FIRST AID FOR THE®

USMLE STEP 1

2008

A STUDENT-TO-STUDENT GUIDE

- Student advice from the 2007 exam
- 1000+ frequently tested facts and mnemonics
- 24 pages of high-yield color images
- Student reviews of 300+ review products

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USMLE STEP 1 2008

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PREFACE

With the 2008 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 a major revision in many ways and includes:

- A revised and updated exam preparation guide for the USMLE Step 1. Includes detailed analysis as well as study and test-taking strategies for the FRED format.
- Revisions and new material based on student experience with the 2007 administrations of the computerized USMLE Step 1.
- Expanded USMLE advice for international medical graduates, osteopathic medical students, podiatry students, and students with disabilities.
- Over a thousand frequently tested facts and useful mnemonics, including hundreds of new or revised entries.
- A high-yield collection of over 175 glossy photos similar to those appearing on the USMLE Step 1 exam.
- An in-depth guide to hundreds of recommended basic science review and sample examination books, based on a nationwide survey of randomly selected third-year medical students.

The 2008 edition would not have been possible without the help of the hundreds of students and faculty members who contributed their feedback and suggestions. We invite students and faculty to continue sharing their thoughts and ideas to help us improve *First Aid for the® USMLE Step 1*. (See How to Contribute, p. xv.)

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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 books as study guides for first-year medical school courses.

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 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 crammable subjects first. Review subject-by-subject emphasis and clinical vignette format.
- ☐ Simulate the USMLE Step 1 to pinpoint strengths and weaknesses in knowledge and test-taking skills.
- ☐ Evaluate and choose study methods and materials (e.g., review books, practice tests, software).
- ☐ Ask advice from those who have recently taken the USMLE Step 1.

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.
- ☐ Light review of 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. You will not be allowed to take the exam unless the names match EXACTLY.

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 at **www.firstaidteam.com.**

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SECTION II

High-Yield General Principles

- Behavioral Science
- Biochemistry
- Embryology
- Microbiology
- Immunology
- Pathology
- Pharmacology

"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

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The 2008 edition of *First Aid for the USMLE Step 1* contains a revised and expanded database of basic science material that student authors and faculty have identified as high yield for board reviews. The information is presented in a partially organ-based format. Hence, Section II is devoted to pathology, the foundational principles of behavioral science, biochemistry, embryology, microbiology and 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. At the beginning of each subsection, we list supplementary high-yield clinical vignettes and topics that have appeared on recent exams in order to help focus your review.

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." 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 content as well as to expand our database of information. However, we must note that inevitably many other very high yield entries and topics are not yet included in our database.

We actively encourage medical students and faculty to submit entries and 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 diagrams, charts, and computer-based tutorials (see How to Contribute, p. xv).

Disclaimer

The entries in this section reflect student opinions of what is high yield. Owing to 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. All errors and omissions will gladly be corrected if brought to the attention of the authors, either through the publisher or directly by e-mail.

HIGH-YIELD PRINCIPLES IN

Behavioral Science

"It's psychosomatic. You need a lobotomy. I'll get a saw."
—Calvin, "Calvin & Hobbes"

- High-Yield Clinical Vignettes
- Epidemiology/ Biostatistics
- Ethics
- Development
- Physiology

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

Behavioral science questions may seem less concrete than questions from other disciplines, requiring an awareness of the social 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, and we have included several examples in the high-yield clinical vignettes. 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 specificity and predictive values in a problem-solving format.

BEHAVIORAL SCIENCE—HIGH-YIELD CLINICAL VIGNETTES

▪ Woman with anxiety about a gynecologic exam is told to relax and to imagine going through the steps of the exam.	What process does this exemplify?	Systematic desensitization.
▪ 65-year-old man is diagnosed with incurable metastatic pancreatic adenocarcinoma. His family asks you, the doctor, not to tell the patient.	What do you do?	Assess whether telling the patient will negatively affect his health. If not, tell him.
▪ Man admitted for chest pain is medicated for ventricular tachycardia. The next day he jumps out of bed and does 50 push-ups to show the nurses he has not had a heart attack.	What defense mechanism is he using?	Denial.
▪ You find yourself attracted to your 26-year-old patient.	What do you say?	Nothing! The tone of the interview must be very professional; it is not acceptable to have any sort of romantic relationship with patients. If you feel your actions may be misinterpreted, invite a chaperone into the room.
▪ Large group of people is followed over 10 years. Every 2 years, it is determined who develops heart disease and who does not.	What type of study is this?	Cohort study.
▪ Girl can groom herself, can hop on one foot, and has an imaginary friend.	How old is she?	Four years old.
▪ Man has flashbacks about his girlfriend's death 2 months ago following a hit-and-run accident. He often cries and wishes for the death of the culprit.	What is the diagnosis?	Normal bereavement.
▪ 36-year-old woman with a strong family history of breast cancer refuses a mammogram because she heard it hurts.	What do you do?	Discuss the risks and benefits of not having a mammogram. Each patient must give her own informed consent to each procedure; if the patient refuses, you must abide by her wishes.

BEHAVIORAL SCIENCE—HIGH-YIELD CLINICAL VIGNETTES (*continued*)

▪ 4-year-old girl complains of a burning feeling in her genitalia; otherwise, she behaves and sleeps normally. A smear of the discharge shows *N. gonorrhoeae*.	How was she infected?	Sexual abuse.
▪ 72-year-old man insists on stopping treatment for his heart condition because it makes him feel "funny."	What do you do?	Although you want to encourage the patient to take his medication, the patient has the final say in his own treatment regimen. You should investigate the "funny" feeling and determine if there are drugs available that don't elicit this particular side effect.
▪ During a particular stage of sleep, man has variable blood pressure and EEG together with penile tumescence.	What stage of sleep is he in?	REM sleep.
▪ A certain screening test has a 2% false-negative rate.	What is the sensitivity of the test?	Sensitivity is 98%.
▪ The prevalence of influenza in population A is 2 times the prevalence of influenza in population B. The incidence is the same in populations A and B.	What can be assumed about the disease course in population A versus population B?	The disease duration is 2 times longer in population A.

Types of studies

Study type	Design	Measures/example
Case-control study Observational and retrospective	Compares a group of people with disease to a group without. Asks, "What happened?"	**Odds ratio** (OR). "Patients with COPD had higher odds of a history of smoking than those without COPD."
Cohort study Observational and prospective	Compares a group with a given risk factor to a group without to assess whether the risk factor ↑ the likelihood of disease. Asks, "What will happen?"	**Relative risk** (RR). "Smokers had a higher risk of developing COPD than did nonsmokers."
Cross-sectional study Observational	Collects data from a group of people to assess frequency of disease (and related risk factors) at a particular point in time. Asks, "What is happening?"	**Disease prevalence.** Can show risk factor association with disease, but does not establish causality.
Twin concordance study	Compares the frequency with which both monozygotic twins or both dizygotic twins develop a disease.	Measures heritability.
Adoption study	Compares siblings raised by biologic vs. adoptive parents.	Measures heritability and influence of environmental factors.

Clinical trial — Experimental study involving humans. Compares therapeutic benefits of 2 or more treatments, or of treatment and placebo. Highest-quality study when randomized, controlled, and double-blinded.

	Study sample	Purpose
Phase I	Small number of patients, usually healthy volunteers.	Assesses safety, toxicity, and pharmacokinetics.
Phase II	Small number of patients with disease of interest.	Assesses treatment efficacy, optimal dosing, and adverse effects.
Phase III	Large number of patients randomly assigned either to the treatment under investigation or to the best available treatment (or placebo).	Compares the new treatment to the current standard of care. Is more convincing if double-blinded (i.e., neither patient nor doctor knows if the patient is in the treatment or control group).

Meta-analysis — Pools data from several studies to come to an overall conclusion. Achieves greater statistical power and integrates results of similar studies. Highest echelon of clinical evidence. May be limited by quality of individual studies or bias in study selection.

Prevalence vs. incidence

$$\text{Prevalence} = \frac{\text{total cases in population at a given time}}{\text{total population at risk}}$$

$$\text{Incidence} = \frac{\text{new cases in population over a given time period}}{\text{total population at risk during that time}}$$

Incidence is new **incidents.**

Prevalence ≅ incidence × disease duration.

Prevalence > incidence for chronic diseases (e.g., diabetes).

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

When calculating incidence, don't forget that people previously positive for a disease are no longer considered at risk.

Evaluation of diagnostic tests

Uses 2 × 2 table comparing test results with the actual presence of disease.

		Disease ⊕	Disease ⊖
Test	⊕	a	b
	⊖	c	d

Sensitivity	Proportion of all people with disease who test positive. Value approaching 1 is desirable for ruling **out** disease and indicates a low false-negative rate. Used for screening in diseases with low prevalence.	= a / (a + c) = 1 – false-negative rate **SNOUT** = **S**e**N**sitivity rules **OUT.**
Specificity	Proportion of all people without disease who test negative. Value approaching 1 is desirable for ruling **in** disease and indicates a low false-positive rate. Used as a confirmatory test after a positive screening test. Example: HIV testing. Screen with ELISA (sensitive, high false-positive rate, low threshold); confirm with Western blot (specific, high false-negative rate, high threshold).	= d / (d + b) = 1 – false-positive rate **SPIN** = **SP**ecificity rules **IN.**
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. (Note: If the prevalence of a disease in a population is low, even tests with high specificity or high sensitivity will have low positive predictive values!)	= a / (a + b)
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.	= d / (c+ d)

Odds ratio vs. relative risk

Odds ratio (OR) for case control studies	Odds of having disease in exposed group divided by odds of having disease in unexposed group. Approximates relative risk if prevalence of disease is not too high.
Relative risk (RR) for cohort studies	Relative probability of getting a disease in the exposed group compared to the unexposed group. Calculated as percent with disease in exposed group divided by percent with disease in unexposed group.
Attributable risk	The difference in risk between exposed and unexposed groups, or the proportion of disease occurrences that are a result of the exposure (e.g., smoking causes one-third of cases of pneumonia).

$$\text{Odds ratio} = \frac{a/b}{c/d} = \frac{ad}{bc}$$

$$\text{Relative risk} = \frac{a/(a+b)}{c/(c+d)}$$

$$\text{Attributable risk} = \frac{a}{a+b} - \frac{c}{c+d}$$

Risk factor	Disease ⊕	Disease ⊖
⊕	a	b
⊖	c	d

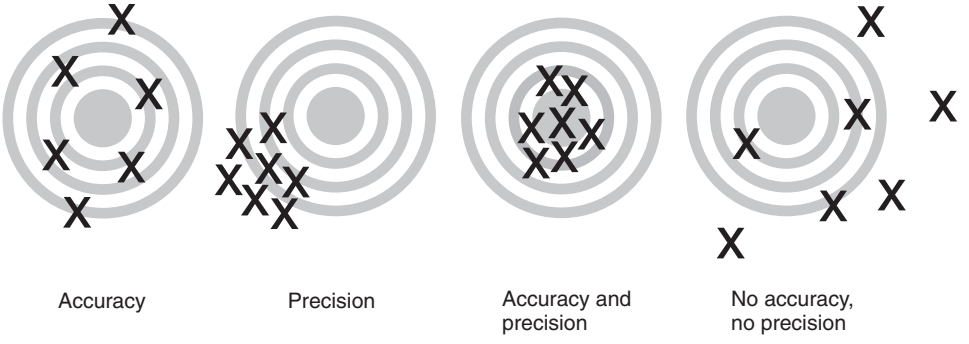
Precision vs. accuracy

Precision is:
1. The consistency and reproducibility of a test (reliability)
2. The absence of random variation in a test

Random error—reduced precision in a test.

Accuracy is the trueness of test measurements (validity).

Systematic error—reduced accuracy in a test.



Bias

Occurs when 1 outcome is systematically favored over another. Systematic errors.
1. **Selection bias**—nonrandom assignment to study group
2. **Recall bias**—knowledge of presence of disorder alters recall by subjects
3. **Sampling bias**—subjects are not representative relative to general population; therefore, results are not generalizable
4. **Late-look bias**—information gathered at an inappropriate time
5. **Procedure bias**—subjects in different groups are not treated the same—e.g., more attention is paid to treatment group, stimulating greater compliance

Ways to reduce bias:
1. Blind studies (double blind is better)
2. Placebo responses
3. Crossover studies (each subject acts as own control)
4. Randomization

Statistical distribution

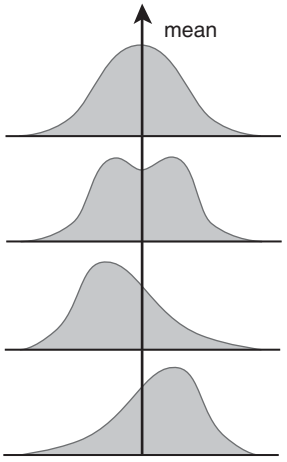
Terms that describe statistical distributions:

Normal ≈ Gaussian ≈ bell-shaped (mean = median = mode).

Bimodal is simply 2 humps.

Positive skew—mean > median > mode. Asymmetry with tail on right.

Negative skew—mean < median < mode. Asymmetry with tail on left.



Statistical hypotheses

Null (H_0): Hypothesis of no difference (e.g., there is no association between the disease and the risk factor in the population).

Alternative (H_1): Hypothesis that there is some difference (e.g., there is some association between the disease and the risk factor in the population).

Study results \ Reality	H_1	H_0
H_1	Power ($1 - \beta$)	α
H_0	β	

Error types

Type I error (α): Stating that there **is** an effect or difference when none exists (to mistakenly accept the experimental hypothesis and reject the null hypothesis). p = probability of making a type I error. p is judged against α, a preset level of significance (usually < .05).

If $p < .05$, then there is less than a 5% chance that the data will show something that is not really there.

α = you "saw" a difference that did not exist—for example, convicting an innocent man.

Type II error (β): Stating that there **is not** an effect or difference when one exists (to fail to reject the null hypothesis when in fact H_0 is false).

β is the probability of making a type II error.

β = you did not "see" a difference that does exist—for example, setting a guilty man free.

Power ($1 - \beta$)

Probability of rejecting null hypothesis when it is in fact false, or the likelihood of finding a difference if one in fact exists. It depends on:

1. Total number of end points experienced by population
2. Difference in compliance between treatment groups (differences in the mean values between groups)
3. Size of expected effect

If you ↑ sample size, you ↑ power. There is power in numbers.

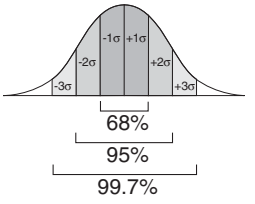
Power = $1 - \beta$.

► BEHAVIORAL SCIENCE–EPIDEMIOLOGY/BIOSTATISTICS *(continued)*

Standard deviation vs. standard error

n = sample size.
σ = standard deviation.
SEM = standard error of the mean.
SEM = $\sigma/\sqrt{n}$.
Therefore, SEM < σ and SEM decreases as n increases.

Normal (Gaussian) distribution:



Confidence interval

Range of values in which a specified probability of the means of repeated samples would be expected to fall.
CI = confidence interval.
CI = range from [mean – Z(SEM)] to [mean + Z(SEM)].
The 95% CI (corresponding to $p = .05$) is often used. For the 95% CI, Z = 1.96.

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.

_t_-test vs. ANOVA vs. χ^2

***t*-test** checks difference between the **means** of 2 groups.
ANOVA checks difference between the means of 3 or more groups.
χ^2 checks difference between 2 or more percentages or proportions of categorical outcomes (not mean values).

Mr. **T** is **mean.**

ANOVA = **AN**alysis **O**f **VA**riance of 3 or more variables.
χ^2 = compare percentages (%) or proportions.

Correlation coefficient (r)

r is always between −1 and +1. The closer the absolute value of r is to 1, the stronger the correlation between the two variables.
Coefficient of determination = r^2 (value that is usually reported).

Disease prevention

1°—prevent disease occurrence (e.g., vaccination).
2°—early detection of disease (e.g., Pap smear).
3°—reduce disability from disease (e.g., exogenous insulin for diabetes).

PDR:
Prevent
Detect
Reduce disability

Important prevention measures

Risk factor	Services
Diabetes	Eye, foot exams; urine tests
Drug use	Hepatitis immunizations; HIV, TB tests
Alcoholism	Influenza, pneumococcal immunizations; TB test
Overweight	Blood sugar tests for diabetes
Homeless, recent immigrant, inmate	TB test
High-risk sexual behavior	HIV, hepatitis B, syphilis, gonorrhea, chlamydia tests

Reportable diseases	Only some infectious diseases are reportable in all states, including AIDS, chickenpox, gonorrhea, hepatitis A and B, measles, mumps, rubella, salmonella, shigella, syphilis, and TB. Other diseases (including HIV) vary by state.	**H**ep, **H**ep, **H**ep, **H**ooray, the **SSSMMART Chick** is **Gon**e! **H**ep B **H**ep A **H**ep C **H**IV **S**almonella **S**higella **S**yphilis **M**easles **M**umps **A**IDS **R**ubella **T**uberculosis **Chick**enpox **Gon**orrhea

Leading causes of death in the United States by age

Infants	Congenital anomalies, short gestation/low birth weight, sudden infant death syndrome, maternal complications of pregnancy, respiratory distress syndrome.
Age 1–14	Injuries, cancer, congenital anomalies, homicide, heart disease.
Age 15–24	Injuries, homicide, suicide, cancer, heart disease.
Age 25–64	Cancer, heart disease, injuries, suicide, stroke.
Age 65+	Heart disease, cancer, stroke, COPD, pneumonia, influenza.

Medicare and Medicaid	Medicare and Medicaid are federal programs that originated from amendments to the Social Security Act. Medicare Part A = hospital; Part B = doctor bills. Medicaid is federal and state assistance for very low income people.	Medicar**E** is for **E**lderly. Medicai**D** is for **D**estitute.

► BEHAVIORAL SCIENCE–ETHICS

Core ethical principles

Autonomy	Obligation to respect patients as individuals and to honor their preferences in medical care.
Beneficence	Physicians have a special ethical (fiduciary) duty to act in the patient's best interest. May conflict with autonomy. If the patient can make an informed decision, ultimately the patient has the right to decide.
Nonmaleficence	"Do no harm." However, if the benefits of an intervention outweigh the risks, a patient may make an informed decision to proceed (most surgeries fall into this category).
Justice	To treat persons fairly.

Informed consent	Legally requires: 1. Discussion of pertinent information 2. Patient's agreement to the plan of care 3. Freedom from coercion	Patients must understand the risks, benefits, and alternatives, which include no intervention.

► BEHAVIORAL SCIENCE–ETHICS *(continued)*

Exceptions to informed consent	1. Patient lacks decision-making capacity or is legally incompetent 2. Implied consent in an emergency 3. Therapeutic privilege—withholding information when disclosure would severely harm the patient or undermine informed decision-making capacity 4. Waiver—patient waives the right of informed consent
Consent for minors	Parental consent must be obtained unless minor is married or otherwise emancipated.
Decision-making capacity	1. Patient makes and communicates a choice 2. Patient is informed 3. Decision remains stable over time 4. Decision is consistent with patient's values and goals 5. Decision is not a result of delusions or hallucinations The patient's family cannot require that a doctor withhold information from the patient.
Oral advance directive	Incapacitated patient's prior oral statements commonly used as guide. Problems arise from variance in interpretation. If patient was informed, directive is specific, patient made a choice, and decision was repeated over time, the oral directive is more valid.
Written advance directive	Living will—describes treatments the patient wishes to receive or not receive if he/she becomes incapacitated and cannot communicate about treatment decisions. Usually, patient directs physician to withhold or withdraw life-sustaining treatment if he/she develops a terminal disease or enters a persistent vegetative state. Durable power of attorney—patient designates a surrogate to make medical decisions in the event that he/she loses decision-making capacity. Patient may also specify decisions in clinical situations. Surrogate retains power unless revoked by patient. More flexible than a living will.
Confidentiality	Confidentiality respects patient privacy and autonomy. Disclosing information to family and friends should be guided by what the patient would want. The patient may waive the right to confidentiality (e.g., insurance companies).
Exceptions to confidentiality	1. Potential harm to others is serious 2. Likelihood of harm to self is great 3. No alternative means exist to warn or to protect those at risk 4. Physicians can take steps to prevent harm Examples include: 1. Infectious diseases—physicians may have a duty to warn public officials and identifiable people at risk 2. The Tarasoff decision—law requiring physician to directly inform and protect potential victim from harm; may involve breach of confidentiality 3. Child and/or elder abuse 4. Impaired automobile drivers 5. Suicidal/homicidal patients—physicians may hold patients involuntarily for a period of time

Malpractice

Civil suit under negligence requires:
1. Physician had a duty to the patient (**D**uty)
2. Physician breached that duty (**D**ereliction)
3. Patient suffers harm (**D**amage)
4. The breach of the duty was what caused the harm (**D**irect)

The most common factor leading to litigation is poor communication between physician and patient.

The **4 D's.**

Unlike a criminal suit, in which the burden of proof is "beyond a reasonable doubt," the burden of proof in a malpractice suit is "more likely than not."

Good Samaritan law

Relieves health care workers, as well as laypersons in some instances, from liability in certain emergency situations with the objective of encouraging health care workers to offer assistance.

Ethical situations

Situation	Appropriate response
Patient is noncompliant.	Work to improve the physician-patient relationship.
Patient has difficulty taking medications.	Provide written instructions; attempt to simplify treatment regimens.
Family members ask for information about patient's prognosis.	Avoid discussing issues with relatives without the permission of the patient.
A 17-year-old girl is pregnant and requests an abortion.	Many states require parental notification or consent for minors for an abortion. Parental consent is **not** required for emergency situations, treatment of STDs, medical care during pregnancy, and management of drug addiction.
A terminally ill patient requests physician assistance in ending his life.	In the overwhelming majority of states, refuse involvement in any form of physician-assisted suicide. Physicians may, however, prescribe medically appropriate analgesics that coincidentally shorten the patient's life.
Patient states that he finds you attractive.	Ask direct, closed-ended questions and use a chaperone if necessary. Romantic relationships with patients are **never** appropriate.
Patient refuses a necessary procedure or desires an unnecessary one.	Attempt to understand why the patient wants/does not want the procedure. Address the underlying concerns. Avoid performing unnecessary procedures.
Patient is angry about the amount of time he spent in the waiting room.	Apologize to the patient for any inconvenience. Stay away from efforts to explain the delay.
Patient is upset with the way he was treated by another doctor.	Suggest that the patient speak directly to that physician regarding his/her concerns. If the problem is with a member of the office staff, tell the patient you will speak to that individual.
A child wishes to know more about his illness.	Ask what the parents have told the child about his illness. Parents of a child decide what information can be relayed about the illness.
Patient continues to smoke, believing that cigarettes are good for him.	Ask how the patient feels about his/her smoking. Offer advice on cessation if the patient seems willing to make an effort to quit.
Minor (under age 18) requests condoms.	Physicians can provide counsel and contraceptives to minors without a parent's knowledge or consent.

► BEHAVIORAL SCIENCE–DEVELOPMENT

Apgar score — A 10-point scale evaluated at 1 minute and 5 minutes.

	0 points	1 point	2 points
Appearance	Blue	Trunk pink	All pink
Pulse	None	< 100/min	> 100/min
Grimace	None	Grimace	Grimace + cough
Activity	Limp	Some	Active
Respiration	None	Irregular	Regular

Low birth weight — Defined as < 2500 g. Associated with greater incidence of physical and emotional problems. Caused by prematurity or intrauterine growth retardation. Complications include infections, respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, and persistent fetal circulation.

Developmental milestones

Approximate age	Motor milestone	Cognitive/social milestone
Infant		
Birth–3 mo	Rooting reflex	
3 mo	Holds head up, Moro reflex disappears	Social smile
4–5 mo	Rolls front to back, sits when propped	Recognizes people
7–9 mo	Sits alone, crawls	Stranger anxiety, orients to voice
12–14 mo	Upgoing Babinski disappears	
15 mo	Walks	Few words, separation anxiety
Toddler		
12–24 mo	Climbs stairs, stacks 3 blocks	Object permanence; 200 words and **2**-word sentences at age **2**
18–24 mo	Stacks 6 blocks	Rapprochement
24–48 mo		Parallel play
24–36 mo		Core gender identity
Preschool		
30–36 mo	Stacks 9 blocks (number of blocks stacked = age in years × 3)	Toilet training ("**pee** at age **3**").
3 yrs	Rides tricycle (rides **3**-cycle at age **3**); copies line or circle drawing	900 words and complete sentences
4 yrs	Simple drawings (stick figure), hops on 1 foot	Cooperative play, imaginary friends, grooms self, brushes teeth
School age		
6–11 yrs		Reads; understands death Development of conscience (superego), same-sex friends, identification with same-sex parent
Adolescence (puberty)		
11 yrs (girls) 13 yrs (boys)		Abstract reasoning (formal operations), formation of personality

Changes in the elderly	1. Sexual changes: Men—slower erection/ejaculation, longer refractory period Women—vaginal shortening, thinning, and dryness 2. Sleep patterns— ↓ REM sleep, ↓ slow-wave sleep, ↑ sleep latency, ↑ awakenings during the night 3. Common medical conditions—arthritis, hypertension, heart disease, osteoporosis 4. Psychiatric disorders (excluding comorbidities) are found at a lower prevalence among the healthy elderly than at other life stages 5. ↑ suicide rate (males 65–74 years of age have the highest suicide rate in the United States) 6. ↓ vision, hearing, immune response, bladder control 7. ↓ renal, pulmonary, GI function 8. ↓ muscle mass, ↑ fat	Sexual interest does not ↓. Intelligence does not ↓.

Tanner stages of sexual development

1. Childhood
2. Pubic hair begins to develop (adrenarche), ↑ size of testes, breast tissue elevation
3. ↑ pubic hair, darkens, becomes curly, ↑ penis size/length
4. ↑ penis width, darker scrotal skin, development of glans, raised areolae
5. Adult; areolae are no longer raised

Grief	Normal bereavement characterized by shock, denial, guilt, and somatic symptoms. Typically lasts 6 months to 1 year. May experience illusions. Pathologic grief includes excessively intense or prolonged grief or grief that is delayed, inhibited, or denied. May experience depressive symptoms, delusions, and hallucinations.	
Kübler-Ross grief stages	**D**enial, **A**nger, **B**argaining, **G**rieving, **A**cceptance. Stages do not necessarily occur in this order, and > 1 stage can be present at once.	**D**eath **A**rrives **B**ringing **G**rave **A**djustments.

► BEHAVIORAL SCIENCE—PHYSIOLOGY

Stress effects	Stress induces production of free fatty acids, 17-OH corticosteroids, lipids, cholesterol, catecholamines; affects water absorption, muscular tonicity, gastrocolic reflex, and mucosal circulation.
Sexual dysfunction	Differential diagnosis includes: 1. Drugs (e.g., antihypertensives, neuroleptics, SSRIs, ethanol) 2. Diseases (e.g., depression, diabetes) 3. Psychological (e.g., performance anxiety)

► BEHAVIORAL SCIENCE–PHYSIOLOGY *(continued)*

Body-mass index (BMI)

BMI is a measure of weight adjusted for height.

$$\text{BMI} = \frac{\text{weight in kg}}{(\text{height in meters})^2}$$

< 18.5 underweight;
18.5–24.9 normal;
25.0–29.9 overweight;
> 30.0 obese.

Sleep stages

Stage (% of total sleep time in young adults)	Description	EEG waveform
	Awake (eyes open), alert, active mental concentration	**B**eta (highest frequency, lowest amplitude)
	Awake (eyes closed)	**A**lpha
1 (5%)	Light sleep	**T**heta
2 (45%)	Deeper sleep	**S**leep spindles and K complexes
3–4 (25%)	Deepest, non-REM sleep; sleepwalking; night terrors; bedwetting (slow-wave sleep)	**D**elta (lowest frequency, highest amplitude)
REM (25%)	Dreaming, loss of motor tone, possibly a memory processing function, erections, ↑ brain O_2 use	**B**eta At night, **BATS D**rink **B**lood.

1. Serotonergic predominance of raphe nucleus key to initiating sleep
2. NE reduces REM sleep
3. Extraocular movements during REM due to activity of PPRF (paramedian pontine reticular formation/conjugate gaze center)
4. REM sleep having the same EEG pattern as while awake and alert has spawned the terms "paradoxical sleep" and "desynchronized sleep"
5. Benzodiazepines shorten stage 4 sleep; thus useful for night terrors and sleepwalking
6. Imipramine is used to treat enuresis because it ↓ stage 4 sleep

REM sleep

↑ and variable pulse, REM, ↑ and variable blood pressure, penile/clitoral tumescence. Occurs every 90 minutes; duration ↑ through the night. ACh is the principal neurotransmitter involved in REM sleep. REM sleep ↓ with age.

REM sleep is like sex:
↑ pulse, penile/clitoral tumescence,
↓ with age.

Narcolepsy

Disordered regulation of sleep-wake cycles. May include hypnagogic (just before sleep) or hypnopompic (just before awakening) hallucinations. The patient's nocturnal and narcoleptic sleep episodes start off with REM sleep. **Cataplexy** (loss of all muscle tone following a strong emotional stimulus) in some patients. Strong genetic component. Treat with stimulants (e.g., amphetamines).

HIGH-YIELD PRINCIPLES IN

Biochemistry

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

—Mike Adams

"World, world, O world!
But that thy strange mutations make us hate thee,
Life would not yield to age."

—William Shakespeare, *King Lear,* Act IV, Scene I

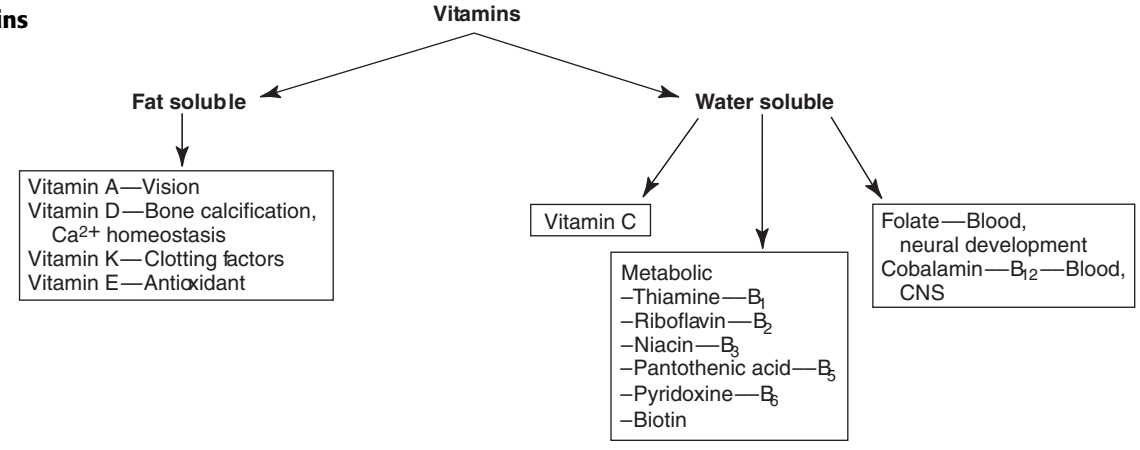
- High-Yield Clinical Vignettes
- Nutrition
- Molecular
- Cellular
- Metabolism
- Laboratory Techniques
- Genetics

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. 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, and physical chemistry. Detailed chemical structures are infrequently tested. Familiarity with the latest biochemical techniques that have medical relevance—such as enzyme-linked immunosorbent assay (ELISA), immunoelectrophoresis, Southern blotting, and PCR—is useful. Beware if you placed out of your medical school's biochemistry class, for the emphasis of the test differs from that of many undergraduate courses. Review the related biochemistry when studying pharmacology or genetic diseases as a way to reinforce and integrate the material.

BIOCHEMISTRY—HIGH-YIELD CLINICAL VIGNETTES

▪ Full-term neonate of an uneventful delivery becomes mentally retarded and hyperactive and has a musty odor.	What is the diagnosis?	PKU.
▪ Stressed executive comes home from work, consumes 7 or 8 martinis in rapid succession before dinner, and becomes hypoglycemic.	What is the mechanism?	NADH ↑ prevents gluconeogenesis by shunting pyruvate and oxaloacetate to lactate and malate.
▪ 2-year-old girl has an ↑ in abdominal girth, failure to thrive, and skin and hair depigmentation.	What is the diagnosis?	Kwashiorkor.
▪ Alcoholic develops a rash, diarrhea, and altered mental status.	What is the vitamin deficiency?	Vitamin B_3 (pellagra).
▪ 51-year-old man has black spots in his sclera and has noted that his urine turns black upon standing.	What is the diagnosis?	Alkaptonuria.
▪ 25-year-old man complains of severe chest pain and has xanthomas of his Achilles tendons.	What is the disease, and where is the defect?	Familial hypercholesterolemia; LDL receptor.
▪ Woman complains of intense muscle cramps and darkened urine after exercise.	What is the diagnosis?	McArdle's disease.
▪ 2 parents with albinism have a son who is normal.	What genetic mechanism could explain why the son is not affected?	Locus heterogeneity.
▪ 40-year-old man has chronic pancreatitis with pancreatic insufficiency.	What vitamins are likely deficient?	A, D, E, and K.
▪ Child exhibits weakness and enlarged calves.	What is the disease, and how it is inherited?	Duchenne's muscular dystrophy; X-linked recessive.

Vitamins



Vitamins: fat soluble	A, D, E, K. Absorption dependent on gut (ileum) and pancreas. Toxicity more common than for water-soluble vitamins, because these accumulate in fat.	Malabsorption syndromes (steatorrhea), such as cystic fibrosis and sprue, or mineral oil intake can cause fat-soluble vitamin deficiencies.
Vitamins: water soluble	B_1 (thiamine: TPP) B_2 (riboflavin: FAD, FMN) B_3 (niacin: NAD^+) B_5 (pantothenic acid: CoA) B_6 (pyridoxine: PLP) B_{12} (cobalamin) C (ascorbic acid) Biotin Folate	All wash out easily from body except B_{12} and folate (stored in liver). B-complex deficiencies often result in dermatitis, glossitis, and diarrhea.
Vitamin A (retinol)		
Deficiency	Night blindness, dry skin.	**Retinol** is vitamin **A**, so think **Retin-A** (used topically for wrinkles and acne). Found in leafy vegetables.
Function	Constituent of visual pigments (retinal).	
Excess	Arthralgias, fatigue, headaches, skin changes, sore throat, alopecia.	
Vitamin B_1 (thiamine)		
Deficiency	Beriberi and Wernicke-Korsakoff syndrome. Seen in alcoholism and malnutrition.	Spell beriberi as **B**er**1B**er**1.** Dry beriberi—polyneuritis, symmetrical muscle wasting. Wet beriberi—high-output cardiac failure (dilated cardiomyopathy), edema.
Function	In thiamine pyrophosphate, a cofactor for oxidative decarboxylation of α-ketoacids (pyruvate, α-ketoglutarate) and branched-chain AA dehydrogenase, and a cofactor for transketolase in the HMP shunt.	

► BIOCHEMISTRY–NUTRITION *(continued)*

Vitamin B_2 (riboflavin)

Deficiency	Angular stomatitis (inflammation of oral mucous linings), **C**heilosis (inflammation of lips), **C**orneal vascularization.	The **2 C's.** **F**AD and **F**MN are derived from ribo**F**lavin (B_2 = **2** ATP).
Function	Cofactor in oxidation and reduction (e.g., $FADH_2$).	

Vitamin B_3 (niacin)

Deficiency	Niacin is made by the body from tryptophan. Synthesis requires B_6. Pellagra can be caused by Hartnup disease (↓ tryptophan absorption), malignant carcinoid syndrome (↑ tryptophan metabolism), and INH (↓ vitamin B_6).	Pellagra's symptoms are the **3 D's: D**iarrhea, **D**ermatitis, **D**ementia (also beefy glossitis). **N**AD derived from **N**iacin (B_3 = **3** ATP).
Function	Constituent of NAD^+, $NADP^+$ (used in redox reactions). Derived from tryptophan using vitamin B_6.	

Vitamin B_5 (pantothenate)

Deficiency	Dermatitis, enteritis, alopecia, adrenal insufficiency.	
Function	Constituent of CoA (a cofactor for acyl transfers) and component of fatty acid synthase.	Pantothen-**A** is in Co-**A.**

Vitamin B_6 (pyridoxine)

Deficiency	Convulsions, hyperirritability (deficiency inducible by INH and oral contraceptives), peripheral neuropathy.
Function	Converted to pyridoxal phosphate, a cofactor used in transamination (e.g., ALT and AST), decarboxylation reactions, glycogen phosphorylase, and heme synthesis. Required for the synthesis of niacin from tryptophan.

Vitamin B_{12} (cobalamin)

Deficiency	Macrocytic, megaloblastic anemia; neurologic symptoms (optic neuropathy, subacute combined degeneration, paresthesia); glossitis.	Found only in animal products. Vitamin B_{12} deficiency is usually caused by malabsorption (sprue, enteritis, *Diphyllobothrium latum*), lack of intrinsic factor (pernicious anemia, gastric bypass surgery), or absence of terminal ileum (Crohn's disease). Use Schilling test to detect the etiology of the deficiency. Abnormal myelin is seen in B_{12} deficiency, possibly due to ↓ methionine or ↑ methylmalonic acid (from metabolism of accumulated methylmalonyl-CoA).
Function	Cofactor for homocysteine methyltransferase (transfers CH_3 groups as methylcobalamin) and methylmalonyl-CoA mutase. Stored primarily in the liver. Very large reserve pool (several years). Synthesized only by microorganisms.	

$$\text{Homocysteine + N-methyl THF} \xrightarrow{B_{12}} \text{Methionine + THF}$$

$$\text{Methylmalonyl-CoA} \xrightarrow{B_{12}} \text{Succinyl-CoA}$$

Folic acid		
Deficiency	Most common vitamin deficiency in the United States. Macrocytic, megaloblastic anemia (often no neurologic symptoms, as opposed to vitamin B_{12} deficiency).	**FOL**ate from **FOL**iage. Eat green leaves (because folic acid is not stored very long). Supplemental folic acid in early pregnancy reduces neural tube defects.
Function	Coenzyme (THF) for 1-carbon transfer; involved in methylation reactions. Important for the synthesis of nitrogenous bases in DNA and RNA.	
Biotin		
Deficiency	Dermatitis, enteritis. Caused by antibiotic use, excessive ingestion of raw eggs.	"**AVID**in in egg whites **AVID**ly binds biotin."
Function	Cofactor for carboxylations: 1. Pyruvate → oxaloacetate 2. Acetyl-CoA → malonyl-CoA 3. Propionyl-CoA → methylmalonyl-CoA	
Vitamin C (ascorbic acid)		
Deficiency	Scurvy—swollen gums, bruising, anemia, poor wound healing.	British sailors carried limes to prevent scurvy (origin of the word "limey").
Function	Necessary for hydroxylation of proline and lysine in collagen synthesis. Facilitates iron absorption by keeping iron in Fe^{2+} reduced state (more absorbable). Necessary as a cofactor for dopamine β-hydroxylase, which converts dopamine to NE.	
Vitamin D	D_2 = ergocalciferol, consumed in milk. D_3 = cholecalciferol, formed in sun-exposed skin. 25-OH D_3 = storage form. 1,25 $(OH)_2$ D_3 (calcitriol) = active form.	Remember that drinking milk (fortified with vitamin D) is good for bones.
Deficiency	Rickets in children (bending bones), osteomalacia in adults (soft bones), and hypocalcemic tetany.	
Function	↑ intestinal absorption of calcium and phosphate.	
Excess	Hypercalcemia, loss of appetite, stupor. Seen in sarcoidosis, a disease where the epithelioid macrophages convert vitamin D into its active form.	
Vitamin E		
Deficiency	↑ fragility of erythrocytes, neurodysfunction.	**V**itamin **E** is for **E**rythrocytes.
Function	Antioxidant (protects erythrocytes from hemolysis).	

► BIOCHEMISTRY–NUTRITION *(continued)*

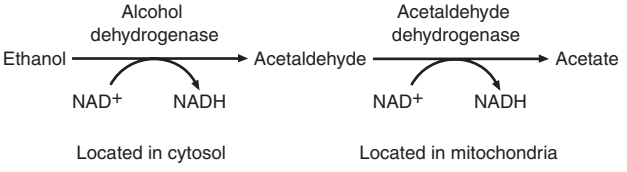
Vitamin K

Deficiency	Neonatal hemorrhage with ↑ PT and ↑ aPTT but normal bleeding time, because neonates have sterile intestines and are unable to synthesize vitamin K.	**K** for **K**oagulation. Note that the vitamin K–dependent clotting factors are II, VII, IX, X, and protein C and S. Warfarin is a vitamin K antagonist.
Function	Catalyzes γ-carboxylation of glutamic acid residues on various proteins concerned with blood clotting. Synthesized by intestinal flora. Therefore, vitamin K deficiency can occur after the prolonged use of broad-spectrum antibiotics.	Neonates are given vitamin K injection at birth to prevent hemorrhage.

Zinc deficiency

Delayed wound healing, hypogonadism, ↓ adult hair (axillary, facial, pubic); may predispose to alcoholic cirrhosis.

Ethanol metabolism

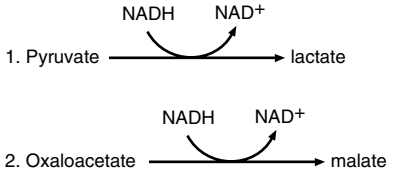


NAD^+ is the limiting reagent.
Alcohol dehydrogenase operates via zero-order kinetics.

Fomepizole inhibits alcohol dehydrogenase.
Disulfiram (Antabuse) inhibits acetaldehyde dehydrogenase (acetaldehyde accumulates, contributing to hangover symptoms).

Ethanol hypoglycemia

Ethanol metabolism ↑ $NADH/NAD^+$ ratio in liver, causing diversion of pyruvate to lactate and OAA to malate, thereby inhibiting gluconeogenesis and leading to hypoglycemia. This altered $NADH/NAD^+$ ratio is responsible for the hepatic fatty change (hepatocellular steatosis) seen in chronic alcoholics (shunting away from glycolysis and toward fatty acid synthesis, which normalizes the ratio).



Kwashiorkor vs. marasmus

Kwashiorkor—protein malnutrition resulting in skin lesions, edema, liver malfunction (fatty change). Clinical picture is small child with swollen belly.
Marasmus—energy malnutrition resulting in tissue and muscle wasting, loss of subcutaneous fat, and variable edema.

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

Chromatin structure

Negatively charged DNA loops twice around histone octamer (2 each of the positively charged H2A, H2B, H3, and H4) to form nucleosome bead.

Think of beads on a string.

H1 ties nucleosomes together in a string (30-nm fiber).

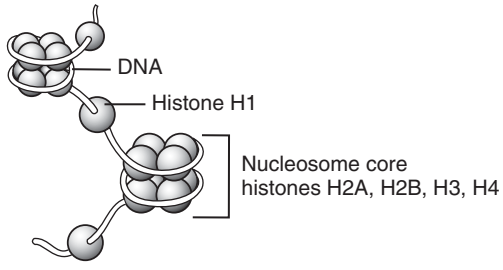
H1 is the only histone that is not in the nucleosome core.

In mitosis, DNA condenses to form mitotic chromosomes.

Heterochromatin — Condensed, transcriptionally inactive.

Euchromatin — Less condensed, transcriptionally active.

Eu = true, "truly transcribed."



Nucleotides

Purines (**A, G**) have 2 rings. Pyrimidines (**C, T, U**) have 1 ring. Guanine has a ketone. Thymine has a methyl. Deamination of cytosine makes uracil.

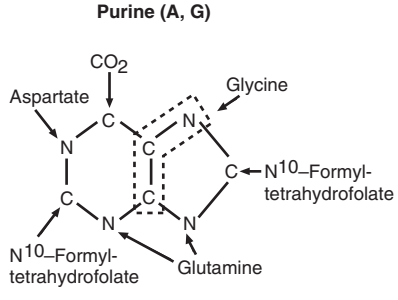
PURe **A**s **G**old: **PUR**ines.

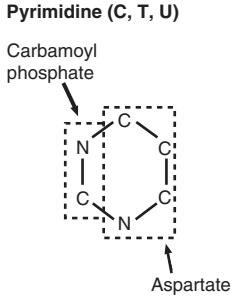
CUT the **PY** (pie): **PY**rimidines.

THYmine has a me**THY**l.

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.





Nucleotides (base + ribose + phosphate) are linked by 3′-5′ phosphodiester bond.

Nucleoside = base + ribose.

Amino acids necessary for purine synthesis:
- **G**lycine
- **A**spartate
- **G**lutamine

De novo nucleotide synthesis:
- Purines are made from IMP precursor.
- Pyrimidines are made from orotate precursor, with PRPP added later.
- Ribonucleotides are synthesized first and are converted to deoxyribonucleotides by ribonucleotide reductase.

► BIOCHEMISTRY–MOLECULAR *(continued)*

Transition vs. transversion

Transition	Substituting purine for purine or pyrimidine for pyrimidine.	Trans**I**tion = **I**dentical type.
Transversion	Substituting purine for pyrimidine or vice versa.	Trans**V**ersion = con**V**ersion between types.

Genetic code features

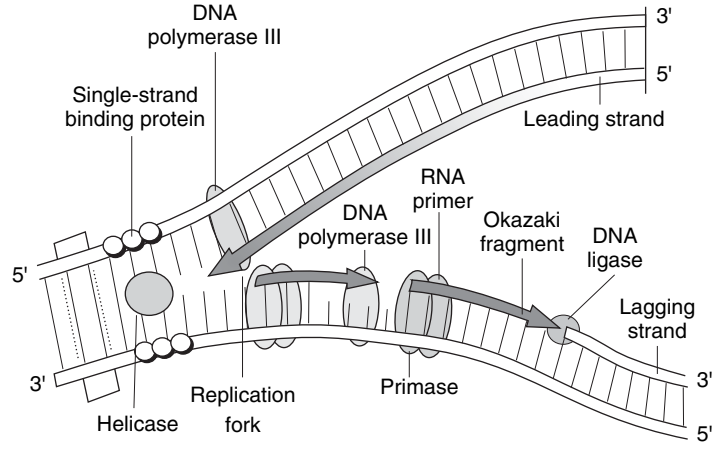
Unambiguous	Each codon specifies only 1 amino acid.	
Degenerate/ redundant	More than 1 codon may code for the same amino acid.	Methionine encoded by only 1 codon (AUG).
Commaless, nonoverlapping	Read from a fixed starting point as a continuous sequence of bases.	Some viruses are an exception.
Universal	Genetic code is conserved throughout evolution.	Exceptions include mitochondria, archaebacteria, *Mycoplasma*, and some yeasts.

Mutations in DNA

Silent	Same aa, often base change in 3rd position of codon (tRNA wobble).	Severity of damage: nonsense > missense > silent.
Missense	Changed aa (conservative—new aa is similar in chemical structure).	
Nonsense	Change resulting in early **stop** codon.	**Stop** the **nonsense!**
Frame shift	Change resulting in misreading of all nucleotides downstream, usually resulting in a truncated protein.	

DNA replication

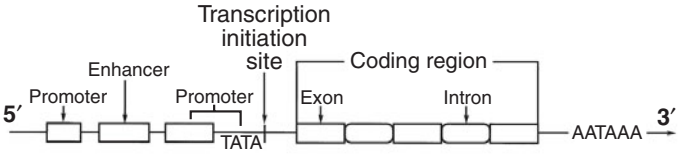
Eukaryotes	Eukaryotic genome has multiple origins of replication. Replication begins at a consensus sequence of AT-rich base pairs.	Eukaryotic DNA replication is more complicated than the prokaryotic process but uses many enzymes analogous to those below.
Prokaryotes	Single origin of replication—continuous bidirectional DNA synthesis on leading strand and discontinuous (Okazaki fragments) on lagging strand.	DNA replication is semiconservative.
Replication fork	Y-shaped region along DNA template where leading and lagging strands are synthesized.	
Helicase	Unwinds DNA template at replication fork. Single-stranded binding (SSB) protein prevents strands from reannealing.	
DNA topoisomerases	Create a nick in the helix to relieve supercoils. DNA gyrase is a specific prokaryotic topoisomerase.	Fluoroquinolones inhibit DNA gyrase.
Primase	Makes an RNA primer on which DNA polymerase III can initiate replication.	
DNA polymerase III	Elongates the chain by adding deoxynucleotides to the 3′ end (leading strand). Elongates lagging strand until it reaches primer of preceding fragment. 3′ → 5′ exonuclease activity "proofreads" each added nucleotide.	DNA polymerase III has 5′ → 3′ synthesis and proofreads with 3′ → 5′ exonuclease. DNA polymerase I and III are prokaryotic.
DNA polymerase I	Degrades RNA primer and fills in the gap with DNA.	DNA polymerase I excises RNA primer with 5′ → 3′ exonuclease.
DNA ligase	Seals.	



► BIOCHEMISTRY–MOLECULAR *(continued)*

DNA repair		
Single strand		
Nucleotide excision repair	Specific endonucleases release the oligonucleotide-containing damaged bases; DNA polymerase and ligase fill and reseal the gap, respectively.	Mutated in **xeroderma pigmentosum** (dry skin with melanoma and other cancers, "children of the night"), which prevents repair of thymidine dimers.
Base excision repair	Specific glycosylases recognize and remove damaged bases, AP endonuclease cuts DNA at apyrimidinic site, empty sugar is removed, and the gap is filled and resealed.	
Mismatch repair	Unmethylated, newly synthesized string is recognized, mismatched nucleotides are removed, and the gap is filled and resealed.	Mutated in **hereditary nonpolyposis colorectal cancer** (HNPCC).
Double strand		
Nonhomologous end joining	Brings together two ends of DNA fragments. No requirement for homology.	
DNA/RNA/protein synthesis direction	DNA and RNA are both synthesized **5′ → 3′.** Remember that the 5′ of the incoming nucleotide bears the triphosphate (energy source for bond). The 3′ hydroxyl of the nascent chain is the target.	mRNA is read 5′ to 3′. Protein synthesis is N to C.
Types of RNA	Of mRNA, rRNA, and tRNA: **m**RNA is the longest type. **r**RNA is the most abundant type. **t**RNA is the smallest type.	**M**assive, **R**ampant, **T**iny.
Start and stop codons		
mRNA initiation codons	AUG (or rarely GUG).	**AUG** in**AUG**urates protein synthesis.
Eukaryotes	Codes for methionine, which may be removed before translation is completed.	
Prokaryotes	Codes for formyl-methionine (f-Met).	
mRNA stop codons	UGA, UAA, UAG.	**UGA** = **U** **G**o **A**way. **UAA** = **U** **A**re **A**way. **UAG** = **U** **A**re **G**one.
Regulation of gene expression		
Promoter	Site where RNA polymerase and multiple other transcription factors bind to DNA upstream from gene locus (AT-rich upstream sequence with TATA and CAAT boxes).	Promoter mutation commonly results in dramatic ↓ in amount of gene transcribed.
Enhancer	Stretch of DNA that alters gene expression by binding transcription factors. 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.	

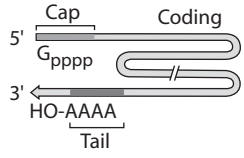
Functional organization of the gene



RNA polymerases

Eukaryotes	RNA polymerase I makes **r**RNA. RNA polymerase II makes **m**RNA. RNA polymerase III makes **t**RNA. No proofreading function, but can initiate chains. RNA polymerase II opens DNA at promoter site. α-amanitin inhibits RNA polymerase II.	I, II, and III are numbered as their products are used in protein synthesis. α-amanitin is found in death cap mushrooms.
Prokaryotes	RNA polymerase (multisubunit complex) makes all 3 kinds of RNA.	

RNA processing (eukaryotes)

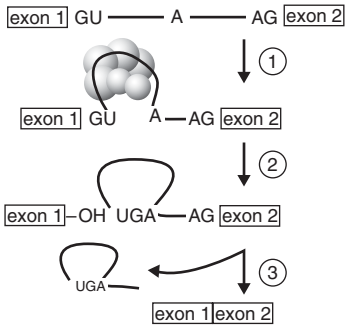


Occurs in nucleus. After transcription:
1. Capping on 5′ end (7-methylguanosine)
2. Polyadenylation on 3′ end (≈ 200 A's)
3. Splicing out of introns

Initial transcript is called heterogeneous nuclear RNA (hnRNA).
Capped and tailed transcript is called mRNA.

Only processed RNA is transported out of the nucleus.
AAUAAA = polyadenylation signal.
Poly-A polymerase does not require a template.

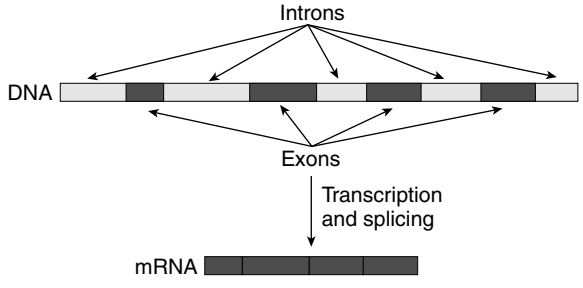
Splicing of pre-mRNA



Pre-mRNA splicing occurs in eukaryotes.
1—Primary transcript combines with snRNPs and other proteins to form spliceosome.
2—Lariat-shaped intermediate is generated.
3—Lariat is released to remove intron precisely and join 2 exons.

Introns vs. exons

Exons contain the actual genetic information coding for protein.
Introns are intervening noncoding segments of DNA.



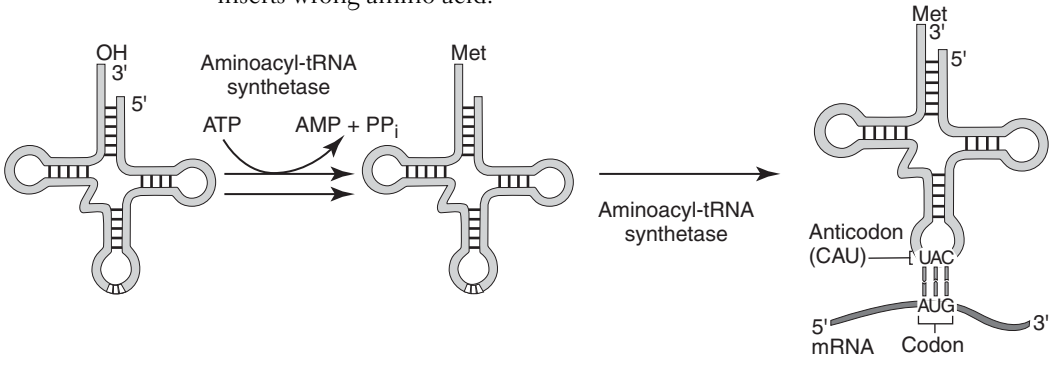
INtrons stay **IN** the nucleus, whereas **EX**ons **EX**it and are **EX**pressed.

Different exons can be combined by **alternative splicing** to make unique proteins in different tissues (e.g., β-thalassemia mutations).

► BIOCHEMISTRY–MOLECULAR *(continued)*

tRNA

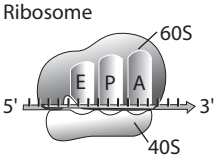
Structure	75–90 nucleotides, 2° structure, cloverleaf form, anticodon end is opposite 3′ aminoacyl end. All tRNAs, both eukaryotic and prokaryotic, have CCA at 3′ end along with a high percentage of chemically modified bases. The amino acid is covalently bound to the 3′ end of the tRNA.	
Charging	Aminoacyl-tRNA synthetase (1 per aa, uses ATP) scrutinizes aa before and after it binds to tRNA. If incorrect, bond is hydrolyzed by synthetase. The aa-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.



tRNA wobble

Accurate base pairing is 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.

Protein synthesis



Initiation	Activated by GTP hydrolysis, initiation factors (eIFs) help assemble the 40S ribosomal subunit with the initiator tRNA and are released when the mRNA and the ribosomal subunit assemble with the complex.	**E**ukaryotes—80S → 60S + 40S (**E**ven). Prokaryotes—70S → 50S + 30S (odd).
Elongation	1. Aminoacyl-tRNA binds to A site except for initiator methionine 2. Peptidyltransferase catalyzes peptide bond formation, transfers growing polypeptide to amino acid in A site 3. Ribosome advances 3 nucleotides toward 3′ end of RNA, moving peptidyl RNA to P site (translocation)	**A**TP—tRNA **A**ctivation (charging). **G**TP—tRNA **G**ripping and **G**oing places (translocation). **A** site = incoming **A**minoacyl tRNA. **P** site = accommodates growing **P**eptide.
Termination	Completed protein is released from ribosome through simple hydrolysis and dissociates.	**E** site = holds **E**mpty tRNA as it **E**xits.

Energy requirements of translation

tRNA aminoacylation	ATP → AMP (2 phosphoanhydride bonds)
Loading tRNA onto ribosome	GTP → GDP
Translocation	GTP → GDP
Total energy expenditure	4 high-energy phosphoanhydride bonds

Posttranslational modifications

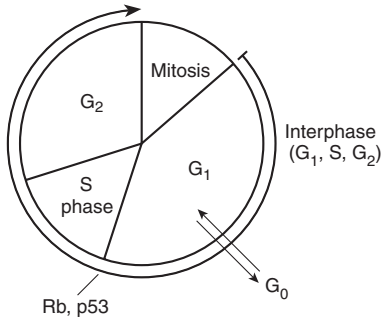
Trimming	Removal of N- or C-terminal propeptides from zymogens to generate mature proteins.
Covalent alterations	Phosphorylation, glycosylation, and hydroxylation.
Proteasomal degradation	Attachment of ubiquitin to defective proteins to tag them for breakdown.

► BIOCHEMISTRY—CELLULAR

Enzyme regulation methods

Enzyme concentration alteration (synthesis and/or destruction), covalent modification (e.g., phosphorylation), proteolytic modification (zymogen), allosteric regulation (e.g., feedback inhibition), pH, temperature, and transcriptional regulation (e.g., steroid hormones).

Cell cycle phases

Checkpoints control transitions between phases; regulated by cyclins, CDKs, and tumor suppressors	Mitosis (shortest phase): prophase-metaphase-anaphase-telophase. G_1 and G_0 are of variable duration. CDKs—constitutive and inactive. Cyclins—phase specific, activate CDKs. Cyclin-CDK complexes must be both activated and inactivated for cell cycle to progress. Rb and p53 tumor suppressors normally inhibit G_1-to-S progression; mutations in these genes result in unrestrained growth.	**G** stands for **G**ap or **G**rowth; **S** for **S**ynthesis. 
Permanent cells	Remain in G_0, regenerate from stem cells.	Neurons, skeletal and cardiac muscle cells, and RBCs remain in G_0.
Stable (quiescent) cells	Enter G_1 from G_0 when stimulated.	Hepatocytes, lymphocytes.
Labile cells	Never go to G_0, divide rapidly with a short G_1.	Bone marrow, gut epithelium, skin, hair follicles.

Rough endoplasmic reticulum (RER)

RER is the site of synthesis of secretory (exported) proteins and of N-linked oligosaccharide addition to many proteins.
Nissl bodies (in neurons)—synthesize enzymes (e.g., ChAT) and peptide neurotransmitters.
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.

► BIOCHEMISTRY–CELLULAR *(continued)*

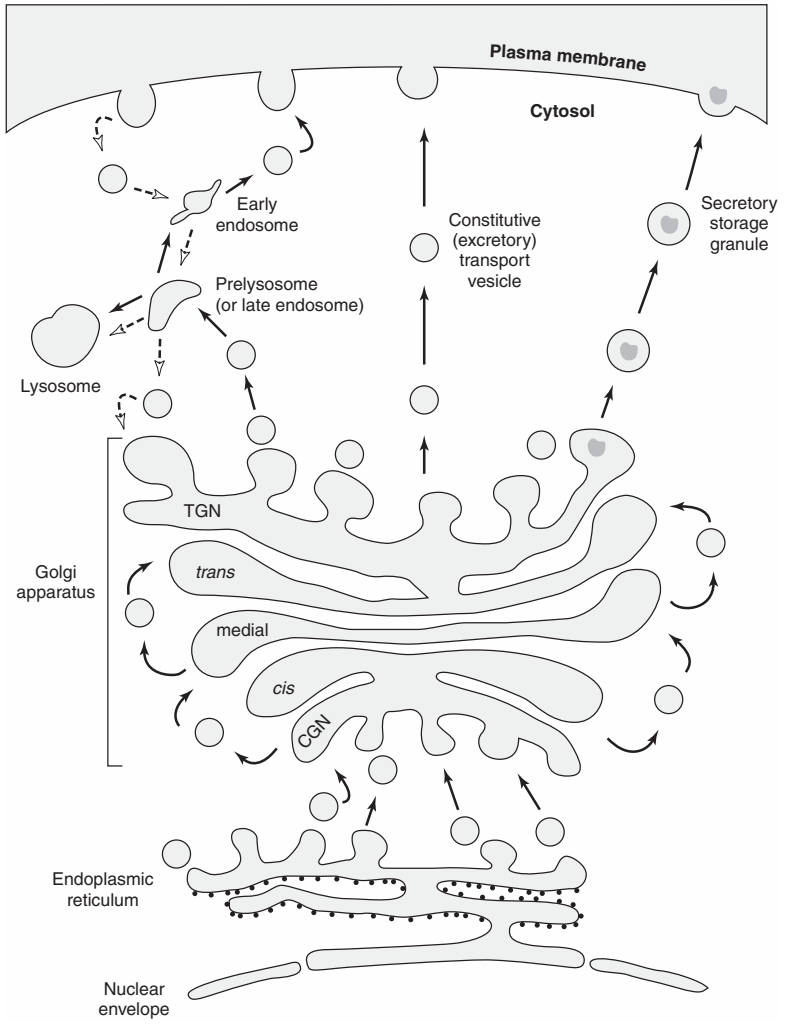
Smooth endoplasmic reticulum (SER)

SER is the site of steroid synthesis and detoxification of drugs and poisons.

