
<th>CHARACTERISTICS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MEN 1</strong></td>
<td>Parathyroid tumors</td>
<td>MEN 1 = 3 P’s: Pituitary, Parathyroid, and Pancreas; remember by drawing a diamond.</td>
</tr>
<tr>
<td></td>
<td>Pituitary tumors (prolactin or GH)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pancreatic endocrine tumors—Zollinger-Ellison syndrome, insulinomas, VIPomas, glucagonomas (rare)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Associated with mutation of MEN1 gene (menin, a tumor suppressor)</td>
<td></td>
</tr>
<tr>
<td><strong>MEN 2A</strong></td>
<td>Parathyroid hyperplasia</td>
<td>MEN 2A = 2 P’s: Parathyroids and Pheochromocytoma; remember by drawing a square.</td>
</tr>
<tr>
<td></td>
<td>Pheochromocytoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medullary thyroid carcinoma (secretes calcitonin)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Associated with marfanoid habitus; mutation in RET gene (codes for receptor tyrosine kinase)</td>
<td></td>
</tr>
<tr>
<td><strong>MEN 2B</strong></td>
<td>Pheochromocytoma</td>
<td>MEN 2B = 1 P: Pheochromocytoma; remember by drawing a triangle.</td>
</tr>
<tr>
<td></td>
<td>Medullary thyroid carcinoma (secretes calcitonin)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral/intestinal ganglioneuromatosis (mucosal neuromas)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Associated with marfanoid habitus; mutation in RET gene</td>
<td></td>
</tr>
</tbody>
</table>

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**Diagram:**

- **MEN 1:** Parathyroid, Pituitary, Pancreas
- **MEN 2A:** Parathyroid, Parathyroid, Parathyroid, Medullary thyroid cancer, Pheochromocytoma
- **MEN 2B:** Pheochromocytoma, Medullary thyroid cancer, Pheochromocytoma, Pheochromocytoma, Medullary thyroid cancer
### Diabetes mellitus drugs

Treatment strategies:
- **Type 1 DM**—low-carbohydrate diet, insulin replacement
- **Type 2 DM**—dietary modification and exercise for weight loss; oral agents, non-insulin injectables, insulin replacement
- **Gestational DM (GDM)**—dietary modifications, exercise, insulin replacement if lifestyle modification fails

<table>
<thead>
<tr>
<th>DRUG CLASSES</th>
<th>ACTION</th>
<th>CLINICAL USE</th>
<th>TOXICITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin preparations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Insulin, short acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Regular</strong></td>
<td></td>
<td>Type 1 DM, type 2 DM, GDM, DKA (IV), hyperkalemia (+ glucose), stress hyperglycemia.</td>
<td></td>
</tr>
<tr>
<td><strong>Insulin, intermediate acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NPH</strong></td>
<td></td>
<td>Type 1 DM, type 2 DM, GDM.</td>
<td></td>
</tr>
<tr>
<td><strong>Insulin, long acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Detemir, Glargine</strong></td>
<td></td>
<td>Type 1 DM, type 2 DM, GDM (basal glucose control).</td>
<td></td>
</tr>
<tr>
<td><strong>Oral hypoglycemic drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Biguanides</strong></td>
<td>Exact mechanism unknown. ↓ gluconeogenesis, ↑ glycolysis, ↑ peripheral glucose uptake (↑ insulin sensitivity).</td>
<td>Oral. First-line therapy in type 2 DM, causes modest weight loss. Can be used in patients without islet function.</td>
<td>GI upset; most serious adverse effect is lactic acidosis (thus contraindicated in renal insufficiency).</td>
</tr>
<tr>
<td><strong>Metformin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sulfonylureas</strong></td>
<td>Close K⁺ channel in β-cell membrane → cell depolarizes → insulin release via ↑ Ca²⁺ influx.</td>
<td>Stimulate release of endogenous insulin in type 2 DM. Require some islet function, so useless in type 1 DM.</td>
<td>Risk of hypoglycemia ↑ in renal failure. First generation: disulfiram-like effects. Second generation: hypoglycemia.</td>
</tr>
<tr>
<td><strong>First generation:</strong> Chlorpropamide, Tolbutamide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Second generation:</strong> Glimepiride, Glipizide, Glyburide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Glitazones/thiazolidinediones</strong></td>
<td>↑ insulin sensitivity in peripheral tissue. Binds to PPAR-γ nuclear transcription regulator.</td>
<td>Used as monotherapy in type 2 DM or combined with above agents.</td>
<td>Weight gain, edema. Hepatotoxicity, HF, ↑ risk of fractures.</td>
</tr>
<tr>
<td><strong>Pioglitazone, Rosiglitazone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Diabetes mellitus drugs (continued)

<table>
<thead>
<tr>
<th>DRUG CLASSES</th>
<th>ACTION</th>
<th>CLINICAL USE</th>
<th>TOXICITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral hypoglycemic drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(continued)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GLP-1 analogs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide, Liraglutide</td>
<td>↑ insulin, ↓ glucagon release.</td>
<td>Type 2 DM.</td>
<td>Nausea, vomiting; pancreatitis.</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linaglaptin, Saxagliptin,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>↑ insulin, ↓ glucagon release.</td>
<td>Type 2 DM.</td>
<td>Mild urinary or respiratory</td>
</tr>
<tr>
<td>Amylin analogs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pramlintide</td>
<td>↓ gastric emptying, ↓ glucagon.</td>
<td>Type 1 DM, type 2 DM.</td>
<td>Hypoglycemia, nausea, diarrhea.</td>
</tr>
<tr>
<td>SGLT-2 inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>Block reabsorption of glucose in PCT.</td>
<td>Type 2 DM.</td>
<td>Glucosuria, UTIs, vaginal</td>
</tr>
<tr>
<td>α-glucosidase inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acarbose, Miglitol</td>
<td>Inhibit intestinal brush-border α-glucosidases. Delayed carbohydrate hydrolysis and glucose absorption → ↓ postprandial hyperglycemia.</td>
<td>Used as monotherapy in type 2 DM or in combination with above agents.</td>
<td>GI disturbances.</td>
</tr>
</tbody>
</table>

*Genes activated by PPAR-γ regulate fatty acid storage and glucose metabolism. Activation of PPAR-γ ↑ insulin sensitivity and levels of adiponectin.

Propylthiouracil, methimazole

| MECHANISM | Block thyroid peroxidase, inhibiting the oxidation of iodide and the organification (coupling) of iodine → inhibition of thyroid hormone synthesis. Propylthiouracil also blocks 5′-deiodinase → ↓ peripheral conversion of T4 to T3. |
| CLINICAL USE | Hyperthyroidism. PTU blocks Peripheral conversion, used in Pregnancy. |
| TOXICITY | Skin rash, agranulocytosis (rare), aplastic anemia, hepatotoxicity (propylthiouracil). Methimazole is a possible teratogen (can cause aplasia cutis). |

Levothyroxine (T4), triiodothyronine (T3)

| MECHANISM | Thyroid hormone replacement. |
| CLINICAL USE | Hypothyroidism, myxedema. Used off-label as weight loss supplements. |
| TOXICITY | Tachycardia, heat intolerance, tremors, arrhythmias. |
### Hypothalamic/pituitary drugs

<table>
<thead>
<tr>
<th>DRUG</th>
<th>CLINICAL USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH antagonists (conivaptan, tolvaptan)</td>
<td>SIADH, block action of ADH at V₂-receptor.</td>
</tr>
<tr>
<td>Desmopressin acetate</td>
<td>Central (not nephrogenic) DI.</td>
</tr>
<tr>
<td>GH</td>
<td>GH deficiency, Turner syndrome.</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>Stimulates labor, uterine contractions, milk let-down; controls uterine hemorrhage.</td>
</tr>
<tr>
<td>Somatostatin (octreotide)</td>
<td>Acromegaly, carcinoid syndrome, gastrinoma, glucagonoma, esophageal varices.</td>
</tr>
</tbody>
</table>

### Demeclocycline

| MECHANISM | ADH antagonist (member of tetracycline family). |
| CLINICAL USE | SIADH. |
| TOXICITY | Nephrogenic DI, photosensitivity, abnormalities of bone and teeth. |

### Glucocorticoids

| MECHANISM | Beclomethasone, dexamethasone, fludrocortisone (mineralocorticoid and glucocorticoid activity), hydrocortisone, methylprednisolone, prednisone, triamcinolone. |
| CLINICAL USE | Metabolic, catabolic, anti-inflammatory, and immunosuppressive effects mediated by interactions with glucocorticoid response elements, inhibition of phospholipase A₂, and inhibition of transcription factors such as NF-κB. |
| TOXICITY | Iatrogenic Cushing syndrome (hypertension, weight gain, moon facies, truncal obesity, buffalo hump, thinning of skin, striae, osteoporosis, hyperglycemia, amenorrhea, immunosuppression), adrenocortical atrophy, peptic ulcers, steroid diabetes, steroid psychosis. Adrenal insufficiency when drug stopped abruptly after chronic use. |

### Cinacalcet

| MECHANISM | Sensitizes Ca²⁺-sensing receptor (CaSR) in parathyroid gland to circulating Ca²⁺ → PTH. |
| CLINICAL USE | Hypercalcemia due to 1° or 2° hyperparathyroidism. |
| TOXICITY | Hypocalcemia. |
“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

“The colon is the playing field for all human emotions.”
—Cyrus Kapadia, MD
GI embryology

Foregut—pharynx to duodenum.
Midgut—duodenum to proximal 2/3 of transverse colon.
Hindgut—distal 1/3 of transverse colon to anal canal above pectinate line.

Developmental defects of anterior abdominal wall due to failure of:
- Rostral fold closure—sternal defects
- Lateral fold closure—omphalocele, gastroschisis
- Caudal fold closure—bladder extrophy

Duodenal atresia—failure to recanalize (trisomy 21).
Jejunal, ileal, colonic atresia—due to vascular accident (apple peel atresia).

Midgut development:
- 6th week—midgut herniates through umbilical ring
- 10th week—returns to abdominal cavity + rotates around superior mesenteric artery (SMA)

Pathology—malrotation of midgut, omphalocele, intestinal atresia or stenosis, volvulus.

Gastrointestinal anomalies

Gastroschisis—extrusion of abdominal contents through abdominal folds; not covered by peritoneum.
Omphalocele—persistance of herniation of abdominal contents into umbilical cord, sealed by peritoneum.

Tracheoesophageal anomalies

Esophageal atresia (EA) with distal tracheoesophageal fistula (TEF) is the most common (85%).
Result in drooling, choking, and vomiting with first feeding. TEF allows air to enter stomach (visible on CXR). Cyanosis is 2° to laryngospasm (to avoid reflux-related aspiration). Clinical test: failure to pass nasogastric tube into stomach.

In H-type, the fistula resembles the letter H. In pure EA the CXR shows gasless abdomen.

Congenital pyloric stenosis

Hypertrophy of the pylorus causes obstruction. Palpable “olive” mass in epigastric region and nonbiliious projectile vomiting at ≈ 2–6 weeks old. Occurs in 1/600 live births, more often in firstborn males. Results in hypokalemic hypochloremic metabolic alkalosis (2° to vomiting of gastric acid and subsequent volume contraction). Treatment is surgical incision (pyloromyotomy).
Pancreas and spleen embryology

Pancreas—derived from foregut. Ventral pancreatic buds contribute to uncinate process and main pancreatic duct. The dorsal pancreatic bud alone becomes the body, tail, isthmus, and accessory pancreatic duct. Both the ventral and dorsal buds contribute to the pancreatic head. **Annular pancreas**—ventral pancreatic bud abnormally encircles 2nd part of duodenum; forms a ring of pancreatic tissue that may cause duodenal narrowing. **Pancreas divisum**—ventral and dorsal parts fail to fuse at 8 weeks. Common anomaly; mostly asymptomatic, but may cause chronic abdominal pain and/or pancreatitis.

Spleen—arises in mesentery of stomach (hence is mesodermal) but is supplied by foregut (celiac artery).

Retroperitoneal structures

Retroperitoneal structures include GI structures that lack a mesentery and non-GI structures. Injuries to retroperitoneal structures can cause blood or gas accumulation in retroperitoneal space.

**SAD PUCKER:**
- Suprarenal (adrenal) glands [not shown]
- 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 GI ligaments

<table>
<thead>
<tr>
<th>LIGAMENT</th>
<th>CONNECTS</th>
<th>STRUCTURES CONTAINED</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falciform</td>
<td>Liver to anterior abdominal wall</td>
<td>Ligamentum teres hepatis (derivative of fetal umbilical vein)</td>
<td>Derivative of ventral mesentery</td>
</tr>
</tbody>
</table>
| Hepatoduodenal      | Liver to duodenum                      | Portal triad: proper hepatic artery, portal vein, common bile duct                     | Pringle maneuver—ligament may be compressed between thumb and index finger placed in omental foramen to control bleeding  
|                     |                                        |                                                                                        | Borders the omental foramen, which connects the greater and lesser sacs                         |
| Gastrohepatic       | Liver to lesser curvature of stomach   | Gastric arteries                                                                        | Separates greater and lesser sacs on the right                                                
|                     |                                        |                                                                                        | May be cut during surgery to access lesser sac                                                 |
| Gastrocolic (not shown) | Greater curvature and transverse colon | Gastroepiploic arteries                                                                 | Part of greater omentum                                                                         |
| Gastroplenic        | Greater curvature and spleen           | Short gastrics, left gastroepiploic vessels                                            | Separates greater and lesser sacs on the left                                                  |
| Splenorenal         | Spleen to posterior abdominal wall     | Splenic artery and vein, tail of pancreas                                              |                                                                                                  |
Digestive tract anatomy

Layers of gut wall (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 the mucosa only.

Frequencies of basal electric rhythm (slow waves):
- **Stomach**—3 waves/min
- **Duodenum**—12 waves/min
- **Ileum**—8–9 waves/min

Digestive tract histology

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus</td>
<td>Nonkeratinized stratified squamous epithelium.</td>
</tr>
<tr>
<td>Stomach</td>
<td>Gastric glands.</td>
</tr>
<tr>
<td>Duodenum</td>
<td>Villi and microvilli † absorptive surface. Brunner glands (HCO$_3^-$-secreting cells of submucosa) and crypts of Lieberkühn.</td>
</tr>
<tr>
<td>Jejunum</td>
<td>Plicae circulares and crypts of Lieberkühn.</td>
</tr>
<tr>
<td>Ileum</td>
<td>Peyer patches (lymphoid aggregates in lamina propria, submucosa), plicae circulares (proximal ileum), and crypts of Lieberkühn. Largest number of goblet cells in the small intestine.</td>
</tr>
<tr>
<td>Colon</td>
<td>Colon has crypts of Lieberkühn but no villi; abundant goblet cells.</td>
</tr>
</tbody>
</table>
Arteries supplying GI structures branch **anteriorly**. Arteries supplying non-GI structures branch **laterally**.

Superior mesenteric artery (SMA) syndrome occurs when the transverse portion (third part) of the duodenum is entrapped between SMA and aorta, causing intestinal obstruction.

**Abdominal aorta and branches**

- Celiac trunk (T12)
- Superior mesenteric artery (L1)
- Right renal artery
- Left renal artery (L1)
- Left testicular/ovarian artery
- Inferior mesenteric artery (L3)
- Right external iliac artery
- Left inferior phrenic artery
- Left middle suprarenal artery
- Right internal iliac artery
- Left inferior phrenic artery
- Left middle suprarenal artery
- Right renal artery
- Left renal artery (L1)
- Left testicular/ovarian artery
- Inferior mesenteric artery (L3)
- "Bifurcation" of abdominal aorta (L4)
- Left common iliac artery
- Right internal iliac artery
- Right external iliac artery
- Median sacral artery

**GI blood supply and innervation**

<table>
<thead>
<tr>
<th>EMBRYONIC GUT REGION</th>
<th>ARtery</th>
<th>PARASYMPATHETIC INNERRATION</th>
<th>VERTEBRAL LEVEL</th>
<th>STRUCTURES SUPPLIED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foregut</td>
<td>Celiac</td>
<td>Vagus</td>
<td>T12/L1</td>
<td>Pharynx (vagus nerve only) and lower esophagus (celiac artery only) to proximal duodenum; liver, gallbladder, pancreas, spleen (mesoderm)</td>
</tr>
<tr>
<td>Midgut</td>
<td>SMA</td>
<td>Vagus</td>
<td>L1</td>
<td>Distal duodenum to proximal 2/3 of transverse colon</td>
</tr>
<tr>
<td>Hindgut</td>
<td>IMA</td>
<td>Pelvic</td>
<td>L3</td>
<td>Distal 1/3 of transverse colon to upper portion of rectum; splenic flexure is a watershed region between SMA and IMA</td>
</tr>
</tbody>
</table>
Celiac trunk

Branches of celiac trunk: common hepatic, splenic, and left gastric. These constitute the main blood supply of the stomach.

Short gastrics have poor anastomoses if splenic artery is blocked.

Strong anastomoses exist between:
- Left and right gastroepiploics
- Left and right gastrics
Portosystemic anastomoses

---

Pathologic blood flow in portal HTN
Flow through TIPS, re-establishing normal flow direction
Normal venous drainage

1. Esophageal varices
2. Caput medusae
3. Rectal varices
4. TIPS

To the azygos vein

<table>
<thead>
<tr>
<th>SITE OF ANASTOMOSIS</th>
<th>CLINICAL SIGN</th>
<th>PORTAL ↔ SYSTEMIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Esophagus</td>
<td>Esophageal varices</td>
<td>Left gastric ↔ esophageal</td>
</tr>
<tr>
<td>2. Umbilicus</td>
<td>Caput medusae</td>
<td>Paraumbilical ↔ small epigastric veins of the anterior abdominal wall.</td>
</tr>
<tr>
<td>3. Rectum</td>
<td>Anorectal varices (not internal hemorrhoids)</td>
<td>Superior rectal ↔ middle and inferior rectal</td>
</tr>
</tbody>
</table>

Varices of gut, butt, and caput (medusae) are commonly seen with portal hypertension.

Treatment with a transjugular intrahepatic portosystemic shunt (TIPS) 4 between the portal vein and hepatic vein relieves portal hypertension by shunting blood to the systemic circulation, bypassing the liver.
**Pectinate (dentate) line**

Formed where endoderm (hindgut) meets ectoderm.

- **Above pectinate line**—internal hemorrhoids, adenocarcinoma.
  - Arterial supply from superior rectal artery (branch of IMA).
  - Venous drainage: superior rectal vein → inferior mesenteric vein → portal system.

  - Internal hemorrhoids receive visceral innervation and are therefore **not painful**.
  - Lymphatic drainage to internal iliac lymph nodes.

- **Below pectinate line**—external hemorrhoids, anal fissures, squamous cell carcinoma.
  - Arterial supply from inferior rectal artery (branch of internal pudendal artery).
  - Venous drainage: inferior rectal vein → internal pudendal vein → internal iliac vein → common iliac vein → IVC.

  - External hemorrhoids receive somatic innervation (inferior rectal branch of pudendal nerve) and are therefore **painful** if thrombosed.
  - Lymphatic drainage to superficial inguinal nodes.

  - Anal fissure—tear in the anal mucosa below the Pectinate line. Pain while Pooping; blood on “toilet” Paper. Located Posteriorly since this area is Poorly Perfused.

**Liver anatomy**

Apical surface of hepatocytes faces bile canaliculi. Basolateral surface faces sinusoids.

- **Zone I**—periportal zone:
  - Affected 1st by viral hepatitis
  - Ingested toxins (e.g., cocaine)

- **Zone II**—intermediate zone:
  - Yellow fever

- **Zone III**—pericentral vein (centrilobular) zone:
  - Affected 1st by ischemia
  - Contains cytochrome P-450 system
  - Most sensitive to metabolic toxins
  - Site of alcoholic hepatitis
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 can cause obstruction of common bile duct alone → painless jaundice.
Inguinal canal

- Parietal peritoneum
- Extraperitoneal tissue
- Transversalis fascia
- Transversus abdominis muscle
- Internal oblique muscle
- Aponeurosis of external oblique muscle
- Inguinal ligament
- Internal inguinal ring: site of protrusion of indirect hernia
- Abdominal wall: site of protrusion of direct hernia
- Inferior epigastric vessels
- Medial umbilical ligament
- Median umbilical ligament
- Rectus abdominis muscle
- Pyramidalis muscle
- Conjoined tendon
- Linea alba
- Spermatic cord
- External spermatic fascia (external oblique)
- Cremasteric muscle and fascia (internal oblique)
- Internal spermatic fascia (transversalis fascia)
- Superficial inguinal ring
- Extraperitoneal tissue
### Hernias

A protrusion of peritoneum through an opening, usually a site of weakness.

#### Diaphragmatic hernia

Abdominal structures enter the thorax; may occur due to congenital defect of pleuroperitoneal membrane, or as a result of trauma. Commonly occurs on left side due to relative protection of right hemidiaphragm by liver. Most commonly a **hiatal hernia**, in which stomach herniates upward through the esophageal hiatus of the diaphragm.

**Sliding hiatal hernia** is most common. Gastroesophageal junction is displaced upward; “hourglass stomach.”

**Paraesophageal hernia**—gastroesophageal junction is usually normal. Fundus protrudes into the thorax.

#### Indirect inguinal hernia

Goes through the internal (deep) inguinal ring, external (superficial) inguinal ring, and into the scrotum. Enters internal inguinal ring lateral to inferior epigastric artery. Occurs in infants owing to failure of processus vaginalis to close (can form hydrocele). Much more common in males.

An indirect inguinal hernia follows the path of descent of the testes. Covered by all 3 layers of spermatic fascia.

#### Direct inguinal hernia

Protrudes through the inguinal (Hesselbach) triangle. Bulges directly through abdominal wall medial to inferior epigastric artery. Goes through the external (superficial) inguinal ring only. Covered by external spermatic fascia. Usually in older men.

MDs don’t **LIE:**

- Medial to inferior epigastric artery = Direct hernia.
- Lateral to inferior epigastric artery = Indirect hernia.

#### Femoral hernia

Protrudes below inguinal ligament through femoral canal below and lateral to pubic tubercle. More common in **females**.

Leading cause of bowel incarceration.

Hesselbach triangle:
- Inferior epigastric vessels
- Lateral border of rectus abdominis
- Inguinal ligament

![Diagram of Hernias](image)
### GI regulatory substances

<table>
<thead>
<tr>
<th>REGULATORY SUBSTANCE</th>
<th>SOURCE</th>
<th>ACTION</th>
<th>REGULATION</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrin</strong></td>
<td>G cells (antrum of stomach, duodenum)</td>
<td>↑ gastric H⁺ secretion</td>
<td>↑ by stomach distention/alkalinization, amino acids, peptides, vagal stimulation&lt;br&gt;↓ by pH &lt; 1.5</td>
<td>↑ in chronic atrophic gastritis (e.g., H. pylori).&lt;br&gt;↑↑ in Zollinger-Ellison syndrome.</td>
</tr>
<tr>
<td><strong>Somatostatin</strong></td>
<td>D cells (pancreatic islets, GI mucosa)</td>
<td>↓ gastric acid and pepsinogen secretion&lt;br&gt;↓ gallbladder contraction&lt;br&gt;↓ insulin and glucagon release</td>
<td>↑ by acid&lt;br&gt;↓ by vagal stimulation</td>
<td>Inhibits secretion of GH, insulin, and other hormones (encourages somato-stasis). Octreotide is an analog used to treat acromegaly, insulinoma, carcinoid syndrome, and variceal bleeding.</td>
</tr>
<tr>
<td><strong>Cholecystokinin</strong></td>
<td>I cells (duodenum, jejunum)</td>
<td>↑ pancreatic secretion&lt;br&gt;↑ gallbladder contraction&lt;br&gt;↑ gastric emptying&lt;br&gt;↑ sphincter of Oddi relaxation</td>
<td>↑ by fatty acids, amino acids</td>
<td>CCK acts on neural muscarinic pathways to cause pancreatic secretion.</td>
</tr>
<tr>
<td><strong>Secretin</strong></td>
<td>S cells (duodenum)</td>
<td>↑ pancreatic HCO₃⁻ secretion&lt;br&gt;↓ gastric acid secretion&lt;br&gt;↑ bile secretion</td>
<td>↑ by acid, fatty acids in lumen of duodenum</td>
<td>↑ HCO₃⁻ neutralizes gastric acid in duodenum, allowing pancreatic enzymes to function.</td>
</tr>
<tr>
<td><strong>Glucose-dependent insulino tropic peptide (GIP)</strong></td>
<td>K cells (duodenum, jejunum)</td>
<td>Exocrine: ↑ gastric H⁺ secretion&lt;br&gt;Endocrine: ↑ insulin release</td>
<td>↑ by fatty acids, amino acids, oral glucose</td>
<td>Also known as gastric inhibitory peptide. Oral glucose load leads to ↑ insulin compared to IV equivalent due to GIP secretion.</td>
</tr>
<tr>
<td><strong>Motilin</strong></td>
<td>Small intestine</td>
<td>Produces migrating motor complexes (MMCs)</td>
<td>↑ in fasting state</td>
<td>Motilin receptor agonists (e.g., erythromycin) are used to stimulate intestinal peristalsis.</td>
</tr>
<tr>
<td><strong>Vasoactive intestinal polypeptide (VIP)</strong></td>
<td>Parasympathetic ganglia in sphincters, gallbladder, small intestine</td>
<td>↑ intestinal water and electrolyte secretion&lt;br&gt;↑ relaxation of intestinal smooth muscle and sphincters</td>
<td>↑ by distention and vagal stimulation&lt;br&gt;↓ by adrenergic input</td>
<td>VIPoma—non-α, non-β islet cell pancreatic tumor that secretes VIP. Copious Watery Diarrhea, Hypokalemia, and Achlorhydria (WDHA syndrome).</td>
</tr>
<tr>
<td><strong>Nitric oxide</strong></td>
<td></td>
<td>↑ smooth muscle relaxation, including lower esophageal sphincter (LES)</td>
<td></td>
<td>Loss of NO secretion is implicated in ↑ LES tone of achalasia.</td>
</tr>
</tbody>
</table>
**Gi secretory products**

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>SOURCE</th>
<th>ACTION</th>
<th>REGULATION</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrinsic factor</td>
<td>Parietal cells (stomach)</td>
<td>Vitamin B₁₂-binding protein (required for B₁₂ uptake in terminal ileum)</td>
<td>Autoimmune destruction of parietal cells → chronic gastritis and pernicious anemia.</td>
<td></td>
</tr>
<tr>
<td>Gastric acid</td>
<td>Parietal cells (stomach)</td>
<td>↓ stomach pH</td>
<td>↑ by histamine, ACh, gastrin ↓ by somatostatin, GIP, prostaglandin, secretin</td>
<td>Gastrinoma: gastrin-secreting tumor that causes high levels of acid and ulcers refractory to medical therapy (i.e., PPI).</td>
</tr>
<tr>
<td>Pepsin</td>
<td>Chief cells (stomach)</td>
<td>Protein digestion</td>
<td>↑ by vagal stimulation, local acid</td>
<td>Pepsinogen (inactive) is converted to pepsin (active) in the presence of H⁺</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>Mucosal cells (stomach, duodenum, salivary glands, pancreas) and Brunner glands (duodenum)</td>
<td>Neutralizes acid</td>
<td>↑ by pancreatic and biliary secretion with secretin</td>
<td>HCO₃⁻ is trapped in mucus that covers the gastric epithelium.</td>
</tr>
</tbody>
</table>

**Locations of Gi 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.
Gastric parietal cell

Pancreatic secretions: Isotonic fluid; low flow → high Cl⁻, high flow → high HCO₃⁻.

<table>
<thead>
<tr>
<th>ENZYME</th>
<th>ROLE</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-amylase</td>
<td>Starch digestion</td>
<td>Secreted in active form</td>
</tr>
<tr>
<td>Lipases</td>
<td>Fat digestion</td>
<td></td>
</tr>
<tr>
<td>Proteases</td>
<td>Protein digestion</td>
<td>Includes trypsin, chymotrypsin, elastase, carboxypeptidases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Secreted as proenzymes also known as zymogens</td>
</tr>
<tr>
<td>Trypsinogen</td>
<td>Converted to active enzyme trypsin</td>
<td>Converted to trypsin by enterokinase/enteropeptidase, a brush-border enzyme on duodenal and jejunal mucosa</td>
</tr>
<tr>
<td></td>
<td>activation of other proenzymes and cleaving of additional trypsinogen molecules into active trypsin (positive feedback loop)</td>
<td></td>
</tr>
</tbody>
</table>

Carbohydrate absorption: Only monosaccharides (glucose, galactose, fructose) are absorbed by enterocytes. Glucose and galactose are taken up by SGLT1 (Na⁺ dependent). Fructose is taken up by facilitated diffusion by GLUT-5. All are transported to blood by GLUT-2. D-xylose absorption test: distinguishes GI mucosal damage from other causes of malabsorption.
Vitamin/mineral absorption

<table>
<thead>
<tr>
<th>Vitamin/mineral</th>
<th>Absorption</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>Absorbed as Fe(^{2+}) in duodenum.</td>
<td>Iron Fist, Bro Clinically relevant in patients with small bowel disease or after resection.</td>
</tr>
<tr>
<td>Folate</td>
<td>Absorbed in small bowel.</td>
<td></td>
</tr>
<tr>
<td>B(_{12})</td>
<td>Absorbed in terminal ileum along with bile salts, requires intrinsic factor.</td>
<td></td>
</tr>
</tbody>
</table>

Peyer patches

Unencapsulated lymphoid tissue found in lamina propria and submucosa of ileum. Contain specialized M cells that sample and present antigens to immune cells. B cells stimulated in germinal centers of Peyer patches differentiate into IgA-secreting plasma cells, which ultimately reside in lamina propria. IgA receives protective secretory component and is then transported across the epithelium to the gut to deal with intraluminal antigen.

Think of IgA, the Intra-gut Antibody. And always say “secretory IgA.”

Bile

Composed of bile salts (bile acids conjugated to glycine or taurine, making them water soluble), phospholipids, cholesterol, bilirubin, water, and ions. Cholesterol 7α-hydroxylase catalyzes rate-limiting step of bile synthesis.

Functions:
- Digestion and absorption of lipids and fat-soluble vitamins
- Cholesterol excretion (body’s only means of eliminating cholesterol)
- Antimicrobial activity (via membrane disruption)
Bilirubin

Heme is metabolized by heme oxygenase to biliverdin, which is subsequently reduced to bilirubin. Unconjugated bilirubin is removed from blood by liver, conjugated with glucuronate, and excreted in bile. Direct bilirubin—conjugated with glucuronic acid; water soluble. Indirect bilirubin—unconjugated; water insoluble.

Salivary gland tumors

Generally benign and occur in parotid gland:
- Pleomorphic adenoma (benign mixed tumor)—most common salivary gland tumor. Presents as painless, mobile mass. Composed of chondromyxoid stroma and epithelium and recurs if incompletely excised or ruptured intraoperatively.
- Mucoepidermoid carcinoma—most common malignant tumor, has mucinous and squamous components. Typically presents as painless, slow-growing mass.
- Warthin tumor (papillary cystadenoma lymphomatosum)—benign cystic tumor with germinal centers.

Achalasia

Failure of relaxation of LES due to loss of myenteric (Auerbach) plexus. High LES resting pressure and uncoordinated peristalsis → progressive dysphagia to solids and liquids (vs. obstruction—solids only). Barium swallow shows dilated esophagus with an area of distal stenosis. Associated with ↑ risk of esophageal squamous cell carcinoma. A-chalasia = absence of relaxation. “Bird’s beak” on barium swallow. 2° achalasia may arise from Chagas disease (T. cruzi infection) or malignancies (mass effect or paraneoplastic).
Esophageal pathologies

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boerhaave syndrome</td>
<td>Transmural, usually distal esophageal with pneumomediastinum (arrows) due to violent retching; surgical emergency.</td>
</tr>
<tr>
<td>Eosinophilic esophagitis</td>
<td>Infiltration of eosinophils in the esophagus in atopic patients. Food allergens → dysphagia, heartburn, strictures. Unresponsive to GERD therapy.</td>
</tr>
<tr>
<td>Esophageal strictures</td>
<td>Associated with lye ingestion and acid reflux.</td>
</tr>
<tr>
<td>Esophageal varices</td>
<td>Dilated submucosal veins in lower 1/4 of esophagus 2° to portal hypertension. Common in alcoholics, may be source of upper GI bleeding.</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>Associated with reflux, infection in immunocompromised (Candida: white pseudomembrane; HSV-1: punched-out ulcers; CMV: linear ulcers), or chemical ingestion.</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>Commonly presents as heartburn and regurgitation upon lying down. May also present with nocturnal cough and dyspnea, adult-onset asthma. Decrease in LES tone.</td>
</tr>
<tr>
<td>Mallory-Weiss syndrome</td>
<td>Mucosal lacerations at the gastroesophageal junction due to severe vomiting. Leads to hematemesis. Usually found in alcoholics and bulimics.</td>
</tr>
<tr>
<td>Plummer-Vinson syndrome</td>
<td>Triad of Dysphagia, Iron deficiency anemia, and Esophageal webs. May be associated with glossitis. Increased risk of esophageal squamous cell carcinoma (&quot;Plumbers’ DIE&quot;).</td>
</tr>
<tr>
<td>Sclerodermal esophageal dysmotility</td>
<td>Esophageal smooth muscle atrophy → ↓ LES pressure and dysmotility → acid reflux and dysphagia → stricture, Barrett esophagus, and aspiration. Part of CREST syndrome.</td>
</tr>
</tbody>
</table>

**Barrett esophagus**

Glandular metaplasia—replacement of nonkeratinized stratified squamous epithelium with intestinal epithelium (nonciliated columnar with goblet cells) in distal esophagus. Due to chronic acid reflux (GERD). Associated with esophagitis, esophageal ulcers, and ↑ risk of esophageal adenocarcinoma.
**Esophageal cancer**

Can be squamous cell carcinoma or adenocarcinoma. Typically presents with progressive dysphagia (first solids, then liquids) and weight loss; poor prognosis. Risk factors include:

- Achalasia
- Alcohol—squamous
- Barrett esophagus—adenocarcinoma
- Cigarettes—both
- Diverticula (e.g., Zenker)—squamous
- Esophageal web—squamous
- Familial
- Fat (obesity)—adenocarcinoma
- GERD—adenocarcinoma
- Hot liquids—squamous

**Gastritis**

**Acute gastritis (erosive)**

Disruption of mucosal barrier $\rightarrow$ inflammation. Can be caused by:

- NSAIDs $\rightarrow$ PGE$_2$ $\rightarrow$ gastric mucosa protection
- Burns (Curling ulcer) $\rightarrow$ plasma volume sloughing of gastric mucosa
- Brain injury (Cushing ulcer) $\rightarrow$ vagal stimulation $\rightarrow$ ACh $\rightarrow$ H$^+$ production

Especially common among alcoholics and patients taking daily NSAIDs (e.g., patients with rheumatoid arthritis).

Burned by the Curling iron.

Always Cushion the brain.

**Chronic gastritis (nonerosive)**

**Type A (fundus/body)**

Autoimmune disorder characterized by autoantibodies to parietal cells, pernicious anemia, and achlorhydria. Associated with other autoimmune disorders.

A comes before B:

- Type A—Autoimmune; first part of the stomach (fundus/body).
- Type B—H. pylori bacteria; second part of the stomach (antrum).

**Type B (antrum)**

Most common type. Caused by *H. pylori* infection. ↑ risk of MALT lymphoma.

**Ménétrier disease**

Gastric hyperplasia of mucosa $\rightarrow$ hypertrophied rugae, excess mucus production with resultant protein loss and parietal cell atrophy with acid production. Precancerous. Rugae of stomach are so hypertrophied that they look like brain gyri.
**Stomach cancer**

Commonly gastric adenocarcinoma; lymphoma; carcinoid (rare). Early aggressive local spread with node/liver metastases. Often presents with weight loss, early satiety, and in some cases acanthosis nigricans.

- **Intestinal**—associated with *H. pylori*, dietary nitrosamines (smoked foods), tobacco smoking, achlorhydria, chronic gastritis. Commonly on lesser curvature; looks like ulcer with raised margins.
- **Diffuse**—not associated with *H. pylori*; signet ring cells (mucin-filled cells with peripheral nuclei); stomach wall grossly thickened and leathery (limitis plastica).

**Virchow node**—involvement of left supraclavicular node by metastasis from stomach.

**Krukenberg tumor**—bilateral metastases to ovaries. Abundant mucin-secreting, signet ring cells.

**Sister Mary Joseph nodule**—subcutaneous periumbilical metastasis.

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**Peptic ulcer disease**

<table>
<thead>
<tr>
<th></th>
<th>Gastric ulcer</th>
<th>Duodenal ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PAIN</strong></td>
<td>Can be Greater with meals—weight loss</td>
<td>Decreases with meals—weight gain</td>
</tr>
<tr>
<td><strong>H. Pylori Infection</strong></td>
<td>In 70%</td>
<td>In almost 100%</td>
</tr>
<tr>
<td><strong>MECHANISM</strong></td>
<td>(\downarrow) mucosal protection against gastric acid</td>
<td>(\downarrow) mucosal protection or (\uparrow) gastric acid secretion</td>
</tr>
<tr>
<td><strong>OTHER CAUSES</strong></td>
<td>NSAIDs</td>
<td>Zollinger-Ellison syndrome</td>
</tr>
<tr>
<td><strong>RISK OF CARCINOMA</strong></td>
<td>(\uparrow)</td>
<td>Generally benign</td>
</tr>
<tr>
<td><strong>OTHER</strong></td>
<td>Biopsy margins to rule out malignancy</td>
<td>Hypertrophy of Brunner glands</td>
</tr>
</tbody>
</table>

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**Ulcer complications**

**Hemorrhage**

Gastric, duodenal (posterior > anterior). 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.

**Perforation**

Duodenal (anterior > posterior). May see free air under diaphragm → with referred pain to the shoulder via phrenic nerve.
### Malabsorption syndromes

**Celiac disease**
- Autoimmune-mediated intolerance of gliadin (gluten protein found in wheat) → malabsorption and steatorrhea. Associated with HLA-DQ2, HLA-DQ8, northern European descent, dermatitis herpetiformis, ↓ bone density. Findings: anti-endomysial, anti-tissue transglutaminase, and anti-gliadin antibodies; blunting of villi; and lymphocytes in lamina propria. Moderately ↑ risk of malignancy (e.g., T-cell lymphoma).
- Treatment: gluten-free diet.

**Disaccharidase deficiency**
- Most common is lactase deficiency → milk intolerance. Normal-appearing villi. Osmotic diarrhea. Since lactase is located at tips of intestinal villi, self-limited lactase deficiency can occur following injury (e.g., viral enteritis).
- Lactose tolerance test: + for lactase deficiency if administration of lactose produces symptoms and serum glucose rises < 20 mg/dL.

**Pancreatic insufficiency**
- Due to cystic fibrosis, obstructing cancer, chronic pancreatitis. Causes malabsorption of fat and fat-soluble vitamins (A, D, E, K) as well as vitamin B₁₂.
- ↑ neutral fat in stool. D-xylose absorption test: normal urinary excretion in pancreatic insufficiency; ↓ excretion with intestinal mucosa defects or bacterial overgrowth.

**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.

**Whipple disease**
- Infection with *Tropheryma whipplei* (gram positive); PAS + foamy macrophages in intestinal lamina propria, mesenteric nodes. Cardiac symptoms, Arthralgias, and Neurologic symptoms are common. Most often occurs in older men.
- Foamy Whipped cream in a CAN.

---

![Celiac sprue](image1.png)

Celiac sprue. Blunting of villi (single arrow), increased intraepithelial lymphocytes, and crypt hyperplasia (double arrow).

![Whipple disease](image2.png)

Whipple disease. Foamy macrophages (arrow) in lamina propria.
Inflammatory bowel diseases

**Crohn disease**

**LOCATION**
Any portion of the GI tract, usually the terminal ileum and colon. *Skip* lesions, *rectal sparing*.

**GROSS MORPHOLOGY**
Transmural inflammation → fistulas. *Cobblestone* mucosa, creeping *fat*, bowel wall thickening (“string sign” on barium swallow x-ray **A**), linear ulcers, fissures.

**MICROSCOPIC MORPHOLOGY**
Noncaseating *granulomas* and lymphoid aggregates (Th1 mediated).

**COMPLICATIONS**
Strictures (leading to obstruction), fistulas (including enterovesical fistulae, which can cause recurrent polymicrobial UTIs), perianal disease, malabsorption, nutritional depletion, colorectal cancer, gallstones.

**INTESTINAL MANIFESTATION**
Diarrhea that may or may not be bloody.

**EXTRAINTESTINAL MANIFESTATIONS**
Migratory polyarthrits, erythema nodosum, ankylosing spondylitis, pyoderma gangrenosum, aphthous ulcers, uveitis, kidney stones.

**TREATMENT**
Corticosteroids, azathioprine, antibiotics (e.g., ciprofloxacin, metronidazole), infliximab, adalimumab.

For **Crohn**, think of a *fat granny* and an old *crone* skipping down a *cobblestone* road away from the *wreck* (rectal sparing).

**Ulcerative colitis**

**LOCATION**
Colitis = colon inflammation. Continuous colonic lesions, always with rectal involvement.

**GROSS MORPHOLOGY**
Mucosal and submucosal inflammation only. Friable mucosal pseudopolyps (compare normal **A** with diseased **C**), with freely hanging mesentery. Loss of haustra → “lead pipe” appearance on imaging.

**MICROSCOPIC MORPHOLOGY**
Crypt abscesses and ulcers, bleeding, no granulomas (Th2 mediated).

**COMPLICATIONS**
Malnutrition, sclerosing cholangitis, toxic megacolon, colorectal carcinoma (worse with right-sided colitis or pancolitis).

**INTESTINAL MANIFESTATION**
Bloody diarrhea.

**EXTRAINTESTINAL MANIFESTATIONS**
Pyoderma gangrenosum, erythema nodosum, 1° sclerosing cholangitis, ankylosing spondylitis, aphthous ulcers, uveitis.

**TREATMENT**
5-aminosalicylic preparations (e.g., mesalamine), 6-mercaptopurine, infliximab, colectomy.

5-aminosalicylic preparations causes ULCCERS: Ulcers, Large intestine, Continuous, Colorectal carcinoma, Crypt abscesses, Extends proximally, Red diarrhea, Sclerosing cholangitis.

---

**Image Captions**

**A**

**B**

**C**
**Irritable bowel syndrome**  
Recurrent abdominal pain associated with ≥ 2 of the following:  
* Pain improves with defecation  
* Change in stool frequency  
* Change in appearance of stool  
No structural abnormalities. Most common in middle-aged women. Chronic symptoms. May present with diarrhea, constipation, or alternating symptoms. Pathophysiology is multifaceted. Treat symptoms.

**Appendicitis**  
Acute inflammation of the appendix due to obstruction by fecalith (in adults) or lymphoid hyperplasia (in children).  
Initial diffuse periumbilical pain migrates to McBurney point (⅓ the distance from right anterior superior iliac spine to umbilicus). Nausea, fever; may perforate → peritonitis; may elicit psoas, obturator, Rovsing sign, guarding and rebound tenderness on exam.  
Differential: diverticulitis (elderly), ectopic pregnancy (use β-hCG to rule out).  
Treatment: appendectomy.

**Diverticula of the GI tract**

**Diverticulum**  
Blind pouch protruding from the alimentary tract that communicates with the lumen of the gut. Most diverticula (esophagus, stomach, duodenum, colon) are acquired and are termed “false” in that they lack or have an attenuated muscularis externa. Most often in sigmoid colon.

**Diverticulosis**  
Many false diverticula of the colon, commonly sigmoid. Common (in ~ 50% of people > 60 years). Caused by ↑ intraluminal pressure and focal weakness in colonic wall. Associated with low-fiber diets.

**Diverticulitis**  
Inflammation of diverticula classically causing LLQ pain, fever, leukocytosis. May perforate → peritonitis, abscess formation, or bowel stenosis. Give antibiotics.  
May also cause colovesical fistula (fistula with bladder) → pneumaturia.  
Sometimes called “left-sided appendicitis” due to overlapping clinical presentation.
Zenker diverticulum
Pharyngoesophageal false diverticulum. Herniation of mucosal tissue at Killian triangle between the thyropharyngeal and cricopharyngeal parts of the inferior pharyngeal constrictor. Presenting symptoms: dysphagia, obstruction, foul breath from trapped food particles (halitosis). Most common in elderly males.

Meckel diverticulum
True diverticulum. Persistence of the vitelline duct. May contain ectopic acid–secreting gastric mucosa and/or pancreatic tissue. Most common congenital anomaly of GI tract. Can cause melena, RLQ pain, intussusception, volvulus, or obstruction near terminal ileum. Contrast with omphalomesenteric cyst = cystic dilation of vitelline duct. Diagnosis: pertechnetate study for uptake by ectopic gastric mucosa.

Malrotation
Anomaly of midgut rotation during fetal development → improper positioning of bowel, formation of fibrous bands (Ladd bands). Can lead to volvulus, duodenal obstruction.

Volvulus
Twisting of portion of bowel around its mesentery, can lead to obstruction and infarction. Can occur throughout the GI tract. Midgut volvulus more common in infants and children. Sigmoid volvulus more common in elderly.
Intussusception

Telescoping of proximal bowel segment into distal segment, commonly at ileocecal junction. Compromised blood supply → intermittent abdominal pain often with “currant jelly” stools. Unusual in adults (associated with intraluminal mass or tumor that acts as lead point that is pulled into the lumen). Majority of cases occur in children (usually idiopathic; may be associated with recent enteric or respiratory viral infection). Abdominal emergency in early childhood, with bull’s-eye appearance on ultrasound.

Hirschsprung disease

Congenital megacolon characterized by lack of ganglion cells/enteric nervous plexuses (Auerbach and Meissner plexuses) in segment of colon. Due to failure of neural crest cell migration. Associated with mutations in the RET gene. Presents with bilious emesis, abdominal distention, and failure to pass meconium → chronic constipation. Normal portion of the colon proximal to the aganglionic segment is dilated, resulting in a “transition zone.” Involves rectum. Think of Hirschsprung as a giant spring that has sprung in the colon. Risk ↑ with Down syndrome. Diagnosed by rectal suction biopsy. Treatment: resection.

Other intestinal disorders

Acute mesenteric ischemia
Critical blockage of intestinal blood flow (often embolic occlusion of SMA) → small bowel necrosis → abdominal pain out of proportion to physical findings. May see red “currant jelly” stools.

Adhesion
Fibrous band of scar tissue; commonly forms after surgery; most common cause of small bowel obstruction. Can have well-demarcated necrotic zones.

Angiodysplasia
Tortuous dilation of vessels → hematochezia. Most often found in cecum, terminal ileum, ascending colon. More common in older patients. Confirmed by angiography.

Duodenal atresia
Causes early bilious vomiting with proximal stomach distention (“double bubble” on X-ray) because of failure of small bowel recanalization. Associated with Down syndrome.

Ileus
Intestinal hypomotility without obstruction → constipation and ↓ flatus; distended/tympanic abdomen with ↓ bowel sounds. Associated with abdominal surgeries, opiates, hypokalemia, sepsis. Treatment: bowel rest, electrolyte correction, cholinergic drugs (stimulate intestinal motility).

Ischemic colitis

Meconium ileus
In cystic fibrosis, meconium plug obstructs intestine, preventing stool passage at birth.

Necrotizing enterocolitis
Seen in premature, formula-fed infants with immature immune system. Necrosis of intestinal mucosa (primarily colonic) with possible perforation, which can lead to pneumatosis intestinalis, free air in abdomen, portal venous gas.
Colonic polyps

Small growths of tissue within the colon. May be neoplastic or non-neoplastic. Grossly characterized as flat, sessile, or pedunculated (on a stalk) on the basis of protrusion into colonic lumen. Generally classified by histologic type.

<table>
<thead>
<tr>
<th>HISTOLOGIC TYPE</th>
<th>CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplastic</td>
<td>Non-neoplastic. Generally smaller and majority located in rectosigmoid area.</td>
</tr>
<tr>
<td>Hamartomatous</td>
<td>Non-neoplastic; solitary lesions do not have a significant risk of malignant transformation. Growths of normal colonic tissue with distorted architecture. Associated with Peutz-Jeghers syndrome and juvenile polyposis.</td>
</tr>
<tr>
<td>Adenomatous</td>
<td>Neoplastic, via chromosomal instability pathway with mutations in APC and KRAS. Tubular histology has less malignant potential than villous; tubulovillous has intermediate malignant potential.</td>
</tr>
<tr>
<td>Serrated</td>
<td>Premalignant, via CpG hypermethylation phenotype pathway with microsatellite instability and mutations in BRAF. “Saw-tooth” pattern of crypts on biopsy. Up to 20% of cases of sporadic CRC.</td>
</tr>
</tbody>
</table>

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Polyposis syndromes

**Familial adenomatous polyposis (FAP)**

Autosomal dominant mutation of APC tumor suppressor gene on chromosome 5q. 2-hit hypothesis. 100% progress to CRC unless colon is resected. Thousands of polyps arise starting after puberty; pancolonic; always involves rectum.

**Gardner syndrome**

FAP + osseous and soft tissue tumors, congenital hypertrophy of retinal pigment epithelium, impacted/supernumerary teeth.

**Turcot syndrome**

FAP + malignant CNS tumor. Turcot = Turban.

**Peutz-Jeghers syndrome**

Autosomal dominant syndrome featuring numerous hamartomas throughout GI tract, along with hyperpigmented mouth, lips, hands, genitalia. Associated with risk of colorectal, breast, stomach, small bowel, and pancreatic cancers.

**Juvenile polyposis syndrome**

Autosomal dominant syndrome in children (typically < 5 years old) featuring numerous hamartomatous polyps in the colon, stomach, small bowel. Associated with risk of CRC.

**Lynch syndrome**

Previously known as hereditary nonpolyposis colorectal cancer (HNPCC). Autosomal dominant mutation of DNA mismatch repair genes with subsequent microsatellite instability. ~80% progress to CRC. Proximal colon is always involved. Associated with endometrial, ovarian, and skin cancers.

Can be identified clinically in families using 3-2-1 rule: 3 relatives with Lynch syndrome–associated cancers across 2 generations, 1 of whom must be diagnosed before age 50 years.
Colorectal cancer

**EPIDEMIOLOGY**
Most patients are > 50 years old. ~ 25% have a family history.

**RISK FACTORS**
Adenomatous and serrated polyps, familial cancer syndromes, IBD, tobacco use, diet of processed meat with low fiber.

**PRESENTATION**
Rectosigmoid > ascending > descending. Ascending—exophytic mass, iron deficiency anemia, weight loss. Descending—infiltrating mass, partial obstruction, colicky pain, hematochezia. Rarely, presents with *Streptococcus bovis* bacteremia.

**DIAGNOSIS**
Iron deficiency anemia in males (especially > 50 years old) and postmenopausal females raises suspicion. Screen patients > 50 years old with colonoscopy, flexible sigmoidoscopy, or stool occult blood test. “Apple core” lesion seen on barium enema x-ray A. CEA tumor marker: good for monitoring recurrence, not useful for screening.

*Molecular pathogenesis of colorectal cancer*

There are 2 molecular pathways that lead to CRC:
- **Microsatellite instability pathway (≈ 15%):**
  - DNA mismatch repair gene mutations → sporadic and Lynch syndrome. Mutations accumulate, but no defined morphologic correlates.
- **APC/β-catenin (chromosomal instability) pathway (≈ 85%)** → sporadic cancer.

Order of gene events—**AK-53.**

![Flowchart]
Cirrhosis and portal hypertension

Cirrhosis—diffuse bridging fibrosis and nodular regeneration via stellate cells disrupts normal architecture of liver, ↑ risk for hepatocellular carcinoma (HCC).

Etiologies: alcohol (60–70% of cases in the U.S.), chronic viral hepatitis, biliary disease, genetic/metabolic disorders.

Portosystemic shunts partially alleviate portal hypertension:
- Esophageal varices
- Caput medusae
- Anorectal varices

Cirrhosis. CT shows splenomegaly (blue arrow) and nodularity of liver contour (red arrows). ↑ to regenerating macronodules.

<table>
<thead>
<tr>
<th>Serum marker</th>
<th>Major diagnostic use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline phosphatase (ALP)</td>
<td>Cholestatic and obstructive hepatobiliary disease, HCC, infiltrative disorders, bone disease</td>
</tr>
<tr>
<td>Aminotransferases (AST and ALT) (often called “liver enzymes”)</td>
<td>Viral hepatitis (ALT &gt; AST)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylase</td>
<td>Acute pancreatitis, mumps</td>
</tr>
<tr>
<td>Ceruloplasmin</td>
<td>↑ in Wilson disease</td>
</tr>
<tr>
<td>γ-glutamyl transpeptidase (GGT)</td>
<td>↑ in various liver and biliary diseases (just as ALP can), but not in bone disease; associated with alcohol use</td>
</tr>
<tr>
<td>Lipase</td>
<td>Acute pancreatitis (most specific)</td>
</tr>
</tbody>
</table>
**Reye syndrome**
Rare, often fatal childhood hepatic encephalopathy. Findings: mitochondrial abnormalities, fatty liver (microvesicular fatty change), hypoglycemia, vomiting, hepatomegaly, coma. Associated with viral infection (especially VZV and influenza B) that has been treated with aspirin. Mechanism: aspirin metabolites β-oxidation by reversible inhibition of mitochondrial enzymes. Avoid aspirin in children, except in those with Kawasaki disease.

**Alcoholic liver disease**

<table>
<thead>
<tr>
<th>Hepatic steatosis</th>
<th>Macrovesicular fatty change A that may be reversible with alcohol cessation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholic hepatitis</td>
<td>Requires sustained, long-term consumption. Swollen and necrotic hepatocytes with neutrophilic infiltration. Mallory bodies B (intracytoplasmic eosinophilic inclusions of damaged keratin filaments). Make a toAST with alcohol: AST &gt; ALT (ratio usually &gt; 1.5).</td>
</tr>
<tr>
<td>Alcoholic cirrhosis</td>
<td>Final and irreversible form. Micronodular, irregularly shrunken liver with “hobnail” appearance. Sclerosis (arrows in C) around central vein (zone III). Manifestations of chronic liver disease (e.g., jaundice, hypoalbuminemia).</td>
</tr>
</tbody>
</table>

**Non-alcoholic fatty liver disease**
Metabolic syndrome (insulin resistance) → fatty infiltration of hepatocytes → cellular “ballooning” and eventual necrosis. May cause cirrhosis and HCC. Independent of alcohol use.

**Hepatic encephalopathy**
Cirrhosis → portosystemic shunts → ↑ NH₄ metabolism → neuropsychiatric dysfunction. Spectrum from disorientation/asterixis (mild) to difficult arousal or coma (severe). Triggers:
* ↑ NH₄ production and absorption (due to dietary protein, GI bleed, constipation, infection).
* ↓ NH₄ removal (due to renal failure, diuretics, bypassed hepatic blood flow post-TIPS). Treatment: lactulose (↑ NH₄⁺ generation) and rifaximin.
Hepatocellular carcinoma/hepatoma

Most common 1st malignant tumor of liver in adults. Associated with HBV (+/- cirrhosis) and all other causes of cirrhosis (including HCV, alcoholic and non-alcoholic fatty liver disease, autoimmune disease, hemochromatosis, α1-antitrypsin deficiency, Wilson disease) and specific carcinogens (e.g., aflatoxin from Aspergillus). May lead to Budd-Chiari syndrome.

Findings: jaundice, tender hepatomegaly, ascites, polycythemia, anorexia. Spreads hematogenously.

Diagnosis: ↑ α-fetoprotein; ultrasound or contrast CT/MRI, biopsy.

Other liver tumors

Cavernous hemangioma

Common, benign liver tumor typically occurs at age 30–50 years. Biopsy contraindicated because of risk of hemorrhage.

Hepatic adenoma

Rare, benign liver tumor, often related to oral contraceptive or anabolic steroid use; may regress spontaneously or rupture (abdominal pain and shock).

Angiosarcoma

Malignant tumor of endothelial origin; associated with exposure to arsenic, vinyl chloride.

Metastases

GI malignancies, breast and lung cancer. Most common overall.

Budd-Chiari syndrome

Thrombosis or compression of hepatic veins with centrilobular congestion and necrosis → congestive liver disease (hepatomegaly, varices, abdominal pain, eventual 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 \( \rightarrow \) cirrhosis with PAS \( \oplus \) globules \( \mathbb{A} \) in liver. Codominant trait.

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 \( \mathbb{A} \) due to bilirubin deposition. Occurs at high bilirubin levels (> 2.5 mg/dL) in blood \( 2^{\circ} \) to \( \uparrow \) production or defective metabolism.

Unconjugated (indirect) hyperbilirubinemia

Hemolytic, physiologic (newborns), Crigler-Najjar, Gilbert syndrome.

Conjugated (direct) hyperbilirubinemia

Biliary tract obstruction: gallstones, cholangiocarcinoma, pancreatic or liver cancer, liver fluke.

Biliary tract disease:

* \( 1^\circ \) sclerosing cholangitis
* \( 1^\circ \) biliary cirrhosis

Excretion defect: Dubin-Johnson syndrome, Rotor syndrome.

Mixed (direct and indirect) hyperbilirubinemia

Hepatitis, cirrhosis.

Physiologic neonatal jaundice

At birth, immature UDP-glucuronosyltransferase \( \rightarrow \) unconjugated hyperbilirubinemia \( \rightarrow \) jaundice/kernicterus (bilirubin deposition in brain, particularly basal ganglia).

Treatment: phototherapy (converts unconjugated bilirubin to water-soluble form).
### Hereditary hyperbilirubinemas

**1 Gilbert syndrome**
- Mildly ↓ UDP-glucuronosyltransferase conjugation and impaired bilirubin uptake. Asymptomatic or mild jaundice. 
- ↑ unconjugated bilirubin without overt hemolysis. Bilirubin ↑ with fasting and stress.
- Very common. No clinical consequences.

**2 Crigler-Najjar syndrome, type I**
- Absent UDP-glucuronosyltransferase. Presents early in life; patients die within a few years. 
- Findings: jaundice, kernicterus (bilirubin deposition in brain), ↑ unconjugated bilirubin. 
- Treatment: plasmapheresis and phototherapy.
- Type II is less severe and responds to phenobarbital, which ↑ liver enzyme synthesis.

**3 Dubin-Johnson syndrome**
- Conjugated hyperbilirubinemia due to defective liver excretion. Grossly black liver. Benign.

**4 Rotor syndrome** is similar but even milder and does not cause black liver.
**Wilson disease (hepatolenticular degeneration)**

Inadequate hepatic copper excretion and failure of copper to enter circulation as ceruloplasmin. Leads to copper accumulation, especially in liver, brain, cornea, kidneys (Fanconi syndrome), and joints.

Autosomal recessive inheritance (chromosome 13). Copper is normally excreted into bile by hepatocyte copper transporting ATPase (ATP7B gene).

Treatment includes chelation with penicillamine or trientine, oral zinc.

**Characterized by:**
- Ceruloplasmin, Cirrhosis, Corneal deposits (Kayser-Fleischer rings)
- Copper accumulation, Carcinoma (hepatocellular)
- Hemolytic anemia
- Basal ganglia degeneration (parkinsonian symptoms)
- Asterixis
- Dementia, Dyskinesia, Dysarthria

“Copper is Hella BAD.”

---

**Hemochromatosis**

Hemosiderosis is the deposition of hemosiderin (iron), which stains blue. Hemochromatosis is the disease caused by this iron deposition.

Classic triad of micronodular Cirrhosis, Diabetes mellitus, and skin pigmentation → “bronze” diabetes. Results in HF, testicular atrophy, and ↑ risk of HCC. Disease may be 1° (autosomal recessive) or 2° to chronic transfusion therapy (e.g., β-thalassemia major).

↑ ferritin, ↑ iron, ↓ TIBC → ↓ transferrin saturation. Can be identified on biopsy with Prussian blue stain.

Total body iron may reach 50 g, enough to set off metal detectors at airports.

Primary hemochromatosis due to C282Y or H63D mutation on HFE gene. Associated with HLA-A3.

Iron loss through menstruation slows progression in women.

Treatment of hereditary hemochromatosis: repeated phlebotomy, chelation with deferasirox, deferoxamine, deferiprone (oral).
### Biliary tract disease

May present with pruritus, jaundice, dark urine, light-colored stool, hepatosplenomegaly. Typically with cholestatic pattern of LFTs (↑ conjugated bilirubin, ↑ cholesterol, ↑ ALP).

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Epidemiology</th>
<th>Additional Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary biliary cirrhosis</strong></td>
<td>Extrahepatic biliary obstruction → ↑ pressure in intrahepatic ducts → injury/ fibrosis and bile stasis.</td>
<td>Patients with known obstructive lesions (gallstones, biliary strictures, pancreatic carcinoma). May be complicated by ascending cholangitis.</td>
</tr>
<tr>
<td><strong>Primary biliary cirrhosis</strong></td>
<td>Autoimmune reaction → lymphocytic infiltrate + granulomas → destruction of intralobular bile ducts.</td>
<td>Classically in middle-aged women. Anti-mitochondrial antibody ⊕, including IgM. Associated with other autoimmune conditions (e.g., CREST, Sjögren syndrome, rheumatoid arthritis, celiac disease).</td>
</tr>
<tr>
<td><strong>Primary sclerosing cholangitis</strong></td>
<td>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).</td>
<td>Classically in young men with IBD. Hypergammaglobulinemia (IgM). MPO-ANCA/p-ANCA ⊕. Associated with ulcerative colitis. Can lead to 2° biliary cirrhosis, cholangiocarcinoma.</td>
</tr>
</tbody>
</table>
Gallstones (cholelithiasis)

† cholesterol and/or bilirubin, † bile salts, and gallbladder stasis all cause stones A.

2 types of stones:
- Cholesterol stones (radiolucent with 10–20% opaque due to calcifications)—80% of stones. Associated with obesity, Crohn disease, advanced age, clofibrate, estrogen therapy, multiparity, rapid weight loss, Native American origin.
- Pigment stones (black = radiopaque, Ca$_2^+$ bilirubinate, hemolysis; brown = radiolucent, infection)—seen in patients with chronic hemolysis, alcoholic cirrhosis, advanced age, biliary infections, total parenteral nutrition (TPN).

Most often causes cholecystitis; also ascending cholangitis, acute pancreatitis, bile stasis.
Can also lead to biliary colic—neurohormonal activation (e.g., by CCK after a fatty meal) triggers contraction of gallbladder, forcing a stone into the cystic duct. May present without pain (e.g., in diabetics).
Can cause fistula between gallbladder and small intestine, leading to air in biliary tree and allowing the passage of gallstones into the intestinal tract. Gallstone may obstruct ileocecal valve → gallstone ileus.
Diagnose with ultrasound B. Treat with cholecystectomy if symptomatic.

Risk factors (4 F’s):
1. Female
2. Fat
3. Fertile (pregnant)
4. Forty

Charcot triad of cholangitis:
- Jaundice
- Fever
- RUQ pain

Cholecystitis

Acute or chronic inflammation of gallbladder. Usually from cholelithiasis (gallstones A): most commonly blocking the cystic duct → 2$^e$ infection; rarely ischemia or 1$^e$ infection (CMV). Murphy sign ⊕—inspiratory arrest on RUQ palpation due to pain. ↑ ALP if bile duct becomes involved (e.g., ascending cholangitis). Diagnose with ultrasound or cholecintigraphy (HIDA, or hepatobiliary iminodiacetic acid scan).
Porcelain gallbladder
Calcified gallbladder due to chronic cholecystitis; usually found incidentally on imaging A. Treatment: prophylactic cholecystectomy due to high rates of gallbladder carcinoma.

Acute pancreatitis
Autodigestion of pancreas by pancreatic enzymes A. Causes: idiopathic, Gallstones, Ethanol, Trauma, Steroids, Mumps, Autoimmune disease, Scorpion sting, Hypercalcemia/Hypertriglyceridemia (> 1000 mg/dL), ERCP, Drugs (e.g., sulfa drugs, NRTIs, protease inhibitors). GET SMASHED.
Clinical presentation: epigastric abdominal pain radiating to back, anorexia, nausea. Labs: ↑ amylase, lipase (higher specificity). Can lead to DIC, ARDS, diffuse fat necrosis, hypocalcemia (Ca^{2+} collects in pancreatic Ca^{2+} soap deposits), pseudocyst formation B, hemorrhage, infection, multiorgan failure. Complication: pancreatic pseudocyst (lined by granulation tissue, not epithelium; can rupture and hemorrhage).

Chronic pancreatitis
Chronic inflammation, atrophy, calcification of the pancreas A. Major causes are alcohol abuse and idiopathic. Mutations in CFTR (cystic fibrosis) can cause chronic pancreatic insufficiency. Can lead to pancreatic insufficiency → steatorrhea, fat-soluble vitamin deficiency, diabetes mellitus. Amylase and lipase may or may not be elevated (almost always elevated in acute pancreatitis).
Pancreatic adenocarcinoma

Average survival ~ 1 year after diagnosis. Very aggressive tumor arising from pancreatic ducts (disorganized glandular structure with cellular infiltration \( \rightarrow \)); already metastasized at presentation; tumors more common in pancreatic head \( \rightarrow \) (\( \rightarrow \) obstructive jaundice). Associated with CA 19-9 tumor marker (also CEA, less specific).

Risk factors:
* Tobacco use
* Chronic pancreatitis (especially > 20 years)
* Diabetes
* Age > 50 years
* Jewish and African-American males

Often presents with:
* Abdominal pain radiating to back
* Weight loss (due to malabsorption and anorexia)
* Migratory thrombophlebitis—redness and tenderness on palpation of extremities (Trousseau syndrome)
* Obstructive jaundice with palpable, nontender gallbladder (Courvoisier sign)

Treatment: Whipple procedure, chemotherapy, radiation therapy.
### Acid suppression therapy

**H₂ blockers**
- **Cimetidine**, ranitidine, famotidine, nizatidine. Take H₂ blockers before you dine. Think “table for 2” to remember H₂.

**MECHANISM**
Reversible block of histamine H₂-receptors → ↓ H⁺ secretion by parietal cells.

**CLINICAL USE**
Peptic ulcer, gastritis, mild esophageal reflux.

**TOXICITY**
- Cimetidine is a potent inhibitor of cytochrome P-450 (multiple drug interactions); it also has antiandrogenic effects (prolactin release, gynecomastia, impotence, ↓ libido in males); can cross blood-brain barrier (confusion, dizziness, headaches) and placenta. Both cimetidine and ranitidine ↓ renal excretion of creatinine. Other H₂ blockers are relatively free of these effects.

### Proton pump inhibitors
- Omeprazole, lansoprazole, esomeprazole, pantoprazole, dexlansoprazole.

**MECHANISM**
Irreversibly inhibit H⁺/K⁺ ATPase in stomach parietal cells.

**CLINICAL USE**
Peptic ulcer, gastritis, esophageal reflux, Zollinger-Ellison syndrome.

**TOXICITY**
Increased risk of *C. difficile* infection, pneumonia. ↓ serum Mg²⁺ with long-term use.

### Bismuth, sucralfate

**MECHANISM**
Bind to ulcer base, providing physical protection and allowing HCO₃⁻ secretion to reestablish pH gradient in the mucous layer.

**CLINICAL USE**
↑ ulcer healing, travelers’ diarrhea.
### Misoprostol

**MECHANISM**
A PGE₁ analog. ↑ production and secretion of gastric mucous barrier, ↓ acid production.

**CLINICAL USE**
Prevention of NSAID-induced peptic ulcers (NSAIDs block PGE₁ production); maintenance of a PDA. Also used off-label for induction of labor (ripens cervix).

**TOXICITY**
Diarrhea. Contraindicated in women of childbearing potential (abortifacient).

### Octreotide

**MECHANISM**
Long-acting somatostatin analog; inhibits actions of many splanchnic vasoconstriction hormones.

**CLINICAL USE**
Acute variceal bleeds, acromegaly, VIPoma, carcinoid tumors.

**TOXICITY**
Nausea, cramps, steatorrhea.

### Antacid use

Can affect absorption, bioavailability, or urinary excretion of other drugs by altering gastric and urinary pH or by delaying gastric emptying.

All can cause hypokalemia.

Overuse can also cause the following problems.

<table>
<thead>
<tr>
<th>Antacid</th>
<th>Mechanism</th>
<th>Clinical Use</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aluminum hydroxide</strong></td>
<td>Constipation and hypophosphatemia; proximal muscle weakness, osteodystrophy, seizures</td>
<td></td>
<td>Aluminium amount of feces.</td>
</tr>
<tr>
<td><strong>Calcium carbonate</strong></td>
<td>Hypercalcemia, rebound acid ↑</td>
<td>Can chelate and ↓ effectiveness of other drugs (e.g., tetracycline).</td>
<td></td>
</tr>
<tr>
<td><strong>Magnesium hydroxide</strong></td>
<td>Diarrhea, hyporeflexia, hypotension, cardiac arrest</td>
<td>Mg = Must go to the bathroom.</td>
<td></td>
</tr>
</tbody>
</table>

### Osmotic laxatives

Magnesium hydroxide, magnesium citrate, polyethylene glycol, lactulose.

**MECHANISM**
Provide osmotic load to draw water into the GI lumen.

**CLINICAL USE**
Constipation.

Lactulose also treats hepatic encephalopathy since gut flora degrade it into metabolites (lactic acid and acetic acid) that promote nitrogen excretion as NH₄⁺.

**TOXICITY**
Diarrhea, dehydration; may be abused by bulimics.

### Sulfasalazine

**MECHANISM**
A combination of sulfapyridine (antibacterial) and 5-aminosalicylic acid (anti-inflammatory). Activated by colonic bacteria.

**CLINICAL USE**
Ulcerative colitis, Crohn disease (colitis component).

**TOXICITY**
Malaise, nausea, sulfonamide toxicity, reversible oligospermia.
### Ondansetron

**MECHANISM**
5-HT₃ antagonist; ‡ vagal stimulation. Powerful central-acting antiemetic.

**CLINICAL USE**
Control vomiting postoperatively and in patients undergoing cancer chemotherapy.

**TOXICITY**
Headache, constipation, QT interval prolongation.

---

At a party but feeling queasy? Keep **on dancing** with ondansetron!

### Metoclopramide

**MECHANISM**
D₂ receptor antagonist. † resting tone, contractility, LES tone, motility. Does not influence colon transport time.

**CLINICAL USE**
Diabetic and postsurgery gastroparesis, antiemetic.

**TOXICITY**
† parkinsonian effects, tardive dyskinesia. Restlessness, drowsiness, fatigue, depression, diarrhea. Drug interaction with digoxin and diabetic agents. Contraindicated in patients with small bowel obstruction or Parkinson disease (due to D₁-receptor blockade).

### Orlistat

**MECHANISM**
Inhibits gastric and pancreatic lipase → ‡ breakdown and absorption of dietary fats.

**CLINICAL USE**
Weight loss.

**TOXICITY**
Steatorrhea, ‡ absorption of fat-soluble vitamins.
HIGH-YIELD SYSTEMS

Hematology and Oncology

“Of all that is written, I love only what a person has written with his own blood.”

—Friedrich Nietzsche

“I used to get stressed out, but my cancer has put everything into perspective.”

—Delta Goodrem

“The best blood will at some time get into a fool or a mosquito.”

—Austin O’Malley

Study tip: When reviewing oncologic drugs, focus on mechanisms and side effects rather than details of clinical uses, which may be lower yield.
Erythrocyte

Carries O\textsubscript{2} to tissues and CO\textsubscript{2} to lungs. Anucleate and biconcave, with large surface area-to-volume ratio for rapid gas exchange. Life span of 120 days. Source of energy is glucose (90\% used in glycolysis, 10\% used in HMP shunt). Membrane contains Cl\textsuperscript{-}/HCO\textsubscript{3}{-} antiporter, which allows RBCs to export HCO\textsubscript{3}{-} and transport CO\textsubscript{2} from the periphery to the lungs for elimination.

\textit{Eryth} = red; \textit{cyte} = cell.

Erythrocytosis = polycythemia = ↑ hematocrit.
Anisocytosis = varying sizes.
Poikilocytosis = varying shapes.
Reticulocyte = immature RBC; reflects erythroid proliferation.

Thrombocyte (platelet)

Involved in 1° hemostasis. Small cytoplasmic fragment derived from megakaryocytes. Life span of 8–10 days. When activated by endothelial injury, aggregates with other platelets and interacts with fibrinogen to form platelet plug. Contains dense granules (ADP, Ca\textsuperscript{2+}) and \textalpha{} granules (vWF, fibrinogen). Approximately \(\frac{1}{3}\) of platelet pool is stored in the spleen.

Thrombocytopenia or ↓ platelet function results in petechiae.
vWF receptor: GpIb.
Fibrinogen receptor: GpIIb/IIIa.

Leukocyte

Divided into granulocytes (neutrophil, eosinophil, basophil) and mononuclear cells (monocytes, lymphocytes). Responsible for defense against infections. Normally 4000–10,000 cells/mm\textsuperscript{3}.

WBC differential from highest to lowest (normal ranges per USMLE):

\textbf{Neutrophils (54–62\%)}
\textbf{Lymphocytes (25–33\%)}
\textbf{Monocytes (3–7\%)}
\textbf{Eosinophils (1–3\%)}
\textbf{Basophils (0–0.75\%)}

\textit{Leuk} = white; \textit{cyte} = cell.

\textbf{Neutrophils Like Making Everything Better.}

Neutrophil


Hypersegmented polys (5 or more lobes) are seen in vitamin B\textsubscript{12}/folate deficiency. ↑ band cells (immature neutrophils) reflect states of ↑ myeloid proliferation (bacterial infections, CML).

Important neutrophil chemotactic agents: C5a, IL-8, LTB\textsubscript{4}, kallikrein, platelet-activating factor.
**Monocyte**

- Differentiates into macrophage in tissues.
- Large, kidney-shaped nucleus. Extensive “frosted glass” cytoplasm.
- Monocyte: in the blood.

**Macrophage**

- Phagocytoses bacteria, cellular debris, and senescent RBCs. Long life in tissues.
- Macrophages differentiate from circulating blood monocytes. Activated by γ-interferon.
- Can function as antigen-presenting cell via MHC II.

**Eosinophil**

- Produces histaminase and major basic protein (MBP, a helminthotoxin).

**Basophil**

- Mediates allergic reaction. Densely basophilic granules contain heparin (anticoagulant) and histamine (vasodilator). Leukotrienes synthesized and released on demand.

**Mast cell**

- Mediates allergic reaction in local tissues. Mast cells contain basophilic granules and originate from the same precursor as basophils but are not the same cell type. Can bind the Fc portion of IgE to membrane. IgE cross-links upon antigen binding, causing degranulation, which releases histamine, heparin, and eosinophil chemotactic factors.

- Involved in type I hypersensitivity reactions.
- Cromolyn sodium prevents mast cell degranulation (used for asthma prophylaxis).
**Dendritic cell**

Highly phagocytic APC. Functions as link between innate and adaptive immune systems. Expresses MHC class II and Fc receptors on surface. Called Langerhans cell in the skin.

**Lymphocyte**

Refers to B cells, T cells, and NK cells. B cells and T cells mediate adaptive immunity. NK cells are part of the innate immune response. Round, densely staining nucleus with small amount of pale cytoplasm.

**B cell**

Part of humoral immune response. Originates from stem cells in bone marrow and matures in marrow. Migrates to peripheral lymphoid tissue (follicles of lymph nodes, white pulp of spleen, unencapsulated lymphoid tissue). When antigen is encountered, B cells differentiate into plasma cells (which produce antibodies) and memory cells. Can function as an APC via MHC II.

**T cell**

Mediates cellular immune response. Originates from stem cells in the bone marrow, but matures in the thymus. T cells differentiate into cytotoxic T cells (express CD8, recognize MHC I), helper T cells (express CD4, recognize MHC II), and regulatory T cells. CD28 (costimulatory signal) necessary for T-cell activation. The majority of circulating lymphocytes are T cells (80%).

B = Bone marrow.

T is for Thymus.

CD4+ helper T cells are the primary target of HIV.

\[ \text{MHC} \times \text{CD} = 8 \] (e.g., MHC 2 × CD4 = 8, and MHC 1 × CD8 = 8).
### Plasma cell

Plasma cell produces large amounts of antibody specific to a particular antigen. “Clock-face” chromatin distribution, abundant RER, and well-developed Golgi apparatus.

Multiple myeloma is a plasma cell cancer.