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

Functions of Golgi apparatus

1. Distribution center of proteins and lipids from ER to the plasma membrane, lysosomes, and secretory vesicles
2. Modifies N-oligosaccharides on asparagine
3. Adds O-oligosaccharides to serine and threonine residues
4. Addition of mannose-6-phosphate to specific lysosomal proteins, which targets the protein to the lysosome
5. Proteoglycan assembly from proteoglycan core proteins
6. Sulfation of sugars in proteoglycans and of selected tyrosine on proteins



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I-cell disease—failure of addition of mannose-6-phosphate to lysosome proteins; enzymes are secreted outside the cell instead of being targeted to the lysosome.

Characterized by coarse facial features, clouded corneas, restricted joint movement, and high plasma levels of lysosomal enzymes. Often fatal in childhood.

Vesicular trafficking proteins:

COPI: retrograde, Golgi → ER.

COPII: anterograde, RER → cis-Golgi.

Clathrin: trans-Golgi → lysosomes, plasma membrane → endosomes (receptor-mediated endocytosis).

Microtubule

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

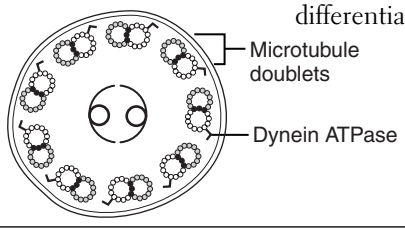
Drugs that act on microtubules:

1. Mebendazole/thiabendazole (antihelminthic)
2. Paclitaxel (Taxol) (anti–breast cancer)
3. Griseofulvin (antifungal)
4. Vincristine/vinblastine (anti-cancer)
5. Colchicine (anti-gout)

Chédiak-Higashi syndrome is due to a microtubule polymerization defect resulting in ↓ phagocytosis.

Cilia structure

9 + 2 arrangement of microtubules.
Dynein is an ATPase that links peripheral 9 doublets and causes bending of cilium by differential sliding of doublets.



Molecular motors:
Dynein = retrograde to microtubule (+ → −).
Kinesin = anterograde to microtubule (− → +).

Kartagener's syndrome

Immotile cilia due to a dynein arm defect. Results in male and female infertility (sperm immotile), bronchiectasis, and recurrent sinusitis (bacteria and particles not pushed out); associated with situs inversus.

Cytoskeletal elements

Actin and myosin	Microvilli, muscle contraction, cytokinesis, adhering junctions.
Microtubule	Cilia, flagella, mitotic spindle, neurons, centrioles.
Intermediate filaments	Vimentin, desmin, cytokeratin, glial fibrillary acid proteins (GFAP), neurofilaments.

Plasma membrane composition

Asymmetric fluid bilayer.
Contains cholesterol (~50%), phospholipids (~50%), sphingolipids, glycolipids, and proteins.
High cholesterol or long saturated fatty acid content → ↑ melting temperature, ↓ fluidity.

Phosphatidylcholine (lecithin) function

Major component of RBC membranes, of myelin, bile, and surfactant (DPPC—dipalmitoyl phosphatidylcholine).
Used in esterification of cholesterol (LCAT is lecithin-cholesterol acyltransferase).

Immunohistochemical stains

Stain	Cell type
Vimentin	Connective tissue
Desmin	Muscle
Cytokeratin	Epithelial cells
GFAP	Neuroglia
Neurofilaments	Neurons

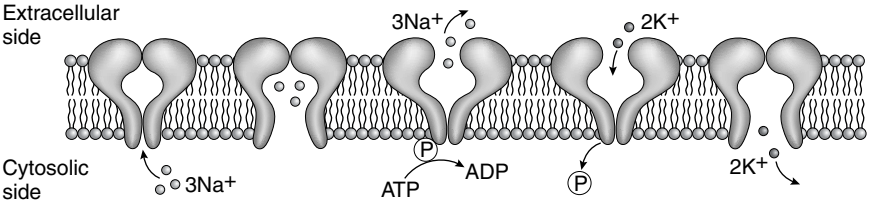
► BIOCHEMISTRY–CELLULAR *(continued)*

Sodium pump

Na^+-K^+ ATPase is located in the plasma membrane with ATP site on cytoplasmic side. For each ATP consumed, 3 Na^+ go out and 2 K^+ come in. During cycle, pump is phosphorylated.

Ouabain inhibits by binding to K^+ site.

Cardiac glycosides (digoxin and digitoxin from foxglove) also inhibit the Na^+-K^+ ATPase, causing ↑ cardiac contractility.



Collagen

Most abundant protein in the human body. Extensively modified.

Organizes and strengthens extracellular matrix.

Type I (90%)—**B**one, **S**kin, **T**endon, dentin, fascia, cornea, late wound repair.

Type II—**C**artilage (including hyaline), vitreous body, nucleus pulposus.

Type III (**R**eticulin)—skin, blood vessels, uterus, fetal tissue, granulation tissue.

Type IV—**B**asement membrane or basal lamina.

Be (**S**o **T**otally) **C**ool, **R**ead **B**ooks.

Type **I**: B**ONE.**

Type **II**: car**TWO**lage.

Type **IV**: Under the **floor** (basement membrane).

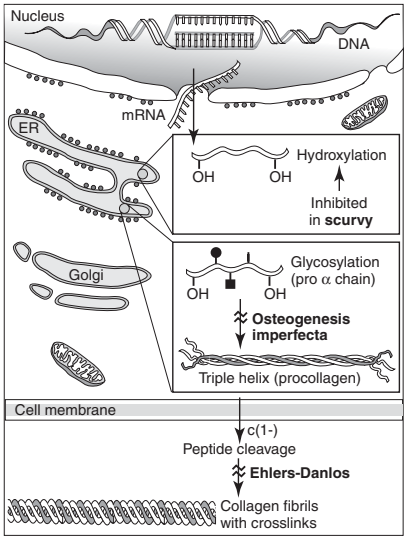
Collagen synthesis and structure

Inside fibroblasts

1. Synthesis (RER) — Translation of collagen α chains **(preprocollagen)**—usually Gly-X-Y polypeptide (X and Y are proline, hydroxyproline, or hydroxylysine).
2. Hydroxylation (ER) — Hydroxylation of specific proline and lysine residues (requires **vitamin C**).
3. Glycosylation (ER) — Glycosylation of pro-α-chain lysine residues and formation of **procollagen** (triple helix of 3 collagen α chains).
4. Exocytosis — Exocytosis of procollagen into extracellular space.

Outside fibroblasts

5. Proteolytic processing — Cleavage of terminal regions of procollagen transforms it into insoluble **tropocollagen.**
6. Cross-linking — Reinforcement of many staggered tropocollagen molecules by covalent lysine-hydroxylysine cross-linkage (by lysyl oxidase) to make **collagen fibrils.**



Ehlers-Danlos syndrome

Faulty collagen synthesis causing:
1. Hyperextensible skin
2. Tendency to bleed (easy bruising)
3. Hypermobile joints

10 types. Inheritance varies. Associated with berry aneurysms.

Type III collagen is most frequently affected (resulting in blood vessel instability).

Osteogenesis imperfecta	Variety of gene defects; all result in abnormal collagen synthesis. Most common form is autosomal-dominant with abnormal collagen type I. 1. **Multiple fractures** occurring with minimal trauma (brittle bone disease), which may occur during the birth process 2. **Blue sclerae** due to the translucency of the connective tissue over the choroid 3. Hearing loss (abnormal middle ear bones) 4. Dental imperfections due to lack of dentin	May be confused with child abuse. Type II is fatal in utero or in the neonatal period. Incidence is 1:10,000.
Elastin	Stretchy protein within lungs, large arteries, elastic ligaments, vocal cords, ligamenta flava (connect vertebrae). Rich in proline and glycine, nonglycosylated forms. Tropoelastin with fibrillin scaffolding. Relaxed and stretched conformations. α_1-antitrypsin inhibits elastase.	Marfan's syndrome is caused by a defect in fibrillin. Emphysema can be caused by excess elastase activity.

► BIOCHEMISTRY–METABOLISM

Metabolism sites

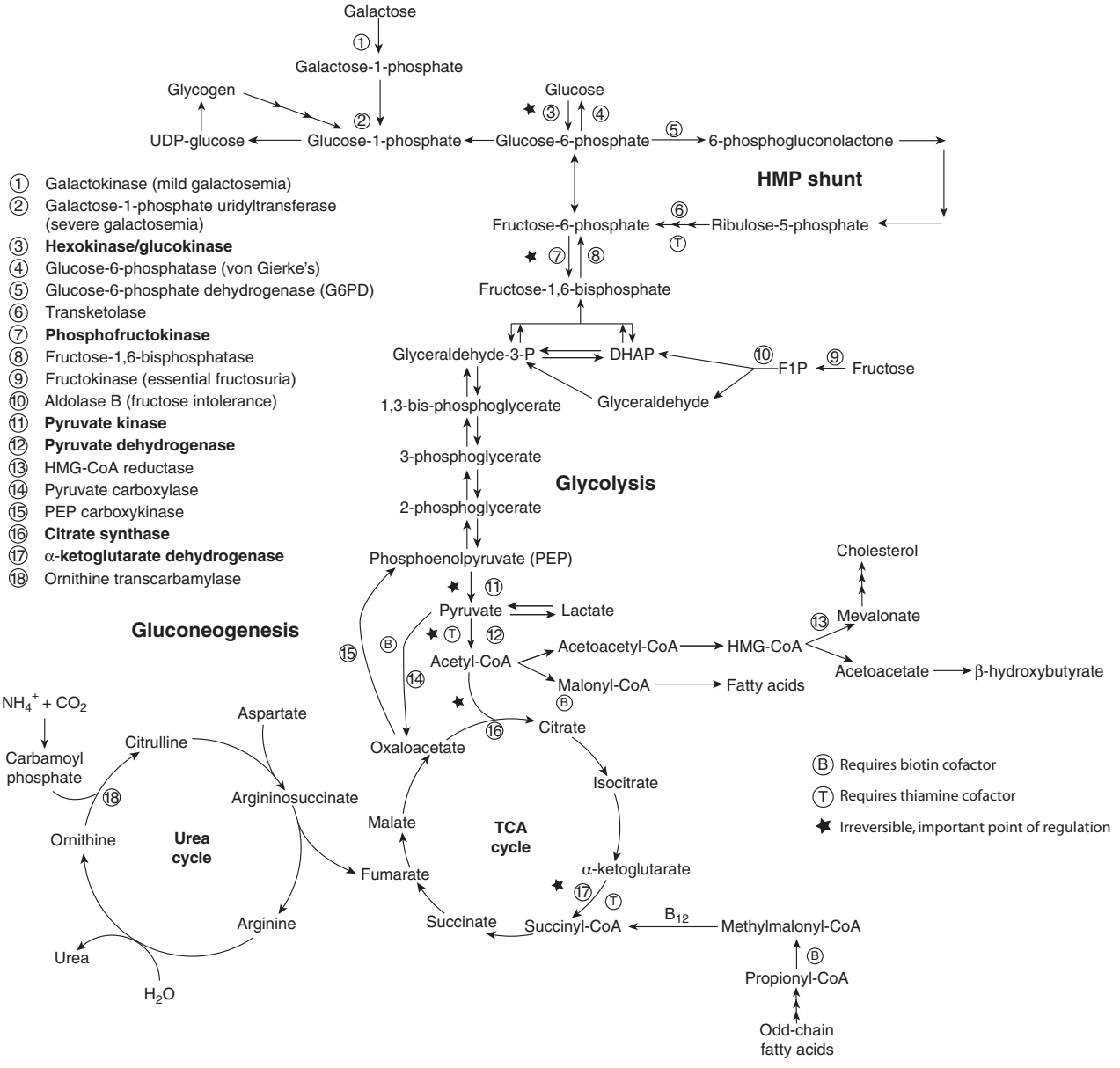
Mitochondria	Fatty acid oxidation (β-oxidation), acetyl-CoA production, Krebs cycle, oxidative phosphorylation.	
Cytoplasm	Glycolysis, fatty acid synthesis, HMP shunt, protein synthesis (RER), steroid synthesis (SER).	
Both	**H**eme synthesis, **U**rea cycle, **G**luconeogenesis.	**HUG**s take **two.**

Rate-determining enzymes of metabolic processes

Process	Enzyme
De novo pyrimidine synthesis	Aspartate transcarbamylase (ATCase)
De novo purine synthesis	Glutamine-PRPP amidotransferase
Glycolysis	Phosphofructokinase-1 (PFK-1)
Gluconeogenesis	Pyruvate carboxylase
TCA cycle	Isocitrate dehydrogenase
Glycogen synthesis	Glycogen synthase
Glycogenolysis	Glycogen phosphorylase
HMP shunt	Glucose-6-phosphate dehydrogenase (G6PD)
Fatty acid synthesis	Acetyl-CoA carboxylase (ACC)
Fatty acid oxidation	Carnitine acyltransferase I
Ketogenesis	HMG-CoA synthase
Cholesterol synthesis	HMG-CoA reductase
Heme synthesis	ALA synthase
Urea cycle	Carbamoyl phosphate synthase I

► BIOCHEMISTRY–METABOLISM *(continued)*

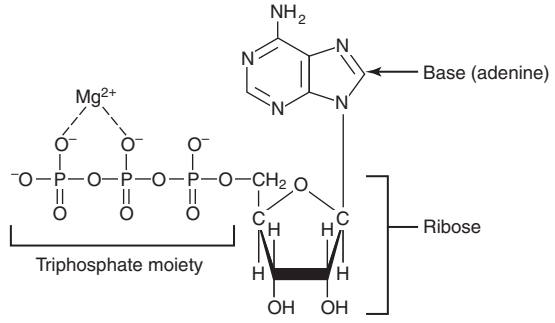
Summary of pathways



① Galactokinase (mild galactosemia)
② Galactose-1-phosphate uridyltransferase (severe galactosemia)
③ **Hexokinase/glucokinase**
④ Glucose-6-phosphatase (von Gierke's)
⑤ Glucose-6-phosphate dehydrogenase (G6PD)
⑥ Transketolase
⑦ **Phosphofructokinase**
⑧ Fructose-1,6-bisphosphatase
⑨ Fructokinase (essential fructosuria)
⑩ Aldolase B (fructose intolerance)
⑪ **Pyruvate kinase**
⑫ **Pyruvate dehydrogenase**
⑬ HMG-CoA reductase
⑭ Pyruvate carboxylase
⑮ PEP carboxykinase
⑯ **Citrate synthase**
⑰ α-**ketoglutarate dehydrogenase**
⑱ Ornithine transcarbamylase

ATP

Aerobic metabolism of glucose produces 32 ATP via malate-aspartate shuttle (heart and liver), 30 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.



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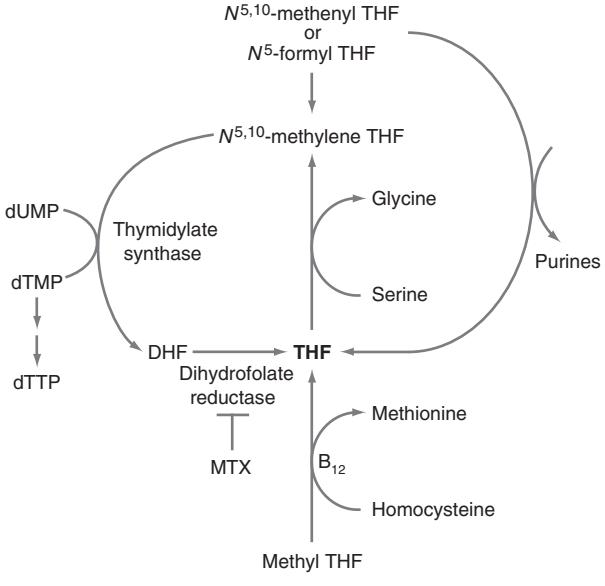
Activated carriers

Phosphoryl (ATP).
Electrons (NADH, NADPH, $FADH_2$).
Acyl (coenzyme A, lipoamide).
CO_2 (biotin).
1-carbon units (tetrahydrofolates).
CH_3 groups (SAM).
Aldehydes (TPP).

***S*-adenosyl-methionine**

ATP + methionine → **SAM.**
SAM transfers methyl units.
Regeneration of methionine (and thus SAM) is dependent on vitamin B_{12} and folate.

SAM the methyl donor man.



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Universal electron acceptors

Nicotinamides (**NAD^+**, **$NADP^+$**) and flavin nucleotides (**FAD^+**).

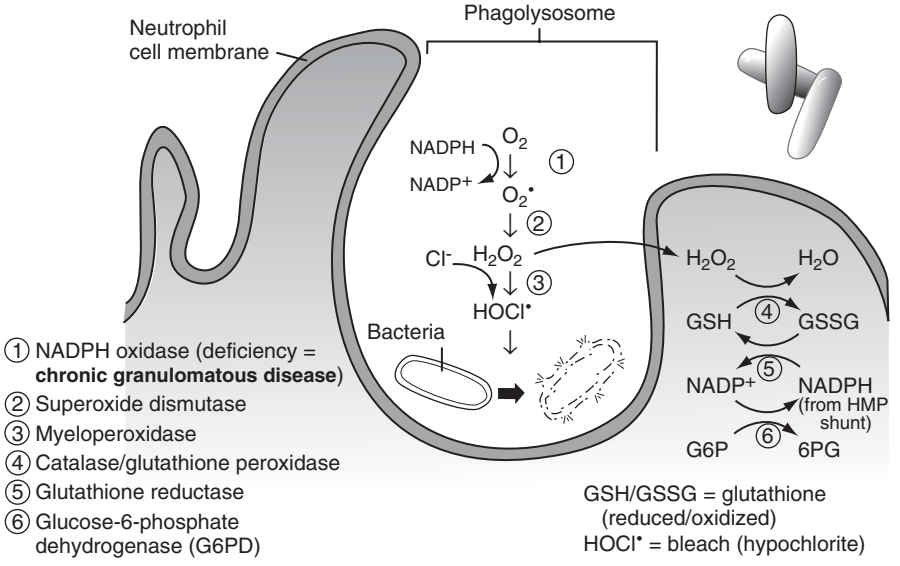
NAD^+ is generally used in **catabolic** processes to carry reducing equivalents away as NADH.

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:
1. Anabolic processes
2. Respiratory burst
3. P-450

Oxygen-dependent respiratory burst



Hexokinase vs. glucokinase

Hexokinase (ubiquitous)	High affinity (low K_m), low capacity (low V_{max}), uninduced by insulin.	Feedback inhibited by glucose-6-phosphate.
Glucokinase (liver and β cells of pancreas)	Low affinity (high K_m), high capacity (high V_{max}). induced by insulin.	No direct feedback inhibition. Phosphorylates excess glucose (e.g., after a meal) to sequester it in the liver.

Glycolysis regulation, key enzymes

Net glycolysis (cytoplasm):
Glucose + 2 P_i + 2 ADP + 2 NAD^+ → 2 Pyruvate + 2 ATP + 2 NADH + $2H^+$ + $2H_2O$.

Require ATP

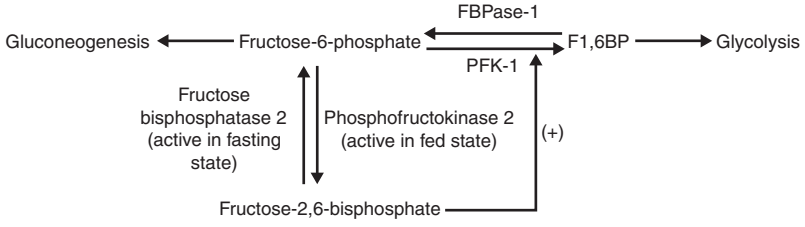
- D-glucose —(Hexokinase/glucokinase*)→ Glucose-6-phosphate — Glucose-6-P ⊖.
- Fructose-6-P —(Phosphofructokinase-1 **(rate-limiting step)**)→ Fructose-1,6-BP — **ATP** ⊖, AMP ⊕, **citrate** ⊖, fructose-2,6-BP ⊕.

Produce ATP

- 1,3-BPG ⇄ 3-PG (Phosphoglycerate kinase)
- Phosphoenolpyruvate —(Pyruvate kinase)→ Pyruvate — **ATP** ⊖, **alanine** ⊖, fructose-1,6-BP ⊕.
- Pyruvate —(Pyruvate dehydrogenase)→ Acetyl-CoA — **ATP** ⊖, **NADH** ⊖, **acetyl-CoA** ⊖.

* Glucokinase in liver; hexokinase in all other tissues.

Regulation by F2,6BP



F2,6BP is the most potent activator of phosphofructokinase (overrides inhibition by ATP and citrate) and is a potent regulator of glycolysis and gluconeogenesis.

Glycolytic enzyme deficiency

Associated with **hemolytic anemia** by decreasing activity of Na^+-K^+ ATPase, leading to RBC swelling and lysis.
Due to deficiencies in pyruvate kinase (95%), phosphoglucose isomerase (4%), and other glycolytic enzymes.

RBCs metabolize glucose anaerobically (no mitochondria) and thus depend solely on glycolysis.

Pyruvate dehydrogenase complex

The complex contains 3 enzymes that require 5 cofactors (the first 4 B vitamins plus lipoic acid):

1. Pyrophosphate (B_1, thiamine; TPP)
2. FAD (B_2, riboflavin)
3. NAD (B_3, niacin)
4. CoA (B_5, pantothenate)
5. Lipoic acid

Reaction: pyruvate + NAD^+ + CoA → acetyl-CoA + CO_2 + NADH.
Activated by exercise:
↑ NAD^+/NADH ratio
↑ ADP
↑ Ca^{2+}

The complex is similar to the α-ketoglutarate dehydrogenase complex (same cofactors, similar substrate and action).

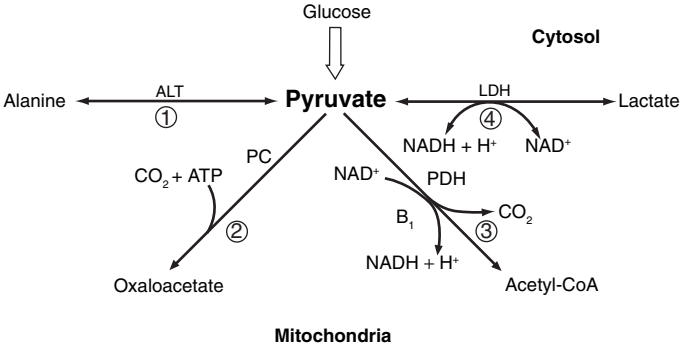
Arsenic inhibits lipoic acid:
Vomiting
Rice water stools
Garlic breath

Pyruvate dehydrogenase deficiency

Causes backup of substrate (pyruvate and alanine), resulting in lactic acidosis. Can be congenital or acquired (as in alcoholics due to B_1 deficiency).
Findings: neurologic defects.
Treatment: ↑ intake of ketogenic nutrients (e.g., high fat content or ↑ lysine and leucine).

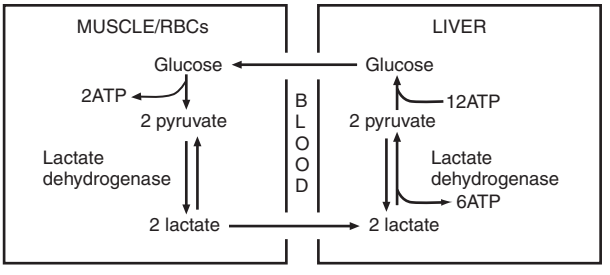
Lysine and **L**eucine—the only purely ketogenic amino acids.

Pyruvate metabolism



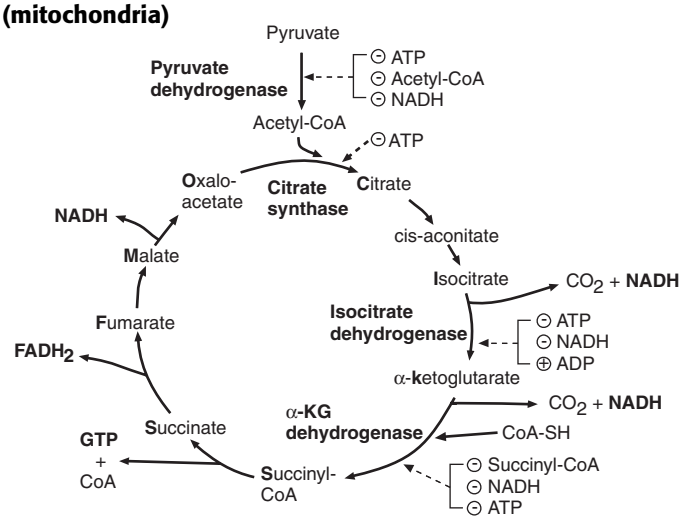
Functions of different pyruvate metabolic pathways:
1. Alanine carries amino groups to the liver from muscle
2. Oxaloacetate can replenish TCA cycle or be used in gluconeogenesis
3. Transition from glycolysis to the TCA cycle
4. End of anaerobic glycolysis (major pathway in RBCs, leukocytes, kidney medulla, lens, testes, and cornea)

Cori cycle



The Cori cycle allows lactate generated during anaerobic metabolism to undergo hepatic gluconeogenesis and become a source of glucose for muscle/RBCs. This comes at the cost of a net loss of 4 ATP/cycle.
Shifts metabolic burden to the liver.

TCA cycle (mitochondria)



* Enzymes in boldface are irreversible.

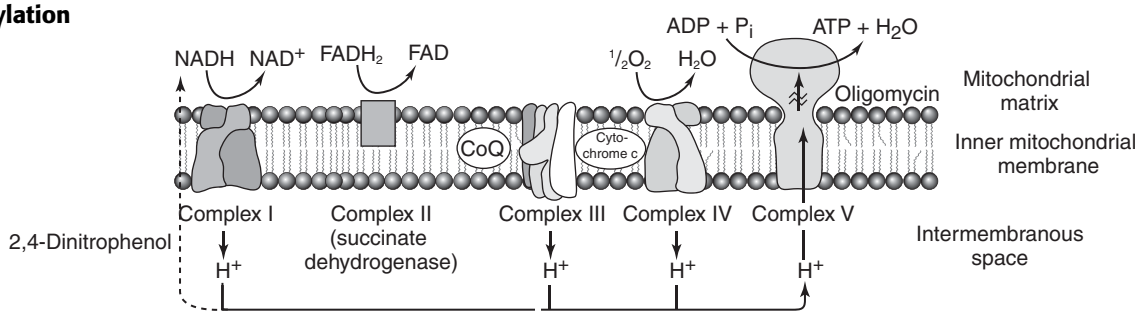
Produces 3 NADH, 1 $FADH_2$, 2 CO_2, 1 GTP per acetyl-CoA = 12 ATP/acetyl-CoA (2× everything per glucose).

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

Citrate **I**s **K**rebs' **S**tarting **S**ubstrate **F**or **M**aking **O**xaloacetate.

Electron transport chain and oxidative phosphorylation

NADH electrons from glycolysis enter mitochondria via malate-aspartate or glycerol-3-phosphate shuttle.



Electron transport chain

1 NADH → 3 ATP; 1 $FADH_2$ → 2 ATP.

Oxidative phosphorylation poisons

Electron transport inhibitors	Directly inhibit electron transport, causing a ↓ proton gradient and block of ATP synthesis.	Rotenone, CN^-, antimycin A, CO.
ATPase inhibitors	Directly inhibit mitochondrial ATPase, causing an ↑ proton gradient, but no ATP is produced because electron transport stops.	Oligomycin.
Uncoupling agents	↑ permeability of membrane, causing a ↓ proton gradient and ↑ O_2 consumption. ATP synthesis stops, but electron transport continues.	2,4-DNP, aspirin, and thermogenin in brown fat.

Gluconeogenesis, irreversible enzymes

Pyruvate carboxylase	In mitochondria. Pyruvate → oxaloacetate. Gluconeogenesis goes through oxaloacetate (vs. glycolysis)	Requires biotin, ATP. Activated by acetyl-CoA.
PEP carboxykinase	In cytosol. Oxaloacetate → phosphoenolpyruvate.	Requires GTP.
Fructose-1,6-bisphosphatase	In cytosol. Fructose-1,6-bisphosphate → fructose-6-P.	
Glucose-6-phosphatase	In ER. Glucose-6-P → glucose.	**P**athway **P**roduces **F**resh **G**lucose.

Above enzymes found only in **liver, kidney, intestinal epithelium.** Muscle cannot participate in gluconeogenesis.

Deficiency of the key gluconeogenic enzymes causes hypoglycemia.

Odd-chain fatty acids yield 1 propionyl-CoA during metabolism, which can enter the TCA cycle, undergo gluconeogenesis, and serve as a glucose source. Even-chain fatty acids cannot produce new glucose, since they yield only acetyl-CoA equivalents.

► BIOCHEMISTRY–METABOLISM *(continued)*

Pentose phosphate pathway (HMP shunt)

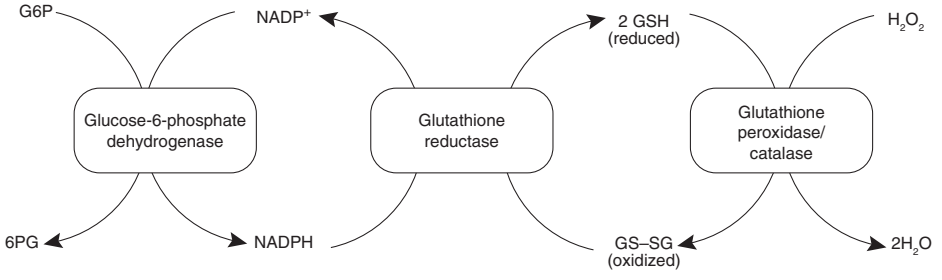
Produces NADPH, which is required for fatty acid and steroid biosynthesis and for glutathione reduction inside RBCs. All reactions of this pathway occur in the cytoplasm. No ATP is used or produced.
Sites: lactating mammary glands, liver, adrenal cortex (sites of fatty acid or steroid synthesis), and RBCs.

Reactions	Key enzymes	Products
Oxidative (irreversible)	Glucose-6-phosphate dehydrogenase	NADPH (for fatty acid and steroid synthesis, glutathione reduction, and cytochrome P-450)
Nonoxidative (reversible)	Transketolases (require thiamine)	Ribose-5-phosphate (for nucleotide synthesis), G3P, F6P (glycolytic intermediates)

Glucose-6-phosphate dehydrogenase deficiency

G6PD is a rate-limiting enzyme in HMP shunt (which yields NADPH). NADPH is necessary to keep glutathione reduced, which in turn detoxifies free radicals and peroxides. ↓ NADPH in RBCs leads to **hemolytic anemia** due to poor RBC defense against oxidizing agents (fava beans, sulfonamides, primaquine) and antituberculosis drugs.

G6PD deficiency is more prevalent among blacks.
Heinz bodies—altered **H**emoglobin precipitates within RBCs. Bite cells result from the phagocytic removal of Heinz bodies from macrophages.
X-linked recessive disorder.
↑ malarial resistance.

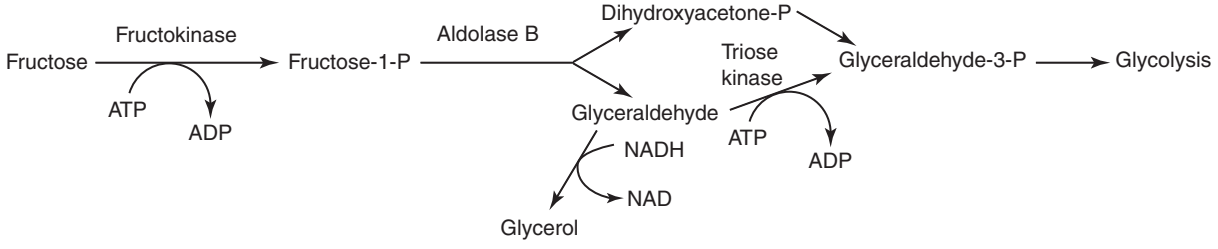


Disorders of fructose metabolism

Fructose intolerance	Hereditary deficiency of **aldolase B** (recessive). Fructose-1-phosphate accumulates, causing a ↓ in available phosphate, which results in inhibition of glycogenolysis and gluconeogenesis. Symptoms: hypoglycemia, jaundice, cirrhosis, vomiting. Treatment: must ↓ intake of both fructose and sucrose (glucose + fructose).
Essential fructosuria	Involves a defect in **fructokinase** and is a benign, asymptomatic condition, since fructose does not enter cells. Symptoms: fructose appears in blood and urine.

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

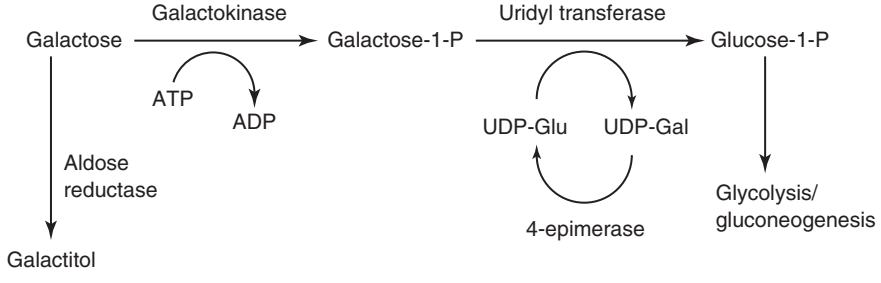
FRUCTOSE METABOLISM (LIVER)



Disorders of galactose metabolism

Galactosemia	Absence of **galactose-1-phosphate uridyltransferase.** Autosomal recessive. Damage is caused by accumulation of toxic substances (including galactitol) rather than absence of an essential compound. Symptoms: cataracts, hepatosplenomegaly, mental retardation. Treatment: exclude galactose and lactose (galactose + glucose) from diet.
Galactokinase deficiency	Causes galactosemia and galactosuria, galactitol accumulation if galactose is present in diet.

GALACTOSE METABOLISM

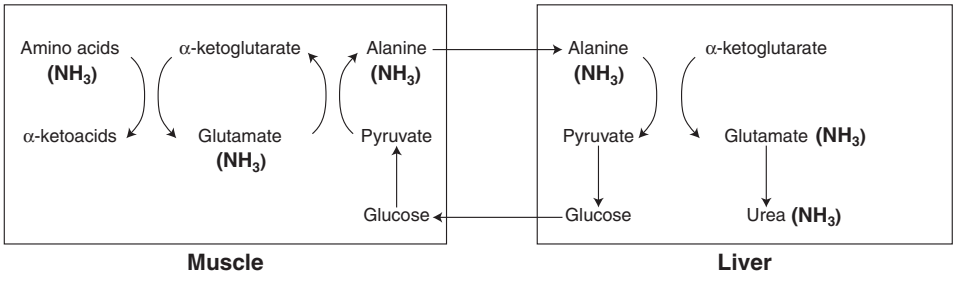


Lactase deficiency	Age-dependent and/or hereditary lactose intolerance (blacks, Asians) due to loss of brush-border enzyme. Symptoms: bloating, cramps, osmotic diarrhea. Treatment: avoid milk or add lactase pills to diet.

► BIOCHEMISTRY–METABOLISM *(continued)*

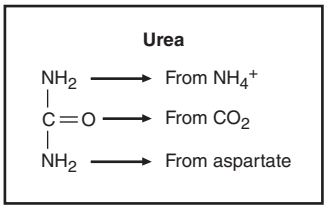
Amino acids	Only L-form amino acids are found in proteins.	
Essential	Ketogenic: Leu, Lys. Glucogenic/ketogenic: Ile, Phe, Tyr, Thr. Glucogenic: Met, Val, Arg, His.	Ketogenic amino acids form ketone bodies. Arg and His are required during periods of growth.
Acidic	Asp and Glu (negatively charged at body pH).	
Basic	Arg, Lys, and His. Arg is most basic. His has no charge at body pH.	Arg and Lys are ↑ in histones, which bind negatively charged DNA.

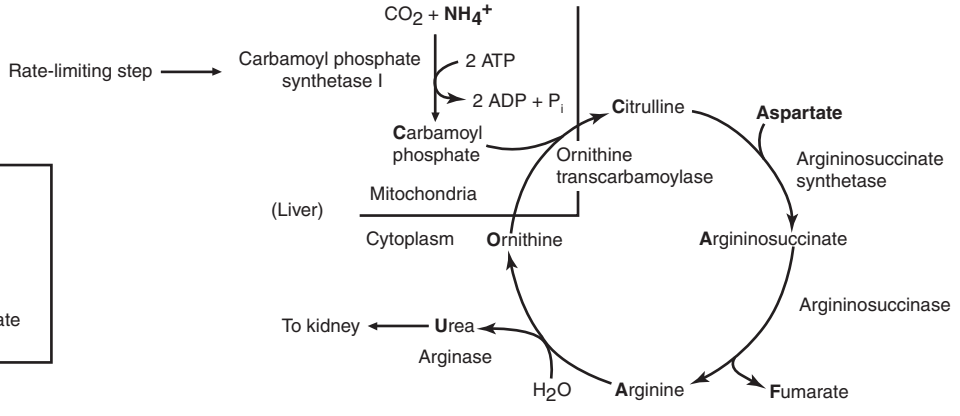
Transport of ammonium by alanine and glutamine



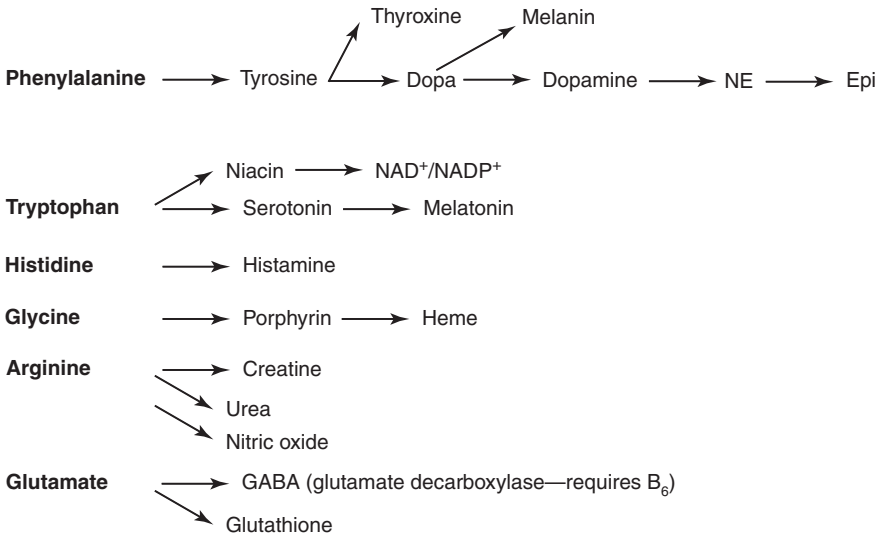
Hyperammonemia	Can be acquired (e.g., liver disease) or hereditary (e.g., ornithine transcarbamoylase deficiency). Excess NH_4^+ depletes α-ketoglutarate, leading to inhibition of TCA cycle. Treatment: benzoate or phenylbutyrate to lower serum ammonia levels.	**Ammonia intoxication:** tremor, slurring of speech, somnolence, vomiting, cerebral edema, blurring of vision.

Urea cycle	The urea cycle does not itself degrade amino acids into amino groups. Instead, it functions to excrete excess nitrogen (NH_4^+) generated by amino acid catabolism.	**O**rdinarily, **C**areless **C**rappers **A**re **A**lso **F**rivolous **A**bout **U**rination.

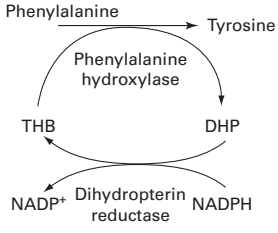




Amino acid derivatives



Phenylketonuria



Normally, phenylalanine is converted into tyrosine (nonessential AA). In PKU, there is ↓ phenylalanine hydroxylase or ↓ tetrahydrobiopterin cofactor. Tyrosine becomes essential and phenylalanine builds up, leading to excess phenylketones in urine.

Findings: mental retardation, growth retardation, fair skin, eczema, musty body odor.

Treatment: ↓ **phenylalanine** (contained in aspartame, e.g., NutraSweet) and ↑ **tyrosine** in diet.

Screened for at birth.

Phenylketones—phenylacetate, phenyllactate, and phenylpyruvate.

Autosomal-recessive disease. Incidence ≈ 1:10,000.

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

Alkaptonuria (ochronosis)

Congenital deficiency of **homogentisic acid oxidase** in the degradative pathway of tyrosine. Resulting alkapton bodies cause urine to turn black on standing. Also, the connective tissue is dark. Benign disease. May have debilitating arthralgias.

Albinism

Congenital deficiency of either of the following:

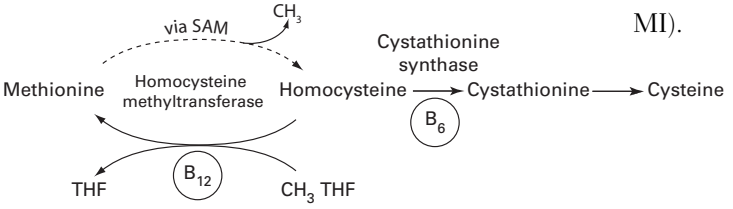
1. Tyrosinase (inability to synthesize melanin from tyrosine)—autosomal recessive
2. Defective tyrosine transporters (↓ amounts of tyrosine and thus melanin)

Can result from a lack of migration of neural crest cells.

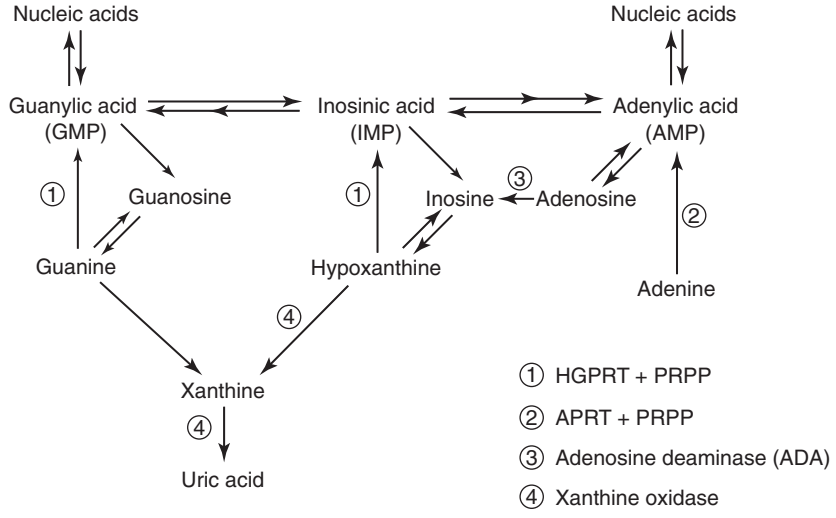
Lack of melanin results in an ↑ risk of skin cancer.

Variable inheritance due to locus heterogeneity.

► BIOCHEMISTRY–METABOLISM *(continued)*

Homocystinuria	3 forms (all autosomal recessive): 1. Cystathionine synthase deficiency (treatment: ↓ Met and ↑ Cys, and ↑ B_{12} and folate in diet) 2. ↓ affinity of cystathionine synthase for pyridoxal phosphate (treatment: ↑↑ vitamin B_6 in diet) 3. Homocysteine methyltransferase deficiency  	All forms result in excess homocysteine, and cysteine becomes essential. Can cause mental retardation, osteoporosis, tall stature, kyphosis, lens subluxation (downward and inward), and atherosclerosis (stroke and MI).
Cystinuria	Common (1:7000) inherited defect of renal tubular amino acid transporter for cysteine, ornithine, lysine, and arginine in the PCT of the kidneys. Excess cystine in urine can lead to the precipitation of **cystine kidney stones** (staghorn calculi).	Treat with acetazolamide to alkalinize the urine. Cystine is made of 2 cysteines connected by a disulfide bond.
Maple syrup urine disease	Blocked degradation of **branched** amino acids (**I**le, **V**al, **L**eu) due to ↓ α-ketoacid dehydrogenase. Causes ↑ α-ketoacids in the blood, especially Leu. Causes severe CNS defects, mental retardation, and death.	Urine smells like maple syrup. **I L**ove **V**ermont maple syrup.

Purine salvage deficiencies



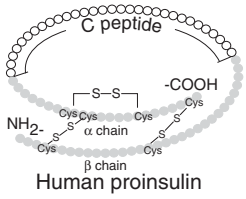
Adenosine deaminase deficiency	ADA deficiency can cause SCID. Excess ATP and dATP imbalances nucleotide pool via feedback inhibition of ribonucleotide reductase. This prevents DNA synthesis and thus ↓ lymphocyte count. 1st disease to be treated by experimental human gene therapy.	SCID—severe combined (T and B) immunodeficiency disease. **SCID** happens to **kids** (i.e., "bubble boy").
Lesch-Nyhan syndrome	Purine salvage problem owing to absence of **HGPRT**, which converts hypoxanthine to IMP and guanine to GMP. X-linked recessive. Results in excess uric acid production. Findings: retardation, self-mutilation, aggression, hyperuricemia, gout, and choreoathetosis.	**H**e's **G**ot **P**urine **R**ecovery **T**rouble.

► BIOCHEMISTRY–METABOLISM *(continued)*

Metabolic fuel use

Exercise	As distances ↑, ATP is obtained from additional sources.	1 g protein or carbohydrate = 4 kcal.
100-meter sprint (seconds)	Stored ATP, creatine phosphate, anaerobic glycolysis.	1 g fat = 9 kcal.
1000-meter run (minutes)	Above + oxidative phosphorylation.	
Marathon (hours)	Glycogen and FFA oxidation; glucose conserved for final sprinting.	
Fasting and starvation	Priorities are to supply sufficient glucose to brain and RBCs and to preserve protein.	
Days 1–3	Blood glucose level maintained by: 1. Hepatic glycogenolysis and glucose release 2. Adipose release of FFA 3. Muscle and liver shifting fuel use from glucose to FFA 4. Hepatic gluconeogenesis from peripheral tissue lactate and alanine, and from adipose tissue glycerol and propionyl-CoA from odd-chain FFA metabolism (the only triacylglycerol components that can contribute to gluconeogenesis)	
After day 3	Muscle protein loss is maintained by hepatic formation of ketone bodies, supplying the brain and heart.	
After several weeks	Ketone bodies become main source of energy for brain, so less muscle protein is degraded than during days 1–3. Survival time is determined by amount of fat stores. After this is depleted, vital protein degradation accelerates, leading to organ failure and death.	

Insulin



Human proinsulin

Made in β cells of pancreas in response to ATP from glucose metabolism acting on K^+ channels and depolarizing cells. Required for adipose and skeletal muscle uptake of glucose.

GLUT2 receptors are found in β cells and GLUT4 in **muscle and fat.** Insulin inhibits glucagon release by α cells of pancreas.

Serum C-peptide is not present with exogenous insulin intake (proinsulin → insulin + C-peptide).

Anabolic effects of insulin:

1. ↑ glucose transport
2. ↑ glycogen synthesis and storage
3. ↑ triglyceride synthesis and storage
4. ↑ Na^+ retention (kidneys)
5. ↑ protein synthesis (muscles)
6. ↑ cellular uptake of K^+

Insulin moves glucose **In**to cells.

BRICK L (don't need insulin for glucose uptake):

Brain
RBCs
Intestine
Cornea
Kidney
Liver

GLUT1: RBCs, brain.

GLUT2 (bidirectional): β islet cells, liver, kidney.

GLUT4 (insulin responsive): adipose tissue, skeletal muscle.

	Fed state	Fasting state	Regulation	
			Liver	Muscle
Glycogen synthase	GS	GS-P	⊕Insulin ⊕Glucose ⊖Glucagon ⊖Epinephrine	⊕Insulin ⊖Epinephrine
Glycogen phosphorylase (in muscle, V)	GP	GP-P	⊕Epinephrine ⊕Glucagon ⊖Insulin	⊕AMP ⊕Epinephrine ⊖ATP ⊖Insulin

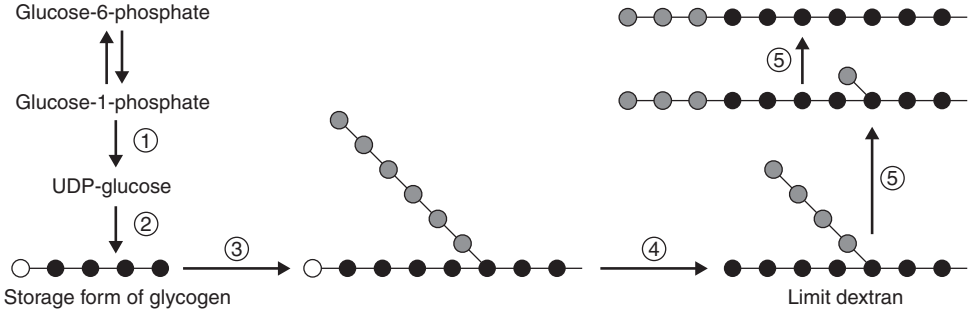
Insulin dephosphorylates (↓ cAMP → ↓ PKA).
Glucagon phosphorylates (↑ cAMP→ ↑ PKA).

Glycogen

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

Skeletal muscle — Glycogen undergoes glycogenolysis to form glucose, which is rapidly metabolized during exercise.

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



① UDP-glucose pyrophosphorylase
② Glycogen synthase
③ Branching enzyme
④ Glycogen phosphorylase
⑤ Debranching enzyme

Note: A small amount of glycogen is degraded in lysosomes by α-1,4-glucosidase

► BIOCHEMISTRY–METABOLISM *(continued)*

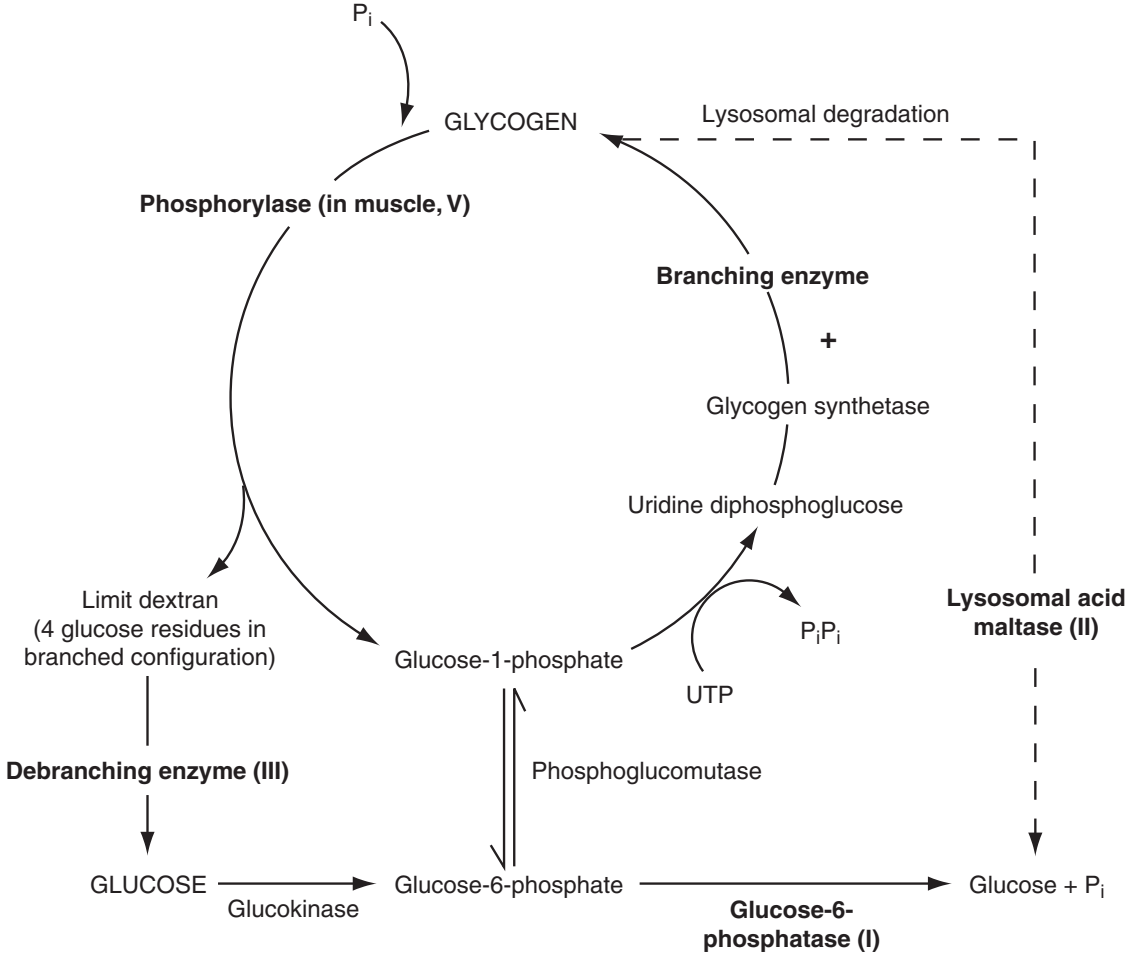
Glycogen storage diseases

12 types, all resulting in abnormal glycogen metabolism and an accumulation of glycogen within cells.

Very **P**oor **C**arbohydrate **M**etabolism.

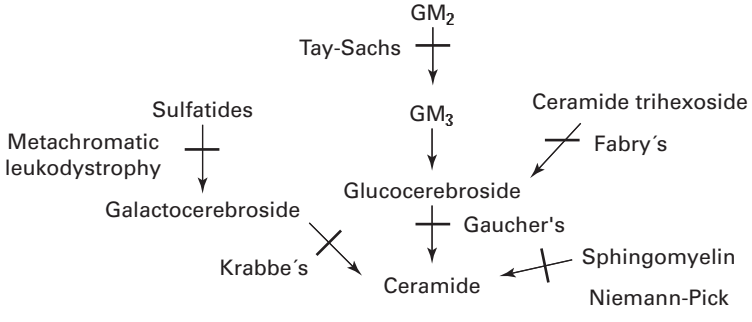
Disease	Findings	Deficient enzyme	Comments
Von Gierke's disease (type I)	Severe fasting hypoglycemia, ↑↑ glycogen in liver, ↑ blood lactate, hepatomegaly	Glucose-6-phosphatase	
Pompe's disease (type II)	Cardiomegaly and systemic findings leading to early death	Lysosomal α-1,4-glucosidase (acid maltase)	**P**ompe's trashes the **P**ump (heart, liver, and muscle).
Cori's disease (type III)	Milder form of type I with normal blood lactate levels	Debranching enzyme α-1,6-glucosidase	Gluconeogenesis is intact.
McArdle's disease (type V)	↑ glycogen in muscle, but cannot break it down, leading to painful muscle cramps, myoglobinuria with strenuous exercise	Skeletal muscle glycogen phosphorylase	**M**cArdle's = **M**uscle.

Glycogenolysis/glycogen synthesis



Lysosomal storage diseases Each is caused by a deficiency in one of the many lysosomal enzymes.

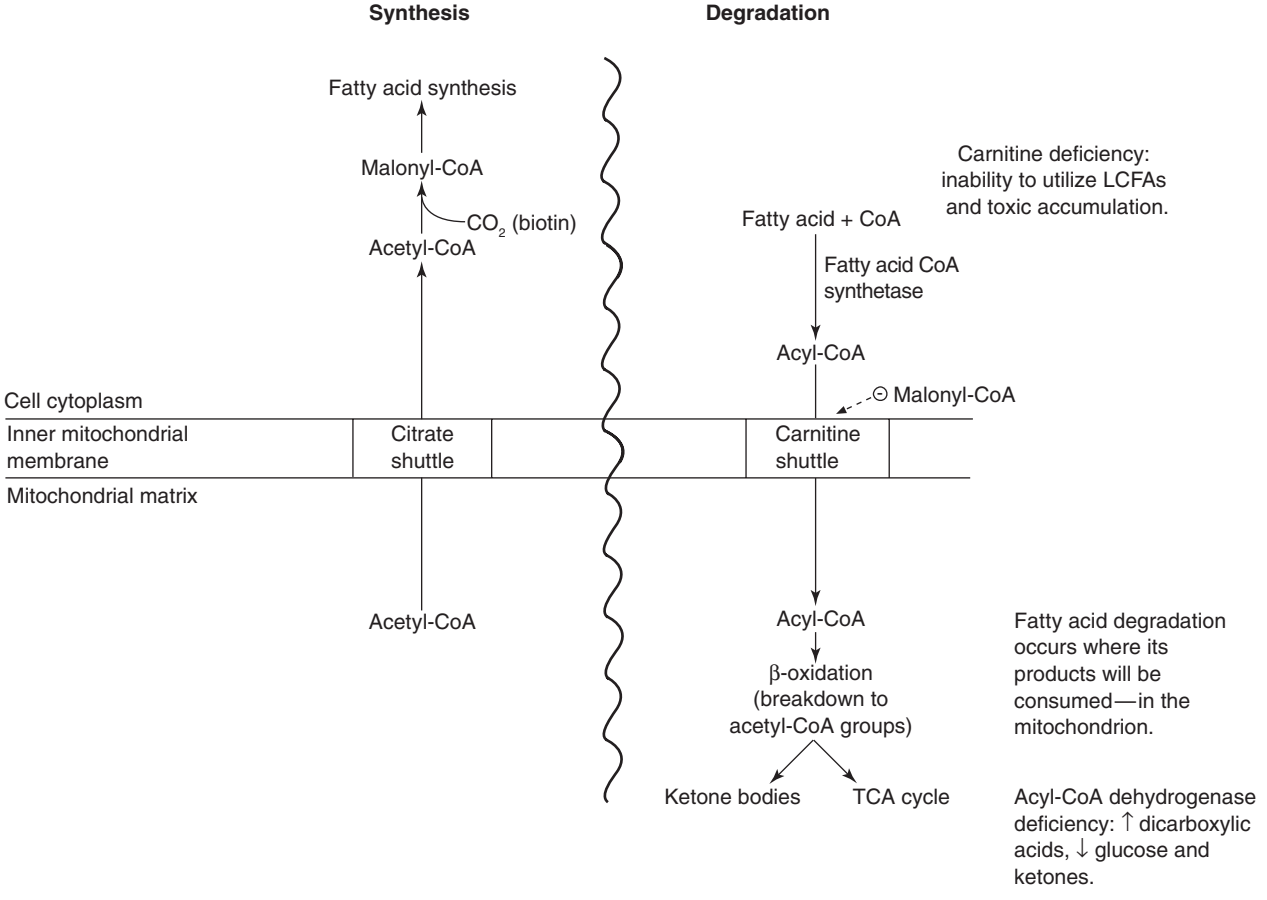
Disease	Findings	Deficient enzyme	Accumulated substrate	Inheritance
Sphingolipidoses				
Fabry's disease	Peripheral neuropathy of hands/feet, angiokeratomas, cardiovascular/renal disease	α-galactosidase A	Ceramide trihexoside	**XR**
Gaucher's disease (most common)	Hepatosplenomegaly, aseptic necrosis of femur, bone crises, Gaucher's cells (macrophages that look like crumpled tissue paper)	β-glucocerebrosidase	Glucocerebroside	AR
Niemann-Pick disease	Progressive neurodegeneration, hepatosplenomegaly, cherry-red spot (on macula), foam cells	Sphingomyelinase	Sphingomyelin	AR
Tay-Sachs disease	Progressive neurodegeneration, developmental delay, cherry-red spot, lysosomes with onion skin	Hexosaminidase A	GM_2 ganglioside	AR
Krabbe's disease	Peripheral neuropathy, developmental delay, optic atrophy, globoid cells	Galactocerebrosidase	Galactocerebroside	AR
Metachromatic leukodystrophy	Central and peripheral demyelination with ataxia, dementia	Arylsulfatase A	Cerebroside sulfate	AR
Mucopolysaccharidoses				
Hurler's syndrome	Developmental delay, gargoylism, airway obstruction, corneal clouding, hepatosplenomegaly	α-L-iduronidase	Heparan sulfate, dermatan sulfate	AR
Hunter's syndrome	Mild Hurler's + aggressive behavior, no corneal clouding	Iduronate sulfatase	Heparan sulfate, dermatan sulfate	**XR**



No man picks (**Niemann-Pick**) his nose with his **sphinger** (**sphing**omyelinase).
Tay-Sa**X** (**Tay-Sachs**) lacks he**X**osaminidase.
Hunters aim for the **X** (**X**-linked recessive).
↑ incidence of Tay-Sachs, Niemann-Pick, and some forms of Gaucher's disease in Ashkenazi Jews.

Fatty acid metabolism sites

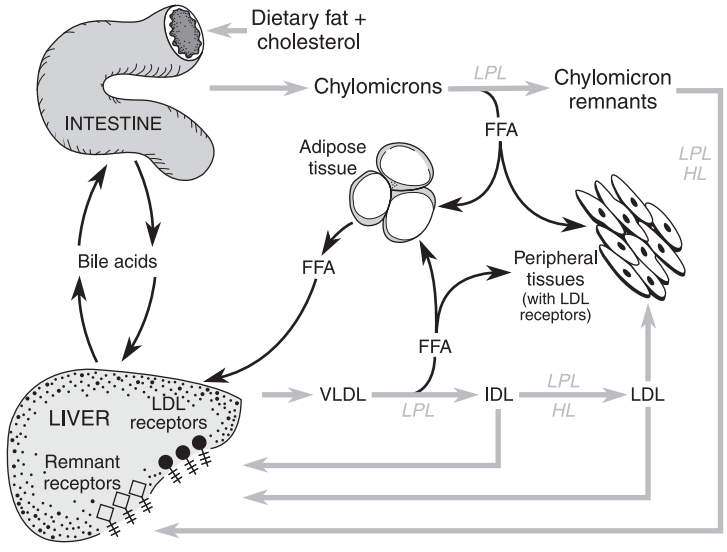
SYtrate = **SY**nthesis.
CARnitine = **CAR**nage of fatty acids.



Ketone bodies	In liver, fatty acid 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 stall the TCA cycle, which shunts glucose and FFA to ketone bodies. Excreted in urine. Made from HMG-CoA. Ketone bodies are metabolized by the brain to 2 molecules of acetyl-CoA.	Breath smells like acetone (fruity odor). Urine test for ketones does not detect β-hydroxybutyrate (favored by high redox state).
Cholesterol synthesis	Rate-limiting step is catalyzed by **HMG-CoA reductase,** which converts HMG-CoA to mevalonate. ⅔ of plasma cholesterol is esterified by lecithin-cholesterol acyltransferase (LCAT).	Statins (e.g., lovastatin) inhibit HMG-CoA reductase.