### Blood groups

<table>
<thead>
<tr>
<th>ABO Classification</th>
<th>Rh Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RBC type</strong></td>
<td><strong>Rh+</strong></td>
</tr>
<tr>
<td><strong>Rh−</strong></td>
<td></td>
</tr>
<tr>
<td><strong>AB</strong></td>
<td></td>
</tr>
<tr>
<td><strong>O</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Group antigens on RBC surface</strong></td>
<td><strong>No anti-D antibody</strong></td>
</tr>
<tr>
<td><strong>A</strong></td>
<td><strong>Rh (D)</strong></td>
</tr>
<tr>
<td><strong>B</strong></td>
<td><strong>Rh (D)</strong></td>
</tr>
<tr>
<td><strong>AB</strong></td>
<td></td>
</tr>
<tr>
<td><strong>None</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Universal donor of RBCs</strong></td>
<td><strong>Universal recipient of plasma</strong></td>
</tr>
<tr>
<td><strong>Universal donor of plasma</strong></td>
<td><strong>Universal recipient of plasma</strong></td>
</tr>
<tr>
<td><strong>Antibodies in plasma</strong></td>
<td><strong>Treat Rh− mothers with Rh(D) immunoglobulin after each pregnancy to prevent anti-D IgG formation</strong></td>
</tr>
<tr>
<td><strong>Anti-B IgM</strong></td>
<td><strong>Anti-D IgG</strong></td>
</tr>
<tr>
<td><strong>Anti-A IgM</strong></td>
<td><strong>None</strong></td>
</tr>
<tr>
<td><strong>None</strong></td>
<td><strong>Anti-D</strong></td>
</tr>
<tr>
<td><strong>Clinical relevance</strong></td>
<td><strong>IgM does not cross placenta; IgG does cross placenta. Rh− mothers exposed to fetal Rh+ blood (often during delivery) may make anti-D IgG. In subsequent pregnancies, anti-D IgG crosses the placenta → hemolytic disease of the newborn (erythroblastosis fetalis) in the next fetus that is Rh+. Prevented by administration of RhoGAM to Rh− pregnant women during third trimester, which prevents maternal anti-Rh IgG production. Rh− mothers have anti-D IgG only if previously exposed to Rh+ blood.</strong></td>
</tr>
</tbody>
</table>

If receive B or AB → hemolytic reaction

If receive A or AB → hemolytic reaction

If receive any non-O → hemolytic reaction

If receive any non-O → hemolytic reaction

If receive any non-O → hemolytic reaction
Coagulation and kinin pathways

Heminology and oncology—Physiology

**Section III**

**386**

**Coagulation and kinin pathways**

- Collagen, basement membrane, activated platelets
- Intrinsics coagulation pathway
- Extrinsic coagulation pathway
- Thromboplastin (tissue factor)
- VII
- VIIa
- XI
- Xa
- IX
- IXa
- X
- II
- Fibrinogen
- Fibrin monomers aggregate
- XIIIa
- XIII
- V
- Thrombin
- Prothrombin
- Kallikrein
- HMWK
- Bradykinin
- Vasodilation
- Permeability
- Pain
- Thrombolysis
- Alteplase
- Retepalase
- Streptokinase
- Tenecteplase

**ANTICOAGULANTS:**
- IIa (thrombin)
  - Heparin (greatest efficacy)
  - LMWH (dalteparin, enoxaparin)
  - Direct thrombin inhibitors (argatroban, bivalirudin, dabigatran)
- Xa
  - LMWH (greatest efficacy)
  - Fondaparinux

**Fibrinolytic system**
- Plasminogen
- tPA
- Aminocaproic acid
- Fibrin degradation products
- Fibrin mesh stabilizes platelet plug

**Hemophilia A:** deficiency of factor VIII (XR)
**Hemophilia B:** deficiency of factor IX (XR)
**Hemophilia C:** deficiency of factor XI (AR)

**Note:** Kallikrein activates bradykinin; ACE inactivates bradykinin

- = require Ca²⁺, phospholipid
- = inhibited by vitamin K antagonist warfarin
- = cofactor
- = activates but not part of coagulation cascade

**Coagulation cascade components**

- **Procoagulation**
  - Oxidized vitamin K → reduced vitamin K (acts as cofactor)
    - precursors of II, VII, IX, X, C, S
    - mature II, VII, IX, X, C, S

- **Anticoagulation**
  - Thrombin-thrombomodulin complex (endothelial cells)
  - Protein S
  - Protein C activated protein C
  - Protein S claves and inactivates Va, VIIIa

- Plasminogen → plasmin
  - Fibrinolysis:
    1. Cleavage of fibrin mesh
    2. Destruction of coagulation factors

**Antithrombin** inhibits activated forms of factors II, VII, IX, X, XI, XII.

Heparin enhances the activity of antithrombin. Principal targets of antithrombin: thrombin and factor Xa.

Factor V Leiden mutation produces a factor V resistant to inhibition by activated protein C.

**tPA** is used clinically as a thrombolytic.

Warfarin inhibits the enzyme vitamin K epoxide reductase. Neonates lack enteric bacteria, which produce vitamin K.

**Vitamin K deficiency:** Impaired synthesis of factors II, VII, IX, X, protein C, protein S.

**vWF** carries/protects VIII.

Oxidized vitamin K → reduced vitamin K (acts as cofactor)

Epicorrelation:

- Oxidized vitamin K
- Reduced vitamin K (acts as cofactor)
- Precursors of II, VII, IX, X, C, S
- Mature II, VII, IX, X, C, S

- Thrombin-thrombomodulin complex (endothelial cells)
- Protein S
- Protein C
- Protein S claves and inactivates Va, VIIIa

- Plasminogen → plasmin
  - Fibrinolysis:
    1. Cleavage of fibrin mesh
    2. Destruction of coagulation factors
Hematology and oncology—Physiology

**Platelet plug formation (primary hemostasis)**

1. **INJURY**
   - Endothelial damage → transient vasoconstriction via neural stimulation reflex and endothelin (released from damaged cell)

2. **EXPOSURE**
   - vWF binds to exposed collagen
   - vWF is from Weibel-Palade bodies of endothelial cells and α-granules of platelets

3. **ADHESION**
   - Platelets bind vWF via GpIIb receptor at the site of injury only (specific) → platelets undergo conformational change
   - Platelets release ADP and Ca²⁺ (necessary for coagulation cascade), TXA₂
   - ADP helps platelets adhere to endothelium

4. **ACTIVATION**
   - ADP binding to receptor induces GpIIb/IIIa expression at platelet surface

5. **AGGREGATION**
   - Fibrinogen binds GpIIb/IIIa receptors and links platelets
   - Balance between Pro-aggregation factors: TXA₂ (released by platelets) ↓ blood flow ↑ platelet aggregation
     - Anti-aggregation factors: PGI₂ (released by endothelial cells) ↑ blood flow ↓ platelet aggregation
   - Temporary plug stops bleeding: unstable, easily dislodged

---

**Thrombogenesis**

Formation of insoluble fibrin mesh.
Aspirin inhibits cyclooxygenase (TXA₂ synthesis).
Clopidogrel, prasugrel, and ticlopidine inhibit ADP-induced expression of GpIIb/IIIa.
Abciximab, eptifibatide, and tirofiban inhibit GpIIb/IIIa directly.
Ristocetin activates vWF to bind GpIIb. Failure of agglutination with ristocetin assay occurs in von Willebrand disease and Bernard-Soulier syndrome.
### Pathologic RBC forms

<table>
<thead>
<tr>
<th>Type</th>
<th>Example</th>
<th>Associated Pathology</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acanthocyte (&quot;spur cell&quot;)</td>
<td><img src="A" alt="Image" /></td>
<td>Liver disease, abetalipoproteinemia (states of cholesterol dysregulation).</td>
<td>Acantho = spiny.</td>
</tr>
<tr>
<td>Basophilic stippling</td>
<td><img src="B" alt="Image" /></td>
<td>Lead poisoning.</td>
<td></td>
</tr>
<tr>
<td>Degmacyte (&quot;bite cell&quot;)</td>
<td><img src="C" alt="Image" /></td>
<td>G6PD deficiency.</td>
<td></td>
</tr>
<tr>
<td>Elliptocyte</td>
<td><img src="D" alt="Image" /></td>
<td>Hereditary elliptocytosis.</td>
<td></td>
</tr>
<tr>
<td>Macro-ovalocyte</td>
<td><img src="E" alt="Image" /></td>
<td>Megaloblastic anemia (also hypersegmented PMNs), marrow failure.</td>
<td></td>
</tr>
<tr>
<td>Ringed sideroblast</td>
<td><img src="F" alt="Image" /></td>
<td>Sideroblastic anemia. Excess iron in mitochondria = pathologic.</td>
<td></td>
</tr>
<tr>
<td>Schistocyte (&quot;helmet cell&quot;)</td>
<td><img src="G" alt="Image" /></td>
<td>DIC, TTP/HUS, HELLP syndrome, mechanical hemolysis (e.g., heart valve prosthesis).</td>
<td></td>
</tr>
</tbody>
</table>
## Pathologic RBC forms (continued)

<table>
<thead>
<tr>
<th>TYPE</th>
<th>EXAMPLE</th>
<th>ASSOCIATED PATHOLOGY</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle cell</td>
<td><img src="sickle_cell.png" alt="Image" /></td>
<td>Sickle cell anemia.</td>
<td>Sickling occurs with dehydration, deoxygenation, and at high altitude.</td>
</tr>
<tr>
<td>Spherocyte</td>
<td><img src="spherocyte.png" alt="Image" /></td>
<td>Hereditary spherocytosis, drug- and infection-induced hemolytic anemia.</td>
<td></td>
</tr>
<tr>
<td>Dacrocyte (“teardrop cell”)</td>
<td><img src="dacrocyte.png" alt="Image" /></td>
<td>Bone marrow infiltration (e.g., myelofibrosis).</td>
<td>RBC “sheds a tear” because it’s mechanically squeezed out of its home in the bone marrow.</td>
</tr>
<tr>
<td>Target cell</td>
<td><img src="target_cell.png" alt="Image" /></td>
<td>HbC disease, Asplenia, Liver disease, Thalassemia.</td>
<td>“HALT,” said the hunter to his target.</td>
</tr>
</tbody>
</table>

## Other RBC pathologies

<table>
<thead>
<tr>
<th>TYPE</th>
<th>EXAMPLE</th>
<th>PROCESS</th>
<th>ASSOCIATED PATHOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heinz bodies</td>
<td><img src="heinz_bodies.png" alt="Image" /></td>
<td>Oxidation of Hb-SH groups to (-S-S-) → Hb precipitation (Heinz bodies A), with subsequent phagocytic damage to RBC membrane → bite cells.</td>
<td>Seen in G6PD deficiency; Heinz body–like inclusions seen in α-thalassemia.</td>
</tr>
<tr>
<td>Howell-Jolly bodies</td>
<td><img src="howell-jolly_bodies.png" alt="Image" /></td>
<td>Basophilic nuclear remnants found in RBCs. Howell-Jolly bodies are normally removed from RBCs by splenic macrophages.</td>
<td>Seen in patients with functional hyposplenia or asplenia.</td>
</tr>
</tbody>
</table>
Microcytic, hypochromic (MCV < 80 fl) anemia

<table>
<thead>
<tr>
<th>DESCRIPTION</th>
<th>FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency</td>
<td>↓ iron due to chronic bleeding (e.g., GI loss, menorrhagia), malnutrition/absorption disorders, or ↑ demand (e.g., pregnancy) → ↓ final step in heme synthesis.</td>
</tr>
</tbody>
</table>
Microcytic, hypochromic (MCV < 80 fl) anemia (continued)

<table>
<thead>
<tr>
<th>DESCRIPTION</th>
<th>FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-thalassemia</strong></td>
<td>Point mutations in splice sites and promoter sequences → ↓ β-globin synthesis. Prevalent in Mediterranean populations.</td>
</tr>
</tbody>
</table>
| | β-thalassemia minor (heterozygote):  
  • β chain is underproduced.  
  • Usually asymptomatic.  
  • Diagnosis confirmed by ↑ HbA₂ (> 3.5%) on electrophoresis.  

**β-thalassemia major** (homozygote):  
  • β chain is absent → severe anemia requiring blood transfusion (2° hemochromatosis).  
  • Marrow expansion (“crew cut” on skull x-ray) → skeletal deformities. “Chipmunk” facies.  
  • Extramedullary hematopoiesis (leads to hepatosplenomegaly). ↑ risk of parvovirus B19–induced aplastic crisis.  

  Major → ↑ HbF (α₂γ₂): HbF is protective in the infant and disease becomes symptomatic only after 6 months.  

| **HbS/β-thalassemia heterozygote** | mild to moderate sickle cell disease depending on amount of β-globin production. |
| **Lead poisoning** | Lead inhibits ferrochelatase and ALA dehydratase → ↓ heme synthesis and ↑ RBC protoporphyrin.  
  Also inhibits rRNA degradation, causing RBCs to retain aggregates of rRNA (basophilic stippling).  
  High risk in old houses with chipped paint. |
| | LEAD:  
  • Lead lines on gingivae (Burton lines) and on metaphyses of long bones on x-ray.  
  • Encephalopathy and erythrocyte basophilic stippling.  
  • Abdominal colic and sideroblastic Anemia.  
  • Drops—wrist and foot drop. Dimercaprol and EDTA are 1st line of treatment.  
  • Sucimer used for chelation for kids (It “sucks” to be a kid who eats lead). |
| **Sideroblastic anemia** | Defect in heme synthesis.  
  Hereditary: X-linked defect in δ-ALA synthase gene.  
  Causes: genetic, acquired (myelodysplastic syndromes), and reversible (alcohol is most common; also lead, vitamin B₆ deficiency, copper deficiency, isoniazid).  
  Ringed sideroblasts (with iron-laden, Prussian blue–stained mitochondria) seen in bone marrow.  
  • ↑ iron, normal/↑ TIBC, ↑ ferritin.  
  Treatment: pyridoxine (B₆, cofactor for δ-ALA synthase). |
Macrocytic (MCV > 100 fl) anemia

<table>
<thead>
<tr>
<th>DESCRIPTION</th>
<th>FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Megaloblastic anemia</td>
<td>Impaired DNA synthesis → maturation of nucleus of precursor cells in bone marrow delayed relative to maturation in cytoplasm. RBC macrocytosis, hypersegmented neutrophils, glossitis.</td>
</tr>
<tr>
<td>Folate deficiency</td>
<td>Causes: malnutrition (e.g., alcoholics), malabsorption, drugs (e.g., methotrexate, trimethoprim, phenytoin), ↑ requirement (e.g., hemolytic anemia, pregnancy). ↑ homocysteine, normal methylmalonic acid. No neurologic symptoms (vs. B₁₂ deficiency).</td>
</tr>
<tr>
<td>B₁₂ (cobalamin) deficiency</td>
<td>Causes: insufficient intake (e.g., veganism), malabsorption (e.g., Crohn disease), pernicious anemia, <em>Diphyllobothrium latum</em> (fish tapeworm), gastrectomy. ↑ homocysteine, ↑ methylmalonic acid. Neurologic symptoms: subacute combined degeneration (due to involvement of B₁₂ in fatty acid pathways and myelin synthesis): spinocerebellar tract, lateral corticospinal tract, dorsal column dysfunction.</td>
</tr>
<tr>
<td>Orotic aciduria</td>
<td>Inability to convert orotic acid to UMP (de novo pyrimidine synthesis pathway) because of defect in UMP synthase. Autosomal recessive. Presents in children as failure to thrive, developmental delay, and megaloblastic anemia refractory to folate and B₁₂. No hyperammonemia (vs. ornithine transcarbamylase deficiency—↑ orotic acid with hyperammonemia). Orotic acid in urine. Treatment: uridine monophosphate to bypass mutated enzyme.</td>
</tr>
<tr>
<td>Nonmegaloblastic macrocytic anemias</td>
<td>Macrocytic anemia in which DNA synthesis is unimpaired. Causes: alcoholism, liver disease, hypothyroidism, reticulocytosis. RBC macrocytosis without hypersegmented neutrophils.</td>
</tr>
</tbody>
</table>
**Normocytic, normochromic anemia**

Normocytic, normochromic anemias are classified as nonhemolytic or hemolytic. The hemolytic anemias are further classified according to the cause of the hemolysis (intrinsic vs. extrinsic to the RBC) and by the location of the hemolysis (intravascular vs. extravascular).

**Intravascular hemolysis**

Findings: ↑ haptoglobin, ↑ LDH, schistocytes and ↑ reticulocytes on blood smear. Characteristic hemoglobinuria, hemosiderinuria, and urobilinogen in urine. Notable causes are mechanical hemolysis (e.g., prosthetic valve), paroxysmal nocturnal hemoglobinuria, microangiopathic hemolytic anemias.

**Extravascular hemolysis**

Findings: macrophages in spleen clear RBCs. Spherocytes in peripheral smear, ↑ LDH, no hemoglobinuria/hemosiderinuria, ↑ unconjugated bilirubin, which can cause jaundice.

### Nonhemolytic, normocytic anemia

<table>
<thead>
<tr>
<th>DESCRIPTION</th>
<th>FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia of chronic disease</td>
<td>↑ inflammation → ↑ hepcidin (released by liver, binds ferroportin on intestinal mucosal cells and macrophages, thus inhibiting iron transport) → ↓ release of iron from macrophages. Associated with conditions such as rheumatoid arthritis, SLE, neoplastic disorders, and chronic kidney disease.</td>
</tr>
<tr>
<td>Pancytopenia characterized by severe anemia, leukopenia, and thrombocytopenia. Normal cell morphology, but hypocellular bone marrow with fatty infiltration (dry bone marrow tap). Symptoms: fatigue, malaise, pallor, purpura, mucosal bleeding, petechiae, infection. Treatment: withdrawal of offending agent, immunosuppressive regimens (e.g., antithymocyte globulin, cyclosporine), bone marrow allograft, RBC/platelet transfusion, bone marrow stimulation (e.g., GM-CSF).</td>
<td></td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>Caused by failure or destruction of myeloid stem cells due to:</td>
</tr>
<tr>
<td>* Radiation and drugs (benzene, chloramphenicol, alkylating agents, antimetabolites)</td>
<td></td>
</tr>
<tr>
<td>* Viral agents (parvovirus B19, EBV, HIV, HCV)</td>
<td></td>
</tr>
<tr>
<td>* Fanconi anemia (DNA repair defect)</td>
<td></td>
</tr>
<tr>
<td>* Idiopathic (immune mediated, ↑ stem cell defect); may follow acute hepatitis</td>
<td></td>
</tr>
<tr>
<td>Treatment: EPO (chronic kidney disease only).</td>
<td></td>
</tr>
</tbody>
</table>

Note: ↑ iron, ↓ TIBC, ↓ ferritin. Normocytic, but can become microcytic.
### Intrinsic hemolytic normocytic anemia

<table>
<thead>
<tr>
<th>DESCRIPTION</th>
<th>FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hereditary spherocytosis (E)</strong></td>
<td>Defect in proteins interacting with RBC membrane skeleton and plasma membrane (e.g., ankyrin, band 3, protein 4.2, spectrin). Results in small, round RBCs with less surface area and no central pallor (↑ MCHC, ↑ red cell distribution width) → premature removal by spleen.</td>
</tr>
<tr>
<td><strong>G6PD deficiency (I/E)</strong></td>
<td>Most common enzymatic disorder of RBCs. X-linked recessive. Defect in G6PD → ↓ glutathione → ↑ RBC susceptibility to oxidant stress. Hemolytic anemia following oxidant stress (e.g., sulfadiazine, antimalarials, infections, fava beans). Back pain, hemoglobinuria a few days after oxidant stress. Labs: blood smear shows RBCs with Heinz bodies and bite cells. “Stress makes me eat bites of fava beans with Heinz ketchup.”</td>
</tr>
<tr>
<td><strong>Pyruvate kinase deficiency (E)</strong></td>
<td>Autosomal recessive. Defect in pyruvate kinase → ↓ ATP → rigid RBCs.</td>
</tr>
<tr>
<td><strong>HbC defect (E)</strong></td>
<td>Glutamic acid–to-lysine mutation in β-globin. Patients with HbSC (1 of each mutant gene) have milder disease than HbSS patients.</td>
</tr>
</tbody>
</table>
| **Sickle cell anemia (E)** | HbS point mutation causes a single amino acid replacement in β chain (substitution of glutamic acid with valine). Pathogenesis: low O₂, high altitude, or acidosis precipitates sickling (deoxygenated HbS polymerizes) → anemia and vaso-occlusive disease. Newborns are initially asymptomatic because of ↑ HbF and ↓ HbS. Heterozygotes (sickle cell trait) also have resistance to malaria. 8% of African Americans carry an HbS allele. Sickle cells are crescent-shaped RBCs. “Crew cut” on skull x-ray due to marrow expansion from ↑ erythropoiesis (also seen in thalassemias). Complications in sickle cell disease:  
  - Aplastic crisis (due to parvovirus B19).  
  - Autosplenectomy (Howell-Jolly bodies)  
  - ↑ risk of infection by encapsulated organisms.  
  - Splenic infarct/sequestration crisis.  
  - Salmonella osteomyelitis.  
  - Painful crises (vaso-occlusive): dactylitis (painful swelling of hands/feet), acute chest syndrome, avascular necrosis, stroke.  
  - Renal papillary necrosis (↑ Po₂ in papilla) and microhematuria (medullary infarcts). Diagnosis: hemoglobin electrophoresis. Treatment: hydroxyurea (↑ HbF), hydration. |
Extrinsic hemolytic normocytic anemia

<table>
<thead>
<tr>
<th>DESCRIPTION</th>
<th>FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autoimmune hemolytic anemia</strong></td>
<td>Warm agglutinin (IgG)—chronic anemia seen in SLE and CLL and with certain drugs (e.g., α-methyldopa) (“warm weather is Great”). Cold agglutinin (IgM)—acute anemia triggered by cold; seen in CLL, Mycoplasma pneumonia infections, and infectious Mononucleosis (“cold weather is MMMiserable”). Many warm and cold AIHAs are idiopathic in etiology. Autoimmune hemolytic anemias are usually Coombs ⊕. Direct Coombs test—anti-Ig antibody (Coombs reagent) added to patient’s blood. RBCs agglutinate if RBCs are coated with Ig. Indirect Coombs test—normal RBCs added to patient’s serum. If serum has anti-RBC surface Ig, RBCs agglutinate when Coombs reagent added.</td>
</tr>
<tr>
<td><strong>Microangiopathic anemia</strong></td>
<td>Pathogenesis: RBCs are damaged when passing through obstructed or narrowed vessel lumina. Seen in DIC, TTP/HUS, SLE, and malignant hypertension. Schistocytes (“helmet cells”) are seen on blood smear due to mechanical destruction of RBCs.</td>
</tr>
<tr>
<td><strong>Macroangiopathic anemia</strong></td>
<td>Prosthetic heart valves and aortic stenosis may also cause hemolytic anemia 2° to mechanical destruction. Schistocytes on peripheral blood smear.</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td>↑ destruction of RBCs (e.g., malaria, Babesia).</td>
</tr>
</tbody>
</table>

Lab values in anemia

<table>
<thead>
<tr>
<th>Iron deficiency</th>
<th>Chronic disease</th>
<th>Hemochromatosis</th>
<th>Pregnancy/OCP use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum iron</td>
<td>↓ (1°)</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Transferrin or TIBC</td>
<td>↑</td>
<td>↓</td>
<td>↑ (1°)</td>
</tr>
<tr>
<td>Ferritin</td>
<td>↓</td>
<td>↑ (1°)</td>
<td>↑ (1°)</td>
</tr>
<tr>
<td>% transferrin saturation (serum iron/TIBC)</td>
<td>↓↓ —</td>
<td>↑↑ ↓</td>
<td></td>
</tr>
</tbody>
</table>

Transferrin—transports iron in blood.
TIBC—indirectly measures transferrin.
Ferritin—1° iron storage protein of body.

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.

Leukopenias

<table>
<thead>
<tr>
<th>CELL TYPE</th>
<th>CELL COUNT</th>
<th>CAUSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>Absolute neutrophil count &lt; 1500 cells/mm³</td>
<td>Sepsis/postinfection, drugs (including chemotherapy), aplastic anemia, SLE, radiation</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>Absolute lymphocyte count &lt; 1500 cells/mm³ (&lt; 3000 cells/mm³ in children)</td>
<td>HIV, DiGeorge syndrome, SCID, SLE, corticosteroids, radiation, sepsis, postoperative</td>
</tr>
<tr>
<td>Eosinopenia</td>
<td>Cushing syndrome, corticosteroids</td>
<td></td>
</tr>
</tbody>
</table>

Corticosteroids cause neutrophilia, despite causing eosinopenia and lymphopenia. Corticosteroids ↑ activation of neutrophil adhesion molecules, impairing migration out of the vasculature to sites of inflammation. In contrast, corticosteroids sequester eosinophils in lymph nodes and cause apoptosis of lymphocytes.
### 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.

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>AFFECTED ENZYME</th>
<th>ACCUMULATED SUBSTRATE</th>
<th>PRESENTING SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead poisoning</td>
<td>Ferrochelatase and ALA dehydratase</td>
<td>Protoporphyrin, δ-ALA (blood)</td>
<td>Microcytic anemia (basophilic stippling), GI and kidney disease. Children—exposure to lead paint → mental deterioration. Adults—environmental exposure (e.g., batteries, ammunition) → headache, memory loss, demyelination.</td>
</tr>
<tr>
<td>Acute intermittent porphyria</td>
<td>Porphobilinogen deaminase</td>
<td>Porphobilinogen, δ-ALA, coproporphobilinogen (urine)</td>
<td>Symptoms (5 P’s):&lt;br&gt; - Painful abdomen&lt;br&gt; - Port wine–colored urine&lt;br&gt; - Polynephropathy&lt;br&gt; - Psychological disturbances&lt;br&gt; - Precipitated by drugs (e.g., cytochrome P-450 inducers), alcohol, starvation&lt;br&gt; Treatment: glucose and heme, which inhibit ALA synthase.</td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td>Uroporphyrinogen decarboxylase</td>
<td>Uroporphyrin (teal-colored urine)</td>
<td>Blistering cutaneous photosensitivity. Most common porphyria.</td>
</tr>
</tbody>
</table>

### Diagram

```
<table>
<thead>
<tr>
<th>Location</th>
<th>Intermediates</th>
<th>Enzymes</th>
<th>Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitochondria</td>
<td>Glycine + succinyl-CoA B6 δ-aminolevulinic acid</td>
<td>δ-aminolevulinic acid synthase: rate-limiting step</td>
<td>Sideroblastic anemia (X linked)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lead poisoning</td>
</tr>
<tr>
<td></td>
<td></td>
<td>δ-aminolevulinic acid dehydratase</td>
<td>Acute intermittent porphyria</td>
</tr>
<tr>
<td></td>
<td>Porphobilinogen</td>
<td>Porphobilinogen deaminase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydroxymethylbilane</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uroporphyrinogen III</td>
<td>Uroporphyrinogen decarboxylase</td>
<td>Porphyria cutanea tarda</td>
</tr>
<tr>
<td></td>
<td>Coproporphyrinogen III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitochondria</td>
<td>Protoporphyrin Fe^{2+} Heme</td>
<td>Ferrochelatase</td>
<td>Lead poisoning</td>
</tr>
</tbody>
</table>

↓ heme → ↑ ALA synthase activity
↑ heme → ↓ ALA synthase activity
```
### Iron poisoning
High mortality rate with accidental ingestion by children (adult iron tablets may look like candy).

**MECHANISM**
Cell death due to peroxidation of membrane lipids.

**SYMPTOMS/SIGNS**
Nausea, vomiting, gastric bleeding, lethargy, scarring leading to GI obstruction.

**TREATMENT**
Chelation (e.g., IV deferoxamine, oral deferasirox) and dialysis.

### Coagulation disorders
PT—tests function of common and extrinsic pathway (factors I, II, V, VII, and X). Defect → ↑ PT.

PTT—tests function of common and intrinsic pathway (all factors except VII and XIII). Defect → ↑ PTT.

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>PT</th>
<th>PTT</th>
<th>MECHANISM AND COMMENTS</th>
</tr>
</thead>
</table>
| Hemophilia A, B, or C     |    | ↑   | Intrinsic pathway coagulation defect.  
  - A: deficiency of factor VIII → ↑ PTT; X-linked recessive.  
  - B: deficiency of factor IX → ↑ PTT; X-linked recessive.  
  - C: deficiency of factor XI → ↑ PTT; autosomal recessive.  
  Macrohemorrhage in hemophilia—hemarthroses (bleeding into joints, such as knee A), easy bruising, bleeding after trauma or surgery (e.g., dental procedures).  
  Treatment: desmopressin + factor VIII concentrate (A); factor IX concentrate (B); factor XI concentrate (C). |
| Vitamin K deficiency      | ↑  | ↑   | General coagulation defect. Bleeding time normal.  
  ↑ activation of factors II, VII, IX, X, protein C, protein S. |

### Platelet disorders
Defects in platelet plug formation → ↑ bleeding time (BT).

Platelet abnormalities → microhemorrhage: mucous membrane bleeding, epistaxis, petechiae, purpura, ↓ bleeding time, possibly decreased platelet count (PC).

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>PC</th>
<th>BT</th>
<th>MECHANISM AND COMMENTS</th>
</tr>
</thead>
</table>
| Bernard-Soulier syndrome        | ↓  | ↑  | Defect in platelet plug formation. Large platelets.  
  ↑ GpIb → defect in platelet-to-vWF adhesion.  
  No agglutination on ristocetin cofactor assay. |
| Glanzmann thrombasthenia        |    | ↑  | Defect in platelet plug formation.  
  ↑ GpIIb/IIIa → defect in platelet-to-platelet aggregation.  
  Labs: blood smear shows no platelet clumping.  
  Agglutination with ristocetin cofactor assay. |
| Immune thrombocytopenia         | ↓  | ↑  | Anti-GpIIb/IIIa antibodies → splenic macrophage consumption of platelet-antibody complex. Commonly due to viral illness.  
  Labs: ↑ megakaryocytes on bone marrow biopsy.  
  Treatment: steroids, intravenous immunoglobulin. |
| Thrombotic thrombocytopenic purpura | ↓  | ↑  | Inhibition or deficiency of ADAMTS 13 (vWF metalloprotease) → ↓ degradation of vWF multimers.  
  Pathogenesis: ↓ large vWF multimers → ↑ platelet adhesion → ↑ platelet aggregation and thrombosis.  
  Labs: schistocytes, ↑ LDH.  
  Symptoms: pentad of neurologic and renal symptoms, fever, thrombocytopenia, and microangiopathic hemolytic anemia.  
  Treatment: plasmapheresis, steroids. |
**Mixed platelet and coagulation disorders**

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>PC</th>
<th>BT</th>
<th>PT</th>
<th>PTT</th>
<th>MECHANISM AND COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>von Willebrand disease</td>
<td>—</td>
<td>†</td>
<td>—</td>
<td>†</td>
<td>Intrinsic pathway coagulation defect: ↓ vWF → ↑ PTT (vWF acts to carry/protect factor VIII). Defect in platelet plug formation: ↓ vWF → defect in platelet-to-vWF adhesion. Autosomal dominant. Mild but most common inherited bleeding disorder. Diagnosed in most cases by ristocetin cofactor assay (agglutination is diagnostic). Treatment: desmopressin, which releases vWF stored in endothelium.</td>
</tr>
<tr>
<td>DIC</td>
<td>↓</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>Widespread activation of clotting → deficiency in clotting factors → bleeding state. Causes: Sepsis (gram-negative), Trauma, Obstetric complications, acute Pancreatitis, Malignancy, Nephrotic syndrome, Transfusion (STOP Making New Thrombi). Labs: schistocytes, ↓ fibrin split products (t-dimers), ↓ fibrinogen, ↓ factors V and VIII.</td>
</tr>
</tbody>
</table>

*PTT may also be normal in von Willebrand disease.

---

**Hereditary thrombosis syndromes leading to hypercoagulability**

| DISEASE                      | DESCRIPTION                                                                                                                                                                                                 |
|------------------------------|--------------------------------------------------------------------------------------------------------------------------------==========================================================================|
| Antithrombin deficiency      | Inherited deficiency of antithrombin: has no direct effect on the PT, PTT, or thrombin time but diminishes the increase in PTT following heparin administration. Can also be acquired: renal failure/nephrotic syndrome → antithrombin loss in urine → ↓ inhibition of factors IIa and Xa. |
| Factor V Leiden              | Production of mutant factor V that is resistant to degradation by activated protein C. Most common cause of inherited hypercoagulability in whites.                                                                 |
| Protein C or S deficiency    | ↓ ability to inactivate factors Va and VIIIa. ↑ risk of thrombotic skin necrosis with hemorrhage following administration of warfarin. Skin and subcutaneous tissue necrosis after warfarin administration → think protein C deficiency. “Protein C Cancels Coagulation.” |
| Prothrombin gene mutation    | Mutation in 3′ untranslated region → ↑ production of prothrombin → ↑ plasma levels and venous clots.                                                                                                      |
### Blood transfusion therapy

<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>DOSAGE EFFECT</th>
<th>CLINICAL USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Packed RBCs</td>
<td>↑ Hb and O₂ carrying capacity</td>
<td>Acute blood loss, severe anemia</td>
</tr>
<tr>
<td>Platelets</td>
<td>↑ platelet count (↑ ~5000/mm³/unit)</td>
<td>Stop significant bleeding (thrombocytopenia, qualitative platelet defects)</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>↑ coagulation factor levels</td>
<td>DIC, cirrhosis, immediate warfarin reversal</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>Contains fibrinogen, factor VIII, factor XIII, vWF, and fibronectin</td>
<td>Coagulation factor deficiencies involving fibrinogen and factor VIII</td>
</tr>
</tbody>
</table>

Blood transfusion risks include infection transmission (low), transfusion reactions, iron overload, hypocalcemia (citrate is a Ca²⁺ chelator), and hyperkalemia (RBCs may lyse in old blood units).

### Leukemia vs. lymphoma

**Leukemia**
- Lymphoid or myeloid neoplasm with widespread involvement of bone marrow. Tumor cells are usually found in peripheral blood.

**Lymphoma**
- Discrete tumor mass arising from lymph nodes. Presentations often blur definitions.

### Leukemoid reaction

Acute inflammatory response to infection. ↑ WBC count with ↑ neutrophils and neutrophil precursors such as band cells (left shift); ↑ leukocyte alkaline phosphatase (LAP). Contrast with CML (also ↑ WBC count with left shift, but ↓ LAP).

### Hodgkin vs. non-Hodgkin lymphoma

<table>
<thead>
<tr>
<th>Hodgkin</th>
<th>Non-Hodgkin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized, single group of nodes; extranodal rare; contiguous spread (stage is strongest predictor of prognosis). Prognosis is much better than with non-Hodgkin lymphoma.</td>
<td>Multiple, peripheral nodes; extranodal involvement common; noncontiguous spread.</td>
</tr>
<tr>
<td>Characterized by Reed-Sternberg cells.</td>
<td>Majority involve B cells (except those of lymphoblastic T-cell origin).</td>
</tr>
<tr>
<td>Bimodal distribution—young adulthood and &gt; 55 years; more common in men except for nodular sclerosing type.</td>
<td>Peak incidence for certain subtypes at 20–40 years old.</td>
</tr>
<tr>
<td>Strongly associated with EBV.</td>
<td>May be associated with HIV and autoimmune diseases.</td>
</tr>
<tr>
<td>Constitutional (“B”) signs/symptoms: low-grade fever, night sweats, weight loss.</td>
<td>Fewer constitutional signs/symptoms.</td>
</tr>
</tbody>
</table>
**Reed-Sternberg cells**

Distinctive tumor giant cell seen in Hodgkin disease; binucleate or bilobed with the 2 halves as mirror images (“owl eyes”). RS cells are CD15+ and CD30+ B-cell origin. Necessary but not sufficient for a diagnosis of Hodgkin disease. Better prognosis with strong stromal or lymphocytic reaction against RS cells. Nodular sclerosing form most common (affects women and men equally). Lymphocyte-rich form has best prognosis. Lymphocyte mixed or depleted forms have worse prognosis.

\[2 \text{ owl eyes } \times 15 = 30.\]

**Non-Hodgkin lymphoma**

<table>
<thead>
<tr>
<th>Type</th>
<th>Occurs in</th>
<th>Genetics</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Burkitt lymphoma</strong></td>
<td>Adolescents or young adults</td>
<td>t(8;14)—translocation of c-my (8) and heavy-chain Ig (14)</td>
<td>“Starry sky” appearance sheets of lymphocytes with interspersed macrophages (arrows). Associated with EBV. Jaw lesion in endemic form in Africa; pelvis or abdomen in sporadic form.</td>
</tr>
<tr>
<td><strong>Diffuse large B-cell lymphoma</strong></td>
<td>Usually older adults, but 20% in children</td>
<td></td>
<td>Most common type of non-Hodgkin lymphoma in adults.</td>
</tr>
<tr>
<td><strong>Follicular lymphoma</strong></td>
<td>Adults</td>
<td>t(14;18)—translocation of heavy-chain Ig (14) and BCL-2 (18)</td>
<td>Indolent course; Bcl-2 inhibits apoptosis. Presents with painless “waxing and waning” lymphadenopathy. Nodular, small cells; cleaved nuclei.</td>
</tr>
<tr>
<td><strong>Mantle cell lymphoma</strong></td>
<td>Older males</td>
<td>t(11;14)—translocation of cyclin D1 (11) and heavy-chain Ig (14)</td>
<td>CD5+.</td>
</tr>
</tbody>
</table>

**Neoplasms of mature T cells**

<table>
<thead>
<tr>
<th>Type</th>
<th>Occurs in</th>
<th>Genetics</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adult T-cell lymphoma</strong></td>
<td>Adults</td>
<td>Caused by HTLV (associated with IV drug abuse)</td>
<td>Adults present with cutaneous lesions; especially affects populations in Japan, West Africa, and the Caribbean. Lytic bone lesions, hypercalcemia.</td>
</tr>
<tr>
<td><strong>Mycosis fungoides/ Sézary syndrome</strong></td>
<td>Adults</td>
<td></td>
<td>Mycosis fungoides presents with skin patches plaques (cutaneous T-cell lymphoma), characterized by atypical CD4+ cells with “cerebriform” nuclei. May progress to Sézary syndrome (T-cell leukemia).</td>
</tr>
</tbody>
</table>
Multiple myeloma

Monoclonal plasma cell ("fried egg" appearance) cancer that arises in the marrow and produces large amounts of IgG (55%) or IgA (25%). Most common 1° tumor arising within bone in people > 40–50 years old. Associated with:

* ↑ susceptibility to infection
* Primary amyloidosis (AL)
* Punched-out lytic bone lesions on x-ray
* M spike on serum protein electrophoresis
* Ig light chains in urine (Bence Jones protein)
* Rouleaux formation (RBCs stacked like poker chips in blood smear)

Numerous plasma cells with "clock-face" chromatin and intracytoplasmic inclusions containing immunoglobulin.

Monoclonal gammopathy of undetermined significance (MGUS)—monoclonal expansion of plasma cells, asymptomatic, may lead to multiple myeloma. No "CRAB" findings. Patients with MGUS develop multiple myeloma at a rate of 1–2% per year.

Think CRAB:

HyperCalcemia
Renal involvement
Anemia
Bone lytic lesions/Back pain

Multiple Myeloma: Monoclonal M protein spike

Distinguish from Waldenström macroglobulinemia → M spike = IgM

→ hyperviscosity syndrome (e.g., blurred vision, Raynaud phenomenon); no "CRAB" findings.

Myelodysplastic syndromes

Stem-cell disorders involving ineffective hematopoiesis → defects in cell maturation of all nonlymphoid lineages. Caused by de novo mutations or environmental exposure (e.g., radiation, benzene, chemotherapy). Risk of transformation to AML.

Pseudo–Pelger-Huet anomaly—neutrophils with bilobed nuclei. Typically seen after chemotherapy.
Leukemias

Unregulated growth and differentiation of WBCs in bone marrow → marrow failure → anemia (↓ RBCs), infections (↓ mature WBCs), and hemorrhage (↓ platelets). ↑ or ↓ number of circulating WBCs.
Leukemic cell infiltration of liver, spleen, lymph nodes, and skin (leukemia cutis) possible.

<table>
<thead>
<tr>
<th>TYPE</th>
<th>PERIPHERAL BLOOD SMEAR</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lymphoid neoplasms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acute lymphoblastic leukemia/lymphoma</strong> (ALL)</td>
<td>Age: &lt; 15 years. T-cell ALL can present as mediastinal mass (presenting as SVC-like syndrome). Associated with Down syndrome. Peripheral blood and bone marrow have ↑↑↑ lymphoblasts A. TdT+ (marker of pre-T and pre-B cells), CD10+ (pre-B cells only). Most responsive to therapy. May spread to CNS and testes. t(12;21) → better prognosis.</td>
<td></td>
</tr>
<tr>
<td><strong>Small lymphocytic lymphoma (SLL)/chronic lymphocytic leukemia (CLL)</strong></td>
<td>Age: &gt; 60 years. Most common adult leukemia. CD20+, CD5+ B-cell neoplasm. Often asymptomatic, progresses slowly; smudge cells B in peripheral blood smear; autoimmune hemolytic anemia. SLL same as CLL except CLL has ↑ peripheral blood lymphocytosis or bone marrow involvement.</td>
<td></td>
</tr>
<tr>
<td><strong>Hairy cell leukemia</strong></td>
<td>Age: Adults. Mature B-cell tumor in the elderly. Cells have filamentous, hair-like projections C. Causes marrow fibrosis → dry tap on aspiration. Stains TRAP (tartrate-resistant acid phosphatase ⊕). TRAP stain largely replaced with flow cytometry. Treatment: cladribine, pentostatin.</td>
<td></td>
</tr>
<tr>
<td><strong>Myeloid neoplasms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acute myelogenous leukemia (AML)</strong></td>
<td>Age: median onset 65 years. Auer rods D; peroxidase ⊕ cytoplasmic inclusions seen mostly in M3 AML; ↑↑ circulating myeloblasts on peripheral smear; adults. Risk factors: prior exposure to alkylating chemotherapy, radiation, myeloproliferative disorders, Down syndrome. t(15;17) → M3 AML subtype responds to all-trans retinoic acid (vitamin A), inducing differentiation of myeloblasts; DIC is a common presentation.</td>
<td></td>
</tr>
<tr>
<td><strong>Chronic myelogenous leukemia (CML)</strong></td>
<td>Age: peak incidence 45–85 years, median age at diagnosis 64 years. Defined by the Philadelphia chromosome (t[9;22], BCR-ABL); myeloid stem cell proliferation; presents with ↑ neutrophils, metamyelocytes, basophils E; splenomegaly; may accelerate and transform to AML or ALL (“blast crisis”). Very low LAP as a result of low activity in mature granulocytes (vs. leukemoid reaction, in which LAP is ↑). Responds to imatinib (a small-molecule inhibitor of the bcr-abl tyrosine kinase).</td>
<td></td>
</tr>
</tbody>
</table>

---

*Images of blood smear and bone marrow aspirate.*
### Chromosomal translocations

<table>
<thead>
<tr>
<th>TRANSLOCATION</th>
<th>ASSOCIATED DISORDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(8;14)</td>
<td>Burkitt lymphoma (c-myc activation)</td>
</tr>
<tr>
<td>t(9;22) (Philadelphia chromosome)</td>
<td>CML (BCR-ABL hybrid)</td>
</tr>
<tr>
<td>t(11;14)</td>
<td>Mantle cell lymphoma (cyclin D1 activation)</td>
</tr>
<tr>
<td>t(14;18)</td>
<td>Follicular lymphoma (BCL-2 activation)</td>
</tr>
<tr>
<td>t(15;17)</td>
<td>M3 type of AML</td>
</tr>
</tbody>
</table>

### Langerhans cell histiocytosis

Collective group of proliferative disorders of dendritic (Langerhans) cells. Presents in a child as lytic bone lesions and skin rash or as recurrent otitis media with a mass involving the mastoid bone. Cells are functionally immature and do not effectively stimulate primary T cells via antigen presentation. Cells express S-100 (mesodermal origin) and CD1a. Birbeck granules ("tennis rackets" or rod shaped on EM) are characteristic.

![Langerhans cell histiocytosis](image_url)
**Chronic myeloproliferative disorders**

The myeloproliferative disorders represent an often-overlapping spectrum, but the classic findings are described below. JAK2 is involved in hematopoietic growth factor signaling. JAK2 gene mutation is often found in chronic myeloproliferative disorders except CML (which has BCR-ABL translocation).

**Polycythemia vera**

Disorder of ↑ hematocrit, often associated with JAK2 mutation. May present as intense itching after hot shower (due to ↑ basophils). Rare but classic symptom is erythromelalgia (severe, burning pain and red-blue coloration) due to episodic blood clots in vessels of the extremities A.

Polycythemia vera is via natural or artificial ↑ in EPO levels.

**Essential thrombocytosis**

Similar to polycythemia vera, but specific for overproduction of abnormal platelets → bleeding, thrombosis. Bone marrow contains enlarged megakaryocytes B.

**Myelofibrosis**

Obliteration of bone marrow due to ↑ fibroblast activity in response to proliferation of monoclonal cell lines C. “Teardrop” RBCs and immature forms of the myeloid line. “Bone marrow is crying because it’s fibrosed and is a dry tap.” Often associated with massive splenomegaly.

<table>
<thead>
<tr>
<th>RBCs</th>
<th>WBCs</th>
<th>PLATELETS</th>
<th>PHILADELPHIA CHROMOSOME</th>
<th>JAK2 MUTATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polycythemia vera</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>⊕</td>
</tr>
<tr>
<td>Essential thrombocytosis</td>
<td>⊕</td>
<td>⊕</td>
<td>⊕</td>
<td>⊕ (30–50%)</td>
</tr>
<tr>
<td>Myelofibrosis</td>
<td>↓</td>
<td>Variable</td>
<td>Variable</td>
<td>⊕</td>
</tr>
<tr>
<td>CML</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>⊕</td>
</tr>
</tbody>
</table>

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**Polycythemia vera**

<table>
<thead>
<tr>
<th>PLASMA VOLUME</th>
<th>RBC MASS</th>
<th>O₂ SATURATION</th>
<th>EPO LEVELS</th>
<th>ASSOCIATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative</td>
<td>↓</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Appropriate absolute</td>
<td>–</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Inappropriate absolute</td>
<td>–</td>
<td>↑</td>
<td>–</td>
<td>↑</td>
</tr>
<tr>
<td>Polycythemia vera</td>
<td>↑</td>
<td>↑↑</td>
<td>–</td>
<td>↓</td>
</tr>
</tbody>
</table>
**HEMATOLOGY AND ONCOLOGY—PHARMACOLOGY**

### Heparin

**MECHANISM**
Activator of antithrombin; inhibits thrombin and factor Xa. Short half-life.

**CLINICAL USE**
Immediate anticoagulation for pulmonary embolism (PE), acute coronary syndrome, MI, deep venous thrombosis (DVT). Used during pregnancy (does not cross placenta). Follow PTT.

**TOXICITY**
Bleeding, thrombocytopenia (HIT), osteoporosis, drug-drug interactions. For rapid reversal (antidote), use protamine sulfate (positively charged molecule that binds negatively charged heparin).

**NOTES**
Low-molecular-weight heparins (e.g., enoxaparin, dalteparin) and fondaparinux act more on factor Xa, have better bioavailability, and 2–4 times longer half-life; can be administered subcutaneously and without laboratory monitoring. Not easily reversible.


### Argatroban, bivalirudin, dabigatran
Bivalirudin is related to hirudin, the anticoagulant used by leeches; inhibit thrombin directly. Alternatives to heparin for anticoagulating patients with HIT.

### Warfarin

**MECHANISM**
Interferes with \( \gamma \)-carboxylation of vitamin K–dependent clotting factors II, VII, IX, and X, and proteins C and S. Metabolism affected by polymorphisms in the gene for vitamin K epoxide reductase complex (VKORC1). In laboratory assay, has effect on EXtrinsic pathway and PT. Long half-life.

**CLINICAL USE**
Chronic anticoagulation (e.g., venous thromboembolism prophylaxis, and prevention of stroke in atrial fibrillation). Not used in pregnant women (because warfarin, unlike heparin, crosses placenta). Follow PT/INR.

**TOXICITY**
Bleeding, teratogenic, skin/tissue necrosis, drug-drug interactions. Proteins C and S have shorter half-lives than clotting factors II, VI, IX, and X, resulting in early transient hypercoagulability with warfarin use. Skin/tissue necrosis believed to be due to small vessel microthromboses.

For reversal of warfarin, give vitamin K. For rapid reversal, give fresh frozen plasma. Heparin “bridging” heparin frequently used when starting warfarin. Heparin’s activation of antithrombin enables anticoagulation during initial, transient hypercoagulable state caused by warfarin. Initial heparin therapy reduces risk of recurrent venous thromboembolism and skin/tissue necrosis.
### Heparin vs. warfarin

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Heparin</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structure</strong></td>
<td>Large, anionic, acidic polymer</td>
<td>Small, amphipathic molecule</td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
<td>Parenteral (IV, SC)</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Site of Action</strong></td>
<td>Blood</td>
<td>Liver</td>
</tr>
<tr>
<td><strong>Onset of Action</strong></td>
<td>Rapid (seconds)</td>
<td>Slow, limited by half-lives of normal clotting factors</td>
</tr>
<tr>
<td><strong>Mechanism of Action</strong></td>
<td>Activates antithrombin, which † the action of IIa (thrombin) and factor Xa</td>
<td>Impairs activation of vitamin K–dependent clotting factors II, VII, IX, and X, and anti-clotting proteins C and S</td>
</tr>
<tr>
<td><strong>Duration of Action</strong></td>
<td>Acute (hours)</td>
<td>Chronic (days)</td>
</tr>
<tr>
<td><strong>Inhibits Coagulation In Vitro</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Agents for Reversal</strong></td>
<td>Protamine sulfate</td>
<td>Vitamin K, fresh frozen plasma</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>PTT (intrinsic pathway)</td>
<td>PT/INR (extrinsic pathway)</td>
</tr>
<tr>
<td><strong>Crosses Placenta</strong></td>
<td>No</td>
<td>Yes (teratogenic)</td>
</tr>
</tbody>
</table>

### Direct factor Xa inhibitors

- **Apixaban, rivaroxaban.**
  - **Mechanism:** Bind to and directly inhibit factor Xa.
  - **Clinical Use:** Treatment and prophylaxis for DVT and PE (rivaroxaban); stroke prophylaxis in patients with atrial fibrillation.
  - **Toxicity:** Bleeding (no reversal agent available).

### Thrombolytics

- **Alteplase (tPA), reteplase (rPA), streptokinase, tenecteplase (TNK-tPA).**
  - **Mechanism:** Directly or indirectly aid conversion of plasminogen to plasmin, which cleaves thrombin and fibrin clots. † PT, † PTT, no change in platelet count.
  - **Clinical Use:** Early MI, early ischemic stroke, direct thrombolysis of severe PE.
  - **Toxicity:** Bleeding. Contraindicated in patients with active bleeding, history of intracranial bleeding, recent surgery, known bleeding diatheses, or severe hypertension. Treat toxicity with aminocaproic acid, an inhibitor of fibrinolysis. Fresh frozen plasma and cryoprecipitate can also be used to correct factor deficiencies.
### Aspirin

**MECHANISM**
Irreversibly inhibits cyclooxygenase (both COX-1 and COX-2) enzyme by covalent acetylation. Platelets cannot synthesize new enzyme, so effect lasts until new platelets are produced: ↑ bleeding time, ↓ TXA₂ and prostaglandins. No effect on PT or PTT.

**CLINICAL USE**
Antipyretic, analgesic, anti-inflammatory, antiplatelet (↓ aggregation).

**TOXICITY**
Gastric ulceration, tinnitus (CN VIII). Chronic use can lead to acute renal failure, interstitial nephritis, and upper GI bleeding. Reye syndrome in children with viral infection. Overdose initially causes hyperventilation and respiratory alkalosis, but transitions to mixed metabolic acidosis–respiratory alkalosis.

### ADP receptor inhibitors
Clopidogrel, prasugrel, ticagrelor (reversible), ticlopidine.

**MECHANISM**
Inhibit platelet aggregation by irreversibly blocking ADP receptors. Prevent expression of glycoproteins IIIb/IIia on platelet surface.

**CLINICAL USE**
Acute coronary syndrome; coronary stenting. ↓ incidence or recurrence of thrombotic stroke.

**TOXICITY**
Neutropenia (ticlopidine). TTP may be seen.

### Cilostazol, dipyridamole

**MECHANISM**
Phosphodiesterase III inhibitor; ↑ cAMP in platelets, resulting in inhibition of platelet aggregation; vasodilators.

**CLINICAL USE**
Intermittent claudication, coronary vasodilation, prevention of stroke or TIs (combined with aspirin), angina prophylaxis.

**TOXICITY**
Nausea, headache, facial flushing, hypotension, abdominal pain.

### GP IIb/IIia inhibitors
Abciximab, eptifibatide, tirofiban.

**MECHANISM**
Bind to the glycoprotein receptor IIb/IIia on activated platelets, preventing aggregation. Abciximab is made from monoclonal antibody Fab fragments.

**CLINICAL USE**
Unstable angina, percutaneous transluminal coronary angioplasty.

**TOXICITY**
Bleeding, thrombocytopenia.


Cancer drugs—cell cycle

Antimetabolites
- Azathioprine
- Cladribine
- Cytarabine
- 5-Fluorouracil
- Hydroxyurea
- Methotrexate
- 6-Mercaptopurine
- 6-Thioguanine

Microtubule inhibitors
- Paclitaxel
- Vinca alkaloids
  - Vinblastine
  - Vincristine

Alkylating agents
- Nitrosoureas
  - Carmustine
  - Cisplatin
  - Lomustine

Interphase
- DNA synthesis
- Cell cycle content
- Double check repair
- G1

Mitosis
- Cytokinesis
- G2 M

Antineoplastics
- Nucleotide synthesis: DNA RNA Cell division
- MTX, 5-FU: ↓ thymidine synthesis
- 6-MP: ↓ de novo purine synthesis
- Hydroxyurea: inhibits ribonucleotide reductase
- Alkylation agents, cisplatin: cross-link DNA
- Bleomycin: DNA strand breakage
- Dactinomycin, doxorubicin: DNA intercalators
- Etoposide: inhibits topoisomerase II
- Irinotecan: inhibits topoisomerase I

Vinca alkaloids: inhibit microtubule formation
- Paclitaxel: inhibits microtubule disassembly
### Antimetabolites

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM*</th>
<th>CLINICAL USE</th>
<th>TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine, 6-mercaptopurine (6-MP), 6-thioguanine (6-TG)</td>
<td>Purine (thiol) analogs → de novo purine synthesis. Activated by HGPRT. Azathioprine is metabolized into 6-MP.</td>
<td>Preventing organ rejection, rheumatoid arthritis, IBD, SLE; used to wean patients off steroids in chronic disease and to treat steroid-refractory chronic disease.</td>
<td>Myelosuppression, GI, liver. Azathioprine and 6-MP are metabolized by xanthine oxidase; thus both have toxicity with allopurinol or febuxostat.</td>
</tr>
<tr>
<td>Cladribine (2-CDA)</td>
<td>Purine analog → multiple mechanisms (e.g., inhibition of DNA polymerase, DNA strand breaks).</td>
<td>Hairy cell leukemia.</td>
<td>Myelosuppression, nephrotoxicity, and neurotoxicity.</td>
</tr>
<tr>
<td>Cytarabine (arabinofuranosyl cytidine)</td>
<td>Pyrimidine analog → inhibition of DNA polymerase.</td>
<td>Leukemias (AML), lymphomas.</td>
<td>Leukopenia, thrombocytopenia, megaloblastic anemia. CYTarabine causes panCYTopenia.</td>
</tr>
<tr>
<td>5-fluorouracil (5-FU)</td>
<td>Pyrimidine analog bioactivated to 5F-dUMP, which covalently complexes folic acid. This complex inhibits thymidylate synthase → dTMP → DNA synthesis.</td>
<td>Colon cancer, pancreatic cancer, basal cell carcinoma (topical).</td>
<td>Myelosuppression, which is not reversible with leucovorin (folinic acid).</td>
</tr>
<tr>
<td>Methotrexate (MTX)</td>
<td>Folic acid analog that competitively inhibits dihydrofolate reductase → dTMP → DNA synthesis.</td>
<td>Cancers: leukemias (ALL), lymphomas, choriocarcinoma, sarcomas. Non-neoplastic: ectopic pregnancy, medical abortion (with misoprostol), rheumatoid arthritis, psoriasis, IBD, vasculitis.</td>
<td>Myelosuppression, which is reversible with leucovorin “rescue.” Hepatotoxicity. Mucositis (e.g., mouth ulcers). Pulmonary fibrosis.</td>
</tr>
</tbody>
</table>

*All are S-phase specific.

![Diagram](image-url)
### Antitumor Antibiotics

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM</th>
<th>CLINICAL USE</th>
<th>TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dactinomycin</strong></td>
<td>Intercalates in DNA.</td>
<td>Wilms tumor, Ewing sarcoma, rhabdomyosarcoma.</td>
<td>Myelosuppression.</td>
</tr>
<tr>
<td><strong>Doxorubicin, daunorubicin</strong></td>
<td>Generate free radicals. Intercalate in DNA → breaks in DNA → ↓ replication.</td>
<td>Solid tumors, leukemias, lymphomas.</td>
<td>Cardiotoxicity (dilated cardiomyopathy), myelosuppression, alopecia. Toxic to tissues following extravasation. Dexrazoxane (iron chelating agent), used to prevent cardiotoxicity.</td>
</tr>
</tbody>
</table>

### Alkylating Agents

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM</th>
<th>CLINICAL USE</th>
<th>TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Busulfan</strong></td>
<td>Cross-links DNA.</td>
<td>CML. Also used to ablate patient’s bone marrow before bone marrow transplantation.</td>
<td>Severe myelosuppression (in almost all cases), pulmonary fibrosis, hyperpigmentation.</td>
</tr>
<tr>
<td><strong>Cyclophosphamide, ifosfamide</strong></td>
<td>Cross-link DNA at guanine N-7. Require bioactivation by liver.</td>
<td>Solid tumors, leukemia, lymphomas.</td>
<td>Myelosuppression; hemorrhagic cystitis, partially prevented with mesna (thiol group of mesna binds toxic metabolites).</td>
</tr>
<tr>
<td><strong>Nitrosoureas</strong></td>
<td>Require bioactivation. Cross blood-brain barrier → CNS. Cross-link DNA.</td>
<td>Brain tumors (including glioblastoma multiforme).</td>
<td>CNS toxicity (convulsions, dizziness, ataxia).</td>
</tr>
</tbody>
</table>
### Microtubule Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Clinical Use</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Paclitaxel, other taxols</strong></td>
<td>Hyperstabilize polymerized microtubules in M phase so that mitotic spindle cannot break down (anaphase cannot occur). “It is taxing to stay polymerized.”</td>
<td>Ovarian and breast carcinomas.</td>
<td>Myelosuppression, alopecia, hypersensitivity.</td>
</tr>
<tr>
<td><strong>Vincristine, vinblastine</strong></td>
<td>Vinca alkaloids that bind β-tubulin and inhibit its polymerization into microtubules → prevent mitotic spindle formation (M-phase arrest).</td>
<td>Solid tumors, leukemias, Hodgkin (vinblastine) and non-Hodgkin (vincristine) lymphomas.</td>
<td>Vincristine: neurotoxicity (areflexia, peripheral neuritis), paralytic ileus. Vinblastine blasts bone marrow (suppression).</td>
</tr>
</tbody>
</table>

### Cisplatin, carboplatin

- **Mechanism**: Cross-link DNA.
- **Clinical Use**: Testicular, bladder, ovary, and lung carcinomas.
- **Toxicity**: Nephrotoxicity, ototoxicity. Prevent nephrotoxicity with amifostine (free radical scavenger) and chloride (saline) diuresis.

### Etoposide, teniposide

- **Mechanism**: Etoposide inhibits topoisomerase II → DNA degradation.
- **Clinical Use**: Solid tumors (particularly testicular and small cell lung cancer), leukemias, lymphomas.
- **Toxicity**: Myelosuppression, GI upset, alopecia.

### Irinotecan, topotecan

- **Mechanism**: Inhibit topoisomerase I and prevent DNA unwinding and replication.
- **Clinical Use**: Colon cancer (irinotecan); ovarian and small cell lung cancers (topotecan).
- **Toxicity**: Severe myelosuppression, diarrhea.

### Hydroxyurea

- **Mechanism**: Inhibits ribonucleotide reductase → DNA Synthesis (S-phase specific).
- **Clinical Use**: Melanoma, CML, sickle cell disease (†HbF).
- **Toxicity**: Severe myelosuppression, GI upset.
### Prednisone, prednisolone

**MECHANISM**  
Various; bind intracytoplasmic receptor; alter gene transcription.

**CLINICAL USE**  
Most commonly used glucocorticoids in cancer chemotherapy. Used in CLL, non-Hodgkin lymphoma (part of combination chemotherapy regimen). Also used as immunosuppressants (e.g., in autoimmune diseases).

**TOXICITY**  
Cushing-like symptoms; weight gain, central obesity, muscle breakdown, cataracts, acne, osteoporosis, hypertension, peptic ulcers, hyperglycemia, psychosis.

---

### Bevacizumab

**MECHANISM**  
Monoclonal antibody against VEGF. Inhibits angiogenesis.

**CLINICAL USE**  
Solid tumors (colorectal cancer, renal cell carcinoma).

**TOXICITY**  
Hemorrhage, blood clots, and impaired wound healing.

---

### Erlotinib

**MECHANISM**  
EGFR tyrosine kinase inhibitor.

**CLINICAL USE**  
Non-small cell lung carcinoma.

**TOXICITY**  
Rash.

---

### Imatinib

**MECHANISM**  
Tyrosine kinase inhibitor of **BCR-ABL** (Philadelphia chromosome fusion gene in CML) and **c-kit** (common in GI stromal tumors).

**CLINICAL USE**  
CML, GI stromal tumors.

**TOXICITY**  
Fluid retention.

---

### Rituximab

**MECHANISM**  
Monoclonal antibody against CD20, which is found on most B-cell neoplasms.

**CLINICAL USE**  
Non-Hodgkin lymphoma, CLL, IBD, rheumatoid arthritis.

**TOXICITY**  
† risk of progressive multifocal leukoencephalopathy.

---

### Tamoxifen, raloxifene

**MECHANISM**  
Selective estrogen receptor modulators (SERMs)—receptor antagonists in breast and agonists in bone. Block the binding of estrogen to ER \( \oplus \) cells.

**CLINICAL USE**  
Breast cancer treatment (tamoxifen only) and prevention. Raloxifene also useful to prevent osteoporosis.

**TOXICITY**  
Tamoxifen—partial agonist in endometrium, which † the risk of endometrial cancer; “hot flashes.” Raloxifene—no † in endometrial carcinoma because it is an estrogen receptor antagonist in endometrial tissue.
Trastuzumab (Herceptin)

**MECHANISM**
Monoclonal antibody against HER-2 (c-erbB2), a tyrosine kinase receptor. Helps kill cancer cells that overexpress HER-2, through inhibition of HER2-initiated cellular signaling and antibody-dependent cytotoxicity.

**CLINICAL USE**
HER-2 ⊕ breast cancer and gastric cancer (tras2zumab).

**TOXICITY**
Cardiotoxicity. “Heartceptin” damages the heart.

Vemurafenib

**MECHANISM**
Small molecule inhibitor of BRAF oncogene ⊕ melanoma

**CLINICAL USE**
Metastatic melanoma.

Common chemotoxicities

- Cisplatin/Carboplatin → acoustic nerve damage (and nephrotoxicity)
- Vincristine → peripheral neuropathy
- Bleomycin, Busulfan → pulmonary fibrosis
- Doxorubicin → cardiotoxicity
- Trastuzumab → cardiotoxicity
- Cisplatin/Carboplatin → nephrotoxic (and acoustic nerve damage)
- CYclophosphamide → hemorrhagic cystitis
- 5-FU → myelosuppression
- 6-MP → myelosuppression
- Methotrexate → myelosuppression
“Rigid, the skeleton of habit alone upholds the human frame.”
—Virginia Woolf

“Beauty may be skin deep, but ugly goes clear to the bone.”
—Redd Foxx

“The function of muscle is to pull and not to push, except in the case of the genitals and the tongue.”
—Leonardo da Vinci
**Musculoskeletal, skin, and connective tissue—Anatomy and Physiology**

### Knee exam

<table>
<thead>
<tr>
<th>TEST</th>
<th>PROCEDURE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anterior drawer sign</strong></td>
<td>With patient supine, bending knee at 90-degree angle, anterior gliding of tibia due to ACL injury.</td>
</tr>
<tr>
<td><strong>Posterior drawer sign</strong></td>
<td>With patient supine, bending knee at 90-degree angle, posterior gliding of tibia due to PCL injury.</td>
</tr>
<tr>
<td><strong>Abnormal passive abduction</strong></td>
<td>With patient supine and knee either extended or at ~30-degree angle, lateral (valgus) force → medial space widening of tibia → MCL injury.</td>
</tr>
<tr>
<td><strong>Abnormal passive adduction</strong></td>
<td>With patient supine and knee either extended or at ~30-degree angle, medial (varus) force → lateral space widening of tibia → LCL injury.</td>
</tr>
</tbody>
</table>
| **McMurray test**         | With patient supine and knee internally and externally rotated during range of motion:  
  ▪ Pain, “popping” on external rotation → medial meniscal tear  
  ▪ Pain, “popping” on internal rotation → lateral meniscal tear |

### Common knee conditions

**“Unhappy triad”**

Common injury in contact sports due to lateral force applied to a planted leg. Classically, consists of damage to the ACL, MCL, and medial meniscus (attached to MCL); however, lateral meniscus injury is more common. Presents with acute knee pain and signs of joint injury/instability.

**Prepatellar bursitis**

“Housemaid’s knee” (A, left). Can be caused by repeated trauma or pressure from extensive kneeling.

**Baker cyst**

Popliteal fluid collection (A, right) commonly related to chronic joint disease.
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, assessed by “empty/full can” test.
- **Infraspinatus** (suprascapular nerve)—laterally rotates arm; pitching injury.
- **Teres minor** (axillary nerve)—adducts and laterally rotates arm.
- **Subscapularis** (upper and lower subscapular nerves)—medially rotates and adducts arm. Innervated primarily by C5-C6.

Overuse injuries of the elbow

| Medial epicondylitis (golfer’s elbow) | Repetitive flexion (forehand shots) or idiopathic → pain near medial epicondyle. |
| Lateral epicondylitis (tennis elbow)  | Repetitive extension (backhand shots) or idiopathic → pain near lateral epicondyle. |

Wrist bones

- Scaphoid, Lunate, Triquetrum,
  Pisiform, Hamate, Capitate, Trapezoid,
  Trapezium (So Long To Pinky, Here Comes The Thumb).
- Scaphoid (palpated in anatomic snuff box) is the most commonly fractured carpal bone and is prone to avascular necrosis owing to retrograde blood supply.
- Dislocation of lunate may cause acute carpal tunnel syndrome.
- A fall on an outstretched hand that damages the hook of the hamate can cause ulnar nerve injury.

Carpal tunnel syndrome

- Entrapment of median nerve in carpal tunnel; nerve compression → paresthesia, pain, and numbness in distribution of median nerve. Associated with pregnancy, rheumatoid arthritis, hypothyroidism; may be associated with repetitive use.

Guyon canal syndrome

- Compression of ulnar nerve at wrist or hand. Classically seen in cyclists due to pressure from handlebars.
### Upper extremity nerves

<table>
<thead>
<tr>
<th>NERVE</th>
<th>CAUSES OF INJURY</th>
<th>PRESENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axillary (C5-C6)</td>
<td>Fractured surgical neck of humerus; anterior dislocation of humerus</td>
<td>Flattened deltoid&lt;br&gt;Loss of arm abduction at shoulder (&gt; 15 degrees)&lt;br&gt;Loss of sensation over deltoid muscle and lateral arm</td>
</tr>
<tr>
<td>Musculocutaneous (C5-C7)</td>
<td>Upper trunk compression</td>
<td>Loss of forearm flexion and supination&lt;br&gt;Loss of sensation over lateral forearm</td>
</tr>
<tr>
<td>Radial (C5-T1)</td>
<td>Midshaft fracture of humerus; compression of axilla, e.g., due to crutches or sleeping with arm over chair (“Saturday night palsy”)</td>
<td>Wrist drop: loss of elbow, wrist, and finger extension&lt;br&gt;4 grip strength (wrist extension necessary for maximal action of flexors)&lt;br&gt;Loss of sensation over posterior arm/forearm and dorsal hand</td>
</tr>
<tr>
<td>Median (C5-T1)</td>
<td>Supracondylar fracture of humerus (proximal lesion); carpal tunnel syndrome and wrist laceration (distal lesion)</td>
<td>“Ape hand” and “Pope’s blessing”&lt;br&gt;Loss of wrist flexion, flexion of lateral fingers, thumb opposition, lumbricals of 2nd and 3rd digits&lt;br&gt;Loss of sensation over thenar eminence and dorsal and palmar aspects of lateral 31/2 fingers with proximal lesion&lt;br&gt;Tinel sign (tingling on percussion) in carpal tunnel syndrome</td>
</tr>
<tr>
<td>Ulnar (C8-T1)</td>
<td>Fracture of medial epicondyle of humerus “funny bone” (proximal lesion); fractured hook of hamate (distal lesion)</td>
<td>“Ulnar claw” on digit extension&lt;br&gt;Radial deviation of wrist upon flexion (proximal lesion)&lt;br&gt;Loss of wrist flexion, flexion of medial fingers, abduction and adduction of fingers (interossei), actions of medial 2 lumbrical muscles&lt;br&gt;Loss of sensation over medial 11/2 fingers including hypothenar eminence</td>
</tr>
<tr>
<td>Recurrent branch of median nerve (C5-T1)</td>
<td>Superficial laceration of palm</td>
<td>“Ape hand”&lt;br&gt;Loss of thenar muscle group: opposition, abduction, and flexion of thumb&lt;br&gt;No loss of sensation</td>
</tr>
</tbody>
</table>

![Nerve Diagram](image-url)
### Brachial Plexus Lesions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Injury</th>
<th>Causes</th>
<th>Muscle Deficit</th>
<th>Functional Deficit</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erb Palsy</strong></td>
<td>Traction or tear of <strong>upper</strong> trunk: C5-C6 roots</td>
<td>Infants—lateral traction on neck during delivery</td>
<td>Deltoid, infraspinatus</td>
<td>Abduction (arm hangs by side)</td>
<td><a href="#">Erb palsy image</a></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adults—trauma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Infraspinatus</td>
<td>Lateral rotation (arm medially rotated)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Biceps brachii</td>
<td>Flexion, supination (arm extended and pronated)</td>
</tr>
<tr>
<td><strong>Klumpke Palsy</strong></td>
<td>Traction or tear of <strong>lower</strong> trunk: C8-T1 root</td>
<td>Infants—upward force on arm during delivery Adults—trauma (e.g., grabbing a tree branch to break a fall)</td>
<td>Intrinsic hand muscles: lumbricals, interossei, thenar, hypothenar</td>
<td>Total claw hand: lumbricals normally flex MCP joints and extend DIP and PIP joints</td>
<td><a href="#">Klumpke palsy image</a></td>
</tr>
<tr>
<td><strong>Thoracic Outlet Syndrome</strong></td>
<td>Compression of <strong>lower</strong> trunk and subclavian vessels</td>
<td>Cervical rib, Pancoast tumor</td>
<td>Same as Klumpke palsy</td>
<td>Atrophy of intrinsic hand muscles; ischemia, pain, and edema due to vascular compression</td>
<td></td>
</tr>
<tr>
<td><strong>Winged Scapula</strong></td>
<td>Lesion of long thoracic nerve</td>
<td>Axillary node dissection after mastectomy, stab wounds</td>
<td>Serratus anterior</td>
<td>Inability to anchor scapula to thoracic cage → cannot abduct arm above horizontal position</td>
<td><a href="#">Winged scapula image</a></td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>PRESENTATION</th>
<th>CONTEXT</th>
<th>Extending fingers at rest</th>
<th>Making a fist</th>
<th>Extending fingers at rest</th>
<th>Making a fist</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOCATION OF LESION</td>
<td>Distal ulnar nerve</td>
<td>Proximal median nerve</td>
<td>Distal median nerve</td>
<td>Proximal ulnar nerve</td>
<td></td>
</tr>
<tr>
<td>SIGN</td>
<td>“Ulnar claw”</td>
<td>“Pope’s blessing”</td>
<td>“Median claw”</td>
<td>“OK gesture” (with digits 1–3 flexed)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Atrophy of the thenar eminence (unopposable thumb → “ape hand”) can be seen in median nerve lesions, while atrophy of the hypothenar eminence can be seen in ulnar nerve lesions.

Hand muscles
Thenar (median)—Opponens pollicis, Abductor pollicis brevis, Flexor pollicis brevis, superficial head (deep head by ulnar nerve).
Hypothenar (ulnar)—Opponens digiti minimi, Abductor digiti minimi, Flexor digiti minimi brevis.
Dorsal interossei—abduct the fingers.
Palmar interossei—adduct the fingers.
Lumbricals—flex at the MCP joint, extend PIP and DIP joints.

Both groups perform the same functions:
Oppose, Abduct, and Flex (OAF).

DAB = Dorsals ABduct.
PAD = Palmar ADduct.
### Lower extremity nerves

<table>
<thead>
<tr>
<th>NERVE</th>
<th>CAUSE OF INJURY</th>
<th>PRESENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obturator (L2−L4)</td>
<td>Pelvic surgery</td>
<td>↓ thigh sensation (medial) and ↓ adduction.</td>
</tr>
<tr>
<td>Femoral (L2−L4)</td>
<td>Pelvic fracture</td>
<td>↓ thigh flexion and leg extension.</td>
</tr>
<tr>
<td>Common peroneal</td>
<td>Trauma or compression of lateral aspect of leg, fibular neck fracture</td>
<td>Foot drop—inverted and plantarflexed at rest, loss of eversion and dorsiflexion. “Steppage gait.” Loss of sensation on dorsum of foot.</td>
</tr>
<tr>
<td>(L4−S2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tibial (L4−S3)</td>
<td>Knee trauma, Baker cyst (proximal lesion); tarsal tunnel syndrome (distal lesion)</td>
<td>Inability to curl toes and loss of sensation on sole of foot. In proximal lesions, foot everted at rest with loss of inversion and plantarflexion.</td>
</tr>
<tr>
<td>Superior gluteal</td>
<td>Iatrogenic injury during intramuscular injection to upper medial gluteal region</td>
<td>Trendelenburg sign/gait—pelvis tilts because weight-bearing leg cannot maintain alignment of pelvis through hip abduction (superior nerve → medius and minimus). Lesion is contralateral to the side of the hip that drops, ipsilateral to extremity on which the patient stands.</td>
</tr>
<tr>
<td>(L4−S1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior gluteal</td>
<td>Posterior hip dislocation</td>
<td>Difficulty climbing stairs, rising from seated position. Loss of hip extension (inferior nerve → maximus).</td>
</tr>
<tr>
<td>(L5−S2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Superior gluteal nerve innervates gluteus medius and minimus. Inferior gluteal nerve innervates gluteus maximus.

PED = Peroneal Everts and Dorsiflexes; if injured, foot drop PED.

TIP = Tibial Inverts and Plantarflexes; if injured, can’t stand on TIP toes.

Sciatic nerve (L4−S3) innervates posterior thigh, splits into common peroneal and tibial nerves.

Pudendal nerve (S2−S4) innervates perineum. Can be blocked with local anesthetic during childbirth using the ischial spine as a landmark for injection.
Signs of lumbosacral radiculopathy

Paresthesias and weakness in distribution of specific lumbar or sacral spinal nerves. Often due to intervertebral disc herniation in which the nerve association with the inferior vertebral body is impinged (e.g., herniation of L3–L4 disc affects the L4 spinal nerve).

Intervertebral discs generally herniate posterolaterally, due to the thin posterior longitudinal ligament and thicker anterior longitudinal ligament along the midline of the vertebral bodies.

<table>
<thead>
<tr>
<th>DISC LEVEL</th>
<th>FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>L3–L4</td>
<td>Weakness of knee extension, ↓ patellar reflex</td>
</tr>
<tr>
<td>L4–L5</td>
<td>Weakness of dorsiflexion, difficulty in heel-walking</td>
</tr>
<tr>
<td>L5–S1</td>
<td>Weakness of plantarflexion, difficulty in toe-walking, ↓ Achilles reflex</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>LOCATION</th>
<th>NERVE</th>
<th>ARTERY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axilla/lateral thorax</td>
<td>Long thoracic</td>
<td>Lateral thoracic</td>
</tr>
<tr>
<td>Surgical neck of humerus</td>
<td>Axillary</td>
<td>Posterior circumflex</td>
</tr>
<tr>
<td>Midshaft of humerus</td>
<td>Radial</td>
<td>Deep brachial</td>
</tr>
<tr>
<td>Distal humerus/cubital fossa</td>
<td>Median</td>
<td>Brachial</td>
</tr>
<tr>
<td>Popliteal fossa</td>
<td>Tibial</td>
<td>Popliteal</td>
</tr>
<tr>
<td>Posterior to medial malleolus</td>
<td>Tibial</td>
<td>Posterior tibial</td>
</tr>
</tbody>
</table>
Muscle conduction to contraction

1. Action potential depolarization opens presynaptic voltage-gated Ca$^{2+}$ channels, inducing neurotransmitter release. T-tubules (extensions of plasma membrane juxtaposed with terminal cisternae) are part of the sarcoplasmic reticulum.

2. Postsynaptic ligand binding leads to muscle cell depolarization in the motor end plate. In skeletal muscle, 1 T-tubule + 2 terminal cisternae = triad.

3. Depolarization travels along muscle cell and down the T-tubule. In cardiac muscle, 1 T-tubule + 1 terminal cisterna = diad.

4. Depolarization of the voltage-sensitive dihydropyridine receptor, mechanically coupled to the ryanodine receptor on the sarcoplasmic reticulum, induces a conformational change, causing Ca$^{2+}$ release from sarcoplasmic reticulum.

5. Released Ca$^{2+}$ binds to troponin C, causing a conformational change that moves tropomyosin out of the myosin-binding groove on actin filaments.

6. Myosin releases bound ADP and inorganic PO$_4^{3-}$ -- displacement of myosin on the actin filament (power stroke). Contraction results in shortening of H and I bands and between Z lines (HIZ shrinkage), but the A band remains the same length (A band is Always the same length).


Types of muscle fibers

**Type 1 muscle**

- Slow twitch; red fibers resulting from
- ↑ mitochondria and myoglobin concentration
- ↑ oxidative phosphorylation → sustained contraction.
- Think “1 slow red ox.”

**Type 2 muscle**

- Fast twitch; white fibers resulting from
- ↑ mitochondria and myoglobin concentration
- ↑ anaerobic glycolysis; weight training results in hypertrophy of fast-twitch muscle fibers.
Smooth muscle contraction

Bone formation

Endochondral ossification

Bones of axial and 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.

Membranous ossification

Bones of calvarium and facial bones. Woven bone formed directly without cartilage. Later remodeled to lamellar bone.

Cell biology of bone

Osteoblasts

Build bone by secreting collagen and catalyzing mineralization. Differentiate from mesenchymal stem cells in periosteum.

Osteoclasts

Multinucleated cells that dissolve bone by secreting acid and collagenases. Differentiate from monocytes, macrophages.

Parathyroid hormone

At low, intermittent levels, exerts anabolic effects (building bone) on osteoblasts and osteoclasts (indirect). Chronically ↑ PTH levels (1° hyperparathyroidism) cause catabolic effects (osteitis fibrosa cystica).

Estrogen

Estrogen inhibits apoptosis in bone-forming osteoblasts and induces apoptosis in bone-resorbing osteoclasts. Estrogen deficiency (surgical or postmenopausal), excess cycles of remodeling, and bone resorption lead to osteoporosis.
Achondroplasia  
Failure of longitudinal bone growth (endochondral ossification) → short limbs. Membranous ossification is not affected → large head relative to limbs. Constitutive activation of fibroblast growth factor receptor (FGFR3) actually inhibits chondrocyte proliferation. > 85% of mutations occur sporadically; autosomal dominant with full penetrance (homozygosity is lethal). Most common cause of dwarfism.

Primary osteoporosis  
Trabecular (spongy) bone loses mass and interconnections despite normal bone mineralization and lab values (serum Ca2+ and PO43−). Diagnosed by a bone mineral density test (DEXA) with a T-score of ≤−2.5. Can be caused by long-term exogenous steroid use, anticonvulsants, anticoagulants, thyroid replacement therapy. Can lead to vertebral compression fractures—acute back pain, loss of height, kyphosis. Also can present with fractures of femoral neck, distal radius (Colles fracture).

Type I (post-menopausal)  
† bone resorption due to ↓ estrogen levels.  
Prophylaxis: regular weight-bearing exercise and adequate Ca2+ and vitamin D intake throughout adulthood.  
Treatment: bisphosphonates, PTH analogs, SERMs, rarely calcitonin; denosumab (monoclonal antibody against RANKL).

Type II (senile)  
Affects men and women > 70 years old.  
Mild compression fracture  
Normal vertebrae

Osteopetrosis (marble bone disease)  
Failure of normal bone resorption due to defective osteoclasts → thickened, dense bones that are prone to fracture. Bone fills marrow space → pancytopenia, extramedullary hematopoiesis. Mutations (e.g., carbonic anhydrase II) impair ability of osteoclast to generate acidic environment necessary for bone resorption. X-rays show bone-in-bone appearance A. Can result in cranial nerve impingement and palsies as a result of narrowed foramina. Bone marrow transplant is potentially curative as osteoclasts are derived from monocytes.

Osteomalacia/rickets  
Vitamin D deficiency → osteomalacia in adults; rickets in children. Due to defective mineralization/calcification of osteoid → soft bones that bow out.  
↓ vitamin D → ↓ serum Ca2+ → ↑ PTH secretion → ↓ serum PO43−.  
Hyperactivity of osteoblasts → ↑ ALP (osteoblasts require alkaline environment).
Paget disease of bone (osteitis deformans)

Common, localized disorder of bone remodeling caused by ↑ in both osteoblastic and osteoclastic activity. Serum Ca^{2+}, phosphorus, and PTH levels are normal. ↑ ALP. Mosaic pattern of woven and lamellar bone: long bone chalk-stick fractures. ↑ blood flow from arteriovenous shunts may cause high-output heart failure. ↑ risk of osteogenic sarcoma.

Hat size can be increased; hearing loss is common due to auditory foramen narrowing. Stages of Paget disease:
- Lytic—osteoclasts
- Mixed—osteoclasts + osteoblasts
- Sclerotic—osteoblasts
- Quiescent—minimal osteoclast/osteoblast activity

Osteonecrosis (avascular necrosis)

Infarction of bone and marrow, usually very painful. Most common site is femoral head (due to insufficiency of medial circumflex femoral artery). Causes include Alcoholism, Sickle cell disease, Storage, Exogenous/Endogenous corticosteroids, Pancreatitis, Trauma, Idiopathic (Legg-Calvé-Perthes disease), Caisson (“the bends”)—ASEPTIC.
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Serum Ca&lt;sup&gt;2+&lt;/sup&gt;</th>
<th>PO&lt;sub&gt;4&lt;/sub&gt;&lt;sup&gt;3−&lt;/sup&gt;</th>
<th>ALP</th>
<th>PTH</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>↓ bone mass</td>
</tr>
<tr>
<td>Osteopetrosis</td>
<td>−/4</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>Dense, brittle bones. Ca&lt;sup&gt;2+&lt;/sup&gt; ↓ in severe, malignant disease</td>
</tr>
<tr>
<td>Paget disease of bone</td>
<td>−</td>
<td>−</td>
<td>↑</td>
<td>−</td>
<td>Abnormal “mosaic” bone architecture</td>
</tr>
<tr>
<td>Osteomalacia/rickets</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>Soft bones</td>
</tr>
<tr>
<td>Hypervitaminosis D</td>
<td>↑</td>
<td>↑</td>
<td>−</td>
<td>↓</td>
<td>Caused by oversupplementation or granulomatous disease (e.g., sarcoidosis)</td>
</tr>
<tr>
<td>Osteitis fibrosa cystica</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>“Brown tumors” due to fibrous replacement of bone, subperiosteal thinning</td>
</tr>
<tr>
<td>1° hyperparathyroidism</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>Idiopathic or parathyroid hyperplasia, adenoma, carcinoma</td>
</tr>
<tr>
<td>2° hyperparathyroidism</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Often as compensation for ESRD (↓ PO&lt;sub&gt;4&lt;/sub&gt;&lt;sup&gt;3−&lt;/sup&gt; excretion and production of activated vitamin D)</td>
</tr>
</tbody>
</table>
### Primary bone tumors

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Epidemiology/Location</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benign tumors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giant cell tumor</td>
<td>20–40 years old.</td>
<td>Locally aggressive benign tumor often around knee.</td>
</tr>
<tr>
<td></td>
<td>Epiphyseal end of long bones.</td>
<td>“Soap bubble” appearance on x-ray A.</td>
</tr>
<tr>
<td></td>
<td>“Osteoclastoma.”</td>
<td>Multinucleated giant cells.</td>
</tr>
<tr>
<td>Osteochondroma</td>
<td>Most common benign tumor (an exostosis of the bone B).</td>
<td>Mature bone with cartilaginous (chondroid) cap.</td>
</tr>
<tr>
<td></td>
<td>Males &lt; 25 years old.</td>
<td>Rarely transforms to chondrosarcoma.</td>
</tr>
<tr>
<td><strong>Malignant tumors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>2nd most common 1° malignant bone tumor (after multiple myeloma).</td>
<td>Codman triangle (from elevation of periosteum) or sunburst pattern on x-ray.</td>
</tr>
<tr>
<td></td>
<td>Bimodal distribution: 10–20 years old (1°), &gt; 65 (2°).</td>
<td>Aggressive. Treat with surgical en bloc resection (with limb salvage) and chemotherapy.</td>
</tr>
<tr>
<td></td>
<td>Metaphysis of long bones, often around knee C.</td>
<td></td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>Boys &lt; 15 years old.</td>
<td>Anaplastic small blue cell malignant tumor D.</td>
</tr>
<tr>
<td></td>
<td>Commonly appears in diaphysis of long bones, pelvis, scapula, ribs.</td>
<td>Extremely aggressive with early metastases, but responsive to chemotherapy.</td>
</tr>
<tr>
<td></td>
<td>“Onion skin” periosteal reaction in bone.</td>
<td>Associated with t(11;22) translocation causing fusion protein EWS-FLI 1.</td>
</tr>
<tr>
<td></td>
<td>11 + 22 = 33 (Patrick Ewing’s jersey number).</td>
<td></td>
</tr>
</tbody>
</table>
### Osteoarthritis and rheumatoid arthritis

<table>
<thead>
<tr>
<th></th>
<th>Osteoarthritis</th>
<th>Rheumatoid arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ETIOLOGY</strong></td>
<td>Mechanical—joint wear and tear destroys articular cartilage.</td>
<td>Autoimmune—Inflammatory destruction of synovial joints. Mediated by cytokines and type III and type IV hypersensitivity reactions.</td>
</tr>
<tr>
<td><strong>JOINT FINDINGS</strong></td>
<td>Subchondral cysts, sclerosis, osteophytes (bone spurs, eburnation (polished, ivory-like appearance of bone), synovitis, Heberden nodes (DIP), Bouchard nodes (PIP). No MCP involvement.</td>
<td>Pannus (inflammatory granulation tissue) formation in joints (MCP, PIP), subcutaneous rheumatoid nodules (fibrinoid necrosis), ulnar deviation of fingers, subluxation. Rare DIP involvement.</td>
</tr>
<tr>
<td><strong>PREDISPOERING FACTORS</strong></td>
<td>Age, obesity, joint trauma.</td>
<td>Females &gt; males. 80% have rheumatoid factor (anti-IgG antibody); anti–cyclic citrullinated peptide antibody is more specific. Strong association with HLA-DR4.</td>
</tr>
<tr>
<td><strong>CLASSIC PRESENTATION</strong></td>
<td>Pain in weight-bearing joints after use (e.g., at the end of the day), improving with rest. Knee cartilage loss begins medially (“bowlegged”). Noninflammatory. No systemic symptoms.</td>
<td>Morning stiffness lasting &gt; 30 minutes and improving with use, symmetric joint involvement, systemic symptoms (fever, fatigue, weight loss, pleuritis, pericarditis).</td>
</tr>
<tr>
<td><strong>TREATMENT</strong></td>
<td>Acetaminophen, NSAIDs, intra-articular glucocorticoids.</td>
<td>NSAIDs, glucocorticoids, disease-modifying agents (methotrexate, sulfasalazine), biologics (TNF-α inhibitors).</td>
</tr>
</tbody>
</table>

---

**Figures:**

- **A** Osteoarthritis. X-ray of hands shows joint space narrowing and sclerosis (arrows).
- **B** Rheumatoid arthritis. Note boutonnière deformities of PIP joints with ulnar deviation.
Sjögren syndrome

Autoimmune disorder characterized by destruction of exocrine glands (especially lacrimal and salivary) by lymphocytic infiltrates. Predominantly affects females 40–60 years old.

Findings:
- Inflammatory joint pain
- Xerophthalmia (dry tear production and subsequent corneal damage)
- Xerostomia (dry saliva production)
- Presence of antinuclear antibodies: SS-A (anti-Ro) and/or SS-B (anti-La)
- Bilateral parotid enlargement

Gout

Findings

Acute inflammatory monoarthritis caused by precipitation of monosodium urate crystals in joints. More common in males. Associated with hyperuricemia, which can be caused by:
- Underexcretion of uric acid (90% of patients)—largely idiopathic; can be exacerbated by certain medications (e.g., thiazide diuretics).
- Overproduction of uric acid (10% of patients)—Lesch-Nyhan syndrome, PRPP excess, fast cell turnover (e.g., tumor lysis syndrome), von Gierke disease.

Crystals are needle shaped and birefringent under polarized light (yellow under parallel light, blue under perpendicular light).

Symptoms

Asymmetric joint distribution. Joint is swollen, red, and painful. Classic manifestation is painful MTP joint of big toe (podagra). Tophus formation (often on external ear, olecranon bursa, or Achilles tendon). Acute attack tends to occur after a large meal or alcohol consumption (alcohol metabolites compete for same excretion sites in kidney as uric acid secretion and subsequent buildup in blood).

Treatment

Acute: NSAIDs (e.g., indomethacin), glucocorticoids, colchicine.
Chronic (preventive): xanthine oxidase inhibitors (e.g., allopurinol, febuxostat).
Pseudogout

Presents with pain and effusion in a joint, caused by deposition of calcium pyrophosphate crystals within the joint space (chondrocalcinosis on x-ray). Forms basophilic, rhomboid crystals that are weakly birefringent under polarized light. Usually affects large joints (classically the knee). > 50 years old; both sexes affected equally. Diseases associated with pseudogout include hemochromatosis, hyperparathyroidism, osteoarthritis. Treatment includes NSAIDs for sudden, severe attacks; glucocorticoids; colchicine for prophylaxis.

Gout—crystals are yellow when parallel (||) to the light.
Pseudogout—crystals are blue when parallel (||) to the light.
Infectious arthritis

*S. aureus*, *Streptococcus*, and *Neisseria gonorrhoeae* are common causes. Gonococcal arthritis is an STD that presents as a migratory arthritis with an asymmetric pattern. Affected joint is swollen, red, and painful. STD = Synovitis (e.g., knee), Tenosynovitis (e.g., hand), and Dermatitis (e.g., pustules).

Seronegative spondyloarthropathies

Arthritis without rheumatoid factor (no anti-IgG antibody). Strong association with HLA-B27 (gene that codes for MHC class I). Occurs more often in males.

**Psoriatic arthritis**


**Ankylosing spondylitis**

Chronic inflammatory disease of spine and sacroiliac joints → ankylosis (stiff spine due to fusion of joints), uveitis, aortic regurgitation.

**Inflammatory bowel disease**

Crohn disease and ulcerative colitis are often accompanied by ankylosing spondylitis or peripheral arthritis.

**Reactive arthritis (Reiter syndrome)**

Classic triad:
- Conjunctivitis and anterior uveitis
- Urethritis
- Arthritis

“Can’t see, can’t pee, can’t bend my knee.” Post-GI (*Shigella, Salmonella, Yersinia, Campylobacter*) or *Chlamydia* infections.
Systemic lupus erythematosus

**SYMPTOMS**
- Classic presentation: rash, joint pain, and fever, most commonly in a female of reproductive age and African descent.
- Libman-Sacks endocarditis—nonbacterial, wart-like vegetations on both sides of valve.
- Lupus nephritis (type III hypersensitivity reaction):
  - Nephritic—diffuse proliferative glomerulonephritis
  - Nephrotic—membranous glomerulonephritis
- Libman-Sacks endocarditis
- Rash (malar \(\Box\) or discoid)
- Arthritis
- Soft tissues/serositis
- Hematologic disorders (e.g., cytopenias)
- Oral/nasopharyngeal ulcers
- Renal disease, Raynaud phenomenon
- Photosensitivity, Positive VDRL/RPR
- Antinuclear antibodies
- Immunosuppressants
- Neurologic disorders (e.g. seizures, psychosis)

**FINDINGS**
- Antinuclear antibodies (ANA) Sensitive, not specific
- Anti-dsDNA antibodies Specific, poor prognosis (renal disease)
- Anti-Smith antibodies Specific, not prognostic (directed against snRNPs)
- Antihistone antibodies Sensitive for drug-induced lupus
- \(\downarrow\) C3, C4, and CH50 due to immune complex formation.

**TREATMENT**
- NSAIDs, steroids, immunosuppressants, hydroxychloroquine.

**Antiphospholipid syndrome**
- 1\textsuperscript{st} or 2\textsuperscript{nd} autoimmune disorder (most commonly in SLE).
- Diagnose based on clinical criteria including history of thrombosis (arterial or venous) or spontaneous abortion along with laboratory findings of lupus anticoagulant, anticardiolipin, anti-\(\beta_2\) glycoprotein antibodies.
- Treat with systemic anticoagulation.
- Anticardiolipin antibodies and lupus anticoagulant can cause false-positive VDRL and prolonged PTT.
Sarcoidosis

Characterized by immune-mediated, widespread noncaseating granulomas, elevated serum ACE levels, and elevated CD4+/CD8+ ratio. Common in black females. Often asymptomatic except for enlarged lymph nodes. Findings on CXR of bilateral adenopathy and coarse reticular opacities. CT of the chest better demonstrates the extensive hilar and mediastinal adenopathy.

Associated with restrictive lung disease (interstitial fibrosis), erythema nodosum, lupus pernio, Bell palsy, epithelioid granulomas containing microscopic Schaumann and asteroid bodies, uveitis, hypercalcemia (due to 1α-hydroxylase–mediated vitamin D activation in macrophages).

Treatment: steroids.

Polymyalgia rheumatica

| SYMPTOMS | Pain and stiffness in shoulders and hips, often with fever, malaise, weight loss. Does not cause muscular weakness. More common in women > 50 years old; associated with temporal (giant cell) arteritis. |
| FINDINGS | ↑ ESR, ↑ CRP, normal CK. |
| TREATMENT | Rapid response to low-dose corticosteroids. |

Fibromyalgia

Most commonly seen in females 20–50 years old. Chronic, widespread musculoskeletal pain associated with stiffness, paresthesias, poor sleep, fatigue. Treat with regular exercise, antidepressants (TCAs, SNRIs), anticonvulsants.
Polymyositis/dermatomyositis

Polymyositis: Progressive symmetric proximal muscle weakness, characterized by endomysial inflammation with CD8+ T cells. Most often involves shoulders.

Dermatomyositis: Similar to polymyositis, but also involves malar rash (similar to SLE), Gottron papules, heliotrope (erythematous periorbital) rash, “shawl and face” rash, “mechanic’s hands.” Risk of occult malignancy. Perimysial inflammation and atrophy with CD4+ T cells.

Polymyositis:

- CK, ANA, anti-Jo-1, anti-SRP, anti-Mi-2 antibodies. Treatment: steroids followed by long-term immunosuppressant therapy (e.g., methotrexate).

Neuromuscular junction diseases

<table>
<thead>
<tr>
<th>Myasthenia gravis</th>
<th>Lambert-Eaton myasthenic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FREQUENCY</strong></td>
<td>Most common NMJ disorder</td>
</tr>
<tr>
<td><strong>PATHOPHYSIOLOGY</strong></td>
<td>Autoantibodies to postsynaptic ACh receptor</td>
</tr>
<tr>
<td><strong>CLINICAL</strong></td>
<td>Proximal muscle weakness, autonomic symptoms (dry mouth, impotence)</td>
</tr>
<tr>
<td><strong>ASSOCIATED WITH</strong></td>
<td>Thymoma, thymic hyperplasia</td>
</tr>
<tr>
<td><strong>ACH INHIBITOR ADMINISTRATION</strong></td>
<td>Reversal of symptoms</td>
</tr>
<tr>
<td></td>
<td>Small cell lung cancer</td>
</tr>
<tr>
<td></td>
<td>Minimal effect</td>
</tr>
</tbody>
</table>

Myositis ossificans

Metaplasia of skeletal muscle into bone following muscular trauma. Most often seen in upper or lower extremity. May present as suspicious “mass” at site of known trauma or as incidental finding on radiography.

Myositis ossificans.

Heterotopic ossification of elbow (arrows) after injury and prosthetic radial head replacement.
Scleroderma (systemic sclerosis)

Triad of autoimmunity, noninflammatory vasculopathy, and collagen deposition with fibrosis. Commonly sclerosis of skin, manifesting as puffy, taut skin without wrinkles, fingertip pitting. Also sclerosis of renal, pulmonary (most common cause of death), cardiovascular, GI systems. 75% female. 2 major types:

- **Diffuse scleroderma**—widespread skin involvement, rapid progression, early visceral involvement. Associated with anti-Scl-70 antibody (anti-DNA topoisomerase I antibody).

- **Limited scleroderma**—limited skin involvement confined to fingers and face. Also with CREST involvement: Calcinosis, Raynaud phenomenon, Esophageal dysmotility, Sclerodactyly, and Telangiectasia. More benign clinical course. Associated with anti-centromere antibody.

Epidermis layers

Skin has 3 layers: epidermis, dermis, subcutaneous fat (hypodermis, subcutis). From surface to base:

- **Stratum Corneum** (keratin)
- **Stratum Lucidum**
- **Stratum Granulosum**
- **Stratum Spinosum** (desmosomes)
- **Stratum Basale** (stem cell site)

Californians Like Girls in String Bikinis.
Epithelial cell junctions

- **Tight junction** (zonula occludens)—prevents paracellular movement of solutes; composed of claudins and occludins.
- **Adherens junction** (zonula adherens)—below tight junction, forms “belt” connecting actin cytoskeletons of adjacent cells with E-cadherins (Ca²⁺-dependent adhesion proteins). Loss of E-cadherin promotes metastasis.
- **Desmosome** (macula adherens)—structural support via keratin interactions. Autoantibodies in pemphigus vulgaris.
- **Gap junction**—channel proteins called connexons permit electrical and chemical communication between cells.

**Integrins**—membrane proteins that maintain integrity of basolateral membrane by binding to collagen and laminin in basement membrane.

**Hemidesmosome**—connects keratin in basal cells to underlying basement membrane. Autoantibodies in bullous pemphigoid. (Hemidesmosomes are down “bullo”.

---

**Epidermal cell junctions**

**Apical**
- E-cadherin
- Actin filaments
- Keratin
- Desmoplakin
- Connexon with central channel

**Basolateral**
- Cell membrane
- Basement membrane
- Hemidesmosomes

**Integrins**—membrane proteins that maintain integrity of basolateral membrane by binding to collagen and laminin in basement membrane.

---

**Dermatologic macroscopic terms (morphology)**

<table>
<thead>
<tr>
<th>LESION</th>
<th>CHARACTERISTICS</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macule</td>
<td>Flat lesion with well-circumscribed change in skin color &lt; 1 cm</td>
<td>Freckle, labial macule A</td>
</tr>
<tr>
<td>Patch</td>
<td>Macule &gt; 1 cm</td>
<td>Large birthmark (congenital nevus) B</td>
</tr>
<tr>
<td>Papule</td>
<td>Elevated solid skin lesion &lt; 1 cm</td>
<td>Mole (nevus) C, acne</td>
</tr>
<tr>
<td>Plaque</td>
<td>Papule &gt; 1 cm</td>
<td>Psoriasis D</td>
</tr>
<tr>
<td>Vesicle</td>
<td>Small fluid-containing blister &lt; 1 cm</td>
<td>Chickenpox (varicella), shingles (zoster) E</td>
</tr>
<tr>
<td>Bulla</td>
<td>Large fluid-containing blister &gt; 1 cm</td>
<td>Bullous pemphigoid F</td>
</tr>
<tr>
<td>Pustule</td>
<td>Vesicle containing pus</td>
<td>Pustular psoriasis G</td>
</tr>
<tr>
<td>Wheal</td>
<td>Transient smooth papule or plaque</td>
<td>Hives (urticaria) H</td>
</tr>
<tr>
<td>Scale</td>
<td>Flaking off of stratum corneum</td>
<td>Eczema, psoriasis, SCC I</td>
</tr>
<tr>
<td>Crust</td>
<td>Dry exudate</td>
<td>Impetigo J</td>
</tr>
</tbody>
</table>
### Dermatologic microscopic terms

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Characteristics</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperkeratosis</td>
<td>↑ thickness of stratum corneum</td>
<td>Psoriasis, calluses</td>
</tr>
<tr>
<td>Parakeratosis</td>
<td>Hyperkeratosis with retention of nuclei in stratum corneum</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>Spongiosis</td>
<td>Epidermal accumulation of edematous fluid in intercellular spaces</td>
<td>Eczematous dermatitis</td>
</tr>
<tr>
<td>Acantholysis</td>
<td>Separation of epidermal cells</td>
<td>Pemphigus vulgaris</td>
</tr>
<tr>
<td>Acanthosis</td>
<td>Epidermal hyperplasia (↑ spinous)</td>
<td>Acanthosis nigricans</td>
</tr>
</tbody>
</table>

### Pigmented skin disorders

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albinism</td>
<td>Normal melanocyte number with ↓ melanin production due to ↓ tyrosinase activity or defective tyrosine transport. Can also be caused by failure of neural crest cell migration during development. ↑ risk of skin cancer.</td>
</tr>
<tr>
<td>Melasma (chloasma)</td>
<td>Hyperpigmentation associated with pregnancy (“mask of pregnancy”) or OCP use.</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>Irregular areas of complete depigmentation. Caused by autoimmune destruction of melanocytes.</td>
</tr>
</tbody>
</table>

![Images of skin conditions](image-url)
Common skin disorders

**Acne**
Obstructive and inflammatory disease of the pilosebaceous unit predominantly found on the face and trunk. Most common in adolescents but can occur at any age.

**Atopic dermatitis (eczema)**
Pruritic eruption, commonly on skin flexures. Often associated with other atopic diseases (asthma, allergic rhinitis). Usually starts on the face in infancy and often appears in antecubital fossae thereafter.

**Allergic contact dermatitis**
Type IV hypersensitivity reaction that follows exposure to allergen. Lesions occur at site of contact (e.g., nickel, poison ivy, neomycin).

**Melanocytic nevus**
Common mole. Benign, but melanoma can arise in congenital or atypical moles. Intradermal nevi are papular. Junctional nevi are flat macules.

**Psoriasis**
Papules and plaques with silvery scaling, especially on knees and elbows. Acanthosis with parakeratotic scaling (nuclei still in stratum corneum). Stratum spinosum, stratum granulosum. Auspitz sign (arrow in)—pinpoint bleeding spots from exposure of dermal papillae when scales are scraped off. Can be associated with nail pitting and psoriatic arthritis.

**Rosacea**
Inflammatory facial skin disorder characterized by erythematous papules and pustules, but no comedones. May be associated with facial flushing in response to external stimuli (e.g., alcohol, heat). Chronic inflammatory changes may result in rhinophyma (bulbous deformation of nose).

**Seborrheic keratosis**
Flat, greasy, pigmented squamous epithelial proliferation with keratin-filled cysts (horn cysts). Looks “stuck on.” Lesions occur on head, trunk, and extremities. Common benign neoplasm of older persons. Leser-Trelat sign—sudden appearance of multiple seborrheic keratoses, indicating an underlying malignancy (e.g., GI, lymphoid).

**Verrucae**

**Urticaria**
Hives. Pruritic wheals that form after mast cell degranulation. Characterized by superficial dermal edema and lymphatic channel dilation.
Skin infections

Bacterial infections

**Impetigo**
Very superficial skin infection. Usually from *S. aureus* or *S. pyogenes*. Highly contagious. Honey-colored crusting. **Bullous impetigo** has bullae and is usually caused by *S. aureus*.

**Cellulitis**
Acute, painful, spreading infection of deeper dermis and subcutaneous tissues. Usually from *S. pyogenes* or *S. aureus*. Often starts with a break in skin from trauma or another infection.

**Erysipelas**
Infection involving upper dermis and superficial lymphatics, usually from *S. pyogenes*. Presents with well-defined demarcation between infected and normal skin.

**Abscess**
Collection of pus from a walled-off infection within deeper layers of skin. Offending organism is almost always *S. aureus*, which is frequently methicillin resistant.

**Necrotizing fasciitis**
Deeper tissue injury, usually from anaerobic bacteria or *S. pyogenes*. Results in crepitus from methane and CO₂ production. “Flesh-eating bacteria.” Causes bullae and a purple color to the skin.

**Staphylococcal scalded skin syndrome**
Exotoxin destroys keratinocyte attachments in stratum granulosum only (vs. toxic epidermal necrolysis, which destroys epidermal-dermal junction). Characterized by fever and generalized erythematous rash with sloughing of the upper layers of the epidermis that heals completely. Seen in newborns and children, adults with renal insufficiency.

Viral infections

**Herpes**
Herpes virus infections (HSV1 and HSV2) of skin can occur anywhere from mucosal surfaces to normal skin. These include herpes labialis, herpes genitalis, herpetic whitlow (finger).

**Molluscum contagiosum**
Umblicated papules caused by a poxvirus. While frequently seen in children, it may be sexually transmitted in adults.

**Varicella zoster virus**
Causes varicella (chickenpox) and zoster (shingles). Varicella presents with multiple crops of lesions in various stages from vesicles to crusts. Zoster is a reactivation of the virus in dermatomal distribution (unless it is disseminated).

**Hairy leukoplakia**
Irregular, white, painless plaques on tongue that cannot be scraped off. EBV mediated. Occurs in HIV-positive patients, organ transplant recipients. Contrast with thrush (scrapable) and leukoplakia (precancerous).
**Blistering skin disorders**

**Pemphigus vulgaris**
Potentially fatal autoimmune skin disorder with IgG antibody against desmoglein (component of desmosomes).
Flaccid intraepidermal bullae caused by acantholysis (keratinocytes in stratum spinosum are connected by desmosomes); oral mucosa also involved.
Immunofluorescence reveals antibodies around epidermal cells in a reticular (net-like) pattern. Nikolsky sign \(\oplus\) (separation of epidermis upon manual stroking of skin).

**Bullous pemphigoid**
Less severe than pemphigus vulgaris. Involves IgG antibody against hemidesmosomes (epidermal basement membrane; antibodies are “bullous” the epidermis).
Tense blisters containing eosinophils affect skin but spare oral mucosa.
Immunofluorescence reveals linear pattern at epidermal-dermal junction. Nikolsky sign \(\ominus\).

**Dermatitis herpetiformis**
Pruritic papules, vesicles, and bullae (often found on elbows). Deposits of IgA at tips of dermal papillae. Associated with celiac disease.

**Erythema multiforme**
Associated with infections (e.g., *Mycoplasma pneumoniae*, HSV), drugs (e.g., sulfa drugs, \(\beta\)-lactams, phenytoin), cancers, autoimmune disease. Presents with multiple types of lesions—macules, papules, vesicles, target lesions (look like targets with multiple rings and dusky center showing epithelial disruption).

**Stevens-Johnson syndrome**
Characterized by fever, bullae formation and necrosis, sloughing of skin, high mortality rate. Typically 2 mucous membranes are involved, and targetoid skin lesions may appear, as seen in erythema multiforme. Usually associated with adverse drug reaction. A more severe form of Stevens-Johnson syndrome (SJS) with > 30% of the body surface area involved is toxic epidermal necrolysis (TEN). 10–30% involvement denotes SJS-TEN.
Miscellaneous skin disorders

**Acanthosis nigricans**
Epidermal hyperplasia causing symmetric, hyperpigmented thickening of skin, especially in axilla or on neck. Associated with hyperinsulinemia (e.g., diabetes, obesity, Cushing syndrome), visceral malignancy (e.g., gastric adenocarcinoma).

**Actinic keratosis**
Premalignant lesions caused by sun exposure. Small, rough, erythematous or brownish papules or plaques. Risk of squamous cell carcinoma is proportional to degree of epithelial dysplasia.

**Erythema nodosum**
Painful inflammatory lesions of subcutaneous fat, usually on anterior shins. Often idiopathic, but can be associated with sarcoidosis, coccidioidomycosis, histoplasmosis, TB, streptococcal infections, leprosy, Crohn disease.

**Lichen Planus**
Pruritic, purplish, polygonal papules and plaques are the 6 P's of lichen Planus. Mucosal involvement manifests as Wickham striae (reticular white lines). Sawtooth infiltrate of lymphocytes at dermal-epidermal junction. Associated with hepatitis C.

**Pityriasis rosea**
“Herald patch” followed days later by other scaly erythematous plaques, often in a “Christmas tree” distribution. Multiple plaques with collarette scale. Self-resolving in 6–8 weeks.

**Sunburn**
Acute cutaneous inflammatory reaction due to excessive UV irradiation. Causes DNA mutations, inducing apoptosis of keratinocytes. UVA is dominant in tanning and photoaging. UVB in sunburn. Can lead to impetigo, skin cancers (basal cell carcinoma, squamous cell carcinoma, melanoma).
Skin cancer

Basal cell carcinoma
Most common skin cancer. Found in sun-exposed areas of body. Locally invasive, but rarely metastasizes. Pink, pearly nodules, commonly with telangiectasias, rolled borders, central crusting or ulceration. BCCs also appear as nonhealing ulcers with infiltrating growth or as a scaling plaque (superficial BCC). Basal cell tumors have “palisading” nuclei.

Squamous cell carcinoma
Second most common skin cancer. Associated with excessive exposure to sunlight, immunosuppression, and occasionally arsenic exposure. Commonly appears on face, lower lip, ears, hands. Locally invasive, may spread to lymph nodes, and will rarely metastasize. Ulcerative red lesions with frequent scale. Associated with chronic draining sinuses. Histopathology: keratin “pearls.”

Actinic keratosis, a scaly plaque, is a precursor to squamous cell carcinoma. Keratoacanthoma is a variant that grows rapidly (4–6 weeks) and may regress spontaneously over months.

Melanoma
Common tumor with significant risk of metastasis. S-100 tumor marker. Associated with sunlight exposure; fair-skinned persons are at risk. Depth of tumor correlates with risk of metastasis. Look for the ABCDEs: Asymmetry, Border irregularity, Color variation, Diameter > 6 mm, and Evolution over time. At least 4 different types of melanoma, including superficial spreading, nodular, lentigo maligna, and acral lentiginous. Often driven by activating mutation in BRAF kinase. Primary treatment is excision with appropriately wide margins. Metastatic or unresectable melanoma in patients with BRAF V600E mutation may benefit from vemurafenib, a BRAF kinase inhibitor.
Inflammatory mediators

**Leukotriene Synthesis (5-Lipoxygenase)**

- Zileuton
- Montelukast
- Zafirlukast

**Leukotriene Receptor Antagonists**

- Montelukast
- Zafirlukast

**MEMBRANE PHOSPHOLIPIDS**

- Phospholipase A₂
- Arachidonic acid

**Lipoxigenase**

**5-HPETE**

**Cyclooxygenase 1 (COX-1)**

**Cyclooxygenase 2 (COX-2)**

**Cyclic endoperoxides**

**Prostacyclin**

**Prostaglandins**

- PGI₂
  - ↓ Platelet aggregation
  - ↓ Vascular tone
- PGE₁
  - Vascular tone
- PGE₂
  - Uterine tone
- PGF₂α
  - Uterine tone

**Thromboxane**

- TXA₂
  - ↑ Platelet aggregation
  - ↑ Vascular tone

**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.

**Toxicity**

Overdose produces hepatic necrosis; acetaminophen metabolite (NAPQI) depletes glutathione and forms toxic tissue byproducts in liver. N-acetylcysteine is antidote—regenerates glutathione.

**Leukotrienes**

- LTC₄
  - ↑ Bronchial tone
- LTD₄
  - ↑ Neutrophil chemotaxis
- LTE₄

**Neutrophils**

Arrive “B₄” others. platelet-aggregation inhibitor.

**Acetaminophen**

- 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.
  - Toxicity: Overdose produces hepatic necrosis; acetaminophen metabolite (NAPQI) depletes glutathione and forms toxic tissue byproducts in liver. N-acetylcysteine is antidote—regenerates glutathione.
### Aspirin

**MECHANISM**
Irreversibly inhibits cyclooxygenase (both COX-1 and COX-2) via acetylation, which \( \uparrow \) synthesis of TXA\(_2\) and prostaglandins. \( \uparrow \) bleeding time. No effect on PT, PTT. A type of NSAID.

**CLINICAL USE**

**TOXICITY**
Gastric ulceration, tinnitus (CN VIII). Chronic use can lead to acute renal failure, interstitial nephritis, GI bleeding. Risk of Reye syndrome in children treated with aspirin for viral infection. Causes respiratory alkalosis early, but transitions to mixed metabolic acidosis-respiratory alkalosis.

### Celecoxib

**MECHANISM**
Reversibly inhibits specifically the cyclooxygenase (COX) isoform 2, which is found in inflammatory cells and vascular endothelium and mediates inflammation and pain; spares COX-1, which helps maintain gastric mucosa. Thus, does not have the corrosive effects of other NSAIDs on the GI lining. Spares platelet function as TXA\(_2\) production is dependent on COX-1.

**CLINICAL USE**
Rheumatoid arthritis, osteoarthritis.

**TOXICITY**
\( \uparrow \) risk of thrombosis. Sulfa allergy.

### NSAIDs

Ibuprofen, naproxen, indomethacin, ketorolac, diclofenac.

**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.

**TOXICITY**
Interstitial nephritis, gastric ulcer (prostaglandins protect gastric mucosa), renal ischemia (prostaglandins vasodilate afferent arteriole).

### Bisphosphonates

Alendronate, other -dronates.

**MECHANISM**
Pyrophosphate analogs; bind hydroxyapatite in bone, inhibiting osteoclast activity.

**CLINICAL USE**
Osteoporosis, hypercalcemia, Paget disease of bone.

**TOXICITY**
Corrosive esophagitis (patients are advised to take with water and remain upright for 30 minutes), osteonecrosis of jaw.

### Teriparatide

**MECHANISM**
Recombinant PTH analog given subcutaneously daily. \( \uparrow \) osteoblastic activity.

**CLINICAL USE**
Osteoporosis. Causes \( \uparrow \) bone growth compared to antiresorptive therapies (e.g., bisphosphonates).

**TOXICITY**
Transient hypercalcemia. May increase risk of osteosarcoma (seen in rodent studies).
Gout drugs

**Chronic gout drugs (preventive)**

**Allopurinol**
Inhibits xanthine oxidase after being converted to alloxanthine, conversion of xanthine to uric acid. Also used in lymphoma and leukemia to prevent tumor lysis–associated urate nephropathy. Also used in lymphoma and leukemia to prevent tumor lysis–associated urate nephropathy. Also used in lymphoma and leukemia to prevent tumor lysis–associated urate nephropathy. Also used in lymphoma and leukemia to prevent tumor lysis–associated urate nephropathy.

**Febuxostat**
Inhibits xanthine oxidase.

**Pegloticase**
Recombinant uricase that catalyze metabolism of uric acid to allantoin (a more water-soluble product).

**Probenecid**
Inhibits reabsorption of uric acid in proximal convoluted tubule (also inhibits secretion of penicillin). Can precipitate uric acid calculi.

**Acute gout drugs**

**NSAIDs**
Naproxen, indomethacin.

**Gluocorticoids**
Oral or intra-articular.

**Colchicine**
Binds and stabilizes tubulin to inhibit microtubule polymerization, impairing neutrophil chemotaxis and degranulation. Acute and prophylactic value. GI side effects.

Do not give salicylates; all but the highest doses depress uric acid clearance. Even high doses (5–6 g/day) have only minor uricosuric activity.

**TNF-α inhibitors**
All TNF-α inhibitors predispose to infection, including reactivation of latent TB, since TNF is important in granuloma formation and stabilization.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM</th>
<th>CLINICAL USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>Fusion protein (receptor for TNF-α + IgG1 Fc), produced by recombinant DNA.</td>
<td>Rheumatoid arthritis, psoriasis, ankylosing spondylitis</td>
</tr>
<tr>
<td>Infliximab,</td>
<td>Anti-TNF-α monoclonal antibody.</td>
<td>Inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis,</td>
</tr>
<tr>
<td>adalimumab</td>
<td></td>
<td>psoriasis</td>
</tr>
</tbody>
</table>
“Estimated amount of glucose used by an adult human brain each day, expressed in M&Ms: 250.”
—Harper’s Index

“He has two neurons held together by a spirochete.”
—Anonymous

“I never came upon any of my discoveries through the process of rational thinking.”
—Albert Einstein

“I like nonsense; it wakes up the brain cells.”
—Dr. Seuss
**NEUROLOGY—EMBRYOLOGY**

**Neural development**

Notochord induces overlying ectoderm to differentiate into neuroectoderm and form neural plate. Neural plate gives rise to neural tube and neural crest cells.

Notochord becomes nucleus pulposus of intervertebral disc in adults.

Alar plate (dorsal): sensory  
Basal plate (ventral): motor  
Same orientation as spinal cord.

---

**Regional specification of developing brain**

Three primary vesicles

<table>
<thead>
<tr>
<th>Adult derivatives of:</th>
<th>Walls</th>
<th>Cavities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral hemispheres</td>
<td>Lateral ventricles</td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>Third ventricle</td>
<td></td>
</tr>
<tr>
<td>Midbrain</td>
<td>Aqueduct</td>
<td></td>
</tr>
<tr>
<td>Pons</td>
<td>Upper part of fourth ventricle</td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>Lower part of fourth ventricle</td>
<td></td>
</tr>
<tr>
<td>Medulla</td>
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</tr>
</tbody>
</table>

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**CNS/PNS origins**

Neuroectoderm—CNS neurons, ependymal cells (inner lining of ventricles, make CSF), oligodendroglia, astrocytes.

Neural crest—PNS neurons, Schwann cells.

Mesoderm—Microglia (like Macrophages, originate from Mesoderm).
Neural tube defects

Neuropores fail to fuse (4th week) → persistent connection between amniotic cavity and spinal canal. Associated with low folic acid intake before conception and during pregnancy.

1 α-fetoprotein (AFP) in amniotic fluid and maternal serum. 1 acetylcholinesterase (AChE) in amniotic fluid is a helpful confirmatory test (fetal AChE in CSF transudates across defect into amniotic fluid).

Spina bifida occulta

Failure of bony spinal canal to close, but no structural herniation. Usually seen at lower vertebral levels. Dura is intact. Associated with tuft of hair or skin dimple at level of bony defect. Normal AFP.

Meningocele

Meninges (but no neural tissue) herniate through bony defect.

Meningomyelocele

Meninges and neural tissue herniate through bony defect.

Forebrain anomalies

Anencephaly


Holoprosencephaly

Failure of left and right hemispheres to separate; usually occurs during weeks 5–6. May be related to mutations in sonic hedgehog signaling pathway. Moderate form has cleft lip/palate, most severe form results in cyclopia. Seen in Patau syndrome and fetal alcohol syndrome.

Posterior fossa malformations

Chiari II

Significant herniation of cerebellar tonsils and vermis through foramen magnum with aqueductal stenosis and hydrocephalus. Often presents with lumbosacral meningomyelocele, paralysis below the defect.

Dandy-Walker

Agenesis of cerebellar vermis with cystic enlargement of 4th ventricle (fills the enlarged posterior fossa ▶). Associated with hydrocephalus, spina bifida.
Syringomyelia

Cystic cavity (syrinx) within spinal cord \( \text{A} \) (if central canal \( \rightarrow \) hydromyelia). Crossing anterior spinal commissural fibers are typically damaged first. Results in a “cape-like,” bilateral loss of pain and temperature sensation in upper extremities (fine touch sensation is preserved). Associated with Chiari malformations, trauma, and tumors.

Syrinx = tube, as in syringe.

Most common at C8–T1.

Chiari I malformation— cerebellar tonsillar ectopia > 3–5 mm; congenital, usually asymptomatic in childhood, manifests with headaches and cerebellar symptoms.

Tongue development

1st and 2nd branchial arches form anterior \( \frac{2}{3} \) (thus sensation via CN V\(_3\), taste via CN VII).

3rd and 4th branchial arches form posterior \( \frac{1}{3} \) (thus sensation and taste mainly via CN IX, extreme posterior via CN X).

Motor innervation is via CN XII to hyoglossus (retracts and depresses tongue), genioglossus (protrudes tongue), and styloglossus (draws sides of tongue upward to create a trough for swallowing).

Motor innervation is via CN X to palatoglossus (elevates posterior tongue during swallowing).

Taste—CN VII, IX, X (solitary nucleus).

Pain—CN V\(_3\), IX, X.

Motor—CN X, XII.
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 Nissle staining (stains RER). RER is not present in the axon. Injury to axon → Wallerian degeneration—degeneration distal to injury and axonal retraction proximally; allows for potential regeneration of axon (if in PNS).

Astrocytes

Microglia

HIV-infected microglia fuse to form multinucleated giant cells in CNS.

Myelin
\[ \text{\text{\textbf{Myelin}}} \]
† conduction velocity of signals transmitted down axons → saltatory conduction of action potential at the nodes of Ranvier, where there are high concentrations of Na⁺ channels. CNS—oligodendrocytes; PNS—Schwann cells.

Wraps and insulates axons \[ e \] \: \text{\text{\textbf{\text{\text{\text{space constant \& conduction velocity.}}}}}}

Schwann cells
Each Schwann cell myelinates only 1 PNS axon. Also promote axonal regeneration. Derived from neural crest.

† conduction velocity via saltatory conduction at the nodes of Ranvier, where there is a high concentration of Na⁺ channels.

May be injured in Guillain-Barré syndrome. **Acoustic neuroma**—type of schwannoma. Typically located in internal acoustic meatus (CN VIII). If bilateral, strongly associated with neurofibromatosis type 2.
Oligodendroglia

Myelinate axons of neurons in CNS. Each oligodendrocyte can myelinate many axons (∼30). Predominant type of glial cell in white matter.

Derived from neuroectoderm.

“Fried egg” appearance histologically.

Injured in multiple sclerosis, progressive multifocal leukoencephalopathy (PML), leukodystrophies.

---

**Sensory receptors**

<table>
<thead>
<tr>
<th>RECEPTOR TYPE</th>
<th>DESCRIPTION</th>
<th>LOCATION</th>
<th>SENSES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Free nerve endings</strong></td>
<td>C—slow, unmyelinated fibers</td>
<td>All skin, epidermis, some</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aδ—fast, myelinated fibers</td>
<td>viscera</td>
<td>Pain, temperature</td>
</tr>
<tr>
<td><strong>Meissner corpuscles</strong></td>
<td>Large, myelinated fibers; adapt</td>
<td>Glabrous (hairless) skin</td>
<td>Dynamic, fine/light touch,</td>
</tr>
<tr>
<td></td>
<td>quickly</td>
<td></td>
<td>position sense</td>
</tr>
<tr>
<td><strong>Pacinian corpuscles</strong></td>
<td>Large, myelinated fibers; adapt</td>
<td>Deep skin layers, ligaments,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>quickly</td>
<td>joints</td>
<td>Vibration, pressure</td>
</tr>
<tr>
<td><strong>Merkel discs</strong></td>
<td>Large, myelinated fibers; adapt</td>
<td>Finger tips, superficial skin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>slowly</td>
<td></td>
<td>Pressure, deep static touch</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(e.g., shapes, edges),</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>position sense</td>
</tr>
<tr>
<td><strong>Ruffini corpuscles</strong></td>
<td>Dendritic endings with capsule;</td>
<td>Finger tips, joints</td>
<td>Pressure, slippage of</td>
</tr>
<tr>
<td></td>
<td>adapt slowly</td>
<td></td>
<td>objects along surface of</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>skin, joint angle change</td>
</tr>
</tbody>
</table>

---

**Peripheral nerve**

Endoneurium—invests single nerve fiber layers (inflammatory infiltrate in Guillain-Barré syndrome).

Perineurium (Permeability barrier)—surrounds a fascicle of nerve fibers. Must be rejoined in microsurgery for limb reattachment.

Epineurium—dense connective tissue that surrounds entire nerve (fascicles and blood vessels).

Endo = inner.
Peri = around.
Epi = outer.
### Neurotransmitters

<table>
<thead>
<tr>
<th>Type</th>
<th>Change in Disease</th>
<th>Locations of Synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>↑ in anxiety ↓ in depression</td>
<td>Locus ceruleus (pons)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dopamine</td>
<td>↑ in Huntington disease ↓ in Parkinson disease ↓ in depression</td>
<td>Ventral tegmentum and substantia nigra pars compacta (midbrain)</td>
</tr>
<tr>
<td>5-HT</td>
<td>↓ in anxiety ↓ in depression</td>
<td>Raphe nuclei (pons, medulla, midbrain)</td>
</tr>
<tr>
<td>ACh</td>
<td>↑ in Parkinson disease ↓ in Alzheimer disease ↓ in Huntington disease</td>
<td>Basal nucleus of Meynert</td>
</tr>
<tr>
<td>GABA</td>
<td>↓ in anxiety ↓ in Huntington disease</td>
<td>Nucleus accumbens&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Locus ceruleus—stress and panic.

<sup>b</sup>Nucleus accumbens and septal nucleus—reward center, pleasure, addiction, fear.

---

### Blood-brain barrier

Prevents circulating blood substances (e.g., bacteria, drugs) from reaching the CSF/CNS. Formed by 3 structures:
- Tight junctions between nonfenestrated capillary endothelial cells
- Basement membrane
- Astrocyte foot processes


A few specialized brain regions with fenestrated capillaries and no blood-brain barrier allow molecules in blood to affect brain function (e.g., area postrema—vomiting after chemo; OVLT—osmotic sensing) or neurosecretory products to enter circulation (e.g., neurohypophysis—ADH release). Infarction and/or neoplasm destroys endothelial cell tight junctions → vasogenic edema. Other notable barriers include:
- Blood-testis barrier
- Maternal-fetal blood barrier of placenta
**Hypothalamus**

The hypothalamus wears **TAN HATS**—Thirst and water balance, Adenohypophysis control (regulates anterior pituitary), Neurohypophysis releases hormones produced in the hypothalamus, Hunger, Autonomic regulation, Temperature regulation, Sexual urges.

Inputs (areas not protected by blood-brain barrier): OVLT (organum vasculosum of the lamina terminalis; senses change in osmolarity), area postrema (responds to emetics).

Supraoptic nucleus primarily makes ADH. Neurohypophysis releases hormones produced in the hypothalamus, Hunger, Autonomic regulation, Temperature regulation, Sexual urges.

ADH and oxytocin—are made by hypothalamus but stored and released by posterior pituitary.

### Lateral area
- Hunger. Destruction → anorexia, failure to thrive (infants). Inhibited by leptin.
- If you zap your **lateral** nucleus, you shrink **laterally**.

### Ventromedial area
- Satiety. Destruction (e.g., craniopharyngioma) → hyperphagia. Stimulated by leptin.
- If you zap your **ventromedial** nucleus, you grow **ventrally** and **medially**.

### Anterior hypothalamus
- Cooling, parasympathetic.
- **Anterior** nucleus = cool off (cooling, pArasympathetic). A/C = anterior cooling.

### Posterior hypothalamus
- Heating, sympathetic.
- Posterior nucleus = get fired up (heating, sympathetic). If you zap your posterior hypothalamus, you become a poikilotherm (cold-blooded, like a snake).

### Suprachiasmatic nucleus
- Circadian rhythm.
- You need **sleep** to be **charismatic** (chiasmatic).
**Sleep physiology**

Sleep cycle is regulated by the circadian rhythm, which is driven by suprachiasmatic nucleus (SCN) of hypothalamus. Circadian rhythm controls nocturnal release of ACTH, prolactin, melatonin, norepinephrine: SCN → norepinephrine release → pineal gland → melatonin. SCN is regulated by environment (e.g., light).

Two stages: rapid-eye movement (REM) and non-REM. Extraocular movements during REM sleep due to activity of PPRF (paramedian pontine reticular formation/alias conjugate gaze center). REM sleep occurs every 90 minutes, and duration ↑ through the night.

Alcohol, benzodiazepines, and barbiturates are associated with ↓ REM sleep and delta wave sleep; norepinephrine also ↓ REM sleep.

Treat bedwetting (sleep enuresis) with oral desmopressin (ADH analog); preferred over imipramine because of the latter's adverse effects.

Benzodiazepines are useful for night terrors and sleepwalking.

<table>
<thead>
<tr>
<th>SLEEP STAGE (% OF TOTAL SLEEP TIME IN YOUNG ADULTS)</th>
<th>DESCRIPTION</th>
<th>EEG WAVEFORM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awake (eyes open)</td>
<td>Alert, active mental concentration</td>
<td>Beta (highest frequency, lowest amplitude)</td>
</tr>
<tr>
<td>Awake (eyes closed)</td>
<td>Alert, active mental concentration</td>
<td>Alpha</td>
</tr>
<tr>
<td>Non-REM sleep</td>
<td>Light sleep</td>
<td>Theta</td>
</tr>
<tr>
<td>Stage N1 (5%)</td>
<td>Deeper sleep, when bruxism occurs</td>
<td>Sleep spindles and K complexes</td>
</tr>
<tr>
<td>Stage N2 (45%)</td>
<td>Deepest non-REM sleep (slow-wave sleep); when sleepwalking, night terrors, and bedwetting occur</td>
<td>Delta (lowest frequency, highest amplitude)</td>
</tr>
<tr>
<td>REM sleep (25%)</td>
<td>Loss of motor tone, ↑ brain O₂ use, ↑ and variable pulse and blood pressure; when dreaming and penile/clitoral tumescence occur; may serve memory processing function</td>
<td>Beta</td>
</tr>
</tbody>
</table>

At night, BATS Drink Blood
### Thalamus

Major relay for all ascending sensory information except olfaction.

<table>
<thead>
<tr>
<th>NUCLEUS</th>
<th>INPUT</th>
<th>INFO</th>
<th>DESTINATION</th>
<th>MNEMONIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPL</td>
<td>Spinothalamic and dorsal columns/medial lemniscus</td>
<td>Pain, temperature; pressure, touch, vibration, proprioception</td>
<td>1° somatosensory cortex</td>
<td></td>
</tr>
<tr>
<td>VPM</td>
<td>Trigeminal and gustatory pathway</td>
<td>Face sensation, taste</td>
<td>1° somatosensory cortex</td>
<td>Makeup goes on the <strong>face</strong> (VPM)</td>
</tr>
<tr>
<td>LGN</td>
<td>CN II</td>
<td>Vision</td>
<td>Calcarine sulcus</td>
<td>Lateral = <strong>Light</strong></td>
</tr>
<tr>
<td>MGN</td>
<td>Superior olive and inferior colliculus of tectum</td>
<td>Hearing</td>
<td>Auditory cortex of temporal lobe</td>
<td>Medial = <strong>Music</strong></td>
</tr>
<tr>
<td>VL</td>
<td>Basal ganglia, cerebellum</td>
<td>Motor</td>
<td>Motor cortex</td>
<td></td>
</tr>
</tbody>
</table>

### Limbic system

Collection of neural structures involved in emotion, long-term memory, olfaction, behavior modulation, ANS function. Structures include hippocampus (red arrows in A), amygdala, fornix, mammillary bodies, cingulate gyrus (blue arrows in A). Responsible for **Feeding**, **Fleeing**, **Fighting**, **Feeling**, and **Sex**. The famous **5 F’s**.

### Osmotic demyelination syndrome (central pontine myelinolysis)

Acute paralysis, dysarthria, dysphagia, diplopia, loss of consciousness. Can cause “locked-in syndrome.” Massive axonal demyelination in pontine white matter **2°** to osmotic changes. Commonly iatrogenic, caused by overly rapid correction of hyponatremia. In contrast, correcting hypernatremia too quickly results in cerebral edema/herniation. Correcting serum Na⁺ too fast:

- “From low to high, your pons will die” (osmotic demyelination syndrome)
- “From high to low, your brain will blow” (cerebral edema/herniation)
Cerebellum

Modulates movement; aids in coordination and balance.

Input:
* Contralateral cortex via middle cerebellar peduncle.
* Ipsilateral proprioceptive information via inferior cerebellar peduncle from spinal cord.

Output:
* Sends information to contralateral cortex to modulate movement. Output nerves = Purkinje cells → deep nuclei of cerebellum → contralateral cortex via superior cerebellar peduncle.
* Deep nuclei (lateral → medial)—Dentate, Emboliform, Globose, Fastigial (“Don’t Eat Greasy Foods”).

Lateral lesions—voluntary movement of extremities; when injured, propensity to fall toward injured (ipsilateral) side.

Medial lesions—lesions involving midline structures (vermal cortex, fastigial nuclei) and/or flocculonodular lobe → truncal ataxia (wide-based cerebellar gait), nystagmus, head tilting.

Generally, midline lesions result in bilateral motor deficits affecting axial and proximal limb musculature.
Basal ganglia

Important in voluntary movements and making postural adjustments.
Receives cortical input, provides negative feedback to cortex to modulate movement.
Striatum = putamen (motor) + caudate (cognitive).
Lentiform = putamen + globus pallidus.

\[ \text{D}_1\text{-Receptor} = \text{D}1\text{R ect pathway.} \]
\[ \text{Indirect} = \text{Inhibitory.} \]

\[ \text{SNc} \quad \text{Substantia nigra pars compacta} \]
\[ \text{GPe} \quad \text{Globus pallidus externus} \]
\[ \text{GPi} \quad \text{Globus pallidus internus} \]
\[ \text{STN} \quad \text{Subthalamic nucleus} \]
\[ \text{D}_1 \quad \text{Dopamine D}_1\text{ receptor} \]
\[ \text{D}_2 \quad \text{Dopamine D}_2\text{ receptor} \]

Excitatory pathway—cortical inputs stimulate the striatum, stimulating the release of GABA, which disinhibits the thalamus via the GPi/SNr (↑ motion).
Inhibitory pathway—cortical inputs stimulate the striatum, which disinhibits STN via GPe, and STN stimulates GPi/SNr to inhibit the thalamus (↓ motion).
Dopamine binds to D\(_1\), stimulating the excitatory pathway, and to D\(_2\), inhibiting the inhibitory pathway → ↑ motion.
### Movement disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Presentation</th>
<th>Characteristic Lesion</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Athetosis</td>
<td>Slow, writhing movements; especially seen in fingers</td>
<td>Basal ganglia (e.g., Huntington)</td>
<td>Writhing, snake-like movement.</td>
</tr>
<tr>
<td>Chorea</td>
<td>Sudden, jerky, purposeless movements</td>
<td>Basal ganglia (e.g., Huntington)</td>
<td>Chorea = dancing.</td>
</tr>
<tr>
<td>Dystonia</td>
<td>Sustained, involuntary muscle contractions</td>
<td></td>
<td>Writer’s cramp; blepharospasm (sustained eyelid twitch).</td>
</tr>
<tr>
<td>Essential tremor</td>
<td>High-frequency tremor with sustained posture (e.g., outstretched arms), worsened with movement or when anxious</td>
<td></td>
<td>Often familial. Patients often self-medicate with EtOH, which ↑ tremor amplitude. Treatment: β-blockers, primidone.</td>
</tr>
<tr>
<td>Hemiballismus</td>
<td>Sudden, wild flailing of 1 arm +/- ipsilateral leg</td>
<td>Contralateral subthalamic nucleus (e.g., lacunar stroke)</td>
<td>Pronounce “Half-of-body ballistic.”</td>
</tr>
<tr>
<td>Intention tremor</td>
<td>Slow, zigzag motion when pointing/extend toward a target</td>
<td>Cerebellar dysfunction</td>
<td></td>
</tr>
<tr>
<td>Myoclonus</td>
<td>Sudden, brief, uncontrolled muscle contraction</td>
<td></td>
<td>Jerks; hiccups; common in metabolic abnormalities such as renal and liver failure.</td>
</tr>
<tr>
<td>Resting tremor</td>
<td>Uncontrolled movement of distal appendages (most noticeable in hands), tremor alleviated by intentional movement</td>
<td>Parkinson disease</td>
<td>Occurs at rest; “pill-rolling tremor” of Parkinson disease.</td>
</tr>
</tbody>
</table>

### Parkinson disease

Degenerative disorder of CNS associated with Lewy bodies (composed of α-synuclein—intracellular eosinophilic inclusions) and loss of dopaminergic neurons (i.e., depigmentation) of substantia nigra pars compacta.

Parkinson TRAPS your body:
- Tremor (pill-rolling tremor at rest)
- Rigidity (cogwheel)
- Akinesia (or bradykinesia)
- Postural instability
- Shuffling gait

### Huntington disease

Autosomal dominant trinucleotide repeat disorder on chromosome 4. Symptoms manifest between ages 20 and 50; characterized by choreiform movements, aggression, depression, dementia (sometimes initially mistaken for substance abuse). ↑ dopamine, ↓ GABA, ↓ ACh in brain. Neuronal death via NMDA-R binding and glutamate toxicity. Atrophy of caudate nuclei with ex vacuo dilatation of frontal horns on MRI. Expansion of CAG repeats (anticipation).

Caudate loses ACh and GABA.
### Cerebral cortex functions

<table>
<thead>
<tr>
<th>Area</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premotor area (part of</td>
<td>Principal motor area</td>
</tr>
<tr>
<td>extrapyramidal circuit)</td>
<td>Principal sensory areas</td>
</tr>
<tr>
<td>Sylvian fissure</td>
<td>Motor speech (Broca area; dominant hemisphere)</td>
</tr>
<tr>
<td>Motor speech</td>
<td>Frontal eye fields</td>
</tr>
<tr>
<td>(Broca area; dominant</td>
<td>Principal motor area</td>
</tr>
<tr>
<td>hemisphere)</td>
<td>Principal sensory areas</td>
</tr>
<tr>
<td>Frontal association areas</td>
<td>Principal visual cortex</td>
</tr>
<tr>
<td>Principal auditory cortex</td>
<td>Occipital lobe</td>
</tr>
<tr>
<td>(Wernicke area; dominant</td>
<td>Frontal lobe</td>
</tr>
<tr>
<td>hemisphere)</td>
<td>Temporal lobe</td>
</tr>
<tr>
<td>Associative auditory cortex</td>
<td>Occipital lobe</td>
</tr>
<tr>
<td>(Wernicke area; dominant</td>
<td>Principal visual cortex</td>
</tr>
<tr>
<td>hemisphere)</td>
<td>Occipital lobe</td>
</tr>
</tbody>
</table>

### Aphasia

Aphasia = higher-order inability to speak (language deficit). Dysarthria = motor inability to speak (movement deficit).

- **Broca**
  - Nonfluent aphasia with intact comprehension and impaired repetition. Broca area—inferior frontal gyrus of frontal lobe.
  - Broca = Broken Boca (boca = mouth in Spanish).

- **Wernicke**
  - Fluent aphasia with impaired comprehension and repetition. Wernicke area—superior temporal gyrus of temporal lobe.
  - Wernicke is Wordy but makes no sense.
  - Wernicke = “What?”

- **Conduction**
  - Poor repetition but fluent speech, intact comprehension. Can be caused by damage to arcuate fasciculus.
  - Can’t repeat phrases such as, “No ifs, ands, or buts.”

- **Global**
  - Nonfluent aphasia with impaired comprehension.
  - Arcuate fasciculus, Broca and Wernicke areas affected.

- **Transcortical motor**
  - Nonfluent aphasia with good comprehension and intact repetition.

- **Transcortical sensory**
  - Poor comprehension with fluent speech and intact repetition.

- **Mixed transcortical**
  - Nonfluent speech, poor comprehension, intact repetition.
  - Broca and Wernicke areas involved; arcuate fasciculus not involved.
### Common brain lesions

<table>
<thead>
<tr>
<th>AREA OF LESION</th>
<th>CONSEQUENCE</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amygdala (bilateral)</td>
<td>Klüver-Bucy syndrome—dissinhibited behavior (e.g., hyperphagia, hypersexuality, hyperorality).</td>
<td>Associated with HSV-1.</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>Disinhibition and deficits in concentration, orientation, judgment; may have reemergence of primitive reflexes.</td>
<td></td>
</tr>
<tr>
<td>Nondominant parietal-temporal cortex</td>
<td>Hemispatial neglect syndrome (agnosia of the contralateral side of the world).</td>
<td></td>
</tr>
<tr>
<td>Dominant parietal-temporal cortex</td>
<td>Agraphia, acalculia, finger agnosia, left-right disorientation.</td>
<td>Gerstmann syndrome.</td>
</tr>
<tr>
<td>Reticular activating system (midbrain)</td>
<td>Reduced levels of arousal and wakefulness (e.g., coma).</td>
<td></td>
</tr>
<tr>
<td>Mammillary bodies (bilateral)</td>
<td>Wernicke-Korsakoff syndrome—confusion, ophthalmoplegia, ataxia; memory loss (anterograde and retrograde amnesia), confabulation, personality changes.</td>
<td>Associated with thiamine (B₁) deficiency and excessive EtOH use; can be precipitated by giving glucose without B₁ to a B₁-deficient patient. Wernicke problems come in a CAN of beer: Confusion, Ataxia, Nystagmus.</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>May result in tremor at rest, chorea, athetosis.</td>
<td>Parkinson disease, Huntington disease.</td>
</tr>
<tr>
<td>Cerebellar hemisphere</td>
<td>Intention tremor, limb ataxia, loss of balance; damage to cerebellum → ipsilateral deficits; fall toward side of lesion.</td>
<td>Cerebellar hemispheres are laterally located—affect lateral limbs.</td>
</tr>
<tr>
<td>Cerebellar vermis</td>
<td>Truncal ataxia, dysarthria.</td>
<td>Vermis is centrally located—affects central body.</td>
</tr>
<tr>
<td>Subthalamic nucleus</td>
<td>Contralateral hemiballismus.</td>
<td></td>
</tr>
<tr>
<td>Hippocampus (bilateral)</td>
<td>Anterograde amnesia—inability to make new memories.</td>
<td></td>
</tr>
<tr>
<td>Paramedian pontine reticular formation</td>
<td>Eyes look away from side of lesion.</td>
<td></td>
</tr>
<tr>
<td>Frontal eye fields</td>
<td>Eyes look toward lesion.</td>
<td></td>
</tr>
</tbody>
</table>
Cerebral arteries—cortical distribution

- Anterior cerebral artery (supplies anteromedial surface)
- Middle cerebral artery (supplies lateral surface)
- Posterior cerebral artery (supplies posterior and inferior surfaces)

Watershed zones

Between anterior cerebral/middle cerebral, posterior cerebral/middle cerebral arteries. Damage in severe hypotension → upper leg/upper arm weakness, defects in higher-order visual processing.

Circle of Willis

System of anastomoses between anterior and posterior blood supplies to brain.
**Homunculus**

Topographic representation of motor (shown) and sensory areas in the cerebral cortex. Distorted appearance is due to certain body regions being more richly innervated and thus having † cortical representation.

**Regulation of cerebral perfusion**

Brain perfusion relies on tight autoregulation. Cerebral perfusion is primarily driven by $P_{CO_2}$ ($P_{O_2}$ also modulates perfusion in severe hypoxia).

Therapeutic hyperventilation ($\uparrow P_{CO_2}$) helps $\downarrow$ intracranial pressure (ICP) in cases of acute cerebral edema (stroke, trauma) via vasoconstriction. Fainting in panic attacks due to $\downarrow$ perfusion.

**Cerebral perfusion and blood pressure**

Cerebral perfusion relies on a pressure gradient between mean arterial pressure (MAP) and ICP. $\downarrow$ blood pressure or $\uparrow$ ICP $\rightarrow$ $\downarrow$ cerebral perfusion pressure (CPP).

CPP = MAP − ICP. If CPP = 0, there is no cerebral perfusion $\rightarrow$ brain death.
### Effects of Strokes

<table>
<thead>
<tr>
<th>Artery</th>
<th>Area of Lesion</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anterior circulation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>Motor cortex—upper limb and face. Sensory cortex—upper limb and face. Temporal lobe (Wernicke area); frontal lobe (Broca area).</td>
<td>Contra lateral paralysis—upper limb and face. Contra lateral loss of sensation—upper limb and face. Aphasia if in dominant (usually left) hemisphere. Hemineglect if lesion affects nondominant (usually right) side.</td>
</tr>
<tr>
<td>Lenticulostriate artery</td>
<td>Striatum, internal capsule.</td>
<td>Contra lateral hemiparesis/hemiplegia. Common location of lacunar infarcts, 2° to unmanaged hypertension.</td>
</tr>
<tr>
<td><strong>Posterior circulation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PICA</td>
<td>Lateral medulla—vestibular nuclei, lateral spinothalamic tract, spinal trigeminal nucleus, nucleus ambiguus, sympathetic fibers, inferior cerebellar peduncle.</td>
<td>Vomiting, vertigo, nystagmus; ↓ pain and temperature sensation from ipsilateral face and contralateral body; dysphagia, hoarseness, ↓ gag reflex; ipsilateral Horner syndrome; ataxia, dysmetria. Lateral medullary (Wallenberg) syndrome. Nucleus ambiguus effects are specific to PICA lesions. “Don’t pick a (PICA) horse (hoarseness) that can’t eat (dysphagia).”</td>
</tr>
<tr>
<td>AICA</td>
<td>Lateral pons—cranial nerve nuclei; vestibular nuclei, facial nucleus, spinal trigeminal nucleus, cochlear nuclei, sympathetic fibers. Middle and inferior cerebellar peduncles.</td>
<td>Vomiting, vertigo, nystagmus. <strong>Paralysis of face,</strong> ↓ lacrimation, salivation, ↓ taste from anterior ⅔ of tongue. Ipsilateral ↓ pain and temperature of the face, contralateral ↓ pain and temperature of the body. Ataxia, dysmetria. Lateral pontine syndrome. Facial nucleus effects are specific to AICA lesions. “Facial droop means AICA’s pooped.”</td>
</tr>
<tr>
<td>PCA</td>
<td>Occipital cortex, visual cortex.</td>
<td>Contra lateral hemianopia with macular sparing.</td>
</tr>
<tr>
<td>Basilar artery</td>
<td>Pons, medulla, lower midbrain, corticospinal and corticobulbar tracts, ocular cranial nerve nuclei, paramedian pontine reticular formation.</td>
<td>Preserved consciousness and blinking, quadriplegia, loss of voluntary facial, mouth, and tongue movements. “Locked-in syndrome.”</td>
</tr>
</tbody>
</table>
### Effects of strokes (continued)

<table>
<thead>
<tr>
<th>ARTERY</th>
<th>AREA OF LESION</th>
<th>SYMPTOMS</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACom</td>
<td>Most common lesion is aneurysm. Can lead to stroke. Saccular (berry) aneurysm can impinge cranial nerves.</td>
<td>Visual field defects.</td>
<td>Lesions are typically aneurysms, not strokes.</td>
</tr>
<tr>
<td>PCom</td>
<td>Common site of saccular aneurysm.</td>
<td>CN III palsy—eye is “down and out” with ptosis and mydriasis.</td>
<td>Lesions are typically aneurysms, not strokes.</td>
</tr>
</tbody>
</table>

### Aneurysms

In general, an abnormal dilation of artery due to weakening of vessel wall.

**Saccular (berry) aneurysm**

- Occurs at bifurcations in the circle of Willis. Most common site is junction of anterior communicating artery and anterior cerebral artery. Rupture (most common complication) → subarachnoid hemorrhage (“worst headache of my life”) or hemorrhagic stroke. Can also cause bitemporal hemianopia via compression of optic chiasm. Associated with ADPKD, Ehlers-Danlos syndrome. Other risk factors: advanced age, hypertension, smoking, race (↑ risk in blacks).

**Charcot-Bouchard microaneurysm**

- Associated with chronic hypertension; affects small vessels (e.g., in basal ganglia, thalamus).

**Central post-stroke pain syndrome**

- Neuropathic pain due to thalamic lesions. Initial paresthesias followed in weeks to months by allodynia (ordinarily painless stimuli cause pain) and dysesthesia. Occurs in 10% of stroke patients.
Intracranial hemorrhage

Epidural hematoma
Rupture of middle meningeal artery (branch of maxillary artery), often 2° to fracture of temporal bone. Lucid interval. Rapid expansion under systemic arterial pressure → transtorial herniation, CN III palsy. CT shows biconvex (lentiform), hyperdense blood collection not crossing suture lines. Can cross falx, tentorium.

Axial CT of brain shows lens-shaped collection of epidural blood (left, arrows), with bone windows showing associated skull fracture (right, circle) and scalp hematoma (arrows).

Subdural hematoma

Axial CTs show crescent-shaped subdural blood collections. Left image shows acute bleed (red arrow) with midline shift (subfalcial herniation, blue arrow). Right image shows “acute on chronic” hemorrhage (red, acute; blue, chronic).

Subarachnoid hemorrhage
Rupture of an aneurysm (such as a berry [saccular] aneurysm, as seen in Ehlers-Danlos syndrome, ADPKD) or arteriovenous malformation. Rapid time course. Patients complain of “worst headache of my life (WHOML).” Bloody or yellow (xanthochromic) spinal tap. 2–3 days afterward, risk of vasospasm due to blood breakdown (not visible on CT, treat with nimodipine) and rebleed (visible on CT).

Axial CT of brain shows subarachnoid blood in sulci (left, arrows) and intraventricular blood (right, arrows) layering in posterior horn of lateral ventricles.

Intraparenchymal (hypertensive) hemorrhage
Most commonly caused by systemic hypertension. Also seen with amyloid angiopathy (recurrent lobar hemorrhagic stroke in elderly), vasculitis, neoplasm. Typically occurs in basal ganglia and internal capsule (Charcot-Bouchard aneurysm of lenticulostriate vessels), but can be lobar.

Axial CT of brain shows intraparenchymal hemorrhage in basal ganglia (left) and cerebellum (right).
Ischemic brain disease/stroke

Irreversible damage begins after 5 minutes of hypoxia. Most vulnerable: hippocampus, neocortex, cerebellum, watershed areas. Irreversible neuronal injury.

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. Ischemic hypoxia—“hypocampal” is most vulnerable.

<table>
<thead>
<tr>
<th>TIME SINCE ISCHEMIC EVENT</th>
<th>12–48 HOURS</th>
<th>24–72 HOURS</th>
<th>3–5 DAYS</th>
<th>1–2 WEEKS</th>
<th>&gt; 2 WEEKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histologic features</td>
<td>Red neurons</td>
<td>Necrosis + neutrophils</td>
<td>Macrophages (microglia)</td>
<td>Reactive gliosis + vascular proliferation</td>
<td>Glial scar</td>
</tr>
</tbody>
</table>

Hemorrhagic stroke

Intracerebral bleeding, often due to hypertension, anticoagulation, cancer (abnormal vessels can bleed). May be ≥ to ischemic stroke followed by reperfusion († vessel fragility). Basal ganglia are most common site of intracerebral hemorrhage.

Ischemic stroke

Acute blockage of vessels → disruption of blood flow and subsequent ischemia → liquefactive necrosis.

3 types:
* Thrombotic—due to a clot forming directly at site of infarction (commonly the MCA A), usually over an atherosclerotic plaque.
* Embolic—embolus from another part of the body obstructs vessel. Can affect multiple vascular territories. Examples: atrial fibrillation; DVT with patent foramen ovale.
* Hypoxic—due to hypoperfusion or hypoxemia. Common during cardiovascular surgeries, tends to affect watershed areas.

Treatment: tPA (if within 3–4.5 hr of onset and no hemorrhage/risk of hemorrhage). Reduce risk with medical therapy (e.g., aspirin, clopidogrel); optimum control of blood pressure, blood sugars, lipids; and treat conditions that risk (e.g., atrial fibrillation).

Transient ischemic attack

Brief, reversible episode of focal neurologic dysfunction without acute infarction (MRI), with the majority resolving in < 15 minutes; deficits due to focal ischemia.

Dural venous sinuses

Large venous channels that run through the dura. Drain blood from cerebral veins and receive CSF from arachnoid granulations. Empty into internal jugular vein.
CSF is made by ependymal cells of choroid plexus; it is reabsorbed by arachnoid granulations and then drains into dural venous sinuses.

**Idiopathic intracranial hypertension (pseudotumor cerebri)**

† ICP with no apparent cause on imaging (i.e., hydrocephalus, obstruction of CSF outflow). Patients present with headaches, diplopia (usually from CN VI palsy), no mental status alterations. Papilledema seen on exam. Risk factors include being a woman of childbearing age, vitamin A excess, danazol. Lumbar puncture reveals † opening pressure and provides headache relief. Treatment: weight loss, acetazolamide, topiramate, invasive procedures for refractory cases (e.g., repeat lumbar puncture, CSF shunt placement, optic nerve fenestration surgery).

**Hydrocephalus**

**Communicating (nonobstructive)**

Communicating hydrocephalus

† CSF absorption by arachnoid granulations → † ICP, papilledema, herniation (e.g., arachnoid scarring post-meningitis).

Normal pressure hydrocephalus

Affects the elderly; idiopathic; CSF pressure elevated only episodically; does not result in increased subarachnoid space volume. Expansion of ventricles A distort the fibers of the corona radiata → triad of urinary incontinence, ataxia, and cognitive dysfunction (sometimes reversible). “Wet, wobbly, and wacky.”

**Noncommunicating (obstructive)**

Noncommunicating hydrocephalus

Caused by structural blockage of CSF circulation within ventricular system (e.g., stenosis of aqueduct of Sylvius; colloid cyst blocking foramen of Monro).

Hydrocephalus mimics

Ex vacuo ventriculomegaly

Appearance of † CSF on imaging, is actually due to decreased brain tissue (neuronal atrophy) (e.g., Alzheimer disease, advanced HIV, Pick disease). ICP is normal; triad is not seen.
Spinal nerves

There are 31 pairs of spinal nerves in total: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, 1 coccygeal. Nerves C1–C7 exit above the corresponding vertebra. C8 spinal nerve exits below C7 and above T1. All other nerves exit below (e.g., C3 exits above the 3rd cervical vertebra; L2 exits below the 2nd lumbar vertebra).

31, just like 31 flavors of Baskin-Robbins ice cream!

Vertebral disc herniation — nucleus pulposus (soft central disc) herniates through annulus fibrosus (outer ring); usually occurs posterolaterally at L4–L5 or L5–S1.

Spinal cord — lower extent

In adults, spinal cord extends to lower border of L1–L2 vertebrae. Subarachnoid space (which contains the CSF) extends to lower border of S2 vertebra. Lumbar puncture is usually performed between L3–L4 or L4–L5 (level of cauda equina).