Essential fatty acids	Linoleic and linolenic acids. Arachidonic acid, if linoleic acid is absent.	Eicosanoids are dependent on essential fatty acids.

Lipoproteins



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Pancreatic lipase—degradation of dietary TG in small intestine.
Lipoprotein lipase (LPL)—degradation of TG circulating in chylomicrons and VLDLs.
Hepatic TG lipase (HL)—degradation of TG remaining in IDL.
Hormone-sensitive lipase—degradation of TG stored in adipocytes.
Lecithin-cholesterol acyltransferase (LCAT)—catalyzes esterification of cholesterol.
Cholesterol ester transfer protein (CETP)—mediates transfer of cholesterol esters to other lipoprotein particles.

Major apolipoproteins	**A**-I—**A**ctivates LCAT. **B**-100—**B**inds to LDL receptor, mediates VLDL secretion. **C**-II—**C**ofactor for lipoprotein lipase. B-48—Mediates chylomicron secretion. **E**—Mediates **E**xtra (remnant) uptake.

► BIOCHEMISTRY–METABOLISM *(continued)*

Lipoprotein functions

Lipoproteins are composed of varying proportions of cholesterol, triglycerides, and phospholipids.

LDL and HDL carry most cholesterol. LDL transports cholesterol from liver to tissue; HDL transports it from periphery to liver.

HDL is **H**ealthy.
LDL is **L**ousy.

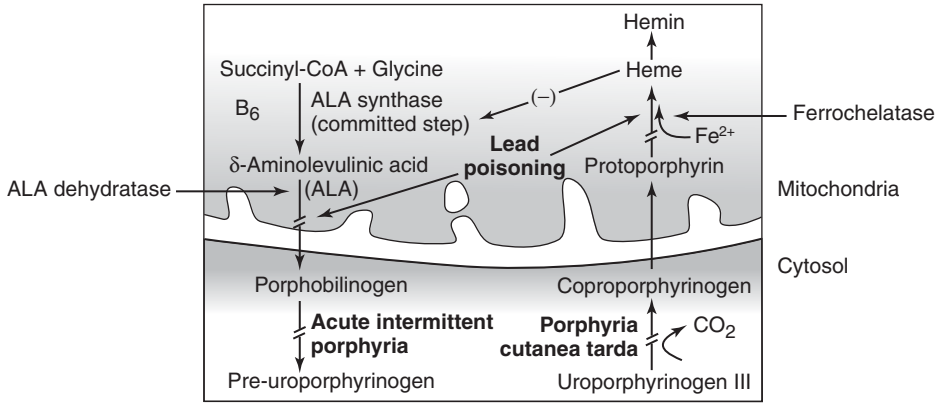
	Function and route	**Apolipoproteins**
Chylomicron	Delivers dietary triglycerides to peripheral tissues. Delivers cholesterol to liver in the form of chylomicron remnants, which are mostly depleted of their triacylglycerols. Secreted by intestinal epithelial cells. Excess causes pancreatitis, lipemia retinalis, and eruptive xanthomas.	B-48, A-IV, C-II, and E
VLDL	Delivers hepatic triglycerides to peripheral tissues. Secreted by liver. Excess causes pancreatitis.	B-100, C-II, and E
IDL	Formed in the degradation of VLDL. Delivers triglycerides and cholesterol to liver, where they are degraded to LDL.	B-100 and E
LDL	Delivers hepatic cholesterol to peripheral tissues. Formed by lipoprotein lipase modification of VLDL in the peripheral tissue. Taken up by target cells via receptor-mediated endocytosis. Excess causes atherosclerosis, xanthomas, and arcus corneae.	B-100
HDL	Mediates centripetal transport of cholesterol (reverse cholesterol transport, from periphery to liver). Acts as a repository for apoC and apoE (which are needed for chylomicron and VLDL metabolism). Secreted from both liver and intestine.	

Familial dyslipidemias

Type	**Increased**	**Elevated blood levels**	**Pathophysiology**
I—hyperchylomicronemia	Chylomicrons	TG, cholesterol	Lipoprotein lipase deficiency or altered apolipoprotein C-II
IIa—hypercholesterolemia	LDL	Cholesterol	↓ LDL receptors
IV—hypertriglyceridemia	VLDL	TG	Hepatic overproduction of VLDL

Heme synthesis

Underproduction of heme causes microcytic hypochromic anemia. Accumulation of intermediates causes porphyrias.



Porphyrias

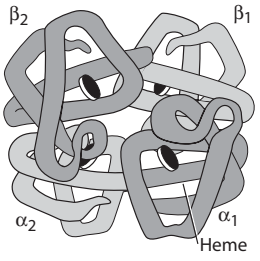
	Affected enzyme	Accumulated substrate in urine	
Lead poisoning	Ferrochelatase and ALA dehydratase	Coproporphyrin and δ-ALA	
Acute intermittent porphyria	Porphobilinogen deaminase	Porphobilinogen and δ-ALA	Symptoms = 5 **P**'s: **P**ainful abdomen **P**ink urine **P**olyneuropathy **P**sychological disturbances **P**recipitated by drugs
Porphyria cutanea tarda	Uroporphyrinogen decarboxylase	Uroporphyrin (tea-colored)	

Heme catabolism

Heme is scavenged from RBCs and Fe^{2+} is reused. Heme → biliverdin → bilirubin (sparingly water soluble, toxic to CNS, transported by albumin). Bilirubin is removed from blood by liver, conjugated with glucuronate, and excreted in bile. Some urobilinogen, an intestinal intermediate, is reabsorbed into blood and excreted as urobilin into urine. Biliverdin gives bruises their blue-green color. Jaundiced newborns are exposed to UV light, which converts bilirubin to urine-soluble products.

► BIOCHEMISTRY–METABOLISM *(continued)*

Hemoglobin



Hemoglobin is composed of 4 polypeptide subunits (2 α and 2 β) and exists in 2 forms:
1. T (taut) form has low affinity for O_2.
2. R (relaxed) form has high affinity for O_2 (300×). Hemoglobin exhibits positive cooperativity and negative allostery (accounts for the sigmoid-shaped O_2 dissociation curve for hemoglobin), unlike myoglobin.

↑ Cl^-, H^+, CO_2, 2,3-BPG, and temperature favor T form over **R** form (shifts dissociation curve to right, leading to ↑ O_2 unloading).

Fetal hemoglobin (2α and 2γ subunits) has lower affinity for 2,3-BPG than adult hemoglobin (HbA) and thus has higher affinity for O_2.

When you're **R**elaxed, you do your job better (carry O_2).

CO_2 transport in blood

CO_2 that is transported in blood and not bound to hemoglobin is primarily in bicarbonate form.

CO_2 (primarily as carbamate) binds to amino acids in globin chain at N terminus, but not to heme.

CO_2 binding favors T (taut) form of hemoglobin, promoting O_2 unloading (negative allosteric regulation).

CO_2 must be transported from tissue to lungs, the reverse of O_2.

Hemoglobin modifications

Lead to tissue hypoxia from ↓ O_2 saturation and ↓ O_2 content.

Methemoglobin

Oxidized form of hemoglobin (ferric, Fe^{3+}) that does not bind O_2 as readily, but has ↑ affinity for CN^-.

Iron in hemoglobin is normally in a reduced state (ferrous, Fe^{2+}).

To treat cyanide poisoning, use nitrites to oxidize hemoglobin to methemoglobin, which binds cyanide, allowing cytochrome oxidase to function. Use thiosulfate to bind this cyanide, forming thiocyanate, which is renally excreted.

METHemoglobinemia can be treated with **METH**ylene blue.

Carboxyhemoglobin

Form of hemoglobin bound to CO in place of O_2.

CO has 200× greater affinity than O_2 for hemoglobin.

Polymerase chain reaction (PCR)

Molecular biology laboratory procedure that is used to synthesize many copies of a desired fragment of DNA.

Steps:

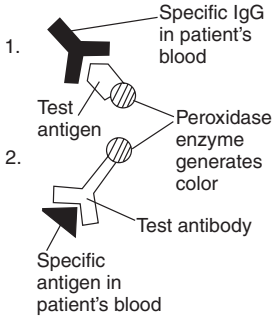
1. DNA is denatured by heating to generate 2 separate strands
2. During cooling, excess premade DNA primers anneal to a specific sequence on each strand to be amplified
3. Heat-stable DNA polymerase replicates the DNA sequence following each primer

These steps are repeated multiple times for DNA sequence amplification.

Molecular biology techniques

Southern blot	A **DNA** sample is electrophoresed on a gel and then transferred to a filter. The filter is then soaked in a denaturant and subsequently exposed to a labeled 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.	**SNoW DRoP:** **S**outhern = **D**NA **N**orthern = **R**NA **W**estern = **P**rotein
Northern blot	Similar technique, except that Northern blotting involves radioactive DNA probe binding to sample **RNA.**	
Western blot	Sample protein is separated via gel electrophoresis and transferred to a filter. Labeled antibody is used to bind to relevant **protein.**	
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.	

Enzyme-linked immunosorbent assay (ELISA)



A rapid immunologic technique testing for **antigen-antibody** reactivity.

Patient's blood sample is probed with either

1. Test antigen (coupled to color-generating enzyme)—to see if immune system recognizes it; or
2. Test antibody (coupled to color-generating enzyme)—to see if a certain antigen is present

If the target substance is present in the sample, the test solution will have an intense color reaction, indicating a positive test result.

ELISA is 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 the specificity of ELISA approach 100%, but both false-positive and false-negative results do occur.

Fluorescence in situ hybridization (FISH)

Fluorescent probe binds to specific gene site of interest.

Specific localization of genes and direct visualization of anomalies (e.g., microdeletions) at molecular level.

► BIOCHEMISTRY—LABORATORY TECHNIQUES *(continued)*

Cloning methods

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

1. DNA fragments are inserted into bacterial plasmids that contain antibiotic resistance genes. These plasmids can be selected for by using media containing the antibiotic, and amplified. Restriction enzymes ligate DNA at 4- to 6-bp palindromic sequences (the sequence on 1 strand reads the same in the same direction on the complementary strand), allowing for insertion of a fragment into a plasmid.
2. Tissue mRNA is isolated and exposed to reverse transcriptase, forming a cDNA (lacks introns) library.

Sanger DNA sequencing

Dideoxynucleotides halt DNA polymerization at each base, generating sequences of various lengths that encompass the entire original sequence. The terminated fragments are electrophoresed and the original sequence can be deduced.

Model systems

Transgenic strategies in mice involve:

1. Random insertion of gene into mouse genome (constitutive).
2. Targeted insertion or deletion of gene through homologous recombination with mouse gene (constitutive). Knock-out = removing a gene. Knock-in = inserting a gene. Gene can be manipulated at specific developmental points using an inducible Cre-lox system with an antibiotic-controlled promoter (e.g., to study a gene whose deletion causes an embryonic lethal).

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

Genetic terms

Codominance	Neither of 2 alleles is dominant (e.g., blood groups).
Variable expression	Nature and severity of the phenotype varies from 1 individual to another.
Incomplete penetrance	Not all individuals with a mutant genotype show the mutant phenotype.
Pleiotropy	1 gene has > 1 effect on an individual's phenotype.
Imprinting	Differences in phenotype depend on whether the mutation is of maternal or paternal origin (e.g., Angel**M**an's syndrome [**M**aternal], **P**rader-Willi syndrome [**P**aternal]).
Anticipation	Severity of disease worsens or age of onset of disease is earlier in succeeding generations (e.g., Huntington's disease).
Loss of heterozygosity	If a patient inherits or develops a mutation in a tumor suppressor gene, the complementary allele must be deleted/mutated before cancer develops. This is not true of oncogenes.
Dominant negative mutation	Exerts a **dominant effect.** A heterozygote produces a nonfunctional altered protein that also prevents the normal gene product from functioning.
Linkage disequilibrium	Tendency for certain alleles at 2 linked loci to occur together more often than expected by chance. Measured in a population, not in a family, and often varies in different populations.
Mosaicism	Occurs when cells in the body have different genetic makeup (e.g., lyonization—random X inactivation in females).
Locus heterogeneity	Mutations at different loci can produce the same phenotype (e.g., albinism).
Heteroplasmy	Presence of both normal and mutated mtDNA, resulting in variable expression in mitochondrial inherited diseases.
Uniparental disomy	Offspring receives 2 copies of a chromosome from 1 parent and no copies from the other parent.

Hardy-Weinberg population genetics

If a population is in Hardy-Weinberg equilibrium, then:

Disease prevalence: $p^2 + 2pq + q^2 = 1$

Allele prevalence: $p + q = 1$

p and q are separate alleles; 2pq = heterozygote prevalence. The prevalence of an X-linked recessive disease in males = q and in females = q^2.

Hardy-Weinberg law assumes:

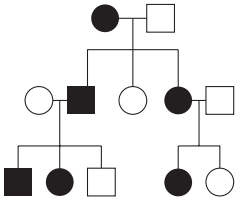
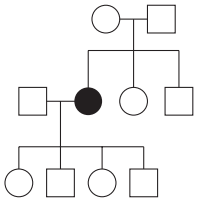
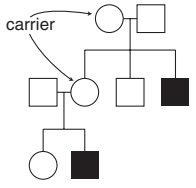
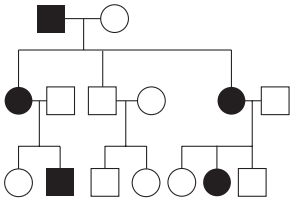
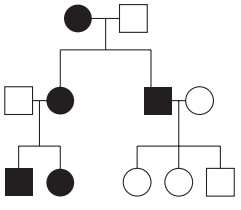
1. There is no mutation occurring at the locus
2. There is no selection for any of the genotypes at the locus
3. Mating is completely random
4. There is no migration into or out of the population being considered

Imprinting

At a single locus, only 1 allele is active; the other is inactive (imprinted/inactivated by methylation).

	Deletion of the active allele → disease.	Can also occur as a result of uniparental disomy.
Prader-Willi syndrome	Deletion of normally active paternal allele.	Mental retardation, obesity, hypogonadism, hypotonia.
Angelman's syndrome	Deletion of normally active maternal allele.	Mental retardation, seizures, ataxia, inappropriate laughter (happy puppet).

Modes of inheritance

Autosomal dominant 	Often due to defects in structural genes. Many generations, both male and female, affected.	Often pleiotropic and, in many cases, present clinically after puberty. Family history crucial to diagnosis.
Autosomal recessive 	25% of offspring from 2 carrier parents are affected. Often due to enzyme deficiencies. Usually seen in only 1 generation.	Commonly more severe than dominant disorders; patients often present in childhood.
X-linked recessive 	Sons of heterozygous mothers have a 50% chance of being affected. No male-to-male transmission.	Commonly more severe in males. Heterozygous females may be affected.
X-linked dominant 	Transmitted through both parents. Either male or female offspring of the affected mother may be affected, while **all** female offspring of the affected father are diseased.	Hypophosphatemic rickets.
Mitochondrial inheritance 	Transmitted only through mother. All offspring of affected females may show signs of disease.	Leber's hereditary optic neuropathy; mitochondrial myopathies. Variable expression in population due to heteroplasmy.

Autosomal-dominant diseases

Adult polycystic kidney disease	**Always bilateral,** massive enlargement of kidneys due to multiple large cysts. Patients present with pain, hematuria, hypertension, progressive renal failure. 90% of cases are due to mutation in *APKD1* (chromosome 16). Associated with polycystic liver disease, **berry aneurysms,** mitral valve prolapse. Juvenile form is recessive.
Familial hypercholesterolemia (hyperlipidemia type IIA)	Elevated LDL owing to defective or absent LDL receptor. Heterozygotes (1:500) have cholesterol ≈ 300 mg/dL. Homozygotes (very rare) have cholesterol ≈ 700+ mg/dL, severe atherosclerotic disease early in life, and tendon xanthomas (classically in the Achilles tendon); MI may develop before age 20.
Marfan's syndrome	Fibrillin gene mutation → connective tissue disorders. Skeletal abnormalities—tall with long extremities, pectus excavatum, hyperextensive joints, and long, tapering fingers and toes (arachnodactyly; see Figure 110). Cardiovascular—cystic medial necrosis of aorta → aortic incompetence and dissecting aortic aneurysms. Floppy mitral valve. Ocular—subluxation of lenses.
Neurofibromatosis type 1 (von Recklinghausen's disease)	Findings: café-au-lait spots, neural tumors, Lisch nodules (pigmented iris hamartomas). Also marked by skeletal disorders (e.g., scoliosis), optic pathway gliomas, pheochromocytoma, and ↑ tumor susceptibility. On long arm of chromosome **17; 17** letters in von Recklinghausen.
Neurofibromatosis type 2	Bilateral acoustic neuroma, juvenile cataracts. *NF***2** gene on chromosome **22;** type **2** = **22.**
Tuberous sclerosis	Findings: facial lesions (adenoma sebaceum), hypopigmented "ash leaf spots" on skin, cortical and retinal hamartomas, seizures, mental retardation, renal cysts and renal angiomyolipomas, cardiac rhabdomyomas, ↑ incidence of astrocytomas. Incomplete penetrance, variable presentation.
von Hippel–Lindau disease	Findings: hemangioblastomas of retina/cerebellum/medulla; about half of affected individuals develop multiple bilateral renal cell carcinomas and other tumors. Associated with deletion of *VHL* gene (tumor suppressor) on chromosome 3 (3p). Von Hippel–Lindau = **3** words for chromosome **3.**
Huntington's disease	Findings: depression, progressive dementia, choreiform movements, caudate atrophy, and ↓ levels of GABA and ACh in the brain. Symptoms manifest in affected individuals between the ages of 20 and 50. Gene located on chromosome **4;** triplet repeat disorder. "Hunting **4** food."
Familial adenomatous polyposis	Colon becomes covered with adenomatous polyps after puberty. Progresses to colon cancer unless resected. Deletion on chromosome **5** (***APC* gene**); **5** letters in "polyp."
Hereditary spherocytosis	Spheroid erythrocytes; hemolytic anemia; ↑ MCHC. Splenectomy is curative.
Achondroplasia	Autosomal-dominant cell-signaling defect of fibroblast growth factor (FGF) receptor 3. Results in dwarfism; short limbs, but head and trunk are normal size. Associated with advanced paternal age.

Autosomal-recessive diseases

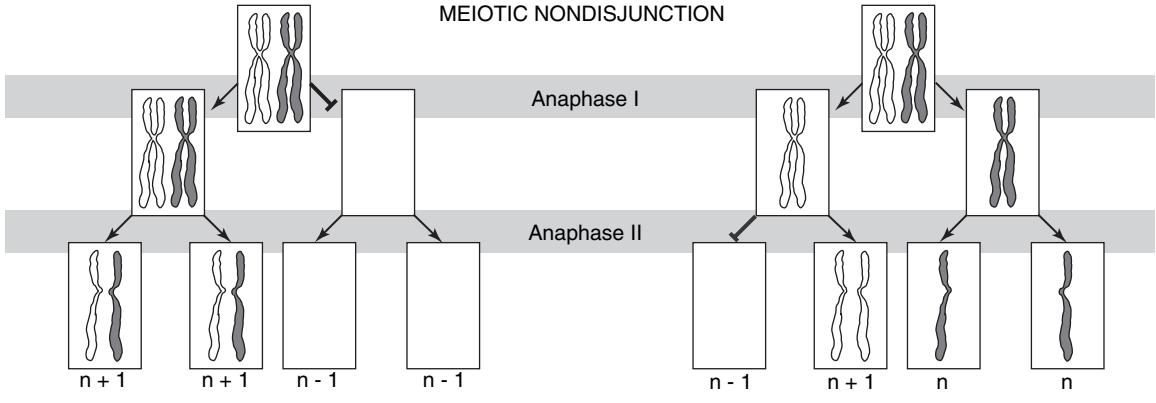
Cystic fibrosis, albinism, α_1-antitrypsin deficiency, phenylketonuria, thalassemias, sickle cell anemias, glycogen storage diseases, mucopolysaccharidoses (except Hunter's), sphingolipidoses (except Fabry's), infant polycystic kidney disease, hemochromatosis.

► BIOCHEMISTRY–GENETICS *(continued)*

Cystic fibrosis	Autosomal-recessive defect in *CFTR* gene on chromosome 7, commonly deletion of Phe 508. CFTR channel actively secretes Cl^- in lungs and GI tract and actively reabsorbs Cl^- from sweat. Defective Cl^- channel → secretion of abnormally thick mucus that plugs lungs, pancreas, and liver → recurrent pulmonary infections (*Pseudomonas* species and S. *aureus*), chronic bronchitis, bronchiectasis, pancreatic insufficiency (malabsorption and steatorrhea), meconium ileus in newborns. ↑ concentration of Cl^- ions in sweat test is diagnostic.	Infertility in males due to bilateral absence of vas deferens. Fat-soluble vitamin deficiencies (A, D, E, K). Can present as failure to thrive in infancy. Most common lethal genetic disease of Caucasians. Treatment: *N*-acetylcysteine to loosen mucous plugs.
X-linked recessive disorders	**B**ruton's agammaglobulinemia, **W**iskott-Aldrich syndrome, **F**ragile X, **G**6PD deficiency, **O**cular albinism, **L**esch-Nyhan syndrome, **D**uchenne's muscular dystrophy, **H**emophilia A and B, **F**abry's disease, **H**unter's syndrome. Female carriers of X-linked recessive disorders are rarely affected because of random inactivation of X chromosomes in each cell.	**B**e **W**ise, **F**ool's **GOLD H**eeds **F**alse **H**ope.
Muscular dystrophies		
Duchenne's (X-linked)	Frame-shift mutation → deletion of dystrophin gene → accelerated muscle breakdown. Onset before 5 years of age. Weakness begins in pelvic girdle muscles and progresses superiorly. Pseudohypertrophy of calf muscles due to fibrofatty replacement of muscle; cardiac myopathy. The use of Gowers' maneuver, requiring assistance of the upper extremities to stand up, is characteristic (indicates proximal lower limb weakness).	**D**uchenne's = **D**eleted **D**ystrophin. Diagnose muscular dystrophies by ↑ CPK and muscle biopsy.
Becker's	Mutated dystrophin gene is less severe than Duchenne's.	
Fragile X syndrome	X-linked defect affecting the methylation and expression of the *FMR1* gene. Associated with chromosomal breakage. The 2nd most common cause of genetic mental retardation (the most common cause is Down syndrome). Associated with macro-orchidism (enlarged testes), long face with a large jaw, large everted ears, and autism.	Triplet repeat disorder $(CGG)_n$ that may show genetic anticipation (germline expansion in females). Fragile **X** = e**X**tra-large testes, jaw, ears.
Trinucleotide repeat expansion diseases	**Hunting**ton's disease, **my**otonic dystrophy, **Fried**reich's ataxia, fragile **X** syndrome. May show anticipation (disease severity ↑ and age of onset ↓ in successive generations).	**Try** (**tri**nucleotide) **hunting** for **my fried** eggs (**X**).

Autosomal trisomies

Disorder	Down syndrome	Edwards' syndrome	Patau's syndrome
Trisomy	21 (**D**rinking age = 21)	18 (**E**lection age = 18)	13 (**P**uberty = 13)
Incidence	1:700; **most common chromosomal disorder**	1:8000	1:15,000
↑ with maternal age	Yes	Yes	Yes
Genetics	95% meiotic nondisjunction; 4% robertsonian translocation; 1% mosaicism (nonmaternal)	—	—
Prenatal screening	↑ α-fetoprotein, ↓ β-hCG, ↑ nuchal translucency	—	—
Other disease risks	ALL, Alzheimer's > age 35	—	—
Life expectancy	45–50 years	< 1 year	< 1 year
Mental retardation	Yes, **most common cause**	Severe	Severe
Head	Flat facial profile, prominent epicanthal folds	Prominent occiput, micrognathia (small jaw), low-set ears	Microphthalmia, microcephaly, cleft lip/palate
Congenital heart defects	Yes, especially septum primum–type ASD due to endocardial cushion defects	Yes	Yes
Hands	Simian crease (see Image 111)	Clenched hands	Polydactyly
Feet	Gap between first 2 toes	Rocker-bottom feet	Rocker-bottom feet



► BIOCHEMISTRY–GENETICS *(continued)*

Chromosomal inversions

Pericentric	Involves centromere; proceeds through meiosis.
Paracentric	Does not involve centromere; does not proceed through meiosis.

Cri-du-chat syndrome	Congenital deletion of short arm of chromosome 5 (46,XX or XY, 5p–). Findings: microcephaly, severe mental retardation, high-pitched crying/mewing, epicanthal folds, cardiac abnormalities.	*Cri du chat* = cry of the cat.
22q11 syndromes	**C**left palate, **A**bnormal facies, **T**hymic aplasia → T-cell deficiency, **C**ardiac defects, **H**ypocalcemia 2° to parathyroid aplasia, microdeletion at chromosome **22**q11. Variable presentation as DiGeorge syndrome (thymic, parathyroid, and cardiac defects) or velocardiofacial syndrome (palate, facial, and cardiac defects).	**CATCH-22.**

HIGH-YIELD PRINCIPLES IN

Embryology

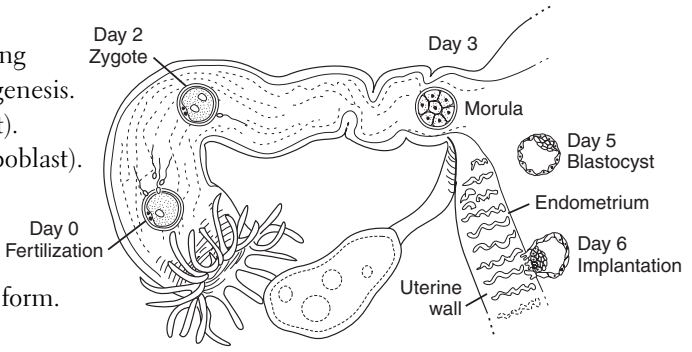
"Zygote. This cell, formed by the union of an ovum and a sperm, represents the beginning of a human being."

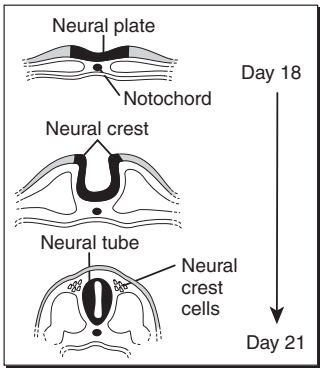
—Keith Moore and Vid Persaud,
Before We Are Born

Embryology is traditionally one of the higher-yield areas within anatomy. This topic can be crammed closer to the exam date. Many questions focus on underlying mechanisms of congenital malformations (e.g., failure of fusion of the maxillary and medial nasal processes leading to cleft lip).

Fetal landmarks

Day 0	Fertilization by sperm forming zygote, initiating embryogenesis.
Within week 1	Implantation (as a blastocyst).
Within week 2	Bilaminar disk (epiblast, hypoblast).
Within week 3	Gastrulation.
	Primitive streak, notochord, and neural plate begin to form.
Weeks 3–8	Neural tube formed.
	Organogenesis.
	Extremely susceptible to teratogens.
Week 4	Heart begins to beat.
	Upper and lower limb buds begin to form.
Week 8	Fetal movement; fetus looks like a baby.
Week 10	Genitalia have male/female characteristics.
Alar plate (dorsal)	Sensory
Basal plate (ventral)	Motor





Early development

Rule of 2's for 2nd week	2 germ layers (bilaminar disk): epiblast, hypoblast. 2 cavities: amniotic cavity, yolk sac. 2 components to placenta: cytotrophoblast, syncytiotrophoblast.	The epiblast (precursor to ectoderm) invaginates to form primitive streak. Cells from the primitive streak give rise to both intraembryonic mesoderm and endoderm.
Rule of 3's for 3rd week	3 germ layers (gastrula): ectoderm, mesoderm, endoderm.	
Rule of 4's for 4th week	4 heart chambers. 4 limb buds grow.	

Embryologic derivatives

Ectoderm	
Surface ectoderm	Adenohypophysis; lens of eye; epithelial linings of skin, ear, eye, and nose; epidermis.
Neuroectoderm	Neurohypophysis, CNS neurons, oligodendrocytes, astrocytes, ependymal cells, pineal gland.
Neural crest	ANS, dorsal root ganglia, melanocytes, chromaffin cells of adrenal medulla, enterochromaffin cells, pia and arachnoid, celiac ganglion, Schwann cells, odontoblasts, parafollicular (C) cells of thyroid, laryngeal cartilage, bones of the skull.
Endoderm	Gut tube epithelium and derivatives (e.g., lungs, liver, pancreas, thymus, parathyroid, thyroid follicular cells).
Mesoderm	Dura mater, connective tissue, muscle, bone, cardiovascular structures, lymphatics, blood, urogenital structures, serous linings of body cavities (e.g., peritoneal), spleen, adrenal cortex, kidneys.
	Notochord induces ectoderm to form neuroectoderm (neural plate). Its postnatal derivative is the nucleus pulposus of the intervertebral disk.
	Mesodermal defects = **VACTERL: V**ertebral defect, **A**nal atresia, **C**ardiac defects, **T**racheo-**E**sophageal fistula, **R**enal defects, **L**imb defects (bone and muscle).

Teratogens

Most susceptible in 3rd–8th weeks (organogenesis) of pregnancy.

Examples	Effects on fetus
Alcohol	(See the discussion of fetal alcohol syndrome below)
ACE inhibitors	Renal damage
Cocaine	Abnormal fetal development and fetal addiction
Diethylstilbestrol (DES)	Vaginal clear cell adenocarcinoma
Iodide	Congenital goiter or hypothyroidism
Vitamin A	Extremely high risk for birth defects
Thalidomide	Limb defects ("flipper" limbs)
Tobacco	Preterm labor, placental problems, attention-deficit hyperactivity disorder (ADHD)
Warfarin, x-rays, anticonvulsants	Multiple anomalies

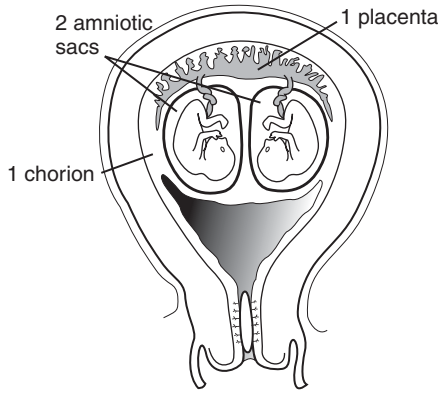
Fetal infections can also cause congenital malformations. (Other medications contraindicated in pregnancy are shown in the pharmacology section.)

Fetal alcohol syndrome

Leading cause of congenital malformations in the United States. Newborns of mothers who consumed significant amounts of alcohol during pregnancy have an ↑ incidence of congenital abnormalities, including pre- and postnatal developmental retardation, microcephaly, facial abnormalities, limb dislocation, and heart and lung fistulas. Mechanism may include inhibition of cell migration.

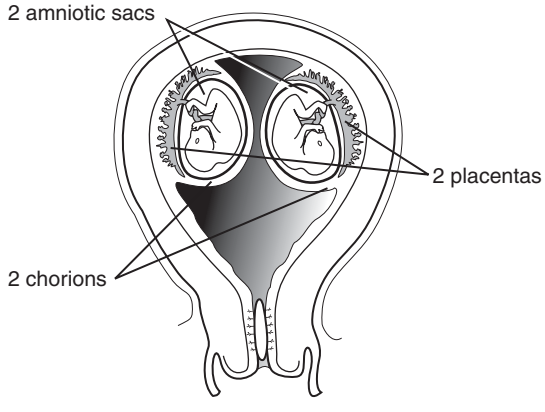
Twinning

Monozygotic



1 zygote splits evenly to develop 2 amniotic sacs with a single common chorion and placenta.

Dizygotic (fraternal) or monozygotic



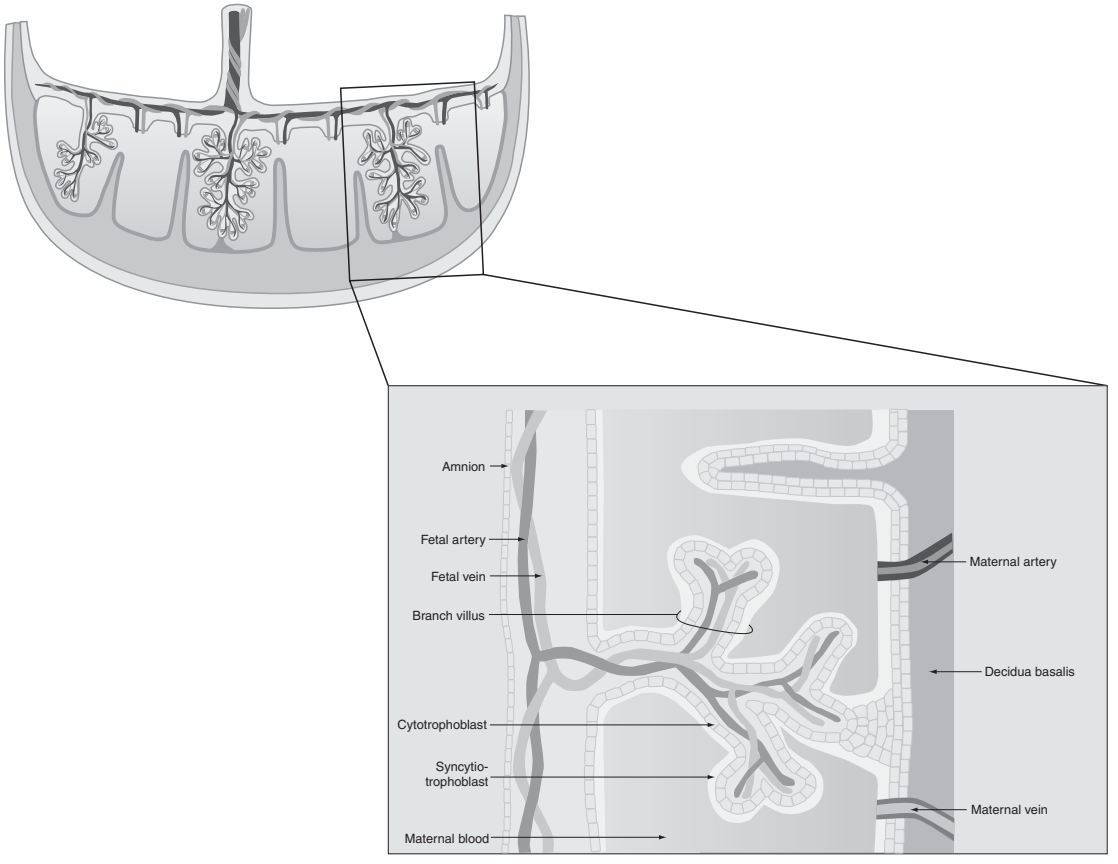
Monozygotes that split early develop 2 placentas (separate/fused), chorions, and amniotic sacs.

Dizygotes develop individual placentas, chorions, and amniotic sacs.

Placental development 1° site of nutrient and gas exchange between mother and fetus.

Fetal component: Cytotrophoblast composes the inner layer of chorionic villi. Syncytiotrophoblast is the outer layer and secretes hCG.

Maternal component: Decidua basalis derived from the endometrium.



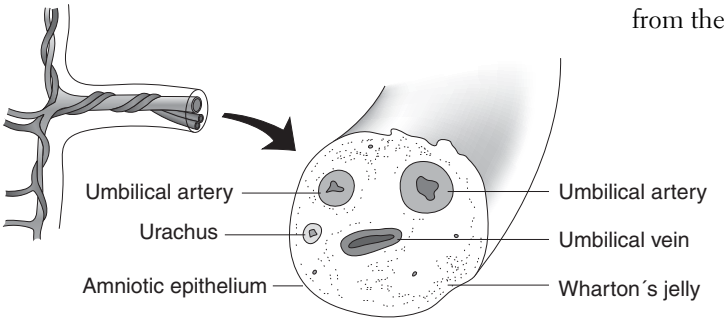
Umbilical cord

Contains 2 umbilical arteries, which return deoxygenated blood from fetal internal iliac arteries, and 1 umbilical vein, which supplies oxygenated blood from the placenta to the fetus.

Urachus removes nitrogenous waste from fetal bladder (like a urethra).

Single umbilical artery is associated with congenital and chromosomal anomalies.

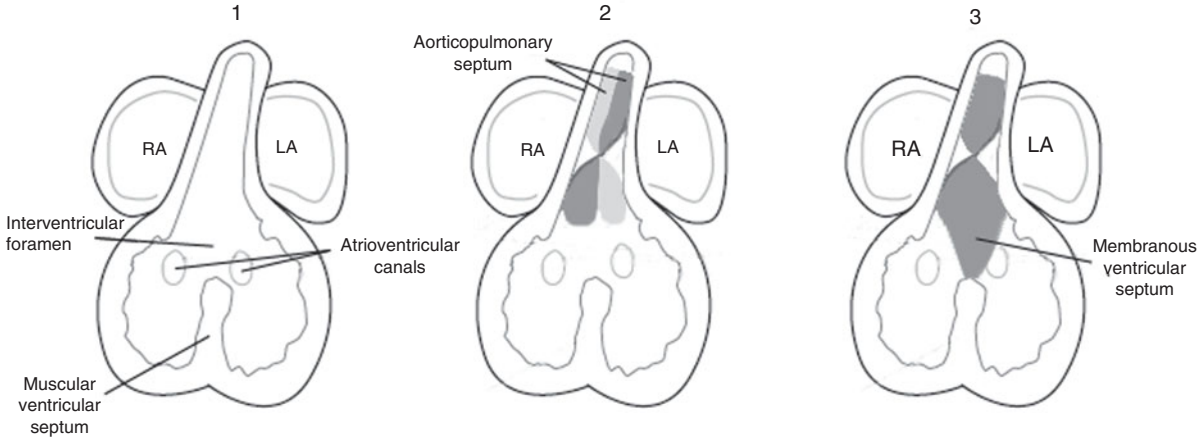
Urachus connects fetal bladder with allantois. Umbilical arteries and veins are derived from the allantois.



Heart embryology

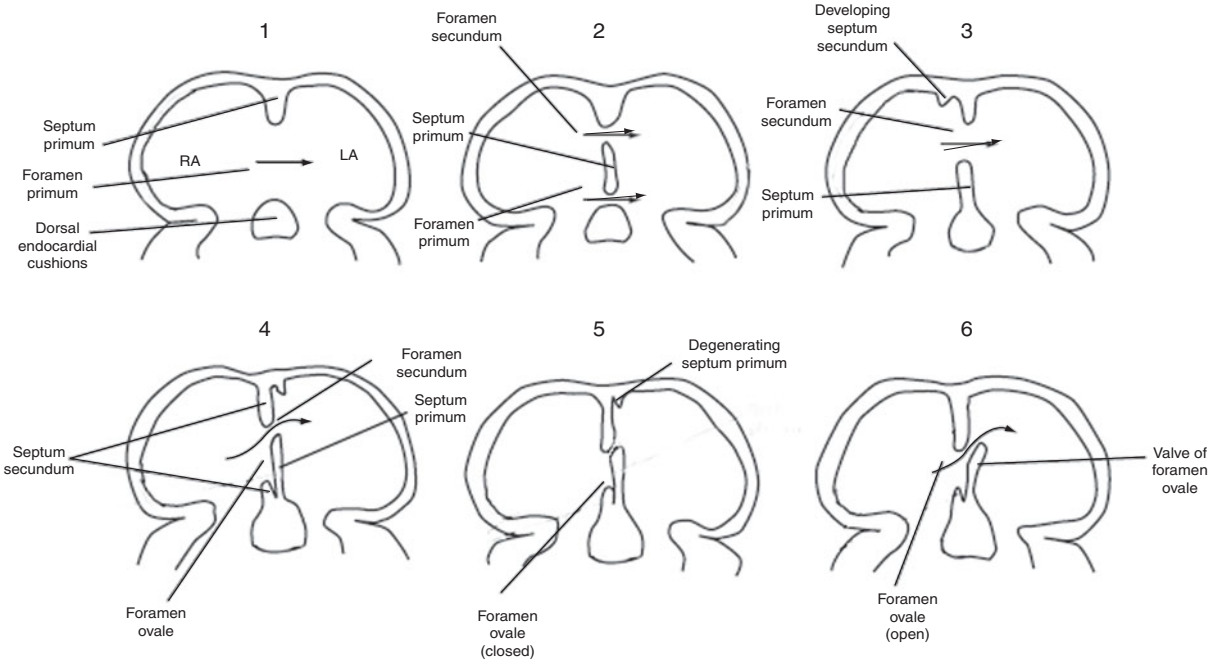
Embryonic structure	Gives rise to
Truncus arteriosus (TA)	Ascending aorta and pulmonary trunk
Bulbus cordis	Smooth parts of left and right ventricle
Primitive ventricle	Trabeculated parts of left and right ventricle
Primitive atria	Trabeculated left and right atrium
Left horn of sinus venosus (SV)	Coronary sinus
Right horn of SV	Smooth part of right atrium
Right common cardinal vein and right anterior cardinal vein	SVC

Interventricular septum development



1. Muscular ventricular septum forms. Opening is called the interventricular foramen.
2. The aorticopulmonary septum divides the TA into the aortic and pulmonary trunks.
3. The aorticopulmonary septum meets and fuses with the muscular ventricular septum to form the membranous interventricular septum, closing the interventricular foramen.

Interatrial septum development



1. Foramen primum narrows as the septum primum grows toward the endocardial cushions.
2. Perforations in the septum primum form the foramen secundum as the foramen primum disappears.
3. The foramen secundum maintains the right-to-left shunt as the septum secundum begins to grow.
4. The septum secundum contains a permanent opening called the foramen ovale.
5. The foramen secundum enlarges and the upper part of the septum primum degenerates.
6. The remaining portion of the septum primum is now called the valve of the foramen ovale.

Fetal erythropoiesis

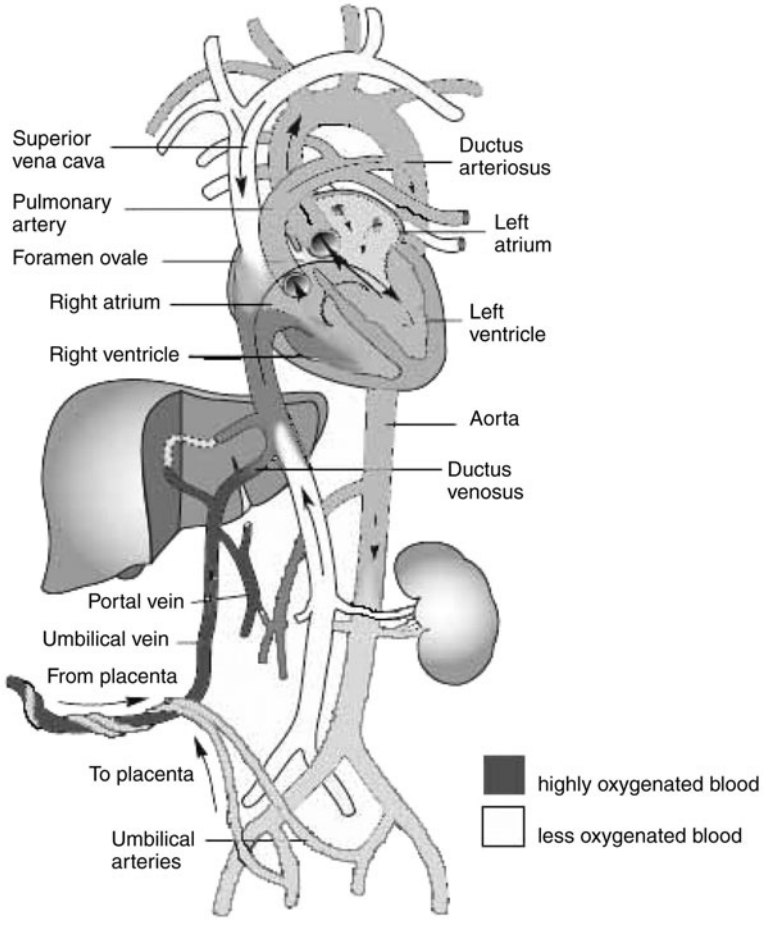
Fetal erythropoiesis occurs in:

1. **Y**olk sac (3–8 wk)
2. **L**iver (6–30 wk)
3. **S**pleen (9–28 wk)
4. **B**one marrow (28 wk onward)

Young **L**iver **S**ynthesizes **B**lood.

Fetal hemoglobin = $\alpha_2\gamma_2$.
Adult hemoglobin = $\alpha_2\beta_2$.

Fetal circulation



(Adapted, with permission, from Ganong WF. *Review of Medical Physiology,* 19th ed. Stamford, CT: Appleton & Lange, 1999: 600.)

Blood in umbilical vein is ≈ 80% saturated with O_2. Umbilical arteries have low O_2 saturation.

3 important shunts:

1. Blood entering the fetus through the umbilical vein is conducted via the **ductus venosus** into the IVC.
2. Most oxygenated blood reaching the heart via the IVC is diverted through the **foramen ovale** and pumped out the aorta to the head and body.
3. Deoxygenated blood from the SVC is expelled into the pulmonary artery and **ductus arteriosus** to the lower body of the fetus.

At birth, infant takes a breath; ↓ resistance in pulmonary vasculature causes ↑ left atrial pressure vs. right atrial pressure; foramen ovale closes (now called fossa ovalis); ↑ in O_2 leads to ↓ in prostaglandins, causing closure of ductus arteriosus.

Indomethacin helps close PDA. Prostaglandins keep PDA open.

Fetal-postnatal derivatives

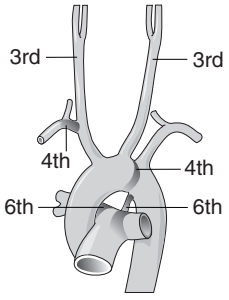
1. Umbilical vein—ligamentum teres hepatis
2. Umbi**L**ical arteries—**mediaL** umbilical ligaments
3. Ductus arteriosus—ligamentum arteriosum
4. Ductus venosus—ligamentum venosum
5. Foramen ovale—fossa ovalis
6. Alla**N**tois—urachus—**mediaN** umbilical ligament
7. Notochord—nucleus pulposus of intervertebral disk

Contained in falciform ligament.

The urachus is the part of the allantoic duct between the bladder and the umbilicus.

Urachal cyst or sinus is a remnant.

Aortic arch derivatives



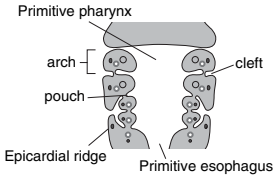
1st—part of **MAX**illary artery.
2nd—**S**tapedial artery and hyoid artery.
3rd—common **C**arotid artery and proximal part of internal carotid artery.
4th—on left, aortic arch; on right, proximal part of right subclavian artery.
6th—proximal part of pulmonary arteries and (on left only) ductus arteriosus.

1st arch is **MAX**imal.
Second = **S**tapedial.
C is 3rd letter of alphabet.

4th arch (4 limbs) = systemic.

6th arch = pulmonary and the pulmonary-to-systemic shunt (ductus arteriosus).

Branchial apparatus



Composed of branchial clefts, arches, and pouches.
Branchial clefts are derived from ectoderm.
Branchial arches are derived from mesoderm and neural crests.
Branchial pouches are derived from endoderm.

CAP covers outside from inside (**C**lefts = ectoderm, **A**rches = mesoderm, **P**ouches = endoderm).
Clefts are also called grooves.
Branchial apparatus is also called pharyngeal apparatus.

Branchial arch 1 derivatives

Meckel's cartilage: **M**andible, **M**alleus, incus, spheno**M**andibular ligament.
Muscles: **M**uscles of **M**astication (temporalis, **M**asseter, lateral and **M**edial pterygoids), **M**ylohyoid, anterior belly of digastric, tensor tympani, tensor veli palatini, anterior ⅔ of tongue.
Nerve: CN V_2 and CN V_3.

Branchial arch 2 derivatives

Reichert's cartilage: **S**tapes, **S**tyloid process, lesser horn of hyoid, **S**tylohyoid ligament.
Muscles: muscles of facial expression, **S**tapedius, **S**tylohyoid, posterior belly of digastric.
Nerve: CN VII.

Branchial arch 3 derivatives

Cartilage: greater horn of hyoid.
Muscle: stylopharyngeus.
Nerve: CN IX.

Think of pharynx: stylo**pharyngeus** innervated by glosso**pharyngeal** nerve.

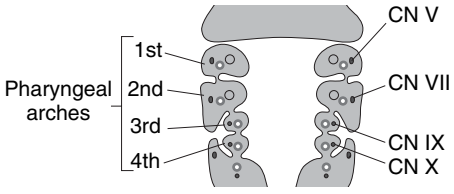
Branchial arches 4–6 derivatives

Cartilages: thyroid, cricoid, arytenoids, corniculate, cuneiform.
Muscles (4th arch): most pharyngeal constrictors, cricothyroid, levator veli palatini.
Muscles (6th arch): all intrinsic muscles of larynx **except cricothyroid.**
Nerve: 4th arch—CN X (superior laryngeal branch); 6th arch—CN X (recurrent laryngeal branch).

Arches 3 and 4 form posterior ⅓ of tongue.
Arch 5 makes no major developmental contributions.

Branchial arch innervation

Arch 1 derivatives supplied by CN V_2 and V_3.
Arch 2 derivatives supplied by CN VII.
Arch 3 derivatives supplied by CN IX.
Arch 4 and 6 derivatives supplied by CN X.
These CNs are the only ones with both sensory and motor components.



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.

Branchial pouch derivatives

1st pouch develops into middle ear cavity, eustachian tube, mastoid air cells.
2nd pouch develops into epithelial lining of palatine tonsil.
3rd pouch (dorsal wings) develops into **inferior** parathyroids.
3rd pouch (ventral wings) develops into thymus.
4th pouch (dorsal wings) develops into **superior** parathyroids.

1st pouch contributes to endoderm-lined structures of ear.
3rd pouch contributes to 3 structures (thymus, left and right inferior parathyroids).
Aberrant development of 3rd and 4th pouches → DiGeorge syndrome → leads to T-cell deficiency (thymic aplasia) and hypocalcemia (failure of parathyroid development).

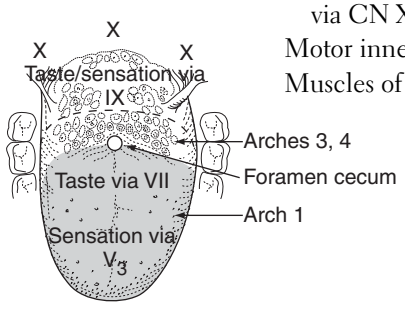
Ear development

Bones	Muscles (innervation)	Origin	Miscellaneous
Malleus/incus	Tensor ty**M**pani (V_3)	1st arch	
Stapes	**S**tapedius (VII)	2nd arch	
		1st cleft	External auditory meatus
		1st branchial membrane	Tympanic membrane

Tongue development

1st branchial arch forms anterior $^2/_3$ (thus sensation via CN V_3, taste via CN VII).
3rd and 4th arches form posterior $^1/_3$ (thus sensation and taste mainly via CN IX, extreme posterior via CN X).
Motor innervation is via CN XII.
Muscles of the tongue are derived from occipital myotomes.

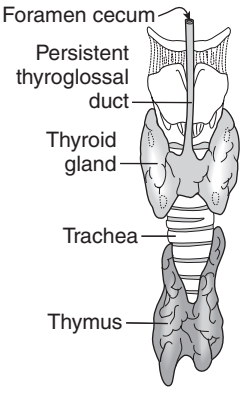
Taste is CN VII, IX, X (solitary nucleus); pain is CN V_3, IX, X; motor is CN XII.



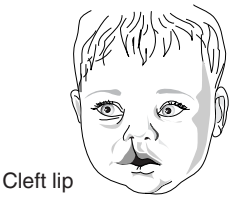
Thyroid development

Thyroid diverticulum arises from floor of primitive pharynx, 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 in midline neck and will move with swallowing (vs. persistent cervical sinus leading to branchial cyst in lateral neck).

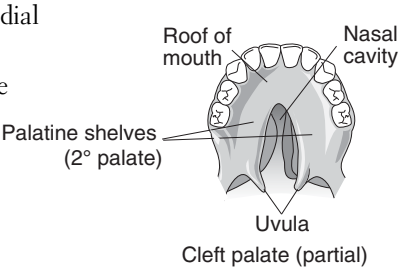


Cleft lip and cleft palate


Cleft lip

Cleft lip—failure of fusion of the maxillary and medial nasal processes (formation of 1° palate).

Cleft palate—failure of fusion of the lateral palatine processes, the nasal septum, and/or the median palatine process (formation of 2° palate).

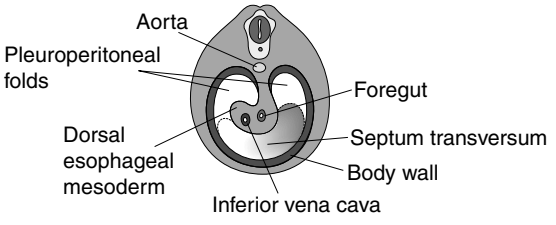


Cleft palate (partial)

Diaphragm embryology

Diaphragm is derived from:

1. **S**eptum transversum
2. **P**leuroperitoneal folds
3. **B**ody wall
4. **D**orsal mesentery of esophagus



Several **P**arts **B**uild **D**iaphragm.

Diaphragm descends during development but maintains innervation from above C3–C5. "**C3, 4, 5** keeps the diaphragm alive."

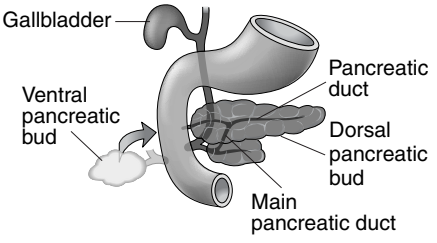
Abdominal contents may herniate into the thorax because of incomplete development (diaphragmatic hernia) → hypoplasia of thoracic organs due to space compression.

Pancreas and spleen embryology

Pancreas is derived from the foregut. Ventral pancreatic bud becomes pancreatic head, uncinate process (lower half of head), and main pancreatic duct. Dorsal pancreatic bud becomes everything else (body, tail, isthmus, and accessory pancreatic duct).

Annular pancreas—ventral pancreatic bud abnormally encircles 2nd part of duodenum; forms a ring of pancreatic tissue that may cause duodenal narrowing.

Spleen arises from dorsal mesentery but is supplied by artery of foregut.



GI embryology

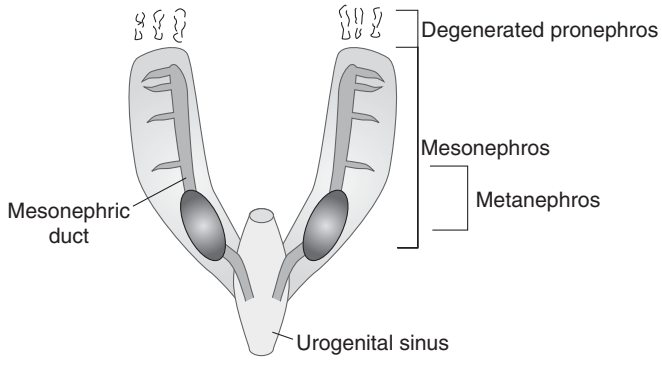
1. Foregut—pharynx to duodenum
2. Midgut—duodenum to transverse colon
3. Hindgut—distal transverse colon to rectum

Gastroschisis—failure of lateral body folds to fuse → extrusion of abdominal contents through abdominal folds.

Omphalocele—persistence of herniation of abdominal contents into umbilical cord.

Kidney embryology

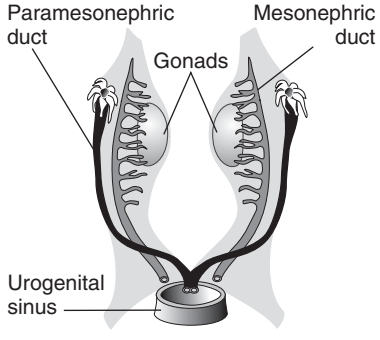
1. Pronephros—week 4; then degenerates
2. Mesonephros—functions as interim kidney for 1st trimester; later contributes to male genital system
3. Metanephros—permanent
4. Urogenital sinus—develops into bladder, urethra, allantois



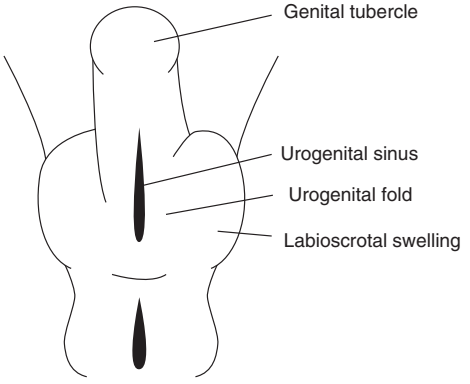
Genital embryology

Female	Default development. Mesonephric duct disappears and paramesonephric duct develops.
Male	*SRY* gene on Y chromosome codes for testis-determining factor. Müllerian inhibiting substance secreted by testes suppresses development of paramesonephric ducts. ↑ androgens → development of mesonephric ducts.
Mesonephric (wolffian) duct	Develops into male internal structures (except prostate)—**S**eminal vesicles, **E**pididymis, **E**jaculatory duct, and **D**uctus deferens.
Paramesonephric (müllerian) duct	Develops into fallopian tube, uterus, and part of vagina.

SEED.



Male/female genital homologues



Male			Female
	Dihydrotestosterone	Estrogen	
Glans penis	←	Genital tubercle →	Glans clitoris
Corpus spongiosum	←	Urogenital sinus →	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

HIGH-YIELD PRINCIPLES IN

Microbiology

- High-Yield Clinical Vignettes
- Clinical Bacteriology
- Bacteriology
- Mycology
- Parasitology
- Virology
- Systems
- Antimicrobials

"What lies behind us and what lies ahead of us are tiny matters compared to what lives within us."

—Oliver Wendell Holmes

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. Learning the distinguishing characteristics, target organs, and method of spread of—as well as relevant laboratory tests for—major pathogens can improve your score substantially.

MICROBIOLOGY—HIGH-YIELD CLINICAL VIGNETTES

■ Alcoholic vomits gastric contents and develops foul-smelling sputum.	What organisms are most likely?	Anaerobes.
■ Middle-age male presents with acute-onset monoarticular joint pain and bilateral Bell's palsy.	What is the likely disease, and how did he get it?	Lyme disease; bite from *Ixodes* tick.
■ UA of patient shows WBC casts.	What is the diagnosis?	Pyelonephritis.
■ Patient presents with "rose gardener's" scenario (thorn prick with ulcers along lymphatic drainage).	What is the infectious bug?	*Sporothrix schenckii*.
■ 25-year-old medical student has a burning feeling in his gut after meals. Biopsy of gastric mucosa shows gram-negative rods.	What is the likely organism?	*Helicobacter pylori*.
■ 32-year-old male has "cauliflower" skin lesions. Tissue biopsy shows broad-based budding yeasts.	What is the likely organism?	*Blastomyces*.
■ Breast-feeding woman suddenly develops redness and swelling of her right breast. On examination, it is found to be a fluctuant mass.	What is the diagnosis?	Mastitis caused by *S. aureus*.
■ 20-year-old college student presents with lymphadenopathy, fever, and hepatosplenomegaly. His serum agglutinates sheep RBCs.	What cell is infected?	B cell (EBV; infectious mononucleosis).
■ 3 hours after eating custard at a picnic, a whole family began to vomit. After 10 hours, they were better.	What is the organism?	*S. aureus* (produces preformed enterotoxin).
■ Infant becomes flaccid after eating honey.	What organism is implicated, and what is the mechanism of action?	*Clostridium botulinum*; inhibited release of ACh.
■ Man presents with squamous cell carcinoma of the penis.	He had exposure to what virus?	HPV.
■ Patient develops endocarditis 3 weeks after receiving a prosthetic heart valve.	What organism is suspected?	*S. epidermidis*.

MICROBIOLOGY—HIGH-YIELD CLINICAL VIGNETTES *(continued)*

■ 55-year-old man who is a smoker and a heavy drinker presents with a new cough and flulike symptoms. Gram stain shows no organisms; silver stain of sputum shows gram-negative rods.	What is the diagnosis?	*Legionella* pneumonia.
■ After taking clindamycin, patient develops toxic megacolon and diarrhea.	What is the mechanism of diarrhea?	*Clostridium difficile* overgrowth.
■ 25-year-old man presents with 3 days of fever, chills, and a painful, swollen knee.	What is the diagnosis, and what is the causative agent?	Septic arthritis; N. *gonorrhoeae*.
■ 19-year-old female college student presents with vaginal itching and a thick, curdy discharge.	What is the causative agent?	*Candida albicans*.
■ 30-year-old woman returns from a camping trip and complains of watery diarrhea and cramps.	What is the causative agent?	*Giardia lamblia*.