Goal of lumbar puncture is to obtain sample of CSF without damaging spinal cord. To keep the cord alive, keep the spinal needle between L3 and L5.

Spinal cord and associated tracts

Legs (Lumbosacral) are lateral in Lateral corticospinal, spinothalamic tracts. Dorsal column is organized as you are, with hands at sides. Arms outside, legs inside.
### Spinal tract anatomy and functions

Remember, ascending tracts synapse and then cross.

<table>
<thead>
<tr>
<th>TRACT AND FUNCTION</th>
<th>1ST-ORDER NEURON</th>
<th>SYNAPSE 1</th>
<th>2ND-ORDER NEURON</th>
<th>SYNAPSE 2</th>
<th>3RD-ORDER NEURON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorsal column</td>
<td>Sensory nerve ending → cell body in dorsal root ganglion → enters spinal cord, ascends ipsilaterally in dorsal column</td>
<td>Ipsilateral nucleus cuneatus or gracilis (medulla)</td>
<td>Decussates in medulla → ascends contralaterally in medial lemniscus</td>
<td>VPL (thalamus)</td>
<td>Sensory cortex</td>
</tr>
<tr>
<td></td>
<td>Spinothalamic tract</td>
<td>Sensory nerve ending (Aδ and C fibers) (cell body in dorsal root ganglion) → enters spinal cord</td>
<td>Ipsilateral gray matter (spinal cord)</td>
<td>Decussates at anterior white commissure → ascends contralaterally</td>
<td>VPL (thalamus)</td>
</tr>
<tr>
<td></td>
<td>Lateral corticospinal tract</td>
<td>UMN: cell body in 1° motor cortex → descends ipsilaterally (through internal capsule), most fibers decussate at caudal medulla (pyramidal decussation) → descends contralaterally</td>
<td>Cell body of anterior horn (spinal cord)</td>
<td>LMN: leaves spinal cord</td>
<td>NMJ</td>
</tr>
</tbody>
</table>

### Motor neuron signs

<table>
<thead>
<tr>
<th>SIGN</th>
<th>UMN LESION</th>
<th>LMN LESION</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness</td>
<td>+</td>
<td>+</td>
<td><strong>Lower MN =</strong> everything lowered (less muscle mass, ↓ muscle tone, ↓ reflexes, downgoing toes).</td>
</tr>
<tr>
<td>Atrophy</td>
<td>−</td>
<td>+</td>
<td><strong>Upper MN =</strong> everything up (tone, DTRs, toes).</td>
</tr>
<tr>
<td>Fasciculations</td>
<td>−</td>
<td>+</td>
<td>Fasciculations = muscle twitching.</td>
</tr>
<tr>
<td>Reflexes</td>
<td>↑</td>
<td>↓</td>
<td>Positive Babinski is normal in infants.</td>
</tr>
<tr>
<td>Tone</td>
<td>↑</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Babinski</td>
<td>+</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Spastic paralysis</td>
<td>+</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Flaccid paralysis</td>
<td>−</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Clasp knife spasticity</td>
<td>+</td>
<td>−</td>
<td></td>
</tr>
</tbody>
</table>
### Spinal cord lesions

<table>
<thead>
<tr>
<th>AREA AFFECTED</th>
<th>DISEASE</th>
<th>CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Poliomyelitis and spinal muscular atrophy (Werdnig-Hoffmann disease)</td>
<td>LMN lesions only, due to destruction of anterior horns; flaccid paralysis.</td>
</tr>
<tr>
<td></td>
<td>Multiple sclerosis</td>
<td>Due to demyelination; mostly white matter of cervical region; random and asymmetric lesions, due to demyelination; scanning speech, intention tremor, nystagmus.</td>
</tr>
<tr>
<td></td>
<td>Amyotrophic lateral sclerosis</td>
<td>Combined UMN and LMN deficits with no sensory or oculomotor deficits; both UMN and LMN signs. Can be caused by defect in superoxide dismutase 1. Commonly presents as fasciculations with eventual atrophy and weakness of hands; fatal. Riluzole treatment modestly ↑ survival by ↓ presynaptic glutamate release. Commonly known as Lou Gehrig disease. For Lou Gehrig disease, give riluzole (a glutamate antagonist).</td>
</tr>
<tr>
<td></td>
<td>Complete occlusion of anterior spinal artery</td>
<td>Spares dorsal columns and Lissauer tract; upper thoracic ASA territory is watershed area, as artery of Adamkiewicz supplies ASA below ~ T8.</td>
</tr>
<tr>
<td></td>
<td>Tabes dorsalis</td>
<td>Caused by 3° syphilis. Results from degeneration (demyelination) of dorsal columns and roots → impaired sensation and proprioception, progressive sensory ataxia (inability to sense or feel the legs → poor coordination). Associated with Charcot joints, shooting pain, Argyll Robertson pupils. Exam will demonstrate absence of DTRs and ⊕ Romberg sign.</td>
</tr>
<tr>
<td></td>
<td>Syringomyelia</td>
<td>Syrinx expands and damages anterior white commissure of spinothalamic tract (2nd-order neurons) → bilateral loss of pain and temperature sensation (usually C8–T1); seen with Chiari I malformation; can expand and affect other tracts.</td>
</tr>
<tr>
<td></td>
<td>Vitamin B₁₂ deficiency</td>
<td>Subacute combined degeneration—demyelination of dorsal columns, lateral corticospinal tracts, and spino cerebellar tracts; ataxic gait, paresthesia, impaired position and vibration sense.</td>
</tr>
</tbody>
</table>
Poliomyelitis

Caused by poliovirus (fecal-oral transmission). Replicates in oropharynx and small intestine before spreading via bloodstream to CNS. Infection causes destruction of cells in anterior horn of spinal cord (LMN death).

**Symptoms**

LMN lesion signs: weakness, hypotonia, flaccid paralysis, fasciculations, hyporeflexia, muscle atrophy. Signs of infection: malaise, headache, fever, nausea, etc.

**Findings**

CSF with ↑ WBCs and slight ↑ of protein (with no change in CSF glucose). Virus recovered from stool or throat.

Spinal muscular atrophy (Werdnig-Hoffmann disease)

Congenital degeneration of anterior horns of spinal cord → LMN lesion. “Floppy baby” with marked hypotonia and tongue fasciculations. Infantile type has median age of death of 7 months. Autosomal recessive inheritance.

Friedreich ataxia

Autosomal recessive trinucleotide repeat disorder (GAA) on chromosome 9 in gene that encodes frataxin (iron binding protein). Leads to impairment in mitochondrial functioning. Degeneration of multiple spinal cord tracts → muscle weakness and loss of DTRs, vibratory sense, proprioception. Staggering gait, frequent falling, nystagmus, dysarthria, pes cavus, hammer toes, diabetes mellitus, hypertrophic cardiomyopathy (cause of death). Presents in childhood with kyphoscoliosis. Friedreich is Fratastic (frataxin): he’s your favorite frat brother, always staggering and falling but has a sweet, big heart.

Brown-Séquard syndrome

Hemisection of spinal cord. Findings:

- Ipsilateral UMN signs below level of lesion (due to corticospinal tract damage)
- Ipsilateral loss of tactile, vibration, proprioception sense below level of lesion (due to dorsal column damage)
- Contralateral pain and temperature loss below level of lesion (due to spinothalamic tract damage)
- Ipsilateral loss of all sensation at level of lesion
- Ipsilateral LMN signs (e.g., flaccid paralysis) at level of lesion

If lesion occurs above T1, patient may present with Horner syndrome due to damage of oculosympathetic pathway.
Landmark dermatomes

- C2 — posterior half of a skull “cap.”
- C3 — high turtleneck shirt.
- C4 — low-collar shirt.
- T4 — at the nipple.
- T7 — at the xiphoid process.
- T10 — at the umbilicus (important for early appendicitis pain referral).
- L1 — at the inguinal ligament.
- L4 — includes the kneecaps.
- S2, S3, S4 — erection and sensation of penile and anal zones.

Diaphragm and gallbladder pain referred to the right shoulder via phrenic nerve.

- T4 at the teat pore.
- T10 at the belly button.
- L1 is IL (Inguinal Ligament). Down on ALL 4’s (L4).
- “S2, 3, 4 keep the penis off the floor.”

Clinical reflexes

- Biceps = C5 nerve root.
- Triceps = C7 nerve root.
- Patella = L4 nerve root.
- Achilles = S1 nerve root.

Reflexes count up in order:
- S1, 2 — “buckle my shoe” (Achilles reflex)
- L3, 4 — “kick the door” (patellar reflex)
- C5, 6 — “pick up sticks” (biceps reflex)
- C7, 8 — “lay them straight” (triceps reflex)

Additional reflexes:
- L1, L2 — “testicles move” (cremaster reflex)
- S3, S4 — “winks galore” (anal wink reflex)

Primitive reflexes

CNS reflexes that are present in a healthy infant, but are absent in a neurologically intact adult. Normally disappear within 1st year of life. These “primitive” reflexes are inhibited by a mature/developing frontal lobe. They may reemerge in adults following frontal lobe lesions → loss of inhibition of these reflexes.

- Moro reflex — “Hang on for life” reflex — abduct/extend arms when startled, and then draw together
- Rooting reflex — Movement of head toward one side if cheek or mouth is stroked (nipple seeking)
- Sucking reflex — Sucking response when roof of mouth is touched
- Palmar reflex — Curling of fingers if palm is stroked
- Plantar reflex — Dorsiflexion of large toe and fanning of other toes with plantar stimulation

Babinski sign — presence of this reflex in an adult, which may signify a UMN lesion

Galant reflex — Stroking along one side of the spine while newborn is in ventral suspension (face down) causes lateral flexion of lower body toward stimulated side
Brain stem—ventral view

CN nuclei that lie medially at brain stem: III, IV, VI, XII. “Factors of 12, except 1 and 2.”

Brain stem—dorsal view (cerebellum removed)

Pineal gland—melatonin secretion, circadian rhythms.
Superior colliculi—conjugate vertical gaze center.
Inferior colliculi—auditory.
Parinaud syndrome—paralysis of conjugate vertical gaze due to lesion in superior colliculi (e.g., stroke, hydrocephalus, pinealoma).

Your eyes are above your ears, and the superior colliculus (visual) is above the inferior colliculus (auditory).

Cranial nerve nuclei

Located in tegmentum portion of brain stem (between dorsal and ventral portions):
- Midbrain—nuclei of CN III, IV
- Pons—nuclei of CN V, VI, VII, VIII
- Medulla—nuclei of CN IX, X, XII
- Spinal cord—nucleus of CN XI

Lateral nuclei = sensory (a Lar plate).
- Sulcus limitans—
- Medial nuclei = Motor (basal plate).
Cranial nerve and vessel pathways

Cribiform plate (CN I).
Middle cranial fossa (CN II–VI)—through sphenoid bone:
- Optic canal (CN II, ophthalmic artery, central retinal vein)
- Superior orbital fissure (CN III, IV, V₁, VI, ophthalmic vein, sympathetic fibers)
- Foramen Rotundum (CN V₂)
- Foramen Ovale (CN V₃)
- Foramen spinosum (middle meningeal artery)

Posterior cranial fossa (CN VII–XII)—through temporal or occipital bone:
- Internal auditory meatus (CN VII, VIII)
- Jugular foramen (CN IX, X, XI, jugular vein)
- Hypoglossal canal (CN XII)
- Foramen magnum (spinal roots of CN XI, brain stem, vertebral arteries)

Divisions of CN V exit owing to Standing Room Only.

Cranial nerves

<table>
<thead>
<tr>
<th>NERVE</th>
<th>CN</th>
<th>FUNCTION</th>
<th>TYPE</th>
<th>MNEMONIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olfactory</td>
<td>I</td>
<td>Smell (only CN without thalamic relay to cortex)</td>
<td>Sensory</td>
<td>Some</td>
</tr>
<tr>
<td>Optic</td>
<td>II</td>
<td>Sight</td>
<td>Sensory</td>
<td>Say</td>
</tr>
<tr>
<td>Oculomotor</td>
<td>III</td>
<td>Eye movement (SR, IR, MR, IO), pupillary constriction (sphincter pupillae: Edinger-Westphal nucleus, muscarinic receptors), accommodation, eyelid opening (levator palpebrae)</td>
<td>Motor</td>
<td>Marry</td>
</tr>
<tr>
<td>Trochlear</td>
<td>IV</td>
<td>Eye movement (SO)</td>
<td>Motor</td>
<td>Money</td>
</tr>
<tr>
<td>Trigeminal</td>
<td>V</td>
<td>Mastication, facial sensation (ophthalmic, maxillary, mandibular divisions), somatosensation from anterior 2/3 of tongue</td>
<td>Both</td>
<td>But</td>
</tr>
<tr>
<td>Abducens</td>
<td>VI</td>
<td>Eye movement (LR)</td>
<td>Motor</td>
<td>My</td>
</tr>
<tr>
<td>Facial</td>
<td>VII</td>
<td>Facial movement, taste from anterior 2/3 of tongue, lacrimation, salvation (submandibular and sublingual glands), eyelid closing (orbicularis oculi), stapedius muscle in ear (note: nerve courses through the parotid gland, but does not innervate it)</td>
<td>Both</td>
<td>Brother</td>
</tr>
<tr>
<td>Vestibulocochlear</td>
<td>VIII</td>
<td>Hearing, balance</td>
<td>Sensory</td>
<td>Says</td>
</tr>
<tr>
<td>Glossopharyngeal</td>
<td>IX</td>
<td>Taste and somatosensation from posterior 1/3 of tongue, swallowing, salivation (parotid gland), monitoring carotid body and sinus chemo- and baroreceptors, and stylopharyngeus (elevates pharynx, larynx)</td>
<td>Both</td>
<td>Big</td>
</tr>
<tr>
<td>Vagus</td>
<td>X</td>
<td>Taste from epiglottic region, swallowing, soft palate elevation, midline uvula, talking, coughing, thoracoabdominal viscera, monitoring aortic arch chemo- and baroreceptors</td>
<td>Both</td>
<td>Brains</td>
</tr>
<tr>
<td>Accessory</td>
<td>XI</td>
<td>Head turning, shoulder shrugging (SCM, trapezius)</td>
<td>Motor</td>
<td>Matter</td>
</tr>
<tr>
<td>Hypoglossal</td>
<td>XII</td>
<td>Tongue movement</td>
<td>Motor</td>
<td>Most</td>
</tr>
</tbody>
</table>
**Vagal nuclei**

**Nucleus Solitarius**
Visceral sensory information (e.g., taste, baroreceptors, gut distention).
VII, IX, X.

**Nucleus ambiguus**
Motor innervation of pharynx, larynx, upper esophagus (e.g., swallowing, palate elevation).
IX, X, XI (cranial portion).

**Dorsal motor nucleus**
Sends autonomic (parasympathetic) fibers to heart, lungs, upper GI.
X.

---

**Cranial nerve reflexes**

<table>
<thead>
<tr>
<th>REFLEX</th>
<th>AFFERENT</th>
<th>EFFERENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corneal</td>
<td>V1 ophthalmic (nasociliary branch)</td>
<td>VII (temporal branch: orbicularis oculi)</td>
</tr>
<tr>
<td>Lacrimation</td>
<td>V1 (loss of reflex does not preclude emotional tears)</td>
<td>VII</td>
</tr>
<tr>
<td>Jaw jerk</td>
<td>V3 (sensory—muscle spindle from masseter)</td>
<td>V3 (motor—masseter)</td>
</tr>
<tr>
<td>Pupillary</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>Gag</td>
<td>IX</td>
<td>X</td>
</tr>
</tbody>
</table>

---

**Common cranial nerve lesions**

- **CN V motor lesion**
  Jaw deviates toward side of lesion due to unopposed force from the opposite pterygoid muscle.

- **CN X lesion**
  Uvula deviates away from side of lesion. Weak side collapses and uvula points away.

- **CN XI lesion**
  Weakness turning head to contralateral side of lesion (SCM). Shoulder droop on side of lesion (trapezius).
The left SCM contracts to help turn the head to the right.

- **CN XII lesion (LMN)**
  Tongue deviates toward side of lesion (“lick your wounds”) due to weakened tongue muscles on affected side.
Cavernous sinus

Collection of venous sinuses on either side of pituitary. Blood from eye and superficial cortex → cavernous sinus → internal jugular vein. CN III, IV, V₁, VI, and occasionally V₂ plus postganglionic sympathetic pupillary fibers en route to orbit all pass through cavernous sinus. Cavernous portion of internal carotid artery is also here.

Nerves that control extraocular muscles (plus V₁ and V₂) pass through the cavernous sinus.

Cavernous sinus syndrome—presents with variable ophthalmoplegia, 4 corneal sensation, Horner syndrome and occasional decreased maxillary sensation. 2° to pituitary tumor mass effect, carotid-cavernous fistula, or cavernous sinus thrombosis related to infection. CN VI is most susceptible to injury.

Auditory physiology

Outer ear
Visible portion of ear (pinna), includes auditory canal and eardrum. Transfers sound waves via vibration of eardrum.

Middle ear
Air-filled space with three bones called the ossicles (malleus, incus, stapes). Ossicles conduct and amplify sound from eardrum to inner ear.

Inner ear
Snail-shaped, fluid-filled cochlea. Contains basilar membrane that vibrates 2⁴ to sound waves. Vibration transduced via specialized hair cells → auditory nerve signaling → brain stem. Each frequency leads to vibration at specific location on basilar membrane (tonotopy):
* Low frequency heard at apex near helicotrema (wide and flexible).
* High frequency heard best at base of cochlea (thin and rigid).

Hearing loss

<table>
<thead>
<tr>
<th>RINNE TEST</th>
<th>WEBBER TEST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conductive</td>
<td>Localizes to affected ear</td>
</tr>
<tr>
<td>Abnormal (bone &gt; air)</td>
<td></td>
</tr>
<tr>
<td>Sensorineural</td>
<td>Localizes to unaffected ear</td>
</tr>
<tr>
<td>Normal (air &gt; bone)</td>
<td></td>
</tr>
<tr>
<td>Noise-induced</td>
<td>Damage to stereociliated cells in organ of Corti; loss of high-frequency hearing 1st; sudden extremely loud noises can produce hearing loss due to tympanic membrane rupture.</td>
</tr>
</tbody>
</table>
**Cholesteatoma**

Overgrowth of desquamated keratin debris within middle ear space may erode ossicles, mastoid air cells → conductive hearing loss.

**Facial lesions**

<table>
<thead>
<tr>
<th>UMN lesion</th>
<th>Lesion of motor cortex or connection between cortex and facial nucleus. Contralateral paralysis of lower face; forehead spared due to bilateral UMN innervation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMN lesion</td>
<td>Ipsilateral paralysis of upper and lower face.</td>
</tr>
<tr>
<td>Facial nerve palsy</td>
<td>Complete destruction of the facial nucleus itself or its branchial efferent fibers (facial nerve proper). Peripheral ipsilateral facial paralysis (absent forehead creases and drooping smile with inability to close eye on involved side). Can occur idiopathically (called Bell palsy); gradual recovery in most cases. Associated with Lyme disease, herpes simplex and (less common) herpes zoster (Ramsay Hunt syndrome), sarcoidosis, tumors, diabetes. Treatment includes corticosteroids.</td>
</tr>
</tbody>
</table>

**Mastication muscles**

3 muscles close jaw: **M**asseter, **tE**mporalis, **M**edial pterygoid. 1 opens: lateral pterygoid. All are innervated by trigeminal nerve (V3).

**M’s Munch**

Lateral Lowers (when speaking of pterygoids with respect to jaw motion). “It takes more muscle to keep your mouth shut.”
Normal eye

Aqueous humor pathway

Refractive errors

<table>
<thead>
<tr>
<th>Error</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperopia</td>
<td>Eye too short for refractive power of cornea and lens → light focused behind retina.</td>
</tr>
<tr>
<td>Myopia</td>
<td>Eye too long for refractive power of cornea and lens → light focused in front of retina.</td>
</tr>
<tr>
<td>Astigmatism</td>
<td>Abnormal curvature of cornea → different refractive power at different axes.</td>
</tr>
<tr>
<td>Presbyopia</td>
<td>Age-related impaired accommodation (focusing on near objects), possibly due to decreased lens elasticity. Often necessitates “reading glasses.”</td>
</tr>
</tbody>
</table>
Cataract
Painless, often bilateral, opacification of lens in vision. Risk factors: age, smoking, EtOH, excessive sunlight, prolonged corticosteroid use, classic galactosemia, galactokinase deficiency, diabetes mellitus (sorbitol), trauma, infection.

Glaucoma
Optic disc atrophy with characteristic cupping (thinning of outer rim of optic nerve head versus normal), usually with elevated intraocular pressure (IOP) and progressive peripheral visual field loss.

Open angle
Associated with age, African-American race, family history. Painless, more common in U.S. Primary—cause unclear. Secondary—blocked trabecular meshwork from WBCs (e.g., uveitis), RBCs (e.g., vitreous hemorrhage), retinal elements (e.g., retinal detachment).

Closed/narrow angle
Primary—enlargement or forward movement of lens against central iris (pupil margin) → obstruction of normal aqueous flow through pupil → fluid builds up behind iris, pushing peripheral iris against cornea and impeding flow through trabecular meshwork. Secondary—hypoxia from retinal disease (e.g., diabetes mellitus, vein occlusion) induces vasoproliferation in iris that contracts angle.

Chronic closure—often asymptomatic with damage to optic nerve and peripheral vision. Acute closure—true ophthalmic emergency. ↑ IOP pushes iris forward → angle closes abruptly. Very painful, red eye, sudden vision loss, halos around lights, rock-hard eye, frontal headache. Do not give epinephrine because of its mydriatic effect.

Uveitis
Inflammation of uvea (e.g., iritis aka anterior uveitis, choroiditis aka posterior uveitis). May have hypopyon (accumulation of pus in anterior chamber) or conjunctival redness. Associated with systemic inflammatory disorders (e.g., sarcoidosis, rheumatoid arthritis, juvenile idiopathic arthritis, HLA-B27–associated conditions).
Age-related macular degeneration

Degeneration of macula (central area of retina). Causes distortion (metamorphopsia) and eventual loss of central vision (scotomas).

- Dry (nonexudative, > 80%)—deposition of yellowish extracellular material in and beneath Bruch membrane and retinal pigment epithelium (“drusen”) with gradual in vision. Prevent progression with multivitamin and antioxidant supplements.

- Wet (exudative, 10–15%)—rapid loss of vision due to bleeding 2º to choroidal neovascularization. Treat with anti-VEGF (vascular endothelial growth factor) injections (e.g., ranibizumab) or laser.

Diabetic retinopathy

Retinal damage due to chronic hyperglycemia. Two types:

- Nonproliferative—damaged capillaries leak blood lipids and fluid seep into retina hemorrhages and macular edema. Treatment: blood sugar control, macular laser.

- Proliferative—chronic hypoxia results in new blood vessel formation with resultant traction on retina. Treatment: peripheral retinal photocoagulation, anti-VEGF (e.g., bevacizumab).

Retinal vein occlusion

Blockage of central or branch retinal vein due to compression from nearby arterial atherosclerosis. Retinal hemorrhage and venous engorgement 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 2º to retinal breaks, diabetic traction, inflammatory effusions. Visualized on fundoscopy by the splaying and paucity of retinal vessels [blue arrows]. Correlation with cross-sectional “optical ultrasound” shown on inset. Breaks more common in patients with high myopia and are 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)  

Retinitis pigmentosa

Inherited retinal degeneration. Painless, progressive vision loss beginning with night blindness (rods affected first). Bone spicule–shaped deposits around macula  

Retinitis

Retinal edema and necrosis leading to scar  . Often viral (CMV, HSV, HZV). Associated with immunosuppression.  

Papilledema

Optic disc swelling (usually bilateral) due to ↑ ICP (e.g., 2° to mass effect). Enlarged blind spot and elevated optic disc with blurred margins seen on fundoscopic exam  

**Pupillary control**

**Miosis**
Constriction, parasympathetic:
- 1st neuron: Edinger-Westphal nucleus to ciliary ganglion via CN III
- 2nd neuron: short ciliary nerves to pupillary sphincter muscles

**Pupillary light reflex**
Light in either retina sends a signal via CN II to pretectal nuclei (dashed lines in image) in midbrain that activates bilateral Edinger-Westphal nuclei; pupils contract bilaterally (consensual reflex).
Result: illumination of 1 eye results in bilateral pupillary constriction.

**Mydriasis**
Dilation, sympathetic:
- 1st neuron: hypothalamus to ciliospinal center of Budge (C8–T2)
- 2nd neuron: exit at T1 to superior cervical ganglion (travels along cervical sympathetic chain near lung apex, subclavian vessels)
- 3rd neuron: plexus along internal carotid, through cavernous sinus; enters orbit as long ciliary nerve to pupillary dilator muscles. Sympathetic fibers also innervate smooth muscle of eyelids (minor retractor) and sweat glands of forehead and face.

**Marcus Gunn pupil**
Afferent pupillary defect—due to optic nerve damage or severe retinal injury, bilateral pupillary constriction when light is shone in affected eye relative to unaffected eye. Tested with “swinging flashlight test.”

**Horner syndrome**
Sympathetic denervation of face:
- Ptosis (slight drooping of eyelid: superior tarsal muscle)
- Anhidrosis (absence of sweating) and flushing (rubor) of affected side of face
- Miosis (pupil constriction)
Associated with lesion of spinal cord above T1 (e.g., Pancoast tumor, Brown-Séquard syndrome [cord hemisection], late-stage syringomyelia).
Any interruption results in Horner syndrome.
Ocular motility

To test function of each muscle, ask patient to follow a path from 1° position as diagramed (i.e., SO depression function best tested when eye is adducted).

Obliques go Opposite (left SO and IO tested with patient looking right).

IOU: IO tested looking Up.
CN III, IV, VI palsies

**CN III damage**

CN III has both motor (central) and parasympathetic (peripheral) components. Motor output to ocular muscles—affected primarily by vascular disease (e.g., 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 1st affected by compression (e.g., posterior communicating artery aneurysm, uncal herniation). Signs: diminished or absent pupillary light reflex, “blown pupil” often with “down-and-out” gaze.

**CN IV damage**

Eye moves upward, particularly with contralateral gaze and head tilt toward the side of the lesion (problems going down stairs, may present with compensatory head tilt in the opposite direction).

**CN VI damage**

Medially directed eye that cannot abduct.
Visual field defects

1. Right anopia
2. Bitemporal hemianopia (pituitary lesion, chiasm)
3. Left homonymous hemianopia
4. Left upper quadrantic anopia (right temporal lesion, MCA)
5. Left lower quadrantic anopia (right parietal lesion, MCA)
6. Left hemianopia with macular sparing (PCA infarct), macula → bilateral projection to occiput
7. Central scotoma (macular degeneration)

Meyer loop—inferior retina; loops around inferior horn of lateral ventricle.
Dorsal optic radiation—superior retina; takes shortest path via internal capsule.

Internuclear ophthalmoplegia

Medial longitudinal fasciculus (MLF): pair of tracts that allows for crosstalk between CN VI and CN III nuclei. Coordinates both eyes to move in same horizontal direction. Highly myelinated (must communicate quickly so eyes move at same time). Lesions may be unilateral or bilateral (latter classically seen in multiple sclerosis).

Lesion in MLF = internuclear ophthalmoplegia (INO), a conjugate horizontal gaze palsy. Lack of communication such that when CN VI nucleus activates ipsilateral lateral rectus, contralateral CN III nucleus does not stimulate medial rectus to fire. Abducting eye gets nystagmus (CN VI overfires to stimulate CN III). Convergence normal.

MLF in MS.
When looking left, the left nucleus of CN VI fires, which contracts the left lateral rectus and stimulates the contralateral (right) nucleus of CN III via the right MLF to contract the right medial rectus.

Directional term (e.g., right INO, left INO) refers to which eye is paralyzed.
## Dementia

A ↓ in cognitive ability, memory, or function with intact consciousness.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Description</th>
<th>Histologic/Gross Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alzheimer disease</strong></td>
<td>Most common cause in elderly. Down syndrome patients have an ↑ risk of developing Alzheimer. Familiar form (10%) associated with the following altered proteins: * ApoE2: ↓ risk * ApoE4: ↑ risk * APP, presenilin-1, presenilin-2: ↑ risk of early onset</td>
<td>Widespread cortical atrophy. Narrowing of gyri and widening of sulci ↓ ACh Senile plaques ↑β in gray matter: extracellular β-amyloid core; may cause amyloid angiopathy → intracranial hemorrhage; Aβ (amyloid-β) synthesized by cleaving amyloid precursor protein (APP) Neurofibrillary tangles: intracellular, hyperphosphorylated tau protein = insoluble cytoskeletal elements; number of tangles correlates with degree of dementia</td>
</tr>
<tr>
<td><strong>Frontotemporal dementia</strong></td>
<td>Dementia, aphasia, parkinsonian aspects; change in personality. Spares parietal lobe and posterior ⅔ of superior temporal gyrus.</td>
<td>Also called Pick disease. Note the Pick bodies: silver-staining spherical tau protein aggregates Frontotemporal atrophy</td>
</tr>
<tr>
<td><strong>Lewy body dementia</strong></td>
<td>Initially dementia and visual hallucinations (“hallucinations”) followed by parkinsonian features.</td>
<td>α-synuclein defect (Lewy bodies, primarily cortical)</td>
</tr>
<tr>
<td><strong>Creutzfeldt-Jakob disease</strong></td>
<td>Rapidly progressive (weeks to months) dementia with myoclonus (“startle myoclonus”).</td>
<td>Spongiform cortex Prions (PrPsc → PrPc sheet [β-pleated sheet resistant to proteases])</td>
</tr>
<tr>
<td><strong>Other causes</strong></td>
<td>Multi-infarct (aka vascular, 2nd most common cause of dementia in elderly); syphilis; HIV; vitamins B1, B3, or B12 deficiency; Wilson disease; normal pressure hydrocephalus.</td>
<td></td>
</tr>
</tbody>
</table>
Multiple sclerosis

Autoimmune inflammation and demyelination of CNS (brain and spinal cord). Patients can present with optic neuritis (sudden loss of vision resulting in Marcus Gunn pupils), INO, hemiparesis, hemisensory symptoms, bladder/bowel incontinence. Relapsing and remitting course. Most often affects women in their 20s and 30s; more common in whites living further from equator.

Charcot classic triad of MS is a S I N:
- Scanning speech
- Intention tremor (also incontinence and internuclear ophthalmoplegia)
- Nystagmus

Findings

1. Protein (IgG) in CSF. Oligoclonal bands are diagnostic. MRI is gold standard. Periventricular plaques (areas of oligodendrocyte loss and reactive gliosis) with destruction of axons. Multiple white matter lesions separated in space and time.

Treatment

Slow progression with disease-modifying therapies (e.g., β-interferon, natalizumab). Treat acute flares with IV steroids. Symptomatic treatment for neurogenic bladder (catheterization, muscarinic antagonists), spasticity (baclofen, GABA<sub>B</sub> receptor agonists), pain (opioids).

Acute inflammatory demyelinating polyradiculopathy

Most common subtype of Guillain-Barré syndrome. Autoimmune condition that destroys Schwann cells → inflammation and demyelination of peripheral nerves and motor fibers. Results in symmetric ascending muscle weakness/paralysis beginning in lower extremities. Facial paralysis in 50% of cases. May see autonomic dysregulation (e.g., cardiac irregularities, hypertension, hypotension) or sensory abnormalities. Almost all patients survive; the majority recover completely after weeks to months.

Findings:
- CSF protein with normal cell count (albumino cytologic dissociation). Protein may cause papilledema.

Associated with infections (e.g., Campylobacter jejuni, viral) → autoimmune attack of peripheral myelin due to molecular mimicry, inoculations, and stress, but no definitive link to pathogens. Respiratory support is critical until recovery. Additional treatment: plasmapheresis, IV immunoglobulins.
Other demyelinating and dysmyelinating diseases

**Acute disseminated (postinfectious) encephalomyelitis**
Multifocal periventricular inflammation and demyelination after infection (commonly measles or VZV) or certain vaccinations (e.g., rabies, smallpox).

**Charcot-Marie-Tooth disease**
Also known as hereditary motor and sensory neuropathy (HMSN). Group of progressive hereditary nerve disorders related to the defective production of proteins involved in the structure and function of peripheral nerves or the myelin sheath. Typically autosomal dominant inheritance pattern and associated with scoliosis and foot deformities (high or flat arches).

**Krabbe disease**
Autosomal recessive lysosomal storage disease due to deficiency of galactocerebrosidase. Buildup of galactocerebroside and psychosine destroys myelin sheath. Findings: peripheral neuropathy, developmental delay, optic atrophy, globoid cells.

**Metachromatic leukodystrophy**
Autosomal recessive lysosomal storage disease, most commonly due to arylsulfatase A deficiency. Buildup of sulfatides → impaired production and destruction of myelin sheath. Findings: central and peripheral demyelination with ataxia, dementia.

**Progressive multifocal leukoencephalopathy**
Demyelination of CNS due to destruction of oligodendrocytes. Associated with JC virus. Seen in 2–4% of AIDS patients (reactivation of latent viral infection). Rapidly progressive, usually fatal. ↑ risk associated with natalizumab, rituximab.

**Adrenoleukodystrophy**
X-linked genetic disorder typically affecting males. Disrupts metabolism of very-long-chain fatty acids → excessive buildup in nervous system, adrenal gland, testes. Progressive disease that can lead to long-term coma/death and adrenal gland crisis.

Seizures
Characterized by synchronized, high-frequency neuronal firing. Variety of forms.

**Partial (focal) seizures**
Affect single area of the brain. Most commonly originate in medial temporal lobe. Often preceded by seizure aura; can secondarily generalize. Types:
- **Simple partial** (consciousness intact)—motor, sensory, autonomic, psychic
- **Complex partial** (impaired consciousness)

**Generalized seizures**
Diffuse. Types:
- **Absence** (petit mal)—3 Hz, no postictal confusion, blank stare
- **Myoclonic**—quick, repetitive jerks
- **Tonic-clonic** (grand mal)—alternating stiffening and movement
- **Tonic**—stiffening
- **Atonic**—“drop” seizures (falls to floor); commonly mistaken for fainting

**Epilepsy**—a disorder of recurrent seizures (febrile seizures are not epilepsy).
**Status epilepticus**—continuous or recurring seizure(s) that may result in brain injury; variably defined as > 10–30 min.
Causes of seizures by age:
- **Children**—genetic, infection (febrile), trauma, congenital, metabolic
- **Adults**—tumor, trauma, stroke, infection
- **Elderly**—stroke, tumor, trauma, metabolic, infection
### Differentiating headaches

Pain due to irritation of structures such as the dura, cranial nerves, or extracranial structures.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Localization</th>
<th>Duration</th>
<th>Description</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cluster</strong></td>
<td>Unilateral</td>
<td>15 min–3 hr; repetitive</td>
<td>Repetitive brief headaches. Excruciating periorbital pain with lacrimation and rhinorrhea. May induce Horner syndrome. More common in males.</td>
<td>100% O₂, sumatriptan</td>
</tr>
<tr>
<td><strong>Tension</strong></td>
<td>Bilateral</td>
<td>&gt; 30 min (typically 4–6 hr); constant</td>
<td>Steady pain. No photophobia or phonophobia. No aura.</td>
<td>Analgesics, NSAIDs, acetaminophen; amitriptyline for chronic pain</td>
</tr>
<tr>
<td><strong>Migraine</strong></td>
<td>Unilateral</td>
<td>4–72 hr</td>
<td>Pulsating pain with nausea, photophobia, or phonophobia. May have “aura.” Due to irritation of CN V, meninges, or blood vessels (release of substance P, calcitonin gene-related peptide, vasoactive peptides).</td>
<td>Abortive therapies (e.g., triptans, NSAIDs) and prophylaxis (e.g., propranolol, topiramate, Ca²⁺ channel blockers, amitriptyline). POUND—Pulsatile, One-day duration, Unilateral, Nausea, Disabling</td>
</tr>
</tbody>
</table>

Other causes of headache include subarachnoid hemorrhage (“worst headache of my life”), meningitis, hydrocephalus, neoplasia, arteritis.

*Compare with trigeminal neuralgia, which produces repetitive shooting pain in the distribution of CN V that lasts (typically) for < 1 minute.*

### Vertigo

Sensation of spinning while actually stationary. Subtype of “dizziness,” but distinct from “lightheadedness.”

**Peripheral vertigo**

More common. Inner ear etiology (e.g., semicircular canal debris, vestibular nerve infection, Ménière disease). Positional testing ➔ delayed horizontal nystagmus.

**Central vertigo**

Brain stem or cerebellar lesion (e.g., stroke affecting vestibular nuclei or posterior fossa tumor). Findings: directional change of nystagmus, skew deviation, diplopia, dysmetria. Positional testing ➔ immediate nystagmus in any direction; may change directions. Focal neurologic findings.
Neurocutaneous disorders

<table>
<thead>
<tr>
<th>Neurocutaneous disorder</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sturge-Weber syndrome</td>
<td>Congenital, non-inherited (somatic), developmental anomaly of neural crest derivatives (mesoderm/ectoderm) due to activating mutation of GNAQ gene. Affects small (capillary-sized) blood vessels → port-wine stain of the face (nevus flammeus, a non-neoplastic “birthmark” in CN V1/V2 distribution); ipsilateral leptomeningeal angioma → seizures/epilepsy; intellectual disability; and episcleral hemangioma → ↑ IOP → early-onset glaucoma. <strong>STURGE</strong>-Weber: Sporadic, port-wine Stain; Tram track calcifications (opposing gyri); Unilateral; Retardation (intellectual disability); Glaucoma; GNAQ gene; Epilepsy.</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td><strong>HAMARTOMAS</strong>: Hamartomas in CNS and skin; Angiofibromas; Mitral regurgitation; Ash-leaf spots; cardiac Rhabdomyoma; (Tuberous sclerosis); autosomal doMinant; Mental retardation (intellectual disability); renal Angiomyolipoma; Seizures, Shagreen patches. ↑ incidence of subependymal astrocytomas and ungual fibromas.</td>
</tr>
<tr>
<td>Neurofibromatosis type I (von Recklinghausen disease)</td>
<td>Café-au-lait spots; Lisch nodules (pigmented iris hamartomas), cutaneous neurofibromas; optic gliomas, pheochromocytomas. Mutated NF1 tumor suppressor gene (neurofibromin, a negative regulator of RAS) on chromosome 17. Skin tumors of NF-1 are derived from neural crest cells.</td>
</tr>
<tr>
<td>von Hippel-Lindau disease</td>
<td>Hemangioblastomas (high vascularity with hyperchromatic nuclei in retina, brain stem, cerebellum, spine; angiomatosis (e.g., cavernous hemangiomas in skin, mucosa, organs); bilateral renal cell carcinomas; pheochromocytomas.</td>
</tr>
</tbody>
</table>

![Images of various neurological conditions](image_url)
Adult primary brain tumors

Glioblastoma multiforme (grade IV astrocytoma)

Meningioma
Common, typically benign 1° brain tumor. Most often occurs in convexities of hemispheres (near surfaces of brain) and parasagittal region. Arises from arachnoid cells, is extra-axial (external to brain parenchyma), and may have a dural attachment (“tail”). Often asymptomatic; may present with seizures or focal neurologic signs. Resection and/or radiosurgery. Histology: spindle cells concentrically arranged in a whorled pattern; psammoma bodies (laminated calcifications).

Hemangioblastoma
Most often cerebellar. Associated with von Hippel-Lindau syndrome when found with retinal angiomas. Can produce erythropoietin → 2° polycythemia. Histology: closely arranged, thin-walled capillaries with minimal intervening parenchyma.

Schwannoma
Classically at the cerebellopontine angle, but can be along any peripheral nerve. Schwann cell origin; S-100+; often localized to CN VIII → vestibular schwannoma. Resectable or treated with stereotactic radiosurgery. Bilateral vestibular schwannomas found in NF-2.

Oligodendrogloma

Pituitary adenoma
Most commonly prolactinoma. Bitemporal hemianopia shows normal visual field above, patient’s perspective below) due to pressure on optic chiasm. Hyper- or hypopituitarism are sequelae.
# Childhood primary brain tumors

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Description</th>
<th>Prognosis/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilocytic (low-grade) astrocytoma</td>
<td>Usually well circumscribed. In children, most often found in posterior fossa (e.g., cerebellum). May be supratentorial. GFAP. Benign; good prognosis.</td>
<td>Rosenthal fibers—eosinophilic, corkscrew fibers. Cystic + solid (gross).</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>Ependymal cell tumors most commonly found in 4th ventricle. Can cause hydrocephalus. Poor prognosis.</td>
<td>Characteristic perivascular rosettes. Rod-shaped blepharoplasts (basal ciliary bodies) found near nucleus.</td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>Benign childhood tumor, may be confused with pituitary adenoma (both can cause bitemporal hemianopia). Most common childhood supratentorial tumor.</td>
<td>Derived from remnants of Rathke pouch. Calcification is common (tooth enamel–like).</td>
</tr>
</tbody>
</table>

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### Herniation syndromes

1. **Cingulate (subfalcine) herniation under falk cerebi**
   - Can compress anterior cerebral artery.

2. **Downward transtentorial (central) herniation**
   - Caudal displacement of brain stem → rupture of paramedian basilar artery branches → Duret hemorrhages. Usually fatal.

3. **Uncal herniation**
   - Uncus = medial temporal lobe. Compresses ipsilateral CN III (blown pupil, “down-and-out” gaze), ipsilateral PCA (contralateral homonymous hemianopia), contralateral crus cerebri at the Kernohan notch (ipsilateral paresis; a “false localization” sign).

4. **Cerebellar tonsillar herniation into the foramen magnum**
   - Coma and death result when these herniations compress the brain stem.
### Glaucoma drugs

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM</th>
<th>SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>α-agonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine (α₁)</td>
<td>↓ aqueous humor synthesis via vasoconstriction</td>
<td>Mydriasis (αᵢ); do not use in closed-angle glaucoma</td>
</tr>
<tr>
<td>Brimonidine (α₂)</td>
<td>↓ aqueous humor synthesis</td>
<td>Blurry vision, ocular hyperemia, foreign body sensation, ocular allergic reactions, ocular pruritus</td>
</tr>
<tr>
<td><strong>β-blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timolol, betaxolol, carteolol</td>
<td>↓ aqueous humor synthesis</td>
<td>No pupillary or vision changes</td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>↓ aqueous humor synthesis via inhibition of</td>
<td>No pupillary or vision changes</td>
</tr>
<tr>
<td></td>
<td>carbonic anhydrase</td>
<td></td>
</tr>
<tr>
<td><strong>Cholinomimetics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct (pilocarpine, carbachol)</td>
<td>↑ outflow of aqueous humor via contraction of ciliary muscle and opening of trabecular meshwork</td>
<td>Miosis and cyclospasm (contraction of ciliary muscle)</td>
</tr>
<tr>
<td>Indirect (physostigmine, echothiophate)</td>
<td>Use pilocarpine in emergencies—very effective at opening meshwork into canal of Schlemm</td>
<td></td>
</tr>
<tr>
<td><strong>Prostaglandin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latanoprost (PGF₂α)</td>
<td>↑ outflow of aqueous humor</td>
<td>Darkens color of iris (browning)</td>
</tr>
</tbody>
</table>

### Opioid analgesics

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>CLINICAL USE</th>
<th>TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine, fentanyl, codeine, loperamide, methadone, meperidine, dextromethorphan, diphenoxylate, pentazocine.</td>
<td>Pain, cough suppression (dextromethorphan), diarrhea (loperamide, diphenoxylate), acute pulmonary edema, maintenance programs for heroin addicts (methadone, buprenorphine + naloxone).</td>
<td>Addiction, respiratory depression, constipation, miosis (pinpoint pupils), additive CNS depression with other drugs. Tolerance does not develop to miosis and constipation. Toxicity treated with naloxone or naltraxone (opioid receptor antagonist).</td>
</tr>
</tbody>
</table>
### Butorphanol

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>κ-opioid receptor agonist and μ-opioid receptor partial agonist; produces analgesia.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>Severe pain (e.g., migraine, labor). Causes less respiratory depression than full opioid agonists.</td>
</tr>
<tr>
<td>TOXICITY</td>
<td>Can cause opioid withdrawal symptoms if patient is also taking full opioid agonist (competition for opioid receptors). Overdose not easily reversed with naloxone.</td>
</tr>
</tbody>
</table>

### Tramadol

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Very weak opioid agonist; also inhibits 5-HT and norepinephrine reuptake (works on multiple neurotransmitters—“tram it all” in with tramadol).</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>Chronic pain.</td>
</tr>
<tr>
<td>TOXICITY</td>
<td>Similar to opioids. Decreases seizure threshold. Serotonin syndrome.</td>
</tr>
</tbody>
</table>
## Epilepsy drugs

<table>
<thead>
<tr>
<th><strong>Epilepsy drugs</strong></th>
<th><strong>PARTIAL (FOCAL)</strong></th>
<th><strong>GENERALIZED</strong></th>
<th><strong>MECHANISM</strong></th>
<th><strong>SIDE EFFECTS</strong></th>
<th><strong>NOTES</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethosuximide</td>
<td>*</td>
<td>✓</td>
<td>Blocks thalamic T-type Ca²⁺ channels</td>
<td>GI, fatigue, headache, urticaria, Stevens-Johnson syndrome.</td>
<td>Sucks to have Silent (absence) Seizures</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>**</td>
<td>✓</td>
<td>† GABAδ action</td>
<td>Sedation, tolerance, dependence, respiratory depression</td>
<td>Also for eclampsia seizures (1st line is MgSO₄)</td>
</tr>
<tr>
<td>(diazepam, lorazepam)</td>
<td>✓</td>
<td>✓</td>
<td>† Na⁺ channel inactivation; zero-order kinetics</td>
<td>Nystagmus, diplopia, ataxia, sedation, gingival hyperplasia, hirsutism, peripheral neuropathy, megaloblastic anemia, teratogenesis (fetal hydantoin syndrome), SLE-like syndrome, induction of cytochrome P-450, lymphadenopathy, Stevens-Johnson syndrome, osteopenia</td>
<td>Fosphenytoin for parenteral use</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>✓</td>
<td>✓</td>
<td>† Na⁺ channel inactivation</td>
<td>Diplopia, ataxia, blood dyscrasias (agranulocytosis, aplastic anemia), liver toxicity, teratogenesis, induction of cytochrome P-450, SIADH, Stevens-Johnson syndrome</td>
<td>1st line for trigeminal neuralgia</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>✓</td>
<td>✓</td>
<td>† Na⁺ channel inactivation, † GABA concentration by inhibiting GABA transaminase</td>
<td>GI, distress, rare but fatal hepatotoxicity (measure LFTs), neural tube defects (e.g., spina bifida), tremor, weight gain, contraindicated in pregnancy</td>
<td>Also used for myoclonic seizures, bipolar disorder</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>✓</td>
<td>✓</td>
<td>Primarily inhibits high-voltage-activated Ca²⁺ channels, designed as GABA analog</td>
<td>Sedation, ataxia</td>
<td>Also used for peripheral neuropathies, postherpetic neuralgia</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>✓</td>
<td>✓</td>
<td>† GABAδ action</td>
<td>Sedation, tolerance, dependence, induction of cytochrome P-450, cardiorespiratory depression</td>
<td>1st line in neonates</td>
</tr>
<tr>
<td>Topiramate</td>
<td>✓</td>
<td>✓</td>
<td>Blocks Na⁺ channels, † GABA action</td>
<td>Sedation, mental dulling, kidney stones, weight loss</td>
<td>Also used for migraine prevention</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>✓</td>
<td>✓</td>
<td>Blocks voltage-gated Na⁺ channels</td>
<td>Stevens-Johnson syndrome (must be titrated slowly)</td>
<td></td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>✓</td>
<td>✓</td>
<td>Unknown; may modulate GABA and glutamate release</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiagabine</td>
<td>✓</td>
<td>✓</td>
<td>† GABA by inhibiting reuptake</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>✓</td>
<td>✓</td>
<td>† GABA by irreversibly inhibiting GABA transaminase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stevens-Johnson syndrome</td>
<td>✓</td>
<td>✓</td>
<td>Prodrome of malaise and fever followed by rapid onset of erythematous/purpuric macules (oral, ocular, genital). Skin lesions progress to epidermal necrosis and sloughing</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* = 1st line; ** = 1st line for acute; *** = 1st line for prophylaxis.
### Barbiturates

| MECHANISM | Facilitate GABA<sub>A</sub> action by ↓ duration of Cl<sup>-</sup> channel opening, thus ↓ neuron firing (barbiturates ↓ duration). Contraindicated in porphyria. |
| CLINICAL USE | Sedative for anxiety, seizures, insomnia, induction of anesthesia (thiopental). |
| TOXICITY | Respiratory and cardiovascular depression (can be fatal); CNS depression (can be exacerbated by EtOH use); dependence; drug interactions (induces cytochrome P-450). Overdose treatment is supportive (assist respiration and maintain BP). |

### Benzodiazepines

| MECHANISM | Facilitate GABA<sub>A</sub> action by ↑ frequency of Cl<sup>-</sup> channel opening. ↑ REM sleep. Most have long half-lives and active metabolites (exceptions: Alprazolam, Triazolam, Oxazepam, and Midazolam are short acting → higher addictive potential). |
| CLINICAL USE | Anxiety, spasticity, status epilepticus (lorazepam and diazepam), detoxification (especially alcohol withdrawal–DTs), night terrors, sleepwalking, general anesthetic (amnesia, muscle relaxation), hypnotic (insomnia). |
| TOXICITY | Dependence, additive CNS depression effects with alcohol. Less risk of respiratory depression and coma than with barbiturates. Treat overdose with flumazenil (competitive antagonist at GABA benzodiazepine receptor). |

### Nonbenzodiazepine hypnotics

| MECHANISM | Act via the BZ1 subtype of the GABA receptor. Effects reversed by flumazenil. |
| CLINICAL USE | Insomnia. |
| TOXICITY | Ataxia, headaches, confusion. Short duration because of rapid metabolism by liver enzymes. Unlike older sedative-hypnotics, cause only modest day-after psychomotor depression and few amnestic effects. ↓ dependence risk than benzodiazepines. |

### Anesthetics—general principles

CNS drugs must be lipid soluble (cross the blood-brain barrier) or be actively transported. Drugs with ↓ solubility in blood = rapid induction and recovery times. Drugs with ↑ solubility in lipids = ↑ potency = 1/MAC

MAC = Minimal Alveolar Concentration (of inhaled anesthetic) required to prevent 50% of subjects from moving in response to noxious stimulus (e.g., skin incision). Examples: nitrous oxide (N<sub>2</sub>O) has ↓ blood and lipid solubility, and thus fast induction and low potency. Halothane, in contrast, has ↑ lipid and blood solubility, and thus high potency and slow induction.
### Inhaled anesthetics

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Effects</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane, enflurane, isoflurane, sevoflurane, methoxyflurane, N₂O.</td>
<td>Myocardial depression, respiratory depression, nausea/emesis, ↑ cerebral blood flow (↓ cerebral metabolic demand).</td>
<td>Hepatotoxicity (halothane), nephrotoxicity (methoxyflurane), proconvulsant (enflurane), expansion of trapped gas in a body cavity (N₂O). Can cause malignant hyperthermia—rare, life-threatening hereditary condition in which inhaled anesthetics (except N₂O) and succinylcholine induce fever and severe muscle contractions. Treatment: dantrolene.</td>
</tr>
</tbody>
</table>

### Intravenous anesthetics

#### Barbiturates

- Thiopental—high potency, high lipid solubility, rapid entry into brain. Used for induction of anesthesia and short surgical procedures. Effect terminated by rapid redistribution into tissue (i.e., skeletal muscle) and fat. ↓ cerebral blood flow.

#### Benzodiazepines

- Midazolam most common drug used for endoscopy; used adjunctively with gaseous anesthetics and narcotics. May cause severe postoperative respiratory depression, ↓ BP (treat overdose with flumazenil), anterograde amnesia.

#### Arylcyclohexylamines (Ketamine)

- PCP analogs that act as dissociative anesthetics. Block NMDA receptors. Cardiovascular stimulants. Cause disorientation, hallucination, bad dreams. ↑ cerebral blood flow.

#### Opioids

- Morphine, fentanyl used with other CNS depressants during general anesthesia.

#### Propofol

- Used for sedation in ICU, rapid anesthesia induction, short procedures. Less postoperative nausea than thiopental. Potentiates GABA₄.
### Local anesthetics

| Mechanism | Esters—procaine, cocaine, tetracaine. Amides—lidoca\(\text{in}\), mepto\(\text{acaine}\), bup\(\text{ivacaine}\) (am\(\text{ides}\) have 2 Is in name). 

| Principle | Block Na\(^+\) channels by binding to specific receptors on inner portion of channel. Preferentially bind to activated Na\(^+\) channels, so most effective in rapidly firing neurons. 3° amine local anesthetics penetrate membrane in uncharged form, then bind to ion channels as charged form. 

| Clinical use | Can be given with vasoconstrictors (usually epinephrine) to enhance local action—↓ bleeding, ↑ anesthesia by ↓ systemic concentration. 

| Toxicity | In infected (acidic) tissue, alkaline anesthetics are charged and cannot penetrate membrane effectively → need more anesthetic. 

| Order of nerve blockade: small-diameter fibers > large diameter. Myelinated fibers > unmyelinated fibers. Overall, size factor predominates over myelination such that small myelinated fibers > small unmyelinated fibers > large myelinated fibers > large unmyelinated fibers. 

| Order of loss: (1) pain, (2) temperature, (3) touch, (4) pressure. If allergic to esters, give amides. 

### Neuromuscular blocking drugs

| Muscle paralysis in surgery or mechanical ventilation. Selective for motor (vs. autonomic) nicotinic receptor. 

| Depolarizing | Succinylcholine—strong ACh receptor agonist; produces sustained depolarization and prevents muscle contraction. Reversal of blockade: 
* Phase I (prolonged depolarization)—no antidote. Block potentiated by cholinesterase inhibitors. 
* Phase II (repolarized but blocked; ACh receptors are available, but desensitized)—antidote is cholinesterase inhibitors. Complications include hypercalcemia, hyperkalemia, malignant hyperthermia. 

| Nondepolarizing | Tubocurarine, atracurium, mivacurium, pancuronium, vecuronium, rocuronium—competitive antagonists—compete with ACh for receptors. Reversal of blockade—neostigmine (must be given with atropine to prevent muscarinic effects such as bradycardia), edrophonium, and other cholinesterase inhibitors. 

| Dantrolene | Prevents release of Ca\(^{2+}\) from the sarcoplasmic reticulum of skeletal muscle. 

| Clinical use | Malignant hyperthermia and neuroleptic malignant syndrome (a toxicity of antipsychotic drugs). 

| Baclofen | Inhibits GABA\(_B\) receptors at spinal cord level, inducing skeletal muscle relaxation. 

| Clinical use | Muscle spasms (e.g., acute low back pain). 

| Cyclobenzaprine | Centrally acting skeletal muscle relaxant. Structurally related to TCAs, similar anticholinergic side effects. 

| Clinical use | Muscle spasms. 

| CNS excitation, severe cardiovascular toxicity (bupivacaine), hypertension, hypotension, arrhythmias (cocaine), methemoglobinemia (benzocaine).
Parkinson disease drugs

<table>
<thead>
<tr>
<th>STRATEGY</th>
<th>AGENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinsonism is due to loss of dopaminergic neurons and excess cholinergic activity.</td>
<td></td>
</tr>
</tbody>
</table>
| Dopamine agonists | Ergot—Bromocriptine  
                   | Non-ergot (preferred)—pramipexole, ropinirole                           |
| ↑ dopamine availability | Amantadine (↑ dopamine release and  
                              ↓ dopamine reuptake); also used as an antiviral  
                              against influenza A and rubella; toxicity =  
                              ataxia, livedo reticularis. |
| ↑ t-DOPA availability | Agents prevent peripheral (pre-BBB) l-DOPA degradation → ↑ l-DOPA entering CNS  
                              → ↑ central l-DOPA available for conversion to dopamine.  
                              * Levodopa (l-dopa)/carbidopa—carbidopa  
                                  blocks peripheral conversion of l-DOPA  
                                  to dopamine by inhibiting DOPA decarboxylase. Also reduces side effects of  
                                  peripheral l-dopa conversion into dopamine (e.g., nausea, vomiting).  
                              * Entacapone, tolcapone—prevent peripheral  
                                  l-dopa degradation to 3-O-methyldopa (3-OMD) by inhibiting COMT. |
| Prevent dopamine breakdown | Agents act centrally (post-BBB) to block breakdown of dopamine → ↑ available dopamine.  
                              * Selegiline—blocks conversion of dopamine into 3-MT by selectively inhibiting MAO-B.  
                              * Tolcapone—blocks conversion of dopamine to DOPAC by inhibiting central COMT. |
| Curb excess cholinergic activity | Benztropine (Antimuscarinic; improves  
                              tremor and rigidity but has little effect on bradykinesia). |
|                   | **BALSA:**  
                              * Bromocriptine  
                              * Amantadine  
                              * Levodopa (with carbidopa)  
                              * Selegiline (and COMT inhibitors)  
                              * Antimuscarinics |

Park your Mercedes-Benz.
Parkinson disease drugs (continued)

**L-dopa (levodopa)/carbidopa**

**MECHANISM**
† level of dopamine in brain. Unlike dopamine, L-dopa can cross blood-brain barrier and is converted by dopa decarboxylase in the CNS to dopamine. Carbidopa, a peripheral DOPA decarboxylase inhibitor, is given with L-dopa to † the bioavailability of L-dopa in the brain and to limit peripheral side effects.

**CLINICAL USE** Parkinson disease.

**TOXICITY** Arrhythmias from † peripheral formation of catecholamines. Long-term use can lead to dyskinesia following administration ("on-off" phenomenon), akinesia between doses.

**Selegiline**

**MECHANISM** Selectively inhibits MAO-B, which preferentially metabolizes dopamine over norepinephrine and 5-HT, thereby † the availability of dopamine.

**CLINICAL USE** Adjunctive agent to L-dopa in treatment of Parkinson disease.

**TOXICITY** May enhance adverse effects of L-dopa.
### Alzheimer drugs

**Memantine**

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>NMDA receptor antagonist; helps prevent excitotoxicity (mediated by Ca(^{2+})).</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOXICITY</td>
<td>Dizziness, confusion, hallucinations.</td>
</tr>
</tbody>
</table>

**Donepezil, galantamine, rivastigmine, tacrine**

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>AChE inhibitors.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOXICITY</td>
<td>Nausea, dizziness, insomnia.</td>
</tr>
</tbody>
</table>

### Huntington disease drugs

Neurotransmitter changes in Huntington disease: ↓ GABA, ↑ ACh, ↑ dopamine.

Treatments:
- Tetrabenazine and reserpine—inhibit vesicular monoamine transporter (VMAT); limit dopamine vesicle packaging and release.
- Haloperidol—D\(_2\) receptor antagonist.

### Triptans

**Sumatriptan**

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>5-HT(_{1B/1D}) agonists. Inhibit trigeminal nerve activation; prevent vasoactive peptide release; induce vasoconstriction.</th>
<th>A SUMo wrestler TRIPs ANd falls on your head.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>Acute migraine, cluster headache attacks.</td>
<td></td>
</tr>
<tr>
<td>TOXICITY</td>
<td>Coronary vasospasm (contraindicated in patients with CAD or Prinzmetal angina), mild paresthesia.</td>
<td></td>
</tr>
</tbody>
</table>
HIGH-YIELD PRINCIPLES IN

Psychiatry

“A Freudian slip is when you say one thing but mean your mother.”
—Anonymous

“Men will always be mad, and those who think they can cure them are the maddest of all.”
—Voltaire

“Anyone who goes to a psychiatrist ought to have his head examined.”
—Samuel Goldwyn

The DSM-5 was released by the American Psychiatric Association in 2013, reclassifying several psychiatric conditions and updating diagnostic criteria. We have updated this chapter to reflect certain DSM-5 revisions.
## Classical conditioning
Learning in which a natural response (salivation) is elicited by a conditioned, or learned, stimulus (bell) that previously was presented in conjunction with an unconditioned stimulus (food).

Usually deals with **involuntary** responses. Pavlov’s classical experiments with dogs—ringing the bell provoked salivation.

## Operant conditioning
Learning in which a particular action is elicited because it produces a punishment or reward. Usually deals with **voluntary** responses.

<table>
<thead>
<tr>
<th>Positive reinforcement</th>
<th>Desired reward produces action (mouse presses button to get food).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative reinforcement</td>
<td>Target behavior (response) is followed by removal of aversive stimulus (mouse presses button to turn off continuous loud noise).</td>
</tr>
<tr>
<td>Punishment</td>
<td>Repeated application of aversive stimulus extinguishes unwanted behavior.</td>
</tr>
<tr>
<td>Extinction</td>
<td>Discontinuation of reinforcement (positive or negative) eventually eliminates behavior. Can occur in operant or classical conditioning.</td>
</tr>
</tbody>
</table>

## Transference and countertransference

<table>
<thead>
<tr>
<th>Transference</th>
<th>Patient projects feelings about formative or other important persons onto physician (e.g., psychiatrist is seen as parent).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Countertransference</td>
<td>Doctor projects feelings about formative or other important persons onto patient (e.g., patient reminds physician of younger sibling).</td>
</tr>
</tbody>
</table>

## Ego defenses
Unconscious mental processes used to resolve conflict and prevent undesirable feelings (e.g., anxiety, depression).

<table>
<thead>
<tr>
<th>IMMATURE DEFENSES</th>
<th>DESCRIPTION</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acting out</td>
<td>Expressing unacceptable feelings and thoughts through actions.</td>
<td>Tantrums.</td>
</tr>
<tr>
<td>Denial</td>
<td>Avoiding the awareness of some painful reality.</td>
<td>A common reaction in newly diagnosed AIDS and cancer patients.</td>
</tr>
<tr>
<td>Displacement</td>
<td>Transferring avoided ideas and feelings to a neutral person or object (vs. projection).</td>
<td>Mother yells at her child, because her husband yelled at her.</td>
</tr>
<tr>
<td>Dissociation</td>
<td>Temporary, drastic change in personality, memory, consciousness, or motor behavior to avoid emotional stress.</td>
<td>Extreme forms can result in dissociative identity disorder (multiple personality disorder).</td>
</tr>
<tr>
<td>Fixation</td>
<td>Partially remaining at a more childish level of development (vs. regression).</td>
<td>Adults fixating on video games.</td>
</tr>
<tr>
<td>Identification</td>
<td>Modeling behavior after another person who is more powerful (though not necessarily admired).</td>
<td>Abused child identifies with an abuser.</td>
</tr>
<tr>
<td>Isolation (of affect)</td>
<td>Separating feelings from ideas and events.</td>
<td>Describing murder in graphic detail with no emotional response.</td>
</tr>
</tbody>
</table>
### Ego defenses (continued)

<table>
<thead>
<tr>
<th>IMMATURE DEFENSES</th>
<th>DESCRIPTION</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passive aggression</td>
<td>Expressing negativity and performing below what is expected as an indirect show of opposition.</td>
<td>Disgruntled employee is repeatedly late to work.</td>
</tr>
<tr>
<td>Projection</td>
<td>Attributing an unacceptable internal impulse to an external source (vs. displacement).</td>
<td>A man who wants another woman thinks his wife is cheating on him.</td>
</tr>
<tr>
<td>Rationalization</td>
<td>Proclaiming logical reasons for actions actually performed for other reasons, usually to avoid self-blame.</td>
<td>After getting fired, claiming that the job was not important anyway.</td>
</tr>
<tr>
<td>Reaction formation</td>
<td>Replacing a warded-off idea or feeling by an (unconsciously derived) emphasis on its opposite (vs. sublimation).</td>
<td>A patient with libidinous thoughts enters a monastery.</td>
</tr>
<tr>
<td>Regression</td>
<td>Turning back the maturational clock and going back to earlier modes of dealing with the world (vs. fixation).</td>
<td>Seen in children under stress such as illness, punishment, or birth of a new sibling (e.g., bedwetting in a previously toilet-trained child when hospitalized).</td>
</tr>
<tr>
<td>Repression</td>
<td>Involuntarily withholding an idea or feeling from conscious awareness (vs. suppression).</td>
<td>A 20-year-old does not remember going to counseling during his parents’ divorce 10 years earlier.</td>
</tr>
<tr>
<td>Splitting</td>
<td>Believing that people are either all good or all bad at different times due to intolerance of ambiguity. Commonly seen in borderline personality disorder.</td>
<td>A patient says that all the nurses are cold and insensitive but that the doctors are warm and friendly.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MATURE DEFENSES</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Altruism</td>
<td>Alleviating negative feelings via unsolicited generosity.</td>
</tr>
<tr>
<td>Humor</td>
<td>Appreciating the amusing nature of an anxiety-provoking or adverse situation.</td>
</tr>
<tr>
<td>Sublimation</td>
<td>Replacing an unacceptable wish with a course of action that is similar to the wish but does not conflict with one’s value system (vs. reaction formation).</td>
</tr>
<tr>
<td>Suppression</td>
<td>Intentionally withholding an idea or feeling from conscious awareness (vs. repression); temporary.</td>
</tr>
</tbody>
</table>

Mature adults wear a **SASH**: Sublimation, Altruism, Suppression, Humor.
Infant deprivation effects

- Long-term deprivation of affection results in:
  - Failure to thrive
  - Poor language/socialization skills
  - Lack of basic trust
  - Anaclitic depression (infant withdrawn/unresponsive)

The 4 W's: Weak, Wordless, Wanting (socially), Wary.

- Deprivation for > 6 months can lead to irreversible changes.
- Severe deprivation can result in infant death.

Child abuse

<table>
<thead>
<tr>
<th>Physical abuse</th>
<th>Sexual abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence</td>
<td>Genital, anal, or oral trauma; STDs; UTIs.</td>
</tr>
<tr>
<td>Spiral fractures (or multiple fractures at different stages of healing), burns (e.g., cigarette, buttocks/thighs), subdural hematomas, posterior rib fractures, retinal detachment.</td>
<td></td>
</tr>
<tr>
<td>During exam, children often avoid eye contact.</td>
<td></td>
</tr>
<tr>
<td>Abuser</td>
<td>Usually biological mother.</td>
</tr>
<tr>
<td>Known to victim, usually male.</td>
<td></td>
</tr>
<tr>
<td>Epidemiology</td>
<td>40% of deaths in children &lt; 1 year old.</td>
</tr>
<tr>
<td>Peak incidence 9–12 years old.</td>
<td></td>
</tr>
</tbody>
</table>

Child neglect

- Failure to provide a child with adequate food, shelter, supervision, education, and/or affection.
- Most common form of child maltreatment. Evidence: poor hygiene, malnutrition, withdrawal, impaired social/emotional development, failure to thrive.
- As with child abuse, child neglect must be reported to local child protective services.

Childhood and early-onset disorders

- **Attention-deficit hyperactivity disorder**
  - Onset before age 12. Limited attention span and poor impulse control. Characterized by hyperactivity, impulsivity, and/or inattention in multiple settings (school, home, places of worship, etc.). Normal intelligence, but commonly coexists with difficulties in school. Continues into adulthood in as many as 50% of individuals. Associated with 4 frontal lobe volume/metabolism. Treatment: stimulants (e.g., methylphenidate) +/- cognitive behavioral therapy (CBT); atomoxetine may be an alternative to stimulants in selected patients.

- **Conduct disorder**
  - Repetitive and pervasive behavior violating the basic rights of others (e.g., physical aggression, destruction of property, theft). After age 18, many of these patients will meet criteria for diagnosis of antisocial personality disorder. Treatment for both: CBT.

- **Oppositional defiant disorder**
  - Enduring pattern of hostile, defiant behavior toward authority figures in the absence of serious violations of social norms. Treatment: CBT.

- **Separation anxiety disorder**
  - Common onset at 7–9 years. Overwhelming fear of separation from home or loss of attachment figure. May lead to factitious physical complaints to avoid going to or staying at school. Treatment: CBT, play therapy, family therapy.

- **Tourette syndrome**
  - Onset before age 18. Characterized by sudden, rapid, recurrent, nonrhythmic, stereotyped motor and vocal tics that persist for > 1 year. Coprolalia (involuntary obscene speech) found in only 10–20% of patients. Associated with OCD and ADHD. Treatment: psychoeducation, behavioral therapy. For intractable tics, low-dose high-potency antipsychotics (e.g., fluphenazine, pimozide), tetrabenazine, and clonidine may be used.
Pervasive developmental disorders

Characterized by difficulties with language and failure to acquire or early loss of social skills.

Autism spectrum disorder

Characterized by poor social interactions, communication deficits, repetitive/ritualized behaviors, restricted interests. Must present in early childhood. May or may not be accompanied by intellectual disability; rarely accompanied by unusual abilities (savants). More common in boys.

Rett syndrome

X-linked disorder seen almost exclusively in girls (affected males die in utero or shortly after birth). Symptoms usually become apparent around ages 1–4, including regression characterized by loss of development, loss of verbal abilities, intellectual disability, ataxia, stereotyped hand-wraring.

Neurotransmitter changes with disease

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>NEUROTRANSMITTER CHANGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer disease</td>
<td>↓ ACh</td>
</tr>
<tr>
<td></td>
<td>↑ glutamate</td>
</tr>
<tr>
<td>Anxiety</td>
<td>↑ norepinephrine</td>
</tr>
<tr>
<td></td>
<td>↓ GABA, ↓ 5-HT</td>
</tr>
<tr>
<td>Depression</td>
<td>↓ norepinephrine</td>
</tr>
<tr>
<td></td>
<td>↓ 5-HT, ↓ dopamine</td>
</tr>
<tr>
<td>Huntington disease</td>
<td>↓ GABA, ↑ ACh</td>
</tr>
<tr>
<td></td>
<td>↑ dopamine</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>↓ dopamine</td>
</tr>
<tr>
<td></td>
<td>↑ ACh</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>↑ dopamine</td>
</tr>
</tbody>
</table>

Understanding these changes can help guide pharmacologic treatment choice.

Orientation

Patient’s ability to know who he or she is, where he or she is, and the date and time.

Common causes of loss of orientation: alcohol, drugs, fluid/electrolyte imbalance, head trauma, hypoglycemia, infection, nutritional deficiencies.

Order of loss: 1st—time; 2nd—place; last—person.

Amnesias

Retrograde amnesia

Inability to remember things that occurred before a CNS insult.

Anterograde amnesia

Inability to remember things that occurred after a CNS insult (↑ acquisition of new memory).

Korsakoff syndrome

Amnesia (anterograde > retrograde) caused by vitamin B₁ deficiency and associated destruction of mammillary bodies. Seen in alcoholics. Confabulations are characteristic.

Dissociative amnesia

Inability to recall important personal information, usually subsequent to severe trauma or stress. May be accompanied by dissociative fugue (abrupt travel or wandering during a period of dissociative amnesia, associated with traumatic circumstances).
Delirium

“Waxing and waning” level of consciousness with acute onset; rapid ↓ in attention span and level of arousal. Characterized by disorganized thinking, hallucinations (often visual), illusions, misperceptions, disturbance in sleep-wake cycle, cognitive dysfunction. Usually 2° to other illness (e.g., CNS disease, infection, trauma, substance abuse/withdrawal, metabolic/electrolyte disturbances, hemorrhage, urinary/fecal retention). Most common presentation of altered mental status in inpatient setting. Abnormal EEG. Treatment is aimed at identifying and addressing underlying condition. Haloperidol may be used as needed. Use benzodiazepines for alcohol withdrawal.

Dementia

↓ in intellectual function without affecting level of consciousness. Characterized by memory deficits, apraxia, aphasia, agnosia, loss of abstract thought, behavioral/personality changes, impaired judgment. A patient with dementia can develop delirium (e.g., patient with Alzheimer disease who develops pneumonia is at ↑ risk for delirium). Irreversible causes: Alzheimer disease, Lewy body dementia, Huntington disease, Pick disease, cerebral infarct, Creutzfeldt-Jakob disease, chronic substance abuse (due to neurotoxicity of drugs). Reversible causes: hypothyroidism, depression, vitamin B₁₂ deficiency, normal pressure hydrocephalus. ↑ incidence with age. EEG usually normal.

Psychosis

A distorted perception of reality characterized by delusions, hallucinations, and/or disorganized thinking. Psychosis can occur in patients with medical illness, psychiatric illness, or both.

Hallucinations

Perceptions in the absence of external stimuli (e.g., seeing a light that is not actually present).

Delusions

Unique, false beliefs about oneself or others that persist despite the facts (e.g., thinking aliens are communicating with you).

Disorganized speech

Words and ideas are strung together based on sounds, puns, or “loose associations.”
Hallucination types

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual</td>
<td>More commonly a feature of medical illness (e.g., drug intoxication) than psychiatric illness.</td>
</tr>
<tr>
<td>Auditory</td>
<td>More commonly a feature of psychiatric illness (e.g., schizophrenia) than medical illness.</td>
</tr>
<tr>
<td>Olfactory</td>
<td>Often occur as an aura of psychomotor epilepsy and in brain tumors.</td>
</tr>
<tr>
<td>Gustatory</td>
<td>Rare, but seen in epilepsy.</td>
</tr>
<tr>
<td>Tactile</td>
<td>Common in alcohol withdrawal (e.g., formication—the sensation of bugs crawling on one’s skin). Also seen in cocaine abusers (“cocaine crawlies”).</td>
</tr>
<tr>
<td>Hypnagogic</td>
<td>Occurs while going to sleep. Sometimes seen in narcolepsy.</td>
</tr>
<tr>
<td>Hypnopompic</td>
<td>Occurs while waking from sleep (“pompous upon awakening”). Sometimes seen in narcolepsy.</td>
</tr>
</tbody>
</table>

Schizophrenia

Chronic mental disorder with periods of psychosis, disturbed behavior and thought, and decline in functioning lasting > 6 months. Associated with ↑ dopaminergic activity, ↑ dendritic branching.

Diagnosis requires 2 or more of the following (first 4 are “positive symptoms”):
- Delusions
- Hallucinations—often auditory
- Disorganized speech (loose associations)
- Disorganized or catatonic behavior
- “Negative symptoms”—flat affect, social withdrawal, lack of motivation, lack of speech or thought

**Brief psychotic disorder**—lasting < 1 month, usually stress related.

**Schizophreniform disorder**—lasting 1–6 months.

**Schizoaffective disorder**—lasting > 2 weeks; psychotic symptoms with episodic superimposed major depression or mania (or both). Psychosis is present with and without mood disorder, but mood disorder is present only with psychosis.

Genetics and environment contribute to the etiology of schizophrenia.

Frequent cannabis use is associated with psychosis/schizophrenia in teens.

Lifetime prevalence—1.5% (males = females, blacks = whites). Presents earlier in men (late teens to early 20s vs. late 20s to early 30s in women). Patients are at ↑ risk for suicide.

Treatment: atypical antipsychotics (e.g., risperidone) are first line.

Delusional disorder

Fixed, persistent, false belief system lasting > 1 month. Functioning otherwise not impaired.

Example: a woman who genuinely believes she is married to a celebrity when, in fact, she is not.
Dissociative disorders

Dissociative identity disorder
Formerly known as multiple personality disorder. Presence of 2 or more distinct identities or personality states. More common in women. Associated with history of sexual abuse, PTSD, depression, substance abuse, borderline personality, somatoform conditions.

Depersonalization/derealization disorder
Persistent feelings of detachment or estrangement from one’s own body, thoughts, perceptions, and actions (depersonalization) or one’s environment (derealization).

Mood disorder
Chartered by an abnormal range of moods or internal emotional states and loss of control over them. Severity of moods causes distress and impairment in social and occupational functioning. Includes major depressive disorder, bipolar disorder, dysthymic disorder, and cyclothymic disorder. Episodic superimposed psychotic features (delusions or hallucinations) may be present.

Manic episode
Distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently ↑ activity or energy lasting at least 1 week. Often disturbing to patient. Diagnosis requires hospitalization or at least 3 of the following (manics DIG FAST):
- Distractibility
- Irresponsibility—seeks pleasure without regard to consequences (hedonistic)
- Grandiosity—inflated self-esteem
- Flight of ideas—racing thoughts
- ↑ in goal-directed Activity/psychomotor Agitation
- ↓ need for Sleep
- Talkativeness or pressured speech

Hypomanic episode
Like manic episode except mood disturbance is not severe enough to cause marked impairment in social and/or occupational functioning or to necessitate hospitalization. No psychotic features. Lasts at least 4 consecutive days.

Bipolar disorder (manic depression)
Bipolar I defined by presence of at least 1 manic episode with or without a hypomanic or depressive episode.
Bipolar II defined by presence of a hypomanic and a depressive episode.
Patient’s mood and functioning usually return to normal between episodes. Use of antidepressants can precipitate mania. High suicide risk. Treatment: mood stabilizers (e.g., lithium, valproic acid, carbamazepine), atypical antipsychotics.
Cyclothymic disorder—dysthymia and hypomania; milder form of bipolar disorder lasting at least 2 years.
**Major depressive disorder**
May be self-limited disorder, with major depressive episodes usually lasting 6–12 months. Episodes characterized by at least 5 of the following 9 symptoms for 2 or more weeks (symptoms must include patient-reported depressed mood or anhedonia). Treatment: CBT and SSRIs are first line. SNRIs, mirtazapine, bupropion can also be considered. Electroconvulsive therapy (ECT) in select patients.