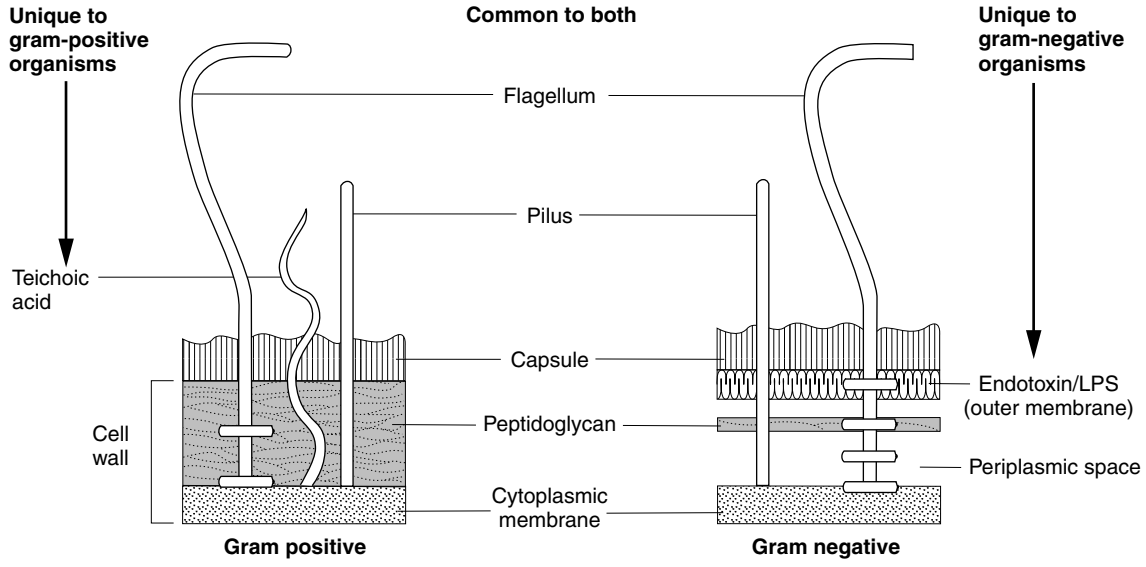
Bacterial structures

Structure	Function	Chemical composition
Peptidoglycan	Gives rigid support, protects against osmotic pressure.	Sugar backbone with cross-linked peptide side chains.
Cell wall/cell membrane (gram positives)	Major surface antigen.	Peptidoglycan for support. Teichoic acid induces TNF and IL-1.
Outer membrane (gram negatives)	Site of endotoxin (lipopolysaccharide); major surface antigen.	Lipid A induces TNF and IL-1; polysaccharide is the antigen.
Plasma membrane	Site of oxidative and transport enzymes.	Lipoprotein bilayer.
Ribosome	Protein synthesis.	50S and 30S subunits.
Periplasm	Space between the cytoplasmic membrane and outer membrane in gram-negative bacteria.	Contains many hydrolytic enzymes, including β-lactamases.
Capsule	Protects against phagocytosis.	Polysaccharide (except *Bacillus anthracis*, which contains D-glutamate).
Pilus/fimbria	Mediates adherence of bacteria to cell surface; sex pilus forms attachment between 2 bacteria during conjugation.	Glycoprotein.
Flagellum	Motility.	Protein.
Spore	Provides resistance to dehydration, heat, and chemicals.	Keratin-like coat; dipicolinic acid.
Plasmid	Contains a variety of genes for antibiotic resistance, enzymes, and toxins.	DNA.
Glycocalyx	Mediates adherence to surfaces, especially foreign surfaces (e.g., indwelling catheters).	Polysaccharide.

Bacteria with unusual cell membranes/walls

Mycoplasma	Contain sterols and have no cell wall.
Mycobacteria	Contain mycolic acid. High lipid content.

Cell walls

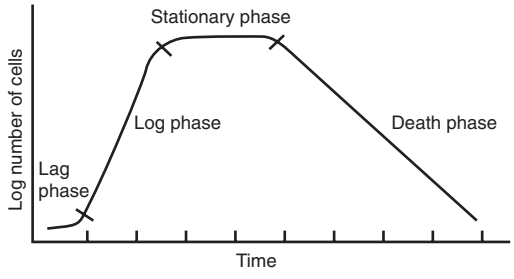


(Adapted, with permission, from Levinson W, Jawetz E. *Medical Microbiology and Immunology: Examination and Board Review,* 9th ed. New York: McGraw-Hill, 2006: 7.)

Gram stain limitations

These bugs do not Gram stain well:	**T**hese **R**ascals **M**ay **M**icroscopically **L**ack **C**olor.
***T**reponema* (too thin to be visualized).	Treponemes—darkfield microscopy and fluorescent antibody staining.
***R**ickettsia* (intracellular parasite).	
Mycobacteria (high-lipid-content cell wall requires acid-fast stain).	Mycobacteria—acid fast.
***M**ycoplasma* (no cell wall).	
***L**egionella pneumophila* (primarily intracellular).	*Legionella*—silver stain.
***C**hlamydia* (intracellular parasite; lacks muramic acid in cell wall).	

Bacterial growth curve



(Adapted, with permission, from Levinson W. *Medical Microbiology and Immunology: Examination and Board Review,* 9th ed. New York: McGraw-Hill, 2006: 15.)

Lag—metabolic activity without division.
Log—rapid cell division.
Stationary—nutrient depletion slows growth. Spore formation in some bacteria.
Death—prolonged nutrient depletion and buildup of waste products lead to death.

Main features of exotoxins and endotoxins

Property	Exotoxin	Endotoxin
Source	Certain species of some gram-positive and gram-negative bacteria	Outer cell membrane of most gram-negative bacteria and *Listeria*
Secreted from cell	Yes	No
Chemistry	Polypeptide	Lipopolysaccharide
Location of genes	Plasmid or bacteriophage	Bacterial chromosome
Toxicity	High (fatal dose on the order of 1 μg)	Low (fatal dose on the order of hundreds of micrograms)
Clinical effects	Various effects (see text)	Fever, shock
Mode of action	Various modes (see text)	Includes TNF and IL-1
Antigenicity	Induces high-titer antibodies called antitoxins	Poorly antigenic
Vaccines	Toxoids used as vaccines	No toxoids formed and no vaccine available
Heat stability	Destroyed rapidly at 60°C (except staphylococcal enterotoxin)	Stable at 100°C for 1 hour
Typical diseases	Tetanus, botulism, diphtheria	Meningococcemia, sepsis by gram-negative rods

(Adapted, with permission, from Levinson W. *Medical Microbiology and Immunology: Examination and Board Review,* 8th ed. New York: McGraw-Hill, 2004: 39.)

Bacterial virulence factors	These promote evasion of host immune response.
S. aureus protein A	Binds Fc region of Ig.
IgA protease	Enzyme that cleaves IgA. Polysaccharide capsules also inhibit phagocytosis. Secreted by *S. pneumoniae*, *H. influenzae*, and *Neisseria*.
Group A streptococcal M protein	Helps prevent phagocytosis.

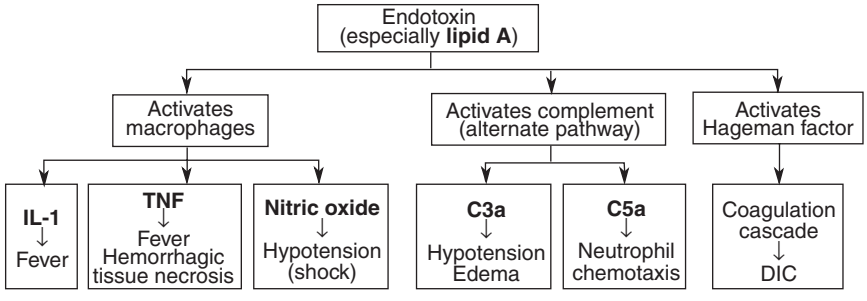
Bugs with exotoxins

Superantigens	Bind directly to MHC II and T-cell receptor simultaneously, activating large numbers of T cells to stimulate release of IFN-γ and IL-2.
S. aureus	TSST-1 superantigen causes toxic shock syndrome (fever, rash, shock). Other *S. aureus* toxins include enterotoxins that cause food poisoning as well as exfoliatin, which causes staphylococcal scalded skin syndrome.
S. pyogenes	Scarlet fever–erythrogenic toxin causes toxic shock–like syndrome.
ADP ribosylating A-B toxins	Interfere with host cell function. B (binding) component binds to a receptor on surface of host cell, enabling endocytosis. A (active) component then attaches an ADP-ribosyl to a host cell protein (ADP ribosylation), altering protein function.
Corynebacterium diphtheriae	Inactivates elongation factor (EF-2) (similar to *Pseudomonas* exotoxin A); causes pharyngitis and "pseudomembrane" in throat.
Vibrio cholerae	ADP ribosylation of G protein stimulates adenylyl cyclase; ↑ pumping of Cl^- into gut and ↓ Na^+ absorption. H_2O moves into gut lumen; causes voluminous rice-water diarrhea.
E. coli	Heat-labile toxin stimulates **A**denylate cyclase. Heat-stable toxin stimulates **G**uanylate cyclase. Both cause watery diarrhea. "Labile like the **A**ir, stable like the **G**round."
Bordetella pertussis	Increases cAMP by inhibiting $G\alpha_i$; causes whooping cough; inhibits chemokine receptor, causing lymphocytosis.
Other toxins	
Clostridium perfringens	α toxin causes gas gangrene; get double zone of hemolysis on blood agar.
C. tetani	Blocks the release of inhibitory neurotransmitters GABA and glycine; causes "lockjaw."
C. botulinum	Blocks the release of acetylcholine; causes anticholinergic symptoms, CNS paralysis, especially cranial nerves; spores found in canned food, honey (causes floppy baby).
Bacillus anthracis	1 toxin in the toxin complex is an adenylate cyclase.
Shigella	Shiga toxin (also produced by *E. coli* O157:H7) cleaves host cell rRNA; also enhances cytokine release, causing HUS.
S. pyogenes	Streptolysin O is a hemolysin; antigen for ASO antibody, which is used in the diagnosis of rheumatic fever.

Endotoxin

A lipopolysaccharide found in cell wall of gram-negative bacteria.

N-dotoxin is an integral part of gram-**N**egative cell wall. Endotoxin is heat stable.



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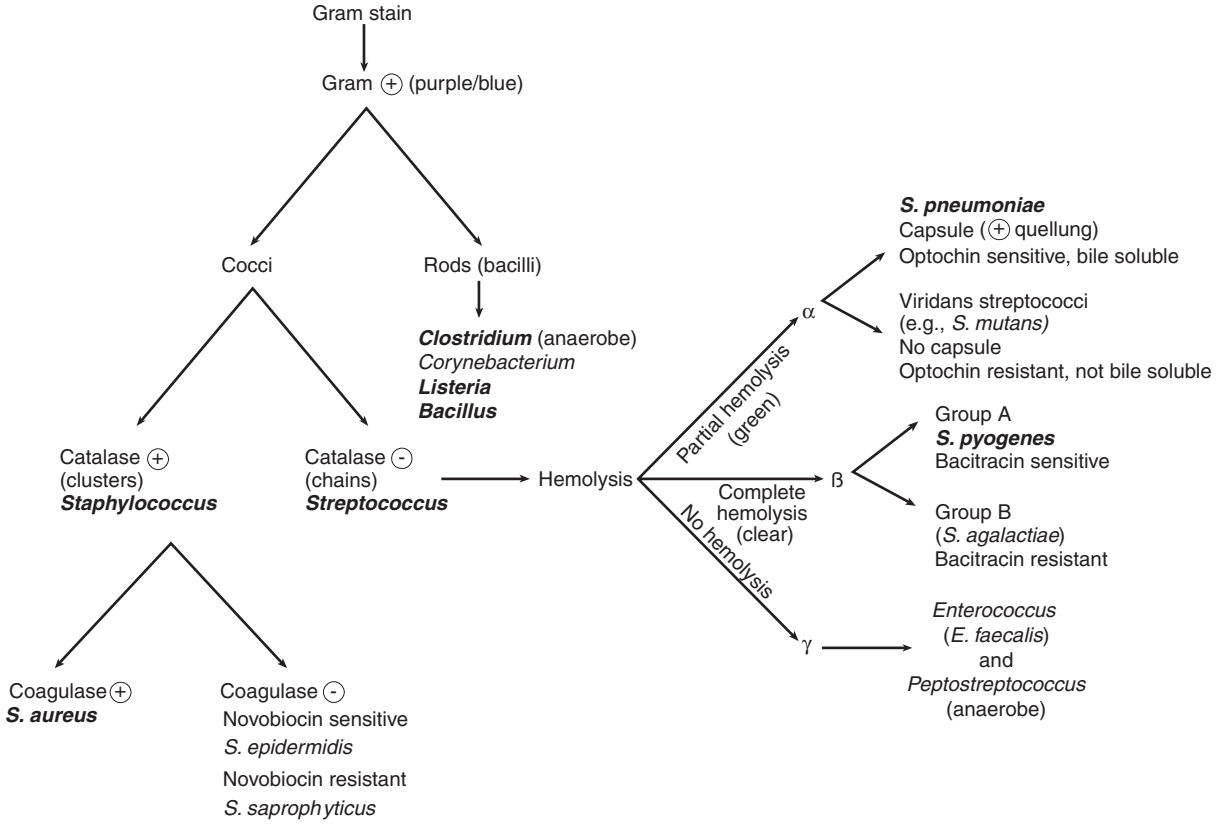
► MICROBIOLOGY–CLINICAL BACTERIOLOGY *(continued)*

Fermentation patterns of *Neisseria*	The pathogenic *Neisseria* species are differentiated on the basis of sugar fermentation (see Color Image 4).	**M**enin**G**ococci ferment **M**altose and **G**lucose. **G**onococci ferment **G**lucose.
Pigment-producing bacteria	*S. aureus*—yellow pigment. *Pseudomonas* ***aerug****inosa*—blue-**green** pigment. *Serratia marcescens*—red pigment.	*Aureus* (Latin) = gold. **AERUG**ula is **green.** *Serratia marcescens*—think red maraschino cherries!

Gram-positive lab algorithm

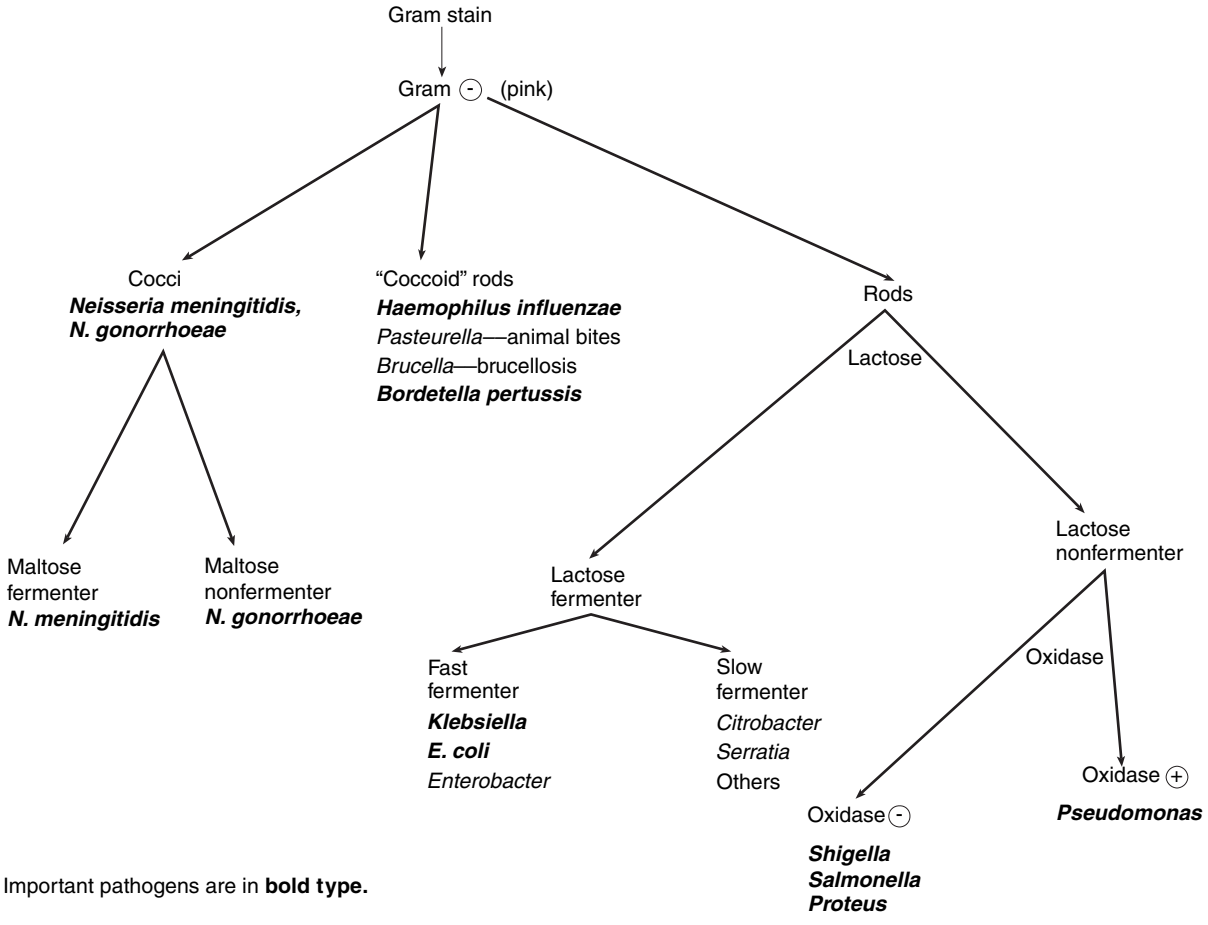


Important pathogens are in **bold type.**
Note: *Enterococcus* is either α- or γ-hemolytic.

Identification of gram-positive bacteria

Staphylococci	**NO**vobiocin—***S****aprophyticus* is **R**esistant; *Epidermidis* is **S**ensitive.	**NO StRES.**
Streptococci	**O**ptochin—*Viridans* is **R**esistant; *P**neumoniae* is **S**ensitive.	**OVRPS** (overpass).
	Bacitracin—group **B** strep are **R**esistant; group **A** strep are **S**ensitive.	**B-BRAS.**

Gram-negative lab algorithm



Important pathogens are in **bold type.**

Special culture requirements

Bug	Media used for isolation
H. influenzae	Chocolate agar with factors V (NAD) and X (hematin)
N. gonorrhoeae	Thayer-Martin media
B. pertussis	Bordet-Gengou (potato) agar
C. diphtheriae	Tellurite plate, Löffler's media
M. tuberculosis	Löwenstein-Jensen agar
Lactose-fermenting enterics	Pink colonies on MacConkey's agar
Legionella	Charcoal yeast extract agar buffered with ↑ iron and cysteine
Fungi	Sabouraud's agar

Stains

Congo red	Amyloid; apple-green birefringence in polarized light (because of β-pleated sheets).
Giemsa's	*Borrelia*, *Plasmodium*, trypanosomes, *Chlamydia*.
PAS (periodic acid-Schiff)	Stains glycogen, mucopolysaccharides; used to diagnose Whipple's disease.
Ziehl-Neelsen	Acid-fast bacteria.
India ink	*Cryptococcus neoformans.*
Silver stain	Fungi, *Legionella*.

► MICROBIOLOGY–CLINICAL BACTERIOLOGY *(continued)*

Bacterial genetics

Transformation	DNA taken up directly from environment by competent prokaryotic and eukaryotic cells. Any DNA can be used.
Conjugation	
$F^+ \times F^-$	F^+ plasmid contains genes required for conjugation process. Bacteria without this plasmid are termed F^-. Plasmid is replicated and transferred through pilus from F^+ cell. Plasmid DNA only; no transfer of chromosomal genes.
Hfr × F^-	F^+ plasmid can become incorporated into bacterial chromosomal DNA, termed Hfr cell. Replication of incorporated plasmid DNA may include some flanking chromosomal DNA. Transfer of plasmid and chromosomal genes.
Transduction	
Generalized	Lytic phage infects bacterium, leading to cleavage of bacterial DNA and synthesis of viral proteins. Parts of bacterial chromosomal DNA may become packaged in viral capsid. Phage infects another bacterium, transferring these genes.
Specialized	Lysogenic phage infects bacterium; viral DNA incorporated into bacterial chromosome. When phage DNA is excised, flanking bacterial genes may be excised with it. DNA is packaged into phage viral capsid and can infect another bacterium.
Transposition	Segment of DNA that can "jump" (excision and reincorporation) 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.

Lysogeny

Genetic code for a bacterial toxin encoded in a lysogenic phage.

Shig**A**-like toxin
Botulinum toxin (certain strains)
Cholera toxin
Diphtheria toxin
Erythrogenic toxin of *Streptococcus pyogenes*

ABCDE.

► MICROBIOLOGY–BACTERIOLOGY

Obligate aerobes

Use an O_2-dependent system to generate ATP.
Examples include ***N****ocardia*, ***P****seudomonas aeruginosa*, ***M****ycobacterium tuberculosis*, and ***B****acillus*.
M. tuberculosis has a predilection for the apices of the lung, which have the highest P_{O_2}.

Nagging **P**ests **M**ust **B**reathe.
*P. **AER**uginosa* is an **AER**obe seen in burn wounds, nosocomial pneumonia, and pneumonias in cystic fibrosis patients.

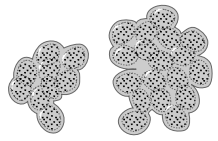
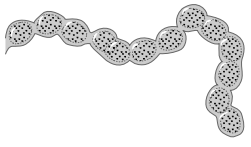
Obligate anaerobes

Examples include ***A****ctinomyces*. ***B****acteroides*, and ***C****lostridium*. They lack catalase and/or superoxide dismutase and are thus susceptible to oxidative damage. Generally foul smelling (short-chain fatty acids), are difficult to culture, and produce gas in tissue (CO_2 and H_2).

Anaerobes know their **ABC**s.
Anaerobes are normal flora in GI tract, pathogenic elsewhere. Amin**O_2**glycosides are ineffective against anaerobes because these antibiotics require **O_2** to enter into bacterial cell.

Intracellular bugs		
Obligate intracellular	***R**ickettsia*, ***C**hlamydia*. Can't make own ATP.	Stay inside (cells) when it is **R**eally **C**old.
Facultative intracellular	***S**almonella*, ***N**eisseria*, ***B**rucella*, ***M**ycobacterium*, ***L**isteria*, ***F**rancisella*, ***L**egionella*, ***Y**ersinia*.	**S**ome **N**asty **B**ugs **M**ay **L**ive **F**acultative**LY.**
Encapsulated bacteria	Positive **quellung** reaction—if encapsulated bug is present, capsule **swells** when specific anticapsular antisera are added. Examples are *Streptococcus pneumoniae*, *Haemophilus influenzae* (especially B serotype), *Neisseria meningitidis*, and *Klebsiella pneumoniae*. Their polysaccharide capsule is an antiphagocytic virulence factor.	**Quellung** = capsular "**swellung.**" Capsule serves as antigen in vaccines (Pneumovax, *H. influenzae* B, meningococcal vaccines). Conjugation with protein ↑ immunogenicity and T-cell-dependent response.
Spores: bacterial	Only certain gram-positive rods form spores when nutrients are limited (at end of stationary phase). Spores are highly resistant to destruction by heat and chemicals. Have dipicolinic acid in their core. Have no metabolic activity. Must autoclave to kill spores (as is done to surgical equipment).	Gram-positive spores found in soil: *Bacillus anthracis*, *Clostridium perfringens*, *C. tetani*. Other spore formers include *B. cereus*, *C. botulinum*.
Urease-positive bugs	*H. pylori*, *Proteus*, *Klebsiella*, *Ureaplasma*.	
α-hemolytic bacteria	Form green ring around colonies on blood agar. Include the following organisms: 1. *Streptococcus pneumoniae* (catalase negative and optochin sensitive) (see Color Image 1) 2. Viridans streptococci (catalase negative and optochin resistant)	
β-hemolytic bacteria	Form clear area of hemolysis on blood agar. Include the following organisms: 1. *Staphylococcus aureus* (catalase and coagulase positive) 2. *Streptococcus pyogenes*—group A strep (catalase negative and bacitracin sensitive) 3. *Streptococcus agalactiae*—group B strep (catalase negative and bacitracin resistant) 4. *Listeria monocytogenes* (tumbling motility, meningitis in newborns, unpasteurized milk)	
Catalase/coagulase (gram-positive cocci)	Catalase degrades H_2O_2, an antimicrobial product of PMNs. H_2O_2 is a substrate for myeloperoxidase. Staphylococci make catalase, whereas streptococci do not. *S. aureus* makes coagulase, whereas *S. epidermidis* and *S. saprophyticus* do not.	**Staph** make catalase because they have more "**staff.**" Bad staph (*aureus*, because *epidermidis* is skin flora) make coagulase and toxins.

► MICROBIOLOGY–BACTERIOLOGY *(continued)*

Staphylococcus aureus 	Protein A (virulence factor) binds Fc-IgG, inhibiting complement fixation and phagocytosis. Causes: 1. Inflammatory disease—skin infections, organ abscesses, pneumonia 2. Toxin-mediated disease—toxic shock syndrome (TSST-1 toxin), scalded skin syndrome (exfoliative toxin), rapid-onset food poisoning (enterotoxins) (see Color Image 3) 3. MRSA (methicillin-resistant *S. aureus*) infection—important cause of serious nosocomial and community-acquired infections. Resistant to β-lactams due to altered penicillin-binding protein.	TSST is a superantigen that binds to MHC II and T-cell receptor, resulting in polyclonal T-cell activation. *S. aureus* food poisoning is due to ingestion of preformed toxin. Causes acute bacterial endocarditis, osteomyelitis.
***Streptococcus pyogenes* (group A β-hemolytic streptococci) sequelae**	Causes: 1. Pyogenic—pharyngitis, cellulitis, impetigo 2. Toxigenic—scarlet fever, toxic shock syndrome 3. Immunologic—rheumatic fever, acute glomerulonephritis Bacitracin sensitive. Antibodies to **M protein** enhance host defenses against *S. pyogenes* but can give rise to rheumatic fever. ASO titer detects recent *S. pyogenes* infection.	**PH**aryngitis gives you rheumatic "**PH**ever" and glomerulone**PH**ritis. No "**rheum**" for **SPEC**Culation: **S**ubcutaneous nodules, **P**olyarthritis, **E**rythema marginatum, **C**horea, **C**arditis.
Streptococcus pneumoniae	Most common cause of: **M**eningitis **O**titis media (in children) **P**neumonia **S**inusitis Encapsulated. IgA protease.	*S. pneumoniae* **MOPS** are **M**ost **OP**tochin **S**ensitive. Pneumococcus is associated with "rusty" sputum, sepsis in sickle cell anemia and splenectomy.
Group B streptococci	Bacitracin resistant, β-hemolytic; cause pneumonia, meningitis, and sepsis, mainly in babies.	
Enterococci 	Enterococci (*Enterococcus faecalis* and *E. faecium*) are penicillin G resistant and cause UTI and subacute endocarditis. 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, hardier than nonenterococcal group D, can thus grow in 6.5% NaCl (lab test). *Entero* = intestine, *faecalis* = feces, *strepto* = twisted (chains), *coccus* = berry.
Staphylococcus epidermidis	Infects prosthetic devices and catheters. Component of normal skin flora; contaminates blood cultures.	

Viridans group streptococci	Viridans streptococci are α-hemolytic. They are normal flora of the oropharynx and cause dental caries (*Streptococcus mutans*) and subacute bacterial endocarditis (*S. sanguis*). Resistant to optochin, differentiating them from *S. pneumoniae*, which is α-hemolytic but is optochin sensitive.	*Sanguis* (Latin) = blood. There is lots of blood in the heart (endocarditis). Viridans group strep live in the mouth because they are not afraid **of-the-chin** (**op-to-chin** resistant).
Clostridia (with exotoxins)	Gram-positive, spore-forming, obligate anaerobic bacilli. *Clostridium tetani* produces an exotoxin causing tetanus. *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 bacterial spores in honey causes disease. *C. perfringens* produces α toxin (lecithinase) that can cause myonecrosis (gas gangrene) and hemolysis. *C. difficile* produces a cytotoxin, an exotoxin that kills enterocytes, causing pseudomembranous colitis. Often 2° to antibiotic use, especially clindamycin or ampicillin.	**TET**anus is **TET**anic paralysis (blocks glycine release [inhibitory neurotransmitter]) from Renshaw cells in spinal cord. ***BOT**ulinum* is from bad **BOT**tles of food and honey (causes a flaccid paralysis). ***PERF**ringens* **PERF**orates a gangrenous leg. ***DI**fficile* causes **DI**arrhea. Treat with metronidazole.
Diphtheria (and exotoxin)	Caused by *Corynebacterium diphtheriae* via exotoxin encoded by β-prophage. Potent exotoxin inhibits protein synthesis via ADP ribosylation of EF-2. Symptoms include pseudomembranous pharyngitis (grayish-white membrane) with lymphadenopathy. Lab diagnosis based on gram-positive rods with metachromatic granules.	*Coryne* = club shaped. Grows on tellurite agar. **ABCDEFG:** **A**DP ribosylation **B**eta-prophage ***C**orynebacterium* ***D**iphtheriae* **E**longation **F**actor 2 **G**ranules
Anthrax	Caused by *Bacillus anthracis*, a gram-positive, spore-forming rod that produces anthrax toxin. The only bacterium with a protein capsule. Contact → malignant pustule (painless ulcer); can progress to bacteremia and death. Inhalation of spores → flulike symptoms that rapidly progress to fever, pulmonary hemorrhage, mediastinitis, and shock.	Black skin lesions—vesicular papules covered by black eschar. Woolsorters' disease—inhalation of spores from contaminated wool.

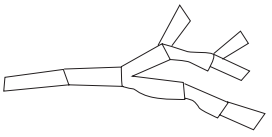
► MICROBIOLOGY–BACTERIOLOGY *(continued)*

Listeria monocytogenes

Acquired by ingestion of unpasteurized milk/cheese or by vaginal transmission during birth. Form "actin rockets" by which they move from cell to cell.

Can cause amnionitis, septicemia, and spontaneous abortion in pregnant women; granulomatosis infantiseptica; neonatal meningitis; meningitis in immunocompromised patients; mild gastroenteritis in healthy individuals.

Actinomyces* vs. *Nocardia



Both are gram-positive rods forming long branching filaments resembling fungi.

Actinomyces israelii, a gram-positive anaerobe, causes oral/facial abscesses that may drain through sinus tracts in skin. Normal oral flora.

Nocardia asteroides, a gram-positive and also a weakly acid-fast aerobe in soil, causes pulmonary infection in immunocompromised patients.

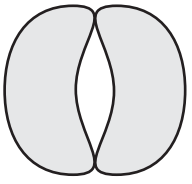
A. israelii forms yellow "sulfur granules" in sinus tracts.

SNAP:
Sulfa for *N*ocardia;
*A*ctinomyces use **P**enicillin

Penicillin and gram-negative bugs

Gram-negative bugs are resistant to benzylpenicillin G but may be susceptible to penicillin derivatives such as ampicillin. The gram-negative outer membrane layer inhibits entry of penicillin G and vancomycin.

Neisseria



Gram-negative cocci. Both ferment glucose and produce IgA proteases.

Gonococci
No polysaccharide capsule
No maltose fermentation
No vaccine
Sexually transmitted
Causes gonorrhea, septic arthritis, neonatal conjunctivitis, PID

Meningococci
Polysaccharide capsule
Maltose fermentation
Vaccine
Respiratory and oral secretions
Causes meningococcemia and meningitis, Waterhouse-Friderichsen syndrome

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Haemophilus influenzae

HaEMOPhilus causes **E**piglottitis, **M**eningitis, **O**titis media, and **P**neumonia. Small gram-negative (coccobacillary) rod. Aerosol transmission. Most invasive disease caused by capsular type B. Produces IgA protease. Culture on **chocolate agar** requires factors **V** (NAD) and **X** (hematin) for growth. Treat meningitis with ceftriaxone. Rifampin prophylaxis in close contacts. Does not cause the flu (influenza virus does).

When a child has "flu," mom goes to five (**V**) and dime (**X**) store to buy some **chocolate.** Vaccine contains type B capsular polysaccharide conjugated to diphtheria toxoid or other protein. Given between 2 and 18 months of age.

Enterobacteriaceae

Diverse family including *E. coli*, *Salmonella*, *Shigella*, *Klebsiella*, *Enterobacter*, *Serratia*, *Proteus*.

All species have somatic (O) antigen (which is the polysaccharide of endotoxin). The capsular (K) antigen is related to the virulence of the bug. The flagellar (H) antigen is found in motile species. All ferment glucose and are oxidase negative.

Think **COFFEe:**
Capsular
O antigen
Flagellar antigen
Ferment glucose
Enterobacteriaceae

Klebsiella	Pneumonia in alcoholics and diabetics. Red currant jelly sputum. Also cause of nosocomial UTIs.	3 **A**'s: **A**spiration pneumonia **A**bscess in lungs **A**lcoholics
Lactose-fermenting enteric bacteria	These bacteria grow pink colonies on MacConkey's agar. Examples include ***K****lebsiella*, ***E****. coli*, ***E****nterobacter*, and C*itrobacter*.	Lactose is **KEE.** Test with MacCon**KEE**'s agar.
Salmonella* vs. *Shigella	Both are non–lactose fermenters; both invade intestinal mucosa and can cause bloody diarrhea. ***Salmon****ella* have flagella and can disseminate hematogenously. Only S*almonella* produce H_2S. Symptoms of salmonellosis may be prolonged with antibiotic treatments, and there is typically a monocytic response. S*higella* is more virulent (10^1 organisms) than S*almonella* (10^5 organisms). S*almonella typhi* causes typhoid fever—fever, diarrhea, headache, rose spots on abdomen. Can remain in gallbladder chronically.	**Salmon swim** (motile and disseminate). Most species of S*almonella* have an animal reservoir; S*higella* do not have flagella but can propel themselves while within a cell by actin polymerization. Transmission is via "**F**ood, **F**ingers, **F**eces, and **F**lies."
Yersinia enterocolitica	Usually transmitted from pet feces (e.g., puppies), contaminated milk, or pork. Outbreaks are common in day-care centers. Can mimic Crohn's or appendicitis.	
Bugs causing food poisoning	*Vibrio parahaemolyticus* and *V. vulnificus* in contaminated seafood. *V. vulnificus* can also cause wound infections from contact with contaminated water or shellfish. *Bacillus cereus* in reheated rice. *S. aureus* in meats, mayonnaise, custard. *Clostridium perfringens* in reheated meat dishes. *C. botulinum* in improperly canned foods (bulging cans). *E. coli* O157:H7 in undercooked meat. *Salmonella* in poultry, meat, and eggs.	*S. aureus* and *B. cereus* food poisoning starts quickly and ends quickly. "Food poisoning from reheated rice? **Be serious!**" **(*B. cereus*).**

Bugs causing diarrhea

Type	Species	Findings
Bloody diarrhea	*Campylobacter*	Comma- or S-shaped organisms; growth at 42°C; oxidase positive
	Salmonella	Lactose negative; flagellar motility
	Shigella	Lactose negative; very low ID_{50}; produces Shiga toxin
	Enterohemorrhagic *E. coli*	O157:H7; can cause HUS; makes Shiga-like toxin
	Enteroinvasive *E. coli*	Invades colonic mucosa
	Yersinia enterocolitica	Day-care outbreaks, pseudoappendicitis
	C. difficile (can cause both watery and bloody diarrhea)	Pseudomembranous colitis
	Entamoeba histolytica	Protozoan
Watery diarrhea	Enterotoxigenic *E. coli*	Traveler's diarrhea; produces ST and LT toxins
	Vibrio cholerae	Comma-shaped organisms; rice-water diarrhea
	C. perfringens	Also causes gas gangrene
	Protozoa	*Giardia*, *Cryptosporidium* (in immunocompromised)
	Viruses	Rotavirus, adenovirus, Norwalk virus (norovirus)

cAMP inducers

1. *Vibrio cholerae* toxin permanently activates G_s, causing rice-water diarrhea.
2. Pertussis toxin permanently disables G_i, causing whooping cough.
3. *E. coli*—heat-labile toxin.
4. *Bacillus anthracis* toxin includes edema factor, a bacterial adenylate cyclase (↑ cAMP).

Cholera, pertussis, and *E. coli* toxins act via ADP ribosylation to permanently activate adenylate cyclase (↑ cAMP), while the anthrax edema factor is itself an adenylate cyclase.

Cholera turns the "on" on.
Pertussis turns the "off" off.
Pertussis toxin also promotes lymphocytosis by inhibiting chemokine receptors.

Legionella pneumophila

Legionnaires' disease = severe pneumonia. Pontiac fever = mild influenza.

Gram-negative rod. Gram stains poorly—use silver stain. Grow on charcoal yeast extract culture with iron and cysteine. Aerosol transmission from environmental water source habitat. No person-to-person transmission. Treat with erythromycin.

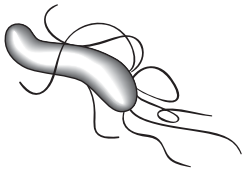
Think of a French legionnaire (soldier) with his silver helmet, sitting around a campfire (charcoal) with his iron dagger—he is no **sissy** (**cysteine**).

Pseudomonas aeruginosa

PSEUDOmonas is associated with wound and burn infections, **P**neumonia (especially in cystic fibrosis), **S**epsis (black lesions on skin), **E**xternal otitis (swimmer's ear), **U**TI, **D**rug use and **D**iabetic **O**steomyelitis, and hot tub folliculitis. Aerobic gram-negative rod. Non–lactose fermenting, oxidase positive. Produces pyocyanin (blue-green) pigment; has a grapelike odor. Water source. Produces endotoxin (fever, shock) and exotoxin A (inactivates EF-2). Treat with aminoglycoside plus extended-spectrum penicillin (e.g., piperacillin, ticarcillin).

AERuginosa—**AER**obic. Think water connection and blue-green pigment.
Think *Pseudomonas* in burn victims.

Helicobacter pylori



Causes gastritis and up to 90% of duodenal ulcers. Risk factor for peptic ulcer, gastric adenocarcinoma, and lymphoma. Gram-negative rod. Urease positive (e.g., urease breath test). Creates alkaline environment. Treat with triple therapy: (1) bismuth (Pepto-Bismol), metronidazole, and either tetracycline or amoxicillin; or (2) (more costly) metronidazole, omeprazole, and clarithromycin.

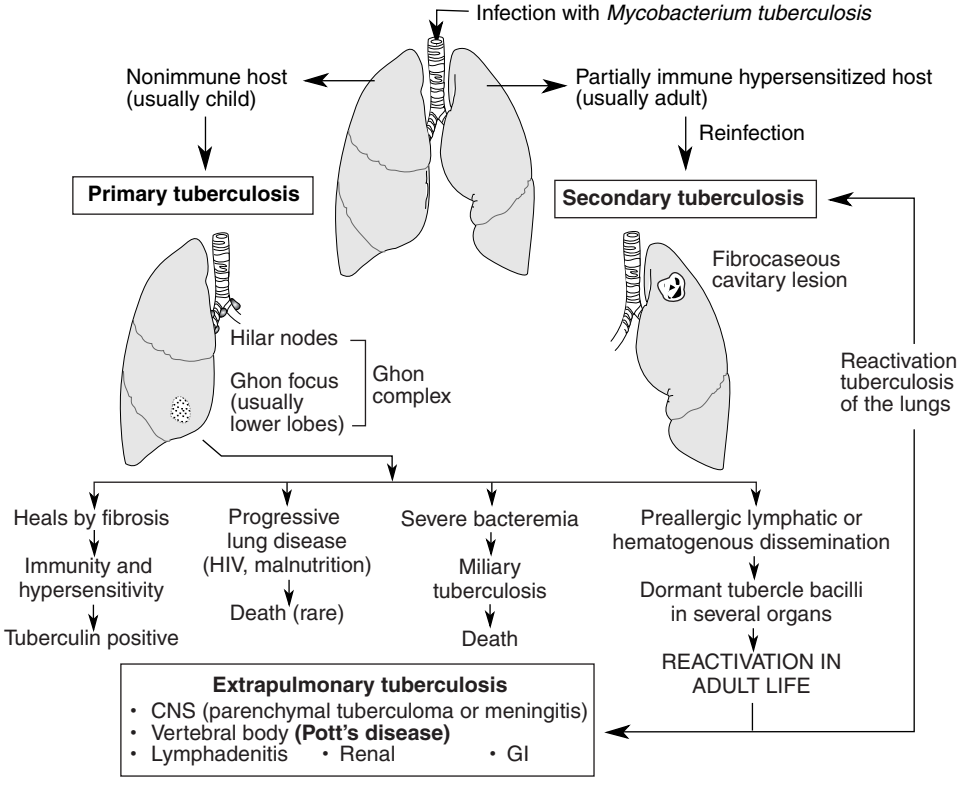
Zoonotic bacteria

Species	Disease	Transmission and source	
***B**artonella henselae*	Cat scratch fever	Cat scratch	**B**ig **B**ad **B**ugs **F**rom **Y**our **P**et.
***B**orrelia burgdorferi*	Lyme disease	Tick bite; *Ixodes* ticks that live on deer and mice	
***B**rucella* spp.	Brucellosis/ **U**ndulant fever	Dairy products, contact with animals	**Un**pasteurized dairy products give you **Un**dulant fever.
***F**rancisella tularensis*	Tularemia	Tick bite; rabbits, deer	
***Y**ersinia pestis*	Plague	Flea bite; rodents, especially prairie dogs	
***P**asteurella multocida*	Cellulitis	Animal bite; cats, dogs	

Gardnerella vaginalis

A pleomorphic, gram-variable rod that causes vaginosis—off-white/gray vaginal discharge with fishy smell; nonpainful. *Mobiluncus*, an anaerobe, is also involved. Sexually transmitted. Treat with metronidazole. Clue cells, or vaginal epithelial cells covered with bacteria, are visible under the microscope (see Color Image 13).

1° and 2° tuberculosis



(Adapted, with permission, from Chandrasoma P, Taylor CR. *Concise Pathology,* 3rd ed. Stamford, CT: Appleton & Lange, 1998: 523.)

PPD+ if current infection, past exposure, or BCG vaccinated.
PPD– if no infection or anergic (steroids, malnutrition, immunocompromise, sarcoidosis).

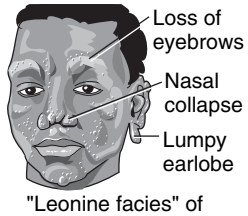
Ghon complex

TB granulomas (Ghon focus) with lobar and perihilar lymph node involvement. Reflects 1° infection or exposure.

Mycobacteria

Mycobacterium tuberculosis (TB, often resistant to multiple drugs).
M. kansasii (pulmonary TB-like symptoms).
M. scrofulaceum (cervical lymphadenitis in kids).
M. avium–intracellulare (often resistant to multiple drugs; causes disseminated disease in AIDS).
All mycobacteria are acid-fast organisms.

TB symptoms include fever, night sweats, weight loss, and hemoptysis (see Color Image 2).

Leprosy (Hansen's disease)  "Leonine facies" of lepromatous leprosy	Caused by *Mycobacterium leprae*, an acid-fast bacillus that likes cool temperatures (infects skin and superficial nerves) and cannot be grown in vitro. Reservoir in United States: armadillos. Treatment: long-term oral dapsone; toxicity is hemolysis and methemoglobinemia. Alternate treatments include rifampin and combination of clofazimine and dapsone.	Hansen's disease has 2 forms: lepromatous and tuberculoid; lepromatous is worse (failed cell-mediated immunity); tuberculoid is self-limited. **LE**promatous = **LE**thal.
Rickettsiae	Rickettsiae are obligate intracellular parasites that need CoA and NAD. All except *Coxiella* are transmitted by an arthropod vector and cause headache, fever, and rash; *Coxiella* is an atypical rickettsia because it is transmitted by aerosol and causes pneumonia. Tetracycline is the treatment of choice for most rickettsial infections.	Classic triad—headache, fever, rash (vasculitis).
Rickettsial diseases and vectors	Rocky Mountain spotted fever (tick)—*Rickettsia rickettsii*. Endemic typhus (fleas)—*R. typhi*. Epidemic typhus (human body louse)—*R. prowazekii*. Ehrlichiosis (tick)—*Ehrlichia*. Q fever (inhaled aerosols)—*Coxiella burnetii*. Treatment for all: tetracycline.	Rickettsial rash starts on hands and feet; typhus rash starts centrally and spreads out: "**R**ickettsia on the w**R**ists, **T**yphus on the **T**runk." **Q** fever is **Q**ueer because it has no rash, has no vector, and has negative Weil-Felix, and its causative organism can survive outside for a long time and does not have *Rickettsia* as its genus name.
Rocky Mountain spotted fever	Caused by *Rickettsia rickettsii*. Symptoms: rash on palms and soles (migrating to wrists, ankles, then trunk), headache, fever. Endemic to East Coast (in spite of name).	Palm and sole rash is seen in Rocky Mountain spotted fever, syphilis, and coxsackievirus A infection (hand, foot, and mouth disease).
Weil-Felix reaction	Weil-Felix reaction assays for antirickettsial antibodies, which cross-react with *Proteus* antigen. Weil-Felix is usually positive for typhus and Rocky Mountain spotted fever but negative for Q fever.	

Chlamydiae

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

1. **E**lementary body (small, dense), which **E**nters cell via endocytosis
2. Initial or **R**eticulate body, which **R**eplicates in cell by fission

Chlamydia trachomatis causes reactive arthritis, conjunctivitis, nongonococcal urethritis, and pelvic inflammatory disease (PID).

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

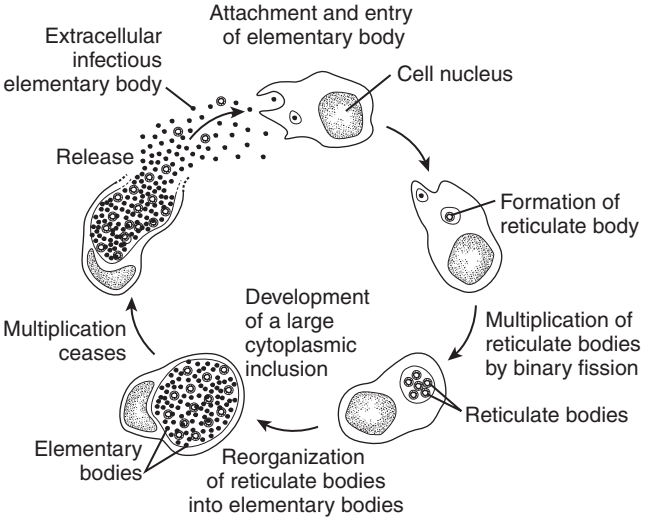
Treatment: erythromycin or tetracycline.

Chlamys = cloak (intracellular).

Chlamydia psittaci—notable for an avian reservoir.

The chlamydial cell wall is unusual in that it lacks muramic acid.

Lab diagnosis: cytoplasmic inclusions seen on Giemsa or fluorescent antibody–stained smear.



***Chlamydia trachomatis* serotypes**

Types A, B, and C—chronic infection, cause blindness in Africa.

Types D–K—urethritis/PID, ectopic pregnancy, neonatal pneumonia, or neonatal conjunctivitis.

Types L1, L2, and L3—lymphogranuloma venereum (acute lymphadenitis—positive Frei test).

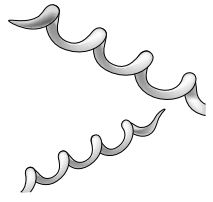
ABC = **A**frica/**B**lindness/**C**hronic infection.

L1–3 = **L**ymphogranuloma venereum.

D–K = everything else.

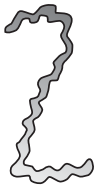
Neonatal disease can be acquired during passage through infected birth canal. Treat with oral erythromycin.

Spirochetes

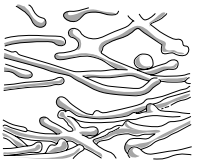


The spirochetes are spiral-shaped bacteria with axial filaments and include ***B****orrelia* (big size), ***L****eptospira*, and ***T****reponema*. Only *Borrelia* can be visualized using aniline dyes (Wright's or Giemsa stain) in light microscopy. *Treponema* is visualized by dark-field microscopy.

BLT. B is **B**ig.

Leptospira interrogans 	Question mark–shaped bacteria found in water contaminated with animal urine. Leptospirosis includes flulike symptoms, fever, headache, abdominal pain, and jaundice. Most prevalent in the tropics. Weil's 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 tick *Ixodes*. Classic symptom is erythema chronicum migrans, an expanding "bull's eye" red rash with central clearing. Also affects joints, CNS, and heart. Mice are important reservoirs. Deer required for tick life cycle. Treat with doxycycline. Named after Lyme, Connecticut; disease is common in northeastern United States. Transmission is most common in summer months.	3 stages of Lyme disease: Stage 1—erythema chronicum migrans, flulike symptoms. Stage 2—neurologic and cardiac manifestations. Stage 3—chronic monoarthritis, and migratory polyarthritis. **BAKE** a Key **Lyme** pie: **B**ell's palsy, **A**rthritis, **K**ardiac block, **E**rythema migrans.
Treponemal disease	Treponemes are spirochetes. *Treponema pallidum* causes syphilis. *T. pertenue* causes yaws (a tropical infection that is not an STD, although VDRL test is positive).	
Syphilis 1° syphilis 2° syphilis 3° syphilis Congenital syphilis	Caused by spirochete *Treponema pallidum*. Presents with painless chancre (localized disease). Disseminated disease with constitutional symptoms, maculopapular rash (palms and soles), condylomata lata. Many treponemes are present in chancres of 1° and 2° syphilis. Gummas, aortitis, neurosyphilis (tabes dorsalis), Argyll Robertson pupil (see Color Image 12). Saber shins, saddle nose, CN VIII deafness, Hutchinson's teeth.	Treat with penicillin G. **S**econdary syphilis = **S**ystemic. Signs: broad-based ataxia, positive Romberg, Charcot joints, stroke without hypertension.
Argyll Robertson pupil	Argyll Robertson pupil constricts with accommodation but is not reactive to light. Associated with 3° syphilis.	"Prostitute's pupil"—accommodates but does not react.
VDRL vs. FTA-ABS	FTA-ABS is specific for treponemes, turns positive earliest in disease, and remains positive longest. **VDRL** **FTA** **Interpretation** + + Active infection + – Probably false positive – + Successfully treated	**FTA-ABS** = **F**ind **T**he **A**ntibody-**ABS**olutely: 1. Most specific 2. Earliest positive 3. Remains positive the longest

► MICROBIOLOGY–BACTERIOLOGY *(continued)*

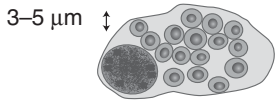
VDRL false positives	VDRL detects nonspecific antibody that reacts with beef cardiolipin. Used for diagnosis of syphilis, but many biologic false positives, including viral infection (mononucleosis, hepatitis), some drugs, rheumatic fever, SLE, and leprosy.	**VDRL:** **V**iruses (mono, hepatitis) **D**rugs **R**heumatic fever **L**upus and leprosy
Mycoplasma pneumoniae 	Classic cause of atypical "walking" pneumonia (insidious onset, headache, nonproductive cough, diffuse interstitial infiltrate). X-ray looks worse than patient. High titer of cold agglutinins (IgM). Grown on Eaton's agar. Treatment: tetracycline or erythromycin (bugs are penicillin resistant because they have no cell wall).	No cell wall. Not seen on gram stain. Only bacterial membrane containing cholesterol. Mycoplasmal pneumonia is more common in patients < 30 years of age. Frequent outbreaks in military recruits and prisons.

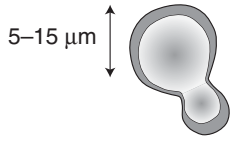
► MICROBIOLOGY–MYCOLOGY

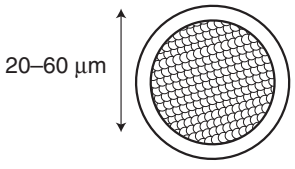
Spores: fungal	Most fungal spores are asexual. Both coccidioidomycosis and histoplasmosis are transmitted by inhalation of asexual spores.	Conidia—asexual fungal spores (e.g., blastoconidia, arthroconidia).
Candida albicans	Systemic or superficial fungal infection (budding yeast with pseudohyphae in culture at 20°C; germ tube formation at 37°C). Thrush esophagitis in immunocompromised patients, endocarditis in IV drug users, vaginitis (post-antibiotic), diaper rash. Transmission occurs by inhalation of spores. No person-to-person spread. Treatment: nystatin for superficial infection; amphotericin B for serious systemic infection.	*Alba* = **white.**

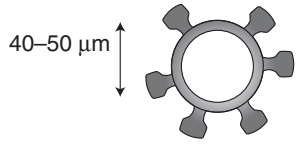
Systemic mycoses

Disease	Endemic location and pathologic features	Notes
Histoplasmosis	Mississippi and Ohio river valleys. Causes pneumonia.	Bird or bat droppings; intracellular (tiny yeast inside macrophages).
Blastomycosis	States east of Mississippi River and Central America. Causes inflammatory lung disease and can disseminate to skin and bone. Forms granulomatous nodules.	**B**ig, **B**road-**B**ased **B**udding. **Cold = Mold.** **Heat = Yeast.** Culture on Sabouraud's agar.
Coccidioidomycosis	Southwestern United States, California. Causes pneumonia and meningitis; can disseminate to bone and skin.	San Joaquin Valley or desert (desert bumps) "valley fever" (see Color Image 7).
Paracoccidioidomycosis	Rural Latin America.	"Captain's wheel" appearance.





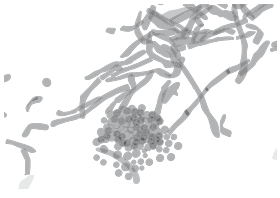




All of the above are caused by **dimorphic** fungi, which are mold in soil (at lower temperature) and yeast in tissue (at higher/body temperature: 37°C) except coccidioidomycosis, which is a spherule in tissue. All can cause pneumonia and can disseminate. Treat with fluconazole or ketoconazole for local infection; amphotericin B for systemic infection. Systemic mycoses can mimic TB (granuloma formation).

Cutaneous mycoses

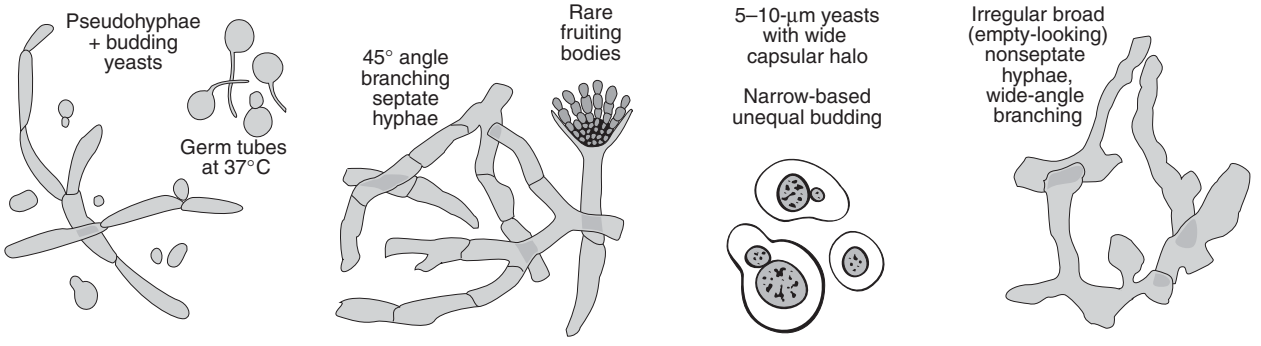
Tinea versicolor — Caused by *Malassezia furfur.* Occurs in hot, humid weather. Treat with topical miconazole, selenium sulfide (Selsun). "Spaghetti and meatball" appearance on KOH prep.



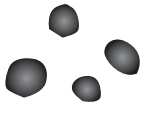
Tinea pedis, cruris, corporis, capitis — Pruritic lesions with central clearing resembling a ring, caused by dermatophytes (*Microsporum*, *Trichophyton*, and *Epidermophyton*). See mold hyphae in KOH prep, not dimorphic. Pets are a reservoir for *Microsporum* and can be treated with topical azoles.

Opportunistic fungal infections

Candida albicans	Thrush in immunocompromised (neonates, steroids, diabetes, AIDS), vulvovaginitis (high pH, diabetes, use of antibiotics), disseminated candidiasis (to any organ), chronic mucocutaneous candidiasis (see Color Image 9). Germ tube test is diagnostic.
Aspergillus fumigatus	Allergic bronchopulmonary aspergillosis, lung cavity aspergilloma ("fungus ball"), invasive aspergillosis, especially in immunocompromised individuals and those with chronic granulomatous disease. **Mold** with septate hyphae that branch at a V-shaped (45°) angle. Not dimorphic.
Cryptococcus neoformans	Cryptococcal meningitis, cryptococcosis. Heavily encapsulated **yeast.** Not dimorphic. Found in soil, pigeon droppings. Culture on Sabouraud's agar. Stains with India ink. Latex agglutination test detects polysaccharide capsular antigen (see Color Image 8). "Soap bubble" lesions in brain.
Mucor and *Rhizopus* spp.	Mucormycosis. **Mold** with irregular nonseptate hyphae branching at wide angles (≥ 90°). Disease mostly in ketoacidotic diabetic and leukemic patients. Fungi also proliferate in the walls of blood vessels and cause infarction and necrosis of distal tissue. Rhinocerebral, frontal lobe abscesses.

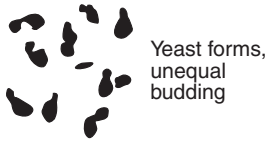


***Pneumocystis jiroveci* (formerly *carinii*)**



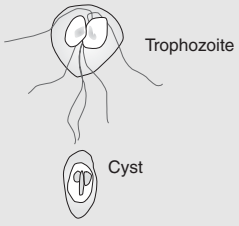
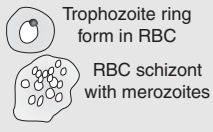
Causes diffuse interstitial pneumonia (PCP). Yeast (originally classified as protozoan). Inhaled. Most infections asymptomatic. Immunosuppression (e.g., AIDS) predisposes to disease. Diffuse, bilateral CXR appearance. Diagnosed by lung biopsy or lavage. Identified by methenamine silver stain of lung tissue. Treat with TMP-SMX, pentamidine, dapsone. Start prophylaxis when CD4 drops < 200 cells/mL in HIV patients (see Color Image 17).

Sporothrix schenckii

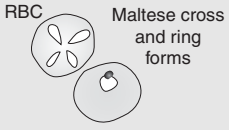
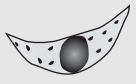
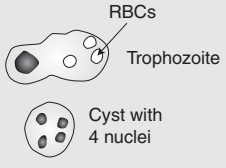
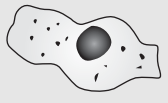


Sporotrichosis. Dimorphic fungus that lives on vegetation. When traumatically introduced into the skin, typically by a thorn ("rose gardener's" disease), causes local pustule or ulcer with nodules along draining lymphatics (ascending lymphangitis). Little systemic illness. Cigar-shaped budding yeast visible in pus. Treat with itraconazole or potassium iodide.

Medically important protozoa—single-celled organisms

Organism	Disease	Transmission	Diagnosis	Treatment
Giardia lamblia (see Color Image 5) 	Giardiasis: bloating, flatulence, foul-smelling diarrhea (often seen in campers/hikers)	Cysts in water	Trophozoites or cysts in stool	Metronidazole
Trichomonas vaginalis (see Color Image 10)	Vaginitis: foul-smelling, greenish discharge; itching and burning	Sexual	Trophozoites (motile) on wet mount	Metronidazole
Trypanosoma cruzi	Chagas' disease (dilated cardiomyopathy, megacolon, megaesophagus); predominantly in South America	Reduviid bug	Blood smear	Nifurtimox
Trypanosoma *T. gambiense* *T. rhodesiense*	African sleeping sickness	Tsetse fly	Blood smear	Suramin for blood-borne disease or melarsoprol for CNS penetration
Leishmania donovani	Visceral leishmaniasis (kala-azar): spiking fevers, hepatosplenomegaly, pancytopenia	Sandfly	Macrophages containing amastigotes	Sodium stibogluconate
Plasmodium *P. vivax* *P. ovale* *P. malariae* *P. falciparum* 	Malaria: cyclic fever, headache, anemia, splenomegaly Malaria—severe (cerebral) with *P. falciparum* *P. vivax* and *P. ovale* have dormant forms in liver (hypnozoites) → relapsing malaria	Mosquito (*Anopheles*)	Blood smear	Chloroquine (primaquine to prevent relapse caused by *P. vivax*, *P. ovale*), sulfadoxine + pyrimethamine, mefloquine, quinine

Medically important protozoa—single-celled organisms *(continued)*

Organism	Disease	Transmission	Diagnosis	Treatment
Babesia 	Babesiosis: fever and hemolytic anemia; predominantly in northeastern United States	*Ixodes* tick	Blood smear, no RBC pigment, appears as "Maltese cross"	Quinine, clindamycin
Cryptosporidium	Severe diarrhea in AIDS Mild disease (watery diarrhea) in non-immunocompromised	Cysts in water	Cysts on acid-fast stain	None
Toxoplasma gondii 	Brain abscess in HIV, birth defects (ring-enhancing brain lesions)	Cysts in meat or cat feces; crosses placenta (pregnant women should avoid cats)	Serology, biopsy	Sulfadiazine + pyrimethamine
Entamoeba histolytica 	Amebiasis: bloody diarrhea, (dysentery), liver abscess, RUQ pain	Cysts in water	Serology and/or trophozoites or cysts in stool; RBCs in cytoplasm of entamoeba	Metronidazole and iodoquinol
Naegleria fowleri 	Rapidly fatal meningoencephalitis	Swimming in freshwater lakes (enter via cribriform plate)	Amoebas in spinal fluid	None

Medically important helminths Multicellular organisms. Life cycle involves stages in other organisms.

Organism	Transmission/disease	Treatment
Nematodes (roundworms)		
Enterobius vermicularis (pinworm)	Food contaminated with eggs; intestinal infection; causes anal pruritus (the Scotch tape test).	Mebendazole/pyrantel pamoate
Ascaris lumbricoides (giant roundworm)	Eggs are visible in feces; intestinal infection.	Mebendazole/pyrantel pamoate
Trichinella spiralis	Undercooked meat, usually pork; inflammation of muscle (larvae encyst in muscle), periorbital edema.	Thiabendazole
Strongyloides stercoralis	Larvae in soil penetrate the skin; intestinal infection; causes vomiting, diarrhea, and anemia.	Ivermectin/thiabendazole
Ancylostoma duodenale, *Necator americanus* (hookworms)	Larvae penetrate skin of feet; intestinal infection can cause anemia (sucks blood from intestinal walls).	Mebendazole/pyrantel pamoate (worms are **BEND**y; treat with me**BEND**azole)
Dracunculus medinensis	In drinking water; skin inflammation and ulceration.	Niridazole
Onchocerca volvulus	Transmitted by female blackflies; causes **river** blindness, with skin nodules and "lizard skin." Can have allergic reaction to microfilaria.	**Iver**mectin (**IVER**mectin for r**IVER** blindness)
Loa loa	Transmitted by deer fly, horse fly, and mango fly; causes swelling in skin (can see worm crawling in conjunctiva).	Diethylcarbamazine
Wuchereria bancrofti	Female mosquito; causes blockage of lymphatic vessels (elephantiasis).	Diethylcarbamazine
Toxocara canis	Food contaminated with eggs; causes granulomas (if in retina → blindness) and visceral larva migrans.	Diethylcarbamazine
Cestodes (tapeworms)		
Taenia solium	Ingestion of larvae encysted in undercooked pork leads to intestinal tapeworms. Ingestion of eggs causes cysticercosis and neurocysticercosis, mass lesions in brain ("swiss cheese" appearance).	Praziquantel for intestinal worms and cysticercosis; albendazole for neurocysticercosis
Echinococcus granulosus	Eggs in dog feces when ingested can cause cysts in liver; causes anaphylaxis if echinococcal antigens are released from cysts (see Image 112).	Albendazole
Trematodes (flukes)		
Schistosoma	Snails are host; cercariae penetrate skin of humans; causes granulomas, fibrosis, and inflammation of the spleen and liver.	Praziquantel
Clonorchis sinensis	Undercooked fish; causes inflammation of the biliary tract → pigmented gallstones. Also associated with cholangiocarcinoma.	Praziquantel
Paragonimus westermani	Undercooked crab meat; causes inflammation and 2° bacterial infection of the lung.	Praziquantel

► MICROBIOLOGY–PARASITOLOGY *(continued)*

Nematode routes of infection	Ingested—***E**nterobius*, ***A**scaris*, ***T**richinella*. Cutaneous—***S**trongyloides*, ***A**ncylostoma*, ***N**ecator*.	You'll get sick if you **EAT** these! These get into your feet from the **SAN**d.

Parasite hints	**Findings**	**Organism**
	Brain cysts, seizures	*Taenia solium* (cysticercosis)
	Liver cysts	*Echinococcus granulosus*
	B_{12} deficiency	*Diphyllobothrium latum*
	Biliary tract disease	*Clonorchis sinensis*
	Hemoptysis	*Paragonimus westermani*
	Portal hypertension	*Schistosoma mansoni*
	Hematuria, bladder cancer	*Schistosoma haematobium*
	Microcytic anemia	*Ancylostoma*, *Necator*
	Perianal pruritus	*Enterobius*

"Tricky T's"

Typhoid fever—caused by bacterium *Salmonella typhi*.
Typhus—caused by bacteria *Rickettsia rickettsii* (endemic) and *Rickettsia prowazekii* (epidemic).
*Chlamydia **trach**omatis*—bacteria, STD.
***Trep**onema*—spirochete; causes syphilis (*T. pallidum*) or yaws (*T. pertenue*).
***Trich**omonas vaginalis*—protozoan, STD.
***Tryp**anosoma*—protozoan, causes Chagas' disease (*T. cruzi*) or African sleeping sickness.
***T**oxoplasma*—protozoan, a TORCH infection.
***Trich**inella spiralis*—nematode in undercooked meat.

► MICROBIOLOGY–VIROLOGY

DNA viral genomes	All DNA viruses except the Parvoviridae are dsDNA. All are linear except papilloma, polyoma, and hepadnaviruses (circular).	All are dsDNA (like our cells), except "**part-of-a-virus**" (**parvovirus**) is ssDNA.
RNA viral genomes	All RNA viruses except Reoviridae are ssRNA.	All are ssRNA (like our mRNA), except "**r**epeat**o**-virus" (**reo**virus) is dsRNA.
Naked viral genome infectivity	Purified nucleic acids of most dsDNA (except poxviruses and HBV) and (+) strand ssRNA (≈ mRNA) viruses are infectious. Naked nucleic acids of (−) strand ssRNA and dsRNA viruses are not infectious. They require enzymes contained in the complete virion.	

Viral envelopes	**N**aked (nonenveloped) viruses include **C**alicivirus, **P**icornavirus, **R**eovirus, **P**arvovirus, **A**denovirus, **P**apilloma, and **P**olyoma. Generally, enveloped viruses acquire their envelopes from plasma membrane when they exit from cell. Exceptions are herpesviruses, which acquire envelopes from nuclear membrane.	**Naked CPR** and **PAPP** smear.

Virus ploidy	All viruses are haploid (with 1 copy of DNA or RNA) except retroviruses, which have 2 identical ssRNA molecules (≈ diploid).

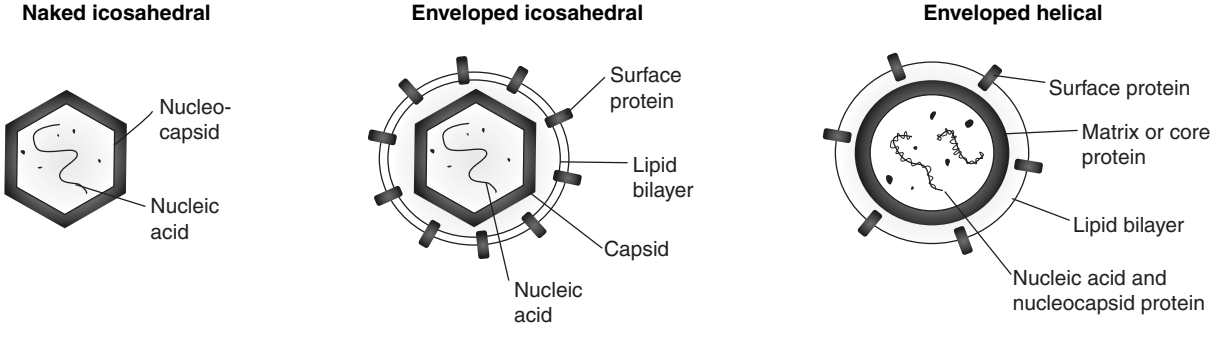
Viral replication

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

Viral pathogens

Structure	Viruses
DNA enveloped viruses	Herpesviruses (HSV types 1 and 2, VZV, CMV, EBV), HBV, smallpox virus
DNA nucleocapsid viruses	Adenovirus, papillomaviruses, parvovirus
RNA enveloped viruses	Influenza virus, parainfluenza virus, RSV, measles virus, mumps virus, rubella virus, rabies virus, HTLV, HIV
RNA nucleocapsid viruses	Enteroviruses (poliovirus, coxsackievirus, echovirus, HAV), rhinovirus, reovirus (rotavirus)

Viral structure—general features



► MICROBIOLOGY–VIROLOGY *(CONTINUED)*

DNA virus characteristics

Some general rules—all DNA viruses:

1. Are **HHAPPPP**y viruses	**H**epadna, **H**erpes, **A**deno, **P**ox, **P**arvo, **P**apilloma, **P**olyoma.
2. Are double stranded	EXCEPT parvo (single stranded).
3. Are linear	EXCEPT papilloma and polyoma (circular, supercoiled) and hepadna (circular, incomplete).
4. Are icosahedral	EXCEPT pox (complex).
5. Replicate in the nucleus	EXCEPT pox (carries own DNA-dependent RNA polymerase).

DNA viruses

Viral Family	Envelope	DNA Structure	Medical Importance
Herpesviruses	Yes	DS – linear	HSV-1—oral (and some genital) lesions, keratoconjunctivitis HSV-2—genital (and some oral) lesions VZV—chickenpox, zoster, shingles EBV—mononucleosis, Burkitt's lymphoma CMV—infection in immunosuppressed patients, especially transplant recipients; congenital defects HHV-6—roseola (exanthem subitum) HHV-8—Kaposi's sarcoma–associated herpesvirus (KSHV)
Hepadnavirus	Yes	DS – partial circular	HBV Acute or chronic hepatitis Vaccine available—use has increased tremendously Not a retrovirus but has reverse transcriptase
Adenovirus	No	DS – linear	Febrile pharyngitis—sore throat Pneumonia Conjunctivitis—"pink eye"
Parvovirus	No	SS – linear (–) (smallest DNA virus)	B19 virus—aplastic crises in sickle cell disease, "slapped cheeks" rash—erythema infectiosum (fifth disease), hydrops fetalis
Papillomavirus*	No	DS – circular	HPV—warts, CIN, cervical cancer
Polyomavirus*	No	DS – circular	JC—progressive multifocal leukoencephalopathy (PML) in HIV
Poxvirus	Yes	DS – linear (largest DNA virus)	Smallpox, although eradicated, could be used in germ warfare Vaccinia—cowpox ("milkmaid's blisters") Molluscum contagiosum

*Papillomavirus and polyomavirus are two new classifications originally grouped as "papovavirus."

RNA viruses

Viral Family	Envelope	RNA Structure	Capsid Symmetry	Medical Importance
Picornaviruses	No	SS + linear	Icosahedral	**P**oliovirus—polio-Salk/Sabin vaccines—IPV/OPV **E**chovirus—aseptic meningitis **R**hinovirus—"common cold" **C**oxsackievirus—aseptic meningitis herpangina—febrile pharyngitis hand, foot, and mouth disease myocarditis **H**AV—acute viral hepatitis
Caliciviruses	No	SS + linear	Icosahedral	HEV Norwalk virus—viral gastroenteritis
Reoviruses	No	DS linear 10–12 segments	Icosahedral (double)	Reovirus—Colorado tick fever Rotavirus—#1 cause of fatal diarrhea in children
Flaviviruses	Yes	SS + linear	Icosahedral	HCV Yellow fever* Dengue* St. Louis encephalitis* West Nile virus*
Togaviruses	Yes	SS + linear	Icosahedral	Rubella (German measles) Eastern equine encephalitis* Western equine encephalitis*
Retroviruses	Yes	SS + linear	Icosahedral	Have reverse transcriptase HIV—AIDS HTLV—T-cell leukemia
Coronaviruses	Yes	SS + linear	Helical	Coronavirus—"common cold" and SARS
Orthomyxoviruses	Yes	SS – linear 8 segments	Helical	Influenza virus
Paramyxoviruses	Yes	SS – linear Nonsegmented	Helical	**P**a**R**a**M**yxovirus: **P**arainfluenza—croup **R**SV—bronchiolitis in babies; Rx—ribavirin Rubeola (**M**easles) **M**umps
Rhabdoviruses	Yes	SS – linear	Helical	Rabies
Filoviruses	Yes	SS – linear	Helical	Ebola/Marburg hemorrhagic fever—often fatal!
Arenaviruses	Yes	SS – circular	Helical	LCV—lymphocytic choriomeningitis Lassa fever encephalitis—spread by mice
Bunyaviruses	Yes	SS – circular 3 segments	Helical	California encephalitis* Sandfly/Rift Valley fevers Crimean-Congo hemorrhagic fever* Hantavirus—hemorrhagic fever, pneumonia
Deltavirus	Yes	SS – circular	Helical	HDV
SS, single-stranded; DS, double-stranded; +, + sense; –, – sense; *= arbovirus				

(Adapted, with permission, from Levinson W, Jawetz E. *Medical Microbiology and Immunology: Examination and Board Review,* 6th ed. New York: McGraw-Hill, 2000: 182.)

► MICROBIOLOGY–VIROLOGY *(continued)*

Viral vaccines	Live attenuated vaccines induce humoral and cell-mediated immunity but have reverted to virulence on rare occasions. Killed vaccines induce only humoral immunity but are stable.	Dangerous to give live vaccines to immunocompromised patients or their close contacts.
	Live attenuated—measles, mumps, rubella, Sabin polio, VZV, yellow fever, smallpox.	MMR = measles, mumps, rubella.
	Killed—**R**abies, **I**nfluenza, Salk **P**olio, and HA**V** vaccines.	Sal**K** = **K**illed.
	Recombinant—HBV (antigen = recombinant HBsAg).	**RIP** **A**lways.

Viral genetics	
Recombination	Exchange of genes between 2 chromosomes by crossing over within regions of significant base sequence homology.
Reassortment	When viruses with segmented genomes (e.g., influenza virus) exchange segments. High-frequency recombination. Cause of worldwide influenza pandemics.
Complementation	When 1 of 2 viruses that infect the cell has a mutation that results in a nonfunctional protein. The nonmutated virus "complements" the mutated one by making a functional protein that serves both viruses.
Phenotypic mixing	Occurs with simultaneous infection of a cell with 2 viruses. Genome of virus A can be partially or completely coated (forming pseudovirion) with the surface proteins of virus B. Type B protein coat determines the infectivity of the phenotypically mixed virus. However, the progeny from this infection have a type A coat that is encoded by its type A genetic material.

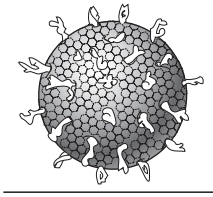
Negative-stranded viruses	Must transcribe negative strand to positive using RNA polymerase. They include **A**renaviruses, **B**unyaviruses, **P**aramyxoviruses, **O**rthomyxoviruses, **F**iloviruses, **R**habdoviruses, and **H**epatitis delta virus.	**A**lways **B**ring **P**olymerase **O**r **F**ail **R**eplication **H**orribly.
Segmented viruses	All are RNA viruses. They include **B**unyaviruses, **O**rthomyxoviruses (influenza viruses), **A**renaviruses, and **R**eoviruses. Influenza virus consists of 8 segments of negative-stranded RNA. These segments can undergo reassortment, causing antigenic shifts that lead to worldwide pandemics of the flu.	**BOAR.**

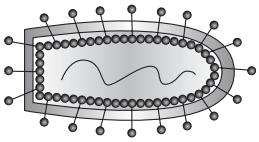
Herpesviruses

Virus	Diseases	Route of transmission	
HSV-1	Gingivostomatitis, keratoconjunctivitis, temporal lobe encephalitis, herpes labialis	Respiratory secretions, saliva	Get herpes in a **CHEV**rolet: **C**MV **H**SV **E**BV **V**ZV
HSV-2	Herpes genitalis (see Color Image 11), neonatal herpes	Sexual contact, perinatal	
VZV	Varicella-zoster (shingles), encephalitis, pneumonia (see Color Image 15)	Respiratory secretions	
EBV	Infectious mononucleosis, Burkitt's lymphoma	Respiratory secretions, saliva	
CMV	Congenital infection, mononucleosis (negative Monospot), pneumonia. Infected cells have characteristic "owl's eye" appearance (see Color Image 6)	Congenital, transfusion, sexual contact, saliva, urine, transplant	
HHV-8	Kaposi's sarcoma (HIV patients)	Sexual contact	

HSV identification	Tzanck test—a smear of an opened skin vesicle to detect multinucleated giant cells. Used to assay for HSV-1, HSV-2, and VZV. Infected cells also have intranuclear Cowdry A inclusions.	**Tzanck** heavens I do not have herpes.
EBV	A herpesvirus. Can cause mononucleosis. Infects B cells. Characterized by fever, hepatosplenomegaly, pharyngitis, and lymphadenopathy (especially posterior auricular nodes). Peak incidence 15–20 years old. Positive heterophil antibody test. Abnormal circulating cytotoxic T cells (atypical lymphocytes). Also associated with development of Hodgkin's and endemic Burkitt's lymphomas.	Most common during peak kissing years ("kissing disease"). Monospot test—heterophil antibodies detected by agglutination of sheep RBCs.
Picornavirus	Includes **P**oliovirus, **E**chovirus, **R**hinovirus, **C**oxsackievirus, **H**AV. RNA is translated into 1 large polypeptide that is cleaved by proteases into functional viral proteins. Can cause aseptic (viral) meningitis (except rhinovirus and HAV).	Pico**RNA**virus = small **RNA** virus. **PERCH** on a "**peak**" (pico).
Rhinovirus	A picornavirus. Nonenveloped RNA virus. Cause of common cold; > 100 serologic types.	**Rhino** has a runny nose.
Yellow fever virus	A flavivirus (also an arbovirus) transmitted by *Aedes* mosquitos. Virus has a monkey or human reservoir. Symptoms: high fever, black vomitus, and jaundice. Councilman bodies (acidophilic inclusions) may be seen in liver.	*Flavi* = yellow.

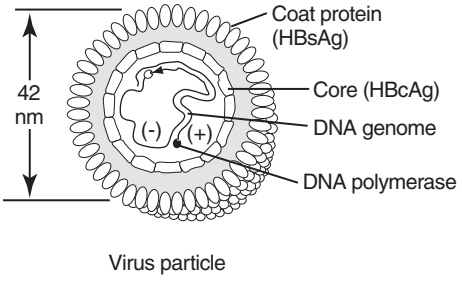
► MICROBIOLOGY–VIROLOGY *(continued)*

Rubella virus	A togavirus. Causes German (3-day) measles. Fever, lymphadenopathy, arthralgias, fine truncal rash. Causes mild disease in children but serious congenital disease (a TORCH infection).	
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. Villous destruction with atrophy leads to ↓ absorption of Na^+ and water.	**ROTA** = **R**ight **O**ut **T**he **A**nus.
Influenza viruses	Orthomyxoviruses. Enveloped, single-stranded RNA viruses with segmented genome. Contain hemagglutinin and neuraminidase antigens. Responsible for worldwide influenza epidemics; patients at risk for fatal bacterial superinfection. Rapid genetic changes.	Killed viral vaccine is major mode of protection; reformulated vaccine offered each fall to elderly, health-care workers, etc.
Genetic shift (pandemic)	Reassortment of viral genome (such as when human flu A virus recombines with swine flu A virus).	**S**udden **S**hift is more deadly than gra**D**ual **D**rift.
Genetic drift (epidemic)	Minor (antigenic drift) changes based on random mutation.	
Treatment	Amantadine and rimantadine useful for influenza A (especially prophylaxis). High level of resistance to these drugs; no longer used. Zanamivir and oseltamivir (neuraminidase inhibitors) useful for both influenza A and B.	
Paramyxoviruses	Paramyxoviruses cause disease in children. They include those that cause parainfluenza (croup), mumps, and measles as well as RSV, which causes respiratory tract infection (bronchiolitis, pneumonia) in infants.	
Rubeola (measles) virus	A paramyxovirus that causes measles. Koplik spots (red spots with blue-white center on buccal mucosa) are diagnostic. SSPE (years later), encephalitis (1:2000), and giant cell pneumonia (rarely, in immunosuppressed) are possible sequelae. Rash spreads from head to toe.	3 **C**'s of measles: **C**ough **C**oryza **C**onjunctivitis Also look for **K**oplik spots.
Mumps virus	A paramyxovirus. Symptoms: **P**arotitis, **O**rchitis (inflammation of testes), and aseptic **M**eningitis. Can cause sterility (especially after puberty).	Mumps makes your parotid glands and testes as big as **POM**-poms.

Rabies virus 	Negri bodies (see Image 113) are characteristic cytoplasmic inclusions in neurons infected by rabies virus. Has bullet-shaped capsid. Rabies has long incubation period (weeks to months). Causes fatal encephalitis with seizures, hydrophobia, hypersalivation, and pharyngeal spasm. More commonly from bat, raccoon, and skunk bites than from dog bites in the United States.	Travels to the CNS by migrating in a retrograde fashion up nerve axons.
Arboviruses	Transmitted by arthropods (mosquitoes, ticks). Classic examples are dengue fever (also known as break-bone fever) and yellow fever. A variant of dengue fever in Southeast Asia is hemorrhagic shock syndrome.	**ARBO**virus—**AR**thropod-**BO**rne virus, including some members of **F**lavivirus, **T**ogavirus, and **B**unyavirus. **F**ever **T**ransmitted by **B**ites.
"Lots of spots"		
Rubella	Togavirus; German 3-day measles.	
Rubeola	Paramyxovirus; measles.	
Varicella	Herpesvirus; chickenpox and zoster.	
Variola	Poxvirus; smallpox (no longer present outside of labs).	
Vaccinia	Poxvirus; strain used for smallpox vaccine.	
Hepatitis viruses	The hepatitis viruses belong to 5 different viral families.	
	HAV (RNA picornavirus) is transmitted primarily by fecal-oral route. Short incubation (3 weeks). No carriers.	Hep **A**: **A**symptomatic (usually), **A**cute, **A**lone (no carriers).
	HBV (DNA hepadnavirus) is transmitted primarily by parenteral, sexual, and maternal-fetal routes. Long incubation (3 months). Carriers. Cellular RNA polymerase transcribes RNA from DNA template. Reverse transcriptase transcribes DNA genome from RNA intermediate. However, the virion enzyme is a DNA-dependent DNA polymerase.	Hep **B**: **B**lood borne.
	HCV (RNA flavivirus) is transmitted primarily via blood and resembles HBV in its course and severity. Carriers. Common cause of hepatitis among IV drug users in the United States.	Hep **C**: **C**hronic, **C**irrhosis, **C**arcinoma, **C**arriers.
	HDV (delta agent) is a defective virus that requires HBsAg as its envelope. HDV can coinfect with HBV or superinfect; the latter has a worse prognosis. Carriers.	Hep **D**: **D**efective, **D**ependent on HBV.
	HEV (RNA calicivirus) is transmitted enterically and causes water-borne epidemics. Resembles HAV in course, severity, incubation. High mortality rate in pregnant women.	Hep **E**: **E**nteric, **E**xpectant mothers, **E**pidemics.
	Both HBV and HCV predispose a patient to chronic active hepatitis, cirrhosis, and hepatocellular carcinoma.	A and E by fecal-oral route: "The **vowels** hit your **bowels**."

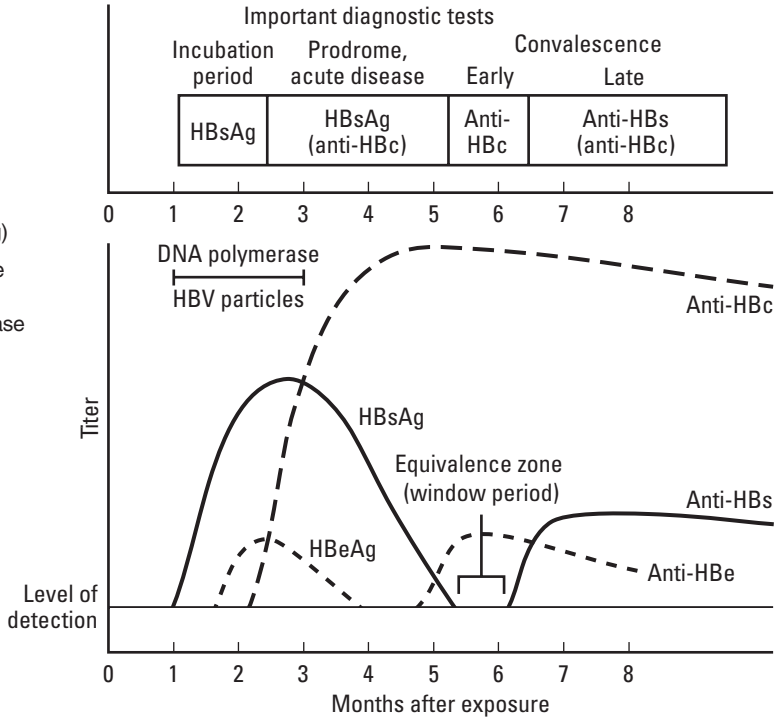
Hepatitis serologic markers

IgG HAVAb	Indicates prior infection; protective against reinfection.
IgM HAVAb	IgM antibody to HAV; best test to detect active hepatitis A.
HBsAg	Antigen found on surface of HBV; continued presence indicates carrier state.
HBsAb	Antibody to HBsAg; **provides immunity** to hepatitis B.
HBcAg	Antigen associated with core of HBV.
HBcAb	Antibody to HBcAg; positive during **window period.** IgM HBcAb is an indicator of recent disease. IgG HBcAb signifies chronic disease.
H**Be**Ag	A second, different antigenic determinant in the HBV core. Important indicator of active viral replication and therefore transmissibility (**Be**ware!)
HBeAb	Antibody to e antigen; indicates low transmissibility.



Virus particle

In viral hepatitis, ALT > AST.
In alcoholic hepatitis, AST > ALT.

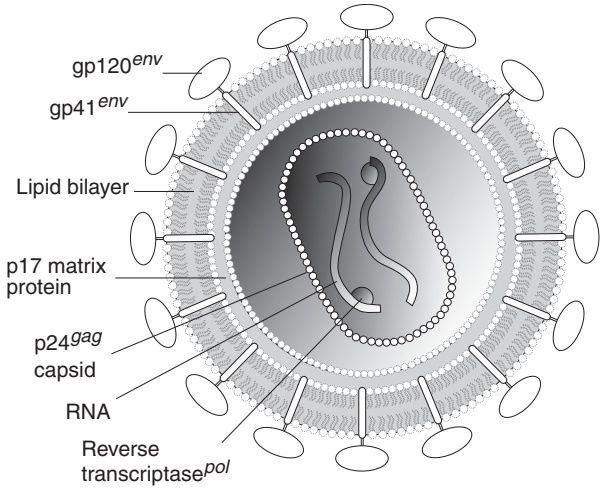


Test	Acute Disease	Window Phase	Complete Recovery	Chronic Carrier	Immunized
HBsAg	+	–	–	+	–
HBsAb	–	–[b]	+	–	+
HBcAb	+[a]	+	+	+	–

[a]IgM in acute stage; IgG in chronic or recovered stage.

[b]Patient has surface antibody but available antibody is bound to HBsAg, so not detected in assay.

HIV



(Adapted, with permission, from Levinson W. *Medical Microbiology and Immunology: Examination and Board Review,* 8th ed. New York: McGraw-Hill, 2004: 314.)

Diploid genome (2 molecules of RNA).
p24 = rectangular capsid protein.
gp41 and gp120 = envelope proteins.

Reverse transcriptase synthesizes dsDNA from RNA; dsDNA integrates into host genome.

Virus binds CXCR4 and CD4 on T cells; binds CCR5 and CD4 on macrophages. 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); positive results are then confirmed with Western blot assay (specific, high false-negative rate and high threshold, RULE IN test).
HIV PCR/viral load tests are increasing in popularity: they allow physician to monitor the effect of drug therapy on viral load.
AIDS diagnosis ≤ 200 CD4+, HIV positive with AIDS indicator condition (e.g., PCP), or CD4/CD8 ratio < 1.5.

ELISA/Western blot tests look for antibodies to viral proteins; these tests are often 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).

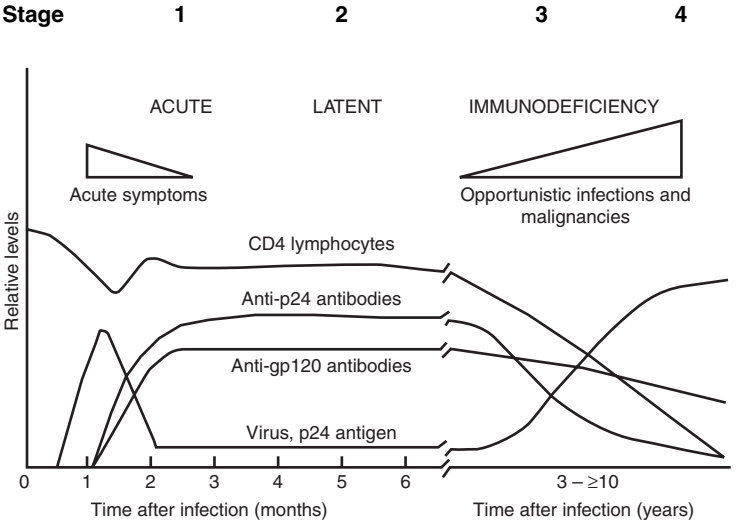
► MICROBIOLOGY–VIROLOGY *(continued)*

Time course of HIV infection

4 stages of infection:

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

During latent phase, virus replicates in lymph nodes.



(Adapted, with permission, from Levinson W. *Medical Microbiology and Immunology: Examination and Board Review,* 8th ed. New York: McGraw-Hill, 2004: 318.)

Opportunistic infections and disease in AIDS

Organ system	Infection/disease
Brain	Cryptococcal meningitis, toxoplasmosis, CMV encephalopathy, AIDS dementia, PML (JC virus)
Eyes	CMV retinitis
Mouth and throat	Thrush (*Candida albicans*), HSV, CMV, oral hairy leukoplakia (EBV)
Lungs	*Pneumocystis jiroveci* pneumonia (PJP), TB, histoplasmosis
GI	Cryptosporidiosis, *Mycobacterium avium–intracellulare* complex, CMV colitis, non-Hodgkin's lymphoma (EBV), *Isospora belli*
Skin	Shingles (VZV), Kaposi's sarcoma (HHV-8)
Genitals	Genital herpes, warts, and cervical cancer (HPV)

HIV-associated infections and CD4 count

Risk increases at CD4 level of:	Infection
< 400	Oral thrush, tinea pedis, reactivation VZV, reactivation tuberculosis, other bacterial infections (e.g., *H. influenzae*, *S. pneumoniae*, *Salmonella*)
< 200	Reactivation HSV, cryptosporidiosis, *Isospora*, disseminated coccidioidomycosis, *Pneumocystis* pneumonia
< 100	Candidal esophagitis, toxoplasmosis, histoplasmosis
< 50	CMV retinitis and esophagitis, disseminated *M. avium–intracellulare*, cryptococcal meningoencephalitis

Neoplasms associated with HIV — Kaposi's sarcoma (HHV-8), invasive cervical carcinoma (HPV), 1° CNS lymphoma, non-Hodgkin's lymphoma.

HIV encephalitis — Occurs late in the course of HIV infection. Virus gains CNS access via infected macrophages. Microglial nodules with multinucleated giant cells.

Prions Infectious agents that do not contain RNA or DNA (consist only of proteins); encoded by cellular genes. Diseases include Creutzfeldt-Jakob disease (CJD—rapid progressive dementia), kuru, scrapie (sheep), and "mad cow disease." Prions are associated with spongiform encephalopathy. Normal prions have α-helix conformation; pathologic prions (like CJD) are β-pleated sheets.

► MICROBIOLOGY–SYSTEMS

Normal flora: dominant

Skin—*Staphylococcus epidermidis.*
Nose—*S. Epidermidis*; colonized by *S. aureus.*
Oropharynx—Viridans group streptococci.
Dental plaque—*Streptococcus mutans.*
Colon—*Bacteroides fragilis* > *E. coli.*
Vagina—*Lactobacillus*, colonized by *E. coli* and group B strep.

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

Common causes of pneumonia

Neonates (< 4 wk)	Children (4 wk–18 yr)	Adults (18–40 yr)	Adults (40–65 yr)	Elderly
Group B streptococci	Viruses (**R**SV)	*Mycoplasma*	*S. pneumoniae*	*S. pneumoniae*
E. coli	***M**ycoplasma*	*C. pneumoniae*	*H. influenzae*	Viruses
	***C**hlamydia pneumoniae*	*S. pneumoniae*	Anaerobes	Anaerobes
	***S**treptococcus pneumoniae*		Viruses	*H. influenzae*
	Runts **M**ay **C**ough **S**putum		*Mycoplasma*	Gram-negative rods

Special groups:

Nosocomial (hospital acquired)	*Staphylococcus*, gram-negative rods
Immunocompromised	*Staphylococcus*, gram-negative rods, fungi, viruses, *Pneumocystis jiroveci*—with HIV
Aspiration	Anaerobes
Alcoholic/IV drug user	*S. pneumoniae, Klebsiella, Staphylococcus*
Postviral	*Staphylococcus, H. influenzae*
Atypical	*Mycoplasma, Legionella, Chlamydia*

Common causes of meningitis

Newborn (0–6 mos)	Children (6 mos–6 yrs)	6–60 yrs	60 yrs +
Group B streptococci	*Streptococcus pneumoniae*	*N. meningitidis*	*S. pneumoniae*
E. coli	*Neisseria meningitidis*	Enteroviruses	Gram-negative rods
Listeria	*Haemophilus influenzae* type B	*S. pneumoniae*	*Listeria*
	Enteroviruses	HSV	

Viral causes of meningitis—enteroviruses (esp. coxsackievirus), HSV, HIV, West Nile virus, VZV.
In HIV—*Cryptococcus*, CMV, toxoplasmosis (brain abscess), JC virus (PML).
Note: Incidence of *H. influenzae* meningitis has ↓ greatly with introduction of *H. influenzae* vaccine in last 10–15 years.

CSF findings in meningitis

	Pressure	Cell type	Protein	Sugar
Bacterial	↑	↑ PMNs	↑	↓
Fungal/TB	↑	↑ lymphocytes	↑	↓
Viral	Normal/↑	↑ lymphocytes	Normal	Normal

Osteomyelitis

Most people—*S. aureus*.
Sexually active—*Neisseria gonorrhoeae* (rare), septic arthritis more common.
Diabetics and drug addicts—*Pseudomonas aeruginosa*.
Sickle cell—*Salmonella*.
Prosthetic replacement—*S. aureus* and *S. epidermidis*.
Vertebral—*Mycobacterium tuberculosis* (Pott's disease).
Cat and dog bites or scratches—*Pasteurella multocida*.

Assume *S. aureus* if no other information.
Most osteomyelitis occurs in children.
Elevated CRP and ESR classic but nonspecific.

Urinary tract infections

Ambulatory—*E. coli* (50–80%), *Klebsiella* (8–10%).
Staphylococcus saprophyticus (10–30%) is the 2nd most common cause of UTI in young, sexually active, ambulatory women.
Hospital—*E. coli*, *Proteus*, *Klebsiella*, *Serratia*, *Pseudomonas*.
Epidemiology: women to men—10:1 (short urethra colonized by fecal flora).
Predisposing factors: flow obstruction, kidney surgery, catheterization, gynecologic abnormalities, diabetes, and pregnancy.

UTIs mostly caused by ascending infections. In males: babies with congenital defects; elderly with enlarged prostates.
UTI—dysuria, frequency, urgency, suprapubic pain.
Pyelonephritis—fever, chills, flank pain, and CVA tenderness.

UTI bugs

Species	Features of the organism	
Serratia marcescens	Some strains produce a red pigment; often nosocomial and drug resistant.	**SSEEK PP.** Diagnostic markers: Leukocyte esterase—positive = bacterial. Nitrite test—positive = gram negative.
Staphylococcus saprophyticus	2nd leading cause of community-acquired UTI in sexually active women.	
Escherichia coli	Leading cause of UTI. Colonies show metallic sheen on EMB agar.	
Enterobacter cloacae	Often nosocomial and drug resistant.	
Klebsiella pneumoniae	Large mucoid capsule and viscous colonies.	
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.	

ToRCHeS infections

These important infections are transmitted in utero or during vaginal birth.

Major clinical manifestations

- ***T****oxoplasma gondii*—"classic triad" of chorioretinitis, intracranial calcifications, and hydrocephalus. May be asymptomatic at birth.
- **R**ubella—deafness, cataracts, heart defects (PDA, pulmonary artery stenosis), and mental retardation.
- **C**MV—petechial rash, intracranial calcifications, mental retardation, hepatosplenomegaly, microcephaly, jaundice. 90% are asymptomatic at birth.
- **H**IV—hepatosplenomegaly, neurologic abnormalities, frequent infections.
- **H**SV type 2—encephalitis, conjunctivitis, vesicular skin lesions. Often asymptomatic at birth.
- **S**yphilis—cutaneous lesions, hepatosplenomegaly, jaundice, saddle nose, saber shins, Hutchinson teeth, CN VIII deafness, rhinitis ("snuffles").

Other important congenital infections

Listeria, *E. coli*, and group B streptococci can be acquired placentally or from birth canal.

Sexually transmitted diseases

Disease	Clinical features	Organism
Gonorrhea	Urethritis, cervicitis, PID, prostatitis, epididymitis, arthritis, creamy purulent discharge	*Neisseria gonorrhoeae*
1° syphilis	Painless chancre	*Treponema pallidum*
2° syphilis	Fever, lymphadenopathy, skin rashes, condylomata lata	
3° syphilis	Gummas, tabes dorsalis, general paresis, aortitis, Argyll Robertson pupil	
Genital herpes	Painful penile, vulvar, or cervical ulcers; can cause systemic symptoms such as fever, headache, myalgia.	HSV-2
Chlamydia	Urethritis, cervicitis, conjunctivitis, Reiter's syndrome, PID	*Chlamydia trachomatis* (D–K)
Lymphogranuloma venereum	Ulcers, lymphadenopathy, rectal strictures	*C. trachomatis* (L1–L3)
Trichomoniasis	Vaginitis, strawberry-colored mucosa	*Trichomonas vaginalis*
AIDS	Opportunistic infections, Kaposi's sarcoma, lymphoma	HIV
Condylomata acuminata	Genital warts, koilocytes	HPV 6 and 11
Hepatitis B	Jaundice	HBV
Chancroid	Painful genital ulcer, inguinal adenopathy	*Haemophilus ducreyi*
Bacterial vaginosis	Noninflammatory, malodorous discharge (fishy smell); positive whiff test, clue cells	*Gardnerella vaginalis*

Pelvic inflammatory disease	Top bugs—*Chlamydia trachomatis* (subacute, often undiagnosed), *Neisseria gonorrhoeae* (acute, high fever). *C. trachomatis* is the most common STD in the United States (3–4 million cases per year). 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. Other STDs include *Gardnerella* (clue cells) and *Trichomonas* (motile on wet prep).

Nosocomial infections

Pathogen	Risk factor	Notes
CMV, RSV	Newborn nursery	The 2 most common causes of nosocomial infections are *E. coli* (UTI) and *S. aureus* (wound infection).
E. coli, Proteus mirabilis	Urinary catheterization	
Pseudomonas aeruginosa	Respiratory therapy equipment	Presume *Pseudomonas* ***AIR****uginosa* when **AIR** or burns are involved.
HBV	Work in renal dialysis unit	
Candida albicans	Hyperalimentation	
Legionella	Water aerosols	*Legionella* when water source is involved.

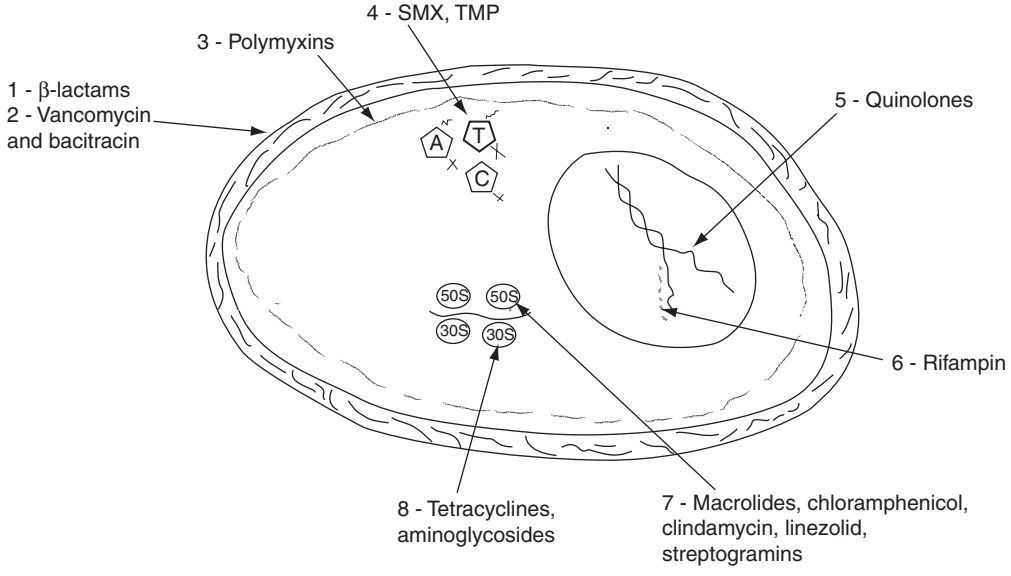
Bug hints (if all else fails)

Pus, empyema, abscess—*S. aureus*.
Pediatric infection—*Haemophilus influenzae* (including epiglottitis).
Pneumonia in cystic fibrosis, burn infection—*Pseudomonas aeruginosa*.
Branching rods in oral infection—*Actinomyces israelii*.
Traumatic open wound—*Clostridium perfringens*.
Surgical wound—*S. aureus*.
Dog or cat bite—*Pasteurella multocida*.
Currant jelly sputum—*Klebsiella*.
Sepsis/meningitis in newborn—group B strep.

► MICROBIOLOGY–ANTIMICROBIALS

Antimicrobial therapy

Mechanism of action	Drugs
1. Block cell wall synthesis by inhibition of peptidoglycan cross-linking	Penicillin, ampicillin, ticarcillin, piperacillin, imipenem, aztreonam, cephalosporins
2. Block peptidoglycan synthesis	Bacitracin, vancomycin
3. Disrupt bacterial cell membranes	Polymyxins
4. Block nucleotide synthesis	Sulfonamides, trimethoprim
5. Block DNA topoisomerases	Quinolones
6. Block mRNA synthesis	Rifampin
7. Block protein synthesis at 50S ribosomal subunit	Chloramphenicol, macrolides, clindamycin, streptogramins (quinupristin, dalfopristin), linezolid
8. Block protein synthesis at 30S ribosomal subunit	Aminoglycosides, tetracyclines



► MICROBIOLOGY–ANTIMICROBIALS *(continued)*

Bacteriostatic vs. bactericidal antibiotics

Bacteriostatic	**E**rythromycin, **C**lindamycin, **S**ulfamethoxazole, **T**rimethoprim, **T**etracyclines, **C**hloramphenicol.	"We're **ECST**a**T**i**C** about bacteriostatics."
Bactericidal	**V**ancomycin, **F**luoroquinolones, **P**enicillin, **A**minoglycosides, **C**ephalosporins, **M**etronidazole.	"**V**ery **F**inely **P**roficient **A**t **C**ell **M**urder."

Penicillin

Penicillin G (IV form), penicillin V (oral). Prototype β-lactam antibiotics.

Mechanism	1. Bind penicillin-binding proteins 2. Block transpeptidase cross-linking of cell wall 3. Activate autolytic enzymes
Clinical use	Bactericidal for gram-positive cocci, gram-positive rods, gram-negative cocci, and spirochetes. Not penicillinase resistant.
Toxicity	Hypersensitivity reactions, hemolytic anemia.

Methicillin, nafcillin, dicloxacillin (penicillinase-resistant penicillins)

Mechanism	Same as penicillin. Narrow spectrum; penicillinase resistant because of bulkier R group.	"Use **naf** (nafcillin) for **staph.**"
Clinical use	*S. aureus* (except MRSA; resistant because of altered penicillin-binding protein target site).	
Toxicity	Hypersensitivity reactions; methicillin—interstitial nephritis.	

Ampicillin, amoxicillin (aminopenicillins)

Mechanism	Same as penicillin. Wider spectrum; penicillinase sensitive. Also combine with clavulanic acid (penicillinase inhibitor) to enhance spectrum. Am**O**xicillin has greater **O**ral bioavailability than ampicillin.	
Clinical use	Extended-spectrum penicillin—certain gram-positive bacteria and gram-negative rods (***H**aemophilus influenzae*, ***E**. coli*, ***L**isteria monocytogenes*, ***P**roteus mirabilis*, ***S**almonella*, enterococci).	Coverage: ampicillin/amoxicillin **HELPS** kill enterococci.
Toxicity	Hypersensitivity reactions; ampicillin rash; pseudomembranous colitis.	

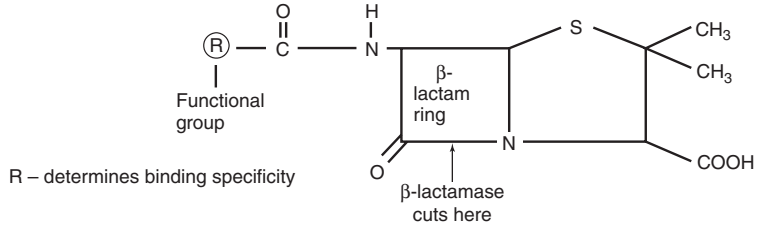
Ticarcillin, carbenicillin, piperacillin (antipseudomonals)

Mechanism	Same as penicillin. Extended spectrum.	**TCP: T**akes **C**are of ***P**seudomonas*.
Clinical use	*Pseudomonas* spp. and gram-negative rods; susceptible to penicillinase; use with clavulanic acid.	
Toxicity	Hypersensitivity reactions.	

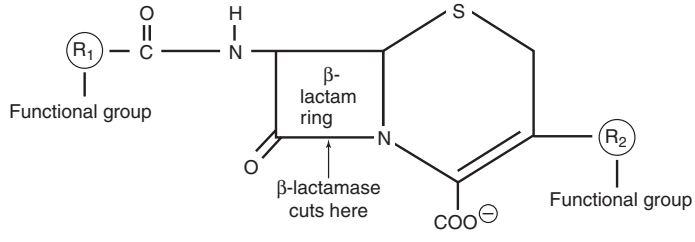
Cephalosporins

Mechanism	β-lactam drugs that inhibit cell wall synthesis but are less susceptible to penicillinases. Bactericidal.	
Clinical use	1st generation (cefazolin, cephalexin)—gram-positive cocci, ***P**roteus mirabilis*, ***E. c**oli*, ***K**lebsiella pneumoniae*.	1st generation—**PEcK.**
	2nd generation (cefoxitin, cefaclor, cefuroxime)—gram-positive cocci, ***H**aemophilus influenzae*, ***E**nterobacter aerogenes*, ***N**eisseria* spp., ***P**roteus mirabilis*, ***E. c**oli*, ***K**lebsiella pneumoniae*, ***S**erratia marcescens*.	2nd generation—**HEN PEcKS.**
	3rd generation (ceftriaxone, cefotaxime, ceftazidime)—serious gram-negative infections resistant to other β-lactams; meningitis (most penetrate the blood-brain barrier). Examples: ceftazidime for *Pseudomonas*; ceftriaxone for gonorrhea.	
	4th generation (cefepime)—↑ activity against *Pseudomonas* and gram-positive organisms.	
Toxicity	Hypersensitivity reactions. Cross-hypersensitivity with penicillins occurs in 5–10% of patients. ↑ nephrotoxicity of aminoglycosides; disulfiram-like reaction with ethanol (in cephalosporins with a methylthiotetrazole group, e.g., cefamandole).	

Penicillin



Cephalosporin



Aztreonam

Mechanism	A monobactam resistant to β-lactamases. Inhibits cell wall synthesis (binds to PBP3). Synergistic with aminoglycosides. No cross-allergenicity with penicillins.
Clinical use	Gram-negative rods—*Klebsiella* spp., *Pseudomonas* spp., *Serratia* spp. 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. No cross-sensitivity with penicillins or cephalosporins.

Imipenem/cilastatin, meropenem

Mechanism	Imipenem is a broad-spectrum, β-lactamase-resistant carbapenem. Always administered with cilastatin (inhibitor of renal dihydropeptidase I) to ↓ inactivation in renal tubules.	With imipenem, "the kill is **LASTIN**' with ci**LASTATIN**."
Clinical use	Gram-positive cocci, gram-negative rods, and anaerobes. Drug of choice for *Enterobacter*. The significant side effects limit use to life-threatening infections, or after other drugs have failed. Meropenem, however, has a reduced risk of seizures and is stable to dihydropeptidase I.	
Toxicity	GI distress, skin rash, and CNS toxicity (seizures) at high plasma levels.	

Vancomycin

Mechanism	Inhibits cell wall mucopeptide formation by binding D-ala D-ala portion of cell wall precursors. Bactericidal. Resistance occurs with amino acid change of D-ala D-ala to D-ala D-lac.
Clinical use	Used for serious, gram-positive multidrug-resistant organisms, including *S. aureus* and *Clostridium difficile* (pseudomembranous colitis).
Toxicity	**N**ephrotoxicity, **O**totoxicity, **T**hrombophlebitis, diffuse flushing—"red man syndrome" (can largely prevent by pretreatment with antihistamines and slow infusion rate). Well tolerated in general—does **NOT** have many problems.

Protein synthesis inhibitors

"Buy **AT 30, CCELL** (sell) at **50**."

30S inhibitors:

A = **A**minoglycosides (streptomycin, gentamicin, tobramycin, amikacin) [bactericidal]

T = **T**etracyclines [bacteriostatic]

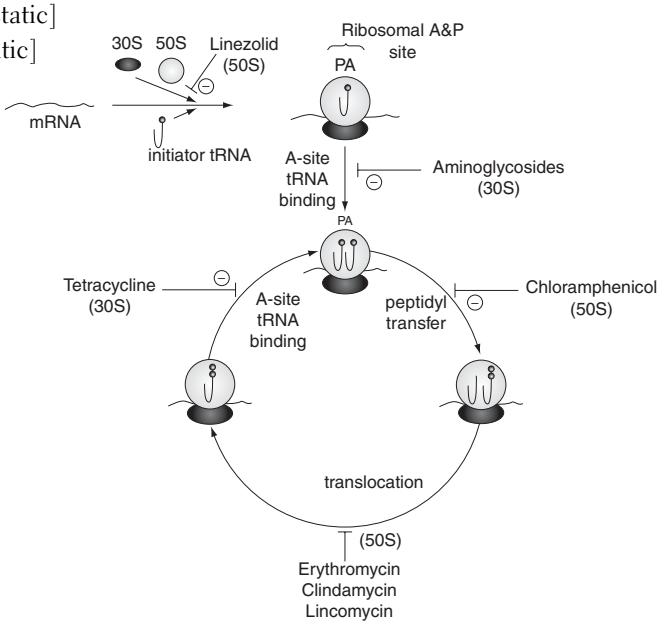
50S inhibitors:

C = **C**hloramphenicol, **C**lindamycin [bacteriostatic]

E = **E**rythromycin [bacteriostatic]

L = **L**incomycin [bacteriostatic]

L = **L**inezolid [variable]



Aminoglycosides	**G**entamicin, **N**eomycin, **A**mikacin, **T**obramycin, **S**treptomycin.	"**Mean**" **GNATS** can**NOT** kill anaerobes.
Mechanism	Bactericidal; inhibit formation of initiation complex and cause misreading of mRNA. Require O_2 for uptake; therefore ineffective against anaerobes.	
Clinical use	Severe gram-negative rod infections. Synergistic with β-lactam antibiotics. Neomycin for bowel surgery.	
Toxicity	**N**ephrotoxicity (especially when used with cephalosporins), **O**totoxicity (especially when used with loop diuretics). **T**eratogen.	
Tetracyclines	Tetracycline, doxycycline, demeclocycline, minocycline.	**D**emeclocycline—ADH antagonist; acts as a **D**iuretic in SIADH.
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. Must NOT take with milk, antacids, or iron-containing preparations because divalent cations inhibit its absorption in the gut.	
Clinical use	***V**ibrio cholerae*, **A**cne, ***C**hlamydia*, ***U**reaplasma **U**realyticum*, ***M**ycoplasma pneumoniae*, **T**ularemia, ***H. pylori***, ***B**orrelia burgdorferi* (Lyme disease), ***R**ickettsia*.	**VACUUM THe BedRoom.**
Toxicity	GI distress, discoloration of teeth and inhibition of bone growth in children, photosensitivity. Contraindicated in pregnancy.	
Macrolides	Erythromycin, azithromycin, clarithromycin.	
Mechanism	Inhibit protein synthesis by blocking translocation; bind to the 23S rRNA of the 50S ribosomal subunit. Bacteriostatic.	
Clinical use	URIs, pneumonias, STDs—gram-positive cocci (streptococcal infections in patients allergic to penicillin), *Mycoplasma*, *Legionella*, *Chlamydia*, *Neisseria*.	
Toxicity	GI discomfort (most common cause of noncompliance), acute cholestatic hepatitis, eosinophilia, skin rashes. Increases serum concentration of theophyllines, oral anticoagulants.	
Chloramphenicol		
Mechanism	Inhibits 50S peptidyltransferase activity. Bacteriostatic.	
Clinical use	Meningitis (*Haemophilus influenzae*, *Neisseria meningitidis*, *Streptococcus pneumoniae*). Conservative use owing to toxicities.	
Toxicity	Anemia (dose dependent), aplastic anemia (dose independent), gray baby syndrome (in premature infants because they lack liver UDP-glucuronyl transferase).	

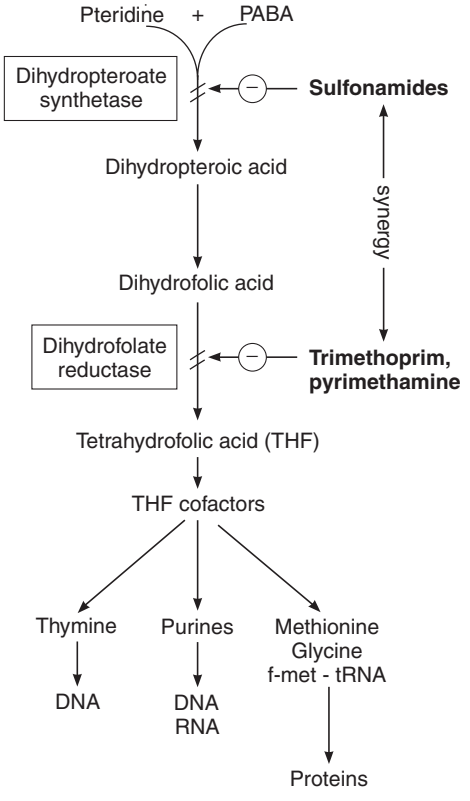
► MICROBIOLOGY–ANTIMICROBIALS *(continued)*

Clindamycin

Mechanism	Blocks peptide bond formation at 50S ribosomal subunit. Bacteriostatic.	Treats anaerobes above the diaphragm.
Clinical use	Treat anaerobic infections (e.g., *Bacteroides fragilis*, *Clostridium perfringens*).	
Toxicity	Pseudomembranous colitis (*C. difficile* overgrowth), fever, diarrhea.	

Sulfonamides — Sulfamethoxazole (SMX), sulfisoxazole, triple sulfas, sulfadiazine.

Mechanism	PABA antimetabolites inhibit dihydropteroate synthetase. Bacteriostatic.
Clinical use	Gram-positive, gram-negative, *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).



(Adapted, with permission, from Katzung BG. *Basic and Clinical Pharmacology,* 7th ed. Stamford, CT: Appleton & Lange, 1997: 762.)

Trimethoprim		
Mechanism	Inhibits bacterial dihydrofolate reductase. Bacteriostatic.	**T**rimethoprim = **TMP:** "**T**reats **M**arrow **P**oorly."
Clinical use	Used in combination with sulfonamides (trimethoprim-sulfamethoxazole [TMP-SMX]), causing sequential block of folate synthesis. Combination used for recurrent UTIs, *Shigella*, *Salmonella*, *Pneumocystis jiroveci* pneumonia.	
Toxicity	Megaloblastic anemia, leukopenia, granulocytopenia. (May alleviate with supplemental folinic acid.)	
Sulfa drug allergies	Patients who do not tolerate sulfa drugs should not be given sulfonamides or other sulfa drugs, such as sulfasalazine, sulfonylureas, thiazide diuretics, acetazolamide, or furosemide.	
Fluoroquinolones	Ciprofloxacin, norfloxacin, ofloxacin, sparfloxacin, moxifloxacin, gatifloxacin, enoxacin (fluoroquinolones), nalidixic acid (a quinolone).	
Mechanism	Inhibit DNA gyrase (topoisomerase II). Bactericidal. Must not be taken with antacids.	Fluoroquino**LONES** hurt attachments to your **BONES.**
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. Contraindicated in pregnant women and in children because animal studies show damage to cartilage. Tendonitis and tendon rupture in adults; leg cramps and myalgias in kids.	
Metronidazole		
Mechanism	Forms toxic metabolites in the bacterial cell that damage DNA. Bactericidal.	
Clinical use	Antiprotozoal. ***G**iardia*, ***E**ntamoeba*, ***T**richomonas*, ***G**ardnerella vaginalis*, **A**naerobes (*Bacteroides*, *Clostridium*). Used with bismuth and amoxicillin (or tetracycline) for "triple therapy" against *H. **P**ylori*.	**GET GAP** on the **Metro!** Anaerobic infection below the diaphragm.
Toxicity	Disulfiram-like reaction with alcohol; headache, metallic taste.	
Polymyxins	Polymyxin B, polymyxin E.	**'MYXins MIX up** membranes.
Mechanism	Bind to cell membranes of bacteria and disrupt their osmotic properties. Polymyxins are cationic, basic proteins that act like detergents.	
Clinical use	Resistant gram-negative infections.	
Toxicity	Neurotoxicity, acute renal tubular necrosis.	

Antimycobacterial drugs

Bacterium	Prophylaxis	Treatment
M. tuberculosis	Isoniazid	Isoniazid, rifampin, ethambutol, pyrazinamide
M. avium–intracellulare	Azithromycin	Azithromycin, rifampin, ethambutol, streptomycin
M. leprae	N/A	Dapsone, rifampin, clofazimine

Anti-TB drugs

Streptomycin, **P**yrazinamide, **I**soniazid (INH), **R**ifampin, **E**thambutol.
Cycloserine (2nd-line therapy).
Important side effect of ethambutol is optic neuropathy (red-green color blindness). For other drugs, hepatotoxicity.

INH-SPIRE (inspire).

Isoniazid (INH)

Mechanism	↓ synthesis of mycolic acids.	**INH I**njures **N**eurons and **H**epatocytes.
Clinical use	*Mycobacterium tuberculosis.* The only agent used as solo prophylaxis against TB.	Different INH half-lives in fast vs. slow acetylators.
Toxicity	Hemolysis if G6PD deficient, neurotoxicity, hepatotoxicity, SLE-like syndrome. Pyridoxine (vitamin B_6) can prevent neurotoxicity.	

Rifampin

Mechanism	Inhibits DNA-dependent RNA polymerase.	**R**ifampin's **4 R's:**
Clinical use	*Mycobacterium tuberculosis*; delays resistance to dapsone when used for leprosy. Used for meningococcal prophylaxis and chemoprophylaxis in contacts of children with *Haemophilus influenzae* type B.	**R**NA polymerase inhibitor **R**evs up microsomal P-450 **R**ed/orange body fluids **R**apid resistance if used alone
Toxicity	Minor hepatotoxicity and drug interactions (↑ P-450); orange body fluids (nonhazardous side effect).	

Resistance mechanisms for various antibiotics

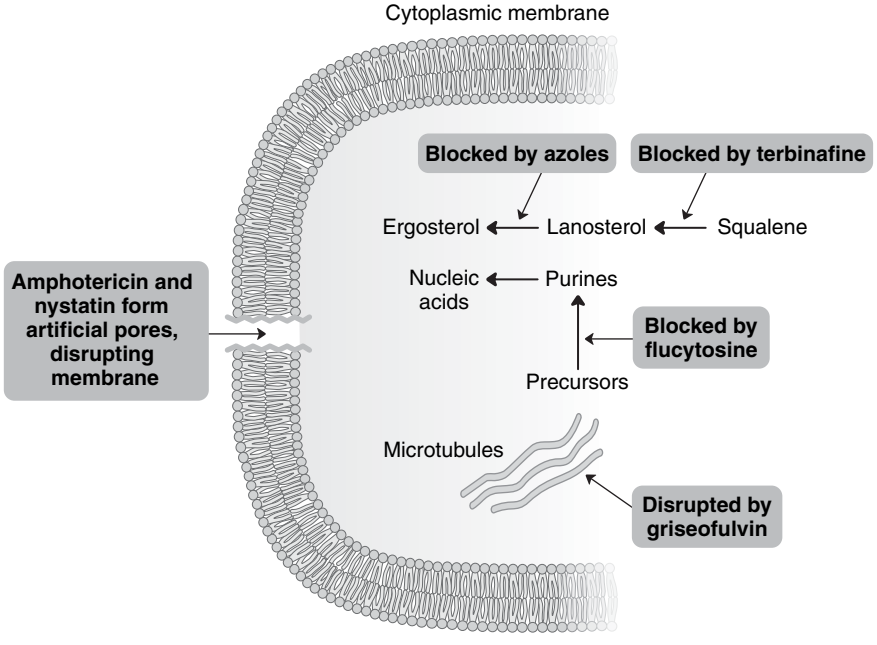
Drug	Most common mechanism
Penicillins/cephalosporins	β-lactamase cleavage of β-lactam ring, or altered PBP in case of MRSA
Aminoglycosides	Modification via acetylation, adenylation, or phosphorylation
Vancomycin	Terminal D-ala of cell wall component replaced with D-lac; ↓ affinity
Chloramphenicol	Modification via acetylation
Macrolides	Methylation of rRNA near erythromycin's ribosome-binding site
Tetracycline	↓ uptake or ↑ transport out of cell
Sulfonamides	Altered enzyme (bacterial dihydropteroate synthetase), ↓ uptake, or ↑ PABA synthesis
Quinolones	Altered gyrase or reduced uptake

Nonsurgical antimicrobial prophylaxis

Meningococcal infection	Rifampin (drug of choice), minocycline.
Gonorrhea	Ceftriaxone.
Syphilis	Benzathine penicillin G.
History of recurrent UTIs	TMP-SMX.
Pneumocystis jiroveci pneumonia	TMP-SMX (drug of choice), aerosolized pentamidine.
Endocarditis with surgical or dental procedures	Penicillins.

Treatment of highly resistant bacteria	MRSA—vancomycin. VRE—linezolid and streptogramins (quinupristin/dalfopristin).

Antifungal therapy



(Adapted, with permission, from Katzung BG, Trevor AJ. *USMLE Road Map: Pharmacology*, 1st ed. New York: McGraw-Hill, 2003: 120.)

► MICROBIOLOGY–ANTIMICROBIALS *(continued)*

Amphotericin B

Mechanism	Binds ergosterol (unique to fungi); forms membrane pores that allow leakage of electrolytes.	Amphotericin "tears" holes in the fungal membrane by forming pores.
Clinical use	Used for wide spectrum of systemic mycoses. *Cryptococcus*, *Blastomyces*, *Coccidioides*, *Aspergillus*, *Histoplasma*, *Candida*, *Mucor* (systemic mycoses). Intrathecally for fungal meningitis; does not cross blood-brain barrier.	
Toxicity	Fever/chills ("shake and bake"), hypotension, nephrotoxicity, arrhythmias, anemia, IV phlebitis ("amphoterrible"). Hydration reduces nephrotoxicity. Liposomal amphotericin reduces toxicity.	

Nystatin

Mechanism	Binds to ergosterol, disrupting fungal membranes. Too toxic for systemic use.
Clinical use	"Swish and swallow" for oral candidiasis (thrush); topical for diaper rash or vaginal candidiasis.

Azoles

Fluconazole, ketoconazole, clotrimazole, miconazole, itraconazole, voriconazole.