**Persistent depressive disorder (dysthymia)**
Depression, often milder, lasting at least 2 years.

**SIG E CAPS:**
- Sleep disturbance
- Loss of interest (anhedonia)
- Guilt or feelings of worthlessness
- Energy loss and fatigue
- Concentration problems
- Appetite/weight changes
- Psychomotor retardation or agitation
- Suicidal ideations
- Depressed mood

Patients with depression typically have the following changes in their sleep stages:
- ↓ slow-wave sleep
- ↑ REM latency
- ↑ REM early in sleep cycle
- ↑ total REM sleep
- Repeated nighttime awakenings
- Early-morning wakening (terminal insomnia)

**Atypical depression**
Differs from classical forms of depression. Characterized by mood reactivity (being able to experience improved mood in response to positive events, albeit briefly), “reversed” vegetative symptoms (hypersomnia, hyperphagia), leaden paralysis (heavy feeling in arms and legs), long-standing interpersonal rejection sensitivity. Most common subtype of depression. Treatment: CBT and SSRIs are first line. MAO inhibitors are effective but not first line because of their risk profile.

**Postpartum mood disturbances**
Onset within 4 weeks of delivery.

**Maternal (postpartum) “blues”**
50–85% incidence rate. Characterized by depressed affect, tearfulness, and fatigue starting 2–3 days after delivery. Usually resolves within 10 days. Treatment: supportive. Follow up to assess for possible postpartum depression.

**Postpartum depression**
10–15% incidence rate. Characterized by depressed affect, anxiety, and poor concentration starting within 4 weeks after delivery. Treatment: CBT and SSRIs are first line.

**Postpartum psychosis**
0.1–0.2% incidence rate. Characterized by mood-congruent delusions, hallucinations, and thoughts of harming the baby or self. Risk factors include history of bipolar or psychotic disorder, first pregnancy, family history, recent discontinuation of psychotropic medication. Treatment: hospitalization and initiation of atypical antipsychotic; if insufficient, ECT may be used.
Pathologic grief
Normal bereavement characterized by shock, denial, guilt, and somatic symptoms. Duration varies widely. Pathologic grief lasts > 6 months, satisfies major depressive criteria (e.g., weight loss, anhedonia, passive death wish), and/or includes psychotic symptoms (e.g., delusions). Hallucinations (e.g., hearing the voice of a deceased loved one) in the absence of other psychotic symptoms are not considered pathologic.

Electroconvulsive therapy
Used mainly for treatment-refractory depression, depression with psychotic symptoms, and acutely suicidal patients. Produces grand mal seizure in an anesthetized patient. Adverse effects include disorientation, temporary headache, partial anterograde/retrograde amnesia usually resolving in 6 months.

Risk factors for suicide completion
Sex (male), Age (teenager or elderly), Depression, Previous attempt, Ethanol or drug use, loss of Rational thinking, Sickness (medical illness, 3 or more prescription medications), Organized plan, No spouse (divorced, widowed, or single, especially if childless), Social support lacking. Women try more often; men succeed more often. SAD PERSONS are more likely to complete suicide.

Anxiety disorder
Inappropriate experience of fear/worry and its physical manifestations (anxiety) incongruent with the magnitude of the perceived stressor. Symptoms interfere with daily functioning. Includes panic disorder, phobias, generalized anxiety disorder, PTSD. Treatment: CBT, SSRIs, SNRIs.

Panic disorder
Defined by recurrent panic attacks (periods of intense fear and discomfort peaking in 10 minutes with at least 4 of the following): Palpitations, Paresthesias, Abdominal distress, Nausea, Intense fear of dying or losing control, Light-headedness, Chest pain, Chills, Choking, disConnectedness, Sweating, Shaking, Shortness of breath. Strong genetic component. Treatment: CBT, SSRIs, and venlafaxine are first line. Benzodiazepines occasionally used in acute setting. PANICS. Diagnosis requires attack followed by 1 month (or more) of 1 (or more) of the following:
* Persistent concern of additional attacks
* Worrying about consequences of attack
* Behavioral change related to attacks
Symptoms are the systemic manifestations of fear.
**Specific phobia**
Fear that is excessive or unreasonable and interferes with normal function. Cued by presence or anticipation of a specific object or situation. Person recognizes fear is excessive. Can treat with systematic desensitization.

**Social anxiety disorder**—exaggerated fear of embarrassment in social situations (e.g., public speaking, using public restrooms). Treatment: CBT, SSRIs.

**Agoraphobia**—exaggerated fear of open or enclosed places, using public transportation, being in line or in crowds, or leaving home alone. Treatment: CBT, SSRIs, MAO inhibitors.

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**Generalized anxiety disorder**
Anxiety **lasting > 6 months** unrelated to a specific person, situation, or event. Associated with sleep disturbance, fatigue, GI disturbance, difficulty concentrating. Treatment: CBT, SSRIs, SNRIs are first line. Buspirone, TCAs, benzodiazepines are second line.

**Adjustment disorder**—emotional symptoms (anxiety, depression) causing impairment following an identifiable psychosocial stressor (e.g., divorce, illness) and **lasting < 6 months** (> 6 months in presence of chronic stressor). Treatment: CBT, SSRIs.

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**Obsessive-compulsive disorder**
Recurring intrusive thoughts, feelings, or sensations (obsessions) that cause severe distress; relieved in part by the performance of repetitive actions (compulsions). Ego-dystonic: behavior inconsistent with one's own beliefs and attitudes (vs. obsessive-compulsive personality disorder). Associated with Tourette syndrome. Treatment: CBT, SSRIs, and clomipramine are first line.

**Body dysmorphic disorder**—preoccupation with minor or imagined defect in appearance significant emotional distress or impaired functioning; patients often repeatedly seek cosmetic surgery. Treatment: CBT.

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**Post-traumatic stress disorder**
Persistent reexperiencing of a previous traumatic event (e.g., war, rape, robbery, serious accident, fire). May involve nightmares or flashbacks, intense fear, helplessness, horror. Leads to avoidance of stimuli associated with the trauma and persistently 1 arousal. Disturbance **lasts > 1 month** and impairs social-occupational functioning. Treatment: CBT, SSRIs, and venlafaxine are first line.

**Acute stress disorder**—**lasts between 3 days and 1 month**. Treatment: CBT; pharmacotherapy is usually not indicated.
Malingering
Patient **consciously** fakes, profoundly exaggerates, or claims to have a disorder in order to attain a specific 2° (external) gain (e.g., avoiding work, obtaining compensation). Poor compliance with treatment or follow-up of diagnostic tests. Complaints cease after gain (vs. factitious disorder).

![Diagram of Malingering]

**Factitious disorders**
Patient **consciously** creates physical and/or psychological symptoms in order to assume “sick role” and to get medical attention (1° [internal] gain).

**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.

**Munchausen syndrome by proxy**
Illness in a child or elderly patient is caused or fabricated by the caregiver. Motivation is to assume a sick role by proxy. Form of child/elder abuse.

**Somatic symptom and related disorders**
Category of disorders characterized by physical symptoms with no identifiable physical cause. Both illness production and motivation are **unconscious** drives. Symptoms not intentionally produced or feigned. More common in women.

**Conversion disorder**
Loss of sensory or motor function (e.g., paralysis, blindness, mutism), often following an acute stressor; patient is aware of but sometimes indifferent toward symptoms (“la belle indifférence”); more common in females, adolescents, and young adults.

**Illness anxiety disorder (hypochondriasis)**
Preoccupation with and fear of having a serious illness despite medical evaluation and reassurance.

**Somatic symptom disorder**
Variety of complaints in one or more organ systems lasting for months to years. Associated with excessive, persistent thoughts and anxiety about symptoms. May co-occur with medical illness.

**Personality**

**Personality trait**
An enduring, repetitive pattern of perceiving, relating to, and thinking about the environment and oneself.

**Personality disorder**
Inflexible, maladaptive, and rigidly pervasive pattern of behavior causing subjective distress and/or impaired functioning; person is usually not aware of problem. Usually presents by early adulthood.
Three clusters, A, B, and C; remember as **Weird, Wild, and Worried** based on symptoms.
### Cluster A personality disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paranoid</td>
<td>Pervasive distrust and suspiciousness; projection is the major defense mechanism.</td>
<td></td>
</tr>
<tr>
<td>Schizoid</td>
<td>Voluntary social withdrawal, limited emotional expression, content with social isolation (vs. avoidant).</td>
<td>Schizoid = distant.</td>
</tr>
<tr>
<td>Schizotypal</td>
<td>Eccentric appearance, odd beliefs or magical thinking, interpersonal awkwardness.</td>
<td>Schizotypal = magical thinking.</td>
</tr>
</tbody>
</table>

### Cluster B personality disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antisocial</td>
<td>Disregard for and violation of rights of others, criminality, impulsivity; males &gt; females; must be ≥ 18 years old and have history of conduct disorder before age 15. Conduct disorder if &lt; 18 years old.</td>
<td>Antisocial = sociopath.</td>
</tr>
<tr>
<td>Borderline</td>
<td>Unstable mood and interpersonal relationships, impulsivity, self-mutilation, boredom, sense of emptiness; females &gt; males; splitting is a major defense mechanism.</td>
<td>Treatment: dialectical behavior therapy.</td>
</tr>
<tr>
<td>Histrionic</td>
<td>Excessive emotionality and excitability, attention seeking, sexually provocative, overly concerned with appearance.</td>
<td></td>
</tr>
<tr>
<td>Narcissistic</td>
<td>Grandiosity, sense of entitlement; lacks empathy and requires excessive admiration; often demands the “best” and reacts to criticism with rage.</td>
<td></td>
</tr>
</tbody>
</table>

### Cluster C personality disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoidant</td>
<td>Hypersensitive to rejection, socially inhibited, timid, feelings of inadequacy, desires relationships with others (vs. schizoid).</td>
<td></td>
</tr>
<tr>
<td>Obsessive-compulsive</td>
<td>Preoccupation with order, perfectionism, and control; ego-syntonic: behavior consistent with one’s own beliefs and attitudes (vs. OCD).</td>
<td></td>
</tr>
<tr>
<td>Dependent</td>
<td>Submissive and clingy, excessive need to be taken care of, low self-confidence.</td>
<td>Patients often get stuck in abusive relationships.</td>
</tr>
</tbody>
</table>
Keeping "schizo-" straight

Schizoid < Schizotypal < Schizophrenic < Schizoaffective
(schizoid + odd thinking) (greater odd thinking than schizotypal) (schizophrenic psychotic symptoms + bipolar or depressive mood disorder)

Schizophrenia time course:
< 1 mo—brief psychotic disorder, usually stress related
1–6 mo—schizophreniform disorder
> 6 mo—schizophrenia

Eating disorders

Anorexia nervosa
Excessive dieting +/- purging; intense fear of gaining weight and body image distortion; BMI < 18.5. Associated with bone density, severe weight loss, metatarsal stress fractures, amenorrhea, lanugo, anemia, electrolyte disturbances. Seen primarily in adolescent girls. Commonly coexists with excessive exercise and/or depression. Psychotherapy and nutritional rehabilitation are first line. Refeeding syndrome (hypophosphatemia) can occur in significantly malnourished patients.

Bulimia nervosa
Binge eating with recurrent inappropriate compensatory behaviors (e.g., self-induced vomiting, using laxatives or diuretics, fasting, excessive exercise) occurring weekly for at least 3 months. Body weight often maintained within normal range. Associated with parotitis, enamel erosion, electrolyte disturbances, alkalosis, dorsal hand calluses from induced vomiting (Russell sign). Seen predominantly in adolescent girls.

Gender dysphoria
Strong, persistent cross-gender identification. Characterized by persistent discomfort with one’s sex assigned at birth, causing significant distress and/or impaired functioning. Affected individuals are often referred to as transgender.

Transsexualism—desire to live as the opposite sex, often through surgery or hormone treatment.

Transvestism—paraphilia, not gender dysphoria. Wearing clothes (e.g., vest) of the opposite sex (cross-dressing).

Sexual dysfunction
Includes sexual desire disorders (hypoactive sexual desire or sexual aversion), sexual arousal disorders (erectile dysfunction), orgasmic disorders (anorgasmia, premature ejaculation), sexual pain disorders (dyspareunia, vaginismus).
Differential diagnosis includes:
- Drugs (e.g., antihypertensives, neuroleptics, SSRIs, ethanol)
- Diseases (e.g., depression, diabetes, STIs)
- Psychological (e.g., performance anxiety)

Sleep terror disorder
Periods of terror with screaming in the middle of the night; occurs during slow-wave sleep. Most common in children. Occurs during non-REM sleep (no memory of arousal) as opposed to nightmares that occur during REM sleep (memory of a scary dream). Cause unknown, but triggers include emotional stress, fever, or lack of sleep. Usually self limited.
Narcolepsy

Disordered regulation of sleep-wake cycles; 1st characteristic is excessive daytime sleepiness.
Caused by deficient hypocretin (orexin) production in lateral hypothalamus.
Also associated with:
- Hypnagogic (just before sleep) or hypnopompic (just before awakening) hallucinations.
- Nocturnal and narcoleptic sleep episodes that start with REM sleep.
- Cataplexy (loss of all muscle tone following strong emotional stimulus, such as laughter) in some patients.

Strong genetic component. Treatment: daytime stimulants (e.g., amphetamines, modafinil) and nighttime sodium oxybate (GHB).

Substance use disorder

Maladaptive pattern of substance use defined as 2 or more of the following signs in 1 year:
- Tolerance—need more to achieve same effect
- Withdrawal
- Substance taken in larger amounts, or over longer time, than desired
- Persistent desire or unsuccessful attempts to cut down
- Significant energy spent obtaining, using, or recovering from substance
- Important social, occupational, or recreational activities reduced because of substance use
- Continued use despite knowing substance causes physical and/or psychological problems
- Craving
- Recurrent use in physically dangerous situations
- Failure to fulfill major obligations at work, school, or home due to use
- Social or interpersonal conflicts related to substance use

Stages of change in overcoming substance addiction

1. Precontemplation—not yet acknowledging that there is a problem
2. Contemplation—acknowledging that there is a problem, but not yet ready or willing to make a change
3. Preparation/determination—getting ready to change behaviors
4. Action/willpower—changing behaviors
5. Maintenance—maintaining the behavior changes
6. Relapse—returning to old behaviors and abandoning new changes
### Psychoactive drug intoxication and withdrawal

<table>
<thead>
<tr>
<th>DRUG</th>
<th>INTOXICATION</th>
<th>WITHDRAWAL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depressants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>Emotional lability, slurred speech, ataxia, coma, blackouts. Serum γ-glutamyltransferase (GGT) — sensitive indicator of alcohol use. AST value is twice ALT value.</td>
<td>Mild alcohol withdrawal: symptoms similar to other depressants. Severe alcohol withdrawal can cause autonomic hyperactivity and DTs (5–15% mortality rate). Treatment for DTs: benzodiazepines.</td>
</tr>
<tr>
<td>Opioids (e.g., morphine, heroin, methadone)</td>
<td>Euphoria, respiratory and CNS depression, ↓ gag reflex, pupillary constriction (pinpoint pupils), seizures (overdose). Treatment: naloxone, naltrexone.</td>
<td>Sweating, dilated pupils, piloerection (“cold turkey”), fever, rhinorrhea, yawning, nausea, stomach cramps, diarrhea (“flu-like” symptoms). Treatment: long-term support, methadone, buprenorphine.</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Low safety margin, marked respiratory depression. Treatment: symptom management (e.g., assist respiration, ↑ BP).</td>
<td>Delirium, life-threatening cardiovascular collapse.</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Greater safety margin. Ataxia, minor respiratory depression. Treatment: flumazenil (benzodiazepine receptor antagonist, but rarely used as it can precipitate seizures).</td>
<td>Sleep disturbance, depression, rebound anxiety, seizure.</td>
</tr>
<tr>
<td><strong>Stimulants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>Impaired judgment, pupillary dilation, hallucinations (including tactile), paranoid ideations, angina, sudden cardiac death. Treatment: α-blockers, benzodiazepines. β-blockers not recommended.</td>
<td>Hypersomnia, malaise, severe psychological craving, depression/suicidality.</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Restlessness, ↑ diuresis, muscle twitching.</td>
<td>Lack of concentration, headache.</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Restlessness.</td>
<td>Irritability, anxiety, craving. Treatment: nicotine patch, gum, or lozenges; bupropion/varenicline.</td>
</tr>
</tbody>
</table>
### Psychoactive drug intoxication and withdrawal (continued)

<table>
<thead>
<tr>
<th>DRUG</th>
<th>INTOXICATION</th>
<th>WITHDRAWAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallucinogens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCP</td>
<td>Belligerence, impulsivity, fever, psychomotor agitation, analgesia, vertical</td>
<td>Depression, anxiety, irritability, restlessness, anergia, disturbances of</td>
</tr>
<tr>
<td></td>
<td>and horizontal nystagmus, tachycardia, homicidality, psychosis, delirium,</td>
<td>thought and sleep.</td>
</tr>
<tr>
<td></td>
<td>seizures. Treatment: benzodiazepines, rapid-acting antipsychotic.</td>
<td></td>
</tr>
<tr>
<td>LSD</td>
<td>Perceptual distortion (visual, auditory), depersonalization, anxiety,</td>
<td>Irritability, depression, insomnia, nausea, anorexia. Most symptoms peak</td>
</tr>
<tr>
<td></td>
<td>paranoia, psychosis, possible flashbacks.</td>
<td>in 48 hours and last for 5–7 days. Generally detectable in urine for up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>to 1 month.</td>
</tr>
<tr>
<td>Marijuana (cannabinoid)</td>
<td>Euphoria, anxiety, paranoid delusions, perception of slowed time, impaired</td>
<td></td>
</tr>
<tr>
<td></td>
<td>judgment, social withdrawal, ↑ appetite, dry mouth, conjunctival injection,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hallucinations. Pharmaceutical form is dronabinol (tetrahydrocannabinol isomer): used as antiemetic (chemotherapy) and appetite stimulant (in AIDS).</td>
<td></td>
</tr>
<tr>
<td>Heroin addiction</td>
<td>Users at ↑ risk for hepatitis, HIV, abscesses, bacteremia, right-heart</td>
<td></td>
</tr>
<tr>
<td></td>
<td>endocarditis. Treatment is described below.</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>Long-acting oral opiate used for heroin detoxification or long-term</td>
<td></td>
</tr>
<tr>
<td></td>
<td>maintenance.</td>
<td></td>
</tr>
<tr>
<td>Naloxone + buprenorphine</td>
<td>Antagonist + partial agonist. Naloxone is not orally bioavailable, so</td>
<td></td>
</tr>
<tr>
<td></td>
<td>withdrawal symptoms occur only if injected (lower abuse potential).</td>
<td></td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Long-acting opioid antagonist used for relapse prevention once detoxified.</td>
<td></td>
</tr>
<tr>
<td>Alcoholism</td>
<td>Physiologic tolerance and dependence with symptoms of withdrawal (tremor,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>tachycardia, hypertension, malaise, nausea, DTs) when intake is interrupted.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Complications: alcoholic cirrhosis, hepatitis, pancreatitis, peripheral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>neuropathy, testicular atrophy. Treatment: disulfiram (to condition the</td>
<td></td>
</tr>
<tr>
<td></td>
<td>patient to abstain from alcohol use), acamprosate, naltrexone, supportive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>care. Support groups such as Alcoholics Anonymous are helpful in sustaining</td>
<td></td>
</tr>
<tr>
<td></td>
<td>abstinence and supporting patient and family.</td>
<td></td>
</tr>
<tr>
<td>Wernicke-Korsakoff syndrome</td>
<td>Caused by vitamin B1 deficiency. Triad of confusion, ophthalmoplegia,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ataxia (Wernicke encephalopathy). May progress to irreversible memory</td>
<td></td>
</tr>
<tr>
<td></td>
<td>loss, confabulation, personality change (Korsakoff psychosis). Associated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>with periventricular hemorrhage/necrosis of mammillary bodies. Treatment:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV vitamin B1.</td>
<td></td>
</tr>
<tr>
<td>Mallory-Weiss syndrome</td>
<td>Partial thickness tear at gastroesophageal junction caused by excessive/forceful vomiting. Often presents with hematemesis and misdiagnosed as ruptured esophageal varices.</td>
<td></td>
</tr>
<tr>
<td>Delirium tremens (DTs)</td>
<td>Life-threatening alcohol withdrawal syndrome that peaks 2–4 days after last</td>
<td></td>
</tr>
<tr>
<td></td>
<td>drink. Characterized by autonomic hyperactivity (e.g., tachycardia, tremors,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>anxiety, seizures). Classically occurs in hospital setting (e.g., 2–4 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>postsurgery) in alcoholics not able to drink as inpatients. Treatment:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>benzodiazepines. Alcoholic hallucinosis is a distinct condition characterized</td>
<td></td>
</tr>
<tr>
<td></td>
<td>by visual hallucinations 12–48 hours after last drink. Treatment: long-acting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>benzodiazepines (e.g., chlordiazepoxide, lorazepam, diazepam).</td>
<td></td>
</tr>
</tbody>
</table>
### Medications for selected psychiatric conditions

<table>
<thead>
<tr>
<th>Psychiatric Condition</th>
<th>Preferred Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>Stimulants (e.g., methylphenidate)</td>
</tr>
<tr>
<td>Alcohol withdrawal</td>
<td>Long-acting benzodiazepines (e.g., chlordiazepoxide, lorazepam, diazepam)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>Lithium, valproic acid, atypical antipsychotics</td>
</tr>
<tr>
<td>Bulimia</td>
<td>SSRIs</td>
</tr>
<tr>
<td>Depression</td>
<td>SSRIs</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>SSRIs, SNRIs</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>SSRIs, clomipramine</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>SSRIs, venlafaxine, benzodiazepines</td>
</tr>
<tr>
<td>PTSD</td>
<td>SSRIs, venlafaxine</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Atypical antipsychotics</td>
</tr>
<tr>
<td>Social phobias</td>
<td>SSRIs, β-blockers</td>
</tr>
<tr>
<td>Tourette syndrome</td>
<td>Antipsychotics (e.g., fluphenazine, pimozide), tetrabenazine, clonidine</td>
</tr>
</tbody>
</table>

### CNS stimulants

- **Mechanism**: ↑ catecholamines in the synaptic cleft, especially norepinephrine and dopamine.
- **Clinical Use**: ADHD, narcolepsy, appetite control.
### Antipsyhtics (neuroleptics)

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>All typical antipsychotics block dopamine D₂ receptors († cAMP).</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>Schizophrenia (primarily positive symptoms), psychosis, acute mania, Tourette syndrome.</td>
</tr>
<tr>
<td>TOXICITY</td>
<td>Highly lipid soluble and stored in body fat; thus, very slow to be removed from body. Extrapyramidal system side effects (e.g., dyskinesias). Treatment: benzotropine or diphenhydramine. Endocrine side effects (e.g., dopamine receptor antagonism → hyperprolactinemia → galactorrhea). Side effects arising from blocking muscarinic (dry mouth, constipation), α₁ (hypotension), and histamine (sedation) receptors. Can cause QT prolongation.</td>
</tr>
<tr>
<td>OTHER TOXICITIES</td>
<td>Neuroleptic malignant syndrome (NMS) — rigidity, myoglobinuria, autonomic instability, hyperpyrexia. Treatment: dantrolene, D₂ agonists (e.g., bromocriptine). Tardive dyskinesia—stereotypic oral-facial movements as a result of long-term antipsychotic use.</td>
</tr>
</tbody>
</table>

### High potency: Trifluoperazine, Fluphenazine, Haloperidol (Try to Fly High)—neurologic side effects (e.g., Huntington disease, delirium, EPS symptoms).

### Low potency: Chlorpromazine, Thioridazine (Cheating Thieves are low)—non-neurologic side effects (anticholinergic, antihistamine, and α₁-blockade effects).

Chlorpromazine—Corneal deposits; Thioridazine—retinal deposits; haloperidol—NMS, tardive dyskinesia.

Evolution of EPS side effects:
- 4 hr acute dystonia (muscle spasm, stiffness, oculogyric crisis)
- 4 day akathisia (restlessness)
- 4 wk bradykinesia (parkinsonism)
- 4 mo tardive dyskinesia

For NMS, think FEVER:
- Fever
- Encephalopathy
- Vitals unstable
- Enzymes †
- Rigidity of muscles

### Atypical antipsychotics

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Not completely understood. Varied effects on 5-HT₂, dopamine, and α- and H₁-receptors.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>Schizophrenia—both positive and negative symptoms. Also used for bipolar disorder, OCD, anxiety disorder, depression, mania, Tourette syndrome.</td>
</tr>
<tr>
<td>TOXICITY</td>
<td>Fewer extrapyramidal and anticholinergic side effects than traditional antipsychotics. Olanzapine/clozapine may cause significant weight gain. Clozapine may cause agranulocytosis (requires weekly WBC monitoring) and seizure. Risperidone may increase prolactin (causing lactation and gynecomastia) → GnRH, LH, and FSH (causing irregular menstruation and fertility issues). All may prolong QT interval.</td>
</tr>
</tbody>
</table>

It's atypical for old closets to quietly risper from A to Z.

Must watch clozapine clozely!
**Lithium**

**MECHANISM**
Not established; possibly related to inhibition of phosphoinositol cascade.

**CLINICAL USE**
Mood stabilizer for bipolar disorder; blocks relapse and acute manic events. Also SIADH.

**TOXICITY**
Tremor, hypothyroidism, polyuria (causes nephrogenic diabetes insipidus), teratogenesis. Causes Ebstein anomaly in newborn if taken by pregnant mother. Narrow therapeutic window requires close monitoring of serum levels. Almost exclusively excreted by kidneys; most is reabsorbed at PCT with Na+. Thiazide use is implicated in lithium toxicity in bipolar patients.

**LMNOP—Lithium side effects:**
- Movement (tremor)
- Nephrogenic diabetes insipidus
- Hypothyroidism
- Pregnancy problems

**Buspirone**

**MECHANISM**
Stimulates 5-HT\textsubscript{1A} receptors.

**CLINICAL USE**
Generalized anxiety disorder. Does not cause sedation, addiction, or tolerance. Takes 1–2 weeks to take effect. Does not interact with alcohol (vs. barbiturates, benzodiazepines).

"I'm always anxious if the bus will be on time, so I take buspirone."

**Antidepressants**

**NORADRENERGIC**
- MAO inhibitors
- Bupropion
- NE reuptake
- NE receptor
- TCA, SNRIs
- Metabolites

**SEROTONERGIC**
- MAO
- Bupropion
- 5-HT reuptake
- 5-HT receptor
- TCA, SSRI, SNRI, trazodone
- Metabolites

This diagram illustrates the mechanisms of action for different classes of antidepressants, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and MAO inhibitors. The diagram shows how these medications target various neuronal pathways to treat mood disorders.
### SSRIs

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>5-HT-specific reuptake inhibitors.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>Depression, generalized anxiety disorder, panic disorder, OCD, bulimia, social phobias, PTSD.</td>
</tr>
<tr>
<td>TOXICITY</td>
<td>Fewer than TCAs. GI distress, SIADH, sexual dysfunction (anorgasmia, ↓ libido). Serotonin syndrome with any drug that ↑ 5-HT (e.g., MAO inhibitors, SNRIs, TCAs)—hyperthermia, confusion, myoclonus, cardiovascular instability, flushing, diarrhea, seizures. Treatment: cyproheptadine (5-HT₂ receptor antagonist).</td>
</tr>
</tbody>
</table>

### SNRIs

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Inhibit 5-HT and norepinephrine reuptake.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>Depression. Venlafaxine is also used in generalized anxiety disorder, panic disorder, PTSD. Duloxetine is also indicated for diabetic peripheral neuropathy.</td>
</tr>
<tr>
<td>TOXICITY</td>
<td>↑ BP most common; also stimulant effects, sedation, nausea.</td>
</tr>
</tbody>
</table>

### Tricyclic antidepressants

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Block reuptake of norepinephrine and 5-HT.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>Major depression, OCD (clomipramine), peripheral neuropathy, chronic pain, migraine prophylaxis.</td>
</tr>
<tr>
<td>TOXICITY</td>
<td>Sedation, α₁-blocking effects including postural hypotension, and atropine-like (anticholinergic) side effects (tachycardia, urinary retention, dry mouth). 3° TCAs (amitriptyline) have more anticholinergic effects than 2° TCAs (nortriptyline). Can prolong QT interval. Tri-C’s: Convulsions, Coma, Cardiotoxicity (arrhythmias); also respiratory depression, hyperpyrexia. Confusion and hallucinations in elderly due to anticholinergic side effects (use nortriptyline). Treatment: NaHCO₃ to prevent arrhythmia.</td>
</tr>
</tbody>
</table>

### Monoamine oxidase (MAO) inhibitors

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Nonselective MAO inhibition ↑ levels of amine neurotransmitters (norepinephrine, 5-HT, dopamine).</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>Atypical depression, anxiety.</td>
</tr>
<tr>
<td>TOXICITY</td>
<td>Hypertensive crisis (most notably with ingestion of tyramine, which is found in many foods such as wine and cheese); CNS stimulation. Contraindicated with SSRIs, TCAs, St. John's wort, meperidine, dextromethorphan (to prevent serotonin syndrome).</td>
</tr>
</tbody>
</table>

**Flashbacks paralyze senior citizens.** It normally takes 4–8 weeks for antidepressants to have an effect.
### Atypical antidepressants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
<th>Toxicity</th>
</tr>
</thead>
</table>
| **Bupropion** | Also used for smoking cessation. ↑ norepinephrine and dopamine via unknown mechanism.  
Toxicity: stimulant effects (tachycardia, insomnia), headache, seizures in anorexic/bulimic patients. No sexual side effects. |                                                                                                   |
| **Mirtazapine** | α2-antagonist (↑ release of norepinephrine and 5-HT) and potent 5-HT2 and 5-HT3 receptor antagonist. Toxicity: sedation (which may be desirable in depressed patients with insomnia), ↑ appetite, weight gain (which may be desirable in elderly or anorexic patients), dry mouth. |                                                                                                   |
| **Trazodone**   | Primarily blocks 5-HT2 and α1-adrenergic receptors. Used primarily for insomnia, as high doses are needed for antidepressant effects. Toxicity: sedation, nausea, priapism, postural hypotension. Called trazobone due to male-specific side effects. |                                                                                                   |
“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
Kidney embryology

- Pronephros—week 4; then degenerates.
- Mesonephros—functions as interim kidney for 1st trimester; later contributes to male genital system.
- Metanephros—permanent; first appears in 5th week of gestation; nephrogenesis continues through 32–36 weeks of gestation.
  - Ureteric bud—derived from caudal end of mesonephric duct; gives rise to ureter, pelvices, calyces, collecting ducts; fully canalized by 10th week
  - Metanephric mesenchyme—ureteric bud interacts with this tissue; interaction induces differentiation and formation of glomerulus through to distal convoluted tubule (DCT)
  - Aberrant interaction between these 2 tissues may result in several congenital malformations of the kidney
- Ureteropelvic junction—last to canalize → most common site of obstruction (hydronephrosis) in fetus.

Potter sequence (syndrome)

Oligohydramnios → compression of developing fetus → limb deformities, facial anomalies (e.g., low-set ears and retrognathia [arrows in A]), compression of chest and lack of amniotic fluid aspiration into fetal lungs → pulmonary hypoplasia (cause of death).

Causes include ARPKD, obstructive uropathy (e.g., 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. As they ascend from pelvis during fetal development, horseshoe kidneys get trapped under inferior mesenteric artery and remain low in the abdomen. Kidneys function normally. Associated with ureteropelvic junction obstruction, hydronephrosis, renal stones, infection, chromosomal aneuploidy syndromes (e.g., Edwards, Down, Patau, Turner), and rarely renal cancer.

Multicystic dysplastic kidney

Due to abnormal interaction between ureteric bud and metanephric mesenchyme. Leads to a nonfunctional kidney consisting of cysts and connective tissue. If unilateral (most common), generally asymptomatic with compensatory hypertrophy of contralateral kidney. Often diagnosed prenatally via ultrasound.

Duplex collecting system

Bifurcation of ureteric bud before it enters metanephric blastema creates Y-shaped bifid ureter. Can alternatively occur when two ureteric buds reach and interact with metanephric blastema. Strongly associated with vesicoureteral reflux and/or ureteral obstruction, ↑ risk for UTIs.
Renal — Anatomy

Kidney anatomy and glomerular structure

Left kidney is taken during donor transplantation because it has a longer renal vein.
Afferent = Arriving.
Efferent = Exiting.

Ureters: course

Ureters pass under uterine artery and under ductus deferens (retroperitoneal).
“Water (ureters) under the bridge (uterine artery, vas deferens).”
Gynecologic procedures involving ligation of uterine vessels traveling in cardinal ligament may damage ureter → ureteral obstruction or leak.
Fluid compartments

- **Total body water (TBW)**: 60% of body mass = ~42 L = 42 kg
- **Non water mass (NWM)**: 40% of body mass = ~28 kg

**Extracellular fluid (ECF)**: ~ 14 kg (20% of 70 kg)

**Intracellular fluid (ICF)**: ~ 28 kg (40% of 70 kg)

- 2/3
- 1/3

**Interstitial fluid** = 75% ECF ~ 10.5 L = 10.5 kg

**Blood volume** ~6 L

- **Plasma** = 25% ECF = 3.5 L = 3.5 kg

**Body mass**: ~70 kg

**RBC volume** = ~2.8 L

**HCT (%) ~ 3** [Hb] in g/dL

Normal HCT = 45%

**HIKIN**: High K INtracellularly.

60–40–20 rule (% of body weight for average person):
- 60% total body water
- 40% ICF
- 20% ECF

Plasma volume measured by radiolabeled albumin.

Extracellular volume measured by inulin.

Osmolality = 285–295 mOsm/kg H₂O.

**Glomerular filtration barrier**

- Responsible for filtration of plasma according to size and net charge.
- Composed of:
  - Fenestrated capillary endothelium (size barrier)
  - Fused basement membrane with heparan sulfate (negative charge barrier)
  - Epithelial layer consisting of podocyte foot processes

**Charge barrier is lost in nephrotic syndrome** → albuminuria, hypoproteinemia, generalized edema, hyperlipidemia.

**Renal clearance**

\[ C_x = U_x \times V / P_x = \text{volume of plasma from which the substance is completely cleared per unit time.} \]

\[ C_x < \text{GFR}: \text{net tubular reabsorption of } X. \]

\[ C_x > \text{GFR}: \text{net tubular secretion of } X. \]

\[ C_x = \text{GFR}: \text{no net secretion or reabsorption.} \]

Be familiar with calculations.

- \( C_x \) = clearance of X (mL/min).
- \( U_x \) = urine concentration of X (e.g., mg/mL).
- \( P_x \) = plasma concentration of X (e.g., mg/mL).
- \( V \) = urine flow rate (mL/min).

**Glomerular filtration rate**

Inulin clearance can be used to calculate GFR because it is freely filtered and is neither reabsorbed nor secreted.

\[ \text{GFR} = U_{\text{inulin}} \times V / P_{\text{inulin}} = C_{\text{inulin}} = K_f \cdot [P_{\text{GC}} - P_{\text{BS}}] - (\pi_{\text{GC}} - \pi_{\text{BS}})] \]

(GC = glomerular capillary; BS = Bowman space.) \( \pi_{\text{BS}} \) normally equals zero.

Normal GFR = 100 mL/min.

Creatinine clearance is an approximate measure of GFR. Slightly overestimates GFR because creatinine is moderately secreted by renal tubules.

Incremental reductions in GFR define the stages of chronic kidney disease.
**Effective renal plasma flow**

Effective renal plasma flow (eRPF) can be estimated using \( \text{para}-\text{aminohippuric acid (PAH)} \) clearance because it is both filtered and secreted in the proximal collecting tubule (PCT), resulting in near 100% excretion of all PAH entering kidney.

\[
eRPF = U_{\text{PAH}} \times \frac{V}{P_{\text{PAH}}} = C_{\text{PAH}}.
\]

\[
RBF = \frac{\text{RPF}}{(1 - \text{Hct})}.
\]

eRPF underestimates true renal plasma flow (RPF) by ~10%.

**Filtration**

Filtration fraction (FF) = GFR/RPF.

Normal FF = 20%.

Filtered load (mg/min) = GFR (mL/min) \times \text{plasma concentration (mg/mL)}.

GFR can be estimated with creatinine clearance.

RPF is best estimated with PAH clearance.

**Changes in glomerular dynamics**

<table>
<thead>
<tr>
<th>Effect</th>
<th>GFR</th>
<th>RPF</th>
<th>FF (GFR/RPF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afferent arteriole constriction</td>
<td>↓</td>
<td>↓</td>
<td>—</td>
</tr>
<tr>
<td>Efferent arteriole constriction</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>↑ plasma protein concentration</td>
<td>↓</td>
<td>—</td>
<td>↑</td>
</tr>
<tr>
<td>↓ plasma protein concentration</td>
<td>↑</td>
<td>—</td>
<td>↓</td>
</tr>
<tr>
<td>Constriction of ureter</td>
<td>↓</td>
<td>—</td>
<td>↓</td>
</tr>
</tbody>
</table>
### Calculation of reabsorption and secretion rate

- **Filtered load** = \( \text{GFR} \times P_x \)
- **Excretion rate** = \( V \times U_x \)
- **Reabsorption** = filtered – excreted.
- **Secretion** = excreted – filtered.

### Glucose clearance

Glucose at a normal plasma level is completely reabsorbed in PCT by Na\(^+\)/glucose cotransport. At plasma glucose of \( \sim 200 \text{ mg/dL} \), glucosuria begins (threshold). At \( \sim 375 \text{ mg/dL} \), all transporters are fully saturated (\( T_m \)).

Glucosuria is an important clinical clue to diabetes mellitus. Normal pregnancy may decrease ability of PCT to reabsorb glucose and amino acids \( \rightarrow \) glucosuria and aminoaciduria.

### Amino acid clearance

Na\(^+\)-dependent transporters in PCT reabsorb amino acids. **Hartnup disease** — autosomal recessive. Deficiency of neutral amino acid (e.g., tryptophan) transporters in proximal renal tubular cells and on enterocytes \( \rightarrow \) neutral aminoaciduria and absorptions from the gut \( \rightarrow \) tryptophan for conversion to niacin \( \rightarrow \) pellagra-like symptoms. Treat with high-protein diet and nicotinic acid.
Early PCT—contains brush border. Reabsorbs all glucose and amino acids and most $\text{HCO}_3^-$, $\text{Na}^+$, $\text{Cl}^-$, $\text{PO}_4^{3-}$, $\text{K}^+$, and $\text{H}_2\text{O}$. Isotonic absorption. Generates and secretes $\text{NH}_3$, which acts as a buffer for secreted $\text{H}^+$. PTH—inhibits Na$^+/\text{PO}_4^{3-}$ cotransport $\rightarrow \text{PO}_4^{3-}$ excretion. AT II—stimulates Na$^+/\text{H}^+$ exchange $\rightarrow$ Na$^+$, H$_2\text{O}$, and HCO$_3^-$ reabsorption (permitting contraction alkalosis). 65–80% Na$^+$ reabsorbed.


Thick ascending loop of Henle—reabsorbs Na$^+$, K$^+$, and Cl$^-$. Indirectly induces paracellular reabsorption of Mg$^{2+}$ and Ca$^{2+}$ through (+) lumen potential generated by K$^+$ backleak. Impermeable to H$_2$O. Makes urine less concentrated as it ascends. 10–20% Na$^+$ reabsorbed.

Collecting tubule—reabsorbs Na$^+$ in exchange for secreting K$^+$ and H$^+$ (regulated by aldosterone). Aldosterone—acts on mineralocorticoid receptor $\rightarrow$ mRNA $\rightarrow$ protein synthesis. In principal cells: ↑ apical K$^+$ conductance, ↑ Na$^+/\text{K}^+$ pump, ↑ ENaC channels $\rightarrow$ lumen negativity $\rightarrow$ K$^+$ loss. In α-intercalated cells: ↑ H$^+$ ATPase activity $\rightarrow$ ↑ HCO$_3^-$/Cl$^-$ exchanger activity. ADH—acts at V$_2$ receptor $\rightarrow$ insertion of aquaporin H$_2$O channels on apical side. 3–5% Na$^+$ reabsorbed.
Renal tubular defects

The kidneys put out FABulous Glittering LiquidS:
- Fanconi syndrome is the 1st defect (PCT)
- Bartter syndrome is next (thick ascending loop of Henle)
- Gitelman syndrome is after Bartter (DCT)
- Liddle syndrome is last (collecting tubule)
- Syndrome of apparent mineralocorticoid excess (collecting tubule)

Fanconi syndrome
Generalized reabsorptive defect in PCT.
Associated with † excretion of nearly all amino acids, glucose, HCO₃⁻, and PO₄³⁻. May result in metabolic acidosis (proximal renal tubular acidosis).
Causes include hereditary defects (e.g., Wilson disease, tyrosinemia, glycogen storage disease), ischemia, multiple myeloma, nephrotoxins/drugs (e.g., expired tetracyclines, tenofovir), lead poisoning.

Bartter syndrome
Results in hypokalemia and metabolic alkalosis with hypercalciuria.

Gitelman syndrome
Reabsorptive defect of NaCl in DCT.
Autosomal recessive. Less severe than Bartter syndrome. Leads to hypokalemia, hypomagnesemia, metabolic alkalosis, hypocalciuria.

Liddle syndrome
Gain of function mutation → † Na⁺ reabsorption in collecting tubules († activity of epithelial Na⁺ channel).
Autosomal dominant. Results in hypertension, hypokalemia, metabolic alkalosis, aldosterone. Treatment: Amiloride.

Syndrome of apparent mineralocorticoid excess
Hereditary deficiency of 11β-hydroxysteroid dehydrogenase, which normally converts cortisol into cortisone in mineralocorticoid receptor–containing cells before cortisol can act on the mineralocorticoid receptors. Excess cortisol in these cells from enzyme deficiency → † mineralocorticoid receptor activity → hypertension, hypokalemia, metabolic alkalosis. Low serum aldosterone levels. Can acquire disorder from glycyrrhetic acid (present in licorice), which blocks activity of 11β-hydroxysteroid dehydrogenase.

Relative concentrations along proximal convoluted tubules

TF/P > 1 when: Solute is reabsorbed less quickly than water
TF/P = 1 when: Solute and water are reabsorbed at same rate
TF/P < 1 when: Solute is reabsorbed more quickly than water

TF/P = [Tubular fluid] /[Plasma]

Neither secreted nor reabsorbed; concentration increases as water is reabsorbed.

Tubular insulin † in concentration (but not amount) along the PCT as a result of water reabsorption. Cl⁻ reabsorption occurs at a slower rate than Na⁺ in early PCT and then matches the rate of Na⁺ reabsorption more distally. Thus, its relative concentration † before it plateaus.
Renin-angiotensin-aldosterone system

AT II
Affects baroreceptor function; limits reflex bradycardia, which would normally accompany its pressor effects. Helps maintain blood volume and blood pressure.

ANP, BNP
Released from atria (ANP) and ventricles (BNP) in response to ↑ volume; may act as a “check” on renin-angiotensin-aldosterone system; relaxes vascular smooth muscle via cGMP → ↑ GFR, ↓ renin.

ADH
Primarily regulates osmolarity; also responds to low blood volume states.

Aldosterone
Primarily regulates ECF volume and Na⁺ content; responds to low blood volume states.
**Juxtaglomerular apparatus**

Consists of mesangial cells, JG cells (modified smooth muscle of afferent arteriole) and the macula densa (NaCl sensor, part of DCT). JG cells secrete renin in response to ↓ renal blood pressure and ↑ sympathetic tone (β₁). Macula densa cells sense ↓ NaCl delivery to DCT → adenosine release → vasoconstriction.

JGA maintains GFR via renin-angiotensin-aldosterone system. β-blockers can decrease BP by inhibiting β₁-receptors of the JGA → ↓ renin release.

---

**Kidney endocrine functions**

<table>
<thead>
<tr>
<th>Erythropoietin</th>
<th>Released by interstitial cells in peritubular capillary bed in response to hypoxia.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,25-(OH)₂ D₃</td>
<td>PCT cells convert 25-OH vitamin D to 1,25-(OH)₂ vitamin D (active form).</td>
</tr>
<tr>
<td></td>
<td>25-OH D₃ → 1α-hydroxylase → 1,25-(OH)₂ D₃</td>
</tr>
<tr>
<td></td>
<td>PTH</td>
</tr>
<tr>
<td>Renin</td>
<td>Secreted by JG cells in response to ↓ renal arterial pressure and ↑ renal sympathetic discharge (β₁ effect).</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Paracrine secretion vasodilates the afferent arterioles to ↑ RBF.</td>
</tr>
<tr>
<td></td>
<td>NSAIDs block renal-protective prostaglandin synthesis → constriction of afferent arteriole and ↓ GFR; this may result in acute renal failure.</td>
</tr>
</tbody>
</table>
**Hormones acting on kidney**

- **Atrial natriuretic peptide (ANP)**
  - Synthesized in response to ↑ atrial pressure.
  - Causes ↑ GFR and ↓ Na⁺ filtration with no compensatory Na⁺ reabsorption in distal nephron.
  - Net effect: Na⁺ loss and volume loss.

- **Parathyroid hormone (PTH)**
  - Secreted in response to ↓ plasma [Ca²⁺], ↑ plasma [PO₄³⁻], or ↓ plasma 1,25-(OH)₂D₃.
  - Causes ↑ Ca²⁺ reabsorption (DCT), ↓ PO₄³⁻ reabsorption (PCT), and ↑ 1,25-(OH)₂D₃ production (↑ Ca²⁺ and PO₄³⁻ absorption from gut via vitamin D).

- **Aldosterone**
  - Secreted in response to ↓ blood volume (via AT II) and ↑ plasma [K⁺]; causes ↑ Na⁺ reabsorption, ↑ K⁺ secretion, and H⁺ secretion.

- **ADH (vasopressin)**
  - Secreted in response to ↑ plasma osmolarity and ↓ blood volume.
  - Binds to receptors on principal cells, causing ↑ number of aquaporins and ↑ H₂O reabsorption.

**Potassium shifts**

**Shifts K⁺ out of cell (causing hyperkalemia):**
- Digitalis (blocks Na⁺/K⁺ ATPase)
- Hyperosmolarity
- Lysis of cells (e.g., crush injury, rhabdomyolysis, cancer)
- Acidosis
- β-blocker
- High blood Sugar (insulin deficiency)

**Shifts K⁺ into cell (causing hypokalemia):**
- Hypo-osmolarity
- Alkalosis
- β-adrenergic agonist (↑ Na⁺/K⁺ ATPase)
- Insulin (↑ Na⁺/K⁺ ATPase)
- Insulin shifts K⁺ into cells

**Patient with hyperkalemia? DO LABS.**
**Electrolyte disturbances**

<table>
<thead>
<tr>
<th>ELECTROLYTE</th>
<th>LOW SERUM CONCENTRATION</th>
<th>HIGH SERUM CONCENTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>Nausea and malaise, stupor, coma, seizures</td>
<td>Irritability, stupor, coma</td>
</tr>
<tr>
<td>K⁺</td>
<td>U waves on ECG, flattened T waves, arrhythmias, muscle spasm</td>
<td>Wide QRS and peaked T waves on ECG, arrhythmias, muscle weakness</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>Tetany, seizures, QT prolongation</td>
<td>Stones (renal), bones (pain), groans (abdominal pain), thrones († urinary frequency), psychiatric overtones (anxiety, altered mental status), but not necessarily calciuria</td>
</tr>
<tr>
<td>Mg²⁺</td>
<td>Tetany, torsades de pointes, hypokalemia</td>
<td>↓ DTRs, lethargy, bradycardia, hypotension, cardiac arrest, hypocalcemia</td>
</tr>
<tr>
<td>PO₄³⁻</td>
<td>Bone loss, osteomalacia (adults), rickets (children)</td>
<td>Renal stones, metastatic calcifications, hypocalcemia</td>
</tr>
</tbody>
</table>
**Acid-base physiology**

<table>
<thead>
<tr>
<th></th>
<th>pH</th>
<th>Pco2</th>
<th>[HCO3−]</th>
<th>Compensatory Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic acidosis</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Hyperventilation (immediate)</td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Hypoventilation (immediate)</td>
</tr>
<tr>
<td>Respiratory acidosis</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↑ renal [HCO3−] reabsorption (delayed)</td>
</tr>
<tr>
<td>Respiratory alkalosis</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓ renal [HCO3−] reabsorption (delayed)</td>
</tr>
</tbody>
</table>

Key: ↓ ↓ = 1st disturbance; ↑ ↑ = compensatory response.

Henderson-Hasselbalch equation: $\text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.05 \text{P}_{\text{CO}_2}}$

Predicted respiratory compensation for a simple metabolic acidosis can be calculated using the Winters formula. If measured $\text{P}_{\text{CO}_2}$ differs significantly from predicted $\text{P}_{\text{CO}_2}$, then a mixed acid-base disorder is likely present:

$$\text{P}_{\text{CO}_2} = 1.5 [\text{HCO}_3^-] + 8 \pm 2$$

**Acidosis/alkalosis**

- **Check arterial pH**
  - pH < 7.35: Acidemia
    - $\text{P}_{\text{CO}_2} > 40 \text{ mmHg}$: Respiratory acidosis
    - Hypoventilation
      - Airway obstruction
      - Acute lung disease
      - Chronic lung disease
      - Opioids, sedatives
      - Weakening of respiratory muscles
  - $\text{P}_{\text{CO}_2} < 40 \text{ mmHg}$: Metabolic acidosis with compensation (hyperventilation)
    - Check anion gap
      - Anion gap $= \text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$
      - Anion gap
        - MUDPILES:
          - Methanol (formic acid)
          - Uremia
          - Diabetic ketoacidosis
          - Propylene glycol
          - Iron tablets or isoniazid
          - Lactic acidosis
          - Ethylene glycol (oxalic acid)
          - Salicylates (late)
        - Normal anion gap (8-12 mEq/L)
          - HARD-ASS:
            - Hyperalimentation
            - Addison disease
            - Renal tubular acidosis
            - Diarrhea
            - Acetazolamide
            - Spironolactone
            - Saline infusion
- **Check arterial pH**
  - pH > 7.45: Alkalemia
    - $\text{P}_{\text{CO}_2} < 40 \text{ mmHg}$: Respiratory alkalosis
      - Hyperventilation
        - Hysteria
        - Hypoxemia (e.g., high altitude)
        - Salicylates (early)
        - Tumor
        - Pulmonary embolism
    - $\text{P}_{\text{CO}_2} > 40 \text{ mmHg}$: Metabolic alkalosis with compensation (hypoventilation)
      - Loop/thiazide diuretics
      - Vomiting
      - Antacid use
      - Hyperaldosteronism
Renal tubular acidosis

A disorder of the renal tubules that leads to normal anion gap (hyperchloremic) metabolic acidosis.

<table>
<thead>
<tr>
<th>RTA TYPE</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Distal (type 1), urine pH &gt; 5.5</strong></td>
<td>Defect in ability of α-intercalated cells to secrete H⁺ → no new HCO₃⁻ is generated → metabolic acidosis. Associated with hypokalemia, ↑ risk for calcium phosphate kidney stones (due to ↑ urine pH and ↑ bone turnover). Causes: amphotericin B toxicity, analgesic nephropathy, congenital anomalies (obstruction) of urinary tract.</td>
</tr>
<tr>
<td><strong>Proximal (type 2), urine pH &lt; 5.5</strong></td>
<td>Defect in PCT HCO₃⁻ reabsorption → ↑ excretion of HCO₃⁻ in urine and subsequent metabolic acidosis. Urine is acidified by α-intercalated cells in collecting tubule. Associated with hypokalemia, ↑ risk for hypophosphatemic rickets. Causes: Fanconi syndrome and carbonic anhydrase inhibitors.</td>
</tr>
<tr>
<td><strong>Hyperkalemic (type 4), urine pH &lt; 5.5</strong></td>
<td>Hypoaldosteronism → hyperkalemia → ↓ NH₃ synthesis in PCT → ↓ NH₄⁺ excretion. Causes: ↓ aldosterone production (e.g., diabetic hyporeninism, ACE inhibitors, ARBs, NSAIDs, heparin, cyclosporine, adrenal insufficiency) or aldosterone resistance (e.g., K⁺-sparing diuretics, nephropathy due to obstruction, TMP/SMX).</td>
</tr>
</tbody>
</table>

RENAL—PATHOLOGY

Casts in urine

Presence of casts indicates that hematuria/pyuria is of glomerular or renal tubular origin.

- **RBC casts**: Glomerulonephritis, malignant hypertension.
- **WBC casts**: Tubulointerstitial inflammation, acute pyelonephritis, transplant rejection.
- **Fatty casts (“oval fat bodies”)**: Nephrotic syndrome.
- **Granular (“muddy brown”) casts**: Acute tubular necrosis.
- **Waxy casts**: End-stage renal disease/chronic renal failure.
- **Hyaline casts**: Nonspecific, can be a normal finding, often seen in concentrated urine samples.
### Nomenclature of glomerular disorders

<table>
<thead>
<tr>
<th>Type</th>
<th>Characteristics</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal</td>
<td>&lt; 50% of glomeruli are involved</td>
<td>Focal segmental glomerulosclerosis</td>
</tr>
<tr>
<td>Diffuse</td>
<td>&gt; 50% of glomeruli are involved</td>
<td>Diffuse proliferative glomerulonephritis</td>
</tr>
<tr>
<td>Proliferative</td>
<td>Hypercellular glomeruli</td>
<td>Membranoproliferative glomerulonephritis</td>
</tr>
<tr>
<td>Membranous</td>
<td>Thickening of glomerular basement membrane (GBM)</td>
<td>Membranous nephropathy</td>
</tr>
<tr>
<td>1° glomerular disease</td>
<td>A 1° disease of the kidney specifically impacting the glomeruli</td>
<td>Minimal change disease</td>
</tr>
<tr>
<td>2° glomerular disease</td>
<td>A systemic disease or disease of another organ system that also impacts the glomeruli</td>
<td>SLE, diabetic nephropathy</td>
</tr>
</tbody>
</table>

### Glomerular diseases

**Nephritic syndrome**—due to GBM disruption. Hypertension, ↑ BUN and creatine, oliguria, hematuria, RBC casts in urine. Proteinuria often in the subnephrotic range (< 3.5 g/day) but in severe cases may be in nephrotic range.
- Acute poststreptococcal glomerulonephritis
- Rapidly progressive glomerulonephritis
- IgA nephropathy (Berger disease)
- Alport syndrome
- Membranoproliferative glomerulonephritis

**Nephrotic syndrome**—podocyte disruption → charge barrier impaired. Massive proteinuria (> 3.5 g/day) with hypoalbuminemia, hyperlipidemia, edema. May be 1° (direct podocyte damage) or 2° (podocyte damage from systemic process e.g., diabetes).
- Focal segmental glomerulosclerosis (1° or 2°)
- Minimal change disease (1° or 2°)
- Membranous nephropathy (1° or 2°)
- Amyloidosis (2°)
- Diabetic glomerulonephropathy (2°)

**Nephritic-nephrotic syndrome**—severe nephritic syndrome with profound GBM damage that damages the glomerular filtration charge barrier → nephrotic-range proteinuria (> 3.5 g/day) and concomitant features of nephrotic syndrome. Can occur with any form of nephritic syndrome, but is most commonly seen with:
- Diffuse proliferative glomerulonephritis
- Membranoproliferative glomerulonephritis

### GRAMS OF PROTEIN EXcretED PER DAY (g/day)

<table>
<thead>
<tr>
<th>Grams of Protein Excreted PER Day (g/day)</th>
<th>0.25</th>
<th>3.5</th>
<th>&gt; 3.5</th>
</tr>
</thead>
</table>

**Nephritic syndrome**

Nephritic syndrome = Inflammatory process. When it involves glomeruli, it leads to hematuria and RBC casts in urine. Associated with azotemia, oliguria, hypertension (due to salt retention), proteinuria.

**Acute poststreptococcal glomerulonephritis**

LM—glomeruli enlarged and hypercellular. IF—("starry sky") granular appearance ("lumpy-bumpy"). Due to IgG, IgM, and C3 deposition along GBM and mesangium. EM—subepithelial immune complex (IC) humps.

Most frequently seen in children. Occurs ~ 2 weeks after group A streptococcal infection of pharynx or skin. Resolves spontaneously. Type III hypersensitivity reaction.

 Presents with peripheral and periordial edema, cola-colored urine, hypertension.

↑ anti-DNase B titers, ↓ complement levels.
### Nephritic syndrome (continued)

<table>
<thead>
<tr>
<th>Rapidly progressive (crescentic) glomerulonephritis (RPGN)</th>
<th>LM and IF—crescent moon shape. Crescents consist of fibrin and plasma proteins (e.g., C3b) with glomerular parietal cells, monocytes, macrophages. Several disease processes may result in this pattern, in particular:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Goodpasture syndrome</strong>—type II hypersensitivity; antibodies to GBM and alveolar basement membrane → linear IF</td>
<td></td>
</tr>
<tr>
<td><strong>Granulomatosis with polyangiitis (Wegener)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Microscopic polyangiitis</strong></td>
<td></td>
</tr>
<tr>
<td>Poor prognosis. Rapidly deteriorating renal function (days to weeks).</td>
<td></td>
</tr>
<tr>
<td>Hematuria/hemoptysis.</td>
<td></td>
</tr>
<tr>
<td>Treatment: emergent plasmapheresis.</td>
<td></td>
</tr>
<tr>
<td>PR3-ANCA/c-ANCA.</td>
<td></td>
</tr>
<tr>
<td>MPO-ANCA/p-ANCA.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diffuse proliferative glomerulonephritis (DPGN)</th>
<th>Due to SLE or membranoproliferative glomerulonephritis. LM—“wire looping” of capillaries. EM—subendothelial and sometimes intramembranous IgG-based ICs often with C3 deposition. IF—granular.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor prognosis. Rapidly deteriorating renal function (days to weeks).</td>
<td></td>
</tr>
<tr>
<td>Diffuse proliferative glomerulonephritis (DPGN)</td>
<td></td>
</tr>
<tr>
<td>Due to SLE or membranoproliferative glomerulonephritis. LM—“wire looping” of capillaries. EM—subendothelial and sometimes intramembranous IgG-based ICs often with C3 deposition. IF—granular.</td>
<td></td>
</tr>
<tr>
<td>Most common cause of death in SLE (think “wire lupus”). DPGN and MPGN often present as nephrotic syndrome and nephritic syndrome concurrently.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IgA nephropathy (Berger disease)</th>
<th>LM—mesangial proliferation. EM—mesangial IC deposits. IF—IgA-based IC deposits in mesangium. Renal pathology of Henoch-Schönlein purpura.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Often presents with renal insufficiency or acute gastroenteritis. Episodic hematuria with RBC casts. Not to be confused with Buerger disease (thromboangiitis obliterans).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alport syndrome</th>
<th>Mutation in type IV collagen → thinning and splitting of glomerular basement membrane. Most commonly X-linked.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye problems (e.g., retinopathy, lens dislocation), glomerulonephritis, sensorineural deafness; “can’t see, can’t pee, can’t hear a buzzing bee.” “Basket-weave” appearance on EM.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Membrano-proliferative glomerulonephritis (MPGN)</th>
<th>Type I—subendothelial immune complex (IC) deposits with granular IF; “tram-track” appearance on PAS stain and H&amp;E stain due to GBM splitting caused by mesangial ingrowth. Type II—intramembranous IC deposits, “dense deposits.”</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPGN is a nephritic syndrome that often copresents with nephrotic syndrome. Type I may be 2° to hepatitis B or C infection. May also be idiopathic. Type II is associated with C3 nephritic factor (stabilizes C3 convertase → ↓ serum C3 levels).</td>
<td></td>
</tr>
</tbody>
</table>

---

LM = light microscopy; EM = electron microscopy; IF = immunofluorescence.
### Nephrotic syndrome

Nephrotic syndrome—massive proteinuria (> 3.5 g/day) with hypoalbuminemia, resulting edema, hyperlipidemia. Frothy urine with fatty casts. Due to podocyte damage disrupting glomerular filtration charge barrier. May be 1° (direct sclerosis of podocytes) or 2° (systemic process [e.g., diabetes] secondarily damages podocytes). Severe nephritic syndrome may present with nephrotic syndrome features (nephritic-nephrotic syndrome) if damage to GBM is severe enough to damage charge barrier. Associated with hypercoagulable state (e.g., thromboembolism) due to antithrombin (AT) III loss in urine and risk of infection (due to loss of immunoglobulins in urine and soft tissue compromise by edema).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Light Microscopy (LM)</th>
<th>Immunofluorescence (IF)</th>
<th>Electron Microscopy (EM)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Focal segmental glomerulosclerosis</strong></td>
<td>Segmental sclerosis and hyalinosis</td>
<td>Nonspecific for focal deposits of IgM, C3, C1.</td>
<td>Effacement of foot process similar to minimal change disease.</td>
</tr>
<tr>
<td><strong>Minimal change disease (lipoid nephrosis)</strong></td>
<td>Normal glomeruli (lipid may be seen in PCT cells).</td>
<td></td>
<td>Effacement (fusion) of foot processes.</td>
</tr>
<tr>
<td><strong>Membranous nephropathy</strong></td>
<td>Diffuse capillary and GBM thickening</td>
<td>Granular as a result of immune complex deposition.</td>
<td>“Spike and dome” appearance with subepithelial deposits.</td>
</tr>
</tbody>
</table>
Nephrotic syndrome (continued)

Amyloidosis

LM—Congo red stain shows apple-green birefringence under polarized light. Kidney is the most commonly involved organ (systemic amyloidosis). Associated with chronic conditions (e.g., multiple myeloma, TB, rheumatoid arthritis).

Diabetic glomerulonephropathy

# Kidney stones

Can lead to severe complications, such as hydronephrosis, pyelonephritis. Presents with unilateral flank tenderness, colicky pain radiating to groin, hematuria. Treat and prevent by encouraging fluid intake.

<table>
<thead>
<tr>
<th>CONTENT</th>
<th>PRECIPITATES AT</th>
<th>X-RAY FINDINGS</th>
<th>URINE CRYSTAL</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (80%)</td>
<td>↑ pH (calcium phosphate)</td>
<td>Radiopaque</td>
<td>Envelope- or dumbbell-shaped calcium oxalate</td>
<td>Oxalate crystals can result from ethylene glycol (antifreeze) ingestion, vitamin C abuse, hypocitraturia, malabsorption (e.g., Crohn disease). Most common kidney stone presentation: calcium oxalate stone in patient with hypercalciumia and normocalcemia. Treatment: hydration, thiazides, citrate.</td>
</tr>
<tr>
<td>Ammonium magnesium phosphate (15%)</td>
<td>↑ pH</td>
<td>Radiopaque</td>
<td>Coffin lid</td>
<td>Also known as struvite. Caused by infection with urease bugs (e.g., Proteus mirabilis, Staphylococcus saprophyticus, Klebsiella) that hydrolyze urea to ammonia urine alkalinization. Commonly form staghorn calculi. Treatment: eradication of underlying infection, surgical removal of stone.</td>
</tr>
<tr>
<td>Uric acid (5%)</td>
<td>↓ pH</td>
<td>Radiolucent</td>
<td>Rhomboid or rosettes</td>
<td>Risk factors: ↓ urine volume, arid climates, acidic pH. Visible on CT and ultrasound, but not x-ray. Strong association with hyperuricemia (e.g., gout). Often seen in diseases with ↑ cell turnover, such as leukemia. Treatment: alkalinization of urine, allopurinol.</td>
</tr>
<tr>
<td>Cystine (1%)</td>
<td>↓ pH</td>
<td>Radiolucent</td>
<td>Hexagonal</td>
<td>Hereditary (autosomal recessive) condition in which cystine-reabsorbing PCT transporter loses function, causing cystinuria. Cystine is poorly soluble, thus stones form in urine. Mostly seen in children. Can form staghorn calculi. Sodium cyanide nitroprusside test ⊕. “SIXtine” stones have SIX sides. Treatment: alkalinization of urine.</td>
</tr>
</tbody>
</table>


Hydronephrosis

Distention/dilation of renal pelvis and calyces. Usually caused by urinary tract obstruction (e.g., renal stones, BPH, cervical cancer, injury to ureter); other causes include retroperitoneal fibrosis, vesicoureteral reflux. Dilation occurs proximal to site of pathology. Serum creatinine becomes elevated only if obstruction is bilateral or if patient has only one kidney. Leads to compression and possible atrophy of renal cortex and medulla.

Renal cell carcinoma

Originates from PCT cells — polygonal clear cells filled with accumulated lipids and carbohydrates. Most common in men 50–70 years old. Incidence with smoking and obesity. Manifests clinically with hematuria, palpable mass, secondary polycythemia, flank pain, fever, weight loss. Invades renal vein then IVC and spreads hematogenously; metastasizes to lung and bone.

Treatment: resection if localized disease. Immunotherapy or targeted therapy for advanced/metastatic disease. Resistant to chemotherapy and radiation therapy.

Most common 1° renal malignancy. Associated with gene deletion on chromosome 3 (sporadic or inherited as von Hippel-Lindau syndrome). RCC = 3 letters = chromosome 3. Associated with paraneoplastic syndromes (e.g., ectopic EPO, ACTH, PTHrP).

“Silent” cancer because commonly presents as a metastatic neoplasm.
Renal oncocytoma

Benign epithelial cell tumor (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 (e.g., renal cell carcinoma).

Wilms tumor (nephroblastoma)

Most common renal malignancy of early childhood (ages 2–4). Contains embryonic glomerular structures. Presents with large, palpable, unilateral flank mass (A) and/or hematuria. “Loss of function” mutations of tumor suppressor genes WT1 or WT2 on chromosome 11. May be part of Beckwith-Wiedemann syndrome (Wilms tumor, macroglossia, organomegaly, hemihypertrophy) or WAGR complex: Wilms tumor, Aniridia, Genitourinary malformation, mental Retardation (intellectual disability).
Transitional cell carcinoma


Squamous cell carcinoma of the bladder

Chronic irritation of urinary bladder → squamous metaplasia → dysplasia and squamous cell carcinoma. Risk factors include Schistosoma haematobium infection (Middle East), chronic cystitis, smoking, chronic nephrolithiasis. Presents with painless hematuria.

Urinary tract infection (acute bacterial cystitis)

Inflammation of urinary bladder. Presents as suprapubic pain, dysuria, urinary frequency, urgency. Systemic signs (e.g., high fever, chills) are usually absent. Risk factors include female gender (short urethra), sexual intercourse (“honeymoon cystitis”), indwelling catheter, diabetes mellitus, impaired bladder emptying. Causes:
  * E. coli (most common).
  * Staphylococcus saprophyticus—seen in sexually active young women (E. coli is still more common in this group).
  * Klebsiella.
  * Proteus mirabilis—urine has ammonia scent.
Lab findings: ++ leukocyte esterase, + nitrites for gram-negative organisms (especially E. coli). Sterile pyuria and + urine cultures suggest urethritis by Neisseria gonorrhoeae or Chlamydia trachomatis.
Pyelonephritis

Acute

Neutrophils infiltrate renal interstitium. Affects cortex with relative sparing of glomeruli/vessels. Presents with fevers, flank pain (costovertebral angle tenderness). Causes include ascending UTI (E. coli is most common), hematogenous spread to kidney. Presents with WBCs in urine +/- WBC casts. CT shows striated parenchymal enhancement (arrow in 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

The result of recurrent episodes of acute pyelonephritis. Typically requires predisposition to infection such as vesicoureteral reflux or chronically obstructing kidney stones. Coarse, asymmetric corticomedullary scarring, blunted calyx. Tubules can contain eosinophilic casts resembling thyroid tissue (thyroidization of kidney).

Drug-induced interstitial nephritis

Acute interstitial renal inflammation. Pyuria (classically eosinophils) and azotemia occurring after administration of drugs that act as haptons, inducing hypersensitivity. Nephritis typically occurs 1–2 weeks after certain drugs (e.g., diuretics, penicillin derivatives, proton pump inhibitors, sulfonamides, rifampin), but can occur months after starting NSAIDs. Associated with fever, rash, hematuria, and costovertebral angle tenderness, but can be asymptomatic.

Diffuse cortical necrosis

Acute generalized cortical infarction of both kidneys. Likely due to a combination of vasospasm and DIC. Associated with obstetric catastrophes (e.g., abruptio placentae), septic shock.
**Acute tubular necrosis**  
Most common cause of acute kidney injury in hospitalized patients. Spontaneously resolves in many cases. Can be fatal, especially during initial oliguric phase. ↑ FENa.  
Key finding: granular (“muddy brown”) casts.  
3 stages:  
1. Inciting event  
2. Maintenance phase—oliguric; lasts 1–3 weeks; risk of hyperkalemia, metabolic acidosis, uremia  
3. Recovery phase—polyuric; BUN and serum creatinine fall; risk of hypokalemia  
Can be caused by ischemic or nephrotoxic injury:  
* Ischemic—2° to ↓ renal blood flow (e.g., hypotension, shock, sepsis, hemorrhage, HF). Results in death of tubular cells that may slough into tubular lumen (PCT and thick ascending limb are highly susceptible to injury).  
* Nephrotoxic—2° to injury resulting from toxic substances (e.g., aminoglycosides, radiocontrast agents, lead, cisplatin), crush injury (myoglobinuria), hemoglobinuria. PCT is particularly susceptible to injury.

![Muddy brown casts in acute tubular necrosis](image1)  
Inset shows magnified image of cast.  

**Renal papillary necrosis**  
Sloughing of necrotic renal papillae → gross hematuria and proteinuria. May be triggered by recent infection or immune stimulus. Associated with sickle cell disease or trait, acute pyelonephritis, NSAIDs, diabetes mellitus.  
SAAD pap with papillary necrosis:  
- Sickle cell disease or trait  
- Acute pyelonephritis  
- Analgesics (NSAIDs)  
- Diabetes mellitus
Acute kidney injury (acute renal failure)  
Acute kidney injury is defined as an abrupt decline in renal function as measured by ↑ creatinine and ↑ BUN.

Prerenal azotemia  
Due to ↓ RBF (e.g., hypotension) → ↓ GFR. Na+/H2O and BUN retained by kidney in an attempt to conserve volume → ↑ BUN/creatinine ratio (BUN is reabsorbed, creatinine is not) and ↓ FENa.

Intrinsic renal failure  
Generally due to acute tubular necrosis or ischemia/toxins; less commonly due to acute glomerulonephritis (e.g., RPGN, hemolytic uremic syndrome). In ATN, patchy necrosis → debris obstructing tubule and fluid backflow across necrotic tubule → ↓ GFR. Urine has epithelial/granular casts. BUN reabsorption is impaired → ↑ BUN/creatinine ratio.

Postrenal azotemia  
Due to outflow obstruction (stones, BPH, neoplasia, congenital anomalies). Develops only with bilateral obstruction.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prerenal</th>
<th>Intrinsic Renal</th>
<th>Postrenal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine osmolality (mOsm/kg)</td>
<td>&gt; 500</td>
<td>&lt; 350</td>
<td>&lt; 350</td>
</tr>
<tr>
<td>Urine Na⁺ (mEq/L)</td>
<td>&lt; 20</td>
<td>&gt; 40</td>
<td>&gt; 40</td>
</tr>
<tr>
<td>FENa</td>
<td>&lt; 1%</td>
<td>&gt; 2%</td>
<td>&gt; 1% (mild)</td>
</tr>
<tr>
<td>Serum BUN/Cr</td>
<td>&gt; 20</td>
<td>&lt; 15</td>
<td>Varies</td>
</tr>
</tbody>
</table>

Consequences of renal failure  
Inability to make urine and excrete nitrogenous wastes.  
Consequences (MAD HUNGER):  
- Metabolic Acidosis  
- Dyslipidemia (especially ↑ triglycerides)  
- Hyperkalemia  
- Uremia—clinical syndrome marked by ↑ BUN:  
  - Nausea and anorexia  
  - Pericarditis  
  - Asterixis  
  - Encephalopathy  
  - Platelet dysfunction  
- Na⁺/H₂O retention (HF, pulmonary edema, hypertension)  
- Growth retardation and developmental delay  
- Erythropoietin failure (anemia)  
- Renal osteodystrophy

2 forms of renal failure: acute (e.g., ATN) and chronic (e.g., hypertension, diabetes mellitus, congenital anomalies).

Renal osteodystrophy  
Failure of vitamin D hydroxylation, hypocalcemia, and hyperphosphatemia → 2° hyperparathyroidism. Hyperphosphatemia also independently ↓ serum Ca²⁺ by causing tissue calcifications, whereas ↓ 1,25-(OH)₂ D₃ → ↓ intestinal Ca²⁺ absorption. Causes subperiosteal thinning of bones.
### Renal cyst disorders

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADPKD</strong></td>
<td>Formerly adult polycystic kidney disease. Numerous cysts causing bilateral enlarged kidneys ultimately destroy kidney parenchyma. Presents with flank pain, hematuria, hypertension, urinary infection, progressive renal failure. Autosomal Dominant; mutation in PKD1 (85% of cases, chromosome 16) or PKD2 (15% of cases, chromosome 4). Death from complications of chronic kidney disease or hypertension (caused by renin production). Associated with berry aneurysms, mitral valve prolapse, benign hepatic cysts.</td>
</tr>
<tr>
<td><strong>ARPKD</strong></td>
<td>Formerly infantile polycystic kidney disease. Presents in infancy. Autosomal Recessive. 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.</td>
</tr>
<tr>
<td><strong>Medullary cystic disease</strong></td>
<td>Inherited disease causing tubulointerstitial fibrosis and progressive renal insufficiency with inability to concentrate urine. Medullary cysts usually not visualized; shrunken kidneys on ultrasound. Poor prognosis.</td>
</tr>
<tr>
<td><strong>Simple vs. complex renal cysts</strong></td>
<td>Simple cysts are filled with ultrafiltrate (anechoic on ultrasound). Very common and account for majority of all renal masses. Found incidentally and typically asymptomatic. Complex cysts, including those that are septated, enhanced, or have solid components on imaging require follow-up or removal due to risk of renal cell carcinoma.</td>
</tr>
</tbody>
</table>
Diuretics: site of action

- Acetazolamide
- Thiazides
- Mannitol
- Loop diuretics
- Potassium-sparking diuretics
- ADH antagonists

**Diuretics**

- **Thiazides**
  - NaCl
  - Ca^{2+}
  - Mg^{2+}
  - K^+
  - H^+
  - NaHCO_3

- **Mannitol**
  - NaCl
  - K^+
  - 2Cl^-

- **Loop diuretics**
  - NaCl
  - K^+
  - 2Cl^-
  - H_2O
  - H^+

- **Potassium-sparking diuretics**
  - NaCl
  - K^+
  - H^+

- **ADH antagonists**
  - H_2O
  - (+ADH)

- **Acetazolamide**

- **Mannitol**

- **Thiazides**

- **Loop diuretics**

- **Potassium-sparking diuretics**

- **ADH antagonists**
### Mannitol

**MECHANISM**
Osmotic diuretic. ↑ tubular fluid osmolarity → ↑ urine flow, ↓ intracranial/intraocular pressure.

**CLINICAL USE**
Drug overdose, elevated intracranial/intraocular pressure.

**TOXICITY**
Pulmonary edema, dehydration. Contraindicated in anuria, HF.

### Acetazolamide

**MECHANISM**
Carbonic anhydrase inhibitor. Causes self-limited NaHCO₃ diuresis and ↓ total body HCO₃⁻ stores.

**CLINICAL USE**
Glaucoma, urinary alkalinization, metabolic alkalosis, altitude sickness, pseudotumor cerebri.

**TOXICITY**
Hyperchloremic metabolic acidosis, paresthesias, NH₃ toxicity, sulfa allergy. "ACID"azolamide causes ACIDosis.

### Loop diuretics

**Furosemide, bumetanide, torsemide**

**MECHANISM**
Sulfonamide loop diuretics. Inhibit cotransport system (Na⁺/K⁺/2Cl⁻) of thick ascending limb of loop of Henle. Abolish hypertonicity of medulla, preventing concentration of urine. Stimulate PGE release (vasodilatory effect on afferent arteriole), inhibited by NSAIDs. ↑ Ca²⁺ excretion. Loops Lose Ca²⁺:

**CLINICAL USE**
Edematous states (HF, cirrhosis, nephrotic syndrome, pulmonary edema), hypertension, hypercalcemia.

**TOXICITY**
Otitotoxicity, Hypokalemia, Dehydration, Allergy (sulfa), Nephritis (interstitial), Gout. OH DANG!

### Ethacryninc acid

**MECHANISM**
Phenoxyacetic acid derivative (not a sulfonamide). Essentially same action as furosemide.

**CLINICAL USE**
Diuresis in patients allergic to sulfa drugs.

**TOXICITY**
Similar to furosemide; can cause hyperuricemia; never use to treat gout.
### Thiazide diuretics

**Chlorthalidone, hydrochlorothiazide.**

**Mechanism**
Inhibit NaCl reabsorption in early DCT → ↓ diluting capacity of nephron. ↓ Ca\(^{2+}\) excretion.

**Clinical Use**
Hypertension, HF, idiopathic hypercalciuria, nephrogenic diabetes insipidus, osteoporosis.

**Toxicity**
Hypokalemic metabolic alkalosis, hyperGLUC, hyperLIPIDEMIA, hyperURICEMIA, hyperCALCEMIA. Sulfur allergy.

### K\(^+\)-sparing diuretics

**Spironolactone and eplerenone; Triamterene, and Amiloride.**

**Mechanism**
Spironolactone and eplerenone are competitive aldosterone receptor antagonists in cortical collecting tubule. Triamterene and amiloride act at the same part of the tubule by blocking Na\(^+\) channels in the cortical collecting tubule.

**Clinical Use**
Hyperaldosteronism, K\(^+\) depletion, HF.

**Toxicity**
Hyperkalemia (can lead to arrhythmias), endocrine effects with spironolactone (e.g., gynecomastia, antiandrogen effects).

### Diuretics: electrolyte changes

| **Urine NaCl** | ↓ with all diuretics except acetazolamide. Serum NaCl may decrease as a result. |
| **Urine K\(^+\)** | ↓ with loop and thiazide diuretics. Serum K\(^+\) may decrease as a result. |
| **Blood pH** | ↓ (acidemia): carbonic anhydrase inhibitors. ↓ HCO\(_3\)\(^-\) reabsorption. K\(^+\) sparing: aldosterone blockade prevents K\(^+\) secretion and H\(^+\) secretion. Additionally, hyperkalemia leads to K\(^+\) entering all cells (via H\(^+\)/K\(^+\) exchanger) in exchange for H\(^+\) exiting cells. |
| **Urine Ca\(^{2+}\)** | ↓ (alkalemia): loop diuretics and thiazides cause alkalosis through several mechanisms: |

- Volume contraction → ↑ AT II → ↑ Na\(^+\)/H\(^+\) exchange in PCT → ↑ HCO\(_3\)\(^-\) reabsorption (“contraction alkalosis”)
- K\(^+\) loss leads to K\(^+\) exiting all cells (via H\(^+\)/K\(^+\) exchanger) in exchange for H\(^+\) entering cells
- In low K\(^+\) state, H\(^+\) (rather than K\(^+\)) is exchanged for Na\(^+\) in cortical collecting tubule → alkalosis and “paradoxical aciduria”

- with loop diuretics; ↓ paracellular Ca\(^{2+}\) reabsorption → hypocalcemia.
- with thiazides: Enhanced Ca\(^{2+}\) reabsorption in DCT.
### ACE inhibitors

**MECHANISM**
Inhibit ACE → ↓ AT II → ↓ GFR by preventing constriction of efferent arterioles. Levels of renin ↑ as a result of loss of feedback inhibition. Inhibition of ACE also prevents inactivation of bradykinin, a potent vasodilator.

**CLINICAL USE**
Hypertension, HF, proteinuria, diabetic nephropathy. Prevent unfavorable heart remodeling as a result of chronic hypertension.

**TOXICITY**
Cough, Angioedema (contraindicated in C1 esterase inhibitor deficiency), Teratogen (fetal renal malformations), ↑ Creatinine (↓ GFR), Hyperkalemia, and Hypotension. Avoid in bilateral renal artery stenosis, because ACE inhibitors will further ↓ GFR → renal failure.

In diabetic nephropathy, ↓ intraglomerular pressure, slowing GBM thickening.

Captopril’s CATCHH.

### Angiotensin II receptor blockers

**MECHANISM**
Selectively block binding of angiotensin II to AT₁ receptor. Effects similar to ACE inhibitors, but ARBs do not increase bradykinin.

**CLINICAL USE**
Hypertension, HF, proteinuria, or diabetic nephropathy with intolerance to ACE inhibitors (e.g., cough, angioedema).

**TOXICITY**
Hyperkalemia, ↓ renal function, hypotension; teratogen.

### Aliskiren

**MECHANISM**
Direct renin inhibitor, blocks conversion of angiotensinogen to angiotensin I.

**CLINICAL USE**
Hypertension.

**TOXICITY**
Hyperkalemia, ↓ renal function, hypotension. Contraindicated in diabetics taking ACE inhibitors or ARBs.
HIGH-YIELD SYSTEMS

Reproductive

“Artificial insemination is when the farmer does it to the cow instead of the bull.”
— Student essay

“Whoever called it necking was a poor judge of anatomy.”
— Groucho Marx

“See, the problem is that God gives men a brain and a penis, and only enough blood to run one at a time.”
— Robin Williams

Embryology 558
Anatomy 569
Physiology 573
Pathology 578
Pharmacology 595
### Important genes of embryogenesis

<table>
<thead>
<tr>
<th>Gene</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sonic hedgehog gene</strong></td>
<td>Produced at base of limbs in zone of polarizing activity. Involved in patterning along anterior-posterior axis. Involved in CNS development; mutation can cause holoprosencephaly.</td>
</tr>
<tr>
<td><strong>Wnt-7 gene</strong></td>
<td>Produced at apical ectodermal ridge (thickened ectoderm at distal end of each developing limb). Necessary for proper organization along dorsal-ventral axis.</td>
</tr>
<tr>
<td><strong>FGF gene</strong></td>
<td>Produced at apical ectodermal ridge. Stimulates mitosis of underlying mesoderm, providing for lengthening of limbs.</td>
</tr>
<tr>
<td><strong>Homeobox (Hox) genes</strong></td>
<td>Involved in segmental organization of embryo in a craniocaudal direction. Code for transcription factors. Hox mutations appendages in wrong locations.</td>
</tr>
</tbody>
</table>

### Early fetal development

<table>
<thead>
<tr>
<th>Timeframe</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 0</strong></td>
<td>Fertilization by sperm, forming zygote, initiating embryogenesis.</td>
</tr>
<tr>
<td><strong>Within week 1</strong></td>
<td>hCG secretion begins around the time of implantation of blastocyst (&quot;it 'sticks' at day 6&quot;).</td>
</tr>
<tr>
<td><strong>Within week 2</strong></td>
<td>Bilaminar disc (epiblast, hypoblast). 2 weeks = 2 layers.</td>
</tr>
<tr>
<td><strong>Within week 3</strong></td>
<td>Trilaminar disc. 3 weeks = 3 layers. Gastrulation, Primitive streak, notochord, mesoderm and its organization, and neural plate begin to form.</td>
</tr>
<tr>
<td><strong>Weeks 3–8 (embryonic period)</strong></td>
<td>Neural tube formed by neuroectoderm and closes by week 4. Organogenesis. Extremely susceptible to teratogens.</td>
</tr>
<tr>
<td><strong>Week 4</strong></td>
<td>Heart begins to beat. Upper and lower limb buds begin to form. 4 weeks = 4 limbs.</td>
</tr>
<tr>
<td><strong>Week 6</strong></td>
<td>Fetal cardiac activity visible by transvaginal ultrasound.</td>
</tr>
<tr>
<td><strong>Week 10</strong></td>
<td>Genitalia have male/female characteristics.</td>
</tr>
</tbody>
</table>

### Gastrulation

Process that forms the trilaminar embryonic disc. Establishes the ectoderm, mesoderm, and endoderm germ layers. Starts with the epiblast invaginating to form the primitive streak.
### Embryologic derivatives

<table>
<thead>
<tr>
<th>Ectoderm</th>
<th>External/outer layer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surface ectoderm</strong></td>
<td>Epidermis; adenohypophysis (from Rathke pouch); lens of eye; epithelial linings of oral cavity, sensory organs of ear, and olfactory epithelium; epidermis; anal canal below the pectinate line; parotid, sweat, and mammary glands.</td>
</tr>
<tr>
<td><strong>Neuroectoderm</strong></td>
<td>Brain (neurohypophysis, CNS neurons, oligodendrocytes, astrocytes, ependymal cells, pineal gland), retina and optic nerve, spinal cord.</td>
</tr>
<tr>
<td><strong>Neural crest</strong></td>
<td>PNS (dorsal root ganglia, cranial nerves, celiac ganglion, Schwann cells, ANS), melanocytes, chromaffin cells of adrenal medulla, parafollicular (C) cells of thyroid, pia and arachnoid, bones of the skull, odontoblasts, aorticopulmonary septum.</td>
</tr>
<tr>
<td><strong>Mesoderm</strong></td>
<td>Muscle, bone, connective tissue, serous linings of body cavities (e.g., peritoneum), spleen (derived from foregut mesentery), cardiovascular structures, lymphatics, blood, wall of gut tube, vagina, kidneys, adrenal cortex, dermis, testes, ovaries. Notochord induces ectoderm to form neuroectoderm (neural plate). Its only postnatal derivative is the nucleus pulposus of the intervertebral disc.</td>
</tr>
<tr>
<td><strong>Endoderm</strong></td>
<td>Gut tube epithelium (including anal canal above the pectinate line), most of urethra (derived from urogenital sinus), luminal epithelial derivatives (e.g., lungs, liver, gallbladder, pancreas, eustachian tube, thymus, parathyroid, thyroid follicular cells).</td>
</tr>
</tbody>
</table>

**Craniopharyngioma**—benign Rathke pouch tumor with cholesterol crystals, calcifications.

**Neuroectoderm**—think CNS.

Neutral crest—think PNS and non-neural structures nearby.

### Middle/"meat" layer.

Mesodermal defects = VACTERL:
- Vertebral defects
- Anal atresia
- Cardiac defects
- Tracheo-Esophageal fistula
- Renal defects
- Limb defects (bone and muscle)

### Types of errors in organ morphogenesis

<table>
<thead>
<tr>
<th>Agenesis</th>
<th>Absent organ due to absent primordial tissue.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aplasia</td>
<td>Absent organ despite presence of primordial tissue.</td>
</tr>
<tr>
<td>Hypoplasia</td>
<td>Incomplete organ development; primordial tissue present.</td>
</tr>
<tr>
<td>Deformation</td>
<td>Extrinsic disruption; occurs after embryonic period.</td>
</tr>
<tr>
<td>Disruption</td>
<td>2° breakdown of previously normal tissue or structure (e.g., amniotic band syndrome).</td>
</tr>
<tr>
<td>Malformation</td>
<td>Intrinsic disruption; occurs during embryonic period (weeks 3–8).</td>
</tr>
<tr>
<td>Sequence</td>
<td>Abnormalities result from a single 1° embryologic event (e.g., oligohydramnios → Potter sequence).</td>
</tr>
</tbody>
</table>
**Teratogens**  
Most susceptible in 3rd–8th weeks (embryonic period—organogenesis) of pregnancy. Before week 3, “all-or-none” effects. After week 8, growth and function affected.

<table>
<thead>
<tr>
<th>Teratogen</th>
<th>Effects on Fetus</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Renal damage</td>
<td></td>
</tr>
<tr>
<td>Alkylating agents</td>
<td>Absence of digits, multiple anomalies</td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>CN VIII toxicity</td>
<td>A mean guy hit the baby in the ear.</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Facial dysmorphism, developmental delay, neural tube defects, phalanx/fingernail hypoplasia</td>
<td></td>
</tr>
<tr>
<td>Diethylstilbestrol (DES)</td>
<td>Vaginal clear cell adenocarcinoma, congenital Mullerian anomalies</td>
<td></td>
</tr>
<tr>
<td>Folate antagonists</td>
<td>Neural tube defects</td>
<td></td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>Multiple severe birth defects</td>
<td>Contraception mandatory</td>
</tr>
<tr>
<td>Lithium</td>
<td>Ebstein anomaly (atrialized right ventricle)</td>
<td></td>
</tr>
<tr>
<td>Methimazole</td>
<td>Aplasia cutis congenita</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Fetal hydantoin syndrome—cleft palate, cardiac defects, phalanx/fingernail hypoplasia</td>
<td></td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Discolored teeth</td>
<td>“Teethracyclines.”</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Limb defects (phocomelia, micromelia—“flipper” limbs)</td>
<td>Limb defects with “tha-limb-domide.”</td>
</tr>
<tr>
<td>Valproate</td>
<td>Inhibition of maternal folate absorption → neural tube defects</td>
<td>Valproate inhibits folate absorption.</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Bone deformities, fetal hemorrhage, abortion, ophthalmologic abnormalities</td>
<td>Do not wage warfare on the baby; keep it happy with heparin (does not cross placenta).</td>
</tr>
<tr>
<td><strong>Substance abuse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>Common cause of birth defects and intellectual disability; fetal alcohol syndrome</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>Abnormal fetal growth and fetal addiction; placental abruption</td>
<td></td>
</tr>
<tr>
<td>Smoking (nicotine, CO)</td>
<td>Low birth weight (leading cause in developed countries), preterm labor, placental problems, IUGR, ADHD</td>
<td>Nicotine → vasoconstriction. CO → impaired O₂ delivery.</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iodine (lack or excess)</td>
<td>Congenital goiter or hypothyroidism (cretinism)</td>
<td></td>
</tr>
<tr>
<td>Maternal diabetes</td>
<td>Caudal regression syndrome (anal atresia to sirenomelia), congenital heart defects, neural tube defects</td>
<td></td>
</tr>
<tr>
<td>Vitamin A (excess)</td>
<td>Extremely high risk for spontaneous abortions and birth defects (cleft palate, cardiac)</td>
<td></td>
</tr>
<tr>
<td>X-rays</td>
<td>Microcephaly, intellectual disability</td>
<td>Minimized by lead shielding.</td>
</tr>
</tbody>
</table>
Fetal alcohol syndrome

Leading cause of intellectual disability in the U.S. Newborns of alcohol-consuming mothers have an incidence of congenital abnormalities, including pre- and postnatal developmental retardation, microcephaly, facial abnormalities (e.g., smooth philtrum, hypertelorism), limb dislocation, heart defects. Heart-lung fistulas and holoprosencephaly in most severe form. Mechanism is failure of cell migration.

Twinning

Dizygotic 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 twins arise from 1 fertilized egg (1 egg + 1 sperm) that splits into 2 zygotes in early pregnancy. The degree of separation between monozygotic twins depends on when the fertilized egg splits into 2 zygotes. The timing of this separation determines the number of chorions and the number of amnions.
**Placenta**

1° site of nutrient and gas exchange between mother and fetus.

<table>
<thead>
<tr>
<th><strong>Fetal component</strong></th>
<th><strong>Maternal component</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytotrophoblast</strong></td>
<td><strong>Decidua basalis</strong></td>
</tr>
<tr>
<td><strong>Syncytiotrophoblast</strong></td>
<td></td>
</tr>
<tr>
<td>Outer layer of chorionic villi; secretes hCG (structurally similar to LH; stimulates corpus luteum to secrete progesterone during first trimester).</td>
<td></td>
</tr>
</tbody>
</table>

Cytophoblast makes cells. Lacks MHC-I expression → ↓ chance of attack by maternal immune system.
**Umbilical cord**

Umbilical arteries (2)—return deoxygenated blood from fetal internal iliac arteries to placenta A.

Umbilical vein (1)—supplies oxygenated blood from placenta to fetus; drains into IVC via liver or via ductus venosus.

Single umbilical artery (2-vessel cord B) is associated with congenital and chromosomal anomalies.

Umbilical arteries and vein are derived from allantois.

---

**Urachus**

In the 3rd week the yolk sac forms the allantois, which extends into urogenital sinus. Allantois becomes the urachus, a duct between fetal bladder and yolk sac.

- **Patent urachus**: Total failure of urachus to obliterate → urine discharge from umbilicus.

- **Urachal cyst**: Partial failure of urachus to obliterate; fluid-filled cavity lined with uroepithelium, between umbilicus and bladder. Can lead to infection, adenocarcinoma.

- **Vesicourachal diverticulum**: Slight failure of urachus to obliterate → outpouching of bladder.

---

**Vitelline duct**

7th week—obliteration of vitelline duct (omphalo-mesenteric duct), which connects yolk sac to midgut lumen.

- **Vitelline fistula**: Vitelline duct fails to close → meconium discharge from umbilicus.

- **Meckel diverticulum**: Partial closure of vitelline duct, with patent portion attached to ileum (true diverticulum). May have heterotopic gastric and/or pancreatic tissue → melena, hematochezia, abdominal pain.
### Aortic arch derivatives

<table>
<thead>
<tr>
<th>Arch</th>
<th>Description</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>Part of maxillary artery (branch of external carotid). 1st arch is maximal.</td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td>Stapedial artery and hyoid artery.</td>
<td>Second = Stapedial.</td>
</tr>
<tr>
<td>3rd</td>
<td>Common Carotid artery and proximal part of internal Carotid artery.</td>
<td>C is 3rd letter of alphabet.</td>
</tr>
<tr>
<td>4th</td>
<td>On left, aortic arch; on right, proximal part of right subclavian artery.</td>
<td>4th arch (4 limbs) = systemic.</td>
</tr>
<tr>
<td>6th</td>
<td>Proximal part of pulmonary arteries and (on left only) ductus arteriosus.</td>
<td>6th arch = pulmonary and the pulmonary-to-systemic shunt (ductus arteriosus).</td>
</tr>
</tbody>
</table>

**Branchial apparatus**  
Also called pharyngeal apparatus. Composed of branchial clefts, arches, pouches.  
Branchial clefts—derived from ectoderm. Also called branchial grooves.  
Branchial arches—derived from mesoderm (muscles, arteries) and neural crest (bones, cartilage).  
Branchial pouches—derived from endoderm.  

**CAP covers outside to inside:**  
Clefts = ectoderm  
Arches = mesoderm  
Pouches = endoderm

**Branchial cleft derivatives**  
1st cleft develops into external auditory meatus.  
2nd through 4th clefts form temporary cervical sinuses, which are obliterated by proliferation of 2nd arch mesenchyme.  
Persistent cervical sinus → branchial cleft cyst within lateral neck.
### Branchial arch derivatives

<table>
<thead>
<tr>
<th>Arch</th>
<th>Cartilage</th>
<th>Muscles</th>
<th>Nerves*</th>
<th>Abnormalities/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st arch</td>
<td>Meckel cartilage: Mandible, Malleus, incus, sphenomandibular ligament</td>
<td>Muscles of Mastication (temporalis, Masseter, lateral and Medial pterygoids), Mylohyoid, anterior belly of digastric, tensor tympani, tensor veli palatini</td>
<td>CN V₂ and V₃ chew</td>
<td>Treacher Collins syndrome—1st-arch neural crest fails to migrate → mandibular hypoplasia, facial abnormalities</td>
</tr>
<tr>
<td>2nd arch</td>
<td>Reichert cartilage: Stapes, Styloid process, lesser horn of hyoid, Stylohyoid ligament</td>
<td>Muscles of facial expression, Stapedius, Stylohyoid, platysma, posterior belly of digastric</td>
<td>CN VII (facial expression) smile</td>
<td>Congenital pharyngocutaneous fistula— persistence of cleft and pouch → fistula between tonsillar area and lateral neck</td>
</tr>
<tr>
<td>3rd arch</td>
<td>Cartilage: greater horn of hyoid</td>
<td>Stylopharyngeus (think of stylopharyngeus innervated by glossopharyngeal nerve)</td>
<td>CN IX (stylopharyngeus) swallow stylishly</td>
<td></td>
</tr>
<tr>
<td>4th–6th arches</td>
<td>Cartilages: thyroid, cricoid, arytenoids, corniculate, cuneiform</td>
<td>4th arch: most pharyngeal constrictors; cricothyroid, levator veli palatini 6th arch: all intrinsic muscles of larynx except cricothyroid</td>
<td>4th arch: CN X (superior laryngeal branch) simply swallow 6th arch: CN X (recurrent laryngeal branch) speak</td>
<td>Arches 3 and 4 form posterior ⅓ of tongue; arch 5 makes no major developmental contributions</td>
</tr>
</tbody>
</table>

*These are the only CNs with both motor and sensory components (except V₂, which is sensory only).

When at the restaurant of the golden arches, children tend to first chew (1), then smile (2), then swallow stylishly (3) or simply swallow (4), and then speak (6).
**Branchial pouch derivatives**

<table>
<thead>
<tr>
<th>POUCH</th>
<th>DERIVATIVES</th>
<th>NOTES</th>
<th>MNEMONIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st pouch</td>
<td>Develops into middle ear cavity, eustachian tube, mastoid air cells.</td>
<td>1st pouch contributes to endoderm-lined structures of ear.</td>
<td>Ear, tonsils, bottom-to-top: 1 (ear), 2 (tonsils), 3 dorsal (bottom for inferior parathyroids), 4 ventral (to = thymus), 5 (top = superior parathyroids).</td>
</tr>
<tr>
<td>2nd pouch</td>
<td>Develops into epithelial lining of palatine tonsil.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd pouch</td>
<td>Dorsal wings—develop into inferior parathyroids. Ventral wings—develop into thymus.</td>
<td>3rd pouch contributes to 3 structures (thymus, left and right inferior parathyroids). 3rd-pouch structures end up below 4th-pouch structures.</td>
<td></td>
</tr>
<tr>
<td>4th pouch</td>
<td>Dorsal wings—develop into superior parathyroids.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**DiGeorge syndrome**

Aberrant development of 3rd and 4th pouches → T-cell deficiency (thymic aplasia) and hypocalcemia (failure of parathyroid development). Associated with cardiac defects (conotruncal anomalies).

**MEN 2A**

Mutation of germline RET (neural crest cells):
- Adrenal medulla (pheochromocytoma).
- Parafollicular cells (medullary thyroid cancer): derived from neural crest cells; associated with 4th/5th pharyngeal pouches.

**Cleft lip and cleft palate**

**Cleft lip**—failure of fusion of the maxillary and medial nasal processes (formation of 1st palate).

**Cleft palate**—failure of fusion of the two lateral palatine processes or failure of fusion of lateral palatine processes with the nasal septum and/or median palatine process (formation of 2nd palate).

Cleft lip and cleft palate have two distinct etiologies, but often occur together.
Genital embryology

**Female**
Default development. Mesonephric duct degenerates and paramesonephric duct develops.

**Male**
SRY gene on Y chromosome—produces testis-determining factor → testes development.
Sertoli cells secrete Müllerian inhibitory factor (MIF) that suppresses development of paramesonephric ducts.
Leydig cells secrete androgens that stimulate development of mesonephric ducts.

**Paramesonephric (Müllerian) duct**
Develops into female internal structures—fallopian tubes, uterus, upper portion of vagina (lower portion from urogenital sinus). **Müllerian agenesis**—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).
In females, remnant of mesonephric duct → Gartner duct.

**SRY gene**
1. No Sertoli cells or lack of Müllerian inhibitory factor → develop both male and female internal genitalia and male external genitalia
2. 5α-reductase deficiency—inaibility to convert testosterone into DHT → male internal genitalia, ambiguous external genitalia until puberty (when ↑ testosterone levels cause masculinization)
Uterine (Müllerian duct) anomalies

**Septate uterus**  Common anomaly vs. normal A uterus. Incomplete resorption of septum B. ↑ fertility. Treat with septoplasty.

**Bicornuate uterus**  Incomplete fusion of Müllerian ducts C. ↑ risk of complicated pregnancy.

**Uterus didelphys**  Complete failure of fusion → double uterus, vagina, and cervix D. Pregnancy possible.

Male/female genital homologs

**Glans penis**  Genital tubercle  Glans clitoris

**Corpus cavernosum and spongiosum**  Genital tubercle  Vestibular bulbs

**Bulbourethral glands (of Cowper)**  Urogenital sinus  Greater vestibular glands (of Bartholin)

**Prostate gland**  Urogenital sinus  Urethral and paraurethral glands (of Skene)

**Ventral shaft of penis (penile urethra)**  Urogenital folds  Labia minora

**Scrotum**  Labioscrotal swelling  Labia majora
Congenital penile abnormalities

**Hypospadias**
- Abnormal opening of penile urethra on ventral surface of penis due to failure of urethral folds to fuse.
- Hypospadias is more common than epispadias. Associated with inguinal hernia and cryptorchidism.
- Hypo is below.

**Epispadias**
- Abnormal opening of penile urethra on dorsal surface of penis due to faulty positioning of genital tubercle.
- Exstrophy of the bladder is associated with Epispadias.
- When you have Epispadias, you hit your Eye when you pee.

Descent of testes and ovaries

<table>
<thead>
<tr>
<th>MALE REMNANT</th>
<th>FEMALE REMNANT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gubernaculum (band of fibrous tissue)</strong></td>
<td>Anchors testes within scrotum.</td>
</tr>
<tr>
<td><strong>Processus vaginalis (evagination of peritoneum)</strong></td>
<td>Forms tunica vaginalis.</td>
</tr>
</tbody>
</table>

Gonadal drainage

**Venous drainage**
- Left ovary/testis → left gonadal vein → left renal vein → IVC.
- Right ovary/testis → right gonadal vein → IVC.

**Lymphatic drainage**
- Ovaries/testes → para-aortic lymph nodes.
- Distal vagina/vulva/scrotum → superficial inguinal nodes.
- Proximal vagina/uterus → obturator, external iliac and hypogastric nodes.

“Left gonadal vein takes the Longest way.”
Because the left spermatic vein enters the left renal vein at a 90° angle, flow is less laminar on left than on right → left venous pressure > right venous pressure → varicocele more common on the left.
Female reproductive anatomy

<table>
<thead>
<tr>
<th>Ligament</th>
<th>Connects</th>
<th>Structures contained</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infundibulopelvic ligament (suspensory ligament of the ovary)</td>
<td>Ovaries to lateral pelvic wall</td>
<td>Ovarian vessels</td>
<td>Ligate vessels during oophorectomy to avoid bleeding.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ureter courses retroperitoneally, close to gonadal vessels → at risk of injury during ligation of ovarian vessels.</td>
</tr>
<tr>
<td>Cardinal ligament (not labeled)</td>
<td>Cervix to side wall of pelvis</td>
<td>Uterine vessels</td>
<td>Ureter at risk of injury during ligation of uterine vessels in hysterectomy.</td>
</tr>
<tr>
<td>Round ligament of the uterus</td>
<td>Uterine fundus to labia majora</td>
<td></td>
<td>Derivative of gubernaculum. Travels through round inguinal canal; above the artery of Sampson.</td>
</tr>
<tr>
<td>Broad ligament</td>
<td>Uterus, fallopian tubes, and ovaries to pelvic side wall</td>
<td>Ovaries, fallopian tubes, round ligaments of uterus</td>
<td>Mesosalpinx, mesometrium, and mesovarium comprise the broad ligament.</td>
</tr>
<tr>
<td>Ovarian ligament</td>
<td>Medial pole of ovary to lateral uterus</td>
<td>—</td>
<td>Derivative of gubernaculum. Ovarian Ligament Latches to Lateral uterus.</td>
</tr>
</tbody>
</table>

Female reproductive epithelial histology

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Histology/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vagina</td>
<td>Stratified squamous epithelium, nonkeratinized</td>
</tr>
<tr>
<td>Ectocervix</td>
<td>Stratified squamous epithelium, nonkeratinized</td>
</tr>
<tr>
<td>Transformation zone</td>
<td>Squamocolumnar junction A (most common area for cervical cancer)</td>
</tr>
<tr>
<td>Endocervix</td>
<td>Simple columnar epithelium</td>
</tr>
<tr>
<td>Uterus</td>
<td>Simple columnar epithelium with long tubular glands in follicular phase; coiled glands in luteal phase</td>
</tr>
<tr>
<td>Fallopian tube</td>
<td>Simple columnar epithelium, ciliated</td>
</tr>
<tr>
<td>Ovary, outer surface</td>
<td>Simple cuboidal epithelium (germinal epithelium covering surface of ovary)</td>
</tr>
</tbody>
</table>
Female sexual response cycle
Most commonly described as phase of excitement (uterus elevates, vaginal lubrication), plateau (expansion of inner vagina), orgasm (contraction of uterus), resolution; mediated by autonomic nervous system. Also causes tachycardia and skin flushing.

Male reproductive anatomy
Pathway of sperm during ejaculation—SEVEN UP:
- Seminiferous tubules
- Epididymis
- Vas deferens
- Ejaculatory ducts
- (Nothing)
- Urethra
- Penis

Urethral injury
Suspect if blood seen at urethral meatus.
Posterior urethra—membranous urethra prone to injury from pelvic fracture; bulbar urethra susceptible to blunt force. Injury can cause urine to leak into retropubic space.
Anterior urethra—penile urethra at risk of damage due to perineal straddle injury. Can cause urine to leak beneath deep fascia of Buck. If fascia is torn, urine escapes into superficial perineal space.

Autonomic innervation of the male sexual response
Erection—Parasympathetic nervous system (pelvic nerve):
- NO → cGMP → smooth muscle relaxation → vasodilation → proerectile.
- Norepinephrine → [Ca^{2+}]_{in} → smooth muscle contraction → vasoconstriction → antierectile.

Emission—Sympathetic nervous system (hypogastric nerve).

Ejaculation—visceral and somatic nerves (pudendal nerve).

Point and Shoot.
PDE-5 inhibitors (e.g., sildenafil) ↓ cGMP breakdown.
### Seminiferous tubules

<table>
<thead>
<tr>
<th>CELL</th>
<th>FUNCTION</th>
<th>LOCATION/NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spermatogonia</strong>&lt;br&gt;(germ cells)</td>
<td>Maintain germ pool and produce 1° spermatocytes.</td>
<td>Line seminiferous tubules [A]</td>
</tr>
<tr>
<td><strong>Sertoli cells</strong>&lt;br&gt;(non–germ cells)</td>
<td>Secrete inhibin → inhibit FSH.&lt;br&gt;Secrete androgen-binding protein → maintain local levels of testosterone.&lt;br&gt;Tight junctions between adjacent Sertoli cells form blood-testis barrier → isolate gametes from autoimmune attack.&lt;br&gt;Support and nourish developing spermatozoa.&lt;br&gt;Regulate spermatogenesis.&lt;br&gt;Produce MIF.&lt;br&gt;Temperature sensitive; ↑ sperm production and ↓ inhibin with ↑ temperature.</td>
<td>Line seminiferous tubules&lt;br&gt;Convert testosterone and androstenedione to estrogens via aromatase&lt;br&gt;Sertoli cells Support Sperm Synthesis&lt;br&gt;Homolog of female granulosa cells</td>
</tr>
<tr>
<td><strong>Leydig cells</strong>&lt;br&gt;(endocrine cells)</td>
<td>Secrete testosterone in the presence of LH; testosterone production unaffected by temperature.</td>
<td>Interstitium&lt;br&gt;Homolog of female theca interna cells</td>
</tr>
</tbody>
</table>

---

![Diagram of spermatogenesis](image)
**REPRODUCTIVE—PHYSIOLOGY**

**Estrogen**

**SOURCE**
- Ovary (17β-estradiol), placenta (estriol), adipose tissue (estriol via aromatization).

**FUNCTION**
- Development of genitalia and breast, female fat distribution.
- Growth of follicle, endometrial proliferation, ↑ myometrial excitability.
- Uptregulation of estrogen, LH, and progesterone receptors; feedback inhibition of FSH and LH, then LH surge; stimulation of prolactin secretion.
- ↑ transport proteins, SHBG; ↑ HDL; ↓ LDL.

**Potency:** estradiol > estrone > estriol

**Pregnancy:**
- 50-fold ↑ in estradiol and estrone
- 1000-fold ↑ in estriol (indicator of fetal well-being)

Estrogen receptors expressed in cytoplasm; translocate to nucleus when bound by estrogen

---

**Progesterone**

**SOURCE**
- Corpus luteum, placenta, adrenal cortex, testes.

**FUNCTION**
- Stimulation of endometrial glandular secretions and spiral artery development.
- Maintenance of pregnancy.
- ↓ myometrial excitability.
- Production of thick cervical mucus, which inhibits sperm entry into uterus.
- ↑ body temperature.
- Inhibition of gonadotropins (LH, FSH).
- Uterine smooth muscle relaxation (preventing contractions).
- ↓ estrogen receptor expression.
- Prevents endometrial hyperplasia.

**Fall in progesterone after delivery disinhibits prolactin → lactation. ↑ progesterone is indicative of ovulation.**

*Progesterone is pro-gestation.*

*Prolactin is pro-lactation.*
Tanner stages of sexual development

Tanner stage is assigned independently to genitalia, pubic hair, and breast (e.g., a person can have Tanner stage 2 genitalia, Tanner stage 3 pubic hair).

I. Childhood (prepubertal)
II. Pubic hair appears (pubarche); breast buds form (thelarche)
III. Pubic hair darkens and becomes curly; penis size/length ↑; breasts enlarge
IV. Penis width ↑, darker scrotal skin, development of glans; raised areolae
V. Adult; areolae are no longer raised

Menstrual cycle

Follicular phase can vary in length. Luteal phase is 14 days. Ovulation day + 14 days = menstruation.
Follicular growth is fastest during 2nd week of proliferative phase.
Estrogen stimulates endometrial proliferation.
Progesterone maintains endometrium to support implantation.
↓ progesterone → ↓ fertility.

Dysmenorrhea  Pain with menses; often associated with endometriosis.
Oligomenorrhea  > 35-day cycle.
Polymenorrhea  < 21-day cycle.
Metrorrhagia  Frequent or irregular menstruation.
Menorrhagia  Heavy menstrual bleeding; > 80 mL blood loss or > 7 days of menses.
Menometrorrhagia  Heavy, irregular menstruation.
Oogenesis

$1^\text{st}$ 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 ($1^\text{st}$ oocytes).

Meiosis II is arrested in metaphase II until fertilization ($2^\text{nd}$ oocytes). If fertilization does not occur within 1 day, the $2^\text{nd}$ oocyte degenerates.

An egg meets a sperm.

If fertilization does not occur within 1 day, the $2^\text{nd}$ oocyte degenerates.

Replication (interphase)
**Ovulation**

† estrogen, † GnRH receptors on anterior pituitary. Estrogen surge then stimulates LH release → ovulation (rupture of follicle). † temperature (progesterone induced).

**Mittelschmerz**—transient mid-cycle ovulatory pain; classically associated with peritoneal irritation (e.g., follicular swelling/rupture, fallopian tube contraction). Can mimic appendicitis.

**Pregnancy**

Fertilization most commonly occurs in upper end of fallopian tube (the ampulla). Occurs within 1 day of ovulation.

Implantation within the wall of the uterus occurs 6 days after fertilization. Syncytiotrophoblasts secrete hCG, which is detectable in blood 1 week after conception and on home test in urine 2 weeks after conception.

**Lactation**

After labor, the ↓ in progesterone and estrogen disinhibits lactation. Suckling is required to maintain milk production, since ↑ nerve stimulation → ↑ oxytocin and prolactin.

Prolactin—induces and maintains lactation and ↓ reproductive function.

Oxytocin—assists in milk letdown; also promotes uterine contractions.

Breast milk is the ideal nutrition for infants < 6 months old. Contains maternal immunoglobulins (conferring passive immunity; mostly IgA), macrophages, lymphocytes. Breast milk reduces infant infections and is associated with ↓ risk for child to develop asthma, allergies, diabetes mellitus, and obesity. Exclusively breastfed infants require vitamin D supplementation.

Breastfeeding ↓ maternal risk of breast and ovarian cancer and facilitates mother-child bonding.

**hCG**

<table>
<thead>
<tr>
<th>SOURCE</th>
<th>Syncytiotrophoblast of placenta.</th>
</tr>
</thead>
<tbody>
<tr>
<td>FUNCTION</td>
<td>Maintains corpus luteum (and thus progesterone) for first 8–10 weeks of pregnancy by acting like LH (otherwise no luteal cell stimulation → abortion). After 8–10 weeks, placenta synthesizes its own estriol and progesterone and corpus luteum degenerates. Used to detect pregnancy because it appears early in urine (see above). Has identical α subunit as LH, FSH, TSH. β subunit is unique (pregnancy tests detect β subunit). hCG is ↑ in multiple gestations, hydatidiform moles, choriocarcinomas, and Down syndrome; hCG is ↓ in ectopic/failing pregnancy, Edward syndrome, and Patau syndrome.</td>
</tr>
</tbody>
</table>

**Menopause**

† estrogen production due to age-linked decline in number of ovarian follicles. Average age at onset is 51 years (earlier in smokers).

Usually preceded by 4–5 years of abnormal menstrual cycles. Source of estrogen (estrone) after menopause becomes peripheral conversion of androgens, ↑ androgens → hirsutism.

↑ FSH is specific for menopause (loss of negative feedback on FSH due to ↓ estrogen). Hormonal changes: ↓ estrogen, ↑ FSH, ↑ LH (no surge), ↑ GnRH.

Menopause causes HAVOCS: Hot flashes, Atrophy of the Vagina, Osteoporosis, Coronary artery disease, Sleep disturbances.

Menopause before age 40 can indicate premature ovarian failure.
**Spermatogenesis**

Spermatogenesis begins at puberty with spermatogonia. Full development takes 2 months. Occurs in seminiferous tubules. Produces spermatids that undergo spermiogenesis (loss of cytoplasmic contents, gain of acrosomal cap) to form mature spermatozoa.

“Gonium” is going to be a sperm; “Zoon” is “Zooming” to egg.

---

**Androgens**

Testosterone, dihydrotestosterone (DHT), androstenedione.

<table>
<thead>
<tr>
<th>Source</th>
<th>DHT and testosterone (tests), Androstenedione (ADrenal)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Function</th>
<th>Testosterone:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>* Differentiation of epididymis, vas deferens, seminal vesicles (genitalia, except prostate).</td>
</tr>
<tr>
<td></td>
<td>* Growth spurt: penis, seminal vesicles, sperm, muscle, RBCs.</td>
</tr>
<tr>
<td></td>
<td>* Deepening of voice.</td>
</tr>
<tr>
<td></td>
<td>* Closing of epiphysial plates (via estrogen converted from testosterone).</td>
</tr>
<tr>
<td></td>
<td>* Libido.</td>
</tr>
</tbody>
</table>

DHT:

| Early—differentiation of penis, scrotum, prostate. |
| Late—prostate growth, balding, sebaceous gland activity. |

Potency: DHT > testosterone > androstenedione.

Testosterone is converted to DHT by 5α-reductase, which is inhibited by finasteride. In the male, androgens are converted to estrogen by cytochrome P-450 aromatase (primarily in adipose tissue and testis). Aromatase is the key enzyme in conversion of androgens to estrogen.

Exogenous testosterone → inhibition of hypothalamic–pituitary–gonadal axis → ↓ intratesticular testosterone → ↓ testicular size → azoospermia.
### Reproductive—Pathology

**Sex chromosome disorders of sexual development**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Description</th>
<th>Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klinefelter syndrome</td>
<td>47,XXY, 1:850, Testicular atrophy, eunuchoid body shape, tall, long extremities, gynecomastia, female hair distribution</td>
<td>May present with developmental delay. Presence of inactivated X chromosome (Barr body). Common cause of hypogonadism seen in infertility work-up.</td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>45,XO, Short stature (if untreated), ovarian dysgenesis, bicuspid aortic valve, preductal coarctation (femoral &lt; brachial pulse), lymphatic defects (result in webbed neck or cystic hygroma; lymphedema in feet, hands), horseshoe kidney</td>
<td>Most common cause of 1° amenorrhea. No Barr body.</td>
</tr>
<tr>
<td>Double Y males</td>
<td>XYY, 1:1000, Phenotypically normal (usually undiagnosed), very tall. Random nondisjunction event (paternal meiosis II); noninherited; normal fertility. May be associated with severe acne, learning disability, autism spectrum disorders.</td>
<td></td>
</tr>
<tr>
<td>True hermaphroditism</td>
<td>46,XX or 47,XXY, Also called ovotesticular disorder of sex development. Both ovarian and testicular tissue present (ovotestis); ambiguous genitalia.</td>
<td></td>
</tr>
</tbody>
</table>
### Diagnosing disorders of sex hormones

<table>
<thead>
<tr>
<th>Testosterone</th>
<th>LH</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑</td>
<td>↑</td>
<td>Defective androgen receptor</td>
</tr>
<tr>
<td>↑</td>
<td>↓</td>
<td>Testosterone-secreting tumor, exogenous steroids</td>
</tr>
<tr>
<td>↓</td>
<td>↑</td>
<td>1° hypogonadism</td>
</tr>
<tr>
<td>↓</td>
<td>↓</td>
<td>Hypogonadotropic hypogonadism</td>
</tr>
</tbody>
</table>

### Other disorders of sex development

Disagreement between the phenotypic (external genitalia) and gonadal (testes vs. ovaries) sex. Include terms pseudohermaphrodite, hermaphrodite, and intersex.

**Female pseudo-hermaphrodite (XX)**
- Ovaries present, but external genitalia are virilized or ambiguous. Due to excessive and inappropriate exposure to androgenic steroids during early gestation (e.g., congenital adrenal hyperplasia or exogenous administration of androgens during pregnancy).

**Male pseudo-hermaphrodite (XY)**
- Testes present, but external genitalia are female or ambiguous. Most common form is androgen insensitivity syndrome (testicular feminization).

### Aromatase deficiency

Inability to synthesize estrogens from androgens. Masculinization of female (46,XX) infants (ambiguous genitalia), ↑ serum testosterone and androstenedione. Can present with maternal virilization during pregnancy (fetal androgens cross the placenta).

### Androgen insensitivity syndrome (46,XY)

Defect in androgen receptor resulting in normal-appearing female; female external genitalia with scant sexual hair, rudimentary vagina; uterus and fallopian absent. Patients develop testes (often found in labia majora; surgically removed to prevent malignancy). ↑ testosterone, estrogen, LH (vs. sex chromosome disorders).

### 5α-reductase deficiency

Autosomal recessive; sex limited to genetic males (46,XY). Inability to convert testosterone to DHT. Ambiguous genitalia until puberty, when ↑ testosterone causes masculinization/↑ growth of external genitalia. Testosterone/estrogen levels are normal; LH is normal or ↑. Internal genitalia are normal.

### Kallmann syndrome

Failure to complete puberty; a form of hypogonadotropic hypogonadism. Defective migration of GnRH cells and formation of olfactory bulb; ↓ synthesis of GnRH in the hypothalamus; anosmia; ↓ GnRH, FSH, LH, testosterone. Infertility (low sperm count in males; amenorrhea in females).
Hydatidiform mole

Cystic swelling of chorionic villi and proliferation of chorionic epithelium (only trophoblast). Associated with theca-lutein cysts, hyperemesis gravidarum, hyperthyroidism. Treatment: dilation and curettage and methotrexate. Monitor β-hCG.

<table>
<thead>
<tr>
<th></th>
<th>Complete mole</th>
<th>Partial mole</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KARYOTYPE</strong></td>
<td>46,XX; 46,XY</td>
<td>69,XXX; 69,XXY; 69,XYY</td>
</tr>
<tr>
<td><strong>hCG</strong></td>
<td>↑↑↑</td>
<td>↑</td>
</tr>
<tr>
<td><strong>UTERINE SIZE</strong></td>
<td>↑</td>
<td>–</td>
</tr>
<tr>
<td><strong>CONVERT TO CHORIOCARCINOMA</strong></td>
<td>2%</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>FETAL PARTS</strong></td>
<td>No</td>
<td>Yes (partial = fetal parts)</td>
</tr>
<tr>
<td><strong>COMPONENTS</strong></td>
<td>Most commonly enucleated egg + single sperm (subsequently duplicates paternal DNA)</td>
<td>2 sperm + 1 egg</td>
</tr>
<tr>
<td><strong>RISK OF COMPLICATIONS</strong></td>
<td>15–20% malignant trophoblastic disease</td>
<td>Low risk of malignancy (&lt; 5%)</td>
</tr>
<tr>
<td><strong>SYMPTOMS</strong></td>
<td>First-trimester bleeding, enlarged uterus, hyperemesis, pre-eclampsia, hyperthyroidism</td>
<td>Vaginal bleeding, abdominal pain</td>
</tr>
<tr>
<td><strong>IMAGING</strong></td>
<td>“Honeycombed” uterus or “clusters of grapes” ![A] “snowstorm” on ultrasound ![B]</td>
<td>Fetal parts</td>
</tr>
<tr>
<td>Hypertension in pregnancy</td>
<td>BP &gt; 140/90 mmHg after 20th week of gestation. No pre-existing hypertension. No proteinuria or end-organ damage.</td>
<td>Treatment: antihypertensives (α-methyldopa, labetalol, hydralazine, nifedipine), deliver at 37-39 weeks.</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Gestational hypertension</strong> (pregnancy-induced hypertension)</td>
<td>New-onset hypertension with either proteinuria or end-organ dysfunction after 20th week of gestation (&lt; 20 weeks suggests molar pregnancy). May proceed to eclampsia (+ seizures) and/or HELLP syndrome. Caused by abnormal placental spiral arteries → endothelial dysfunction, vasoconstriction, ischemia. Incidence ↑ in patients with pre-existing hypertension, diabetes, chronic renal disease, autoimmune disorders. Complications: placental abruption, coagulopathy, renal failure, uteroplacental insufficiency, eclampsia.</td>
<td>Treatment: antihypertensives, IV magnesium sulfate (to prevent seizure); definitive is delivery of fetus.</td>
</tr>
<tr>
<td><strong>Preeclampsia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Eclampsia</strong></td>
<td>Preeclampsia + maternal seizures. Maternal death due to stroke, intracranial hemorrhage, or ARDS.</td>
<td>Treatment: IV magnesium sulfate, antihypertensives, immediate delivery.</td>
</tr>
</tbody>
</table>
Pregnancy complications

**Placental abruption** (abruptio placenta)

Premature separation (partial or complete) of placenta from uterine wall before delivery of infant. Risk factors: trauma (e.g., motor vehicle accident), smoking, hypertension, preeclampsia, cocaine abuse.

Presentation: **abrupt**, painful bleeding (concealed or apparent) in third trimester; possible DIC, maternal shock, fetal distress. Life threatening for mother and fetus.

**Placenta accreta/ increta/percreta**

Defective decidual layer → abnormal attachment and separation after delivery. Risk factors: prior C-section, inflammation, placenta previa. Three types distinguishable by the depth of penetration:

- **Placenta accreta**—placenta attaches to myometrium without penetrating it; most common type.
- **Placenta increta**—placenta penetrates into myometrium.
- **Placenta percreta**—placenta penetrates ("perforates") through myometrium and into uterine serosa (invades entire uterine wall); can result in placental attachment to rectum or bladder.

Presentation: often detected on ultrasound prior to delivery. No separation of placenta after delivery → postpartum bleeding (can cause Sheehan syndrome).

**Placenta previa**

Attachment of placenta to lower uterine segment over (or < 2 cm from) internal cervical os. Risk factors: multiparity, prior C-section. Associated with painless third-trimester bleeding.
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).

Retained placental tissue  May cause postpartum hemorrhage, 1 risk of infection.

Ectopic pregnancy  Most often in ampulla of fallopian tube (A shows 10-mm embryo in oviduct at 7 weeks of gestation). Suspect with history of amenorrhea, lower-than-expected rise in hCG based on dates, and sudden lower abdominal pain; confirm with ultrasound. Often clinically mistaken for appendicitis. Pain with or without bleeding. Risk factors:
- History of infertility
- Salpingitis (PID)
- Ruptured appendix
- Prior tubal surgery

Amniotic fluid abnormalities

Polyhydramnios  Too much (> 1.5–2 L) amniotic fluid; associated with fetal malformations (e.g., esophageal/duodenal atresia, anencephaly; both result in inability to swallow amniotic fluid), maternal diabetes, fetal anemia, multiple gestations.

Oligohydramnios  Too little (< 0.5 L) amniotic fluid; associated with placental insufficiency, bilateral renal agenesis, posterior urethral valves (in males) and resultant inability to excrete urine. Any profound oligohydramnios can cause Potter sequence.

Gynecologic tumor epidemiology
Incidence (U.S.)—endometrial > ovarian > cervical; cervical cancer is more common worldwide due to lack of screening or HPV vaccination. Worst prognosis—ovarian > cervical > endometrial.
### Vaginal tumors

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma (SCC)</td>
<td>Usually 2nd to cervical SCC; 1st vaginal carcinoma rare.</td>
</tr>
<tr>
<td>Clear cell adenocarcinoma</td>
<td>Affects women who had exposure to DES in utero.</td>
</tr>
<tr>
<td>Sarcoma botryoides (rhabdomyosarcoma variant)</td>
<td>Affects girls &lt; 4 years old; spindle-shaped cells; desmin +. Presents with clear, grape-like, polypoid mass emerging from vagina.</td>
</tr>
</tbody>
</table>

### Cervical pathology

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysplasia and carcinoma in situ</td>
<td>Disordered epithelial growth; begins at basal layer of squamocolumnar junction (transition zone) and extends outward. Classified as CIN 1, CIN 2, or CIN 3 (severe dysplasia or carcinoma in situ), depending on extent of dysplasia. Associated with HPV 16 and HPV 18, which produce both the E6 gene product (inhibits p53 suppressor gene) and E7 gene product (inhibits RB suppressor gene). May progress slowly to invasive carcinoma if left untreated. Typically asymptomatic (detected with Pap smear) or presents as abnormal vaginal bleeding (often postcoital). Risk factors: multiple sexual partners (&gt;1), smoking, starting sexual intercourse at young age, HIV infection.</td>
</tr>
<tr>
<td>Invasive carcinoma</td>
<td>Often squamous cell carcinoma. Pap smear can catch cervical dysplasia (koilocytes) before it progresses to invasive carcinoma. Diagnose via colposcopy and biopsy. Lateral invasion can block ureters → renal failure.</td>
</tr>
</tbody>
</table>
Premature ovarian failure

Premature atresia of ovarian follicles in women of reproductive age. Patients present with signs of menopause after puberty but before age 40.

Most common causes of anovulation

Pregnancy, polycystic ovarian syndrome, obesity, HPO axis abnormalities, premature ovarian failure, hyperprolactinemia, thyroid disorders, eating disorders, competitive athletics, Cushing syndrome, adrenal insufficiency.

Polycystic ovarian syndrome (Stein-Leventhal syndrome)

Hyperinsulinemia and/or insulin resistance hypothesized to alter hypothalamic hormonal feedback response → ↑ LH:FSH, ↑ androgens from theca interna cells, ↓ rate of follicular maturation → unruptured follicles (cysts) + anovulation. Common cause of subfertility in women. Enlarged, bilateral cystic ovaries; presents with amenorrhea/oligomenorrhea, hirsutism, acne, subfertility. Associated with obesity. ↑ risk of endometrial cancer 2° to unopposed estrogen from repeated anovulatory cycles. Treatment: weight reduction, OCPs, clomiphene citrate, ketoconazole, spironolactone.

Ovarian cysts

Follicular cyst

Distention of unruptured graafian follicle. May be associated with hyperestrogenism, endometrial hyperplasia. Most common ovarian mass in young women.

Theca-lutein cyst

Often bilateral/multiple. Due to gonadotropin stimulation. Associated with choriocarcinoma and hydatidiform moles.
**Ovarian neoplasms**

Most common adnexal mass in women > 55 years old. Can be benign or malignant. Arise from surface epithelium, germ cells, or sex cord stromal tissue. Majority of malignant tumors are epithelial (serous cystadenocarcinoma most common). Risk ↑ with advanced age, infertility, endometriosis, PCOS, genetic predisposition (*BRCA-1* or *BRCA-2* mutation, hereditary nonpolyposis colorectal cancer [HNPCC], strong family history). Risk ↓ with previous pregnancy, history of breastfeeding, OCPs, tubal ligation. Presents with adnexal mass, abdominal distension, bowel obstruction, pleural effusion. Diagnose surgically. Monitor progression by measuring CA 125 levels (not good for screening).

<table>
<thead>
<tr>
<th>Benign ovarian neoplasms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serous cystadenoma</strong></td>
<td>Most common ovarian neoplasm. Lined with fallopian tube–like epithelium. Often bilateral.</td>
</tr>
<tr>
<td><strong>Mucinous cystadenoma</strong></td>
<td>Multiloculated, large. Lined by mucus-secreting epithelium.</td>
</tr>
<tr>
<td><strong>Endometrioma</strong></td>
<td>Endometriosis (ectopic endometrial tissue) within ovary with cyst formation. Presents with pelvic pain, dysmenorrhea, dyspareunia; symptoms may vary with menstrual cycle. “Chocolate cyst”—endometrioma filled with dark, reddish-brown blood. Complex mass on ultrasound.</td>
</tr>
<tr>
<td><strong>Mature cystic teratoma</strong> (dermoid cyst)</td>
<td>Germ cell tumor, most common ovarian tumor in women 20–30 years old. Cystic mass containing elements from all 3 germ layers (e.g., teeth, hair, sebum). Can present with pain 2° to ovarian enlargement or torsion. Can also contain functional thyroid tissue and present as hyperthyroidism (struma ovarii).</td>
</tr>
<tr>
<td><strong>Brenner tumor</strong></td>
<td>Looks like bladder. Solid tumor that is pale yellow-tan and appears encapsulated. “Coffee bean” nuclei on H&amp;E stain.</td>
</tr>
<tr>
<td><strong>Fibromas</strong></td>
<td>Bundles of spindle-shaped fibroblasts. Meigs syndrome—triad of ovarian fibroma, ascites, hydrothorax. “Pulling” sensation in groin.</td>
</tr>
<tr>
<td><strong>Thecoma</strong></td>
<td>Like granulosa cell tumors, may produce estrogen. Usually presents as abnormal uterine bleeding in a postmenopausal woman.</td>
</tr>
</tbody>
</table>
### Ovarian neoplasms (continued)

#### Malignant ovarian neoplasms

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immature teratoma</strong></td>
<td>Aggressive, contains fetal tissue, neuroectoderm. Immature teratoma is most typically represented by immature/embryonic-like neural tissue. Mature teratoma are more likely to contain thyroid tissue.</td>
</tr>
<tr>
<td><strong>Granulosa cell tumor</strong></td>
<td>Most common malignant stromal tumor. Predominantly women in their 50s. Often produces estrogen and/or progesterone and presents with abnormal uterine bleeding, sexual precocity (in pre-adolescents), breast tenderness. Histology shows Call-Exner bodies (granulosa cells arranged haphazardly around collections of eosinophilic fluid, resembling primordial follicles).</td>
</tr>
<tr>
<td><strong>Serous cystadenocarcinoma</strong></td>
<td>Most common ovarian neoplasm, frequently bilateral. Psammoma bodies.</td>
</tr>
<tr>
<td><strong>Mucinous cystadenocarcinoma</strong></td>
<td>Pseudomyxoma peritonei—intraperitoneal accumulation of mucinous material from ovarian or appendiceal tumor.</td>
</tr>
<tr>
<td><strong>Dysgerminoma</strong></td>
<td>Most common in adolescents. Equivalent to male seminoma but rarer. 1% of all ovarian tumors; 30% of germ cell tumors. Sheets of uniform “fried egg” cells.</td>
</tr>
<tr>
<td><strong>Choriocarcinoma</strong></td>
<td>Rare; can develop during or after pregnancy in mother or baby. Malignancy of trophoblastic tissue (cytotrophoblasts, syncytiotrophoblasts); no chorionic villi present. Frequency of bilateral/multiple theca-lutein cysts. Presents with abnormal β-hCG, shortness of breath, hemoptysis. Hematogenous spread to lungs. Very responsive to chemotherapy.</td>
</tr>
<tr>
<td><strong>Yolk sac (endodermal sinus) tumor</strong></td>
<td>Aggressive, in ovaries or testes (boys) and sacrococcygeal area in young children. Most common tumor in male infants. Yellow, friable (hemorrhagic), solid mass. 50% have Schiller-Duval bodies (resemble glomeruli). AFP = tumor marker.</td>
</tr>
<tr>
<td><strong>Krukenberg tumor</strong></td>
<td>GI malignancy that metastasizes to ovaries → mucin-secreting signet cell adenocarcinoma.</td>
</tr>
</tbody>
</table>
### Endometrial conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polyp</strong></td>
<td>Well-circumscribed collection of endometrial tissue within uterine wall. May contain smooth muscle cells. Can extend into endometrial cavity in the form of a polyp.</td>
</tr>
<tr>
<td><strong>Leiomyoma (fibroid)</strong></td>
<td>Most common tumor in females. Often presents with multiple discrete tumors. Incidence in blacks. Benign smooth muscle tumor; malignant transformation is rare. Estrogen sensitive—tumor size with pregnancy and with menopause. Peak occurrence at 20–40 years old. May be asymptomatic, cause abnormal uterine bleeding, or result in miscarriage. Severe bleeding may lead to iron deficiency anemia. Usually does not progress to leiomyosarcoma. Whorled pattern of smooth muscle bundles with well-demarcated borders.</td>
</tr>
<tr>
<td><strong>Endometriosis</strong></td>
<td>Non-neoplastic endometrial glands/stroma outside endometrial cavity. Can be found anywhere; most common sites are ovary (frequently bilateral), pelvis, peritoneum. In ovary, appears as endometrioma (blood-filled “chocolate cyst”). May be due to retrograde flow, metaplastic transformation of multipotent cells, transportation of endometrial tissue via lymphatic system. Characterized by cyclic pelvic pain, bleeding, dysmenorrhea, dyspareunia, dyschezia (pain with defecation), infertility; normal-sized uterus. Treatment: NSAIDs, OCPs, progestins, GnRH agonists, danazol, laparoscopic removal.</td>
</tr>
<tr>
<td><strong>Endometritis</strong></td>
<td>Inflammation of endometrium associated with retained products of conception following delivery, miscarriage, abortion, or with foreign body (e.g., IUD). Retained material in uterus promotes infection by bacterial flora from vagina or intestinal tract. Treatment: gentamicin + clindamycin with or without ampicillin.</td>
</tr>
<tr>
<td><strong>Endometrial hyperplasia</strong></td>
<td>Abnormal endometrial gland proliferation usually caused by excess estrogen stimulation. Risk for endometrial carcinoma. Presents as postmenopausal vaginal bleeding. Risk factors include anovulatory cycles, hormone replacement therapy, polycystic ovarian syndrome, granulosa cell tumor.</td>
</tr>
<tr>
<td><strong>Endometrial carcinoma</strong></td>
<td>Most common gynecologic malignancy. Peak occurrence at 55–65 years old. Presents with vaginal bleeding. Typically preceded by endometrial hyperplasia. Risk factors include prolonged use of estrogen without progestins, obesity, diabetes, hypertension, nulliparity, late menopause, Lynch syndrome.</td>
</tr>
</tbody>
</table>
Breast pathology

Fibroadenoma
- Small, mobile, firm mass with sharp edges.
- Most common tumor in those < 35 years old.
- Size and tenderness with estrogen (e.g., pregnancy, prior to menstruation). Not a precursor to breast cancer.

Intraductal papilloma
- Small tumor that grows in lactiferous ducts. Typically beneath areola.
- Serous or bloody nipple discharge. Slight (1.5–2×) ↑ in risk for carcinoma.

Phyllodes tumor
- Large, bulky mass of connective tissue and cysts. “Leaf-like” projections.
- Most common in 5th decade.
- Some may become malignant.
## Common breast conditions

### Proliferative breast disease
Most common cause of “breast lumps” from age 25 to menopause. Presents with premenstrual breast pain and multiple lesions, often bilateral. Fluctuation in size of mass. Usually does not indicate increased risk of carcinoma. Histologic types:
- **Fibrosis**—hyperplasia of breast stroma.
- **Cystic**—fluid filled, blue dome. Ductal dilation.
- **Sclerosing adenosis**—acini and intralobular fibrosis. Associated with calcifications. Often confused with cancer. ↑ risk (1.5–2×) of developing cancer.
- **Epithelial hyperplasia**—↑ in number of epithelial cell layers in terminal duct lobule. ↑ risk of carcinoma with atypical cells. Occurs in women > 30 years old.

### Lactational mastitis
During breastfeeding, ↑ risk of bacterial infection through cracks in the nipple; *S. aureus* is most common pathogen. Treat with dicloxacillin and continued breastfeeding.

### Fat necrosis
Benign, usually painless lump; forms as a result of injury to breast tissue. Abnormal calcification on mammography; biopsy shows necrotic fat, giant cells. Up to 50% of patients may not report trauma.

### Gynecomastia
Breast enlargement in males. Results from hyperestrogenism (cirrhosis, testicular tumor, puberty, old age), Klinefelter syndrome, drugs (*Spironolactone, Digoxin, Cimetidine, Alcohol, Ketoconazole*). “Some Drugs Create Awesome Knockers.” Physiologic (not pathologic) at birth, puberty, old age.

## Malignant breast tumors
Commonly postmenopausal. Usually arise from terminal duct lobular unit. Overexpression of estrogen/progesterone receptors or c-erbB2 (HER-2, an EGF receptor) is common; triple negative (ER −, PR −, and Her2/Neu −) more aggressive; type affects therapy and prognosis. Axillary lymph node involvement indicating metastasis is the single most important prognostic factor. Most often located in upper-outter quadrant of breast.

### Risk factors:
- ↑ estrogen exposure, ↑ total number of menstrual cycles, older age at 1st live birth, obesity (↑ estrogen exposure as adipose tissue converts androstenedione to estrone), *BRCA1* and *BRCA2* gene mutations, African American ethnicity (↑ risk for triple − breast cancer).

<table>
<thead>
<tr>
<th>TYPE</th>
<th>CHARACTERISTICS</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Noninvasive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ductal carcinoma in situ (DCIS)</strong></td>
<td>Fills ductal lumen (black arrow in [A] indicates neoplastic cells in duct; blue arrow shows engorged blood vessel). Arises from ductal atypia. Often seen early as microcalcifications on mammography.</td>
<td>Early malignancy without basement membrane penetration.</td>
</tr>
<tr>
<td><strong>Comedocarcinoma</strong></td>
<td>Ductal, central necrosis (arrow in [B]). Subtype of DCIS.</td>
<td></td>
</tr>
<tr>
<td><strong>Paget disease</strong></td>
<td>Results from underlying DCIS or invasive breast cancer. Eczematous patches on nipple [C]. Paget cells = large cells in epidermis with clear halo.</td>
<td>Extramammary Paget disease seen on vulva does not suggest underlying malignancy.</td>
</tr>
</tbody>
</table>
### Malignant breast tumors (continued)

<table>
<thead>
<tr>
<th>Invasive</th>
<th>Description</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Invasive ductal</strong></td>
<td>Firm, fibrous, “rock-hard” mass with sharp margins and small, glandular, duct-like cells.</td>
<td>Worst and most invasive. Most common (~75% of all breast cancers).</td>
</tr>
<tr>
<td><strong>Invasive lobular</strong></td>
<td>Orderly row of cells (“Indian file”), due to E-cadherin expression.</td>
<td>Often bilateral with multiple lesions in the same location.</td>
</tr>
<tr>
<td><strong>Medullary</strong></td>
<td>Fleshy, cellular, lymphocytic infiltrate.</td>
<td>Good prognosis.</td>
</tr>
<tr>
<td><strong>Inflammatory</strong></td>
<td>Dermal lymphatic invasion by breast carcinoma. Peau d’orange (breast skin resembles orange peel), neoplastic cells block lymphatic drainage.</td>
<td>50% survival at 5 years. Often mistaken for mastitis or Paget disease.</td>
</tr>
</tbody>
</table>

![Images](image1.png)
Penile pathology

**Peyronie disease**

**Priapism**
Painful sustained erection lasting > 4 hours. Associated with trauma, sickle cell disease (sickled RBCs get trapped in vascular channels), medications (e.g., sildenafil, trazodone). Treat immediately with corporal aspiration, intracavernosal phenylephrine, or surgical decompression to prevent ischemia.

**Squamous cell carcinoma**
More common in Asia, Africa, South America. Precursor in situ lesions: Bowen disease (in penile shaft, presents as leukoplakia), erythroplasia of Queyrat (cancer of glans, presents as erythroplakia), Bowenoid papulosis (carcinoma in situ of unclear malignant potential, presenting as reddish papules). Associated with HPV, lack of circumcision.

Cryptorchidism
Undescended testis (one or both); impaired spermatogenesis (since sperm develop best at temperatures < 37°C); can have normal testosterone levels (Leydig cells are unaffected by temperature); associated with ↑ risk of germ cell tumors. Prematurity ↑ risk of cryptorchidism. ↓ inhibin, ↑ FSH, ↑ LH; testosterone ↑ in bilateral cryptorchidism, normal in unilateral.

Varicocele
Dilated veins in pampiniform plexus due to ↑ venous pressure; most common cause of scrotal enlargement in adult males; most often on left side because of ↑ resistance to flow from left gonadal vein drainage into left renal vein; can cause infertility because of ↑ temperature; “bag of worms” on palpation; diagnose by ultrasound with Doppler \( A \); does not transilluminate.

Treatment: varicocelectomy, embolization by interventional radiologist.

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.
<table>
<thead>
<tr>
<th><strong>Scrotal masses</strong></th>
<th>Benign scrotal lesions present as testicular masses that can be transilluminated (vs. solid testicular tumors).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Congenital hydrocele</strong></td>
<td>Common cause of scrotal swelling in infants, due to incomplete obliteration of processus vaginalis. Transilluminating swelling.</td>
</tr>
<tr>
<td><strong>Acquired hydrocele</strong></td>
<td>Benign scrotal fluid collection usually 2° to infection, trauma, tumor. If bloody → hematocoele.</td>
</tr>
<tr>
<td><strong>Spermatocele</strong></td>
<td>Cyst due to dilated epididymal duct or rete testis. Paratesticular fluctuant nodule.</td>
</tr>
<tr>
<td><strong>Testicular germ cell tumors</strong></td>
<td>~95% of all testicular tumors. Most often occur in young men. Risk factors: cryptorchidism, Klinefelter syndrome. Can present as a mixed germ cell tumor. Differential diagnosis for testicular mass that does not transilluminate: cancer.</td>
</tr>
<tr>
<td><strong>Seminoma</strong></td>
<td>Malignant; painless, homogenous testicular enlargement; most common testicular tumor, most common in 3rd decade, never in infancy. Large cells in lobules with watery cytoplasm and “fried egg” appearance. ↑ placental ALP. Radiosensitive. Late metastasis, excellent prognosis.</td>
</tr>
<tr>
<td><strong>Yolk sac (endodermal sinus) tumor</strong></td>
<td>Yellow, mucinous. Aggressive malignancy of testes, analogous to ovarian yolk sac tumor. Schiller-Duval bodies resemble primitive glomeruli. ↑ AFP is highly characteristic. Most common testicular tumor in boys &lt; 3 years old.</td>
</tr>
<tr>
<td><strong>Choriocarcinoma</strong></td>
<td>Malignant, ↑ hCG. Disordered syncytiotrophoblastic and cytotrophoblastic elements. Hematogenous metastases to lungs and brain (may present with “hemorrhagic stroke” due to bleeding into metastasis. May produce gynecomastia, symptoms of hyperthyroidism (hCG is structurally similar to LH, FSH, TSH).</td>
</tr>
<tr>
<td><strong>Teratoma</strong></td>
<td>Unlike in females, mature teratoma in adult males may be malignant. Benign in children. ↑ hCG and/or AFP in 50% of cases.</td>
</tr>
<tr>
<td><strong>Embryonal carcinoma</strong></td>
<td>Malignant, hemorrhagic mass with necrosis; painful; worse prognosis than seminoma. Often glandular/papillary morphology. “Pure” embryonal carcinoma is rare; most commonly mixed with other tumor types. May be associated with increased hCG and normal AFP levels when pure (↑ AFP when mixed).</td>
</tr>
<tr>
<td><strong>Testicular non–germ cell tumors</strong></td>
<td>5% of all testicular tumors. Mostly benign.</td>
</tr>
<tr>
<td><strong>Leydig cell</strong></td>
<td>Contains Reinke crystals (eosinophilic cytoplasmic inclusions); usually produce androgens → gynecomastia in men, precocious puberty in boys. Golden brown color.</td>
</tr>
<tr>
<td><strong>Sertoli cell</strong></td>
<td>Androblastoma from sex cord stroma.</td>
</tr>
<tr>
<td><strong>Testicular lymphoma</strong></td>
<td>Most common testicular cancer in older men. Not a 1° cancer; arises from metastatic lymphoma to testes. Aggressive.</td>
</tr>
</tbody>
</table>
**Benign prostatic hyperplasia**

Common in men > 50 years old. Characterized by smooth, elastic, firm nodular enlargement (hyperplasia not hypertrophy) of periurethral (lateral and middle) lobes, which compress the urethra into a vertical slit. Not premalignant. Often presents with ↑ frequency of urination, nocturia, difficulty starting and stopping urine stream, dysuria. May lead to distention and hypertrophy of bladder, hydrenephrosis, UTIs. ↑ free prostate-specific antigen (PSA).

Treatment: $\alpha_1$-antagonists (terazosin, tamsulosin), which cause relaxation of smooth muscle; $5\alpha$-reductase inhibitors (e.g., finasteride); PDE-5 inhibitors.

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**Prostatitis**

Dysuria, frequency, urgency, low back pain. Acute: bacterial (e.g., *E. coli*); chronic: bacterial or abacterial (most common).

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**Prostatic adenocarcinoma**

Common in men > 50 years old. Arises most often from posterior lobe (peripheral zone) of prostate gland and is most frequently diagnosed by ↑ PSA and subsequent needle core biopsies. Prostatic acid phosphatase (PAP) and PSA are useful tumor markers (↑ total PSA, with ↓ fraction of free PSA). Osteoblastic metastases in bone may develop in late stages, as indicated by lower back pain and ↑ serum ALP and PSA.

*Note small neoplastic glands with prominent nucleoli (red arrow) amid normal prostate stroma (blue arrow).*
Control of reproductive hormones

Hypothalamus

via blocking negative feedback

GnRH

Anterior pituitary

LH
FSH

Ovary

FSH
LH

Testis

Testosterone

Androstenedione

Androgen-receptor complex

Gene expression in androgen-responsive cells

Gene expression in estrogen-responsive cells

Oral contraceptives
Danazol

Ketoconazole
Danazol

Anastrozole

Androgen-receptor modulators (SERMs)

Selective estrogen-receptor modulators (SERMs)

P450c17

Testosterone

5α-reductase

Dihydrotestosterone

Flutamide
Cyproterone
Spironolactone

Cyproterone
Spironolactone

P-450c17

Aromatase

Estradiol

Estrone

Androstenedione

Estradiol

Anastrozole

Selective estrogen-receptor modulators (SERMs)

Ketoconazole
Danazol

Oral contraceptives

Ketoconazole
Danazol

Oral contraceptives
**Leuprolide**

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>GnRH analog with agonist properties when used in pulsatile fashion; antagonist properties when used in continuous fashion (downregulates GnRH receptor in pituitary → ↓ FSH/LH).</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>Infertility (pulsatile), prostate cancer (continuous use following androgen receptor blockade with flutamide), uterine fibroids (continuous), precocious puberty (continuous).</td>
</tr>
<tr>
<td>TOXICITY</td>
<td>Antiandrogen, nausea, vomiting.</td>
</tr>
</tbody>
</table>

Leuprolide can be used in lieu of GnRH.

**Estrogens (ethinyl estradiol, DES, mestranol)**

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Bind estrogen receptors.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>Hypogonadism or ovarian failure, menstrual abnormalities, hormone replacement therapy in postmenopausal women; use in men with androgen-dependent prostate cancer.</td>
</tr>
<tr>
<td>TOXICITY</td>
<td>↑ risk of endometrial cancer, bleeding in postmenopausal women, clear cell adenocarcinoma of vagina in females exposed to DES in utero, ↑ risk of thrombi. Contraindications—ER ⊕ breast cancer, history of DVTs.</td>
</tr>
</tbody>
</table>

**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 (e.g., PCOS). May cause hot flashes, ovarian enlargement, multiple simultaneous pregnancies, visual disturbances.

**Tamoxifen**

Antagonist at breast; agonist at bone, uterus; ↑ risk of thromboembolic events and endometrial cancer. Used to treat and prevent recurrence of ER/PR ⊕ breast cancer.

**Raloxifene**

Antagonist at breast, uterus; agonist at bone; ↑ risk of thromboembolic events but no increased risk of endometrial cancer (vs. tamoxifen); used primarily to treat osteoporosis.

**Hormone replacement therapy**

Used for relief or prevention of menopausal symptoms (e.g., hot flashes, vaginal atrophy), osteoporosis (↑ estrogen, ↓ osteoclast activity).

Unopposed estrogen replacement therapy ↑ risk of endometrial cancer, so progesterone is added. Possible increased cardiovascular risk.

**Anastrozole/exemestane**

Aromatase inhibitors used in postmenopausal women with ER ⊕ breast cancer.

**Progestins**

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>Bind progesterone receptors, ↓ growth and ↑ vascularization of endometrium.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL USE</td>
<td>Used in oral contraceptives and to treat endometrial cancer, abnormal uterine bleeding.</td>
</tr>
</tbody>
</table>
**Mifepristone (RU-486)**

**MECHANISM**
Competitive inhibitor of progestins at progesterone receptors.

**CLINICAL USE**
Termination of pregnancy. Administered with misoprostol (PGE₁).

**TOXICITY**
Heavy bleeding, GI effects (nausea, vomiting, anorexia), abdominal pain.

**Oral contraception** (synthetic progestins, estrogen)

Estrogen and progestins inhibit LH/FSH and thus prevent estrogen surge. No estrogen surge → no LH surge → no ovulation.

Progestins cause thickening of cervical mucus, thereby limiting access of sperm to uterus.

Progestins also inhibit endometrial proliferation → endometrium is less suitable to the implantation of an embryo.

Contraindications: smokers > 35 years old (↑ risk of cardiovascular events), patients with history of thromboembolism and stroke or history of estrogen-dependent tumor.

**Terbutaline, ritodrine**
β₂-agonists that relax the uterus; used to ↓ contraction frequency in women during labor.

**Danazol**

**MECHANISM**
Synthetic androgen that acts as partial agonist at androgen receptors.

**CLINICAL USE**
Endometriosis, hereditary angioedema.

**TOXICITY**
Weight gain, edema, acne, hirsutism, masculinization, ↓ HDL levels, hepatotoxicity.

**Testosterone, methyltestosterone**

**MECHANISM**
Agonists at androgen receptors.

**CLINICAL USE**
Treats hypogonadism and promotes development of 2nd sex characteristics; stimulation of anabolism to promote recovery after burn or injury.

**TOXICITY**
Causes masculinization in females; ↓ intratesticular testosterone in males by inhibiting release of LH (via negative feedback) → gonadal atrophy. Premature closure of epiphyseal plates. ↑ LDL, ↓ HDL.

**Antiandrogens**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Clinical Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone 5α-reductase DHT</td>
<td>(more potent).</td>
<td>Inhibits conversion of testosterone to DHT. Useful in BPH and male-pattern baldness.</td>
</tr>
<tr>
<td>Finasteride</td>
<td>A 5α-reductase inhibitor (↓ conversion of testosterone to DHT).</td>
<td>Used in BPH and male-pattern baldness.</td>
</tr>
<tr>
<td>Flutamide</td>
<td>A nonsteroidal competitive inhibitor at androgen receptors.</td>
<td>Used for prostate carcinoma.</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Inhibits steroid synthesis (inhibits 17,20-desmolase).</td>
<td>Inhibits steroid binding, 17α-hydroxylase, and 17,20-desmolase.</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Inhibits steroid synthesis (inhibits 17α-hydroxylase, and 17,20-desmolase).</td>
<td>Ketoconazole and spironolactone are used to treat polycystic ovarian syndrome to reduce androgenic symptoms. Both have side effects of gynecomastia and amenorrhea.</td>
</tr>
</tbody>
</table>
### 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.

### Sildenafil, vardenafil, tadalafil

| MECHANISM | Inhibit PDE-5 → $cGMP$, smooth muscle relaxation in corpus cavernosum, $t$ blood flow, penile erection. | Sildenafil, vardenafil, and tadalafil fill the penis. |

### Minoxidil

| MECHANISM | Direct arteriolar vasodilator. |
| CLINICAL USE | Androgenetic alopecia; severe refractory hypertension. |
“There’s so much pollution in the air now that if it weren’t for our lungs, there’d be no place to put it all.”

—Robert Orben

“Mars is essentially in the same orbit. Somewhat the same distance from the Sun, which is very important. We have seen pictures where there are canals, we believe, and water. If there is water, that means there is oxygen. If there is oxygen, that means we can breathe.”

—Former Vice President Dan Quayle

“None of us is different either as barbarian or as Greek; for we all breathe into the air with mouth and nostrils.”

—Antiphon

“Life is not the amount of breaths you take; it’s the moments that take your breath away.”

—Hitch
Respiratory tree

**Conducting zone**
- Large airways consist of nose, pharynx, larynx, trachea, and bronchi. Small airways consist of bronchioles that further divide into terminal bronchioles (large numbers in parallel → least airway resistance).
- Warms, humidifies, and filters air but does not participate in gas exchange → “anatomic dead space.”
- Cartilage and goblet cells extend to end of bronchi.
- Pseudostratified ciliated columnar cells (clear mucus from lungs) extend to beginning of terminal bronchioles, then transition to cuboidal cells.
- 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.

---

**Pneumocytes**

**Type I cells**
- 97% of alveolar surfaces. Line the alveoli.
- Squamous; thin for optimal gas diffusion.

**Type II cells**
- Secrete pulmonary surfactant → ↓ alveolar surface tension and prevents alveolar collapse (atelectasis). Cuboidal and clustered. Also serve as precursors to type I cells and other type II cells. Type II cells proliferate during lung damage.
- Collapsing pressure ($P$) = \( \frac{2}{\text{radius}} \) \text{(surface tension)}
- Alveoli have ↑ tendency to collapse on expiration as radius ↓ (law of Laplace).
- Pulmonary surfactant is a complex mix of lecithins, the most important of which is dipalmitoylphosphatidylcholine.
- Surfactant synthesis begins around week 26 of gestation, but mature levels are not achieved until around week 35.
- Lecithin-to-sphingomyelin ratio > 2.0 in amniotic fluid indicates fetal lung maturity.

**Club (Clara) cells**
- Nonciliated; low-columnar/cuboidal with secretory granules. Secrete component of surfactant; degrade toxins; act as reserve cells.
Lung relations

Right lung has 3 lobes; Left has Less Lobes (2) and Lingula (homolog of right middle lobe). Right lung is more common site for inhaled foreign body because the right main stem bronchus is wider and more vertical than the left.