Mechanism	Inhibit fungal steroid (ergosterol) synthesis.
Clinical use	Systemic mycoses. Fluconazole for cryptococcal meningitis in AIDS patients (because it can cross blood-brain barrier) and candidal infections of all types (i.e., yeast infections). Ketoconazole for *Blastomyces*, *Coccidioides*, *Histoplasma*, *Candida albicans*; hypercortisolism. Clotrimazole and miconazole for topical fungal infections.
Toxicity	Hormone synthesis inhibition (gynecomastia), liver dysfunction (inhibits cytochrome P-450), fever, chills.

Flucytosine

Mechanism	Inhibits DNA synthesis by conversion to fluorouracil, which competes with uracil.
Clinical use	Used in systemic fungal infections (e.g., *Candida*, *Cryptococcus)* in combination with amphotericin B.
Toxicity	Nausea, vomiting, diarrhea, bone marrow suppression.

Caspofungin

Mechanism	Inhibits cell wall synthesis.
Clinical use	Invasive aspergillosis.
Toxicity	GI upset, flushing.

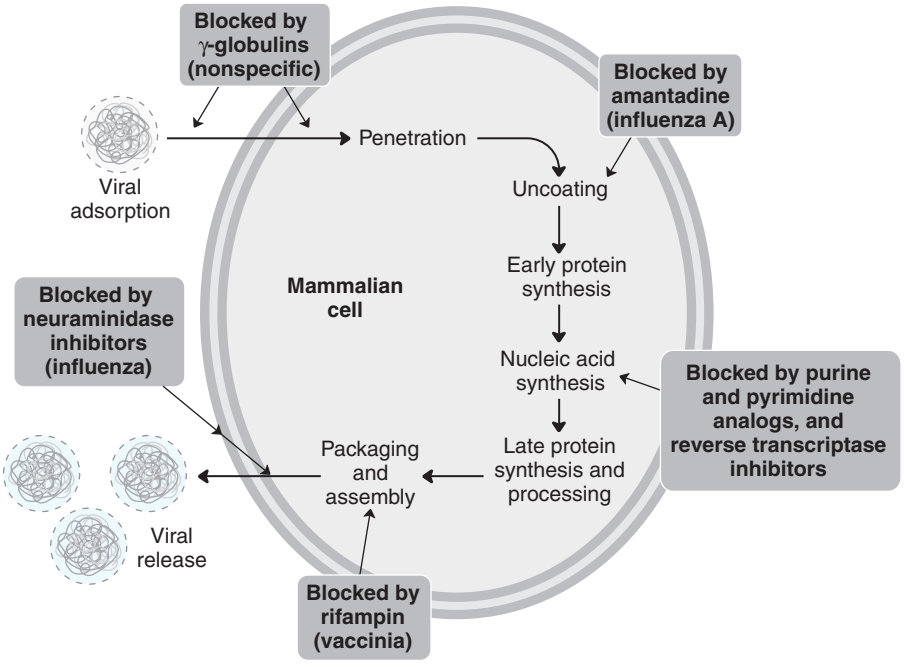
Terbinafine

Mechanism	Inhibits the fungal enzyme squalene epoxidase.
Clinical use	Used to treat dermatophytoses (especially onychomycosis).

Griseofulvin

Mechanism	Interferes with microtubule function; disrupts mitosis. Deposits in keratin-containing tissues (e.g., nails).
Clinical use	Oral treatment of superficial infections; inhibits growth of dermatophytes (tinea, ringworm).
Toxicity	Teratogenic, carcinogenic, confusion, headaches, ↑ P-450 and warfarin metabolism.

Antiviral chemotherapy



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Amantadine

Mechanism	Blocks viral penetration/un**coating** (M2 protein); may buffer pH of endosome. Also causes the release of dopamine from intact nerve terminals.	"**A man to dine**" takes off his **coat.**
Clinical use	Prophylaxis and treatment for influenza A; Parkinson's disease.	**A**mantadine blocks influenza **A** and rubell**A** and causes problems with the cerebell**A.**
Toxicity	Ataxia, dizziness, slurred speech.	
Mechanism of resistance	Mutated M2 protein. 90% of all influenza A strains are resistant to amantadine, so not used.	Rimantidine is a derivative with fewer CNS side effects. Does not cross the blood-brain barrier.

Zanamivir, oseltamivir

Mechanism	Inhibit influenza neuraminidase, decreasing the release of progeny virus.
Clinical use	Both influenza A and B.

Ribavirin

Mechanism	Inhibits synthesis of guanine nucleotides by competitively inhibiting IMP dehydrogenase.
Clinical use	RSV, chronic hepatitis C.
Toxicity	Hemolytic anemia. Severe teratogen.

► MICROBIOLOGY–ANTIMICROBIALS *(continued)*

Acyclovir

Mechanism	Monophosphorylated by HSV/VZV thymidine kinase. Triphosphate formed by cellular enzymes. Preferentially inhibits viral DNA polymerase by chain termination.
Clinical use	HSV, VZV, EBV. Used for HSV-induced mucocutaneous and genital lesions as well as for encephalitis. Prophylaxis in immunocompromised patients. For herpes zoster, use a related agent, famciclovir. No effect on latent forms of HSV and VZV.
Toxicity	Generally well tolerated.
Mechanism of resistance	Lack of thymidine kinase.

Ganciclovir

Mechanism	5'-monophosphate formed by a CMV viral kinase or HSV/VZV thymidine kinase. Triphosphate formed by cellular kinases. Preferentially inhibits viral DNA polymerase.
Clinical use	CMV, especially in immunocompromised patients.
Toxicity	Leukopenia, neutropenia, thrombocytopenia, renal toxicity. More toxic to host enzymes than acyclovir.
Mechanism of resistance	Mutated CMV DNA polymerase or lack of viral kinase.

Foscarnet

Mechanism	Viral DNA polymerase inhibitor that binds to the pyrophosphate-binding site of the enzyme. Does not require activation by viral kinase.	**FOS**carnet = pyro**FOS**phate analog.
Clinical use	CMV retinitis in immunocompromised patients when ganciclovir fails; acyclovir-resistant HSV.	
Toxicity	Nephrotoxicity.	
Mechanism of resistance	Mutated DNA polymerase.	

HIV therapy		
Protease inhibitors	Saqui**navir**, rito**navir**, indi**navir**, nelfi**navir**, ampre**navir**.	All protease inhibitors end in *-navir*.
Mechanism	Inhibit assembly of new virus by blocking protease in progeny virions.	**NAVIR** (never) **TEASE** a **proTEASE**.
Toxicity	GI intolerance (nausea, diarrhea), hyperglycemia, lipodystrophy, thrombocytopenia (indinavir).	
Reverse transcriptase inhibitors		
Nucleosides	Zidovudine (ZDV, formerly AZT), didanosine (ddI), zalcitabine (ddC), stavudine (d4T), lamivudine (3TC), abacavir.	
Non-nucleosides	**N**evirapine, **E**favirenz, **D**elavirdine.	**N**ever **E**ver **D**eliver nucleosides.
Mechanism	Preferentially inhibit reverse transcriptase of HIV; prevent incorporation of DNA copy of viral genome into host DNA.	
Toxicity	Bone marrow suppression (neutropenia, anemia), peripheral neuropathy, lactic acidosis (nucleosides), rash (non-nucleosides), megaloblastic anemia (ZDV).	GM-CSF and erythropoietin can be used to reduce bone marrow suppression.
Clinical use	Highly active antiretroviral therapy (HAART) generally entails combination therapy with protease inhibitors and reverse transcriptase inhibitors. Initiated when patients have low CD4 counts (< 500 cells/mm^3) or high viral load. ZDV is used for general prophylaxis and during pregnancy to reduce risk of fetal transmission.	
Fusion inhibitors	Enfuvirtide.	
Mechanism	Bind viral gp41 subunit; inhibit conformational change required for fusion with CD4 cells. Therefore block entry and subsequent replication.	
Toxicity	Hypersensitivity reactions, reactions at subcutaneous injection site, ↑ risk of bacterial pneumonia.	
Clinical use	In patients with persistent viral replication in spite of antiretroviral therapy. Used in combination with other drugs.	

Interferons	
Mechanism	Glycoproteins from human leukocytes that block various stages of viral RNA and DNA synthesis. Induce ribonuclease that degrades viral mRNA.
Clinical use	IFN-α—chronic hepatitis B and C, Kaposi's sarcoma. IFN-β—MS. IFN-γ—NADPH oxidase deficiency.
Toxicity	Neutropenia.

► MICROBIOLOGY–ANTIMICROBIALS *(continued)*

Antibiotics to avoid in pregnancy	**S**ulfonamides—kernicterus. **A**minoglycosides—ototoxicity. **F**luoroquinolones—cartilage damage. **E**rythromycin—acute cholestatic hepatitis in mom (and clarithromycin—embryotoxic). **M**etronidazole—mutagenesis. **T**etracyclines—discolored teeth, inhibition of bone growth. **R**ibavirin (antiviral)—teratogenic. **G**riseofulvin (antifungal)—teratogenic. **C**hloramphenicol—"gray baby."	**SAFE M**oms **T**ake **R**eally **G**ood **C**are.

HIGH-YIELD PRINCIPLES IN

Immunology

- High-Yield Clinical Vignettes
- Lymphoid Structures
- Lymphocytes
- Immune Responses
- Immunosuppressants

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

"No State shall abridge the privileges or immunities of its citizens."
—The United States Constitution

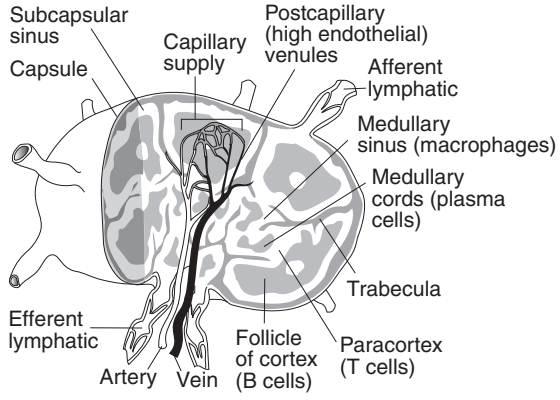
Immunology can be confusing and complicated, but luckily the USMLE tests only basic principles and facts in this area. Cell surface markers are important to know because they are clinically useful (for example, in identifying specific types of immune deficiency or cancer) and are functionally critical 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–HIGH-YIELD CLINICAL VIGNETTES

■ Patient with *Mycoplasma pneumoniae* exhibits cryoagglutinins during recovery phase.	What types of immunoglobulins are reacting?	IgM.
■ Young child presents with tetany and candidiasis. Hypocalcemia and immunosuppression are found.	What immune cell is deficient?	T cell (DiGeorge).
■ Young child has recurrent lung infections and granulomatous lesions.	What enzyme is deficient in neutrophils?	NADPH oxidase (chronic granulomatous disease).
■ Patient presents with recurrent *Neisseria* infections.	What complement proteins are deficient?	C6–C8.
■ Woman complains of a malar rash and arthritis.	The presence of which antibodies are specific for SLE?	Anti-dsDNA and anti-Smith.
■ Patient presents with dermatitis, enteritis, and hepatitis after bone marrow transplantation.	What disease process is occurring?	Graft-versus-host disease.

Lymph node — A 2° lymphoid organ that has many afferents, 1 or more efferents. Encapsulated, with trabeculae. Functions are nonspecific filtration by macrophages, storage and activation of B and T cells, antibody production.

- **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. In an extreme cellular immune response, paracortex becomes greatly enlarged. Not well developed in patients with DiGeorge syndrome.



Paracortex enlarges in an extreme cellular immune response (i.e., viral).

Lymph drainage

Area of body	1° lymph node drainage site
1. Upper limb, lateral breast	1. Axillary
2. Stomach	2. Celiac
3. Duodenum, jejunum	3. Superior mesenteric
4. Sigmoid colon	4. Colic → inferior mesenteric
5. Rectum (lower part), anal canal above pectinate line	5. Internal iliac
6. Anal canal below pectinate line	6. Superficial inguinal
7. Testes	7. Superficial and deep plexuses → para-aortic
8. Scrotum	8. Superficial inguinal
9. Thigh (superficial)	9. Superficial inguinal
10. Lateral side of dorsum of foot	10. Popliteal

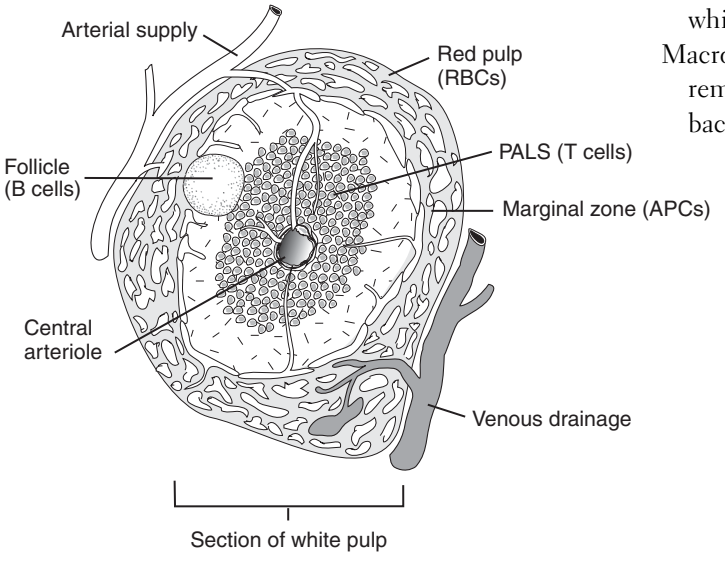
Right lymphatic duct—drains right arm and right half of head.

Thoracic duct—drains everything else.

► IMMUNOLOGY—LYMPHOID STRUCTURES *(continued)*

Sinusoids of spleen

Long, vascular channels in red pulp with fenestrated "barrel hoop" basement membrane. Macrophages found nearby.



T cells are found in the periarterial lymphatic sheath (PALS) and in the red pulp of the spleen. B cells are found in follicles within the white pulp of the spleen.

Macrophages in the spleen remove encapsulated bacteria.

Thymus

Site of T-cell differentiation and maturation. Encapsulated. From epithelium of 3rd branchial pouches. Lymphocytes of mesenchymal origin. Cortex is dense with immature T cells; medulla is pale with mature T cells and epithelial reticular cells and contains Hassall's corpuscles. Positive (MHC restriction) and negative selection (nonreactive to self) occur at the corticomedullary junction.

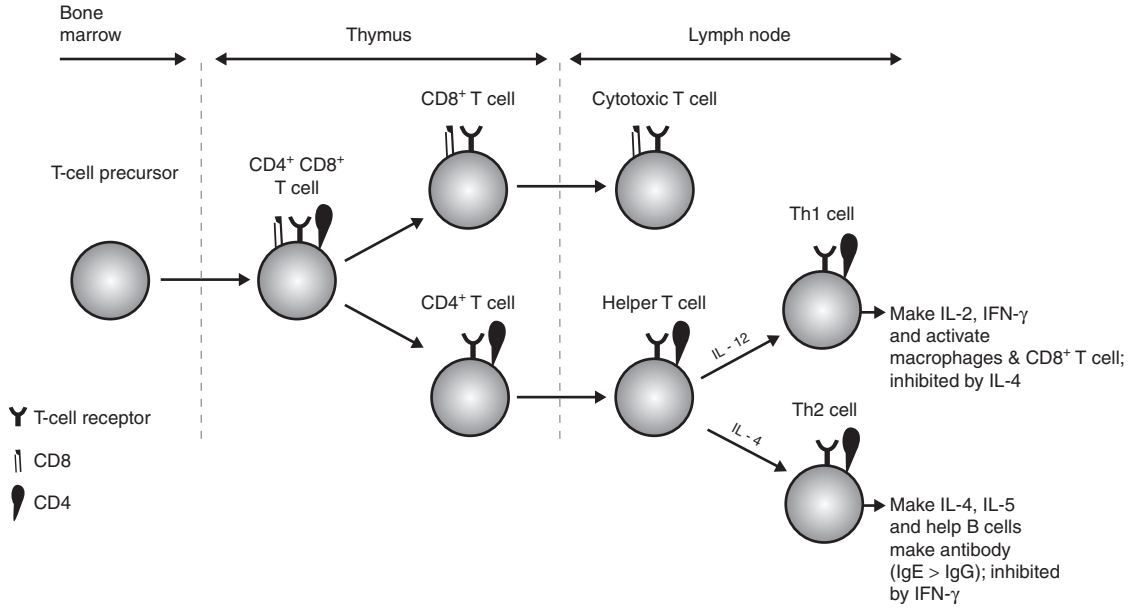
T cells = **T**hymus.
B cells = **B**one marrow.

Innate vs. adaptive immunity

Innate—receptors that recognize pathogens are germline encoded. Response to pathogens is fast and nonspecific. No memory. Consists of neutrophils, macrophages, dendritic cells, and complement.

Adaptive—receptors that recognize pathogens undergo VDJ recombination during lymphocyte development. Response is slow on first exposure, but memory response is faster and more robust. Consists of T cells, B cells, and circulating antibody.

Differentiation of T cells



MHC I and II

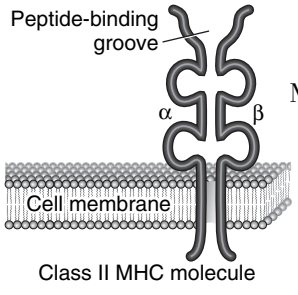
MHC = major histocompatibility complex, encoded by **H**uman **L**eukocyte **A**ntigen (HLA) genes.

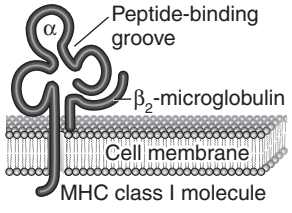
MHC I = HLA-A, HLA-B, HLA-C.
- Expressed on almost all nucleated cells.
- Antigen is loaded in RER of mostly intracellular peptides.
- Mediates viral immunity.
- Pairs with β_2-microglobulin.

MHC II = HLA-DR, HLA-DP, HLA-DQ.
- Expressed only on antigen-presenting cells (APCs).
- Antigen is loaded in an acidified endosome.

MHC I—HLA I letter (A, B, C).

MHC II—HLA II letters (DR, DP, DQ).





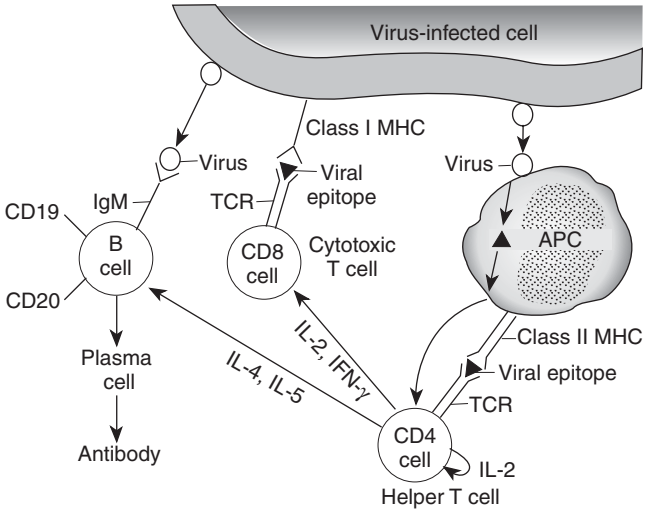
► IMMUNOLOGY–LYMPHOCYTES *(continued)*

Major function of B and T cells

B cells	T cells
Make antibody	$CD4^+$ T cells help B cells make antibody and produce γ-interferon, which activates macrophages
IgG antibodies opsonize bacteria, viruses	Kill virus-infected cells directly ($CD8^+$ T cells)
Allergy (type I hypersensitivity): IgE	Delayed cell-mediated hypersensitivity (type IV)
Cytotoxic (type II) and immune complex (type III) hypersensitivity: IgG	
Antibodies cause organ rejection (hyperacute)	Organ (allograft) rejection (acute and chronic)

T-cell glycoproteins

Helper T cells have CD4, which binds to MHC II on APCs. Cytotoxic T cells have CD8, which binds to MHC I on virus-infected cells.



Product of CD and MHC = 8 (CD**4** × MHC **II** = 8 = CD8 × MHC **I**).

CD3 complex—cluster of polypeptides associated with a T-cell receptor. Important in signal transduction.

APCs:

1. Macrophage
2. B cell
3. Dendritic cell

T-cell activation

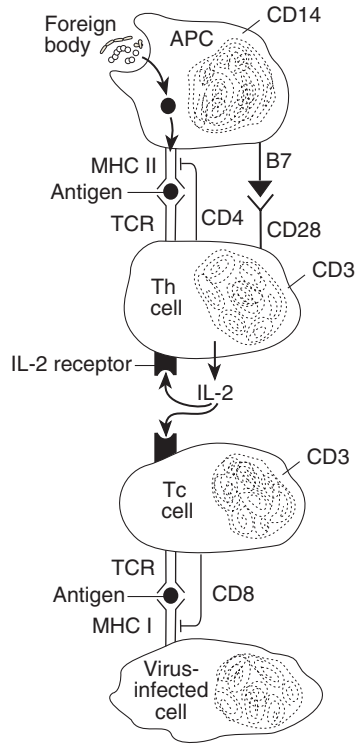
2 signals are required for T-cell activation—signal 1 and signal 2.

Th activation:

1. Foreign body is phagocytosed by APC
2. Foreign antigen is presented on MHC II and recognized by TCR on Th cell (signal 1)
3. "Costimulatory signal" is given by interaction of B7 and CD28 (signal 2)
4. Th cell activated to produce cytokines

Tc activation:

1. Endogenously synthesized (viral or self) proteins are presented on MHC I and recognized by TCR on Tc cell (signal 1)
2. IL-2 from Th cell activates Tc cell to kill virus-infected cell (signal 2)

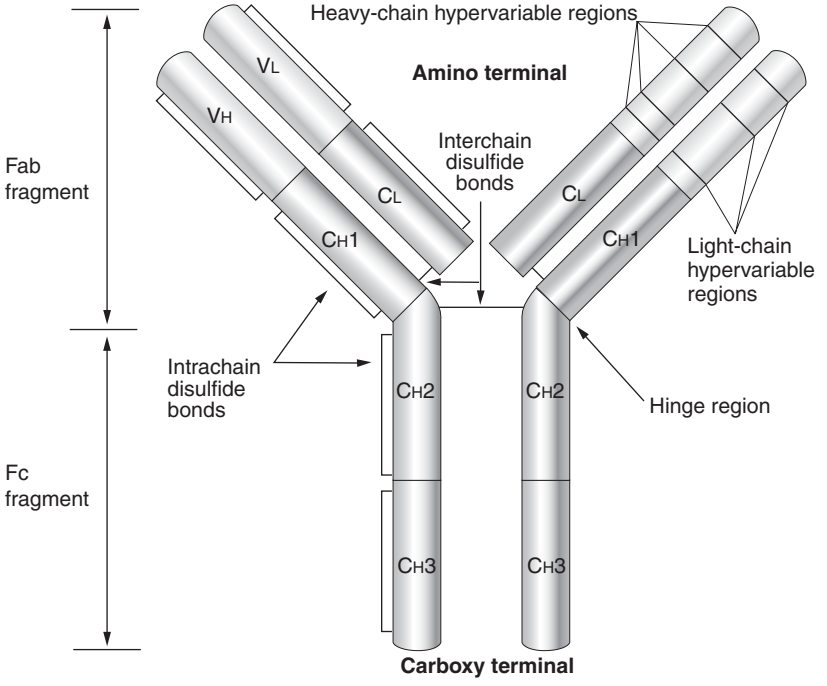


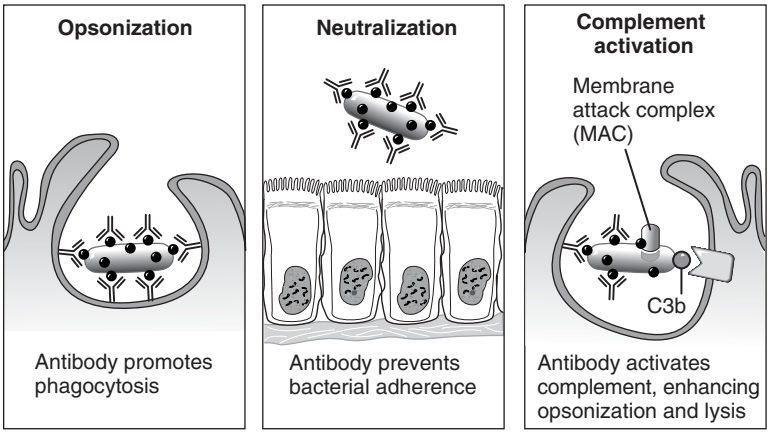
Antibody structure and function

Variable part of L and H chains recognizes antigens. Fc portion of IgM and IgG fixes complement. Heavy chain contributes to Fc and Fab fractions. Light chain contributes only to Fab fraction.

Fab: antigen-binding fragment

Fc:
- **C**onstant
- **C**arboxy terminal
- **C**omplement-binding (IgG + IgM only)
- **C**arbohydrate side chains





Antibody diversity is generated by:
1. Random "recombination" of VJ (light-chain) or VDJ (heavy-chain) genes
2. Random combination of heavy chains with light chains
3. Somatic hypermutation
4. Addition of nucleotides to DNA during "recombination" (see #1) by terminal deoxynucleotidyl transferase

Immunoglobulin isotypes	Mature B lymphocytes express IgM and IgD on their surfaces. They may differentiate by isotype switching (mediated by cytokines and CD40 ligand) into plasma cells that secrete IgA, IgE, or IgG.
IgG	Main antibody in 2° response. Most abundant. Fixes complement, crosses the placenta, opsonizes bacteria, neutralizes bacterial toxins and viruses.
IgA	Prevents attachment of bacteria and viruses to mucous membranes, does not fix complement. Monomer or dimer. Found in secretions. Picks up secretory component from epithelial cells before secretion.
IgM	Produced in the 1° response to an antigen. Fixes complement but does not cross the placenta. Antigen receptor on the surface of B cells. Monomer on B cell or pentamer.
IgD	Unclear function. Found on the surface of many B cells and in serum.
IgE	Mediates immediate (type I) hypersensitivity by inducing the release of mediators from mast cells and basophils when exposed to allergen. Mediates immunity to worms by activating eosinophils. Lowest concentration in serum.

Ig epitopes	**All**otype (polymorphism)—Ig epitope that differs among members of same species. Can be on light chain or heavy chain.	**ALL**otypes represent different **ALL**eles.
	Isotype (IgG, IgA, etc.)—Ig epitope common to a single class of Ig (5 classes, determined by heavy chain).	Isotype = *iso* (same). Common to same class.
	Idiotype (specific for a given antigen)—Ig epitope determined by antigen-binding site.	Idiotype = *idio* (unique). Hypervariable region is unique.

Important cytokines

IL-1	Secreted by macrophages. Causes acute inflammation. Induces chemokine production to recruit leukocytes; activates endothelium to express adhesion molecules. An endogenous pyrogen.	IL-2: stimulates T cells. IL-3: stimulates bone marrow. IL-4: stimulates IgE production. IL-5: stimulates IgA production.
IL-2	Secreted by Th cells. Stimulates growth of helper and cytotoxic T cells.	
IL-3	Secreted by activated T cells. Supports the growth and differentiation of bone marrow stem cells. Has a function similar to GM-CSF.	
IL-4	Secreted by Th2 cells. Promotes growth of B cells. Enhances class switching to IgE and IgG.	
IL-5	Secreted by Th2 cells. Promotes differentiation of B cells. Enhances class switching to IgA. Stimulates production and activation of eosinophils.	
IL-6	Secreted by Th cells and macrophages. Stimulates production of acute-phase reactants and immunoglobulins.	
IL-8	Secreted by macrophages. Major chemotactic factor for neutrophils.	"Clean up on **aisle** 8." Neutrophils are recruited by **IL**-8 to clear infections.
IL-10	Secreted by regulatory T cells. Inhibits actions of activated T cells.	
IL-12	Secreted by B cells and macrophages. Activates NK and Th1 cells.	
γ-interferon	Secreted by Th1 cells. Stimulates macrophages.	
TNF	Secreted by macrophages. Mediates septic shock. Causes leukocyte recruitment, vascular leak.	

Cell surface proteins

Helper T cells	CD4, TCR, CD3, CD28, CD40L.
Cytotoxic T cells	CD8, TCR, CD3.
B cells	IgM, B7, CD19, CD20, CD21, CD40, MHC II.
Macrophages	MHC II, B7, CD40, CD14. Receptors for Fc and C3b.
NK cells	Receptors for MHC I, CD16, CD56.
All cells except mature red cells	MHC I.

Complement

System of proteins that interact to play a role in humoral immunity and inflammation.

Membrane attack complex of complement defends against gram-negative bacteria. Activated by Ig**G** or Ig**M** in the **classic** pathway, and activated by molecules on the surface of microbes (especially endotoxin) in the **alternative** pathway.

C3b and IgG are the two 1° opsonins in bacterial defense.

Decay-accelerating factor (DAF) and C1 esterase inhibitor help prevent complement activation on self-cells.

GM makes **classic** cars.

C1, C2, C3, C4—viral neutralization.

C3**b**—opsonization. **B**inds **B**acteria.

C3**a**, C5**a**—**A**naphylaxis.

C5a—neutrophil chemotaxis.

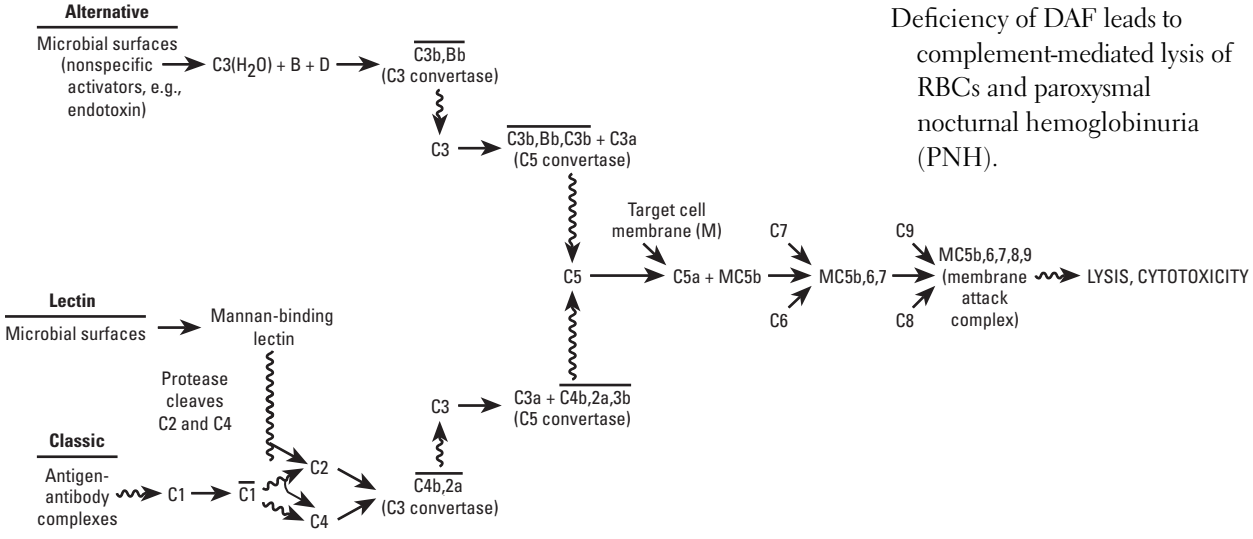
C5b-9—cytolysis by membrane attack complex (MAC).

Deficiency of C1 esterase inhibitor leads to hereditary angioedema.

Deficiency of C3 leads to severe, recurrent pyogenic sinus and respiratory tract infections.

Deficiency of C6–C8 leads to *Neisseria* bacteremia.

Deficiency of DAF leads to complement-mediated lysis of RBCs and paroxysmal nocturnal hemoglobinuria (PNH).



(Adapted, with permission, from Levinson W. *Medical Microbiology and Immunology: Examination and Board Review,* 8th ed. New York: McGraw-Hill, 2004: 432.)

Interferon mechanism

Interferons (α, β, γ) are proteins that place uninfected cells in an antiviral state. Interferons induce the production of a ribonuclease that inhibits viral protein synthesis by degrading viral mRNA (but not host mRNA).

Interferes with viruses:

1. α- and β-interferons inhibit viral protein synthesis
2. γ-interferons ↑ MHC I and II expression and antigen presentation in all cells
3. Activates NK cells to kill virus-infected cells

► IMMUNOLOGY–IMMUNE RESPONSES *(continued)*

Passive vs. active immunity

Active	Induced after exposure to foreign antigens. Slow onset. Long-lasting protection (memory).	After exposure to **T**etanus toxin, **B**otulinum toxin, **H**BV, or **R**abies, patients are given preformed antibodies (passive)—**T**o **B**e **H**ealed **R**apidly.
Passive	Based on receiving preformed antibodies from another host. Rapid onset. Short life span of antibodies (half-life = 3 weeks).	

Antigen variation

Classic examples:
- Bacteria—*Salmonella* (2 flagellar variants), *Borrelia* (relapsing fever), *Neisseria gonorrhoeae* (pilus protein).
- Virus—influenza (major = shift, minor = drift).
- Parasites—trypanosomes (programmed rearrangement).

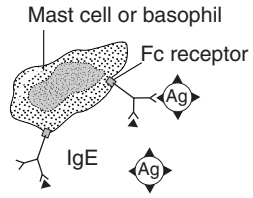
Some mechanisms for variation include DNA rearrangement and RNA segment reassortment (e.g., influenza major shift).

Anergy

Self-reactive T cells become nonreactive without costimulatory molecule.
B cells also become anergic, but tolerance is less complete than in T cells.

Hypersensitivity

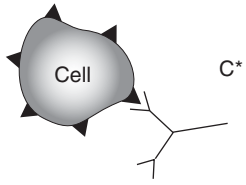
Type I



Anaphylactic and atopic—free antigen cross-links IgE on presensitized mast cells and basophils, triggering release of vasoactive amines (i.e., histamine). Reaction develops rapidly after antigen exposure due to preformed antibody.

First and **F**ast (anaphylaxis). Types I, II, and III are all antibody mediated.

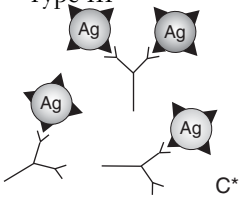
Type II



Antibody mediated—IgM, IgG bind to fixed antigen on "enemy" cell, leading to lysis (by complement) or phagocytosis.

Cy-**2**-toxic.
Antibody and complement lead to membrane attack complex (MAC).

Type III



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

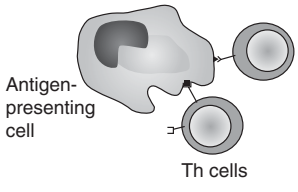
Serum sickness—an immune complex disease (type III) in which antibodies to the foreign proteins are produced (takes 5 days). Immune complexes form and are deposited in membranes, where they fix complement (leads to tissue damage). More common than Arthus reaction.

Arthus reaction—a local subacute antibody-mediated hypersensitivity (type III) reaction. Intradermal injection of antigen induces antibodies, which form antigen-antibody complexes in the skin. Characterized by edema, necrosis, and activation of complement.

Imagine an immune complex as **3** things stuck together: antigen-antibody-complement.
Most serum sickness is now caused by drugs (not serum). Fever, urticaria, arthralgias, proteinuria, lymphadenopathy 5–10 days after antigen exposure.
Antigen-antibody complexes cause the Arthus reaction.

Type IV

Delayed (T-cell-mediated) type—sensitized T lymphocytes encounter antigen and then release lymphokines (leads to macrophage activation).



4th and last—delayed. Cell mediated; therefore, it is not transferable by serum.
4 T's = **T** lymphocytes, **T**ransplant rejections, **T**B skin tests, **T**ouching (contact dermatitis).
ACID:
Anaphylactic and **A**topic (type I)
Cytotoxic (antibody mediated) (type II)
Immune complex (type III)
Delayed (cell mediated) (type IV)

C* = complement

► IMMUNOLOGY–IMMUNE RESPONSES *(continued)*

Diseases caused by hypersensitivity

Reaction	Disorder
Type I	Anaphylaxis
	Allergic rhinitis (hay fever)
Type II	Hemolytic anemia
	Idiopathic thrombocytopenic purpura
	Erythroblastosis fetalis
	Rheumatic fever
	Goodpasture's syndrome
	Bullous pemphigoid
	Graves' disease
	Myasthenia gravis
Type III	SLE
	Rheumatoid arthritis
	Polyarteritis nodosum
	Poststreptococcal glomerulonephritis
	Serum sickness
	Arthus reaction
	Hypersensitivity pneumonitis
Type IV	Type 1 diabetes mellitus
	Multiple sclerosis
	Guillain-Barré syndrome
	Hashimoto's thyroiditis
	Graft-versus-host disease
	PPD (test for *M. tuberculosis*)
	Contact dermatitis

Immune deficiencies

1. **↓ production of:**

B cells—**B**ruton's agammaglobulinemia	X-linked recessive defect in a tyrosine kinase gene associated with low levels of all classes of immunoglobulins. ↓ number of B cells. Associated with recurrent **B**acterial infections after 6 months of age, when levels of maternal IgG antibody decline. Occurs in **B**oys (X-linked).
T cells—Thymic aplasia (DiGeorge syndrome)	Thymus and parathyroids fail to develop owing to failure of development of the 3rd and 4th pharyngeal pouches. Presents with **T**etany owing to hypocalcemia. Recurrent viral and fungal infections due to T-cell deficiency. Congenital defects of heart and great vessels. 22q11 deletion.
B and T cells—severe combined immunodeficiency (SCID)	Defect in early stem-cell differentiation. Presents with recurrent viral, bacterial, fungal, and protozoal infections. May have multiple causes (e.g., failure to synthesize MHC II antigens, defective IL-2 receptors, or adenosine deaminase deficiency).

2. **↓ activation of:**

T cells—IL-12 receptor deficiency	Presents with disseminated mycobacterial infections due to ↓ Th1 response.
B cells—hyper-IgM syndrome	Defect in CD40 ligand on CD4 T helper cells leads to inability to class switch. Presents early in life with severe pyogenic infections. High levels of IgM; very low levels of IgG, IgA, and IgE.
B cells—**W**iskott-Aldrich syndrome	X-linked defect in the ability to mount an IgM response to capsular polysaccharides of bacteria. Associated with elevated IgA levels (**A**ldrich = ↑ Ig**A**), normal IgE levels, and low IgM levels. Triad of symptoms includes recurrent pyogenic **I**nfections, thrombocytopenic **P**urpura, **E**czema (**WIPE**).
Macrophages—Job's syndrome	Failure of IFN-γ production by helper T cells. Neutrophils fail to respond to chemotactic stimuli. Presents with coarse **F**acies, cold (noninflamed) staphylococcal **A**bscesses, retained primary **T**eeth, ↑ Ig**E**, and **D**ermatologic problems (eczema) **(FATED).**

3. **Phagocytic cell deficiency:**

Leukocyte adhesion deficiency syndrome (type 1)	Defect in LFA-1 integrin proteins on phagocytes. Presents early with recurrent bacterial infections, absent pus formation, and delayed separation of umbilicus.
Chédiak-Higashi disease	Autosomal recessive. Defect in microtubular function and lysosomal emptying of phagocytic cells. Presents with recurrent pyogenic infections by staphylococci and streptococci, partial albinism, and peripheral neuropathy.
Chronic granulomatous disease	Defect in phagocytosis of neutrophils owing to lack of NADPH oxidase activity or similar enzymes. Presents with marked susceptibility to opportunistic infections with bacteria, especially *S. aureus*, *E. coli*, and *Aspergillus*. Diagnosis confirmed with negative nitroblue tetrazolium dye reduction test.

4. **Idiopathic dysfunction of:**

T cells—chronic mucocutaneous candidiasis	T-cell dysfunction specifically against *Candida albicans.* Presents with skin and mucous membrane *Candida* infections.
B cells—selective immunoglobulin deficiency	Deficiency in a specific class of immunoglobulins—possibly due to a defect in isotype switching. Selective IgA deficiency is the most common selective immunoglobulin deficiency. Presents with sinus and lung infections; milk allergies and diarrhea are common.
B cells—ataxia-telangiectasia	Defect in DNA repair enzymes with associated IgA deficiency. Presents with cerebellar problems (ataxia) and spider angiomas (telangiectasia).
B cells—common variable immunodeficiency	Normal numbers of circulating B cells, ↓ plasma cells (defect in B-cell maturation), ↓ Ig, can be acquired in 20s–30s.

► IMMUNOLOGY–IMMUNE RESPONSES *(continued)*

Autoantibodies	**Autoantibody**	**Associated disorder**
	Antinuclear antibodies (ANA)	SLE
	Anti-dsDNA, anti-Smith	Specific for SLE
	Antihistone	Drug-induced lupus
	Anti-IgG (rheumatoid factor)	Rheumatoid arthritis
	Anticentromere	Scleroderma (CREST)
	Anti-Scl-70	Scleroderma (diffuse)
	Antimitochondrial	1° biliary cirrhosis
	Antigliadin	Celiac disease
	Anti–basement membrane	Goodpasture's syndrome
	Anti–epithelial cell	Pemphigus vulgaris
	Antimicrosomal, antithyroglobulin	Hashimoto's thyroiditis
	Anti-Jo-1	Polymyositis, dermatomyositis
	Anti-SS-A (anti-Ro)	Sjögren's syndrome
	Anti-SS-B (anti-La)	Sjögren's syndrome
	Anti-U1 RNP (ribonucleoprotein)	Mixed connective tissue disease
	Anti–smooth muscle	Autoimmune hepatitis
	Anti–glutamate decarboxylase	Type 1 diabetes mellitus
	c-ANCA	Wegener's granulomatosis
	p-ANCA	Other vasculitides

HLA subtypes		
B27	**P**soriasis, **A**nkylosing spondylitis, **I**nflammatory bowel disease, **R**eiter's syndrome.	**PAIR.**
B8	Graves' disease, celiac sprue.	
DR2	Multiple sclerosis, hay fever, SLE, Goodpasture's.	
DR3	Diabetes mellitus type 1.	
DR4	Rheumatoid arthritis, diabetes mellitus type 1.	
DR5	Pernicious anemia → B_{12} deficiency, Hashimoto's thyroiditis.	
DR7	Steroid-responsive nephrotic syndrome.	

Grafts	
Autograft	From self.
Syngeneic graft	From identical twin or clone.
Allograft	From nonidentical individual of same species.
Xenograft	From different species.

► IMMUNOLOGY–IMMUNOSUPPRESSANTS

Cyclosporine	
Mechanism	Binds to cyclophilins. Complex blocks the differentiation and activation of T cells by inhibiting calcineurin, thus preventing the production of IL-2 and its receptor.
Clinical use	Suppresses organ rejection after transplantation; selected autoimmune disorders.
Toxicity	Predisposes patients to viral infections and lymphoma; nephrotoxic (preventable with mannitol diuresis).

Tacrolimus (FK506)

Mechanism	Similar to cyclosporine; binds to FK-binding protein, inhibiting secretion of IL-2 and other cytokines.
Clinical use	Potent immunosuppressive used in organ transplant recipients.
Toxicity	Significant—nephrotoxicity, peripheral neuropathy, hypertension, pleural effusion, hyperglycemia.

Azathioprine

Mechanism	Antimetabolite precursor of 6-mercaptopurine that interferes with the metabolism and synthesis of nucleic acids. Toxic to proliferating lymphocytes.
Clinical use	Kidney transplantation, autoimmune disorders (including glomerulonephritis and hemolytic anemia).
Toxicity	Bone marrow suppression. Active metabolite mercaptopurine is metabolized by xanthine oxidase; thus, toxic effects may be ↑ by allopurinol.

Muromonab-CD3 (OKT3)

Mechanism	Monoclonal antibody that binds to CD3 (epsilon chain) on the surface of T cells. Blocks cellular interaction with CD3 protein responsible for T-cell signal transduction.
Clinical use	Immunosuppression after kidney transplantation.
Toxicity	Cytokine release syndrome, hypersensitivity reaction.

Sirolimus (rapamycin)

Mechanism	Binds to mTOR. Inhibits T-cell proliferation in response to IL-2.
Clinical use	Immunosuppression after kidney transplantation in combination with cyclosporine and corticosteroids.
Toxicity	Hyperlipidemia, thrombocytopenia, leukopenia.

Mycophenolate mofetil

Mechanism	Inhibits de novo guanine synthesis and blocks lymphocyte production.

Daclizumab

Mechanism	Monoclonal antibody with high affinity for the IL-2 receptor on activated T cells.

Recombinant cytokines and clinical uses

Agent	Clinical uses
Aldesleukin (interleukin-2)	Renal cell carcinoma, metastatic melanoma
Erythropoietin (epoetin)	Anemias (especially in renal failure)
Filgrastim (granulocyte colony-stimulating factor)	Recovery of bone marrow
Sargramostim (granulocyte-macrophage colony-stimulating factor)	Recovery of bone marrow
α-interferon	Hepatitis B and C, Kaposi's sarcoma, leukemias, malignant melanoma
β-interferon	Multiple sclerosis
γ-interferon	Chronic granulomatous disease
Oprelvekin (interleukin-11)	Thrombocytopenia
Thrombopoietin	Thrombocytopenia

► IMMUNOLOGY–IMMUNOSUPPRESSANTS *(continued)*

Transplant rejection

Hyperacute rejection	Antibody mediated due to the presence of preformed antidonor antibodies in the transplant recipient. Occurs within minutes after transplantation.
Acute rejection	Cell mediated due to cytotoxic T lymphocytes reacting against foreign MHCs. Occurs weeks after transplantation. Reversible with immunosuppressants such as cyclosporine and OKT3.
Chronic rejection	Antibody-mediated vascular damage (fibrinoid necrosis); occurs months to years after transplantation. Irreversible.
Graft-versus-host disease	Grafted immunocompetent T cells proliferate in the irradiated immunocompromised host and reject cells with "foreign" proteins, resulting in severe organ dysfunction. Major symptoms include a maculopapular rash, jaundice, hepatosplenomegaly, and diarrhea.

HIGH-YIELD PRINCIPLES IN

Pathology

- High-Yield Clinical Vignettes
- Inflammation
- Amyloidosis
- Neoplasia

"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 aimed at many different organ systems and are definitely high yield. For example, the concepts of cell injury and inflammation are key to knowing the inflammatory response that follows myocardial infarction, a very common subject of boards questions. Likewise, 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.

► PATHOLOGY—HIGH-YIELD CLINICAL VIGNETTES

■ Prostate biopsy shows neoplastic proliferation of well-differentiated glands with evidence of tumor spread to regional lymph nodes.	What is the Gleason score and stage of the prostate cancer?	Low Gleason score (low "grade") and high stage.
■ Boy presents with mental retardation, facial angiofibromas, and seizures.	What type of cancers are most often associated with his disease?	Cardiac rhabdomyomas and astrocytomas (in tuberous sclerosis).
■ Patient with marked leukocytosis and presence of myeloid blast cells in the peripheral blood is found to have lymphadenopathy and splenomegaly.	What oncogene most likely became translocated in the myeloid stem cells?	*abl* (to form the fusion protein *bcr-abl*).
■ Mother notices that her daughter has a white pupil, which is later confirmed to be inherited retinoblastoma.	Her daughter has an ↑ risk of what other type of cancer?	Osteosarcoma (*Rb* tumor suppressor gene mutation).
■ Woman's Pap smear shows dysplastic changes.	What HPV types are most often associated with cervical carcinoma?	Types 16 and 18.
■ Man complains of joint pain following chemotherapy for AML.	What is the side effect of his cancer treatment?	↑ nucleic acid turnover from dying cancer cells leads to hyperuricemia (tumor lysis syndrome).
■ Elderly woman on chronic hemodialysis treatment has a biopsy of her joint spaces that shows amyloid deposits.	From what protein is the amyloid derived?	β_2-microglobulin.

Apoptosis

Programmed cell death; ATP required. Mediated by caspases.
Characterized by cell shrinkage, chromatin condensation (pyknosis), membrane blebbing, DNA fragmentation (karyorrhexis), nuclear fragmentation (karyolysis), and formation of apoptotic bodies, which are then phagocytosed. No significant inflammation.
Occurs during embryogenesis, hormone induction (menstruation), immune cell–mediated death, injurious stimuli (e.g., radiation, hypoxia), atrophy (e.g., endometrial lining during menopause).

Necrosis

Enzymatic degradation of a cell resulting from exogenous injury.
Characterized by enzymatic digestion and protein denaturation, with release of intracellular components.
Inflammatory.
Morphologically occurs as coagulative (heart, liver, kidney), liquefactive (brain), caseous (tuberculosis), fat (pancreas), fibrinoid (blood vessels), or gangrenous (limbs, GI tract).

Cell injury

Reversible	Irreversible
Cellular swelling	Plasma membrane damage
Nuclear chromatin clumping	Lysosomal rupture
↓ ATP synthesis	Ca^{2+} influx → oxidative phosphorylation
Ribosomal detachment	Nuclear pyknosis, karyolysis, karyorrhexis
Glycogen depletion	Mitochondrial permeability
Fatty change	

Inflammation

Characterized by *rubor* (redness), *dolor* (pain), *calor* (heat), *tumor* (swelling), and *functio laesa* (loss of function).

Fluid exudation	↑ vascular permeability, vasodilation, endothelial injury.	
Leukocyte activation	Emigration (rolling, tight binding, diapedesis); chemotaxis (bacterial products, complement, chemokines); phagocytosis and killing.	
Fibrosis	Fibroblast emigration and proliferation; deposition of ECM.	
Acute	Neutrophil, eosinophil, and antibody mediated.	
Chronic	Mononuclear cell mediated: Characterized by persistent destruction and repair. Granuloma—nodular collections of epithelioid macrophages and giant cells.	Granulomatous diseases: TB (caseating), syphilis, leprosy, *Bartonella*, some fungal pneumonias, sarcoidosis, Crohn's disease.
Resolution	Restoration of normal structure. Granulation tissue—highly vascularized, fibrotic. Abscess—fibrosis surrounding pus. Fistula—abnormal communication. Scarring—collagen deposition resulting in altered structure and function.	

► PATHOLOGY–INFLAMMATION *(continued)*

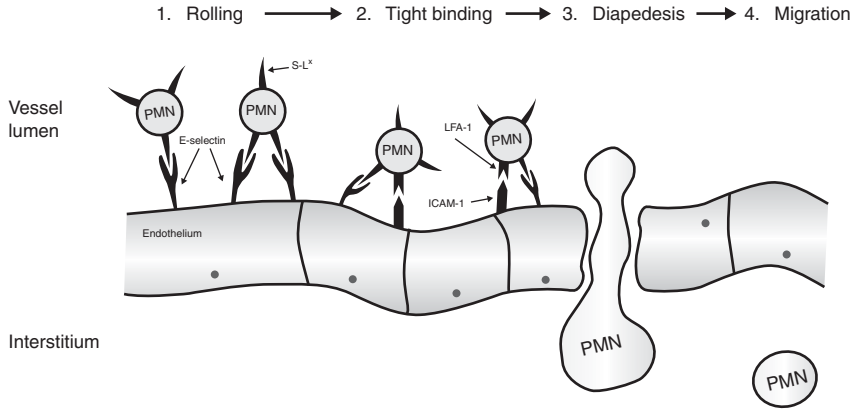
Transudate vs. exudate

Transudate	Exudate
Hypocellular	Cellular
Protein poor	Protein rich
Specific gravity < 1.012	Specific gravity > 1.020
Due to:	Due to:
↑ hydrostatic pressure	Lymphatic obstruction
↑ oncotic pressure	Inflammation
Na^+ retention	

Leukocyte extravasation

Neutrophils exit from blood vessels at sites of tissue injury and inflammation in 4 steps:

1. Rolling—mediated by E-selectin and P-selectin on vascular endothelium binding to sialyl $Lewis^X$ on the leukocyte
2. Tight binding—mediated by **I**CAM-1 on vascular endothelium binding to LFA-1 (**I**ntegrin) on the leukocyte
3. Diapedesis—leukocyte travels between endothelial cells and exits blood vessel
4. Migration—leukocyte travels through the interstitium to the site of injury or infection guided by chemotactic signals (e.g., cytokines)



Free radical injury

Initiated via radiation exposure, metabolism of drugs (phase I), redox reaction, nitric oxide, transition metals, leukocyte oxidative burst.

Induces cell injury through membrane lipid peroxidation, protein modification, DNA breakage.

Free radical degradation produced through enzymes (catalase, superoxide dismutase, glutathione peroxidase), spontaneous decay, antioxidants (vitamins E and A).

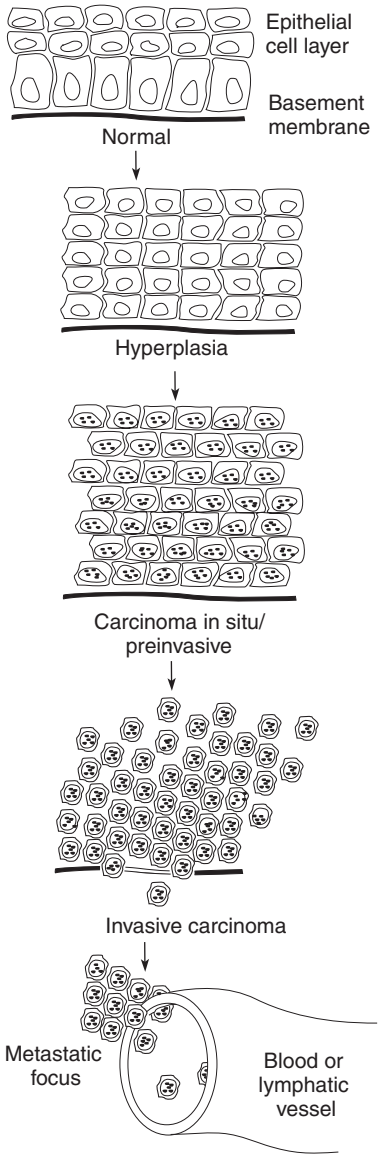
Reperfusion after anoxia induces free radical production (e.g., superoxide) and is a major cause of injury after thrombolytic therapy.

► PATHOLOGY—AMYLOIDOSIS

Structure β-pleated sheet demonstrable by apple-green birefringence of Congo red stain under polarized light; affected tissue has waxy appearance.

Types	Protein	Derived from	
Primary	AL	Ig light chains (multiple myeloma)	A**L** = **L**ight chain.
Secondary	AA	Serum amyloid-associated (SAA) protein (chronic inflammatory disease)	A**A** = **A**cute-phase reactant.
Senile cardiac	Transthyretin	AF	A**F** = old **F**ogies.
Diabetes mellitus type 2	Amylin	AE	A**E** = **E**ndocrine.
Medullary carcinoma of the thyroid	A-CAL	Calcitonin	A-**CAL** = **CAL**citonin.
Alzheimer's disease	Amyloid precursor protein (APP)	β-amyloid	
Dialysis-associated	β_2-microglobulin	MHC class I proteins	

Neoplastic progression



- Normal cells with basal → apical differentiation

- Cells have increased in number—**hyperplasia**
- Abnormal proliferation of cells with loss of size, shape, and orientation—**dysplasia**

- **In situ carcinoma**
- Neoplastic cells have not invaded basement membrane
- High nuclear/cytoplasmic ratio and clumped chromatin
- Neoplastic cells encompass entire thickness
- Tumor cells are monoclonal

- Cells have invaded basement membrane using **collagenases** and **hydrolases**
- Can metastasize if they reach a blood or lymphatic vessel

Metastasis—spread to distant organ
- Must survive immune attack
- "Seed and soil" theory of metastasis
  - Seed = tumor embolus
  - Soil = target organ—liver, lungs, bone, brain. . .
  - Angiogenesis allows for tumor survival

(Adapted, with permission, from McPhee S et al. *Pathophysiology of Disease: An Introduction to Clinical Medicine,* 3rd ed. New York: McGraw-Hill, 2000: 84.)

-plasia definitions

Reversible	Hyperplasia— ↑ in number of cells.
	Metaplasia—1 adult cell type is replaced by another. Often 2° to irritation and/or environmental exposure (e.g., squamous metaplasia in trachea and bronchi of smokers).
	Dysplasia—abnormal growth with loss of cellular orientation, shape, and size in comparison to normal tissue maturation; commonly preneoplastic.
Irreversible	Anaplasia—abnormal cells lacking differentiation; like primitive cells of same tissue, often equated with undifferentiated malignant neoplasms.
	Neoplasia—a clonal proliferation of cells that is uncontrolled and excessive.
	Desmoplasia—fibrous tissue formation in response to neoplasm.

Tumor grade vs. stage

Grade	Degree of cellular differentiation based on histologic appearance of tumor. Usually graded I–IV based on degree of differentiation and number of mitoses per high-power field; character of tumor itself.	Stage usually has more prognostic value than grade. **S**tage = **S**pread. TNM staging system: **T** = size of **T**umor **N** = **N**ode involvement **M** = **M**etastases
Stage	Degree of localization/spread based on site and size of 1° lesion, spread to regional lymph nodes, presence of metastases; spread of tumor in a specific patient.	

Tumor nomenclature

Cell type	Benign	Malignant[a]
Epithelium	Adenoma, papilloma	Adenocarcinoma, papillary carcinoma
Mesenchyme		
Blood cells		Leukemia, lymphoma
Blood vessels	Hemangioma	Angiosarcoma
Smooth muscle	Leiomyoma	Leiomyosarcoma
Skeletal muscle	Rhabdomyoma	Rhabdomyosarcoma
Bone	Osteoma	Osteosarcoma
Fat	Lipoma	Liposarcoma
> 1 cell type	Mature teratoma (women)	Immature teratoma and mature teratoma (men)

[a]The term **carcinoma** implies epithelial origin, whereas **sarcoma** denotes mesenchymal origin. Both terms imply malignancy.

Tumor differences

Benign	Usually well differentiated, slow growing, well demarcated, no metastasis.
Malignant	May be poorly differentiated, erratic growth, locally invasive/diffuse, may metastasize.

► PATHOLOGY–NEOPLASIA *(continued)*

Disease associations with neoplasms

Condition	Neoplasm
1. **Down** syndrome	1. **ALL** (we **ALL** fall **Down**), AML
2. Xeroderma pigmentosum, albinism	2. Melanoma, basal cell carcinoma, and especially squamous cell carcinomas of skin
3. Chronic atrophic gastritis, pernicious anemia, postsurgical gastric remnants	3. Gastric adenocarcinoma
4. Tuberous sclerosis (facial angiofibroma, seizures, mental retardation)	4. Astrocytoma, angiomyolipoma, and cardiac rhabdomyoma
5. Actinic keratosis	5. Squamous cell carcinoma of skin
6. Barrett's esophagus (chronic GI reflux)	6. Esophageal adenocarcinoma
7. Plummer-Vinson syndrome (atrophic glossitis, esophageal webs, anemia; all due to iron deficiency)	7. Squamous cell carcinoma of esophagus
8. Cirrhosis (alcoholic, hepatitis B or C)	8. Hepatocellular carcinoma
9. Ulcerative colitis	9. Colonic adenocarcinoma
10. Paget's disease of bone	10. 2° osteosarcoma and fibrosarcoma
11. Immunodeficiency states	11. Malignant lymphomas
12. AIDS	12. Aggressive malignant lymphomas (non-Hodgkin's) and Kaposi's sarcoma
13. Autoimmune diseases (e.g., Hashimoto's thyroiditis, myasthenia gravis)	13. Benign and malignant lymphomas
14. Acanthosis nigricans (hyperpigmentation and epidermal thickening)	14. Visceral malignancy (stomach, lung, breast, uterus)
15. Dysplastic nevus	15. Malignant melanoma
16. Radiation exposure	16. Sarcoma

Oncogenes Gain of function → cancer. Need damage to only 1 allele.

Gene	Associated tumor
abl	CML
c-*myc*	Burkitt's lymphoma
bcl-2	Follicular and undifferentiated lymphomas (inhibits apoptosis)
erb-B2	Breast, ovarian, and gastric carcinomas
ras	Colon carcinoma
L-*myc*	**L**ung tumor
N-*myc*	**N**euroblastoma
ret	Multiple endocrine neoplasia (MEN) types II and III
c-*kit*	Gastrointestinal stromal tumor (GIST)

Tumor suppressor genes — Loss of function → cancer; both alleles must be lost for expression of disease.

Gene	Chromosome	Associated tumor	
Rb	13q	Retinoblastoma, osteosarcoma	
BRCA1	17q	Breast and ovarian cancer	
BRCA2	13q	Breast cancer	
p*53*	17**p**	Most human cancers, Li-Fraumeni syndrome	
p*16*	9**p**	Melanoma	
APC	5q	Colorectal cancer	
WT1	11p	Wilms' tumor	
NF1	17q	Neurofibromatosis type 1	
NF2	22q	Neurofibromatosis type 2	
DPC	18q	Pancreatic cancer	**DPC**—**D**eleted in **P**ancreatic **C**ancer.
DCC	18q	Colon cancer	**DCC**—**D**eleted in **C**olon **C**ancer.

Tumor markers

PSA	Prostate-specific antigen. Used to screen for prostate carcinoma.	Tumor markers should not be used as the 1° tool for cancer diagnosis. They may be used to confirm diagnosis, to monitor for tumor recurrence, and to monitor response to therapy.
Prostatic acid phosphatase	Prostate carcinoma.	
CEA	Carcinoembryonic antigen. Very nonspecific but produced by ~ 70% of colorectal and pancreatic cancers; also produced by gastric and breast carcinomas.	
α-fetoprotein	Normally made by fetus. Hepatocellular carcinomas. Nonseminomatous germ cell tumors of the testis (e.g., yolk sac tumor).	
β-hCG	**H**ydatidiform moles, **C**horiocarcinomas, and **G**estational trophoblastic tumors.	
CA-125	Ovarian, malignant epithelial tumors.	
S-100	Melanoma, neural tumors, astrocytomas.	
Alkaline phosphatase	Metastases to bone, obstructive biliary disease, Paget's disease of bone.	
Bombesin	Neuroblastoma, lung and gastric cancer.	
TRAP	Tartrate-resistant acid phosphatase. Hairy cell leukemia—a B-cell neoplasm.	
CA-19-9	Pancreatic adenocarcinoma.	

Oncogenic viruses

Virus	Associated cancer
HTLV-1	Adult T-cell leukemia
HBV, HCV	Hepatocellular carcinoma
EBV	Burkitt's lymphoma, nasopharyngeal carcinoma
HPV	Cervical carcinoma (16, 18), penile/anal carcinoma
HHV-8 (Kaposi's sarcoma–associated herpesvirus)	Kaposi's sarcoma, body cavity fluid B-cell lymphoma

Chemical carcinogens

Toxin	Affected organ
Aflatoxins	Liver (hepatocellular carcinoma)
Vinyl chloride	Liver (angiosarcoma)
CCl_4	Liver (centrilobular necrosis, fatty change)
Nitrosamines (e.g., in smoked foods)	Esophagus, stomach
Cigarette smoke	Larynx, lung, renal cell carcinoma, transitional cell carcinoma
Asbestos	Lung (mesothelioma and bronchogenic carcinoma)
Arsenic	Skin (squamous cell carcinoma)
Naphthalene (aniline) dyes	Bladder (transitional cell carcinoma)
Alkylating agents	Blood (leukemia)

Paraneoplastic effects of tumors

Neoplasm	Causes	Effect
Small cell lung carcinoma	ACTH or ACTH-like peptide	Cushing's syndrome
Small cell lung carcinoma and intracranial neoplasms	ADH	SIADH
Squamous cell lung carcinoma, renal cell carcinoma, and breast carcinoma	PTH-related peptide, TGF-β, TNF, IL-1	Hypercalcemia
Renal cell carcinoma, hemangioblastoma	Erythropoietin	Polycythemia
Thymoma, small cell lung carcinoma	Antibodies against presynaptic Ca^{2+} channels at neuromuscular junction	Lambert-Eaton syndrome (muscle weakness)
Leukemias and lymphomas	Hyperuricemia due to excess nucleic acid turnover (i.e., cytotoxic therapy)	Gout, urate nephropathy

Psammoma bodies

Laminated, concentric, calcific spherules seen in:
1. Papillary adenocarcinoma of thyroid
2. Serous papillary cystadenocarcinoma of ovary
3. Meningioma
4. Malignant mesothelioma

PSaMMoma:
Papillary (thyroid)
Serous (ovary)
Meningioma
Mesothelioma

Metastasis to brain

1° tumors that metastasize to brain—**L**ung, **B**reast, **S**kin (melanoma), **K**idney (renal cell carcinoma), **GI**. Overall, approximately 50% of brain tumors are from metastases.

Lots of **B**ad **S**tuff **K**ills **G**lia.
Typically multiple well-circumscribed tumors at gray-white border.

Metastasis to liver

The liver and lung are the most common sites of metastasis after the regional lymph nodes. 1° tumors that metastasize to the liver—**C**olon > **S**tomach > **P**ancreas > **B**reast > **L**ung.

Metastases >> 1° liver tumors.
Cancer **S**ometimes **P**enetrates **B**enign **L**iver.

Metastasis to bone	These 1° tumors metastasize to bone—**P**rostate, **T**hyroid, **T**estes, **B**reast, **L**ung, **K**idney. Metastases from breast and prostate are most common. Metastatic bone tumors are far more common than 1° bone tumors.		**P. T. B**arnum **L**oves **K**ids. **L**ung = **L**ytic. Prostate = blastic. **B**reast = **B**oth lytic and blastic.
Cancer epidemiology			
	Male	**Female**	Deaths from lung cancer have plateaued in males but continue to ↑ in females. Cancer is the 2nd leading cause of death in the United States (heart disease is 1st).
Incidence	Prostate (32%) Lung (16%) Colon and rectum (12%)	Breast (32%) Lung (13%) Colon and rectum (13%)	
Mortality	Lung (33%) Prostate (13%)	Lung (23%) Breast (18%)	

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

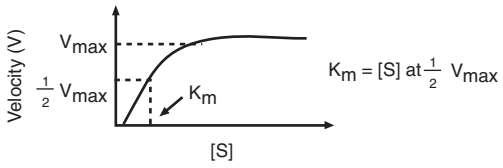
- High-Yield Clinical Vignettes
- Pharmacodynamics
- Autonomic Drugs
- Toxicities and Side Effects
- Miscellaneous

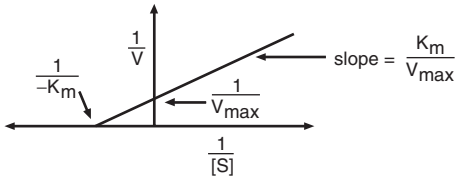
Preparation for questions on pharmacology is straightforward. Memorizing all the key drugs and their characteristics (e.g., mechanisms, clinical use, and important side effects) is high yield. Focus on understanding the prototype drugs in each class. Avoid memorizing obscure derivatives. Learn the "classic" 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 on NSAIDs. Much of the material is clinically relevant. Newer drugs on the market are also fair game.

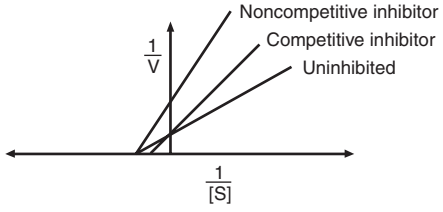
PHARMACOLOGY—HIGH-YIELD CLINICAL VIGNETTES

■ 28-year-old chemist presents with MPTP exposure.	What neurotransmitter is depleted?	Dopamine.
■ Woman taking tetracycline exhibits photosensitivity.	What are the clinical manifestations?	Rash on sun-exposed regions of the body.
■ African-American man who goes to Africa develops a hemolytic anemia after taking malaria prophylaxis.	What is the enzyme deficiency?	Glucose-6-phosphate dehydrogenase.
■ Farmer presents with dyspnea, salivation, miosis, diarrhea, cramping, and blurry vision.	What caused this, and what is the mechanism of action?	Insecticide poisoning; inhibition of acetylcholinesterase.
■ 27-year-old woman with a history of psychiatric illness now has urinary retention due to a neuroleptic.	What do you treat it with?	Bethanechol.
■ Recent kidney transplant patient who is on cyclosporine for immunosuppression requires an antifungal agent for candidiasis.	What antifungal drug would result in cyclosporine toxicity?	Ketoconazole.
■ Patient is on carbamazepine.	What routine workup should always be done?	LFTs.
■ 23-year-old woman who is on rifampin for TB prophylaxis and on birth control (estrogen) gets pregnant.	Why?	Rifampin augments estrogen metabolism in the liver, rendering it less effective.

Enzyme kinetics







K_m reflects the affinity of the enzyme for its substrate.
V_{max} is directly proportional to the enzyme concentration.
The lower the K_m, the higher the affinity.

The higher the y-intercept, the lower the V_{max}.
The further to the right the x-intercept, the greater the K_m.

HINT: Competitive inhibitors cross each other competitively, while noncompetitive inhibitors do not.

	Competitive inhibitors	Noncompetitive inhibitors
Resemble substrate	Yes	No
Overcome by ↑ [S]	Yes	No
Bind active site	Yes	No
Effect on V_{max}	Unchanged	↓
Effect on K_m	↑	Unchanged

Pharmacokinetics

Volume of distribution (V_d)

Relates the amount of drug in the body to the plasma concentration. V_d of plasma protein–bound drugs can be altered by liver and kidney disease.

$$V_d = \frac{\text{amount of drug in the body}}{\text{plasma drug concentration}}$$

Drugs with:
- Low V_d (4–8 L) distribute in blood.
- Medium V_d distribute in extracellular space or body water.
- High V_d (> body weight) distribute in tissues.

Clearance (CL)

Relates the rate of elimination to the plasma concentration.

$$CL = \frac{\text{rate of elimination of drug}}{\text{plasma drug concentration}} = V_d \times K_e \text{ (elimination constant)}$$

Half-life ($t_{1/2}$)

The time required to change the amount of drug in the body by ½ during elimination (or during a constant infusion). A drug infused at a constant rate reaches about 94% of steady state after 4 $t_{1/2}$.

$$t_{1/2} = \frac{0.7 \times V_d}{CL}$$

# of half-lives	1	2	3	4
Concentration	50%	75%	87.5%	93.75%

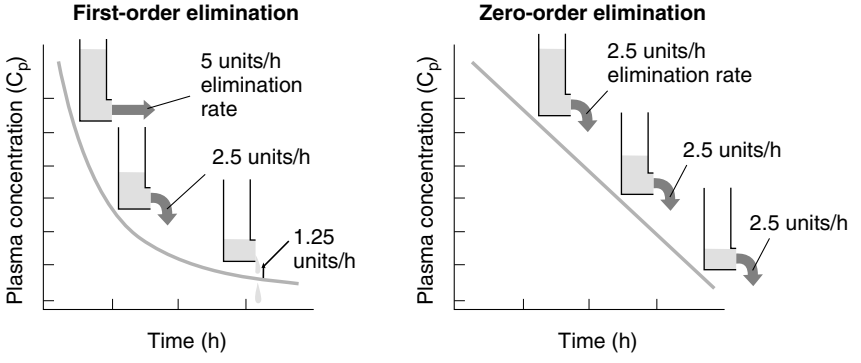
► PHARMACOLOGY–PHARMACODYNAMICS *(continued)*

Dosage calculations

Loading dose = $C_p \times V_d/F$.
Maintenance dose = $C_p \times CL/F$ where C_p = target plasma concentration and F = bioavailability = 1 when drug is given IV.
In patients with impaired renal or hepatic function, the loading dose remains unchanged, although the maintenance dose is ↓.

Elimination of drugs

Zero-order elimination	Rate of elimination is constant regardless of C (i.e., constant **amount** of drug eliminated per unit time). C_p ↓ linearly with time. Examples of drugs—**P**henytoin, **E**thanol, and **A**spirin (at high or toxic concentrations).	**PEA.**
First-order elimination	Rate of elimination is proportional to the drug concentration (i.e., constant **fraction** of drug eliminated per unit time). C_p ↓ exponentially with time.	



(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review,* 5th ed. Stamford, CT: Appleton & Lange, 1998: 5.)

Urine pH and drug elimination

Ionized species get trapped.

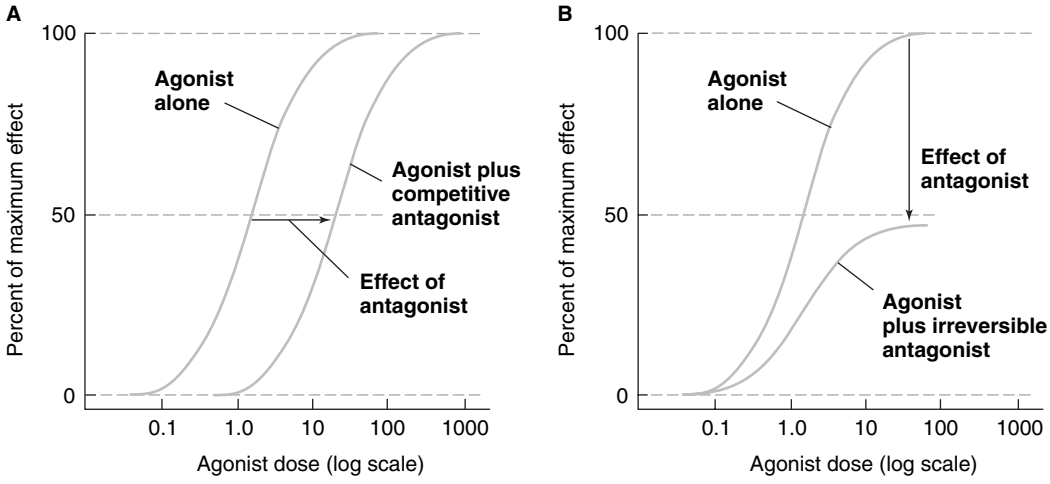
Weak acids	Trapped in basic environments. Treat overdose with bicarbonate.
Weak bases	Trapped in acidic environments. Treat overdose with ammonium chloride.

Phase I vs. phase II metabolism

Phase I (reduction, oxidation, hydrolysis) usually yields slightly polar, water-soluble metabolites (often still active).
Phase II (acetylation, glucuronidation, sulfation) usually yields very polar, inactive metabolites (renally excreted).

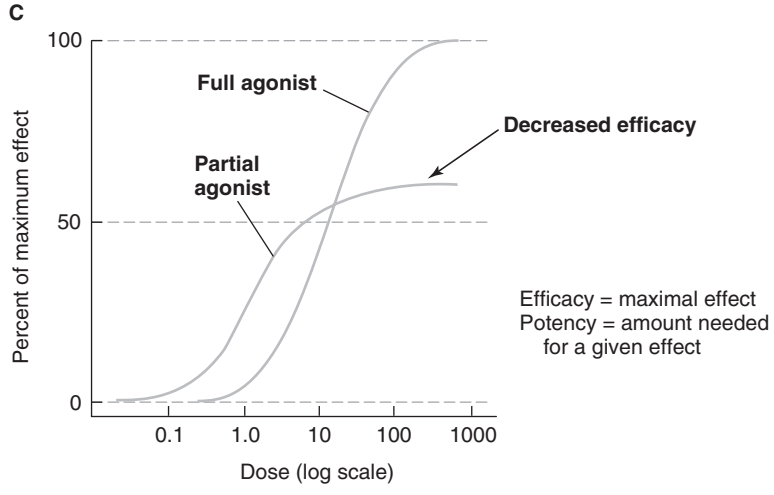
Phase I—cytochrome P-450.
Phase II—conjugation.
Geriatric patients lose phase I first.

Pharmacodynamics



(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review,* 5th ed. Stamford, CT: Appleton & Lange, 1998: 13–14.)

A. A competitive antagonist shifts curve to the right, decreasing potency and increasing EC_{50}. **B.** A noncompetitive antagonist shifts the agonist curve downward, decreasing efficacy.



(Adapted, with permission, from Katzung BG. *Basic and Clinical Pharmacology,* 7th ed. Stamford, CT: Appleton & Lange, 1997: 13.)

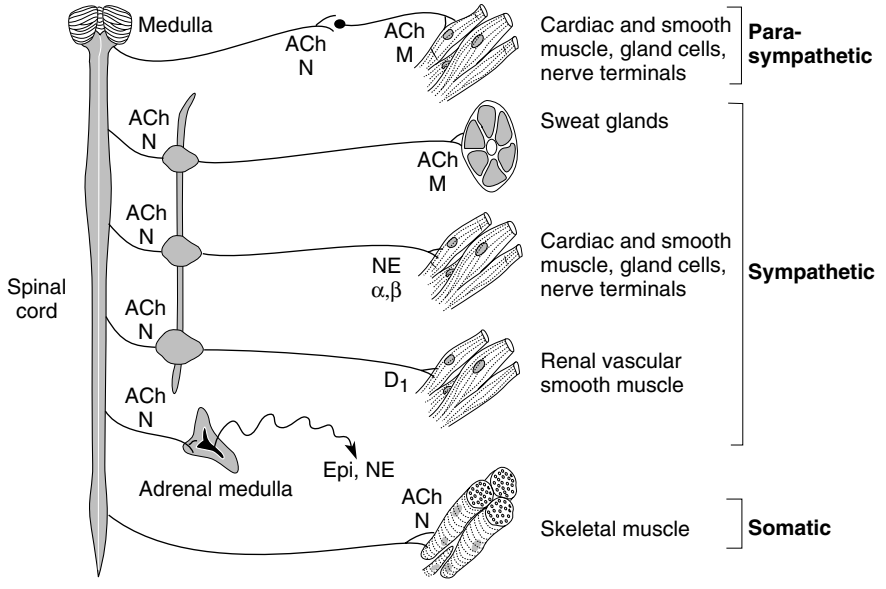
C. Comparison of dose-response curves for a full agonist and a partial agonist. The **partial agonist** acts on the same receptor system as the full agonist but has a **lower maximal efficacy** regardless of the dose. A partial agonist may be more potent (as in the figure), less potent, or equally potent; **potency is an independent factor.**

Therapeutic index

$$\frac{LD_{50}}{ED_{50}} = \frac{\text{median toxic dose}}{\text{median effective dose}}$$

TILE:
TI = LD_{50} / ED_{50}.
Safer drugs have higher TI values.

Central and peripheral nervous system



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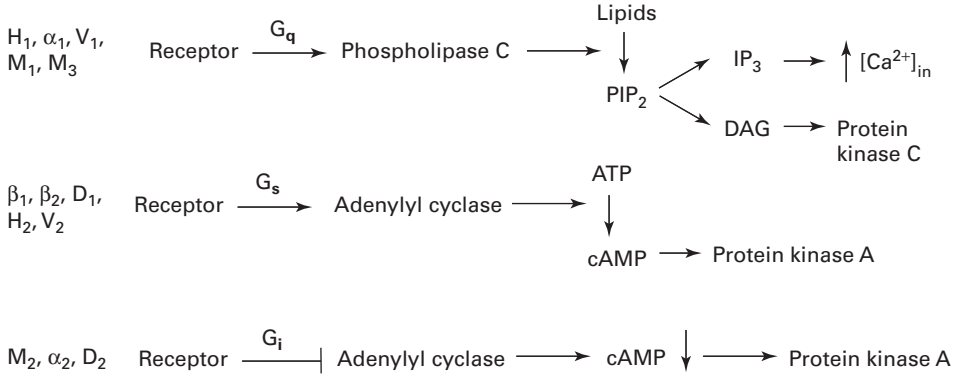
ACh receptors

Nicotinic ACh receptors are ligand-gated Na^+/K^+ channels.
Muscarinic ACh receptors are G-protein-coupled receptors that act through 2nd messengers.

G-protein-linked 2nd messengers

Receptor	G-protein class	Major functions
α_1	q	↑ vascular smooth muscle contraction
α_2	i	↓ sympathetic outflow, ↓ insulin release
β_1	s	↑ heart rate, ↑ contractility, ↑ renin release, ↑ lipolysis, maintains aqueous humor formation
β_2	s	Vasodilation, bronchodilation, ↑ heart rate, ↑ contractility, ↑ lipolysis, ↑ glucagon release
M_1	q	CNS, enteric nervous system
M_2	i	↓ heart rate and contractility
M_3	q	↑ exocrine gland secretions, ↑ gut peristalsis, ↑ bladder contraction
D_1	s	Relaxes renal vascular smooth muscle
D_2	i	Modulates transmitter release, especially in brain
H_1	q	↑ nasal and bronchial mucus production, contraction of bronchioles, pruritus, and pain
H_2	s	↑ gastric acid secretion
V_1	q	↑ vascular smooth muscle contraction
V_2	s	↑ H_2O permeability and reabsorption in the collecting tubules of the kidney

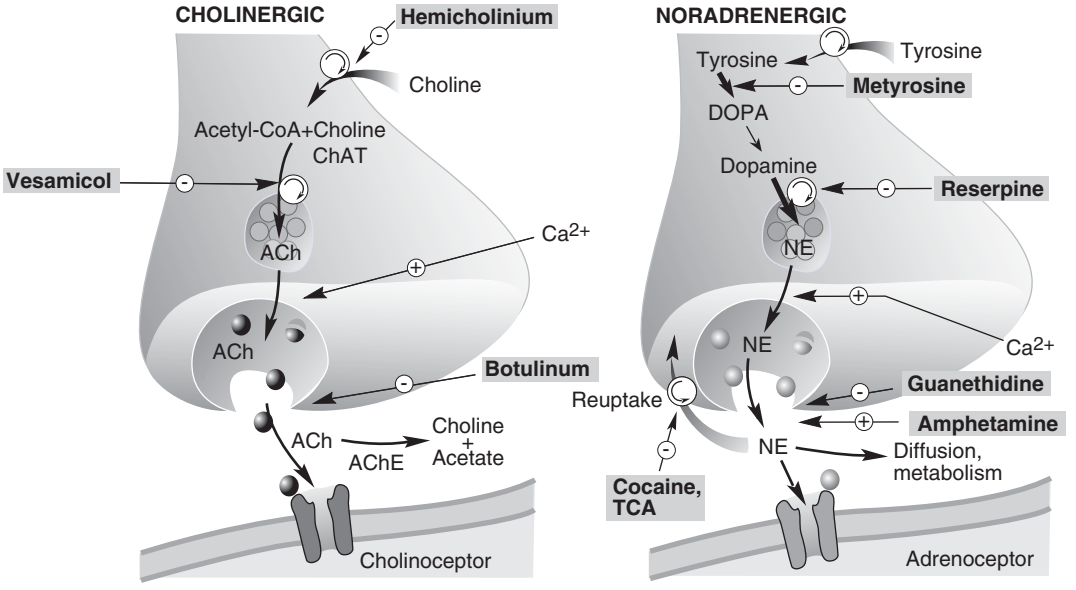
"**Q**iss (kiss) and **qiq** (kick) till you're **siq** (sick) of **sqs** (sex)."



HAVe 1 **M&M.**

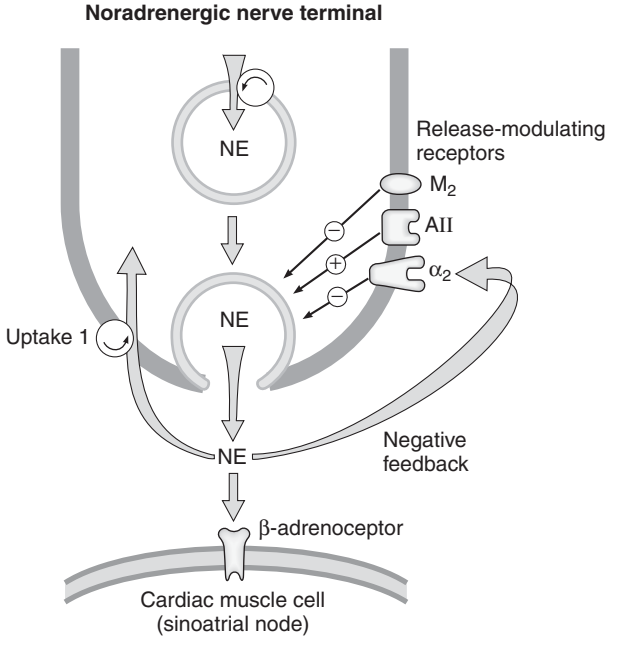
MAD 2's.

Autonomic drugs



(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review,* 5th ed. Stamford, CT: Appleton & Lange, 1998: 42.)

Circles with rotating arrows represent transporters; ChAT, choline acetyltransferase; ACh, acetylcholine; AChE, acetylcholinesterase; NE, norepinephrine.



(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review,* 5th ed. Stamford, CT: Appleton & Lange, 1998: 42.)

Release of NE from a sympathetic nerve ending is modulated by NE itself, acting on presynaptic α_2 autoreceptors, and by ACh, angiotensin II, and other substances.

Cholinergic agents

Drug	Clinical applications	Action
Direct agonists		
Bethanechol	Postoperative and neurogenic ileus and urinary retention	Activates **B**owel and **B**ladder smooth muscle; resistant to AChE. **Beth Anne, call (bethanechol)** me if you want to activate your **B**owels and **B**ladder.
Carbachol	Glaucoma, pupillary contraction, and release of intraocular pressure	
Pilocarpine	Potent stimulator of sweat, tears, saliva	Contracts ciliary muscle of eye (open angle), pupillary sphincter (narrow angle); resistant to AChE. **PILE** on the sweat and tears.
Methacholine	Challenge test for diagnosis of asthma	Stimulates muscarinic receptors in airway when inhaled.
Indirect agonists (anticholinesterases)		
Neostigmine	Postoperative and neurogenic ileus and urinary retention, myasthenia gravis, reversal of neuromuscular junction blockade (postoperative)	↑ endogenous ACh; no CNS penetration. **NEO** CNS = **NO** CNS penetration.
Pyridostigmine	Myasthenia gravis (long acting); does not penetrate CNS	↑ endogenous ACh; ↑ strength.
Edrophonium	Diagnosis of myasthenia gravis (extremely short acting)	↑ endogenous ACh.
Physostigmine	Glaucoma (crosses blood-brain barrier → CNS) and atropine overdose	↑ endogenous ACh. **PHYS** is for **EYES.**
Echothiophate	Glaucoma	↑ endogenous ACh.

Cholinesterase inhibitor poisoning	Symptoms include **D**iarrhea, **U**rination, **M**iosis, **B**ronchospasm, **B**radycardia, **E**xcitation of skeletal muscle and CNS, **L**acrimation, **S**weating, and **S**alivation (also abdominal cramping). Antidote—atropine (muscarinic antagonist) plus pralidoxime (chemical antagonist used to regenerate active cholinesterase).	**DUMBBELSS.** Parathion and other organophosphates. Irreversible inhibitors.

► PHARMACOLOGY—AUTONOMIC DRUGS *(continued)*

Muscarinic antagonists

Drug	Organ system	Application
Atropine, homatropine, tropicamide	Eye	Produce mydriasis and cycloplegia
Benztropine	CNS	**PARK**inson's disease—**PARK** my **BENZ**
Scopolamine	CNS	Motion sickness
Ipratropium	Respiratory	Asthma, COPD
Methscopolamine, oxybutynin, glycopyrrolate	Genitourinary	Reduce urgency in mild cystitis and reduce bladder spasms
Pirenzepine, propantheline	Gastrointestinal	Peptic ulcer treatment

Glaucoma drugs

α_1 stimulation → mydriasis (pupillary dilator muscle); M3 stimulation → miosis (pupillary constrictor muscle) and ciliary muscle contraction.

Drug	Mechanism	Side effects
α-agonists		
Epinephrine	↓ aqueous humor synthesis due to vasoconstriction	Mydriasis, stinging; do not use in closed-angle glaucoma
Brimonidine	↓ aqueous humor synthesis	No pupillary or vision changes
β-blockers		
Timolol, betaxolol, carteolol	↓ aqueous humor secretion	No pupillary or vision changes
Diuretics		
Acetazolamide	↓ aqueous humor secretion due to ↓ HCO_3^- (via inhibition of carbonic anhydrase)	No pupillary or vision changes
Cholinomimetics		
Pilocarpine, carbachol, physostigmine, echothiophate	↑ outflow of aqueous humor; contract ciliary muscle and open trabecular meshwork; use pilocarpine in emergencies; very effective at opening canal of Schlemm	Miosis, cyclospasm
Prostaglandin		
Latanoprost ($PGF_{2\alpha}$)	↑ outflow of aqueous humor	Darkens color of iris (browning)

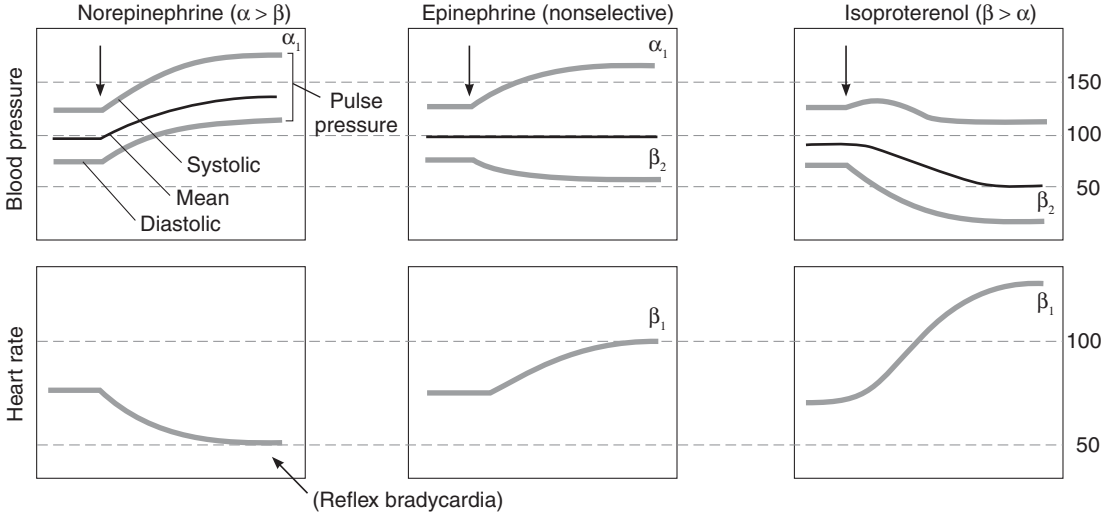
Atropine	Muscarinic antagonist.	
Organ system		
Eye	↑ pupil dilation, cycloplegia.	Blocks **DUMBBELSS.**
Airway	↓ secretions.	
Stomach	↓ acid secretion.	
Gut	↓ motility.	
Bladder	↓ urgency in cystitis.	
Toxicity	↑ body temperature; rapid pulse; dry mouth; dry, flushed skin; cycloplegia; constipation; disorientation. Can cause acute angle-closure glaucoma in elderly, urinary retention in men with prostatic hypertrophy, 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

Hexamethonium	Nicotinic antagonist.
Clinical use	Ganglionic blocker. Used in experimental models to prevent vagal reflex responses to changes in blood pressure—e.g., prevents reflex bradycardia caused by NE.
Toxicity	Severe orthostatic hypotension, blurred vision, constipation, sexual dysfunction.

COMPLETED

Sympathomimetics

Drug	Mechanism/selectivity	Applications
Direct sympathomimetics		
Epinephrine	α_1, α_2, β_1, β_2, low doses selective for β_1	Anaphylaxis, glaucoma (open angle), asthma, hypotension
NE	α_1, $\alpha_2 > \beta_1$	Hypotension (but ↓ renal perfusion)
Isoproterenol	$\beta_1 = \beta_2$	AV block (rare)
Dopamine	$D_1 = D_2 > \beta > \alpha$, inotropic and chronotropic	Shock (↑ renal perfusion), heart failure
Dobutamine	$\beta_1 > \beta_2$, inotropic but not chronotropic	Shock, heart failure, cardiac stress testing
Phenylephrine	$\alpha_1 > \alpha_2$	Pupillary dilation, vasoconstriction, nasal decongestion
Albuterol, terbutaline	$\beta_2 > \beta_1$	Albuterol for acute asthma; terbutaline reduces premature uterine contractions
Ritodrine	β_2	Reduces premature uterine contractions
Indirect sympathomimetics		
Amphetamine	Indirect general agonist, releases stored catecholamines	Narcolepsy, obesity, attention deficit disorder
Ephedrine	Indirect general agonist, releases stored catecholamines	Nasal decongestion, urinary incontinence, hypotension
Cocaine	Indirect general agonist, uptake inhibitor	Causes vasoconstriction and local anesthesia
Sympathoplegics		
Clonidine, α-methyldopa	Centrally acting α_2-agonist, ↓ central adrenergic outflow	Hypertension, especially with renal disease (no ↓ in blood flow to kidney)

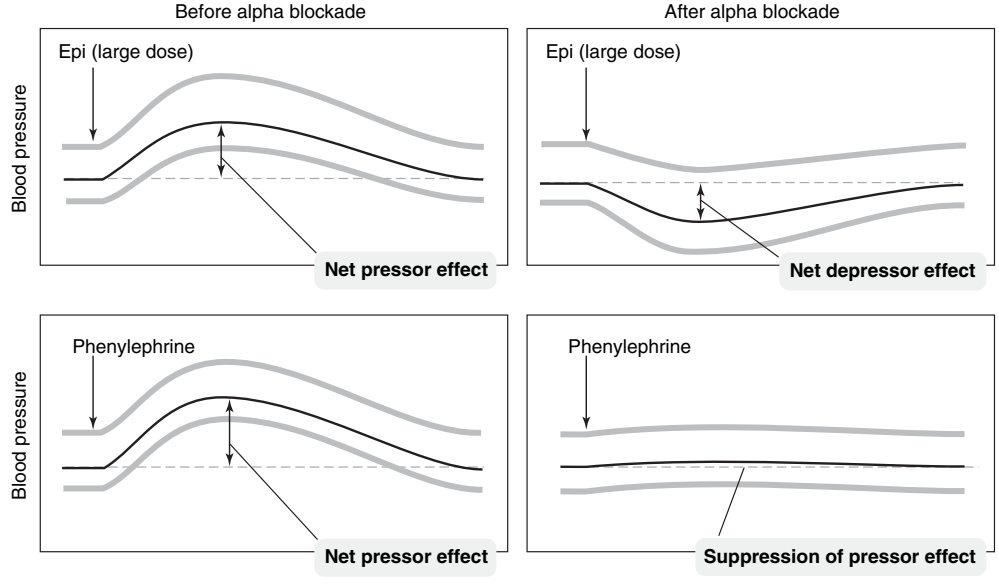


(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review,* 5th ed. Stamford, CT: Appleton & Lange, 1998: 72.)

Selective β_2-agonists	**M**etaproterenol, **A**lbuterol, **S**almeterol, **T**erbutaline.	**MAST.**

α-blockers

Drug	Application	Toxicity
Nonselective		
Phenoxybenzamine (irreversible) and phentolamine (reversible)	Pheochromocytoma (use phenoxybenzamine before removing tumor, since high levels of released catecholamines will not be able to overcome blockage)	Orthostatic hypotension, reflex tachycardia
α_1 selective		
Prazosin, terazosin, doxazosin	Hypertension, urinary retention in BPH	1st-dose orthostatic hypotension, dizziness, headache
α_2 selective		
Mirtazapine	Depression	Sedation, ↑ serum cholesterol, ↑ appetite



(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review,* 5th ed. Stamford, CT: Appleton & Lange, 1998: 80.)

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 β_2 response). The response to phenylephrine is suppressed but not reversed because phenylephrine is a "pure" α-agonist without β action.

► PHARMACOLOGY—AUTONOMIC DRUGS *(continued)*

β-blockers	Propranolol, metoprolol, atenolol, nadolol, timolol, pindolol, esmolol, labetalol.
Application	**Effect**
Hypertension	↓ cardiac output, ↓ renin secretion
Angina pectoris	↓ heart rate and contractility, resulting in ↓ O_2 consumption
MI	β-blockers ↓ mortality
SVT (propranolol, esmolol)	↓ AV conduction velocity (class II antiarrhythmic)
CHF	Slows progression of chronic failure
Glaucoma (timolol)	↓ secretion of aqueous humor
Toxicity	Impotence, exacerbation of asthma, cardiovascular adverse effects (bradycardia, AV block, CHF), CNS adverse effects (sedation, sleep alterations); use with caution in diabetics
Selectivity	Nonselective antagonists ($\beta_1 = \beta_2$)—propranolol, timolol, nadolol, pindolol, and labetalol
	β_1-selective antagonists ($\beta_1 > \beta_2$)—**A**cebutolol (partial agonist), **B**etaxolol, **E**smolol (short acting), **A**tenolol, **M**etoprolol
	Nonselective α- and β-antagonists—carvedilol, labetalol
	Partial β-agonists—acebutolol, pindolol

A BEAM of β_1-blockers.

Specific antidotes

Toxin	Antidote/treatment
1. Acetaminophen	1. N-acetylcysteine
2. Salicylates	2. $NaHCO_3$ (alkalinize urine), dialysis
3. Amphetamines (basic)	3. NH_4Cl (acidify urine)
4. Anticholinesterases, organophosphates	4. Atropine, pralidoxime
5. Antimuscarinic, anticholinergic agents	5. Physostigmine salicylate
6. β-blockers	6. Glucagon
7. Digitalis	7. Stop dig, normalize K^+, lidocaine, anti-dig Fab fragments, Mg^{2+}
8. Iron	8. Deferoxamine
9. Lead	9. CaEDTA, dimercaprol, succimer, penicillamine
10. Arsenic, mercury, gold	10. Dimercaprol (BAL), succimer
11. Copper, arsenic, gold	11. Penicillamine
12. Cyanide	12. Nitrite, hydroxocobalamin, thiosulfate
13. Methemoglobin	13. Methylene blue
14. Carbon monoxide	14. 100% O_2, hyperbaric O_2
15. Methanol, ethylene glycol (antifreeze)	15. Ethanol, dialysis, fomepizole
16. Opioids	16. Naloxone/naltrexone
17. Benzodiazepines	17. Flumazenil
18. TCAs	18. $NaHCO_3$ (serum alkalinization)
19. Heparin	19. Protamine
20. Warfarin	20. Vitamin K, fresh frozen plasma
21. tPA, streptokinase	21. Aminocaproic acid

Lead poisoning

Lead **L**ines on gingivae and on epiphyses of long bones on x-ray.	**LEAD.** High risk in houses with chipped paint.
Encephalopathy and **E**rythrocyte basophilic stippling.	
Abdominal colic and sideroblastic **A**nemia.	
Drops—wrist and foot drop. **D**imercaprol and ED**T**A 1st line of treatment. **Succ**imer for kids.	It "**sucks**" to be a kid who eats lead.

Iron poisoning

Iron overdose is one of the leading causes of fatality from toxicologic agents in children.

Mechanism	Cell death due to peroxidation of membrane lipids.
Symptoms	Acute—gastric bleeding. Chronic—metabolic acidosis, scarring leading to GI obstruction.

Drug reactions

Drug reaction by system	Causal agent
Cardiovascular	
Atropine-like side effects	Tricyclics
Coronary vasospasm	Cocaine, sumatriptan
Cutaneous flushing	Niacin, Ca^{2+} channel blockers, adenosine, vancomycin
Dilated cardiomyopathy	Doxorubicin (Adriamycin), daunorubicin
Torsades des pointes	Class III (sotalol), class IA (quinidine) antiarrhythmics, cisapride
Hematologic	
Agranulocytosis	Clozapine, carbamazepine, colchicine, propylthiouracil, methimazole
Aplastic anemia	Chloramphenicol, benzene, NSAIDs, propylthiouracil, methimazole
Direct Coombs-positive hemolytic anemia	Methyldopa
Gray baby syndrome	Chloramphenicol
Hemolysis in G6PD-deficient patients	**I**soniazid (INH), **S**ulfonamides, **P**rimaquine, **A**spirin, **I**buprofen, **N**itrofurantoin (hemolysis **IS PAIN**)
Thrombotic complications	OCPs (e.g., estrogens and progestins)
Respiratory	
Cough	ACE inhibitors (note: ARBs like losartan—no cough)
Pulmonary fibrosis	Bleomycin, busulfan, amiodarone
GI	
Acute cholestatic hepatitis	Macrolides
Focal to massive hepatic necrosis	Halothane, valproic acid, acetaminophen, *Amanita phalloides*
Hepatitis	INH
Pseudomembranous colitis	Clindamycin, ampicillin
Reproductive/endocrine	
Adrenocortical insufficiency	Glucocorticoid withdrawal (HPA suppression)
Gynecomastia	**S**pironolactone, **D**igitalis, **C**imetidine, chronic **A**lcohol use, estrogens, **K**etoconazole (**S**ome **D**rugs **C**reate **A**wesome **K**nockers)
Hot flashes	Tamoxifen, clomiphene
Musculoskeletal/ connective tissue	
Gingival hyperplasia	Phenytoin
Gout	Furosemide, thiazides
Osteoporosis	Corticosteroids, heparin
Photosensitivity	**S**ulfonamides, **A**miodarone, **T**etracycline (**SAT** for a **photo**)
SLE-like syndrome	**H**ydralazine, **I**NH, **P**rocainamide, **P**henytoin (it's not **HIPP** to have lupus)
Tendonitis, tendon rupture, and cartilage damage (kids)	Fluoroquinolones

Drug reactions *(continued)*

Renal	
Fanconi's syndrome	Expired tetracycline
Interstitial nephritis	Methicillin, NSAIDs
Hemorrhagic cystitis	Cyclophosphamide, ifosfamide (prevent by coadministrating with mesna)
Neurologic	
Cinchonism	Quinidine, quinine
Diabetes insipidus	Lithium, demeclocycline
Seizures	Bupropion, imipenem/cilastatin
Tardive dyskinesia	Antipsychotics
Multiorgan	
Disulfiram-like reaction	Metronidazole, certain cephalosporins, procarbazine, 1st-generation sulfonylureas
Nephrotoxicity/ neurotoxicity	Polymyxins
Nephrotoxicity/ ototoxicity	Aminoglycosides, loop diuretics, cisplatin

P-450 interactions

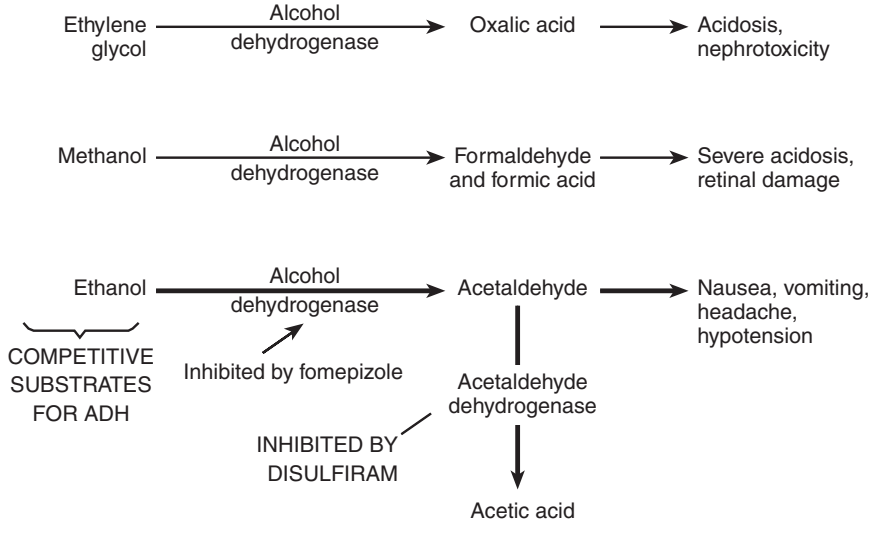
Inducers	**Inhibitors**
Quinidine*	**I**soniazid
Barbiturates	**S**ulfonamides
Phenytoin	**C**imetidine
Rifampin	**K**etoconazole
Griseofulvin	**E**rythromycin
Carbamazepine	**G**rapefruit juice
St. John's wort	

Inducers:
Queen **B**arb takes **P**hen-phen and **R**efuses **G**reasy **C**arb **S**hakes.

Inhibitors:
Inhibitors **S**top **C**yber-**K**ids from **E**ating **G**rapefruit.

*Quinidine can both induce and inhibit different isoforms of P-450. Induction is the more important effect.

Alcohol toxicity



(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review*, 5th ed. Appleton & Lange, 1998: 181.)

► PHARMACOLOGY–TOXICITIES AND SIDE EFFECTS *(continued)*

Sulfa drugs Drugs that can lead to allergies in sulfa-allergic patients—celecoxib, furosemide, thiazides, TMP-SMX, sulfonyureas, sulfasalazine.

► PHARMACOLOGY–MISCELLANEOUS

Herbal agents

Agent	Clinical uses	Toxicities
Echinacea	Common cold	GI distress, dizziness, and headache
Ephedra	As for ephedrine	CNS and cardiovascular stimulation; arrhythmias, stroke, and seizures at high doses
Feverfew	Migraine	GI distress, mouth ulcers, antiplatelet actions
Ginkgo	Intermittent claudication	GI distress, anxiety, insomnia, headache, antiplatelet actions
Kava	Chronic anxiety	GI distress, sedation, ataxia, hepatotoxicity, phototoxicity, dermatotoxicity
Milk thistle	Viral hepatitis	Loose stools
Saw palmetto	Benign prostatic hyperplasia	GI distress, ↓ libido, hypertension
St. John's wort	Mild to moderate depression	GI distress and phototoxicity; serotonin syndrome with SSRIs; induces P-450 system
Dehydroepi-androsterone	Symptomatic improvement in females with SLE or AIDS	Androgenization (premenopausal women), estrogenic effects (postmenopausal), feminization (young men)
Melatonin	Jet lag, insomnia	Sedation, suppresses midcycle LH, hypoprolactinemia

(Adapted, with permission, from Katzung BG, Trevor AJ. *USMLE Road Map: Pharmacology*, 1st ed. New York: McGraw-Hill, 2003.)

Drug name

Ending	Category	Example
-afil	Erectile dysfunction	Sildenafil
-ane	Inhalational general anesthetic	Halothane
-azepam	Benzodiazepine	Diazepam
-azine	Phenothiazine (neuroleptic, antiemetic)	Chlorpromazine
-azole	Antifungal	Ketoconazole
-barbital	Barbiturate	Phenobarbital
-caine	Local anesthetic	Lidocaine
-cillin	Penicillin	Methicillin
-cycline	Antibiotic, protein synthesis inhibitor	Tetracycline
-ipramine	TCA	Imipramine
-navir	Protease inhibitor	Saquinavir
-olol	β-antagonist	Propranolol
-operidol	Butyrophenone (neuroleptic)	Haloperidol
-oxin	Cardiac glycoside (inotropic agent)	Digoxin
-phylline	Methylxanthine	Theophylline
-pril	ACE inhibitor	Captopril
-terol	β_2 agonist	Albuterol
-tidine	H_2 antagonist	Cimetidine
-triptyline	TCA	Amitriptyline
-tropin	Pituitary hormone	Somatotropin
-zosin	α_1 antagonist	Prazosin

SECTION III

High-Yield Organ Systems

- Approaching the Organ Systems
- Cardiovascular
- Endocrine
- Gastrointestinal
- Hematology and Oncology
- Musculoskeletal and Connective Tissue
- Neurology
- Psychiatry
- Renal
- Reproductive
- Respiratory

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In this section, we have divided the High-Yield Facts into the major **Organ Systems.** Within each Organ System are several subsections, including **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 "vertical" framework for learning. Below is some general advice for studying the organ systems by these subsections.

Anatomy

Several topics fall under this heading, including embryology, 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 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 related to specific diseases (e.g., Pancoast's tumor, Horner's 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) also has good yield. Use this as an opportunity to learn associated neuropathology and neurophysiology. Basic embryology (especially congenital malformations) is worth reviewing as well.

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 now 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 increasingly clinical orientation of Step 1, it is no longer sufficient to know only the "trigger word" 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 on NSAIDs. Much of the material is clinically relevant. Newer drugs on the market are also fair game.

Cardiovascular

"As for me, except for an occasional heart attack, I feel as young as I ever did."
—Robert Benchley

"Hearts will never be practical until they are made unbreakable."
—*The Wizard of Oz*

"As the arteries grow hard, the heart grows soft."
—H. L. Mencken

"Nobody has ever measured, not even poets, how much the heart can hold."
—Zelda Fitzgerald

- High-Yield Clinical Vignettes
- Anatomy
- Physiology
- Pathology
- Pharmacology

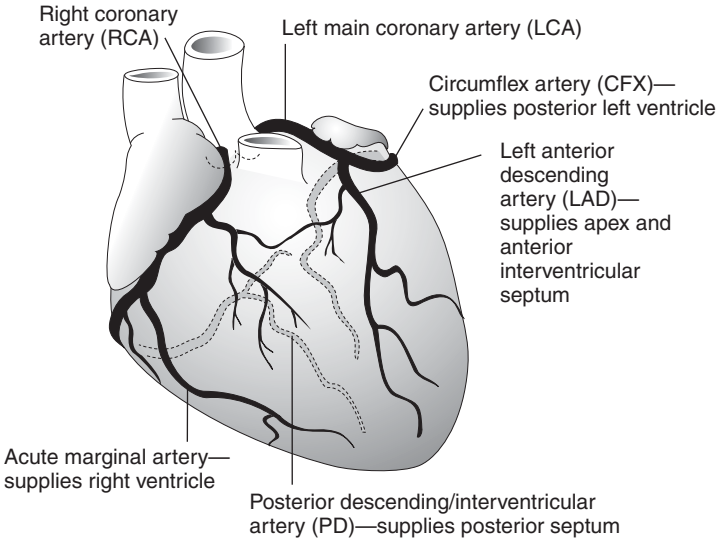
▪ Pregnant woman in 3rd trimester has normal blood pressure when standing and sitting. When supine, blood pressure drops to 90/50.	What is the diagnosis?	Compression of the IVC.
▪ 35-year-old man has high blood pressure in his arms and low pressure in his legs.	What is the diagnosis?	Coarctation of the aorta.
▪ 5-year-old boy presents with a systolic murmur and wide, fixed split S2.	What is the diagnosis?	ASD.
▪ During a game, a young football player collapses and dies immediately.	What is the most likely type of cardiac disease?	Hypertrophic cardiomyopathy.
▪ Patient has a stroke after incurring multiple long bone fractures in trauma stemming from a motor vehicle accident.	What caused the infarct?	Fat emboli.
▪ Elderly woman presents with a headache and jaw pain. Labs show elevated ESR.	What is the diagnosis?	Temporal arteritis.
▪ 80-year-old man presents with a systolic crescendo-decrescendo murmur.	What is the most likely cause?	Aortic stenosis.
▪ Man starts a medication for hyperlipidemia. He then develops a rash, pruritus, and GI upset.	What drug is it?	Niacin.
▪ Patient develops a cough and must discontinue captopril.	What is a good replacement drug, and why doesn't it have the same side effects?	Losartan, an angiotensin II receptor antagonist, does not ↑ bradykinin as captopril does.
▪ Patient presents with ringing in the ears, dizziness, headaches, and GI distress.	What drug is it?	Quinidine.
▪ Patient with a history of hypertension presents with sudden sharp, tearing pain radiating to the back.	What is the CXR finding?	Mediastinal widening.
▪ On auscultation, a pansystolic murmur at the apex with radiation to the axilla is noted.	What is the likely cause?	Mitral insufficiency.

Carotid sheath

3 structures inside:
1. Internal jugular **V**ein (lateral)
2. Common carotid **A**rtery (medial)
3. Vagus **N**erve (posterior)

VAN.

Coronary artery anatomy



(Adapted, with permission, from Ganong WF. *Review of Medical Physiology,* 19th ed. Stamford, CT: Appleton & Lange, 1999: 592.)

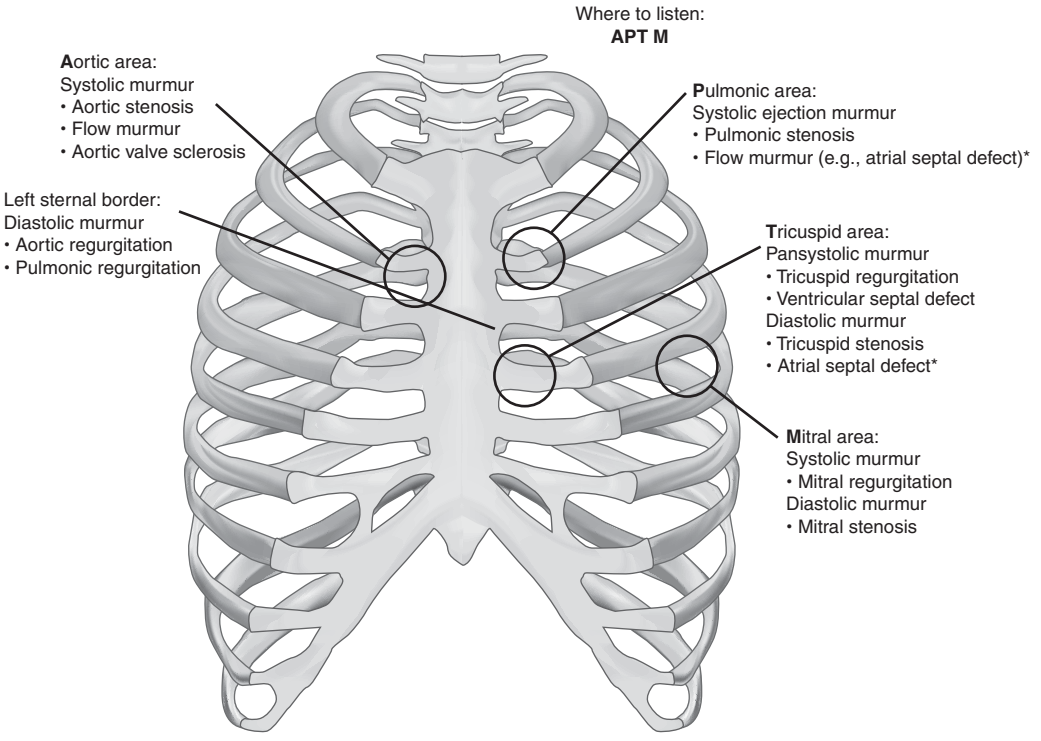
In the majority of cases, the SA and AV nodes are supplied by the RCA. 80% of the time, the RCA supplies the inferior portion of the left ventricle via the PD artery (= right dominant). 20% of the time, the PD arises from the CFX.

Coronary artery occlusion most commonly occurs in the LAD, which supplies the anterior interventricular septum.

Coronary arteries fill during diastole.

The most posterior part of the heart is the left atrium; enlargement can cause dysphagia or hoarseness.

Auscultation of the heart



*ASD commonly presents with a pulmonary flow murmur (↑ flow through pulmonary valve) and a diastolic rumble (↑ flow across tricuspid). The murmur later progresses to a louder diastolic murmur of pulmonic regurgitation from dilatation of the pulmonary artery.

Cardiac output (CO)

Cardiac output (CO) = (stroke volume) × (heart rate).
Fick principle:

$$CO = \frac{\text{rate of } O_2 \text{ consumption}}{\text{arterial } O_2 \text{ content} - \text{venous } O_2 \text{ content}}$$

$$\text{Mean arterial pressure} = \begin{pmatrix}\text{cardiac}\\ \text{output}\end{pmatrix} \times \begin{pmatrix}\text{total peripheral}\\ \text{resistance}\end{pmatrix}$$

MAP = ⅔ diastolic pressure + ⅓ systolic pressure.
Pulse pressure = systolic pressure – diastolic pressure.
Pulse pressure is proportion to stroke volume.

$$SV = \frac{CO}{HR} = EDV - ESV$$

During exercise, CO ↑ initially as a result of an ↑ in SV. After prolonged exercise, CO ↑ as a result of an ↑ in HR.
If HR is too high, diastolic filling is incomplete and CO ↓ (e.g., ventricular tachycardia).

Cardiac output variables

Stroke **V**olume affected by **C**ontractility, **A**fterload, and **P**reload. ↑ SV when ↑ preload, ↓ afterload, or ↑ contractility.

Contractility (and SV) ↑ with:

1. Catecholamines (↑ activity of Ca^{2+} pump in sarcoplasmic reticulum)
2. ↑ intracellular calcium
3. ↓ extracellular sodium
4. Digitalis (↑ intracellular Na^{+}, resulting in ↑ Ca^{2+})

Contractility (and SV) ↓ with:

1. β_1 blockade
2. Heart failure
3. Acidosis
4. Hypoxia/hypercapnea
5. Non-dihydropyridine Ca^{2+} channel blockers

SV CAP.

SV ↑ in anxiety, exercise, and pregnancy.

A failing heart has ↓ SV.

Myocardial O_2 demand is ↑ by:

1. ↑ afterload (∝ arterial pressure)
2. ↑ contractility
3. ↑ heart rate
4. ↑ heart size (↑ wall tension)

Preload and afterload

Preload = ventricular EDV.

Afterload = mean arterial pressure (proportional to peripheral resistance).

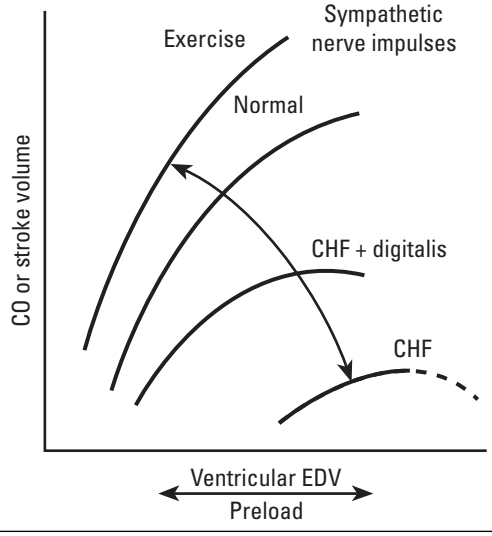
Venodilators (e.g., nitroglycerin) ↓ preload.

Vasodilators (e.g., hydralazine) ↓ afterload.

Preload ↑ with exercise (slightly), ↑ blood volume (overtransfusion), and excitement (sympathetics). Preload pumps up the heart.

Starling curve

Force of contraction is proportional to initial length of cardiac muscle fiber (preload).



CONTRACTILE STATE OF MYOCARDIUM

⊕	⊖
Circulating catecholamines	Pharmacologic depressants
Digitalis	Loss of myocardium (MI)
Sympathetic stimulation	

Ejection fraction (EF)

$$EF = \frac{SV}{EDV} = \frac{EDV - ESV}{EDV}$$

EF is an index of ventricular contractility.

EF is normally ≥ 55%.

Resistance, pressure, flow

$\Delta P = Q \times R$

Similar to Ohm's law: $\Delta V = IR$.

$$\text{Resistance} = \frac{\text{driving pressure } (\Delta P)}{\text{flow } (Q)} = \frac{8\eta \text{ (viscosity)} \times \text{length}}{\pi r^4}$$

Viscosity depends mostly on hematocrit.

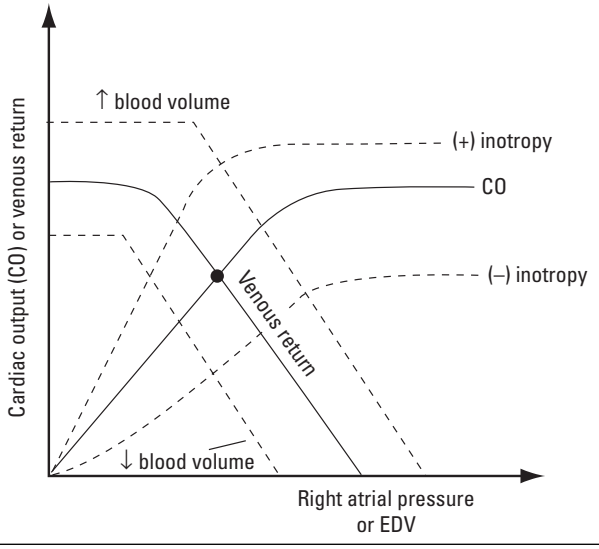
Viscosity ↑ in:

1. Polycythemia
2. Hyperproteinemic states (e.g., multiple myeloma)
3. Hereditary spherocytosis

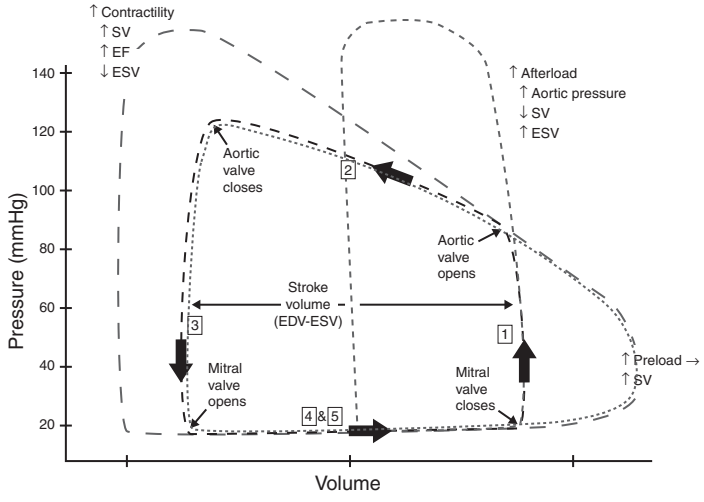
Resistance is directly proportional to viscosity and inversely proportional to the radius to the 4th power.

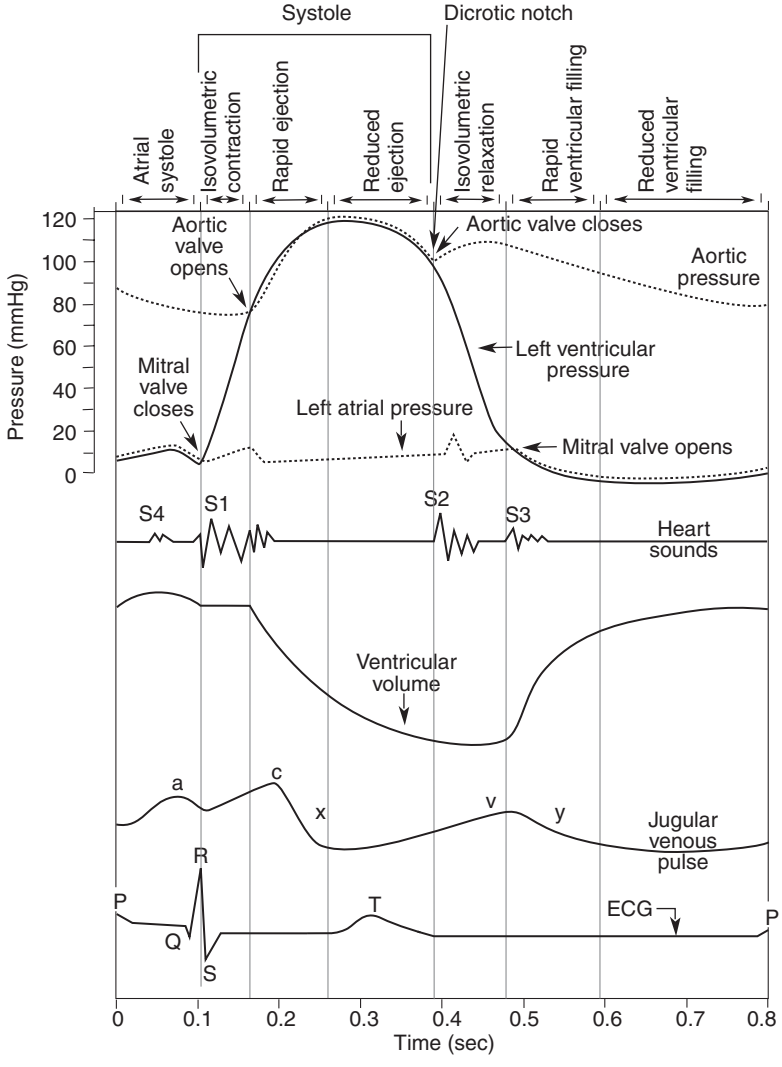
Arterioles account for most of total peripheral resistance → regulate capillary flow.

Cardiac and vascular function curves



Cardiac cycle





(Adapted, with permission, from Ganong WF. *Review of Medical Physiology,* 22nd ed. New York: McGraw-Hill, 2005.)

Phases—left ventricle:

1. Isovolumetric contraction—period between mitral valve closure and aortic valve opening; period of highest O_2 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 closure

Sounds:

S1—mitral and tricuspid valve closure. Loudest at mitral area.

S2—aortic and pulmonary valve closure. Loudest at left sternal border.