If you aspirate a peanut:
- While upright—enters lower portion of right inferior lobe.
- While supine—enters superior portion of right inferior lobe.

Instead of a middle lobe, the left lung has a space occupied by the heart.

The relation of the pulmonary artery to the bronchus at each lung hilum is described by RALS—Right Anterior; Left Superior.

Diaphragm structures

- Structures perforating diaphragm:
  - At T8: IVC
  - At T10: esophagus, vagus (CN 10; 2 trunks)
  - At T12: aorta (red), thoracic duct (white), azygos vein (blue) (“At T-1-2 it’s the red, white, and blue”)

- Diaphragm is innervated by C3, 4, and 5 (phrenic nerve). Pain from diaphragm irritation (e.g., air or blood in peritoneal cavity) can be referred to shoulder (C5) and trapezius ridge (C3, 4).

- Number of letters = T level:
  - T8: vena cava
  - T10: “oesophagus”
  - T12: aortic hiatus

I (IVC) ate (8) ten (10) eggs (esophagus) at (aorta) twelve (12).

C3, 4, 5 keeps the diaphragm alive.

Other bifurcations:
- The common carotid bifurcates at C4.
- The trachea bifurcates at T4.
- The abdominal aorta bifurcates at L4.
**Lung volumes**

<table>
<thead>
<tr>
<th>Volume</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspiratory reserve volume (IRV)</td>
<td>Air that can still be breathed in after normal inspiration</td>
</tr>
<tr>
<td>Tidal volume (TV)</td>
<td>Air that moves into lung with each quiet inspiration, typically 500 mL</td>
</tr>
<tr>
<td>Expiratory reserve volume (ERV)</td>
<td>Air that can still be breathed out after normal expiration</td>
</tr>
<tr>
<td>Residual volume (RV)</td>
<td>Air in lung after maximal expiration; cannot be measured on spirometry</td>
</tr>
<tr>
<td>Inspiratory capacity (IC)</td>
<td>IRV + TV</td>
</tr>
<tr>
<td>Functional residual capacity (FRC)</td>
<td>RV + ERV</td>
</tr>
<tr>
<td>Vital capacity (VC)</td>
<td>TV + IRV + ERV</td>
</tr>
<tr>
<td>Total lung capacity (TLC)</td>
<td>IRV + TV + ERV + RV</td>
</tr>
</tbody>
</table>

**Lung volumes (LITER):**

<table>
<thead>
<tr>
<th>Volume</th>
<th>LITER</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRV</td>
<td>6.0</td>
</tr>
<tr>
<td>TV</td>
<td>2.7</td>
</tr>
<tr>
<td>ERV</td>
<td>2.2</td>
</tr>
<tr>
<td>FRC</td>
<td>1.2</td>
</tr>
<tr>
<td>RV</td>
<td>0</td>
</tr>
</tbody>
</table>

A capacity is a sum of ≥ 2 physiologic volumes.

**Determination of physiologic dead space**

\[ V_D = V_T \times \frac{P_{aco_2} - P_{eco_2}}{P_{aco_2}} \]

\( V_D \) = physiologic dead space = anatomic dead space of conducting airways plus alveolar dead space; apex of healthy lung is largest contributor of alveolar dead space. Volume of inspired air that does not take part in gas exchange.

\( V_T \) = tidal volume.

\( P_{aco_2} \) = arterial Pco₂.

\( P_{eco_2} \) = expired air Pco₂.

**Ventilation**

<table>
<thead>
<tr>
<th>Ventilation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minute ventilation</td>
<td>Total volume of gas entering lungs per minute</td>
</tr>
<tr>
<td>( V_E )</td>
<td>( V_T \times ) respiratory rate (RR)</td>
</tr>
<tr>
<td>Alveolar ventilation</td>
<td>Volume of gas per unit time that reaches alveoli</td>
</tr>
<tr>
<td>( V_A )</td>
<td>( V_T - V_D \times ) RR</td>
</tr>
</tbody>
</table>

Taco, Paco, Peço, Paco (refers to order of variables in equation)
Lung and chest wall

Elastic recoil—tendency for lungs to collapse inward and chest wall to spring outward. At FRC, inward pull of lung is balanced by outward pull of chest wall, and system pressure is atmospheric. Elastic properties of both chest wall and lungs determine their combined volume. At FRC, airway and alveolar pressures are 0, and intrapleural pressure is negative (prevents pneumothorax). PVR is at minimum. Compliance—change in lung volume for a given change in pressure; ↑ in pulmonary fibrosis, pneumonia, pulmonary edema; ↑ in emphysema, normal aging.

Hemoglobin

Hemoglobin (Hb) is composed of 4 polypeptide subunits (2 α and 2 β) and exists in 2 forms:
* T (taut; deoxygenated) form has low affinity for O₂.
* R (relaxed; oxygenated) form has high affinity for O₂ (300×). Hb exhibits positive cooperativity and negative allostery.

↑ Cl⁻, H⁺, CO₂, 2,3-BPG, and temperature favor taut form over relaxed form (shifts dissociation curve right → ↑ O₂ unloading).

Fetal Hb (2 α and 2 γ subunits) has lower affinity for 2,3-BPG than adult Hb and thus has higher affinity for O₂. Taut in Tissues. Relaxed in Respiratory tract.

Hemoglobin acts as buffer for H⁺ ions.
**Hemoglobin modifications**

**Methemoglobin**

Oxidized form of Hb (ferric, Fe\(^{3+}\)) that does not bind \(O_2\) as readily, but has ↑ affinity for cyanide. Iron in Hb is normally in a reduced state (ferrous, Fe\(^{2+}\)). Methemoglobinemia may present with cyanosis and chocolate-colored blood. Induced methemoglobinemia (using nitrates, followed by thiosulfate) may be used to treat cyanide poisoning.

Methemoglobinemia can be treated with methylene blue. Nitrites and benzocaine cause poisoning by oxidizing Fe\(^{2+}\) to Fe\(^{3+}\). Just the 2 of us: ferrous is Fe\(^{2+}\).

**Carboxyhemoglobin**

Form of Hb bound to CO in place of \(O_2\).
- Causes ↓ oxygen-binding capacity with left shift in oxygen-hemoglobin dissociation curve.
- ↓ \(O_2\) unloading in tissues.
- CO binds competitively to Hb and with 200× greater affinity than \(O_2\).
- Treat with 100% \(O_2\) and hyperbaric \(O_2\).

**Oxygen-hemoglobin dissociation curve**

Sigmoidal shape due to positive cooperativity (i.e., tetrameric Hb molecule can bind 4 \(O_2\) molecules and has higher affinity for each subsequent \(O_2\) molecule bound). Myoglobin is monomeric and thus does not show positive cooperativity; curve lacks sigmoidal appearance.

When curve shifts to the right, ↓ affinity of Hb for \(O_2\) (facilitates unloading of \(O_2\) to tissue). An ↑ in all factors (including \(H^+\)) causes a shift of the curve to the right.

A ↓ in all factors (including \(H^+\)) causes a shift of the curve to the left.

Fetal Hb has higher affinity for \(O_2\) than adult Hb, so its dissociation curve is shifted left.
**Oxygen content of blood**

\[ O_2 \text{ content} = (O_2 \text{ binding capacity} \times \% \text{ saturation}) + \text{dissolved } O_2. \]

Normally 1 g Hb can bind 1.34 mL O₂; normal Hb amount in blood is 15 g/dL. Cyanosis results when deoxygenated Hb > 5 g/dL.

\[ O_2 \text{ binding capacity} = 20.1 \text{ mL O}_2/\text{dL}. \]

With ↓ Hb there is ↓ O₂ content of arterial blood, but no change in O₂ saturation and arterial Po₂.

\[ O_2 \text{ delivery to tissues} = \text{cardiac output} \times O_2 \text{ content of blood}. \]

---

<table>
<thead>
<tr>
<th></th>
<th>Hb concentration</th>
<th>% O₂ sat of Hb</th>
<th>Dissolved O₂ (PaO₂)</th>
<th>Total O₂ content</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO poisoning</td>
<td>Normal</td>
<td>↓ (CO competes with O₂)</td>
<td>Normal</td>
<td>↓</td>
</tr>
<tr>
<td>Anemia</td>
<td>↓</td>
<td>Normal</td>
<td>Normal</td>
<td>↓</td>
</tr>
<tr>
<td>Polycythemia</td>
<td>↑</td>
<td>Normal</td>
<td>Normal</td>
<td>↑</td>
</tr>
</tbody>
</table>

---

**Pulmonary circulation**

Normally a low-resistance, high-compliance system. Po₂ and Pco₂ exert opposite effects on pulmonary and systemic circulation. A ↓ in PAO₂ causes a hypoxic vasoconstriction that shifts blood away from poorly ventilated regions of lung to well-ventilated regions of lung.

Perfusion limited—O₂ (normal health), CO₂, N₂O. Gas equilibrates early along the length of the capillary. Diffusion can be ↑ only if blood flow ↑.

Diffusion limited—O₂ (emphysema, fibrosis), CO. Gas does not equilibrate by the time blood reaches the end of the capillary.

A consequence of pulmonary hypertension is cor pulmonale and subsequent right ventricular failure (jugular venous distention, edema, hepatomegaly).

Diffusion: \( V_\text{gas} = A/T \times D_k(P_1 - P_2) \) where

- \( A \) = area,
- \( T \) = alveolar wall thickness,
- \( D_k(P_1 - P_2) \) = difference in partial pressures:
  - ↑ in emphysema.
  - ↓ in pulmonary fibrosis.

---

\[ P_4 = \text{partial pressure of gas in pulmonary capillary blood} \]

\[ P_A = \text{partial pressure of gas in alveolar air} \]
Pulmonary vascular resistance

\[ P_{\text{pulm artery}} - P_{\text{P,atrium}} \]

\[ \frac{\text{cardiac output}}{R} \]

\[ \Delta P = Q \times R, \text{ so } R = \frac{\Delta P}{Q} \]

\[ R = \frac{8 \eta l}{\pi r^4} \]

\( \eta \) = viscosity of blood; \( l \) = vessel length; \( r \) = vessel radius

Alveolar gas equation

\[ PAO_2 = PIo_2 - Paco_2 \]

\[ = 150 \text{ mmHg}^a - \frac{Paco_2}{0.8} \]

\(^a\text{At sea level breathing room air.}\)

\( PAO_2 \) = alveolar \( Po_2 \) (mmHg).
\( PIo_2 \) = \( Po_2 \) in inspired air (mmHg).
\( Paco_2 \) = arterial \( Pco_2 \) (mmHg).
\( R \) = respiratory quotient = \( CO_2 \) produced/\( O_2 \) consumed.
\( A-a \) gradient = \( PAO_2 - PAO_2 \) = 10–15 mmHg.
\( A-a \) gradient may occur in hypoxemia; causes include shunting, \( V/Q \) mismatch, fibrosis (impairs diffusion).

Oxygen deprivation

<table>
<thead>
<tr>
<th>Hypoxemia (↓ ( PAO_2 ))</th>
<th>Hypoxia (↓ ( O_2 ) delivery to tissue)</th>
<th>Ischemia (loss of blood flow)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal A-a gradient</td>
<td>↓ cardiac output</td>
<td>Impeded arterial flow</td>
</tr>
<tr>
<td>High altitude</td>
<td>Hypoxemia</td>
<td>↓ venous drainage</td>
</tr>
<tr>
<td>Hypoventilation (e.g., opioid use)</td>
<td>Anemia</td>
<td></td>
</tr>
<tr>
<td>↑ A-a gradient</td>
<td>CO poisoning</td>
<td></td>
</tr>
<tr>
<td>V/Q mismatch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffusion limitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right-to-left shunt</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

V/Q mismatch

Ideally, ventilation is matched to perfusion (i.e., \( V/Q = 1 \)) for adequate gas exchange.

Lung zones:
- \( V/Q \) at apex of lung = 3 (wasted ventilation)
- \( V/Q \) at base of lung = 0.6 (wasted perfusion)

Both ventilation and perfusion are greater at the base of the lung than at the apex of the lung.

With exercise (↑ cardiac output), there is vasodilation of apical capillaries → \( V/Q \) ratio approaches 1.

Certain organisms that thrive in high \( O_2 \) (e.g., TB) flourish in the apex.

\( V/Q = 0 \) = “airway” obstruction (shunt). In shunt, 100% \( O_2 \) does not improve \( PAO_2 \).

\( V/Q = \infty \) = blood flow obstruction (physiologic dead space). Assuming < 100% dead space, 100% \( O_2 \) improves \( PAO_2 \).
**CO₂ transport**

CO₂ is transported from tissues to lungs in 3 forms:
- HCO₃⁻ (90%).
- Carbaminohemoglobin or HbCO₂ (5%). CO₂ bound to Hb at N-terminus of globin (not heme). CO₂ binding favors taut form (O₂ unloaded).
- Dissolved CO₂ (5%).

In lungs, oxygenation of Hb promotes dissociation of H⁺ from Hb. This shifts equilibrium toward CO₂ formation; therefore, CO₂ is released from RBCs (Haldane effect). In peripheral tissue, ↑ H⁺ from tissue metabolism shifts curve to right, unloading O₂ (Bohr effect).

Majority of blood CO₂ is carried as HCO₃⁻ in the plasma.

---

**Response to high altitude**

↓ atmospheric oxygen (PO₂) → ↓ PaO₂ → ↑ ventilation → ↓ PaCO₂.
Chronic ↑ in ventilation.
↑ erythropoietin → ↑ hematocrit and Hb (chronic hypoxia).
↑ 2,3-BPG (binds to Hb so that Hb releases more O₂).
Cellular changes (↑ mitochondria).
↑ renal excretion of HCO₃⁻ to compensate for respiratory alkalosis (can augment with acetazolamide).

Chronic hypoxic pulmonary vasoconstriction results in RVH.

---

**Response to exercise**

↑ CO₂ production.
↑ O₂ consumption.
↑ ventilation rate to meet O₂ demand.
V/Q ratio from apex to base becomes more uniform.
↑ pulmonary blood flow due to ↑ cardiac output.
↓ pH during strenuous exercise (2° to lactic acidosis).
No change in Pao₂ and Paco₂, but ↑ in venous CO₂ content and ↓ in venous O₂ content.
Rhinosinusitis

Obstruction of sinus drainage into nasal cavity → inflammation and pain over affected area (typically maxillary sinuses in adults). Most common acute cause is viral URI; may cause superimposed bacterial infection, most commonly *S. pneumoniae, H. influenzae, M. catarrhalis.*

Epistaxis

Nose bleed. Most commonly occurs in anterior segment of nostril (Kiesselbach plexus). Life-threatening hemorrhages occur in posterior segment (sphenopalatine artery, a branch of maxillary artery).

Deep venous thrombosis

Blood clot within a deep vein → swelling, redness, warmth, pain. Predisposed by Virchow triad (SHE):
- Stasis
- Hypercoagulability (e.g., defect in coagulation cascade proteins, such as factor V Leiden)
- Endothelial damage (exposed collagen triggers clotting cascade)

Approximately 95% of pulmonary emboli arise from proximal deep veins of lower extremity. Homan sign—dorsiflexion of foot → calf pain. Use unfractionated heparin or low-molecular-weight heparins (e.g., enoxaparin) for prophylaxis and acute management. Use oral anticoagulants (e.g., warfarin, rivaroxaban) for treatment (long-term prevention).
Pulmonary emboli

V/Q mismatch → hypoxemia → respiratory alkalosis. Sudden-onset dyspnea, chest pain, tachypnea, tachycardia. May present as sudden death. Lines of Zahn are interdigitating areas of pink (platelets, fibrin) and red (RBCs) found only in thrombi formed before death; help distinguish pre- and postmortem thrombi.

Types: Fat, Air, Thrombus, Bacteria, Amniotic fluid, Tumor.

Fat emboli—associated with long bone fractures and liposuction; classic triad of hypoxemia, neurologic abnormalities, petechial rash.

Amniotic fluid emboli—can lead to DIC, especially postpartum.

Air emboli—nitrogen bubbles precipitate in ascending divers; treat with hyperbaric O₂.

CT pulmonary angiography is imaging test of choice for PE (look for filling defects).

An embolus moves like a FAT BAT.
Obstructive lung diseases

Obstruction of air flow resulting in air trapping in lungs. Airways close prematurely at high lung volumes → ↑ RV and ↓ FVC. PFTs: ↓ FEV₁, ↓ FVC → ↓ FEV₁/FVC ratio (hallmark), V/Q mismatch. Chronic, hypoxic pulmonary vasoconstriction can lead to cor pulmonale.

<table>
<thead>
<tr>
<th>TYPE</th>
<th>PATHOLOGY</th>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic bronchitis</td>
<td>Hyperplasia of mucus-secreting glands in bronchi → Reid index (thickness of gland layer/total thickness of bronchial wall) &gt; 50%.</td>
<td>Productive cough for &gt; 3 months per year (not necessarily consecutive) for &gt; 2 years. Findings: wheezing, crackles, cyanosis (early-onset hypoxemia due to shunting), late-onset dyspnea, CO₂ retention (hypercapnia), 2° polycythemia.</td>
</tr>
<tr>
<td>Emphysema (&quot;pink puffer&quot;)</td>
<td>Enlargement of air spaces, ↑ recoil, ↑ compliance, ↓ diffusing capacity for CO resulting from destruction of alveolar walls (arrow in A). Two types:</td>
<td>↑ elastase activity → loss of elastic fibers → ↑ lung compliance. Exhalation through pursed lips to ↑ airway pressure and prevent airway collapse during respiration. Barrel-shaped chest D.</td>
</tr>
<tr>
<td>Asthma</td>
<td>Bronchial hyperresponsiveness causes reversible bronchoconstriction. Smooth muscle hypertrophy, Curschmann spirals E (shed epithelium forms whorled mucus plugs), and Charcot-Leyden crystals (eosinophilic, hexagonal, double-pointed, needle-like crystals formed from breakdown of eosinophils in sputum).</td>
<td>Can be triggered by viral URIs, allergens, stress. Test with methacholine challenge. Findings: cough, wheezing, tachypnea, dyspnea, hypoxemia, ↓ inspiratory/expiratory ratio, pulsus paradoxus, mucus plugging F.</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>Chronic necrotizing infection of bronchi → permanently dilated Airways, purulent sputum, recurrent infections, hemoptysis.</td>
<td>Associated with bronchial obstruction, poor ciliary motility (e.g., smoking, Kartagener syndrome), cystic fibrosis G, allergic bronchopulmonary aspergillosis.</td>
</tr>
</tbody>
</table>
Restrictive lung disease

Restricted lung expansion causes ↓ lung volumes (↓ FVC and TLC). PFTs: FEV₁/FVC ratio ≥ 80%.

Types:
- Poor breathing mechanics (extrapulmonary, peripheral hypoventilation, normal A-a gradient):
  - Poor muscular effort—polio, myasthenia gravis
  - Poor structural apparatus—scoliosis, morbid obesity
- Interstitial lung diseases (pulmonary ↓ diffusing capacity, ↑ A-a gradient):
  - Acute respiratory distress syndrome (ARDS)
  - Neonatal respiratory distress syndrome (NRDS, hyaline membrane disease)
  - Pneumoconioses (e.g., anthracosis, silicosis, asbestosis)
  - Sarcoidosis: bilateral hilar lymphadenopathy, noncaseating granuloma; ↑ ACE and Ca²⁺
  - Idiopathic pulmonary fibrosis (repeated cycles of lung injury and wound healing with ↑ collagen deposition)
  - Goodpasture syndrome
  - Granulomatosis with polyangiitis (Wegener)
  - Langerhans cell histiocytosis (eosinophilic granuloma)
  - Hypersensitivity pneumonitis
  - Drug toxicity (bleomycin, busulfan, amiodarone, methotrexate)

Obstructive vs. restrictive lung disease

Note: Obstructive lung volumes > normal (↑ TLC, ↑ FRC, ↑ RV); restrictive lung volumes < normal. In both obstructive and restrictive, FEV₁ and FVC are reduced. In obstructive, however, FEV₁ is more dramatically reduced compared to FVC, resulting in a ↓ FEV₁/FVC ratio.
### Hypersensitivity pneumonitis

Mixed type III/IV hypersensitivity reaction to environmental antigen → dyspnea, cough, chest tightness, headache. Often seen in farmers and those exposed to birds.

### Pneumoconioses

Coal workers’ pneumoconiosis, silicosis, and asbestosis → ↑ risk of cor pulmonale and Caplan syndrome (rheumatoid arthritis and pneumoconioses with intrapulmonary nodules).

#### Asbestosis


Affects lower lobes.

Asbestos (ferruginous) bodies are golden-brown fusiform rods resembling dumbbells C, found in alveolar septum.

#### Berylliosis

Associated with exposure to beryllium in aerospace and manufacturing industries. Granulomatous on histology and therefore occasionally responsive to steroids.

Affects upper lobes.

#### Coal workers’ pneumoconiosis

Prolonged coal dust exposure → macrophages laden with carbon → inflammation and fibrosis. Also known as black lung disease.

Affects upper lobes.

**Anthracosis**—asymptomatic condition found in many urban dwellers exposed to sooty air.

#### Silicosis

Associated with foundries, sandblasting, mines. Macrophages respond to silica and release fibrogenic factors, leading to fibrosis. It is thought that silica may disrupt phagolysosomes and impair macrophages, increasing susceptibility to TB. Also ↑ risk of bronchogenic carcinoma.

Affects upper lobes.

“Eggshell” calcification of hilar lymph nodes. **Asbestos** is from the roof (was common in insulation), but affects the base (lower lobes). **Silica and coal** are from the base (earth), but affect the roof (upper lobes).
**Neonatal respiratory distress syndrome**

Surfactant deficiency → ↑ surface tension → alveolar collapse ("ground-glass" appearance of lung fields). A lecithin:phosphatidylcholine ratio < 1.5 in amniotic fluid is predictive of NRDS. Persistently low O₂ tension → risk of PDA. Therapeutic supplemental O₂ can result in Retinopathy of prematurity, Intraventricular hemorrhage, Bronchopulmonary dysplasia (RIB). Risk factors: prematurity, maternal diabetes (due to ↑ fetal insulin), C-section delivery (↓ release of fetal glucocorticoids).

Complications: metabolic acidosis, PDA, necrotizing enterocolitis.

Treatment: maternal steroids before birth; artificial surfactant for infant.

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**Acute respiratory distress syndrome**

Clinical syndrome characterized by acute onset respiratory failure, bilateral lung opacities, ↓ PaO₂/FiO₂, no HF. May be caused by trauma, sepsis, shock, gastric aspiration, uremia, acute pancreatitis, amniotic fluid embolism. Diffuse alveolar damage → ↑ alveolar capillary permeability → protein-rich leakage into alveoli and noncardiogenic pulmonary edema (normal PCWP). Results in formation of intra-alveolar hyaline membranes. Initial damage due to release of neutrophilic substances toxic to alveolar wall, activation of coagulation cascade, and oxygen-derived free radicals.

Management: mechanical ventilation with low tidal volumes, address underlying cause.

---

**Sleep apnea**

Repeated cessation of breathing > 10 seconds during sleep → disrupted sleep → daytime somnolence. Normal PaO₂ during the day. Nocturnal hypoxia → systemic/pulmonary hypertension, arrhythmias (atrial fibrillation/flutter), sudden death.

**Obstructive sleep apnea**—respiratory effort against airway obstruction. Associated with obesity, loud snoring. Caused by excess parapharyngeal tissue in adults, adenotonsillar hypertrophy in children. Treatment: weight loss, CPAP, surgery.

**Central sleep apnea**—no respiratory effort (due to CNS injury/toxicity.)

---

Hypoxia → ↑ EPO release → ↑ erythropoiesis. **Obesity hypoventilation syndrome**—obesity (BMI ≥ 30 kg/m²) → hypoventilation (↓ respiratory rate) → ↓ PaO₂ and ↑ PaCO₂ during sleep → ↑ PaCO₂ during waking hours (retention).
**Pulmonary hypertension**

Normal mean pulmonary artery pressure = 10–14 mmHg; pulmonary hypertension (PH) \( \geq 25 \) mmHg at rest. Results in arteriosclerosis, medial hypertrophy, intimal fibrosis of pulmonary arteries. Course: severe respiratory distress → cyanosis and RVH → death from decompensated cor pulmonale.

Five classification groups based on cause and treatment options.

**Pulmonary arterial hypertension (PAH)**

Idiopathic PAH; heritable—often due to an inactivating mutation in BMPR2 gene (normally inhibits vascular smooth muscle proliferation); poor prognosis. Includes pulmonary venous occlusive disease and persistent PH of newborn. Other causes include drugs (e.g., amphetamines, cocaine), connective tissue disease, HIV infection, portal hypertension, congenital heart disease, schistosomiasis.

**PH due to left heart disease**

Causes includes systolic/diastolic dysfunction and valvular disease such as mitral stenosis.

**PH due to lung diseases or hypoxia**

Destruction of lung parenchyma (e.g., COPD), hypoxemic vasoconstriction (e.g., obstructive sleep apnea, living in high altitude).

**Chronic thromboembolic PH**

Recurrent microthrombi → ↓ cross-sectional area of pulmonary vascular bed.

**Multifactorial PH**

Causes include hematologic, systemic, and metabolic disorders.

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### Lung—physical findings

<table>
<thead>
<tr>
<th>ABNORMALITY</th>
<th>BREATH SOUNDS</th>
<th>PERCUSSION</th>
<th>FREMITUS</th>
<th>TRACHEAL DEVIAION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural effusion</td>
<td>↓</td>
<td>Dull</td>
<td>↓</td>
<td>— or away from side of lesion (if large)</td>
</tr>
<tr>
<td>Atelectasis (bronchial obstruction)</td>
<td>↓</td>
<td>Dull</td>
<td>↓</td>
<td>Toward side of lesion</td>
</tr>
<tr>
<td>Simple pneumothorax</td>
<td>↓</td>
<td>Hyperresonant</td>
<td>↓</td>
<td>—</td>
</tr>
<tr>
<td>Tension pneumothorax</td>
<td>↓</td>
<td>Hyperresonant</td>
<td>↓</td>
<td>Away from side of lesion</td>
</tr>
<tr>
<td>Consolidation (lobar pneumonia, pulmonary edema)</td>
<td>Bronchial breath sounds; late inspiratory crackles</td>
<td>Dull</td>
<td>↑</td>
<td>—</td>
</tr>
</tbody>
</table>
Pleural effusions: Excess accumulation of fluid between pleural layers. Can be treated with thoracentesis to remove fluid.

Transudate: Protein content. Due to hydrostatic pressure or oncotic pressure (e.g., HF, nephrotic syndrome, hepatic cirrhosis).

Exudate: Protein content, cloudy. Due to malignancy, pneumonia, collagen vascular disease, trauma (occurs in states of vascular permeability). Must be drained due to risk of infection.

Lymphatic: Also known as chylothorax. Due to thoracic duct injury from trauma or malignancy. Milky-appearing fluid; triglycerides.

Pneumothorax: Accumulation of air in pleural space. Unilateral chest pain and dyspnea, unilateral chest expansion, tactile fremitus, hyperresonance, diminished breath sounds, all on the affected side.

Primary spontaneous: Due to rupture of apical blebs or cysts. Occurs most frequently in tall, thin, young males.

Secondary spontaneous: Due to diseased lung (e.g., bullae in emphysema, infections), mechanical ventilation with use of high pressures → barotrauma.

Traumatic pneumothorax: Caused by blunt (e.g., rib fracture) or penetrating (e.g., gunshot) trauma.

Tension: Can be any of the above. Air enters pleural space but cannot exit. Increasing trapped air → tension pneumothorax. Trachea deviates away from affected lung.

Pleur al effusion before treatment. Note small right-sided pleural effusion on CXR (left) and CT (right).

Pleural effusion after treatment. Almost complete resolution after therapy seen on CXR (left) and CT (right).

Pneumothorax. CT shows collapsed left lung.

Tension pneumothorax. Note the hyperlucent left lung field with low left hemidiaphragm (below the field of view) and rightward mediastinal/tracheal shift.
### Pneumonia

<table>
<thead>
<tr>
<th>Type</th>
<th>Typical Organisms</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobar</td>
<td><em>S. pneumoniae</em> most frequently, also <em>Legionella</em>, <em>Klebsiella</em></td>
<td>Intra-alveolar exudate → consolidation A; may involve entire lobe B or lung.</td>
</tr>
<tr>
<td>Bronchopneumonia</td>
<td><em>S. pneumoniae, S. aureus, H. influenza, Klebsiella</em></td>
<td>Acute inflammatory infiltrates C from bronchioles into adjacent alveoli; patchy distribution involving ≥ 1 lobe D.</td>
</tr>
<tr>
<td>Interstitial (atypical) pneumonia</td>
<td>Viruses (influenza, CMV, RSV, adenoviruses), <em>Mycoplasma, Legionella, Chlamydia</em></td>
<td>Diffuse patchy inflammation localized to interstitial areas at alveolar walls; diffuse distribution involving ≥ 1 lobe E. Generally follows a more indolent course (“walking” pneumonia).</td>
</tr>
</tbody>
</table>

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![Images of Pneumonia](images.png)
Lung abscess
Localized collection of pus within parenchyma. Caused by aspiration of oropharyngeal contents (especially in patients predisposed to loss of consciousness [e.g., alcoholics, epileptics]) or bronchial obstruction (e.g., cancer). Treatment: clindamycin.

Air-fluid levels often seen on CXR. Fluid levels common in cavities; presence suggests cavitation. Due to anaerobes (e.g., Bacteroides, Fusobacterium, Peptostreptococcus) or S. aureus.

Mesothelioma
Malignancy of the pleura associated with asbestosis. May result in hemorrhagic pleural effusion (exudative), pleural thickening. Psammoma bodies seen on histology. Smoking not a risk factor.

Pancoast tumor (superior sulcus tumor)
Carcinoma that occurs in apex of lung may cause Pancoast syndrome by invading cervical sympathetic chain, causing Horner syndrome (ipsilateral ptosis, miosis, anhidrosis), SVC syndrome, sensorimotor deficits, hoarseness.

Chest MRI shows mass at right lung apex.
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 (e.g., Pancoast tumor) and thrombosis from indwelling catheters B. Medical emergency. Can raise intracranial pressure (if obstruction is severe) → headaches, dizziness, ↑ risk of aneurysm/rupture of intracranial arteries.
### Lung cancer
Leading cause of cancer death. Presentation: cough, hemoptysis, bronchial obstruction, wheezing, pneumonic “coin” lesion on CXR or noncalcified nodule on CT. Sites of metastases from lung cancer: adrenals, brain, bone (pathologic fracture), liver (jaundice, hepatomegaly). In the lung, metastases (usually multiple lesions) are more common than 1° neoplasms. Most often from breast, colon, prostate, and bladder cancer.

**SPHERE** of complications:
- Superior vena cava syndrome
- Pancoast tumor
- Horner syndrome
- Endocrine (paraneoplastic)
- Recurrent laryngeal nerve compression (hoarseness)
- Effusions (pleural or pericardial)

Risk factors include smoking, secondhand smoke, radon, asbestos, family history. Squamous and Small cell carcinomas are central (central).

<table>
<thead>
<tr>
<th>TYPE</th>
<th>LOCATION</th>
<th>CHARACTERISTICS</th>
<th>HISTOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cell</td>
<td>Central</td>
<td>Undifferentiated → very aggressive. May produce ACTH (Cushing syndrome), SIADH, or Antibodies against presynaptic Ca$^{2+}$ channels (Lambert-Eaton myasthenic syndrome) or neurons (paraneoplastic myelitis/encephalitis). Amplification of myc oncogenes common. Inoperable; treat with chemotherapy.</td>
<td>Neoplasm of neuroendocrine Kulchitsky cells → small dark blue cells A. Chromogranin A A.</td>
</tr>
<tr>
<td>Small cell (oat cell)</td>
<td>Central</td>
<td></td>
<td></td>
</tr>
<tr>
<td>carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>Peripheral</td>
<td>Most common lung cancer in nonsmokers and overall (except for metastases). 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; excellent prognosis.</td>
<td>Glandular pattern on histology, often stains mucin A. Bronchioloalveolar subtype: grows along alveolar septa → apparent “thickening” of alveolar walls.</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>Central</td>
<td>Hilar mass arising from bronchus C. Cavitation; Cigarettes; hyperCalcemia (produces PTHrP).</td>
<td>Keratin pearls A and intercellular bridges.</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>Peripheral</td>
<td>Highly anaplastic undifferentiated tumor; poor prognosis. Less responsive to chemotherapy; removed surgically.</td>
<td>Pleomorphic giant cells. Can secrete β-hCG.</td>
</tr>
<tr>
<td>Bronchial carcinoid</td>
<td></td>
<td>Excellent prognosis; metastasis rare. Symptoms usually due to mass effect; occasionally carcinoid syndrome (5-HT secretion → flushing, diarrhea, wheezing).</td>
<td>Nests of neuroendocrine cells; chromogranin A A.</td>
</tr>
</tbody>
</table>
### RESPIRATORY—PHARMACOLOGY

**H₁ blockers**
- Reversible inhibitors of H₁ histamine receptors.
- **1st generation**
  - Diphenhydramine, dimenhydrinate, chlorpheniramine.
  - Names contain “-en/-ine” or “-en/-ate.”
  - **Clinical Uses**: Allergy, motion sickness, sleep aid.
  - **Toxicity**: Sedation, antimuscarinic, anti-α-adrenergic.

**2nd generation**
- Loratadine, fexofenadine, desloratadine, cetirizine.
  - Names usually end in “-adine.”
  - **Clinical Uses**: Allergy.
  - **Toxicity**: Far less sedating than 1st generation because of lower entry into CNS.

### Expectorants
- **Guaifenesin**
  - Expectorant—thins respiratory secretions; does not suppress cough reflex.
- **N-acetylcysteine**
  - Mucolytic—can loosen mucous plugs in CF patients by disrupting disulfide bonds. Also used as an antidote for acetaminophen overdose.

### Dextromethorphan
- Antitussive (agonizes NMDA glutamate receptors). Synthetic codeine analog. Has mild opioid effect when used in excess. Naloxone can be given for overdose. Mild abuse potential. May cause serotonin syndrome if combined with other serotonergic agents.

### Pseudoephedrine, phenylephrine
- **Mechanism**: α-adrenergic agonists, used as nasal decongestants.
- **Clinical Use**: Reduce hyperemia, edema, nasal congestion; open obstructed eustachian tubes. Pseudoephedrine also illicitly used to make methamphetamine.
- **Toxicity**: Hypertension. Can also cause CNS stimulation/anxiety (pseudoephedrine).

### Pulmonary hypertension drugs
- **Endothelin receptor antagonists**
  - Include bosentan. Competitively antagonize endothelin-1 receptors → ↓ pulmonary vascular resistance.
  - Hepatotoxic (monitor LFTs).
- **PDE-5 inhibitors**
  - Include sildenafil. Inhibit cGMP PDE5 and prolong vasodilatory effect of nitric oxide. Also used to treat erectile dysfunction.
- **Prostacyclin analogs**
  - Include epoprostenol, iloprost. Prostacyclins (PGI₂) with direct vasodilatory effects on pulmonary and systemic arterial vascular beds. Inhibit platelet aggregation. Side effects: flushing, jaw pain.
Asthma drugs  
Bronchoconstriction is mediated by (1) inflammatory processes and (2) parasympathetic tone; therapy is directed at these 2 pathways.

$\beta_2$-agonists  
- **Albuterol**—relaxes bronchial smooth muscle ($\beta_2$). Used during acute exacerbation.
- **Salmeterol, formoterol**—long-acting agents for prophylaxis. Adverse effects are tremor and arrhythmia.

Corticosteroids  
- **Fluticasone, budesonide**—inhibit the synthesis of virtually all cytokines. Inactivate NF-kB, the transcription factor that induces production of TNF-α and other inflammatory agents. 1st-line therapy for chronic asthma.

Muscarinic antagonists  
- **Ipratropium**—competitively blocks muscarinic receptors, preventing bronchoconstriction. Also used for COPD. Tiotropium is long acting.

Antileukotrienes  
- **Montelukast, zafirlukast**—block leukotriene receptors (CysLT1). Especially good for aspirin-induced asthma.
- **Zileuton**—5-lipoxygenase pathway inhibitor. Blocks conversion of arachidonic acid to leukotrienes. Hepatotoxic.

Omalizumab  
- Monoclonal anti-IgE antibody. Binds mostly unbound serum IgE and blocks binding to FcεRI. Used in allergic asthma resistant to inhaled steroids and long-acting $\beta_2$-agonists.

Methylxanthines  
- **Theophylline**—likely causes bronchodilation by inhibiting phosphodiesterase → ↑ cAMP levels due to ↓ cAMP hydrolysis. Usage is limited because of narrow therapeutic index (cardiotoxicity, neurotoxicity); metabolized by cytochrome P-450. Blocks actions of adenosine.

Methacholine  
Muscarinic receptor (M3) agonist. Used in bronchial challenge test to help diagnose asthma.
HIGH-YIELD SYSTEMS

Rapid Review

“Study without thought is vain: thought without study is dangerous.”
—Confucius

“It is better, of course, to know useless things than to know nothing.”
—Lucius Annaeus Seneca

The following tables represent a collection of high-yield associations of diseases with their clinical findings, treatments, and pathophysiology. They serve as a quick review before the exam to tune your senses to commonly tested cases.
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<tr>
<th>CLINICAL PRESENTATION</th>
<th>DIAGNOSIS/DISEASE</th>
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<tr>
<td>Abdominal pain, ascites, hepatomegaly</td>
<td>Budd-Chiari syndrome (posthepatic venous thrombosis)</td>
</tr>
<tr>
<td>Abdominal pain, diarrhea, leukocytosis, recent antibiotic use</td>
<td>Clostridium difficile infection</td>
</tr>
<tr>
<td>Achilles tendon xanthoma</td>
<td>Familial hypercholesterolemia (f LDL receptor signaling)</td>
</tr>
<tr>
<td>Adrenal hemorrhage, hypotension, DIC</td>
<td>Waterhouse-Friderichsen syndrome (meningococcemia)</td>
</tr>
<tr>
<td>Anaphylaxis following blood transfusion</td>
<td>IgA deficiency</td>
</tr>
<tr>
<td>Anterior “drawer sign” ⊕</td>
<td>Anterior cruciate ligament injury</td>
</tr>
<tr>
<td>Arachnodactyly, lens dislocation, aortic dissection, hyperflexible joints</td>
<td>Marfan syndrome (fibrillin defect)</td>
</tr>
<tr>
<td>Athlete with polycythemia</td>
<td>2° to erythropoietin injection</td>
</tr>
<tr>
<td>Back pain, fever, night sweats</td>
<td>Pott disease (vertebral TB)</td>
</tr>
<tr>
<td>Bilateral acoustic schwannomas</td>
<td>Neurofibromatosis type 2</td>
</tr>
<tr>
<td>Bilateral hilar adenopathy, uveitis</td>
<td>Sarcoidosis (noncaseating granulomas)</td>
</tr>
<tr>
<td>Black eschar on face of patient with diabetic ketoacidosis</td>
<td>Mucor or Rhizopus fungal infection</td>
</tr>
<tr>
<td>Blue sclera</td>
<td>Osteogenesis imperfecta (type I collagen defect)</td>
</tr>
<tr>
<td>Bluish line on gingiva</td>
<td>Burton line (lead poisoning)</td>
</tr>
<tr>
<td>Bone pain, bone enlargement, arthritis</td>
<td>Paget disease of bone (↑ osteoblastic and osteoclastic activity)</td>
</tr>
<tr>
<td>Bounding pulses, diastolic heart murmur, head bobbing</td>
<td>Aortic regurgitation</td>
</tr>
<tr>
<td>“Butterfly” facial rash and Raynaud phenomenon in a young female</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Café-au-lait spots, Lisch nodules (iris hamartoma), cutaneous neurofibromas, neurofibromas, pheochromocytomas, optic gliomas</td>
<td>Neurofibromatosis type I, pheochromocytoma, optic gliomas</td>
</tr>
<tr>
<td>Café-au-lait spots (unilateral), polyostotic fibrous dysplasia, precocious puberty, multiple endocrine abnormalities</td>
<td>McCune-Albright syndrome (mosaic G-protein signaling mutation)</td>
</tr>
<tr>
<td>Calf pseudohypertrophy</td>
<td>Muscular dystrophy (most commonly Duchenne, due to X-linked recessive frameshift mutation of dystrophin gene)</td>
</tr>
<tr>
<td>Cervical lymphadenopathy, desquamating rash, coronary aneurysms, red conjunctivae and tongue</td>
<td>Kawasaki disease (treat with IVIG and aspirin)</td>
</tr>
<tr>
<td>“Cherry-red spots” on macula</td>
<td>Tay-Sachs (ganglioside accumulation) or Niemann-Pick (sphingomyelin accumulation), central retinal artery occlusion</td>
</tr>
<tr>
<td>Chest pain on exertion</td>
<td>Angina (stable: with moderate exertion; unstable: with minimal exertion or at rest)</td>
</tr>
<tr>
<td>Chest pain, pericardial effusion/friction rub, persistent fever following MI</td>
<td>Dresser syndrome (autoimmune-mediated post-MI fibrinous pericarditis, 2–12 weeks after acute episode)</td>
</tr>
<tr>
<td>Chest pain with ST depressions on EKG</td>
<td>Unstable angina (troponins –) or NSTEMI (troponins +)</td>
</tr>
<tr>
<td>Child uses arms to stand up from squat</td>
<td>Gowers sign (Duchenne muscular dystrophy)</td>
</tr>
<tr>
<td>Child with fever later develops red rash on face that spreads to body</td>
<td>“Slapped cheeks” (erythema infectiosum/fifth disease: parvovirus B19)</td>
</tr>
<tr>
<td>Chorea, dementia, caudate degeneration</td>
<td>Huntington disease (autosomal dominant CAG repeat expansion)</td>
</tr>
<tr>
<td>Chorioretinitis, hydrocephalus, intracranial calcifications</td>
<td>Congenital toxoplasmossis</td>
</tr>
<tr>
<td>Clinical Presentation</td>
<td>Diagnosis/Disease</td>
</tr>
<tr>
<td>-----------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Chronic exercise intolerance with myalgia, fatigue,</td>
<td>McArdle disease (skeletal muscle glycogen phosphorylase deficiency)</td>
</tr>
<tr>
<td>painful cramps, myoglobinuria</td>
<td></td>
</tr>
<tr>
<td>Cold intolerance</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Conjugate horizontal gaze palsy, horizontal diplopia</td>
<td>Internuclear ophthalmoplegia (damage to MLF; may be unilateral or bilateral)</td>
</tr>
<tr>
<td>Continuous “machine-like” heart murmur</td>
<td>PDA (close with indomethacin; open or maintain with PGE analogs)</td>
</tr>
<tr>
<td>Cutaneous/dermal edema due to connective tissue deposition</td>
<td>Myxedema (caused by hypothyroidism, Graves disease [pretibial])</td>
</tr>
<tr>
<td>Cutaneous flushing, diarrhea, bronchospasm</td>
<td>Carcinoid syndrome (right-sided cardiac valvular lesions, ↑ 5-HIAA)</td>
</tr>
<tr>
<td>Dark purple skin/mouth nodules in a patient with AIDS</td>
<td>Kaposi sarcoma, associated with HHV-8</td>
</tr>
<tr>
<td>Deep, labored breathing/hyperventilation</td>
<td>Kussmaul respirations (diabetic ketoacidosis)</td>
</tr>
<tr>
<td>Dermatitis, dementia, diarrhea</td>
<td>Pellagra (niacin [vitamin B₃] deficiency)</td>
</tr>
<tr>
<td>Dilated cardiomyopathy, edema, alcoholism or malnutrition</td>
<td>Wet beriberi (thiamine [vitamin B₁] deficiency)</td>
</tr>
<tr>
<td>Dog or cat bite resulting in infection</td>
<td>Pasteurella multocida (cellulitis at inoculation site)</td>
</tr>
<tr>
<td>Dry eyes, dry mouth, arthritis</td>
<td>Sjögren syndrome (autoimmune destruction of exocrine glands)</td>
</tr>
<tr>
<td>Dysphagia (esophageal webs), glossitis, iron deficiency</td>
<td>Plummer-Vinson syndrome (may progress to esophageal squamous cell carcinoma)</td>
</tr>
<tr>
<td>anemia</td>
<td></td>
</tr>
<tr>
<td>Elastic skin, hypermobility of joints, ↑ bleeding tendency</td>
<td>Ehlers-Danlos syndrome (type V collagen defect, type III collagen defect seen in vascular subtype of ED)</td>
</tr>
<tr>
<td>Enlarged, hard left supraclavicular node</td>
<td>Virchow node (abdominal metastasis)</td>
</tr>
<tr>
<td>Episodic vertigo, tinnitus, hearing loss</td>
<td>Meniere disease</td>
</tr>
<tr>
<td>Erythroderma, lymphadenopathy, hepatosplenomegaly,</td>
<td>Mycosis fungoides (cutaneous T-cell lymphoma) or Sézary syndrome (mycosis fungoides + malignant T cells in blood)</td>
</tr>
<tr>
<td>atypical T cells</td>
<td></td>
</tr>
<tr>
<td>Facial muscle spasm upon tapping</td>
<td>Chvostek sign (hypocalcemia)</td>
</tr>
<tr>
<td>Fat, female, forty, and fertile</td>
<td>Cholelithiasis (gallstones)</td>
</tr>
<tr>
<td>Fever, chills, headache, myalgia following antibiotic</td>
<td>Jarisch-Herxheimer reaction (rapid lysis of spirochetes results in endotoxin release)</td>
</tr>
<tr>
<td>treatment for syphilis</td>
<td></td>
</tr>
<tr>
<td>Fever, cough, conjunctivitis, corza, diffuse rash</td>
<td>Measles</td>
</tr>
<tr>
<td>Fever, night sweats, weight loss</td>
<td>B symptoms (staging) of lymphoma</td>
</tr>
<tr>
<td>Fibrous plaques in soft tissue of penis with abnormal</td>
<td>Peyronie disease (connective tissue disorder)</td>
</tr>
<tr>
<td>curvature</td>
<td></td>
</tr>
<tr>
<td>Golden brown rings around peripheral cornea</td>
<td>Kayser-Fleischer rings (copper accumulation from Wilson disease)</td>
</tr>
<tr>
<td>Gout, intellectual disability, self-mutilitating behavior</td>
<td>Lesch-Nyhan syndrome (HGPRT deficiency, X-linked recessive)</td>
</tr>
<tr>
<td>in a boy</td>
<td></td>
</tr>
<tr>
<td>Hamartomatous GI polyps, hyperpigmentation of mouth/feet</td>
<td>Peutz-Jeghers syndrome (inherited, benign polyposis can cause bowel obstruction; ↑ cancer risk, mainly GI)</td>
</tr>
<tr>
<td>hands/genitalia</td>
<td></td>
</tr>
<tr>
<td>Hepatosplenomegaly, pancytopenia, osteoporosis, aseptic</td>
<td>Gaucher disease (glucocerebrosidase deficiency)</td>
</tr>
<tr>
<td>necrosis of femur, bone crises</td>
<td></td>
</tr>
<tr>
<td>CLINICAL PRESENTATION</td>
<td>DIAGNOSIS/DISEASE</td>
</tr>
<tr>
<td>-----------------------</td>
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</tr>
<tr>
<td>Hereditary nephritis, sensorineural hearing loss, cataracts</td>
<td>Alport syndrome (mutation in collagen IV)</td>
</tr>
<tr>
<td>Hyperphagia, hypersexuality, hyperorality, hyperdocility</td>
<td>Klüver-Bucy syndrome (bilateral amygdala lesion)</td>
</tr>
<tr>
<td>Hyperreflexia, hypertonia, Babinski sign present</td>
<td>UMN damage</td>
</tr>
<tr>
<td>Hyporeflexia, hypotonia, atrophy, fasciculations</td>
<td>LMN damage</td>
</tr>
<tr>
<td>Hypoxemia, polycythemia, hypercapnia</td>
<td>“Blue bloater” (chronic bronchitis, hyperplasia of mucous cells)</td>
</tr>
<tr>
<td>Indurated, ulcerated genital lesion</td>
<td>Nonpainful: chancre (1° syphilis, Treponema pallidum) Painful, with exudate: chancreoid (Haemophilus ducreyi)</td>
</tr>
<tr>
<td>Infant with “cherry-red” spot on macula, hepatosplenomegaly, and neurodegeneration</td>
<td>Niemann-Pick disease (genetic sphingomyelinase deficiency)</td>
</tr>
<tr>
<td>Infant with cleft lip/palate, microcephaly or holoprosencephaly, polydactyly, cutis aplasia</td>
<td>Patau syndrome (trisomy 13)</td>
</tr>
<tr>
<td>Infant with hypoglycemia, hepatomegaly</td>
<td>Cori disease (debranching enzyme deficiency) or Von Gierke disease (glucose-6-phosphatase deficiency, more severe)</td>
</tr>
<tr>
<td>Infant with microcephaly, rocker-bottom feet, clenched hands, and structural heart defect</td>
<td>Edwards syndrome (trisomy 18)</td>
</tr>
<tr>
<td>Jaundice, palpable distended non-tender gallbladder</td>
<td>Courvoisier sign (distal obstruction of biliary tree)</td>
</tr>
<tr>
<td>Large rash with bull's-eye appearance</td>
<td>Erythema chronicum migrans from Ixodes tick bite (Lyme disease: Borrelia)</td>
</tr>
<tr>
<td>Lucid interval after traumatic brain injury</td>
<td>Epidural hematoma (middle meningeal artery rupture)</td>
</tr>
<tr>
<td>Male child, recurrent infections, no mature B cells</td>
<td>Bruton disease (X-linked agammaglobulinemia)</td>
</tr>
<tr>
<td>Mucosal bleeding and prolonged bleeding time</td>
<td>Glanzmann thrombasthenia (defect in platelet aggregation due to lack of GpIIb/IIIa)</td>
</tr>
<tr>
<td>Muffled heart sounds, distended neck veins, hypotension</td>
<td>Beck triad of cardiac tamponade</td>
</tr>
<tr>
<td>Multiple colon polyps, osteomas/soft tissue tumors, impacted/supernumerary teeth</td>
<td>Gardner syndrome (subtype of FAP)</td>
</tr>
<tr>
<td>Myopathy (infantile hypertrophic cardiomyopathy), exercise intolerance</td>
<td>Pompe disease (lysosomal α-1,4-glucosidase deficiency)</td>
</tr>
<tr>
<td>Neonate with arm paralysis following difficult birth</td>
<td>Erb-Duchenne palsy (superior trunk [C5–C6] brachial plexus injury: “waiter’s tip”)</td>
</tr>
<tr>
<td>No lactation postpartum, absent menstruation, cold intolerance</td>
<td>Sheehan syndrome (pituitary infarction)</td>
</tr>
<tr>
<td>Nystagmus, intention tremor, scanning speech, bilateral internuclear ophthalmoplegia</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Painful blue fingers/toes, hemolytic anemia</td>
<td>Cold agglutinin disease (autoimmune hemolytic anemia caused by Mycoplasma pneumoniae, infectious mononucleosis, CLL)</td>
</tr>
<tr>
<td>Painful fingers/toes changing color from blue to white to red with cold or stress</td>
<td>Raynaud phenomenon (vasospasm in extremities)</td>
</tr>
<tr>
<td>Painful, raised red lesions on pads of fingers/toes</td>
<td>Osler nodes (infective endocarditis, immune complex deposition)</td>
</tr>
<tr>
<td>Clinical Presentation</td>
<td>Diagnosis/Disease</td>
</tr>
<tr>
<td>-----------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Painless erythematous lesions on palms and soles</td>
<td>Janeway lesions (infective endocarditis, septic emboli/microabscesses)</td>
</tr>
<tr>
<td>Painless jaundice</td>
<td>Cancer of the pancreatic head obstructing bile duct</td>
</tr>
<tr>
<td>Palpable purpura on buttocks/legs, joint pain, abdominal</td>
<td>Henoch-Schönlein purpura (IgA vasculitis affecting skin and kidneys)</td>
</tr>
<tr>
<td>pain (child), hematuria</td>
<td></td>
</tr>
<tr>
<td>Pancreatic, pituitary, parathyroid tumors</td>
<td>MEN 1 (autosomal dominant)</td>
</tr>
<tr>
<td>Periorbital and/or peripheral edema, proteinuria,</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>hypoalbuminemia, hypercholesterolemia</td>
<td></td>
</tr>
<tr>
<td>Pink complexion, dyspnea, hyperventilation</td>
<td>“Pink puffer” (emphysema: centriacinar [smoking], panacinar [α1-antitrypsin deficiency])</td>
</tr>
<tr>
<td>Polyuria, renal tubular acidosis type II, growth failure,</td>
<td>Fanconi syndrome (multiple combined dysfunction of the proximal convoluted tubule)</td>
</tr>
<tr>
<td>electrolyte imbalances, hypophosphatemic rickets</td>
<td></td>
</tr>
<tr>
<td>Pruritic, purple, polygonal planar papules and plaques</td>
<td>Lichen planus</td>
</tr>
<tr>
<td>(6 P’s)</td>
<td></td>
</tr>
<tr>
<td>Ptosis, miosis, anhidrosis</td>
<td>Horner syndrome (sympathetic chain lesion)</td>
</tr>
<tr>
<td>Pupil accommodates but doesn’t react</td>
<td>Argyll Robertson pupil (neurosphilitis)</td>
</tr>
<tr>
<td>Rapidly progressive limb weakness that ascends following</td>
<td>Guillain-Barré syndrome (acute inflammatory demyelinating polyradiculopathy subtype)</td>
</tr>
<tr>
<td>upper respiratory infection</td>
<td></td>
</tr>
<tr>
<td>Rash on palms and soles</td>
<td>Coxsackie A, 2° syphilis, Rocky Mountain spotted fever</td>
</tr>
<tr>
<td>Recurrent cold (noninflamed) abscesses, unusual eczema,</td>
<td>Hyper-IgE syndrome (Job syndrome: neutrophil chemotaxis abnormality)</td>
</tr>
<tr>
<td>high serum IgE</td>
<td></td>
</tr>
<tr>
<td>Red “currant jelly” sputum in alcoholic or diabetic</td>
<td>Klebsiella pneumoniae pneumonia</td>
</tr>
<tr>
<td>patients</td>
<td></td>
</tr>
<tr>
<td>Red “currant jelly” stools</td>
<td>Acute mesenteric ischemia (adults), intussusception (children)</td>
</tr>
<tr>
<td>Red, itchy, swollen rash of nipple/areola</td>
<td>Paget disease of the breast (sign of underlying neoplasm)</td>
</tr>
<tr>
<td>Red urine in the morning, fragile</td>
<td>Paroxysmal nocturnal hemoglobinuria</td>
</tr>
<tr>
<td>Renal cell carcinoma (bilateral), angiomatosis,</td>
<td>von Hippel-Lindau disease (dominant tumor suppressor gene mutation)</td>
</tr>
<tr>
<td>angiomatosis, pheochromocytoma</td>
<td></td>
</tr>
<tr>
<td>Resting tremor, rigidity, akinesia, postural instability,</td>
<td>Parkinson disease (loss of dopaminergic neurons in substantia nigra pars compacta)</td>
</tr>
<tr>
<td>shuffling gait</td>
<td></td>
</tr>
<tr>
<td>Retinal hemorrhages with pale centers</td>
<td>Roth spots (bacterial endocarditis)</td>
</tr>
<tr>
<td>Severe jaundice in neonate</td>
<td>Crigler-Najjar syndrome (congenital unconjugated hyperbilirubinemia)</td>
</tr>
<tr>
<td>Severe RLQ pain with palpation of LLQ</td>
<td>Rovsing sign (acute appendicitis)</td>
</tr>
<tr>
<td>Severe RLQ pain with rebound tenderness</td>
<td>McBurney sign (acute appendicitis)</td>
</tr>
<tr>
<td>Short stature, café au lait spots, 1 incidence of tumors</td>
<td>Fanconi anemia (genetic loss of DNA crosslink repair; often progresses to AML)</td>
</tr>
<tr>
<td>leukemia, aplastic anemia</td>
<td></td>
</tr>
<tr>
<td>Single palmar crease</td>
<td>Down syndrome</td>
</tr>
<tr>
<td>Situs inversus, chronic sinusitis, infertility</td>
<td>Kartagener syndrome (dynein arm defect affecting cilia)</td>
</tr>
<tr>
<td>Skin hyperpigmentation, hypotension, fatigue</td>
<td>1° adrenocortical insufficiency (e.g., Addison disease) causes 1 ACTH and 1 α-MSH production</td>
</tr>
<tr>
<td>Slow, progressive muscle weakness in boys</td>
<td>Becker muscular dystrophy (X-linked missense mutation in dystrophin; less severe than Duchenne)</td>
</tr>
</tbody>
</table>
### CLINICAL PRESENTATION

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small, irregular red spots on buccal/lingual mucosa with blue-white centers</td>
<td>Koplik spots (measles; rubeola virus)</td>
</tr>
<tr>
<td>Smooth, moist, painless, wart-like white lesions on genitals</td>
<td>Condylomata lata (2° syphilis)</td>
</tr>
<tr>
<td>Splinter hemorrhages in fingernails</td>
<td>Bacterial endocarditis</td>
</tr>
<tr>
<td>“Strawberry tongue”</td>
<td>Scarlet fever, Kawasaki disease</td>
</tr>
<tr>
<td>Streak ovaries, congenital heart disease, horseshoe kidney, cystic hygroma at birth, short stature, webbed neck, lymphedema</td>
<td>Turner syndrome (45,XO)</td>
</tr>
<tr>
<td>Sudden swollen/painful big toe joint, tophi</td>
<td>Gout/podagra (hyperuricemia)</td>
</tr>
<tr>
<td>Swollen gums, mucosal bleeding, poor wound healing, petechiae</td>
<td>Scurvy (vitamin C deficiency: can’t hydroxylate proline/lysine for collagen synthesis)</td>
</tr>
<tr>
<td>Swollen, hard, painful finger joints</td>
<td>Osteoarthritis (osteo-phytes on PIP [Bouchard nodes], DIP [Heberden nodes])</td>
</tr>
<tr>
<td>Systolic ejection murmur (crescendo-decrescendo)</td>
<td>Aortic stenosis</td>
</tr>
<tr>
<td>Telangiectasias, recurrent epistaxis, skin discoloration, arteriovenous malformations, CI bleeding, hematuria</td>
<td>Osler-Weber-Rendu syndrome</td>
</tr>
<tr>
<td>Thyroid and parathyroid tumors, pheochromocytoma</td>
<td>MEN 2A (autosomal dominant RET mutation)</td>
</tr>
<tr>
<td>Thyroid tumors, pheochromocytoma, ganglioneuromatosis</td>
<td>MEN 2B (autosomal dominant RET mutation)</td>
</tr>
<tr>
<td>Toe extension/fanning upon plantar scrape</td>
<td>Babinski sign (UMN lesion)</td>
</tr>
<tr>
<td>Unilateral facial drooping involving forehead</td>
<td>LMN facial nerve (CN VII) palsy; UMN lesions spare the forehead</td>
</tr>
<tr>
<td>Urethritis, conjunctivitis, arthritis in a male</td>
<td>Reactive arthritis associated with HLA-B27</td>
</tr>
<tr>
<td>Vascular birthmark (port-wine stain) of the face</td>
<td>Nevus flammeus (benign, but associated with Sturge-Weber syndrome)</td>
</tr>
<tr>
<td>Vomiting blood following gastroesophageal lacerations</td>
<td>Mallory-Weiss syndrome (alcoholic and bulimic patients)</td>
</tr>
<tr>
<td>Weight loss, diarrhea, arthritis, fever, adenopathy</td>
<td>Whipple disease (Tropheryma whipplei)</td>
</tr>
<tr>
<td>“Worst headache of my life”</td>
<td>Subarachnoid hemorrhage</td>
</tr>
</tbody>
</table>

### CLASSIC LABS/FINDINGS

<table>
<thead>
<tr>
<th>Laboratory Finding</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticentromere antibodies</td>
<td>Scleroderma (CREST)</td>
</tr>
<tr>
<td>Anti-desmoglein (epithelial) antibodies</td>
<td>Pemphigus vulgaris (blistering)</td>
</tr>
<tr>
<td>Anti–glomerular basement membrane antibodies</td>
<td>Goodpasture syndrome (glomerulonephritis and hemoptysis)</td>
</tr>
<tr>
<td>Antihistone antibodies</td>
<td>Drug-induced SLE (e.g., hydralazine,isoniazid,phenytoin,procaainamide)</td>
</tr>
<tr>
<td>Anti-IgG antibodies</td>
<td>Rheumatoid arthritis (systemic inflammation, joint pannus, boutonnière deformation)</td>
</tr>
<tr>
<td>Antimitochondrial antibodies (AMAs)</td>
<td>1° biliary cirrhosis (female, cholestasis, portal hypertension)</td>
</tr>
<tr>
<td>Antineutrophil cytoplasmic antibodies (ANCAs)</td>
<td>Microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) (MPO-ANCA/p-ANCA); granulomatosis with polyangiitis (Wegener, PR3-ANCA/c-ANCA)</td>
</tr>
<tr>
<td>LAB/DIAGNOSTIC FINDING</td>
<td>DIAGNOSIS/DISEASE</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Antinuclear antibodies (ANAs: anti-Smith and anti-dsDNA)</td>
<td>SLE (type III hypersensitivity)</td>
</tr>
<tr>
<td>Antiplatelet antibodies</td>
<td>Idiopathic thrombocytopenic purpura</td>
</tr>
<tr>
<td>Anti-topoisomerase antibodies</td>
<td>Diffuse systemic scleroderma</td>
</tr>
<tr>
<td>Anti-transglutaminase/anti-gliadin/anti-endomysial antibodies</td>
<td>Celiac disease (diabetes, weight loss)</td>
</tr>
<tr>
<td>“Apple core” lesion on barium enema x-ray</td>
<td>Colorectal cancer (usually left-sided)</td>
</tr>
<tr>
<td>Atypical lymphocytes</td>
<td>EBV</td>
</tr>
<tr>
<td>Azurophilic peroxidase⊕granular inclusions in granulocytes and myeloblasts</td>
<td>Auer rods (AML, especially the promyelocytic [M3] type)</td>
</tr>
<tr>
<td>Bacitracin response</td>
<td>Sensitive: <em>S. pyogenes</em> (group A); resistant: <em>S. agalactiae</em> (group B)</td>
</tr>
<tr>
<td>“Bamboo spine” on x-ray</td>
<td>Ankylosing spondylitis (chronic inflammatory arthritis: HLA-B27)</td>
</tr>
<tr>
<td>Basophilic nuclear remnants in RBCs</td>
<td>Howell-Jolly bodies (due to splenectomy or nonfunctional spleen)</td>
</tr>
<tr>
<td>Basophilic stippling of RBCs</td>
<td>Lead poisoning or sideroblastic anemia</td>
</tr>
<tr>
<td>Bloody or yellow tap on lumbar puncture</td>
<td>Subarachnoid hemorrhage</td>
</tr>
<tr>
<td>“Boot-shaped” heart on x-ray</td>
<td>Tetralogy of Fallot (due to RVH)</td>
</tr>
<tr>
<td>Branching gram-positive rods with sulfur granules</td>
<td>Actinomyces <em>israelii</em></td>
</tr>
<tr>
<td>Bronchogenic apical lung tumor on imaging</td>
<td>Pancoast tumor (can compress cervical sympathetic chain and cause Horner syndrome)</td>
</tr>
<tr>
<td>“Brown” tumor of bone</td>
<td>Hyperparathyroidism or osteitis fibrosa cystica (deposited hemosiderin from hemorrhage gives brown color)</td>
</tr>
<tr>
<td>Cardiomegaly with apical atrophy</td>
<td>Chagas disease (<em>Trypanosoma cruzi</em>)</td>
</tr>
<tr>
<td>Cellular crescents in Bowman capsule</td>
<td>Rapidly progressive crescentic glomerulonephritis</td>
</tr>
<tr>
<td>“Chocolate cyst” of ovary</td>
<td>Endometriosis (frequently involves both ovaries)</td>
</tr>
<tr>
<td>Circular grouping of dark tumor cells surrounding pale neurofibrils</td>
<td>Homer-Wright rosettes (neuroblastoma, medulloblastoma)</td>
</tr>
<tr>
<td>Colonies of mucoid <em>Pseudomonas</em> in lungs</td>
<td>Cystic fibrosis (autosomal recessive mutation in CFTR gene → fat-soluble vitamin deficiency and mucous plugs)</td>
</tr>
<tr>
<td>↓AFP in amniotic fluid/maternal serum</td>
<td>Down syndrome or other chromosomal abnormalities</td>
</tr>
<tr>
<td>Degeneration of dorsal column fibers</td>
<td>Tabes dorsalis (3rd syphilis), subacute combined degeneration (dorsal columns, lateral corticospinal, spino-cerebellar tracts affected)</td>
</tr>
<tr>
<td>“Delta wave” on EKG, short PR interval, supraventricular tachycardia</td>
<td>Wolf-Parkinson-White syndrome (Bundle of Kent bypasses AV node)</td>
</tr>
<tr>
<td>Depigmentation of neurons in substantia nigra</td>
<td>Parkinson disease (basal ganglia disorder: rigidity, resting tremor, bradykinesia)</td>
</tr>
<tr>
<td>Desquamated epithelium casts in sputum</td>
<td>Curschmann spirals (bronchial asthma; can result in whorled mucous plugs)</td>
</tr>
<tr>
<td>Disarrayed granulosa cells arranged around collections of eosinophilic fluid</td>
<td>Call-Exner bodies (granulosa cell tumor of the ovary)</td>
</tr>
<tr>
<td>Dysplastic squamous cervical cells with “raisinoid” nuclei and hyperchromasia</td>
<td>Koilocytes (HPV: predisposes to cervical cancer)</td>
</tr>
<tr>
<td>Lab/Diagnostic Finding</td>
<td>Diagnosis/Disease</td>
</tr>
<tr>
<td>------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Electrical alternans (alternating amplitude on EKG)</td>
<td>Pericardial tamponade</td>
</tr>
<tr>
<td>Enlarged cells with intranuclear inclusion bodies</td>
<td>“Owl eye” appearance of CMV</td>
</tr>
<tr>
<td>Enlarged thyroid cells with ground-glass nuclei with central clearing</td>
<td>“Orphan Annie” eyes nuclei (papillary carcinoma of the thyroid)</td>
</tr>
<tr>
<td>Eosinophilic cytoplasmic inclusion in liver cell</td>
<td>Mallory body (alcoholic liver disease)</td>
</tr>
<tr>
<td>Eosinophilic cytoplasmic inclusion in nerve cell</td>
<td>Lewy body (Parkinson disease)</td>
</tr>
<tr>
<td>Eosinophilic globule in liver</td>
<td>Councilman body (viral hepatitis, yellow fever), represents hepatocyte undergoing apoptosis</td>
</tr>
<tr>
<td>Eosinophilic inclusion bodies in cytoplasm of hippocampal and cerebellar neurons</td>
<td>Negri bodies of rabies</td>
</tr>
<tr>
<td>Extracellular amyloid deposition in gray matter of brain</td>
<td>Senile plaques (Alzheimer disease)</td>
</tr>
<tr>
<td>Giant B cells with bilobed nuclei with prominent inclusions (“owl’s eye”)</td>
<td>Reed-Sternberg cells (Hodgkin lymphoma)</td>
</tr>
<tr>
<td>Glomerulus-like structure surrounding vessel in germ cells</td>
<td>Schiller-Duval bodies (yolk sac tumor)</td>
</tr>
<tr>
<td>“Hair on end” (“Crew-cut”) appearance on x-ray</td>
<td>β-thalassemia, sickle cell disease (marrow expansion)</td>
</tr>
<tr>
<td>hCG elevated</td>
<td>Choriocarcinoma, hydatidiform mole (occurs with and without embryo, and multiple pregnancy)</td>
</tr>
<tr>
<td>Heart nodules (granulomatous)</td>
<td>Aschoff bodies (rheumatic fever)</td>
</tr>
<tr>
<td>Heterophile antibodies</td>
<td>Infectious mononucleosis (EBV)</td>
</tr>
<tr>
<td>Hexagonal, double-pointed, needle-like crystals in bronchial secretions</td>
<td>Bronchial asthma (Charcot-Leyden crystals: eosinophilic granules)</td>
</tr>
<tr>
<td>High level of D-dimers</td>
<td>DVT, PE, DIC</td>
</tr>
<tr>
<td>Hilar lymphadenopathy, peripheral granulomatous lesion in middle or lower lung lobes (can calcify)</td>
<td>Ghon complex (1° TB: Mycobacterium bacilli)</td>
</tr>
<tr>
<td>“Honeycomb lung” on x-ray or CT</td>
<td>Interstitial pulmonary fibrosis</td>
</tr>
<tr>
<td>Hypercoagulability (leading to migrating DVTs and vasculitis)</td>
<td>Trousseau syndrome (adenocarcinoma of pancreas or lung)</td>
</tr>
<tr>
<td>Hypersegmented neutrophils</td>
<td>Megaloblastic anemia (B12 deficiency: neurologic symptoms; folate deficiency: no neurologic symptoms)</td>
</tr>
<tr>
<td>Hypertension, hypokalemia, metabolic alkalosis</td>
<td>Conn syndrome (primary hyperaldosteronism)</td>
</tr>
<tr>
<td>Hypochromic, microcytic anemia</td>
<td>Iron deficiency anemia, lead poisoning, thalassemia (fetal hemoglobin sometimes present)</td>
</tr>
<tr>
<td>Increased AFP in amniotic fluid/maternal serum</td>
<td>Dating error, anencephaly, spina bifida (neural tube defects)</td>
</tr>
<tr>
<td>Increased uric acid levels</td>
<td>Gout, Lesch-Nyhan syndrome, tumor lysis syndrome, loop and thiazide diuretics</td>
</tr>
<tr>
<td>Intranuclear eosinophilic droplet-like bodies</td>
<td>Cowdry type A bodies (HSV or VZV)</td>
</tr>
<tr>
<td>Iron-containing nodules in alveolar septum</td>
<td>Ferruginous bodies (asbestosis: chance of mesothelioma)</td>
</tr>
<tr>
<td>Keratin pearls on a skin biopsy</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>Large granules in phagocytes, immunodeficiency</td>
<td>Chédiak-Higashi disease (congenital failure of phagolysosome formation)</td>
</tr>
<tr>
<td>“Lead pipe” appearance of colon on abdominal imaging</td>
<td>Ulcerative colitis (loss of haustra)</td>
</tr>
<tr>
<td>Linear appearance of IgG deposition on glomerular and alveolar basement membranes</td>
<td>Goodpasture syndrome</td>
</tr>
</tbody>
</table>
### Table: Classic Labs/Findings

<table>
<thead>
<tr>
<th>Lab/Diagnostic Finding</th>
<th>Diagnosis/Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low serum ceruloplasmin</td>
<td>Wilson disease (hepatolenticular degeneration)</td>
</tr>
<tr>
<td>“Lumpy bumpy” appearance of glomeruli on</td>
<td>Poststreptococcal glomerulonephritis (due to deposition of IgG, IgM, and C3)</td>
</tr>
<tr>
<td>immunofluorescence</td>
<td></td>
</tr>
<tr>
<td>Lytic (“punched-out”) bone lesions on x-ray</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Mammary gland (“blue domed”) cyst</td>
<td>Fibrocystic change of the breast</td>
</tr>
<tr>
<td>Monoclonal antibody spike **</td>
<td>Multiple myeloma (usually IgG or IgA)</td>
</tr>
<tr>
<td></td>
<td>Monoclonal gammopathy of undetermined significance (MGUS consequence of aging)</td>
</tr>
<tr>
<td></td>
<td>Waldenström (M protein = IgM) macroglobulinemia</td>
</tr>
<tr>
<td></td>
<td>Primary amyloidosis</td>
</tr>
<tr>
<td>Mucin-filled cell with peripheral nucleus</td>
<td>“Signet ring” (gastric carcinoma)</td>
</tr>
<tr>
<td>Narrowing of bowel lumen on barium x-ray</td>
<td>“String sign” (Crohn disease)</td>
</tr>
<tr>
<td>Necrotizing vasculitis (lungs) and necrotizing</td>
<td>Granulomatosis with polyangiitis (Wegener, PR3-ANCA/c-ANCA) and Goodpasture</td>
</tr>
<tr>
<td>glomerulonephritis</td>
<td>syndrome (anti–basement membrane antibodies)</td>
</tr>
<tr>
<td>Needle-shaped, negatively birefringent crystals</td>
<td>Gout (monosodium urate crystals)</td>
</tr>
<tr>
<td>Nodular hyaline deposits in glomeruli</td>
<td>Kimmelstiel-Wilson nodules (diabetic nephropathy)</td>
</tr>
<tr>
<td>Novobiocin response</td>
<td>Sensitive: <em>S. epidermidis</em>; resistant: <em>S. saprophyticus</em></td>
</tr>
<tr>
<td>“Nutmeg” appearance of liver</td>
<td>Chronic passive congestion of liver due to right heart failure or Budd-Chiari</td>
</tr>
<tr>
<td>“Onion skin” periosteal reaction</td>
<td>syndrome</td>
</tr>
<tr>
<td>Optochin response</td>
<td>Ewing sarcoma (malignant small blue cell tumor)</td>
</tr>
<tr>
<td>Periosteum raised from bone, creating triangular</td>
<td>Codman triangle on x-ray, Ewing sarcoma, pyogenic osteomyelitis</td>
</tr>
<tr>
<td>area</td>
<td></td>
</tr>
<tr>
<td>Podocyte fusion or “effacement” on electron</td>
<td>Minimal change disease (child with nephrotic syndrome)</td>
</tr>
<tr>
<td>microscopy</td>
<td></td>
</tr>
<tr>
<td>Polished, “ivory-like” appearance of bone at</td>
<td>Ehburnation (osteoarthritis resulting in bony sclerosis)</td>
</tr>
<tr>
<td>cartilage erosion</td>
<td></td>
</tr>
<tr>
<td>Protein aggregates in neurons from</td>
<td>Neurofibrillary tangles (Alzheimer disease) and Pick bodies (Pick disease)</td>
</tr>
<tr>
<td>hyperphosphorylation of tau protein</td>
<td></td>
</tr>
<tr>
<td>Psammoma bodies</td>
<td>Meningiomas, papillary thyroid carcinoma, mesothelioma, papillary serous carcinoma</td>
</tr>
<tr>
<td>of neurons</td>
<td>of the endometrium and ovary</td>
</tr>
<tr>
<td>Pseudopalisading tumor cells on brain biopsy</td>
<td>Glioblastoma multiforme</td>
</tr>
<tr>
<td>RBC casts in urine</td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Rectangular, crystal-like, cytoplasmic</td>
<td>Reinke crystals (Leydig cell tumor)</td>
</tr>
<tr>
<td>inclusions in Leydig cells</td>
<td></td>
</tr>
<tr>
<td>Recurrent infections, eczema,</td>
<td>Wiskott-Aldrich syndrome</td>
</tr>
<tr>
<td>thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>Renal epithelial casts in urine</td>
<td>Intrinsic renal failure (e.g., ischemia or toxic injury)</td>
</tr>
<tr>
<td>Rhomboid crystals, positively birefringent</td>
<td></td>
</tr>
<tr>
<td>Rib notching</td>
<td>Pseudogout (calcium pyrophosphate dihydrate crystals)</td>
</tr>
<tr>
<td>Ring-enhancing brain lesion in AIDS</td>
<td>Coarctation of the aorta</td>
</tr>
<tr>
<td>Sheets of medium-sized lymphoid cells with</td>
<td>Toxoplasma gondii, CNS lymphoma</td>
</tr>
<tr>
<td>scattered pale, tingible body–laden</td>
<td></td>
</tr>
<tr>
<td>macrophages (“starry sky” histology)</td>
<td></td>
</tr>
<tr>
<td>Silver-staining spherical aggregation of tau</td>
<td>Pick bodies (Pick disease: progressive dementia, changes in personality)</td>
</tr>
<tr>
<td>proteins in neurons</td>
<td></td>
</tr>
<tr>
<td>LAB/DIAGNOSTIC FINDING</td>
<td>DIAGNOSIS/DISEASE</td>
</tr>
<tr>
<td>------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>“Soap bubble” in femur or tibia on x-ray</td>
<td>Giant cell tumor of bone (generally benign)</td>
</tr>
<tr>
<td>“Spikes” on basement membrane, “dome-like” subepithelial deposits</td>
<td>Membranous nephropathy (nephrotic syndrome)</td>
</tr>
<tr>
<td>Stacks of RBCs</td>
<td>Rouleaux formation (high ESR, multiple myeloma)</td>
</tr>
<tr>
<td>“Steeple” sign on CXR</td>
<td>Group (parainfluenza virus)</td>
</tr>
<tr>
<td>Stippled vaginal epithelial cells</td>
<td>“Clue cells” (Gardnerella vaginalis)</td>
</tr>
<tr>
<td>Streptococcus bovis bacteremia</td>
<td>Colon cancer</td>
</tr>
<tr>
<td>“Tennis racket”-shaped cytoplasmic organelles (EM) in Langerhans cells</td>
<td>Birbeck granules (Langerhans cell histiocytosis)</td>
</tr>
<tr>
<td>Thousands of polyps on colonoscopy</td>
<td>Familial adenomatous polyposis (autosomal dominant, mutation of APC gene)</td>
</tr>
<tr>
<td>Thrombi made of white/red layers</td>
<td>Lines of Zahn (arterial thrombus, layers of platelets/RBCs)</td>
</tr>
<tr>
<td>“Thumb sign” on lateral neck x-ray</td>
<td>Epiglottitis (Haemophilus influenzae)</td>
</tr>
<tr>
<td>Thyroid-like appearance of kidney</td>
<td>Chronic pyelonephritis (usually due to recurrent infections)</td>
</tr>
<tr>
<td>“Tram-track” appearance of capillary loops of glomerular basement membranes on light microscopy</td>
<td>Membranoproliferative glomerulonephritis</td>
</tr>
<tr>
<td>Triglyceride accumulation in liver cell vacuoles</td>
<td>Fatty liver disease (alcoholic or metabolic syndrome)</td>
</tr>
<tr>
<td>“Waxy” casts with very low urine flow</td>
<td>Chronic end-stage renal disease</td>
</tr>
<tr>
<td>WBC casts in urine</td>
<td>Acute pyelonephritis</td>
</tr>
<tr>
<td>WBCs that look “smudged”</td>
<td>CLL (almost always B cell)</td>
</tr>
<tr>
<td>“Wire loop” glomerular capillary appearance on light microscopy</td>
<td>Diffuse proliferative glomerulonephritis (usually seen with lupus)</td>
</tr>
<tr>
<td>Yellowish CSF</td>
<td>Xanthochromia (e.g., due to subarachnoid hemorrhage)</td>
</tr>
</tbody>
</table>

### CLASSIC/RELEVANT TREATMENTS

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>COMMON TREATMENT(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence seizures</td>
<td>Ethosuximide</td>
</tr>
<tr>
<td>Acute gout attack</td>
<td>NSAIDs, colchicine, glucocorticoids</td>
</tr>
<tr>
<td>Acute promyelocytic leukemia (M3)</td>
<td>All-trans retinoic acid</td>
</tr>
<tr>
<td>ADHD</td>
<td>Methylphenidate, CBT, atomoxetine</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>Disulfiram, acamprosate, naltrexone, supportive care</td>
</tr>
<tr>
<td>Alcohol withdrawal</td>
<td>Long-acting benzodiazepines</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Nutrition, psychotherapy, mirtazapine</td>
</tr>
<tr>
<td>Anticoagulation during pregnancy</td>
<td>Heparin</td>
</tr>
<tr>
<td>Arrhythmia in damaged cardiac tissue</td>
<td>Class IB antiarrhythmic (lidocaine, mexiletine)</td>
</tr>
<tr>
<td>B12 deficiency</td>
<td>Vitamin B12 supplementation (work up cause with Schilling test)</td>
</tr>
<tr>
<td>Benign prostatic hyperplasia</td>
<td>α1-antagonists, 5α-reductase inhibitors, PDE-5 inhibitors</td>
</tr>
<tr>
<td>CONDITION</td>
<td>COMMON TREATMENT(S)</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>Mood stabilizers (e.g., lithium, valproic acid, carbamazepine), atypical antipsychotics</td>
</tr>
<tr>
<td>Breast cancer in postmenopausal woman</td>
<td>Aromatase inhibitor (anastrozole)</td>
</tr>
<tr>
<td>Buerger disease</td>
<td>Smoking cessation</td>
</tr>
<tr>
<td>Bulimia nervosa</td>
<td>SSRIs</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>Topical azoles (vaginitis); nystatin, fluconazole, caspofungin (oral/esophageal); fluconazole, caspofungin, amphotericin B (systemic)</td>
</tr>
<tr>
<td>Carcinoid syndrome</td>
<td>Octreotide</td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td>Doxycycline (+ ceftriaxone for gonorrhea coinfection), erythromycin eye drops (prophylaxis in infants)</td>
</tr>
<tr>
<td>Chronic gout</td>
<td>Xanthine oxidase inhibitors (e.g., allopurinol, febuxostat)</td>
</tr>
<tr>
<td>Chronic hepatitis B or C</td>
<td>IFN-α (HBV and HCV); ribavirin, sofosbuvir, peginterferon (HCV)</td>
</tr>
<tr>
<td>Chronic myelogenous leukemia</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Clostridium botulinum</td>
<td>Antitoxin</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>Oral metronidazole; if refractory, oral vancomycin</td>
</tr>
<tr>
<td>Clostridium tetani</td>
<td>Antitoxin</td>
</tr>
<tr>
<td>CMV</td>
<td>Ganciclovir, foscarnet, cidofovir</td>
</tr>
<tr>
<td>Crohn disease</td>
<td>Corticosteroids, infliximab, azathioprine</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>Fluconazole (in AIDS patients)</td>
</tr>
<tr>
<td>Cyclophosphamide-induced hemorrhagic cystitis</td>
<td>Mesna</td>
</tr>
<tr>
<td>Depression</td>
<td>SSRIs (first-line)</td>
</tr>
<tr>
<td>Diabetes insipidius</td>
<td>Desmopressin (central); hydrochlorothiazide, indomethacin, amiloride (nephrogenic)</td>
</tr>
<tr>
<td>Diabetes mellitus type 1</td>
<td>Dietary intervention (low carbohydrate) + insulin replacement</td>
</tr>
<tr>
<td>Diabetes mellitus type 2</td>
<td>Dietary intervention, oral hypoglycemics, and insulin (if refractory)</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>Fluids, insulin, K⁺</td>
</tr>
<tr>
<td>Enterococci</td>
<td>Vancomycin, aminopenicillins/cephalosporins</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>Sildenafil, tadalaafil, vardenafil</td>
</tr>
<tr>
<td>ER + breast cancer</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>Ethylene glycol/methanol intoxication</td>
<td>Fomepizole (alcohol dehydrogenase inhibitor)</td>
</tr>
<tr>
<td>Haemophilus influenzae (B)</td>
<td>Rifampin (prophylaxis)</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>SSRIs, SNRIs (first line); buspirone (second line)</td>
</tr>
<tr>
<td>Granulomatosis with polyangiitis (Wegener)</td>
<td>Cyclophosphamide, corticosteroids</td>
</tr>
<tr>
<td>Heparin reversal</td>
<td>Protamine sulfate</td>
</tr>
<tr>
<td>HER2/neu + breast cancer</td>
<td>Trastuzumab</td>
</tr>
<tr>
<td>Hyperaldosteronism</td>
<td>Spironolactone</td>
</tr>
<tr>
<td>CONDITION</td>
<td>COMMON TREATMENT(S)</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>Statin (first-line)</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>Fibrate</td>
</tr>
<tr>
<td>Immediate anticoagulation</td>
<td>Heparin</td>
</tr>
<tr>
<td>Infertility</td>
<td>Leuprolide, GnRH (pulsatile), clomiphene</td>
</tr>
<tr>
<td>Influenza</td>
<td>Oseltamivir, zanamivir</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>IVIG, high-dose aspirin</td>
</tr>
<tr>
<td><em>Legionella pneumophila</em></td>
<td>Macrolides (e.g., azithromycin)</td>
</tr>
<tr>
<td>Long-term anticoagulation</td>
<td>Warfarin, dabigatran, rivaroxaban and apixaban</td>
</tr>
<tr>
<td>Malaria</td>
<td>Chloroquine, mefloquine, atovaquone/proguanil (for blood schizont), primaquine (for liver hypnozoite)</td>
</tr>
<tr>
<td>Malignant hyperthermia</td>
<td>Dantrolene</td>
</tr>
<tr>
<td>Medical abortion</td>
<td>Mifepristone</td>
</tr>
<tr>
<td>Migraine</td>
<td>Abortive therapies (e.g., sumatriptan, NSAIDs); prophylaxis (e.g., propranolol, topiramate, CCBs, amitriptyline)</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Disease-modifying therapies (e.g., β-interferon, Natalizumab); for acute flares, use IV steroids</td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosi</em></td>
<td>RIPE (rifampin, isoniazid, pyrazinamide, ethambutol)</td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td>Ceftriaxone (add doxycycline to cover likely concurrent <em>C. trachomatis</em>)</td>
</tr>
<tr>
<td><em>Neisseria meningitidis</em></td>
<td>Penicillin/ceftriaxone, rifampin (prophylaxis)</td>
</tr>
<tr>
<td>Neural tube defect prevention</td>
<td>Prenatal folic acid</td>
</tr>
<tr>
<td>Osteomalacia/rickets</td>
<td>Vitamin D supplementation</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Calcium/vitamin D supplementation (prophylaxis); bisphosphonates, PTH analogs, SERMs, calcitonin, denosumab (treatment)</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>Close with indomethacin; open or maintain with PGE analogs</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>α-antagonists (e.g., phenoxybenzamine)</td>
</tr>
<tr>
<td><em>Pneumocystis jiroveci</em></td>
<td>TMP-SMX (prophylaxis in AIDS patient)</td>
</tr>
<tr>
<td>Prolactinoma</td>
<td>Cabergoline/bromocriptine (dopamine agonists)</td>
</tr>
<tr>
<td>Prostate adenocarcinoma/uterine fibroids</td>
<td>Leuprolide, GnRH (continuous)</td>
</tr>
<tr>
<td>Prostate adenocarcinoma</td>
<td>Flutamide</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Antipseudomonal penicillins, aminoglycosides, carbapenems</td>
</tr>
<tr>
<td>Pulmonary arterial hypertension (idiopathic)</td>
<td>Sildenafil, bosentan, epoprostenol</td>
</tr>
<tr>
<td><em>Rickettsia rickettsii</em></td>
<td>Doxycycline, chloramphenicol</td>
</tr>
<tr>
<td>Schizophrenia (negative symptoms)</td>
<td>Atypical antipsychotics</td>
</tr>
<tr>
<td>Schizophrenia (positive symptoms)</td>
<td>Typical and atypical antipsychotics</td>
</tr>
<tr>
<td>SIADH</td>
<td>Fluid restriction, IV hypertonic saline, conivaptan/tolvaptan, demeclocycline</td>
</tr>
</tbody>
</table>
### SECTION III

#### Rapid Review

### Key Associations

<table>
<thead>
<tr>
<th>Condition</th>
<th>Common Treatment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle cell disease</td>
<td>Hydroxyurea (↑ fetal hemoglobin)</td>
</tr>
<tr>
<td><em>Sporothrix schenckii</em></td>
<td>Itraconazole, oral potassium iodide</td>
</tr>
<tr>
<td>Stable angina</td>
<td>Sublingual nitroglycerin</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>MSSA: nafcillin, oxacillin, dicloxacillin (antistaphylococcal penicillins); MRSA: vancomycin, daptomycin, linezolid, ceftaroline</td>
</tr>
<tr>
<td><em>Streptococcus bovis</em></td>
<td>Penicillin prophylaxis; evaluation for colon cancer if linked to endocarditis</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Penicillin/cephalosporin (systemic infection, pneumonia), vancomycin (meningitis)</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>Penicillin prophylaxis</td>
</tr>
<tr>
<td>Temporal arteritis</td>
<td>High-dose steroids</td>
</tr>
<tr>
<td>Tonic-clonic seizures</td>
<td>Levetiracetam, phenytoin, valproate, carbamazepine</td>
</tr>
<tr>
<td><em>Toxoplasma gondii</em></td>
<td>Sulfadiazine + pyrimethamine</td>
</tr>
<tr>
<td>Trichomonas vaginalis</td>
<td>Penicillin</td>
</tr>
<tr>
<td>Trigeminal neuralgia (tic douloureux)</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>5-ASA preparations (e.g., mesalamine), 6-mercaptopurine, infliximab, colectomy</td>
</tr>
<tr>
<td>UTI prophylaxis</td>
<td>TMP-SMX</td>
</tr>
<tr>
<td>Warfarin reversal</td>
<td>Fresh frozen plasma (acute), vitamin K (chronic)</td>
</tr>
</tbody>
</table>

#### Key Associations

<table>
<thead>
<tr>
<th>Disease/Finding</th>
<th>Most Common/Important Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinic (solar) keratosis</td>
<td>Precursor to squamous cell carcinoma</td>
</tr>
<tr>
<td>Acute gastric ulcer associated with CNS injury</td>
<td>Cushing ulcer (↑ intracranial pressure stimulates vagal gastric H+ secretion)</td>
</tr>
<tr>
<td>Acute gastric ulcer associated with severe burns</td>
<td>Curling ulcer (greatly reduced plasma volume results in sloughing of gastric mucosa)</td>
</tr>
<tr>
<td>Alternating areas of transmural inflammation and normal colon</td>
<td>Skip lesions (Crohn disease)</td>
</tr>
<tr>
<td>Aortic aneurysm, abdominal</td>
<td>Atherosclerosis</td>
</tr>
<tr>
<td>Aortic aneurysm, ascending or arch</td>
<td>3rd syphilis (syphilitic aortitis), vasa vasorum destruction</td>
</tr>
<tr>
<td>Aortic aneurysm, thoracic</td>
<td>Marfan syndrome (idiopathic cystic medial degeneration)</td>
</tr>
<tr>
<td>Aortic dissection</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Atrophy of the mammillary bodies</td>
<td>Wernicke encephalopathy (thiamine deficiency causing ataxia, ophthalmoplegia, and confusion)</td>
</tr>
<tr>
<td>Autosplenectomy (fibrosis and shrinkage)</td>
<td>Sickle cell disease (hemoglobin S)</td>
</tr>
<tr>
<td>DISEASE/FINDING</td>
<td>MOST COMMON/IMPORTANT ASSOCIATIONS</td>
</tr>
<tr>
<td>----------------</td>
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</tr>
<tr>
<td>Bacteria associated with gastritis, peptic ulcer disease, and stomach cancer</td>
<td><em>H. pylori</em></td>
</tr>
<tr>
<td>Bacterial meningitis (adults and elderly)</td>
<td><em>S. pneumoniae</em></td>
</tr>
<tr>
<td>Bacterial meningitis (newborns and kids)</td>
<td>Group B streptococcus/ <em>E. coli</em> (newborns), <em>S. pneumoniae/N. meningitidis</em> (kids/teens)</td>
</tr>
<tr>
<td>Bilateral ovarian metastases from gastric carcinoma</td>
<td>Krukenberg tumor (mucin-secreting signet ring cells)</td>
</tr>
<tr>
<td>Bleeding disorder with GpIb deficiency</td>
<td>Bernard-Soulier syndrome (defect in platelet adhesion to von Willebrand factor)</td>
</tr>
<tr>
<td>Brain tumor (adults)</td>
<td>Supratentorial: metastasis, astrocytoma (including glioblastoma multiforme), meningioma, schwannoma</td>
</tr>
<tr>
<td>Brain tumor (kids)</td>
<td>Infratentorial: medulloblastoma (cerebellum) or supratentorial: craniopharyngioma</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Invasive ductal carcinoma</td>
</tr>
<tr>
<td>Breast mass</td>
<td>Fibrocytic change, carcinoma (in postmenopausal women)</td>
</tr>
<tr>
<td>Breast tumor (benign)</td>
<td>Fibroadenoma</td>
</tr>
<tr>
<td>Cardiac 1° tumor (kids)</td>
<td>Rhabdomyoma, often seen in tuberous sclerosis</td>
</tr>
<tr>
<td>Cardiac manifestation of lupus</td>
<td>Marantic/thrombotic endocarditis (nonbacterial)</td>
</tr>
<tr>
<td>Cardiac tumor (adults)</td>
<td>Metastasis, myxoma (90% in left atrium; “ball and valve”)</td>
</tr>
<tr>
<td>Cerebellar tonsillar herniation</td>
<td>Chiari II malformation</td>
</tr>
<tr>
<td>Chronic arrhythmia</td>
<td>Atrial fibrillation (associated with high risk of emboli)</td>
</tr>
<tr>
<td>Chronic atrophic gastritis (autoimmune)</td>
<td>Predisposition to gastric carcinoma (can also cause pernicious anemia)</td>
</tr>
<tr>
<td>Clear cell adenocarcinoma of the vagina</td>
<td>DES exposure in utero</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia, hypotension</td>
<td>21-hydroxylase deficiency</td>
</tr>
<tr>
<td>Congenital cardiac anomaly</td>
<td>VSD</td>
</tr>
<tr>
<td>Congenital conjugated hyperbilirubinemia (black liver)</td>
<td>Dubin-Johnson syndrome (inability of hepatocytes to secrete conjugated bilirubin into bile)</td>
</tr>
<tr>
<td>Constrictive pericarditis</td>
<td>TB (developing world); idiopathic, viral illness (developed world)</td>
</tr>
<tr>
<td>Coronary artery involved in thrombosis</td>
<td>LAD &gt; RCA &gt; circumflex</td>
</tr>
<tr>
<td>Cretinism</td>
<td>Iodine deficit/congenital hypothyroidism</td>
</tr>
</tbody>
</table>
| Cushing syndrome | * Iatrogenic (from corticosteroid therapy)  
* Adrenocortical adenoma (secretes excess cortisol)  
* ACTH-secreting pituitary adenoma (Cushing disease)  
* Paraneoplastic (due to ACTH secretion by tumors) |
<p>| Cyanosis (early; less common) | Tetralogy of Fallot, transposition of great vessels, truncus arteriosus |
| Cyanosis (late; more common) | VSD, ASD, PDA |
| Death in CML | Blast crisis |
| Death in SLE | Lupus nephropathy |</p>
<table>
<thead>
<tr>
<th>DISEASE/FINDING</th>
<th>MOST COMMON/IMPORTANT ASSOCIATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia</td>
<td>Alzheimer disease, multiple infarcts (vascular dementia)</td>
</tr>
<tr>
<td>Demyelinating disease in young women</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>DIC</td>
<td>Severe sepsis, obstetric complications, cancer, burns, trauma, major surgery</td>
</tr>
<tr>
<td>Dietary deficit</td>
<td>Iron</td>
</tr>
<tr>
<td>Diverticulum in pharynx</td>
<td>Zenker diverticulum (diagnosed by barium swallow)</td>
</tr>
<tr>
<td>Ejection click</td>
<td>Aortic stenosis</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>Squamous cell carcinoma (worldwide); adenocarcinoma (U.S.)</td>
</tr>
<tr>
<td>Food poisoning (exotoxin mediated)</td>
<td><em>S. aureus, B. cereus</em></td>
</tr>
<tr>
<td>Glomerulonephritis (adults)</td>
<td>Berger disease (IgA nephropathy)</td>
</tr>
<tr>
<td>Gynecologic malignancy</td>
<td>Endometrial carcinoma (most common in U.S.); cervical carcinoma (most common worldwide)</td>
</tr>
<tr>
<td>Heart murmur, congenital</td>
<td>Mitral valve prolapse</td>
</tr>
<tr>
<td>Heart valve in bacterial endocarditis</td>
<td>Mitral &gt; aortic (rheumatic fever), tricuspid (IV drug abuse)</td>
</tr>
<tr>
<td>Helminth infection (U.S.)</td>
<td><em>Enterobius vermicularis, Ascaris lumbricoides</em></td>
</tr>
<tr>
<td>Hematoma—epidural</td>
<td>Rupture of middle meningeal artery (trauma; lentiform shaped)</td>
</tr>
<tr>
<td>Hematoma—subdural</td>
<td>Rupture of bridging veins (crescent shaped)</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Multiple blood transfusions or hereditary HFE mutation (can result in heart failure, “bronze diabetes,” and ↑ risk of hepatocellular carcinoma)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>Cirrhotic liver (associated with hepatitis B and C and with alcoholism)</td>
</tr>
<tr>
<td>Hereditary bleeding disorder</td>
<td>von Willebrand disease</td>
</tr>
<tr>
<td>Hereditary harmless jaundice</td>
<td>Gilbert syndrome (benign congenital unconjugated hyperbilirubinemia)</td>
</tr>
<tr>
<td>HLA-B27</td>
<td>Ankylosing spondylitis, reactive arthritis, ulcerative colitis, psoriatic arthritis</td>
</tr>
<tr>
<td>HLA-DR3</td>
<td>Diabetes mellitus type 1, SLE, Graves disease, Hashimoto thyroiditis</td>
</tr>
<tr>
<td>HLA-DR4</td>
<td>Diabetes mellitus type 1, rheumatoid arthritis</td>
</tr>
<tr>
<td>Holosystolic murmur</td>
<td>VSD, tricuspid regurgitation, mitral regurgitation</td>
</tr>
<tr>
<td>Hypercoagulability, endothelial damage, blood stasis</td>
<td>Virchow triad (↑ risk of thrombosis)</td>
</tr>
<tr>
<td>Hypertension, 2°</td>
<td>Renal disease</td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>Accidental excision during thyroidectomy</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>Pituitary adenoma (usually benign tumor)</td>
</tr>
<tr>
<td>Infection 2° to blood transfusion</td>
<td>Hepatitis C</td>
</tr>
<tr>
<td>Infections in chronic granulomatous disease</td>
<td><em>S. aureus, E. coli, Aspergillus</em> (catalase ⊕)</td>
</tr>
<tr>
<td>Intellectual disability</td>
<td>Down syndrome, fragile X syndrome</td>
</tr>
<tr>
<td>Disease/Finding</td>
<td>Most Common/Important Associations</td>
</tr>
<tr>
<td>-----------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Kidney stones</td>
<td>- Calcium = radiopaque&lt;br&gt;- Struvite (ammonium) = radiopaque (formed by urease&lt;br&gt; ⊕ organisms such as <em>Klebsiella, Proteus</em> species, and <em>S. saprophyticus</em>)&lt;br&gt;- Uric acid = radiolucent</td>
</tr>
<tr>
<td>Late cyanotic shunt (uncorrected left to right becomes right to left)</td>
<td>Eisenmenger syndrome (caused by ASD, VSD, PDA; results in pulmonary hypertension/polycythemia)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Alcoholic cirrhosis</td>
</tr>
<tr>
<td>Lysosomal storage disease</td>
<td>Gaucher disease</td>
</tr>
<tr>
<td>Male cancer</td>
<td>Prostatic carcinoma</td>
</tr>
<tr>
<td>Malignancy associated with noninfectious fever</td>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td>Malignancy (kids)</td>
<td>ALL, medulloblastoma (cerebellum)</td>
</tr>
<tr>
<td>Metastases to bone</td>
<td>Prostate, breast &gt; lung &gt; thyroid</td>
</tr>
<tr>
<td>Metastases to brain</td>
<td>Lung &gt; breast &gt; genitourinary &gt; melanoma &gt; GI</td>
</tr>
<tr>
<td>Metastases to liver</td>
<td>Colon &gt;&gt; stomach, pancreas</td>
</tr>
<tr>
<td>Mitochondrial inheritance</td>
<td>Disease occurs in both males and females, inherited through females only</td>
</tr>
<tr>
<td>Mitral valve stenosis</td>
<td>Rheumatic heart disease</td>
</tr>
<tr>
<td>Mixed (UMN and LMN) motor neuron disease</td>
<td>Amyotrophic lateral sclerosis</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Coxsackie B</td>
</tr>
<tr>
<td>Nephrotic syndrome (adults)</td>
<td>Focal segmental glomerulosclerosis</td>
</tr>
<tr>
<td>Nephrotic syndrome (kids)</td>
<td>Minimal change disease</td>
</tr>
<tr>
<td>Neuron migration failure</td>
<td>Kallmann syndrome (hypogonadotropic hypogonadism and anosmia)</td>
</tr>
<tr>
<td>Nosocomial pneumonia</td>
<td><em>S. aureus, Pseudomonas,</em> other enteric gram-negative rods</td>
</tr>
<tr>
<td>Obstruction of male urinary tract</td>
<td>BPH</td>
</tr>
<tr>
<td>Opening snap</td>
<td>Mitral stenosis</td>
</tr>
<tr>
<td>Opportunistic infection in AIDS</td>
<td><em>Pneumocystis jirovecii</em> pneumonia</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td><em>S. aureus</em> (most common overall)</td>
</tr>
<tr>
<td>Osteomyelitis in sickle cell disease</td>
<td><em>Salmonella</em></td>
</tr>
<tr>
<td>Osteomyelitis with IV drug use</td>
<td><em>Pseudomonas, Candida, S. aureus</em></td>
</tr>
<tr>
<td>Ovarian tumor (benign, bilateral)</td>
<td>Serous cystadenoma</td>
</tr>
<tr>
<td>Ovarian tumor (malignant)</td>
<td>Serous cystadenocarcinoma</td>
</tr>
<tr>
<td>Pancreatitis (acute)</td>
<td>Gallstones, alcohol</td>
</tr>
<tr>
<td>Pancreatitis (chronic)</td>
<td>Alcohol (adults), cystic fibrosis (kids)</td>
</tr>
<tr>
<td>Pelvic inflammatory disease</td>
<td><em>C. trachomatis, N. gonorrhoeae</em></td>
</tr>
<tr>
<td>Philadelphia chromosome t(9;22) (BCR-ABL)</td>
<td>CML (may sometimes be associated with ALL/AML)</td>
</tr>
<tr>
<td>Pituitary tumor</td>
<td>Prolactinoma, somatotropic adenoma</td>
</tr>
<tr>
<td>1° amenorrhea</td>
<td>Turner syndrome (45,XO)</td>
</tr>
</tbody>
</table>
### Section III

<table>
<thead>
<tr>
<th>Disease/Finding</th>
<th>Most Common/Important Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° bone tumor (adults)</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>1° hyperaldosteronism</td>
<td>Adenoma of adrenal cortex</td>
</tr>
<tr>
<td>1° hyperparathyroidism</td>
<td>Adenomas, hyperplasia, carcinoma</td>
</tr>
<tr>
<td>1° liver cancer</td>
<td>Hepatocellular carcinoma (chronic hepatitis, cirrhosis, hemochromatosis, α1-antitrypsin deficiency, Wilson disease)</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>COPD</td>
</tr>
<tr>
<td>Recurrent inflammation/thrombosis of small/medium vessels in extremities</td>
<td>Buerger disease (strongly associated with tobacco)</td>
</tr>
<tr>
<td>Renal tumor</td>
<td>Renal cell carcinoma: associated with von Hippel-Lindau and cigarette smoking; paraneoplastic syndromes (EPO, renin, PTHrP, ACTH)</td>
</tr>
<tr>
<td>Right heart failure due to a pulmonary cause</td>
<td>Cor pulmonale</td>
</tr>
<tr>
<td>S3 heart sound</td>
<td>↑ ventricular filling pressure (e.g., mitral regurgitation, HF), common in dilated ventricles</td>
</tr>
<tr>
<td>S4 heart sound</td>
<td>Stiff/hypertrophic ventricle (aortic stenosis, restrictive cardiomyopathy)</td>
</tr>
<tr>
<td>2° hyperparathyroidism</td>
<td>Hypocalcemia of chronic kidney disease</td>
</tr>
<tr>
<td>Sexually transmitted disease</td>
<td>C. trachomatis (usually coinfected with N. gonorrhoeae)</td>
</tr>
<tr>
<td>SIADH</td>
<td>Small cell carcinoma of the lung</td>
</tr>
<tr>
<td>Site of diverticula</td>
<td>Sigmoid colon</td>
</tr>
<tr>
<td>Sites of atherosclerosis</td>
<td>Abdominal aorta &gt; coronary artery &gt; popliteal artery &gt; carotid artery</td>
</tr>
<tr>
<td>Stomach cancer</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Stomach ulcerations and high gastrin levels</td>
<td>Zollinger-Ellison syndrome (gastrinoma of duodenum or pancreas)</td>
</tr>
<tr>
<td>t(14;18)</td>
<td>Follicular lymphomas (BCL-2 activation, anti-apoptotic oncogene)</td>
</tr>
<tr>
<td>t(8;14)</td>
<td>Burkitt lymphoma (c-myc fusion, transcription factor oncogene)</td>
</tr>
<tr>
<td>t(9;22)</td>
<td>Philadelphia chromosome, CML (BCR-ABL activation, tyrosine kinase oncogene)</td>
</tr>
<tr>
<td>Temporal arteritis</td>
<td>Risk of ipsilateral blindness due to occlusion of ophthalmic artery; polymyalgia rheumatica</td>
</tr>
<tr>
<td>Testicular tumor</td>
<td>Seminoma (malignant, radiosensitive)</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>Papillary carcinoma</td>
</tr>
<tr>
<td>Tumor in women</td>
<td>Leiomyoma (estrogen dependent, not precancerous)</td>
</tr>
<tr>
<td>Tumor of infancy</td>
<td>Strawberry hemangioma (usually regresses spontaneously by childhood)</td>
</tr>
<tr>
<td>Tumor of the adrenal medulla (adults)</td>
<td>Pheochromocytoma (usually benign)</td>
</tr>
<tr>
<td>Tumor of the adrenal medulla (kids)</td>
<td>Neuroblastoma (malignant)</td>
</tr>
<tr>
<td>Type of Hodgkin lymphoma</td>
<td>Nodular sclerosing (vs. mixed cellularity, lymphocytic predominance, lymphocytic depletion)</td>
</tr>
<tr>
<td>Type of non-Hodgkin lymphoma</td>
<td>Diffuse large B-cell lymphoma</td>
</tr>
</tbody>
</table>
### DISEASE/FINDING

<table>
<thead>
<tr>
<th>DISEASE/FINDING</th>
<th>MOST COMMON/IMPORTANT ASSOCIATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>UTI</td>
<td><em>E. coli, Staphylococcus saprophyticus</em> (young women)</td>
</tr>
<tr>
<td>Vertebral compression fracture</td>
<td>Osteoporosis (type I: postmenopausal woman; type II: elderly man or woman)</td>
</tr>
<tr>
<td>Viral encephalitis affecting temporal lobe</td>
<td>HSV-1</td>
</tr>
<tr>
<td>Vitamin deficiency (U.S.)</td>
<td>Folate (pregnant women are at high risk; body stores only 3- to 4-month supply; prevents neural tube defects)</td>
</tr>
</tbody>
</table>

### EQUATION REVIEW

#### Topic | Equation | Page
---|---|---
Sensitivity | $\text{Sensitivity} = \frac{TP}{(TP + FN)}$ | 49
Specificity | $\text{Specificity} = \frac{TN}{(TN + FP)}$ | 49
Positive predictive value | $PPV = \frac{TP}{(TP + FP)}$ | 49
Negative predictive value | $NPV = \frac{TN}{(FN + TN)}$ | 49
Odds ratio (for case-control studies) | $OR = \frac{\frac{a}{b}}{\frac{c}{d}} = \frac{ad}{bc}$ | 50
Relative risk | $RR = \frac{\frac{a}{a + b}}{\frac{c}{c + d}}$ | 50
Attributable risk | $AR = \frac{a}{a + b} - \frac{c}{c + d}$ | 50
Relative risk reduction | $RRR = 1 - RR$ | 50
Absolute risk reduction | $ARR = \frac{\frac{c}{c + d} - \frac{a}{a + b}}{\frac{c}{c + d}}$ | 50
Number needed to treat | $NNT = \frac{1}{\text{absolute risk reduction}}$ | 50
Number needed to harm | $NNH = \frac{1}{\text{attributable risk}}$ | 50
Hardy-Weinberg equilibrium | $p^2 + 2pq + q^2 = 1$  
$p + q = 1$ | 81
Volume of distribution | $V_d = \frac{\text{amount of drug in the body}}{\text{plasma drug concentration}}$ | 243
Half-life | $t_{1/2} = \frac{0.693 \times V_d}{CL}$ | 243
Drug clearance | $CL = \frac{\text{rate of elimination of drug}}{\text{plasma drug concentration}} = V_d \times K_e$ (elimination constant) | 243
Loading dose | $LD = \frac{C_p \times V_d}{F}$ | 243
Maintenance dose | $D = \frac{C_p \times CL \times \tau}{F}$ | 243
<table>
<thead>
<tr>
<th>Topic</th>
<th>Equation</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output</td>
<td>( CO = \frac{\text{rate of } O_2 \text{ consumption}}{\text{arterial } O_2 \text{ content} - \text{venous } O_2 \text{ content}} )</td>
<td>272</td>
</tr>
<tr>
<td></td>
<td>( CO = \text{stroke volume} \times \text{heart rate} )</td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>( MAP = \text{cardiac output} \times \text{total peripheral resistance} )</td>
<td>272</td>
</tr>
<tr>
<td></td>
<td>( MAP = \frac{2}{3} \text{diastolic} + \frac{1}{3} \text{systolic} )</td>
<td>272</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>( SV = EDV - ESV )</td>
<td>272</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>( EF = \frac{SV}{EDV} = \frac{EDV - ESV}{EDV} )</td>
<td>273</td>
</tr>
<tr>
<td>Resistance</td>
<td>( \text{Resistance} = \frac{\text{driving pressure} (\Delta P)}{\text{flow} (Q)} = \frac{8\eta \text{ (viscosity)} \times \text{length}}{\pi r^4} )</td>
<td>274</td>
</tr>
<tr>
<td>Capillary fluid exchange</td>
<td>( j_c = \text{net fluid flow} = K_f [(P_c - P_i) - \varsigma (\pi_c - \pi_i)] )</td>
<td>287</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>( C_x = \frac{U_x}{P_x} )</td>
<td>529</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td>( \text{GFR} = U_{\text{ulinin}} \times \frac{V}{P_{\text{ulinin}}} = C_{\text{ulinin}} )</td>
<td>529</td>
</tr>
<tr>
<td></td>
<td>( \text{GFR} = K_f [(P_{\text{GC}} - P_{\text{BS}}) - (\pi_{\text{GC}} - \pi_{\text{BS}})] )</td>
<td>530</td>
</tr>
<tr>
<td>Effective renal plasma flow</td>
<td>( \text{eRPF} = U_{\text{PAH}} \times \frac{V}{P_{\text{PAH}}} = C_{\text{PAH}} )</td>
<td>530</td>
</tr>
<tr>
<td>Renal blood flow</td>
<td>( \text{RBF} = \frac{\text{RPF}}{1 - \text{Hct}} )</td>
<td>530</td>
</tr>
<tr>
<td>Filtration fraction</td>
<td>( \text{FF} = \frac{\text{GFR}}{\text{RPF}} )</td>
<td>530</td>
</tr>
<tr>
<td>Henderson-Hasselbalch equation for extracellular pH</td>
<td>( \text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 \text{PCO}_2} )</td>
<td>538</td>
</tr>
<tr>
<td>Winters formula</td>
<td>( \text{PCO}_2 = 1.5 [\text{HCO}_3^-] + 8 \pm 2 )</td>
<td>538</td>
</tr>
<tr>
<td>Physiologic dead space</td>
<td>( V_D = V_T \times \frac{P_{\text{ACO}<em>2} - P</em>{\text{ECO}<em>2}}{P</em>{\text{ACO}_2}} )</td>
<td>602</td>
</tr>
<tr>
<td>Pulmonary vascular resistance</td>
<td>( \text{PVR} = \frac{P_{\text{pulm artery}} - P_{\text{Leftarm}}}{\frac{\text{cardiac output}}{R}} )</td>
<td>606</td>
</tr>
<tr>
<td>Alveolar gas equation</td>
<td>( \text{PAO}<em>2 = \frac{P</em>{\text{LO}<em>2} - P</em>{\text{ACO}_2}}{R} )</td>
<td>606</td>
</tr>
</tbody>
</table>
SECTION IV

Top-Rated Review Resources

“Some books are to be tasted, others to be swallowed, and some few to be chewed and digested.”
—Sir Francis Bacon

“Always read something that will make you look good if you die in the middle of it.”
—P.J. O’Rourke

“So many books, so little time.”
—Frank Zappa

“If one cannot enjoy reading a book over and over again, there is no use in reading it at all.”
—Oscar Wilde

› How to Use the Database 644
› Question Banks 646
› Question Books 646
› Internet Sites 646
› Mobile Apps 647
› Comprehensive 647
› Anatomy, Embryology, and Neuroscience 647
› Behavioral Science 648
› Biochemistry 648
› Cell Biology and Histology 649
› Microbiology and Immunology 649
› Pathology 650
› Pharmacology 651
› Physiology 652
This section is a database of top-rated basic science review books, sample examination books, software, Web sites, and apps that have been marketed to medical students studying for the USMLE Step 1. For each recommended resource, we list (where applicable) the Title, the First Author (or editor), the Current Publisher, the Copyright Year, the Number of Pages, the Approximate List Price, the Format of the resource, and the Number of Test Questions. Finally, each recommended resource receives a Rating. Within each section, resources are arranged first by Rating and then alphabetically by the first author within each Rating group.

For a complete list of resources, including summaries that describe their overall style and utility, go to www.firstaidteam.com/bonus.

A letter rating scale with six different grades reflects the detailed student evaluations for Rated Resources. Each rated resource receives a rating as follows:

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A+</td>
<td>Excellent for boards review.</td>
</tr>
<tr>
<td>A</td>
<td>Very good for boards review; choose among the group.</td>
</tr>
<tr>
<td>A−</td>
<td>Very good for boards review; choose among the group.</td>
</tr>
<tr>
<td>B+</td>
<td>Good, but use only after exhausting better sources.</td>
</tr>
<tr>
<td>B</td>
<td>Good, but use only after exhausting better sources.</td>
</tr>
<tr>
<td>B−</td>
<td>Fair, but there are many better books in the discipline; or low-yield subject material.</td>
</tr>
</tbody>
</table>

The Rating is meant to reflect the overall usefulness of the resource in helping medical students prepare for the USMLE Step 1. This is based on a number of factors, including:

- The cost
- The readability of the text
- The appropriateness and accuracy of the material
- The quality and number of sample questions
- The quality of written answers to sample questions
- The quality and appropriateness of the illustrations (e.g., graphs, diagrams, photographs)
- The length of the text (longer is not necessarily better)
- The quality and number of other resources available in the same discipline
- The importance of the discipline for the USMLE Step 1

Please note that ratings do not reflect the quality of the resources for purposes other than reviewing for the USMLE Step 1. Many books with lower ratings are well written and informative but are not ideal for boards
preparation. We have not listed or commented on general textbooks available in the basic sciences.

Evaluations are based on the cumulative results of formal and informal surveys of thousands of medical students at many medical schools across the country. The ratings represent a consensus opinion, but there may have been a broad range of opinion or limited student feedback on any particular resource.

Please note that the data listed are subject to change in that:

- Publishers’ prices change frequently.
- Bookstores often charge an additional markup.
- New editions come out frequently, and the quality of updating varies.
- The same book may be reissued through another publisher.

We actively encourage medical students and faculty to submit their opinions and ratings of these basic science review materials so that we may update our database. (See p. xix, How to Contribute.) In addition, we ask that publishers and authors submit for evaluation review copies of basic science review books, including new editions and books not included in our database. We also solicit reviews of new books or suggestions for alternate modes of study that may be useful in preparing for the examination, such as flash cards, computer software, commercial review courses, apps, and Web sites.

Disclaimer/Conflict of Interest Statement

No material in this book, including the ratings, reflects the opinion or influence of the publisher. All errors and omissions will gladly be corrected if brought to the attention of the authors through our blog at www.firstaidteam.com. Please note that USMLE-Rx and the entire First Aid for the USMLE series are publications by the senior authors of this book; their ratings are based solely on recommendations from the student authors of this book as well as data from the student survey and feedback forms.
# TOP-RATED REVIEW RESOURCES

## Question Banks

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## Question Books

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## Anatomy, Embryology, and Neuroscience

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<td>Physiology</td>
<td>Costanzo, Saunders, 2013, 520 pp</td>
<td>Text</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>BRS Physiology Cases and Problems</td>
<td>Costanzo, Lippincott Williams &amp; Wilkins, 2012, 368 pp</td>
<td>Cases</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>PreTest Physiology</td>
<td>Metting, McGraw-Hill, 2013, 505 pp</td>
<td>Test/500 q</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>Endocrine Physiology</td>
<td>Molina, McGraw-Hill, 2013, 320 pp</td>
<td>Review</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>Netter's Physiology Flash Cards</td>
<td>Mulroney, Saunders, 2009, 200+ flash cards</td>
<td>Flash cards</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>Case Files: Physiology</td>
<td>Toy, McGraw-Hill, 2008, 456 pp</td>
<td>Cases</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>Pulmonary Pathophysiology: The Essentials</td>
<td>West, Lippincott Williams &amp; Wilkins, 2012, 208 pp</td>
<td>Review/Test/50 q</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>Clinical Physiology Made Ridiculously Simple</td>
<td>Goldberg, MedMaster, 2010, 160 pp</td>
<td>Review</td>
</tr>
</tbody>
</table>
SECTION IV

Commercial Review Courses

- Becker Healthcare 654
- Kaplan Medical 655
- Med School Tutors 655
- Northwestern Medical Review 656
- PASS Program 657
- The Princeton Review 657
- Youel’s™ Prep, Inc. 658
Commercial preparation courses can be helpful for some students, but such courses are expensive and may leave limited time for independent study. They are usually an effective tool for students who feel overwhelmed by the volume of material they must review in preparation for the boards. Also note that while some commercial courses are designed for first-time test takers, others are geared toward students who are repeating the examination. Still other courses have been created for IMGs who want to take all three Steps in a limited amount of time. Finally, student experience and satisfaction with review courses are highly variable, and course content and structure can evolve rapidly. We thus suggest that you discuss options with recent graduates of review courses you are considering. Some student opinions can be found in discussion groups on the Internet.

**Becker Healthcare**

Becker Healthcare provides intensive and comprehensive live, online, and self-study review courses for students preparing for the USMLE. The 7-week live Step 1 reviews are held throughout the year with high student involvement and instructor accessibility. Becker Healthcare uses an active learning system that focuses on comprehension, retention, and application of concepts. Online program components include:

- Over 275 hours of video lectures
- Lecture notes
- Interactive ebooks
- USMLEWorld QBank for 3 months
- Becker’s Step 1 question bank for 6 months
- Clinical vignettes and case studies
- 2 NBME practice exams

Live programs are currently offered in Dallas, Chicago, Fort Lauderdale, and New York City. The fee range is $2799–$6499. The all-inclusive live review program includes all of the above plus:

- Lodging and local hotel shuttle service
- Breakfast and lunch
- Access to a tutor
- High-speed Internet service

Becker’s Self-Study USMLE Step 1 Review Course includes:

- Diagnostic exam
- Streaming video lectures
- Interactive series of ebooks featuring Becker’s new curriculum
- Dual-degree MD and/or PhD instructors
- Becker’s Step 1 Qbank
- Optional full set of color textbooks
- 3-month USMLEWorld or 6-month USMLE Consult Qbank subscription

For more information, contact:

**Becker Healthcare**
3005 Highland Parkway
Downers Grove, IL 60515
Phone: (800) 683-8725
www.becker.com/health
Kaplan Medical

For more than 40 years, Kaplan Medical has helped medical students and physicians in the U.S. and across the world to prepare efficiently for their Boards and match into the residency program of their choice.

USMLE Step 1 Comprehensive Program Live Lectures. Kaplan’s LivePrep offers a highly structured, interactive live lecture series led by all-star faculty and is available at Kaplan centers in major cities with 7-, 14-, and 16-week options. Includes a 7-volume, full-color set of lecture notes.

Live Online Lectures. Kaplan’s Classroom Anywhere™ includes over 240 hours of live, interactive instruction delivered by expert faculty from wherever Internet access is available. Includes a 7-volume set of lecture notes.

Center Study. Kaplan’s CenterPrep provides more than 200 hours of video lectures to study at your own pace at Kaplan centers. Available for 3-, 6-, or 9-month periods and includes a 7-volume set of lecture notes.

On-demand Lectures. Kaplan’s OnlinePrep gives access to over 200 hours of video lectures delivered by expert faculty and is accessible at any time wherever Internet access is available.

USMLE Step 1 High-Yield Program. Utilize Kaplan’s Master Faculty and these key features:

- Review 55 hours of core lectures organized by General Principle and Organ System (39 hours at 1.5× speed)
- Warm up with 28 basic science exercises to review your first year
- Make it stick with clinical correlates, heart sounds, and dynamic visuals throughout your core lectures
- Practice with over 2000 USMLE review exercises in your printed workbook and watch the video explanations
- Connect core lectures with page references to First Aid, Pathoma, and medEssentials
- Strengthen your skills with core lecture quizzes and watch the video explanations
- Prep on-the-go with USMLE Step 1 High Yield on your iPad®

Until Your Test®. Use a structured study guide to map out your schedule for up to 12 months.

USMLE Step 1 High-Yield Program. Includes Step 1 Qbank:

- Master your material with 3000 USMLE practice questions and 200 mini-lectures in Kaplan’s Step 1 Qbank, including diagnostic and 2 simulated exams
- Turn downtime into a higher score with free Qbank mobile app for iPhone® and Android™

To learn more, call 1-800-KAP-TEST or visit www.kaplanmedical.com.

Med School Tutors

Since 2007, Med School Tutors has helped students prepare for Step 1 by working with them one-on-one. Instead of offering courses, lectures, or videos, MST’s approach is tailored to each student’s weaknesses and strengths, according to their learning styles and schedules, and is guided by a personal coach who has scored high on Step 1.

Med School Tutors are medical students and residents who have excelled in their medical studies and training. Their minimum credentials include:

- Training at top medical schools and residency programs
- Superior standardized test scores (e.g., Step 1 > 245)
- Significant and verifiable teaching experience
- Interviewing and training with MST’s most experienced USMLE tutors
Med School Tutors assists students according to their needs. Comprehensive packages include:

- Personal day-by-day study schedule and plan
- Test-taking techniques and confidence-building exercises
- Assessment by question bank performance and NBME test analysis
- Selection and use of high-yield resources
- Integrated review of content with emphasis on student’s weaknesses
- Emphasis on question/vignette-based learning
- Clinical reasoning skills training
- Holistic support throughout study period

Students start with a complimentary consultation and discussion of their needs and goals. This is followed by the tutor matching process and introduction to the tutor. Students then begin formal work with a trial session at half the cost. The trial session encompasses a review of a recent self-assessment (or question block), the first steps in creating a personal study plan, and Q&A. Nearly 80% of MST’s students work with tutors seamlessly online via Web conferences. In-person tutoring is also offered in Manhattan near select universities and medical centers.

For more information, visit www.medschooltutors.com or call (212) 327-0098.

Northwestern Medical Review

Since 1986, Northwestern Medical Review (NMR) has been offering review courses in preparation for the USMLE Step 1 and COMLEX Level I examinations. The curriculum of Northwestern Review allows students to select a variety of live or online courses ranging in length from 5–18 days. The courses are developed in a high-yield and clinically oriented format and address concepts that are commonly tested on the exams. Courses are taught by the authors of the Northwestern Review Books and/or authors of best-selling books. The uniqueness of the NMR curriculum is the multimedia live-lecture TALLP™ instructional methodology that incorporates simulated test items, cartoons, animations, and uplifting mnemonics into the courses. Another feature of the courses is the built-in Adaptive-Flexi-Pass™ teaching methodology that progressively customizes live courses around the academic needs of the participating students. The format of the workbooks allows students to actively and effectively assimilate the presented concepts. In addition to organized lecture notes and review books for all subjects, students will receive access to more than 2500 Web-based question bank items, audio CDs, and a large pool of practice questions and simulated exams. All study plans are available in a customized and onsite format for groups of students. Additionally, public sessions are frequently offered in East Lansing, Philadelphia, Los Angeles, Chicago, New York City, and San Juan. Live courses are also globally available in certain countries. NMR offers a free retake option as well as a liberal cancellation policy.

For more information, contact:

Northwestern Medical Review
P.O. Box 22174
Lansing, MI 48909-2174
Phone: (866) MedPass
Fax: (517) 347-7005
E-mail: contactus@northwesternmedicalreview.com
www.northwesternmedicalreview.com
PASS Program

USMLE and COMLEX Review Program. The PASS Program offers a concept-based, clinically integrated curriculum to help students increase board scores, obtain residencies, and broaden their perspective of medicine. Helpful for a wide spectrum of students, including those trying to maximize scores on the first try and those struggling to stay in medical school. PASS accommodates all types of learners: auditory, visual, or kinesthetic, and, with the help of small class sizes, encourages students to interact and to ask questions.

Live Lectures. PASS offers 4-, 6-, 8-week, or extended-stay programs in Champaign, IL, and St. Augustine, FL. Facilities include computer labs, a state-of-the-art lecture hall, student lounges and study areas, and housing. Drill sessions and small study groups take place throughout the week. Tuition, which includes housing and security deposit, is $4050 for the 4-week course, $6850 for the 6-week course, and $7700 for the 8-week course.

One-on-One Tutoring. Included with tuition, students receive one-on-one tutoring from an MD each week they attend the program. Six-week students receive two sessions per week and 8-week students receive three sessions in weeks 1–5 of the program and five sessions in weeks 6–8.

Online Program. The online program includes new lectures on nearly 40 topics and the current edition of the Course Notes book. Also included are sample questions by topic with video explanations from Dr. Francis, two NBME exams, and a 1-year KISSPharm subscription (www.kisspharm.com). There are weekly drill sessions and a student discussion board, and the program is available for 6- or 12-month access.

For more information, contact:
PASS Program
2302 Moreland Blvd.
Champaign, IL 61822
Phone: (217) 378-8018
Fax: (217) 378-7809
www.passprogram.net

The Princeton Review

The Princeton Review offers two flexible preparation options for the USMLE Step 1: the USMLE Online Course and the USMLE Online Workout.

USMLE Online Courses. The USMLE Online Courses offer the following:

- 75 hours of online review, including lessons, vignettes, and drills
- Complete review of all USMLE Step 1 subjects
- Three full-length CBTs
- Seven 1-hour subject-based tests
- Complete set of print materials
- 24/7 access to technical support
- Three months of access to tests, drills, and lessons

Youel's™ Prep, Inc.

Youel's Prep, Inc., has specialized in medical board preparation for 30 years. The company provides DVDs, audiotapes, videotapes, a CD (PowerPrep Quick Study), books, live lectures, and tutorials for small groups as well as for individuals (TutorialPrep™). All DVDs, videotapes, audiotapes, live lectures, and tutorials are correlated with a three-book set of Prep Notes consisting of two textbooks, Youel's Jewels I and Youel's Jewels II (984 pages), and Case Studies, a question-and-answer book (1854 questions, answers, and explanations).

The Comprehensive DVD program consists of 56 hours of lectures by the systems with a three-book set: Youel's Jewels I and II and Case Studies. Integrated with these programs are pre-tests and post-tests.

All Youel's Prep courses are taught and written by physicians, reflecting the clinical slant of the boards. All programs are systems based. In addition, all programs are updated continuously. Accordingly, books are not printed until the order is received.

Delivery in the United States or overseas is usually within 1 week. Optional express delivery is also available. Youel's Prep Home Study Program™ allows students to own their materials and to use them for repetitive study in the convenience of their homes. Purchasers of any of Youel's Prep materials, programs, or services are enrolled as members of the Youel's Prep Family of Students™, which affords them access to free telephone tutoring at (800) 645-3985. Students may call 24/7. Youel's Prep live lectures are held at select medical schools at the invitation of the school and students.

Programs are custom-designed for content, number of hours, and scheduling to fit students’ needs. First-year students are urged to call early to arrange live-lecture programs at their schools for next year.

For more information, contact:

**Youel's Prep, Inc.**
P.O. Box 31479
Palm Beach Gardens, FL 33420
Phone: (800) 645-3985
Fax: (561) 622-4858
Email: info@youelsprep.com
www.youelsprep.net
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www.exammaster.com

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science@garland.com
www.garlandscience.com

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Lubbock, TX 79410
(806) 773-3197
info@ApolloAudiobooks.com
www.boardprep.net

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Fax: (732) 302-2300
custserv@wiley.com
www.wiley.com

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(800) 527-8378
customer.care@kaplan.com

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www.lww.com

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www.mhprofessional.com

MedMaster, Inc.
P.O. Box 640028
Miami, FL 33164
(800) 355-3480
Fax: (954) 962-4508
mmbks@aol.com
www.medmaster.net

Princeton Review
2315 Broadway
New York, NY 10024
(888) 955-4600
www.princetonreview.com

Thieme Medical Publishers, Inc.
333 Seventh Avenue
New York, NY 10001
(800) 782-3488
Fax: (212) 947-0108
www.thieme.com
customerservice@thieme.com
### Abbreviations and Symbols

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° primary</td>
<td></td>
</tr>
<tr>
<td>2° secondary</td>
<td></td>
</tr>
<tr>
<td>3° tertiary</td>
<td></td>
</tr>
<tr>
<td>A-a</td>
<td>alveolar-arterial [gradient]</td>
</tr>
<tr>
<td>AA</td>
<td>Alcoholics Anonymous, amyloid A</td>
</tr>
<tr>
<td>AAMC</td>
<td>Association of American Medical Colleges</td>
</tr>
<tr>
<td>Ab</td>
<td>antibody</td>
</tr>
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<td>ABP</td>
<td>androgen-binding protein</td>
</tr>
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<td>ACA</td>
<td>anterior cerebral artery</td>
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<td>Acetyl-CoA</td>
<td>acetyl coenzyme A</td>
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<td>ACD</td>
<td>anemia of chronic disease</td>
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<td>ACE</td>
<td>angiotensin-converting enzyme</td>
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<td>ACh</td>
<td>acetylcholine</td>
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<td>AChE</td>
<td>acetylcholinesterase</td>
</tr>
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<td>ACL</td>
<td>anterior cruciate ligament</td>
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<tr>
<td>ACCom</td>
<td>anterior communicating [artery]</td>
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<td>ACTH</td>
<td>adrenocorticotropic hormone</td>
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<td>ADA</td>
<td>adenosine deaminase, Americans with Disabilities Act</td>
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<td>ADH</td>
<td>antiduretic hormone</td>
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<td>ADHD</td>
<td>attention-deficit hyperactivity disorder</td>
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<td>ADP</td>
<td>adenosine diphosphate</td>
</tr>
<tr>
<td>ADPKD</td>
<td>autosomal-dominant polycystic kidney disease</td>
</tr>
<tr>
<td>AFP</td>
<td>α-fetoprotein</td>
</tr>
<tr>
<td>Ag</td>
<td>antigen, silver</td>
</tr>
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<td>AICA</td>
<td>anterior inferior cerebellar artery</td>
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<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>AIHA</td>
<td>autoimmune hemolytic anemia</td>
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<tr>
<td>AL</td>
<td>amyloid light [chain]</td>
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<td>ALA</td>
<td>aminolevulinic acid</td>
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<td>ALL</td>
<td>acute lymphoblastic (lymphocytic) leukemia</td>
</tr>
<tr>
<td>ALP</td>
<td>alkaline phosphatase</td>
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<td>α1, α2</td>
<td>sympathetic receptors</td>
</tr>
<tr>
<td>ALS</td>
<td>amyotrophic lateral sclerosis</td>
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<tr>
<td>ALT</td>
<td>alanine transaminase</td>
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<tr>
<td>AMA</td>
<td>American Medical Association, antimitochondrial antibody</td>
</tr>
<tr>
<td>AML</td>
<td>acute myelogenous (myeloid) leukemia</td>
</tr>
<tr>
<td>AMP</td>
<td>adenosine monophosphate</td>
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<tr>
<td>ANA</td>
<td>antinuclear antibody</td>
</tr>
<tr>
<td>ANCA</td>
<td>antineutrophil cytoplasmic antibody</td>
</tr>
<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
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<tr>
<td>ANP</td>
<td>atrial natriuretic peptide</td>
</tr>
<tr>
<td>ANS</td>
<td>autonomic nervous system</td>
</tr>
<tr>
<td>anti- CCP</td>
<td>anti-cyclic citrullinated peptide</td>
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<tr>
<td>AOA</td>
<td>American Osteopathic Association</td>
</tr>
<tr>
<td>AP</td>
<td>action potential, A &amp; P [ribosomal binding sites]</td>
</tr>
<tr>
<td>A &amp; P</td>
<td>ribosomal binding sites</td>
</tr>
<tr>
<td>APC</td>
<td>antigen-presenting cell, activated protein C</td>
</tr>
<tr>
<td>APP</td>
<td>amyloid precursor protein</td>
</tr>
<tr>
<td>APRT</td>
<td>adenine phosphoribosyltransferase</td>
</tr>
<tr>
<td>APSAC</td>
<td>anistreplase</td>
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<tr>
<td>aPIT</td>
<td>activated partial thromboplastin time</td>
</tr>
<tr>
<td>Apo</td>
<td>apolipoprotein</td>
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<tr>
<td>AR</td>
<td>attributable risk, autosomal recessive, aortic regurgitation</td>
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<tr>
<td>AR-C</td>
<td>arabinofuranosyl cytidine (cytarabine)</td>
</tr>
<tr>
<td>ARB</td>
<td>angiotensin receptor blocker</td>
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<tr>
<td>ARDS</td>
<td>acute respiratory distress syndrome</td>
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<td>Arg</td>
<td>arginine</td>
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<tr>
<td>ARMD</td>
<td>age-related macular degeneration</td>
</tr>
<tr>
<td>ARPKD</td>
<td>autosomal-recessive polycystic kidney disease</td>
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<tr>
<td>AS</td>
<td>aortic stenosis</td>
</tr>
<tr>
<td>ASA</td>
<td>anterior spinal artery</td>
</tr>
<tr>
<td>ASD</td>
<td>atrial septal defect</td>
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<tr>
<td>ASO</td>
<td>anti-streptolysin O</td>
</tr>
<tr>
<td>AT</td>
<td>angiotensin, antithrombin</td>
</tr>
<tr>
<td>ATCase</td>
<td>aspartate transcarbamoylase</td>
</tr>
<tr>
<td>ATN</td>
<td>acute tubular necrosis</td>
</tr>
<tr>
<td>ATP</td>
<td>adenosine triphosphate</td>
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<tr>
<td>ATPase</td>
<td>adenosine triphosphatase</td>
</tr>
<tr>
<td>ATTR</td>
<td>transthyretin-mediated amyloidosis</td>
</tr>
<tr>
<td>AV</td>
<td>atrioventricular</td>
</tr>
<tr>
<td>AZT</td>
<td>azithromycin</td>
</tr>
<tr>
<td>β1, β2</td>
<td>sympathetic receptors</td>
</tr>
<tr>
<td>BAL</td>
<td>British anti-Lewisite [dimercaprol]</td>
</tr>
<tr>
<td>BCG</td>
<td>bacille Calmette-Guérin</td>
</tr>
<tr>
<td>BIMS</td>
<td>Biometric Identity Management System</td>
</tr>
<tr>
<td>BM</td>
<td>basement membrane</td>
</tr>
<tr>
<td>BMI</td>
<td>body-mass index</td>
</tr>
<tr>
<td>BMR</td>
<td>basal metabolic rate</td>
</tr>
<tr>
<td>BP</td>
<td>biphosphatic, blood pressure</td>
</tr>
<tr>
<td>BPG</td>
<td>biphosphoglycerate</td>
</tr>
<tr>
<td>BPH</td>
<td>benign prostatic hyperplasia</td>
</tr>
<tr>
<td>BT</td>
<td>bleeding time</td>
</tr>
<tr>
<td>BUN</td>
<td>blood urea nitrogen</td>
</tr>
<tr>
<td>Ca2+</td>
<td>calcium ion</td>
</tr>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>CAF</td>
<td>common application form</td>
</tr>
<tr>
<td>CALLA</td>
<td>common acute lymphoblastic leukemia antigen</td>
</tr>
<tr>
<td>cAMP</td>
<td>cyclic adenosine monophosphate</td>
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<tr>
<td>Abbreviation</td>
<td>Meaning</td>
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<td>--------------</td>
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</tr>
<tr>
<td>AB</td>
<td>Abbreviation</td>
</tr>
<tr>
<td>CREST</td>
<td>calcinosis, Raynaud phenomenon, esophageal dysfunction, sclerosis, and telangiectasias (syndrome)</td>
</tr>
<tr>
<td>CRH</td>
<td>corticotropin-releasing hormone</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CS</td>
<td>clinical skills</td>
</tr>
<tr>
<td>C-section</td>
<td>cesarean section</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CTP</td>
<td>cytidine triphosphate</td>
</tr>
<tr>
<td>CVA</td>
<td>cerebrovascular accident</td>
</tr>
<tr>
<td>CVID</td>
<td>common variable immunodeficiency</td>
</tr>
<tr>
<td>CXR</td>
<td>chest x-ray</td>
</tr>
<tr>
<td>Cys</td>
<td>cysteine</td>
</tr>
<tr>
<td>DAF</td>
<td>decay-accelerating factor</td>
</tr>
<tr>
<td>DAG</td>
<td>diacylglycerol</td>
</tr>
<tr>
<td>dATP</td>
<td>deoxyadenosine triphosphate</td>
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<td>DCIS</td>
<td>ductal carcinoma in situ</td>
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<td>DHEA</td>
<td>dehydroepiandrosterone</td>
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<td>DHF</td>
<td>dihydrofolic acid</td>
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<td>DHS</td>
<td>Department of Homeland Security</td>
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<td>DHA</td>
<td>dihydrolipoic acid</td>
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<td>dehydroepiandrosterone</td>
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<td>granulocyte colony-stimulating factor</td>
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<td>glomerular filtration rate</td>
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<td>γ-glutamyl transpeptidase</td>
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<td>growth hormone</td>
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<td>glucose transporter</td>
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<td>gonadotropin-releasing hormone</td>
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<td>G protein, S polypeptide</td>
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<td>Hb</td>
<td>hemoglobin</td>
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<td>Hb+</td>
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<td>hepatitis B surface antibody</td>
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<td>human chorionic gonadotropin</td>
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<td>high-density lipoprotein</td>
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<td>hepatitis D virus</td>
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<td>hematoxylin and eosin</td>
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<td>hepatitis E virus</td>
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<td>heart failure</td>
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### Additional Abbreviations

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<td>Integrated Clinical Encounter</td>
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<td>identification</td>
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<td>dose at which pathogen produces infection in 50% of population</td>
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<td>TG</td>
<td>triglyceride</td>
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<td>TG[6]</td>
<td>6-thioguanine</td>
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<td>TGA</td>
<td>trans-Golgi apparatus</td>
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<td>TGF</td>
<td>transforming growth factor</td>
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<td>TGN</td>
<td>trans-Golgi network</td>
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<td>TH cell</td>
<td>helper T cell</td>
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<td>THF</td>
<td>tetrahydrofolic acid</td>
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<td>T1</td>
<td>therapeutic index</td>
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<td>TIA</td>
<td>transient ischemic attack</td>
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<td>TIBC</td>
<td>total iron-binding capacity</td>
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<tr>
<td>TIPS</td>
<td>transjugular intrahepatic portosystemic shunt</td>
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<tr>
<td>TLC</td>
<td>total lung capacity</td>
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<td>Tm max</td>
<td>maximum rate of transport</td>
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<td>TMP</td>
<td>trimethoprim</td>
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<td>TN</td>
<td>true negative</td>
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<td>TNF</td>
<td>tumor necrosis factor</td>
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<td>TNM</td>
<td>tumor, node, metastases [staging]</td>
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<td>TOEFL</td>
<td>Test of English as a Foreign Language</td>
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<td>ToRCH eS</td>
<td>Toxoplasma gondii, rubella, CMV, HIV, HSV-2, syphilis</td>
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<td>TRP</td>
<td>tissue plasminogen activator</td>
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<td>TPR</td>
<td>thiamine pyrophosphate</td>
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<td>TP</td>
<td>true positive</td>
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<td>TR</td>
<td>tricuspid regurgitation</td>
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<td>TRA</td>
<td>tartrate-resistant acid phosphatase</td>
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<td>TRH</td>
<td>thyrotropin-releasing hormone</td>
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<td>tRNA</td>
<td>transfer ribonucleic acid</td>
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<td>TSH</td>
<td>thyroid-stimulating hormone</td>
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<td>TSS</td>
<td>toxic shock syndrome</td>
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<td>TSSR</td>
<td>toxic shock syndrome toxin</td>
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<td>TTP</td>
<td>thrombotic thrombocytopenic purpura</td>
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<td>TTR</td>
<td>transthyretin</td>
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<td>TV</td>
<td>tidal volume</td>
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<td>Tx</td>
<td>translation [factor]</td>
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<td>TXA2</td>
<td>thromboxane A2</td>
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<td>UCV</td>
<td>Underground Clinical Vignettes</td>
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<td>UDP</td>
<td>uridine dipiphosphate</td>
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<td>UMN</td>
<td>upper motor neuron</td>
</tr>
<tr>
<td>UMP</td>
<td>uridine monophosphate</td>
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<tr>
<td>UPD</td>
<td>uniparental disomy</td>
</tr>
<tr>
<td>URI</td>
<td>upper respiratory infection</td>
</tr>
<tr>
<td>ABBREVIATION</td>
<td>MEANING</td>
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<tr>
<td>USMLE</td>
<td>United States Medical Licensing Examination</td>
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<td>UTI</td>
<td>urinary tract infection</td>
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<td>UTP</td>
<td>uridine triphosphate</td>
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<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>V₁, V₂</td>
<td>Vasopressin receptors</td>
</tr>
<tr>
<td>VA</td>
<td>Veterans Affairs</td>
</tr>
<tr>
<td>VC</td>
<td>vital capacity</td>
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<tr>
<td>V₄</td>
<td>volume of distribution</td>
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<tr>
<td>VD</td>
<td>physiologic dead space</td>
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<tr>
<td>V(D)J</td>
<td>heavy-chain hypervariable region [antibody]</td>
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<td>VDRL</td>
<td>Venereal Disease Research Laboratory</td>
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<td>VEGF</td>
<td>vascular endothelial growth factor</td>
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<tr>
<td>VₐH</td>
<td>variable region, heavy chain [antibody]</td>
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<td>VH</td>
<td>von Hippel-Lindau [disease]</td>
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<tr>
<td>VIP</td>
<td>vasoactive intestinal peptide</td>
</tr>
<tr>
<td>VIPoma</td>
<td>vasoactive intestinal polypeptide-secreting tumor</td>
</tr>
<tr>
<td>VJ</td>
<td>light-chain hypervariable region [antibody]</td>
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<tr>
<td>VL</td>
<td>ventral lateral [nucleus]; variable region, light chain [antibody]</td>
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<thead>
<tr>
<th>ABBREVIATION</th>
<th>MEANING</th>
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<td>VLDL</td>
<td>very low density lipoprotein</td>
</tr>
<tr>
<td>VMA</td>
<td>vanillylmandelic acid</td>
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<tr>
<td>Vₐmax</td>
<td>maximum velocity</td>
</tr>
<tr>
<td>VPL</td>
<td>ventral posterior nucleus, lateral</td>
</tr>
<tr>
<td>VPM</td>
<td>ventral posterior nucleus, medial</td>
</tr>
<tr>
<td>VPN</td>
<td>vancomycin, polymyxin, nystatin [media]</td>
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<tr>
<td>V/Q</td>
<td>ventilation/perfusion [ratio]</td>
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<tr>
<td>VRE</td>
<td>vancomycin-resistant enterococcus</td>
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<td>VSD</td>
<td>ventricular septal defect</td>
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<td>Vₜ</td>
<td>tidal volume</td>
</tr>
<tr>
<td>vWF</td>
<td>von Willebrand factor</td>
</tr>
<tr>
<td>VZV</td>
<td>varicella-zoster virus</td>
</tr>
<tr>
<td>WHOML</td>
<td>“worst headache of my life”</td>
</tr>
<tr>
<td>WBC</td>
<td>white blood cell</td>
</tr>
<tr>
<td>XR</td>
<td>X-linked recessive</td>
</tr>
<tr>
<td>XX</td>
<td>normal complement of sex chromosomes for female</td>
</tr>
<tr>
<td>XY</td>
<td>normal complement of sex chromosomes for male</td>
</tr>
<tr>
<td>ZDV</td>
<td>zidovudine [formerly AZT]</td>
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SECTION IV

Image Acknowledgments

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95 Muscular dystrophies. Fibrolary replacement of muscle. Courtesy of the U.S. Department of Health and Human Services and Dr. Lyle Conrad.


108 Alkaptonuria (ochronosis). 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.

108 Cystinuria. Hexagonal stones in cystinuria. This image is a derivative work, adapted from the following source, available under ☑️. Courtesy of Cayla Devine.

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111 Lysosomal storage diseases: Image B. Foam cells in Niemann-Pick disease. This image is a derivative work, adapted from the following source, available under ☑️. Hypercholesterolemia boosts joint destruction in chronic arthritis. An experimental model aggravated by foam macrophage infiltration. Prieto-Potín I, Roam-Blas JA, Martínez-Calatava MJ, et al. Arthritis Res Ther 2013;15:R81. doi 10.1186/ar4261. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

111 Lysosomal storage diseases: Image C. “Cherry-red” spot on macula in Tay-Sachs disease. This image is a derivative work, adapted from the following source, available under ☑️. Courtesy of Dr. Jonathan Trobe.

90 Vitamin A. 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-8, 2008. Available at: http://cnx.org/content/3d3dcb2e-3d3dcb2e-8e98-496f-91c2-fe94e93428a1@3@3/.

93 Vitamin D. Rickets. This image is a derivative work, adapted from the following source, available under ☑️. Courtesy of Dr. Michael L. Richardson.
Microbiology

122 Catalase-positive organisms. Oxygen bubbles released during catalase reaction. This image is a derivative work, adapted from the following source, available under [Creative Commons](https://creativecommons.org/licenses/by/4.0/). Courtesy of Stefano Nase.


128 α-hemolytic bacteria. alpha-hemolysis. This image is a derivative work, adapted from the following source, available under [Creative Commons](https://creativecommons.org/licenses/by-sa/3.0/). Courtesy of Y. Tambe.

128 β-hemolytic bacteria. beta-hemolysis. This image is a derivative work, adapted from the following source, available under [Creative Commons](https://creativecommons.org/licenses/by-sa/4.0/). Courtesy of Y. Tambe.

128 Staphylococcus aureus. Gram stain. [Creative Commons](https://creativecommons.org/licenses/by-sa/3.0/). Courtesy of the U.S. Department of Health and Human Services and Dr. Richard Facklam.

129 Streptococcus pyogenes (group A streptococci). Gram stain. This image is a derivative work, adapted from the following source, available under [Creative Commons](https://creativecommons.org/licenses/by-sa/3.0/). Courtesy of Y. Tambe.

130 Corynebacterium diphtheriae. Pseudomembranous pharyngitis. This image is a derivative work, adapted from the following source, available under [Creative Commons](https://creativecommons.org/licenses/by-sa/4.0/). Courtesy of Wikimedia Commons.

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132 Anthrax: Image A. Gram-positive rods of Bacillus anthracis. [Creative Commons](https://creativecommons.org/licenses/by-sa/4.0/). Courtesy of the U.S. Department of Health and Human Services.

132 Anthrax: Image B. Ulcer with black eschar. [Creative Commons](https://creativecommons.org/licenses/by-sa/4.0/). Courtesy of the U.S. Department of Health and Human Services and James H. Steele.

132 Listeria monocytogenes. Actin rockets. This image is a derivative work, adapted from the following source, available under [Creative Commons](https://creativecommons.org/licenses/by-sa/3.0/). Schuppel M, Loesner MJ. The opportunistic pathogen Listeria monocytogenes: pathogenicity and interaction with the mucosal immune system. Int J Immunol 2010;2010:704321. doi 10.4061/2010/704321.

133 Actinomyces vs. Nocardia: Image A. Actinomyces israelii on Gram stain. [Creative Commons](https://creativecommons.org/licenses/by-sa/4.0/). Courtesy of the U.S. Department of Health and Human Services.


134 Mycobacteria. Acid-fast stain. [Creative Commons](https://creativecommons.org/licenses/by-sa/4.0/). Courtesy of the U.S. Department of Health and Human Services and Dr. Roger Feldman.

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136 Neisseria: Image A. Photomicrograph. [Creative Commons](https://creativecommons.org/licenses/by-sa/4.0/). Courtesy of the U.S. Department of Health and Human Services and Dr. Mike Miller.

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137 Legionella pneumophila. [Creative Commons](https://creativecommons.org/licenses/by-sa/4.0/). Courtesy of Grottola A, Forghieri F, Meacci M, et al. Severe pneumonia caused by Legionella pneumophila serogroup 11, Italy. Emerg Infect Dis 2012. doi 10.3201/eid1811.120216. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

137 Pseudomonas aeruginosa: Image A. Blue-green pigment. This image is a derivative work, adapted from the following source, available under [Creative Commons](https://creativecommons.org/licenses/by-sa/4.0/). Courtesy of Hansen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under [Creative Commons](https://creativecommons.org/licenses/by-sa/4.0/).

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140 **Helicobacter pylori.** Courtesy of the U.S. Department of Health and Human Services, Dr. Patricia Fields, and Dr. Collette Fitzgerald.


141 **Syphilis: Image E.** Condyloma lata. Courtesy of the U.S. Department of Health and Human Services and Susan Lindsay.


141 **Syphilis: Image G.** Congenital syphilis. Courtesy of the U.S. Department of Health and Human Services and Dr. Norman Cole.

141 **Syphilis: Image H.** Hutchinson teeth. Courtesy of the U.S. Department of Health and Human Services and Susan Lindsay.

142 **Gardnerella vaginalis.** Courtesy of the U.S. Department of Health and Human Services and M. Rein.


144 **Mycoplasma pneumoniae.** This image is a derivative work, adapted from the following source, available under [11]. Rottem S, Kosower NS, Korspan JD. Contamination of tissue cultures by *Mycoplasma*. In: Ceccherini-Nelli L, ed: *Biomedical tissue culture*. doi: 10.5772/51518.


145 **Systemic mycoses: Image B.** *Blastomyces*. This image is a derivative work, adapted from the following source, available under [11]. Courtesy of Sarah (Rosenau) Korf. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under [11].


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147 **Opportunistic fungal infections: Image A, left.** Budding yeast of *Candida albicans*. This image is a derivative work, adapted from the following source, available under [11]. Courtesy of Y. Tambe. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under [11].

147 **Opportunistic fungal infections: Image A, right.** Germ tubes of *Candida albicans*. This image is a derivative work, adapted from the following source, available under [11]. Courtesy of Y. Tambe. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under [11].


147 **Opportunistic fungal infections: Image D.** Cryptococci of *Cryptococcus neoformans*. Courtesy of the U.S. Department of Health and Human Services and Dr. Leanor Haley.

147 **Opportunistic fungal infections: Image E.** *Mucor*. Courtesy of the U.S. Department of Health and Human Services and Dr. Libero Ajello.

148 **Pneumocystis jiroveci: Image A.** Pneumocystis pneumonia (PCP). This image is a derivative work, adapted from the following source, available under [11]. Cho JY, Kim D-M, Kwon YE, et al. Newly formed cystic lesions for the development of pneumomediastinum in *Pneumocystis jiroveci* pneumonia. *BMC Infect Dis* 2009;9:171. doi: 10.1186/1471-2334-9-171. 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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152 Protozoa—Others: Image B. *Leishmania donovani*. Courtesy of the U.S. 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.


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160 HSV identification. Positive Tzanck smear in HSV-2 infection. This image is a derivative work, adapted from the following source, available under Creative Commons Attribution License. Courtesy of Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under Creative Commons Attribution License.


171 Prions. Spongiform changes in Creutzfeld-Jacob disease. This image is a derivative work, adapted from the following source, available under Creative Commons Attribution License. Courtesy of DRdoubleB. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under Creative Commons Attribution License.

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Immunology

199 Sinusoids of spleen. Red and white pulp. This image is a derivative work, adapted from the following source, available under Creative Commons Attribution License. Heinrichs S, Conover LF, Bueso-Ramos CE, et al. MYB/LE is a sub-haploinsufficient tumor suppressor gene in myeloid malignancy. elife 2013;2:e00825. doi 10.7554/ elife.00825. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

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Pathology

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Pharmacology


Cardiovascular
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Endocrine

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Gastrointestinal


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Hematology and Oncology

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Musculoskeletal, Skin, and Connective Tissue


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Neurology

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Reproductive


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Respiratory

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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 the founder and editor of the USMLE-Rx test bank and online video series as well as a cofounder of the Underground Clinical Vignettes series. 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 conducting research in asthma education at the University of Louisville.

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Vikas is a writer, editor, entrepreneur, and teleradiologist on sabbatical. In 1990 he conceived and authored the original First Aid for the USMLE Step 1. His entrepreneurial endeavors include a student-focused medical publisher (S2S), an e-learning company (medschool.com/Medsn), and an ER teleradiology practice (24/7 Radiology). Firmly anchored to the Left Coast, Vikas completed a bachelor’s degree at the University of California Berkeley; an MD with thesis at UCSF; and a diagnostic radiology residency at UCLA. His eclectic interests include technology, information design, photography, South Asian diasporic culture, and avoiding a day job. Always finding the long shortcut, Vikas is an adventurer, knowledge seeker, and occasional innovator. He enjoys novice status as a kiteboarder and single father, and strives to raise his children as global citizens.

Matthew Sochat, MD

Matthew began residency training in neurology at New York University in 2014. He earned his medical degree from Brown University in 2013 and completed his undergraduate studies at the University of Massachusetts-Amherst, graduating in 2008 with degrees in biochemistry and the classics. In his (limited) spare time, Matthew enjoys skiing, cooking/baking, traveling, the company of friends/loved ones, and computer/video gaming. Be warned: he also loves to come up with corny jokes at (in)opportune moments.

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Michael is in his sixth and final year of medical school and research at the University of Queensland, Australia. Prior to medical school, he completed an undergraduate degree at Boston University and a research internship at University of Sydney. Michael would be most fortunate for a transitional/preliminary year in order to gain a greater diversity of experience and perspective before committing to any field for the long term. In his (lack of) spare time, he teaches students across the world preparation tactics for the USMLE Step 1 and is an avid member of the Student Doctor Network. Outside of medicine, Michael is interested in chess, artisanal hot sauce, and lexicology.

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