S3—in early diastole during rapid ventricular filling phase. Associated with ↑ filling pressures and more common in dilated ventricles (but normal in children).

S4 ("atrial kick")—high atrial pressure. Associated with ventricular hypertrophy.

a wave—**a**trial contraction.

c wave—RV **c**ontraction (tricuspid valve bulging into atrium).

v wave— ↑ atrial pressure due to filling against closed tricuspid **v**alve.

S2 splitting: aortic valve closes before pulmonic; inspiration ↑ this difference.

Normal:

Expiration | ||
S_1 A_2 P_2
Inspiration | | |

Wide splitting (associated with pulmonic stenosis):

Expiration | | |
S_1 A_2 P_2
Inspiration | | |

Fixed splitting (associated with ASD):

Expiration | | |
S_1 A_2 P_2
Inspiration | | |

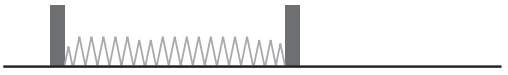
Paradoxical splitting (associated with aortic stenosis):

Expiration | | |
S_1 P_2 A_2
Inspiration | | |

Heart murmurs

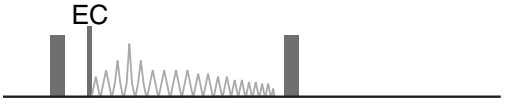
S1 S2

Mitral/tricuspid regurgitation



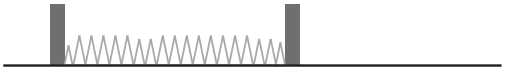
Holosystolic, high-pitched "blowing murmur."
Mitral—loudest at apex and radiates toward axilla.
Tricuspid—loudest at tricuspid area and radiates to right sternal border.

Aortic stenosis



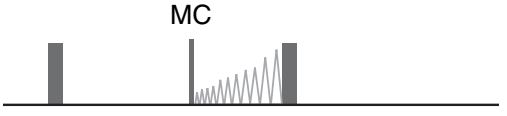
Crescendo-decrescendo systolic ejection murmur following ejection click (EC). LV >> aortic pressure during systole. Radiates to carotids/apex. "Pulsus parvus et tardus"—pulses weak compared to heart sounds.

VSD



Holosystolic, harsh-sounding murmur. Loudest at tricuspid area.

Mitral prolapse

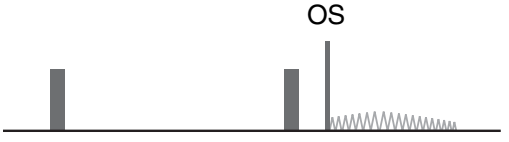


Late systolic murmur with midsystolic click (MC). Most frequent valvular lesion. Loudest at S2.

Aortic regurgitation

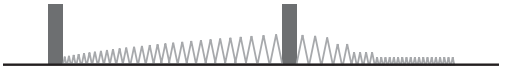
Immediate high-pitched "blowing" diastolic murmur. Wide pulse pressure when chronic.

Mitral stenosis



Follows opening snap (OS). Delayed rumbling late diastolic murmur. LA >> LV pressure during diastole. Tricuspid stenosis differs because it gets louder with inspiration (more blood flows into RA upon inspiration).

PDA



Continuous machine-like murmur. Loudest at time of S2.

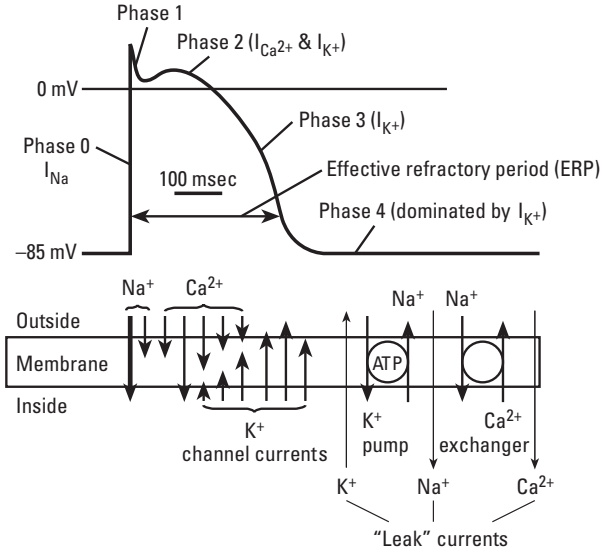
Cardiac myocyte physiology

Cardiac muscle contraction is dependent on extracellular calcium, which enters the cells during plateau of action potential and stimulates calcium release from the cardiac muscle sarcoplasmic reticulum (calcium-induced calcium release).

In contrast to skeletal muscle:

1. Cardiac muscle action potential has a plateau, which is due to Ca^{2+} influx
2. Cardiac nodal cells spontaneously depolarize, resulting in automaticity
3. Cardiac myocytes are electrically coupled to each other by gap junctions

Ventricular action potential



Occurs in atrial and ventricular myocytes and Purkinje fibers.

Phase 0 = rapid upstroke—voltage-gated Na^+ channels open.

Phase 1 = initial repolarization—inactivation of voltage-gated Na^+ channels. Voltage-gated K^+ channels begin to open.

Phase 2 = plateau—Ca^{2+} influx through voltage-gated Ca^{2+} channels balances K^+ efflux. Ca^{2+} influx triggers Ca^{2+} release from sarcoplasmic reticulum and myocyte contraction.

Phase 3 = rapid repolarization—massive K^+ efflux due to opening of voltage-gated slow K^+ channels and closure of voltage-gated Ca^{2+} channels.

Phase 4 = resting potential—high K^+ permeability through K^+ channels.

Pacemaker action potential

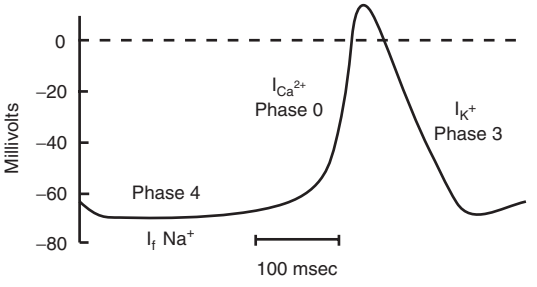
Occurs in the SA and AV nodes. Key differences from the ventricular action potential include:

Phase 0 = upstroke—opening of voltage-gated Ca^{2+} channels. These cells lack fast voltage-gated Na^+ channels. Results in a slow conduction velocity that is used by the AV node to prolong transmission from the atria to ventricles.

Phase 2 = plateau is absent.

Phase 3 = inactivation of the Ca^{2+} channels and ↑ activation of K^+ channels → ↑ K^+ efflux.

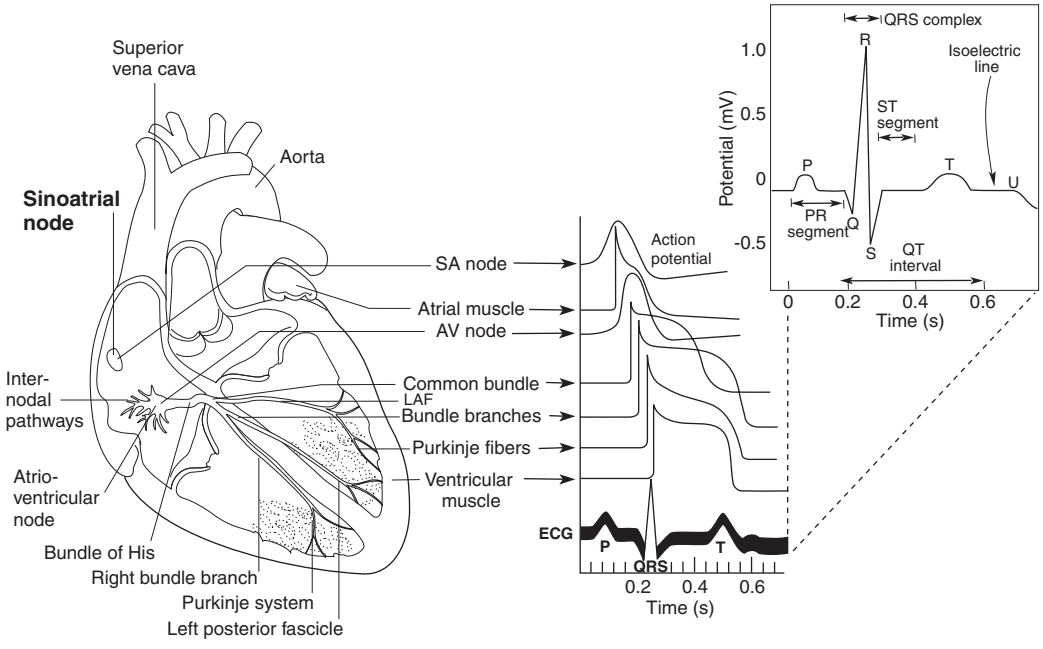
Phase 4 = slow diastolic depolarization—membrane potential spontaneously depolarizes as Na^+ conductance ↑ (I_f different from I_{Na} above). Accounts for automaticity of SA and AV nodes. The slope of phase 4 in the SA node determines heart rate. ACh ↓ the rate of diastolic depolarization and ↓ heart rate, while catecholamines ↑ depolarization and ↑ heart rate.



(Adapted, with permission, from Ganong WF. *Review of Medical Physiology,* 22nd ed. New York: McGraw-Hill, 2005.)

Electrocardiogram

P wave—atrial depolarization.
PR interval—conduction delay through AV node (normally < 200 msec).
QRS complex—ventricular depolarization (normally < 120 msec).
QT interval—mechanical contraction of the ventricles.
T wave—ventricular repolarization.
Atrial repolarization is masked by QRS complex.
ST segment—isoelectric, ventricles depolarized.
U wave—caused by hypokalemia, bradycardia.



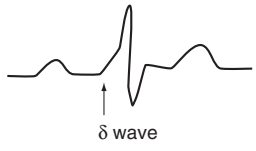
SA node "pacemaker" inherent dominance with slow phase of upstroke
AV node - 100-msec delay - atrioventricular delay

(Adapted, with permission, from Ganong WF. *Review of Medical Physiology,* 22nd ed. New York: McGraw-Hill, 2005: 548, 550.)

Torsades des pointes

Ventricular tachycardia characterized by shifting sinusoidal waveforms on ECG. Can progress to V-fib. Anything that prolongs the QT interval can predispose to torsades des pointes.

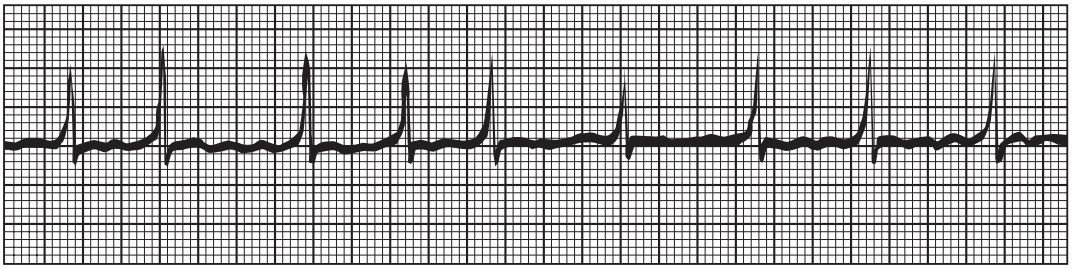
Wolff-Parkinson-White syndrome



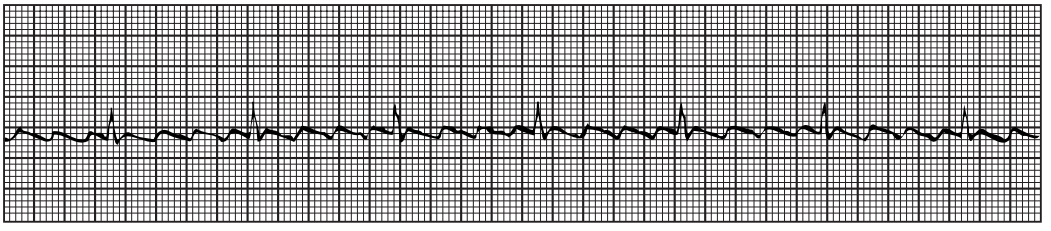
Accessory conduction pathway from atria to ventricle (bundle of Kent), bypassing AV node. As a result, ventricles begin to partially depolarize earlier, giving rise to characteristic delta wave on ECG. May result in reentry current leading to supraventricular tachycardia.

ECG tracings

Atrial fibrillation Chaotic and erratic baseline (irregularly irregular) with no discrete P waves in between irregularly spaced QRS complexes.

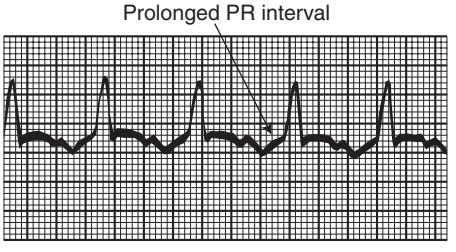


Atrial flutter A rapid succession of identical, back-to-back atrial depolarization waves. The identical appearance accounts for the "sawtooth" appearance of the flutter waves.



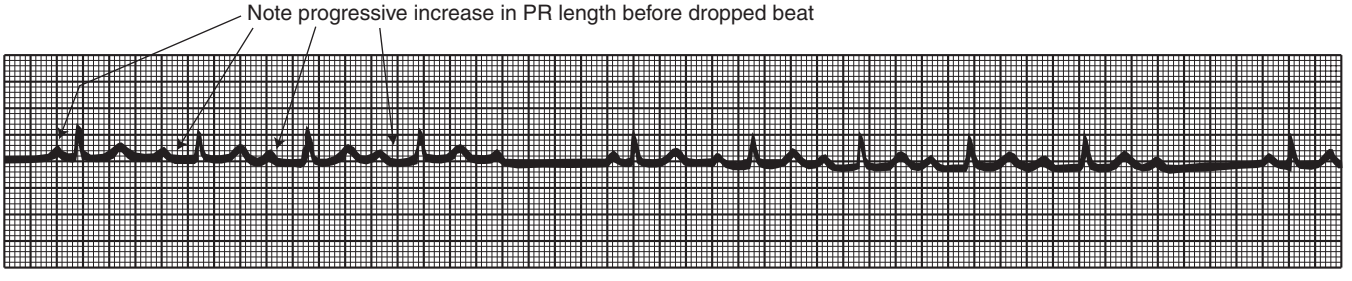
AV block

1st degree The PR interval is prolonged (> 200 msec). Asymptomatic.



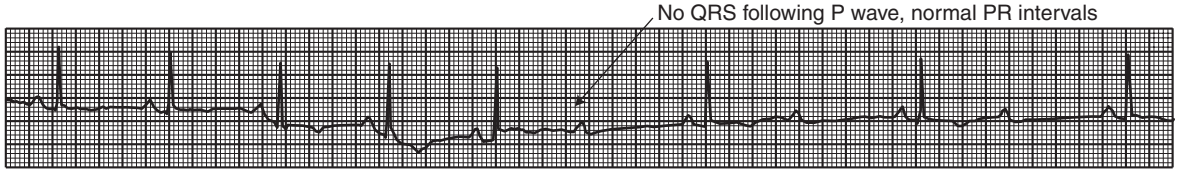
2nd degree

Mobitz type I (Wenckebach) Progressive lengthening of the PR interval until a beat is "dropped" (a P wave not followed by a QRS complex). Usually asymptomatic.

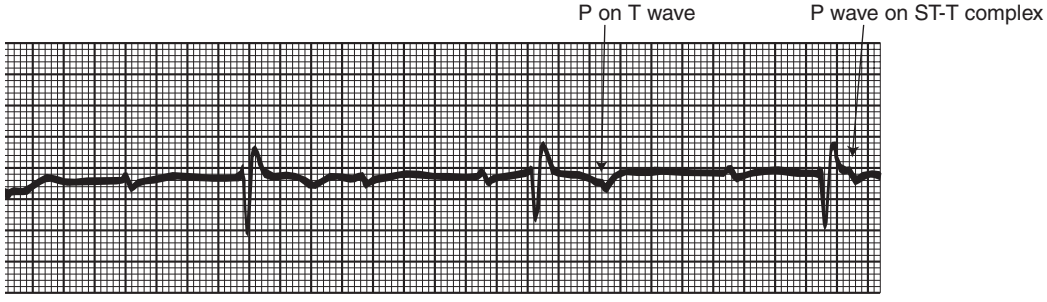


ECG tracings *(continued)*

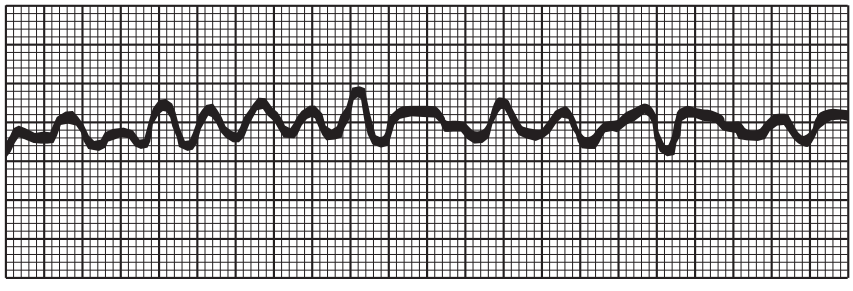
Mobitz type II — Dropped beats that are not preceded by a change in the length of the PR interval (as in type I). These abrupt, nonconducted P waves result in a pathologic condition. It is often found as 2:1 block, where there are 2 P waves to 1 QRS response. May progress to 3rd-degree block.



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. The atrial rate is faster than the ventricular rate. Usually treat with pacemaker.

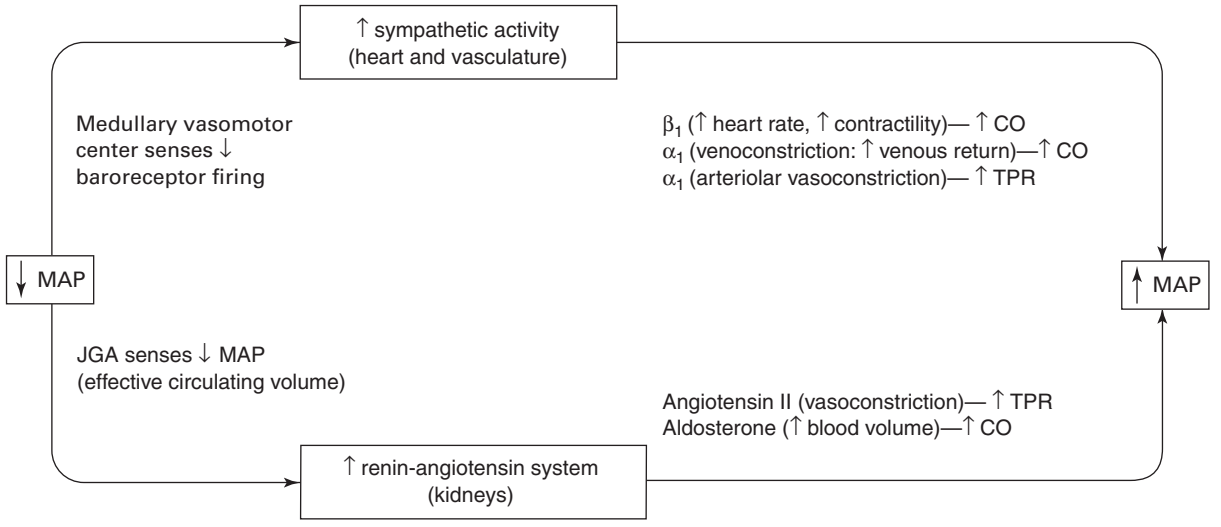


Ventricular fibrillation — A completely erratic rhythm with no identifiable waves. Fatal arrhythmia without immediate CPR and defibrillation.

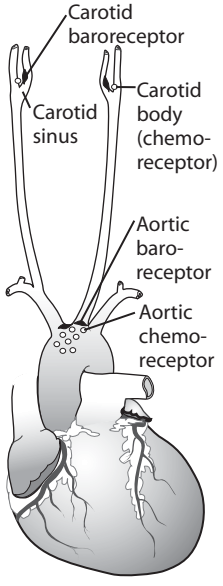


(Adapted, with permission, from Hurst JW. *Introduction to Electrocardiography.* New York: McGraw-Hill, 2001.)

Control of mean arterial pressure



Baroreceptors and chemoreceptors



Receptors:

1. Aortic arch transmits via vagus nerve to medulla (responds only to ↑ BP)
2. Carotid sinus transmits via glossopharyngeal nerve to medulla (responds to ↓ and ↑ in BP).

Baroreceptors:

1. 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.
2. Carotid massage—↑ pressure on carotid artery → ↑ stretch → ↑ afferent baroreceptor firing → ↓ HR.

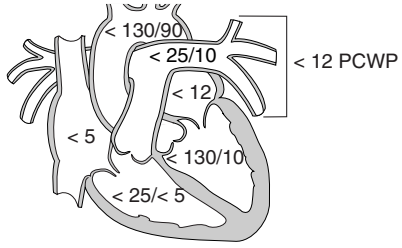
Chemoreceptors:

1. Peripheral—carotid and aortic bodies respond to ↓ P_{O_2} (< 60 mmHg), ↑ P_{CO_2}, and ↓ pH of blood.
2. Central—respond to changes in pH and P_{CO_2} of brain interstitial fluid, which in turn are influenced by arterial CO_2. Do not directly respond to P_{O_2}. Responsible for Cushing reaction— ↑ intracranial pressure constricts arterioles → cerebral ischemia → hypertension (sympathetic response) and reflex bradycardia. Note: Cushing triad = hypertension, bradycardia, respiratory depression.

Circulation through organs

Liver	Largest share of systemic cardiac output.
Kidney	Highest blood flow per gram of tissue.
Heart	Large arteriovenous O_2 difference. ↑ O_2 demand is met by ↑ coronary blood flow, not by ↑ extraction of O_2.

Normal pressures



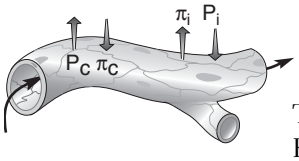
PCWP—pulmonary capillary wedge pressure (in mmHg) is a good approximation of left atrial pressure.
Measured with Swan-Ganz catheter.

Autoregulation

Organ	Factors determining autoregulation
Heart	Local metabolites—O_2, adenosine, NO
Brain	Local metabolites—CO_2 (pH)
Kidneys	Myogenic and tubuloglomerular feedback
Lungs	Hypoxia causes vasoconstriction
Skeletal muscle	Local metabolites—lactate, adenosine, K^+
Skin	Sympathetic stimulation most important mechanism—temperature control

Note: the pulmonary vasculature is unique in that hypoxia causes vasoconstriction. In other organs, hypoxia causes vasodilation.

Capillary fluid exchange



Starling forces determine fluid movement through capillary membranes:
1. P_c = capillary pressure—pushes fluid out of capillary
2. P_i = interstitial fluid pressure—pushes fluid into capillary
3. π_c = plasma colloid osmotic pressure—pulls fluid into capillary
4. π_i = interstitial fluid colloid osmotic pressure—pulls fluid out of capillary

Thus, net filtration pressure = $P_{net} = [(P_c - P_i) - (\pi_c - \pi_i)]$.
K_f = filtration constant (capillary permeability).
Net fluid flow = $(P_{net})(K_f)$.
Edema—excess fluid outflow into interstitium commonly caused by:
1. ↑ capillary pressure (↑ P_c; heart failure)
2. ↓ plasma proteins (↓ π_c; nephrotic syndrome, liver failure)
3. ↑ capillary permeability (↑ K_f; toxins, infections, burns)
4. ↑ interstitial fluid colloid osmotic pressure (↑ π_i; lymphatic blockage)

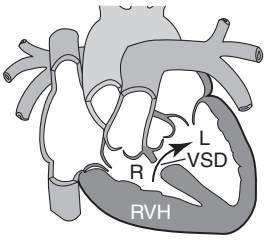
► CARDIOVASCULAR–PATHOLOGY

Congenital heart disease

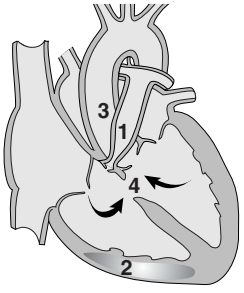
Right-to-left shunts (early cyanosis)—"blue babies"	1. **T**etralogy of Fallot (most common cause of early cyanosis) 2. **T**ransposition of great vessels 3. **T**runcus arteriosus 4. Tricuspid atresia 5. Total anomalous pulmonary venous return (TAPVR)	The **5 T**'s: **T**etralogy **T**ransposition **T**runcus **T**ricuspid **T**APVR Children may squat to ↑ systemic vascular resistance.
Left-to-right shunts (late cyanosis)—"blue kids"	1. VSD (most common congenital cardiac anomaly) 2. ASD (loud S1; wide, fixed split S2) 3. PDA (close with indomethacin)	Frequency—VSD > ASD > PDA. ↑ pulmonary resistance due to arteriolar thickening. → progressive pulmonary hypertension; right-to-left shunt (Eisenmenger's).

Eisenmenger's syndrome

Uncorrected VSD, ASD, or PDA leads to progressive pulmonary hypertension. As pulmonary resistance ↑, the shunt reverses from L → R to R → L, which causes late cyanosis (clubbing and polycythemia).



Tetralogy of Fallot



1. **P**ulmonary stenosis (most important determinant for prognosis)
2. **R**VH
3. **O**verriding aorta (overrides the VSD)
4. **V**SD

Early cyanosis is caused by a right-to-left shunt across the VSD. On x-ray, boot-shaped heart due to RVH. Patients suffer "cyanotic spells."

Tetralogy of Fallot is caused by anterosuperior displacement of the infundibular septum.

PROVe.

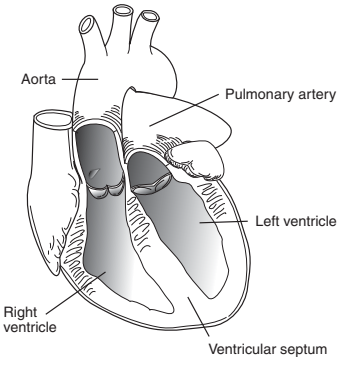
Patient learns to squat to improve symptoms: compression of femoral arteries ↑ pressure, thereby ↓ the right-to-left shunt and directing more blood from the RV to the lungs.

Transposition of great vessels

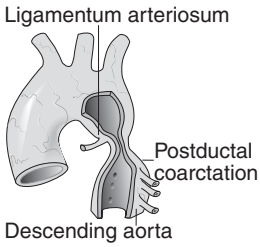
Aorta leaves RV (anterior) and pulmonary trunk leaves LV (posterior) → separation of systemic and pulmonary circulations. Not compatible with life unless a shunt is present to allow adequate mixing of blood (e.g., VSD, PDA, or patent foramen ovale).

Due to failure of the aorticopulmonary septum to spiral.

Without surgical correction, most infants die within the first few months of life.



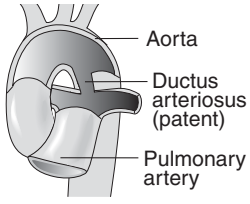
Coarctation of the aorta



Infantile type—aortic stenosis proximal to insertion of ductus arteriosus (preductal).
Adult type—stenosis is distal to ductus arteriosus (postductal). Associated with notching of the ribs (due to collateral circulation), hypertension in upper extremities, weak pulses in lower extremities.
Associated with Turner's syndrome.

Male-to-female ratio 3:1.
Check femoral pulses on physical exam.
INfantile: **IN** close to the heart.
A**D**ult: **D**istal to **D**uctus.

Patent ductus arteriosus



In fetal period, shunt is right to left (normal). In neonatal period, lung resistance ↓ and shunt becomes left to right with subsequent RVH and failure (abnormal). Associated with a continuous, "machine-like" murmur. Patency is maintained by PGE synthesis and low O_2 tension.

Indomethacin is used to close a PDA. PGE is used to keep a PDA open, which may be necessary to sustain life in conditions such as transposition of the great vessels.
PDA is normal in utero and normally closes only after birth.

Congenital cardiac defect associations

Disorder	Defect
22q11 syndromes	Truncus arteriosus, tetralogy of Fallot
Down syndrome	ASD, VSD, AV septal defect (endocardial cushion defect)
Congenital rubella	Septal defects, PDA, pulmonary artery stenosis
Turner's syndrome	Coarctation of aorta
Marfan's syndrome	Aortic insufficiency (late complication)
Offspring of diabetic mother	Transposition of great vessels

Hypertension

Risk factors	↑ age, obesity, diabetes, smoking, genetics, black > white > Asian.
Features	90% of hypertension is 1° (essential) and related to ↑ CO or ↑ TPR; remaining 10% mostly 2° to renal disease. Malignant hypertension is severe and rapidly progressing.
Predisposes to	Atherosclerosis, stroke, CHF, renal failure, retinopathy, and aortic dissection.

Hyperlipidemia signs

Atheromas	Plaques in blood vessel walls.
Xanthomas	Plaques or nodules composed of lipid-laden histiocytes in the skin, especially the eyelids.
Tendinous xanthoma	Lipid deposit in tendon, especially Achilles.
Corneal arcus	Lipid deposit in cornea, nonspecific (arcus senilis).

Arteriosclerosis

Mönckeberg	Calcification in the media of the arteries, especially radial or ulnar. Usually benign; "pipestem" arteries.
Arteriolosclerosis	Hyaline thickening of small arteries in essential hypertension. Hyperplastic "onion skinning" in malignant hypertension.
Atherosclerosis	Fibrous plaques and atheromas form in intima of arteries.

Aortic dissection

Longitudinal intraluminal tear forming a false lumen. Associated with hypertension or cystic medial necrosis (component of Marfan's syndrome). Presents with tearing chest pain radiating to the back. CXR shows mediastinal widening. Can result in aortic rupture and death.

Atherosclerosis

Disease of elastic arteries and large and medium-sized muscular arteries (see Color Image 79).

Risk factors	Smoking, hypertension, diabetes mellitus, hyperlipidemia, family history.
Progression	Endothelial cell dysfunction → macrophage and LDL accumulation → foam cell formation → fatty streaks → smooth muscle migration → fibrous plaque → complex atheromas.
Complications	Aneurysms, ischemia, infarcts, peripheral vascular disease, thrombus, emboli.
Location	Abdominal aorta > coronary artery > popliteal artery > carotid artery.
Symptoms	Angina, claudication, but can be asymptomatic.

Ischemic heart disease

Possible manifestations:

1. **Angina** (CAD narrowing > 75%):
   a. Stable—mostly 2° to atherosclerosis (retrosternal chest pain with exertion)
   b. Prinzmetal's variant—occurs at rest 2° to coronary artery spasm
   c. Unstable/crescendo—thrombosis but no necrosis (worsening chest pain)
2. **Myocardial infarction**—most often acute thrombosis due to coronary artery atherosclerosis; results in myocyte necrosis
3. **Sudden cardiac death**—death from cardiac causes within 1 hour of onset of symptoms, most commonly due to a lethal arrhythmia
4. **Chronic ischemic heart disease**—progressive onset of CHF over many years due to chronic ischemic myocardial damage

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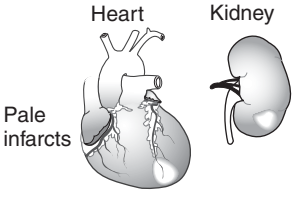
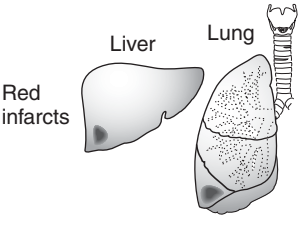
Infarcts: red vs. pale

Red (hemorrhagic) infarcts occur in loose tissues with collaterals, such as liver, lungs, intestine, or liver, or following reperfusion.

Pale infarcts occur in solid tissues with single blood supply, such as heart, kidney, and spleen.

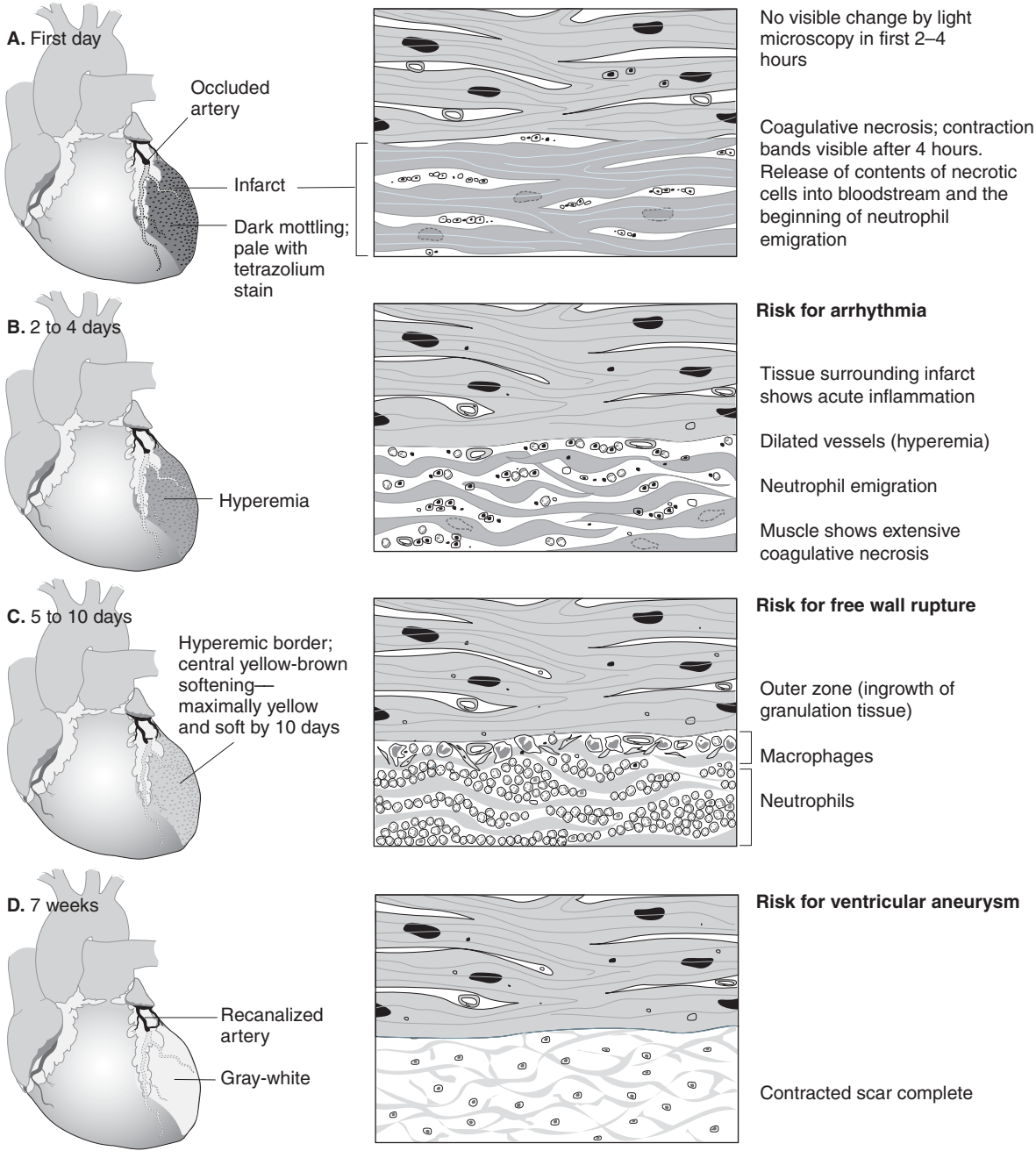
REd = **RE**perfusion.





Evolution of MI

Coronary artery occlusion: LAD > RCA > circumflex.
Symptoms: diaphoresis, nausea, vomiting, severe retrosternal pain, pain in left arm and/or jaw, shortness of breath, fatigue, adrenergic symptoms (see Color Image 80).



(Adapted, with permission, from Chandrasoma P. *Pathology Notes.* Stamford, CT: Appleton & Lange, 1991: 244.)

Diagnosis of MI

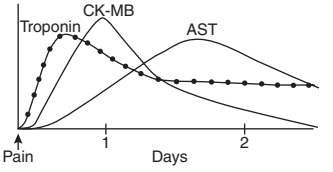
In the first 6 hours, ECG is the gold standard.

Cardiac troponin I rises after 4 hours and is elevated for 7–10 days; more specific than other protein markers.

CK-MB is predominantly found in myocardium but can also be released from skeletal muscle.

AST is nonspecific and can be found in cardiac, liver, and skeletal muscle cells.

ECG changes can include ST elevation (transmural infarct), ST depression (subendocardial infarct), and pathological Q waves (transmural infarct).



MI complications

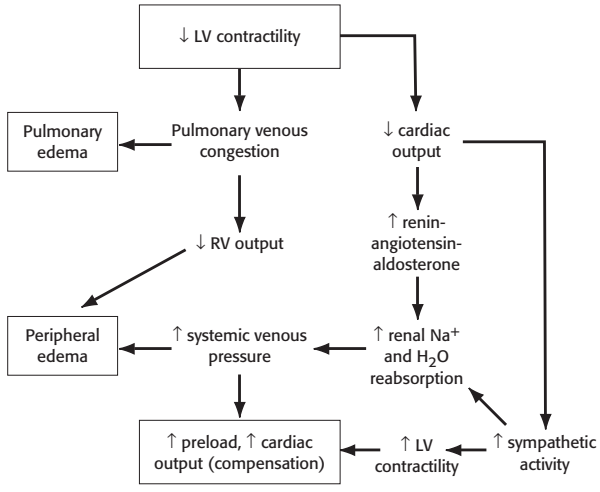
1. Cardiac arrhythmia—important cause of death before reaching hospital; common in first few days
2. LV failure and pulmonary edema
3. Cardiogenic shock (large infarct—high risk of mortality)
4. Ventricular free wall rupture → cardiac tamponade; papillary muscle → severe mitral regurgitation; and interventricular septal rupture → VSD
5. Aneurysm formation—↓ CO, risk of arrhythmia, embolus from mural thrombus
6. Fibrinous pericarditis—friction rub (3–5 days post-MI)
7. Dressler's syndrome—autoimmune phenomenon resulting in fibrinous pericarditis (several weeks post-MI)

Cardiomyopathies

Dilated (congestive) cardiomyopathy	Most common cardiomyopathy (90% of cases). Etiologies include chronic **A**lcohol abuse, **B**eriberi, **C**oxsackie B virus myocarditis, chronic **C**ocaine use, **C**hagas' disease, **D**oxorubicin toxicity, and peripartum cardiomyopathy. Heart dilates and looks like a balloon on chest x-ray.	Systolic dysfunction ensues.
Hypertrophic cardiomyopathy	Hypertrophy often asymmetric and involving the interventricular septum. Normal heart size. 50% of cases are familial, autosomal dominant. Cause of sudden death in young athletes. Findings: loud S4, apical impulses, systolic murmur. Treat with β-blocker or non-dihydropyridine calcium channel blocker (e.g., verapamil).	Diastolic dysfunction ensues.
Restrictive/obliterative cardiomyopathy	Major causes include sarcoidosis, amyloidosis, postradiation fibrosis, endocardial fibroelastosis (thick fibroelastic tissue in endocardium of young children), Löffler's syndrome (endomyocardial fibrosis with a prominent eosinophilic infiltrate), and hemochromatosis (dilated cardiomyopathy can also occur).	Diastolic dysfunction ensues.

CHF

Abnormality	Cause
Dyspnea on exertion	Failure of LV output to ↑ during exercise.
Cardiac dilation	Greater ventricular end-diastolic volume.
Pulmonary edema, paroxysmal nocturnal dyspnea	LV failure → ↑ pulmonary venous pressure → pulmonary venous distention and transudation of fluid. Presence of hemosiderin-laden macrophages ("heart failure" cells) in the lungs.
Orthopnea (shortness of breath when supine)	↑ venous return in supine position exacerbates pulmonary vascular congestion.
Hepatomegaly (nutmeg liver)	↑ central venous pressure → ↑ resistance to portal flow. Rarely, leads to "cardiac cirrhosis."
Ankle, sacral edema	RV failure → ↑ venous pressure → fluid transudation.
Jugular venous distention	Right heart failure → ↑ venous pressure.



Right heart failure most often results from left heart failure. Isolated right heart failure is usually due to cor pulmonale.

Embolus types

Fat, **A**ir, **T**hrombus, **B**acteria, **A**mniotic fluid, **T**umor. Fat emboli are associated with long bone fractures and liposuction. Amniotic fluid emboli can lead to DIC, especially postpartum. Pulmonary embolus—chest pain, tachypnea, dyspnea.

An embolus moves like a **FAT BAT.** Approximately 95% of pulmonary emboli arise from deep leg veins.

Deep venous thrombosis

Predisposed by Virchow's triad:
1. Stasis
2. Hypercoagulability
3. Endothelial damage

Can lead to pulmonary embolism.

Bacterial endocarditis

Fever, Roth's spots (round white spots on retina surrounded by hemorrhage), Osler's nodes (tender raised lesions on finger or toe pads), new **murmur, Janeway lesions** (small erythematous lesions on palm or sole), anemia, **splinter hemorrhages** on nail bed. Valvular damage may cause new murmur. Multiple blood cultures necessary for diagnosis (see Color Image 82).

1. Acute—*S. aureus* (high virulence). Large vegetations on previously normal valves. Rapid onset.
2. Subacute—viridans streptococcus (low virulence). Smaller vegetations on congenitally abnormal or diseased valves. Sequela of dental procedures. More insidious onset.

Endocarditis may also be nonbacterial 2° to malignancy or hypercoagulable state (marantic/thrombotic endocarditis).

Mitral valve is most frequently involved. **Tri**cuspid valve endocarditis is associated with IV **drug** abuse (don't **tri drugs**).

Complications: chordae rupture, glomerulonephritis, suppurative pericarditis, emboli.

Bacteria **FROM JANE:**
Fever
Roth's spots
Osler's nodes
Murmur
Janeway lesions
Anemia
Nail-bed hemorrhage
Emboli

Libman-Sacks endocarditis

Verrucous vegetations occur on both sides of the valve (can be associated with mitral regurgitation and, less commonly, mitral stenosis). Seen in lupus.

SLE causes **LSE.**

Rheumatic heart disease

Rheumatic fever is a consequence of pharyngeal infection with group A β-hemolytic streptococci. Early deaths due to myocarditis. Late sequelae include rheumatic heart disease, which affects heart valves—mitral > aortic >> tricuspid (high-pressure valves affected most). Associated with Aschoff bodies (granuloma with giant cells), Anitschkow's cells (activated histiocytes), migratory polyarthritis, erythema marginatum, elevated ASO titers.

Immune mediated (type II hypersensitivity); not direct effect of bacteria (see Color Image 85).

FEVERSS:
Fever
Erythema marginatum
Valvular damage (vegetation and fibrosis)
ESR ↑
Red-hot joints (polyarthritis)
Subcutaneous nodules (Aschoff bodies)
St. Vitus' dance (chorea)

Cardiac tamponade

Compression of heart by fluid (e.g., blood, effusions) in pericardium, leading to ↓ CO.

Equilibration of diastolic pressures in all 4 chambers.

Findings: hypotension, ↑ venous pressure (JVD), distant heart sounds, ↑ HR, pulsus paradoxus; ECG shows electrical alternans (beat-to-beat alternations of QRS complex height).

Pulsus paradoxus (Kussmaul's pulse)—↓ in amplitude of pulse during inspiration. Seen in severe cardiac tamponade, asthma, obstructive sleep apnea, pericarditis, and croup.

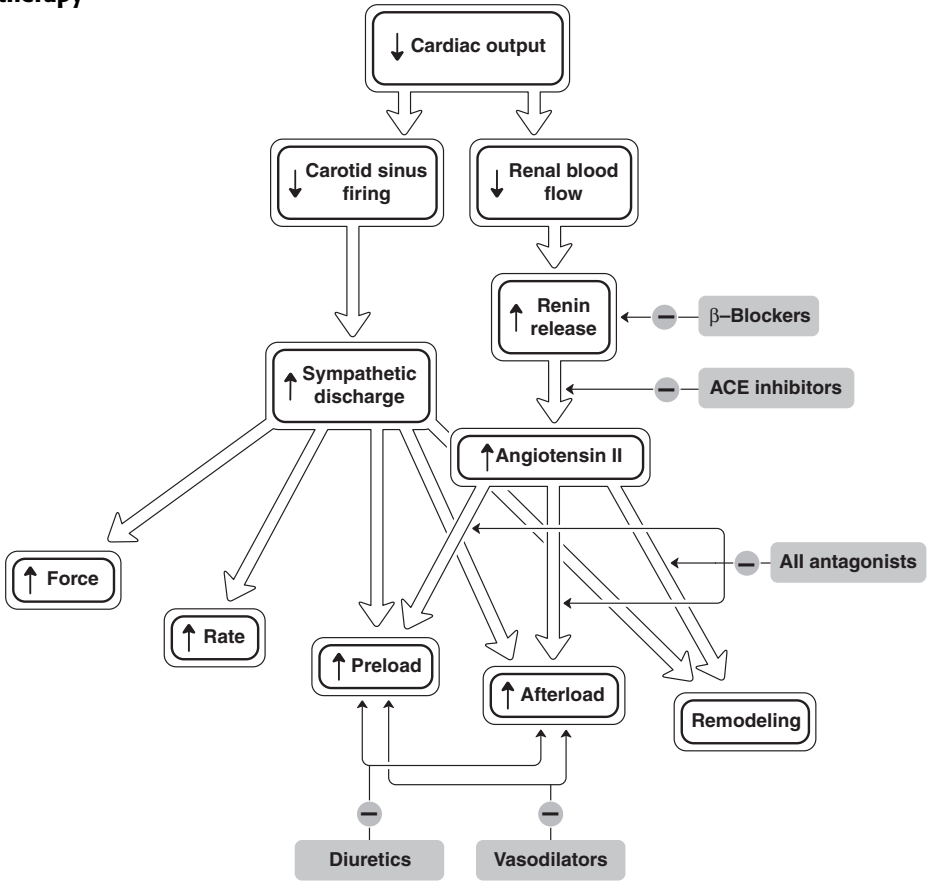
Pericarditis		
Serous	Caused by SLE, rheumatoid arthritis, viral infection, uremia.	
Fibrinous	Uremia, MI (Dressler's syndrome), rheumatic fever.	
Hemorrhagic	TB, malignancy (e.g., melanoma).	
	Findings: pericardial pain, friction rub, pulsus paradoxus, distant heart sounds. Findings include ECG changes with diffuse ST-segment elevation.	
	Can resolve without scarring or lead to chronic adhesive or chronic constrictive pericarditis.	
Syphilitic heart disease	3° syphilis disrupts the vasa vasorum of the aorta with consequent dilation of the aorta and valve ring.	Can result in aneurysm of the ascending aorta or aortic arch and aortic valve incompetence.
	May see calcification of the aortic root and ascending aortic arch. Leads to "tree bark" appearance of the aorta.	
Cardiac tumors	Myxomas are the most common 1° cardiac tumor in adults (see Color Image 88). 90% occur in the atria (mostly LA). Myxomas are usually described as a "ball-valve" obstruction in the LA (associated with multiple syncopal episodes). Rhabdomyomas are the most frequent 1° cardiac tumor in children (associated with tuberous sclerosis).	
	Metastases most common heart tumor (melanoma, lymphoma).	
	Kussmaul's sign: ↑ in jugular venous pressure on inspiration.	
Telangiectasia	Arteriovenous malformation in small vessels. Looks like dilated capillary.	Affects small vessels.
	Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)—autosomal-dominant inheritance. Presents with nosebleeds and skin discolorations.	
Raynaud's disease	↓ blood flow to the skin due to arteriolar vasospasm in response to cold temperature or emotional stress. Most often in the fingers and toes (see Color Image 106). Called Raynaud's phenomenon when 2° to a mixed connective tissue disease, SLE, or CREST syndrome.	Affects small vessels.
Wegener's granulomatosis	Characterized by triad of focal necrotizing vasculitis, necrotizing granulomas in the **lung and upper airway,** and necrotizing glomerulonephritis.	Affects small vessels.
Symptoms	Perforation of nasal septum, chronic sinusitis, otitis media, mastoiditis, cough, dyspnea, hemoptysis, hematuria.	
Findings	**c-ANCA** is a strong marker of disease; chest x-ray may reveal large nodular densities; hematuria and red cell casts.	
Treatment	Cyclophosphamide and corticosteroids.	

Other ANCA-positive vasculitides		
Microscopic polyangiitis	Like Wegener's but lacks granulomas. **p-ANCA.**	All affect small vessels.
1° pauci-immune crescentic glomerulonephritis	Vasculitis limited to kidney. **Pauci-**immune = **pauci**ty of antibodies.	
Churg-Strauss syndrome	Granulomatous vasculitis with eosinophilia. Involves lung, heart, skin, kidneys, nerves. Often seen in atopic patients. **p-ANCA.**	
Sturge-Weber disease	Congenital vascular disorder that affects capillary-sized blood vessels. Manifests with port-wine stain on face and leptomeningeal angiomatosis (intracerebral AVM).	Affects small vessels.
Henoch-Schönlein purpura	Most common form of childhood systemic vasculitis. Skin rash (palpable purpura), arthralgia, intestinal hemorrhage, abdominal pain, and melena. Follows URIs. Multiple lesions of the same age.	Affects small vessels. Common triad: 1. Skin 2. Joints 3. GI
Buerger's disease	Also known as thromboangiitis obliterans; idiopathic, segmental, thrombosing vasculitis of small and medium peripheral arteries and veins. Seen in **heavy smokers.**	Affects small and medium vessels.
Symptoms	Intermittent claudication, superficial nodular phlebitis, cold sensitivity (Raynaud's phenomenon), severe pain in affected part. May lead to gangrene.	
Treatment	Smoking cessation.	
Kawasaki disease	Acute, self-limiting disease of infants/kids. Acute necrotizing vasculitis of small/medium-sized vessels. Fever, congested conjunctiva, changes in lips/oral mucosa ("strawberry tongue"), lymphadenitis. May develop **coronary aneurysms.**	Affects small and medium vessels.
Polyarteritis nodosa	Characterized by necrotizing immune complex inflammation of medium-sized muscular arteries.	Affects medium arteries. Typically involves renal and visceral vessels.
Symptoms	Fever, weight loss, malaise, abdominal pain, melena, headache, myalgia, hypertension, neurologic dysfunction, cutaneous eruptions.	Lesions are of different ages.
Findings	Hepatitis B seropositivity in 30% of patients. Multiple aneurysms and constrictions on arteriogram. Typically not associated with ANCA.	
Treatment	Corticosteroids, cyclophosphamide.	

Takayasu's arteritis	Known as "pulseless disease"—granulomatous thickening of aortic arch and/or proximal great vessels. Associated with an ↑ ESR. Primarily affects Asian females < 40 years old. **F**ever, **A**rthritis, **N**ight sweats, **MY**algia, **SKIN** nodules, **O**cular disturbances, **W**eak pulses in upper extremities.	Affects medium and large arteries. **FAN MY SKIN O**n **W**ednesday.
Temporal arteritis (giant cell arteritis)	Most common vasculitis that affects medium and large arteries, usually branches of carotid artery. Focal, granulomatous inflammation. Affects elderly females.	Affects medium and large arteries. **TEM**poral arteritis has signs near **TEM**ples.
Symptoms	Unilateral headache, jaw claudication, impaired vision (occlusion of ophthalmic artery).	
Findings	Associated with an ↑ ESR. Half of patients have systemic involvement and polymyalgia rheumatica.	
Treatment	High-dose steroids.	

► CARDIOVASCULAR–PHARMACOLOGY

Cardiovascular therapy



(Adapted, with permission, from Katzung BG, Trevor AJ. *USMLE Road Map: Pharmacology*, 1st ed. New York: McGraw-Hill, 2003: 39.)

Antihypertensive drugs

Drug	Adverse effects
Diuretics	
Hydrochlorothiazide	Hypokalemia, mild hyperlipidemia, hyperuricemia, lassitude, hypercalcemia, hyperglycemia
Loop diuretics	Potassium wasting, metabolic alkalosis, hypotension, ototoxicity
Sympathoplegics	
Clonidine	Dry mouth, sedation, severe rebound hypertension
Methyldopa	Sedation, positive Coombs' test
Hexamethonium	Severe orthostatic hypotension, blurred vision, constipation, sexual dysfunction
Reserpine	Sedation, depression, nasal stuffiness, diarrhea
Guanethidine	Orthostatic and exercise hypotension, sexual dysfunction, diarrhea
Prazosin	1st-dose orthostatic hypotension, dizziness, headache
β-blockers	Impotence, asthma, cardiovascular effects (bradycardia, CHF, AV block), CNS effects (sedation, sleep alterations)
Vasodilators	
Hydralazine*	Nausea, headache, lupus-like syndrome, reflex tachycardia, angina, salt retention
Minoxidil*	Hypertrichosis, pericardial effusion, reflex tachycardia, angina, salt retention
Nifedipine, verapamil	Dizziness, flushing, constipation (verapamil), AV block (verapamil), nausea
Nitroprusside	Cyanide toxicity (releases CN)
Diazoxide	Hypoglycemia (reduces insulin release, hypotension)
ACE inhibitors	
Captopril	Hyperkalemia, cough, angioedema, taste changes, hypotension, pregnancy problems (fetal renal damage), rash, ↑ renin
Enalapril	
Fosinopril	
Angiotensin II receptor inhibitors	
Losartan	Fetal renal toxicity, hyperkalemia

*Use with β-blockers to prevent reflex tachycardia, diuretic to block salt retention.

Hydralazine

Mechanism	↑ cGMP → smooth muscle relaxation. Vasodilates arterioles > veins; afterload reduction.
Clinical use	Severe hypertension, CHF. First-line therapy for hypertension in pregnancy, with methyldopa.
Toxicity	Compensatory tachycardia (contraindicated in angina/CAD), fluid retention. Lupus-like syndrome.

Minoxidil

Mechanism	K^+ channel opener—hyperpolarizes and relaxes vascular smooth muscle.
Clinical use	Severe hypertension.
Toxicity	Hypertrichosis, pericardial effusion.

Calcium channel blockers

Nifedipine, verapamil, diltiazem.

Mechanism	Block voltage-dependent L-type calcium channels of cardiac and smooth muscle and thereby reduce muscle contractility. Vascular smooth muscle—nifedipine > diltiazem > verapamil. Heart—verapamil > diltiazem > nifedipine.
Clinical use	Hypertension, angina, arrhythmias (not nifedipine), Prinzmetal's angina, Raynaud's.
Toxicity	Cardiac depression, peripheral edema, flushing, dizziness, and constipation.

Nitroglycerin, isosorbide dinitrate

Mechanism	Vasodilate by releasing nitric oxide in smooth muscle, causing ↑ in cGMP and smooth muscle relaxation. Dilate veins >> arteries. ↓ preload.
Clinical use	Angina, pulmonary edema. Also used as an aphrodisiac and erection enhancer.
Toxicity	Tachycardia, 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, resulting in tachycardia, dizziness, and headache on reexposure.

Malignant hypertension treatment

Nitroprusside	Short acting; ↑ cGMP via direct release of NO.
Fenoldopam	Dopamine D_1 receptor agonist—relaxes renal vascular smooth muscle.
Diazoxide	K^+ channel opener—hyperpolarizes and relaxes vascular smooth muscle.

Antianginal therapy

Goal—reduction of myocardial O_2 consumption (MVO_2) by decreasing 1 or more of the determinants of MVO_2: end diastolic volume, blood pressure, heart rate, contractility, ejection time.

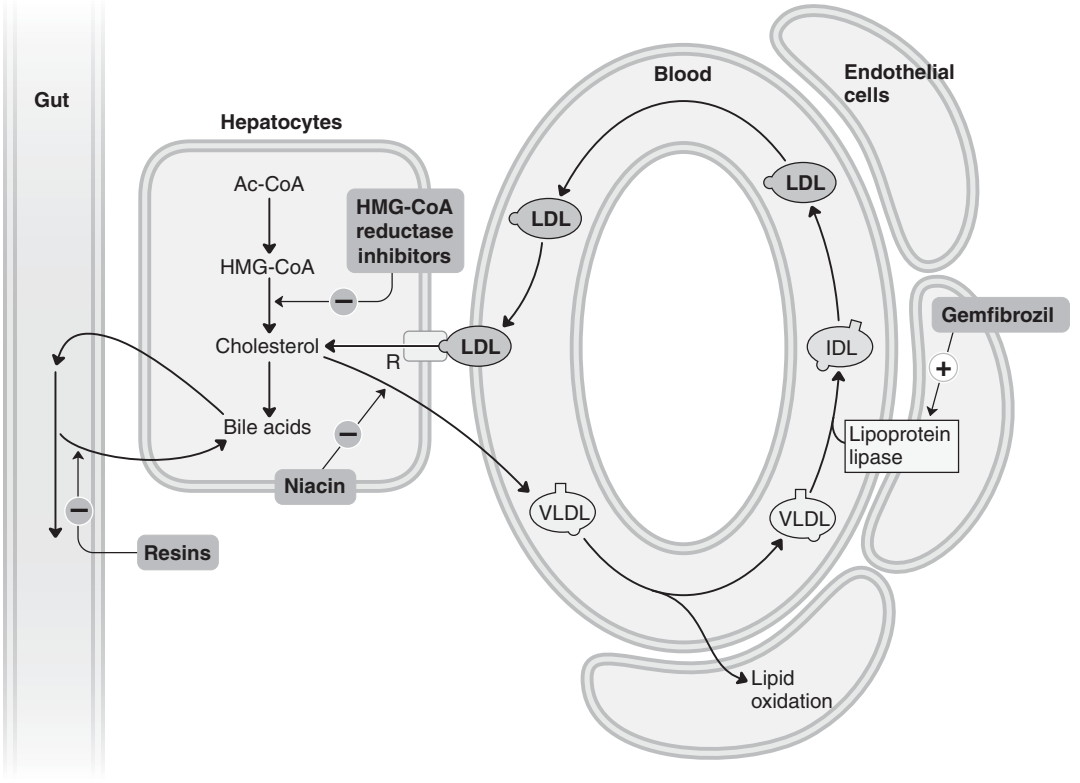
Component	Nitrates (affect preload)	β-blockers (affect afterload)	Nitrates + β-blockers
End diastolic volume	↓	↑	No effect or ↓
Blood pressure	↓	↓	↓
Contractility	↑ (reflex response)	↓	Little/no effect
Heart rate	↑ (reflex response)	↓	↓
Ejection time	↓	↑	Little/no effect
MVO_2	↓	↓	↓↓

Calcium channel blockers—**N**ifedipine is similar to **N**itrates in effect; verapamil is similar to β-blockers in effect.

Note: Labetalol, pindolol, and acebutolol are partial agonists—contraindicated in angina.

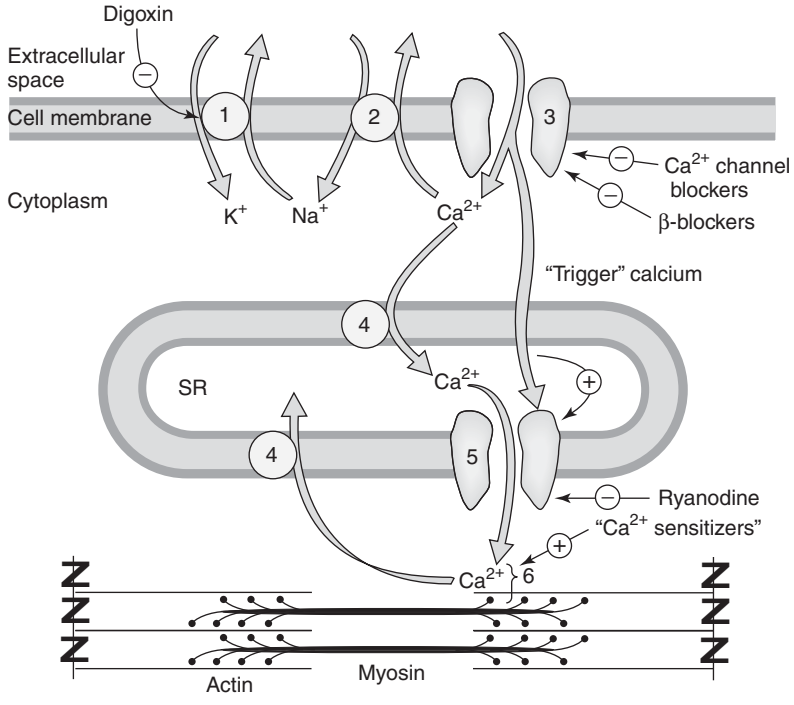
Lipid-lowering agents

Drug	Effect on LDL "bad cholesterol"	Effect on HDL "good cholesterol"	Effect on triglycerides	Mechanisms of action	Side effects/problems
HMG-CoA reductase inhibitors (lovastatin, pravastatin, simvastatin, atorvastatin)	↓↓↓	↑	↓	Inhibit cholesterol precursor, mevalonate	Expensive, reversible ↑ LFTs, myositis
Niacin	↓↓	↑↑	↓	Inhibits lipolysis in adipose tissue; reduces hepatic VLDL secretion into circulation	Red, flushed face, which is ↓ by aspirin or long-term use
Bile acid resins (cholestyramine, colestipol)	↓↓	Slightly ↑	Slightly ↑	Prevent intestinal reabsorption of bile acids; liver must use cholesterol to make more	Patients hate it—tastes bad and causes GI discomfort, ↓ absorption of fat-soluble vitamins
Cholesterol absorption blockers (ezetimibe)	↓↓	—	—	Prevent cholesterol reabsorption at small intestine brush border	Rare ↑ LFTs
"Fibrates" (gemfibrozil, clofibrate, bezafibrate, fenofibrate)	↓	↑	↓↓↓	Upregulate LPL → ↑ TG clearance	Myositis, ↑ LFTs



(Adapted, with permission, from Katzung BG, Trevor AJ. *USMLE Road Map: Pharmacology*, 1st ed. New York: McGraw-Hill, 2003: 56.)

Cardiac drugs: sites of action



(Adapted, with permission, from Katzung BG. *Basic and Clinical Pharmacology,* 7th ed. Stamford, CT: Appleton & Lange, 1997: 198.)

Cardiac sarcomere is shown above with the cellular components involved in excitation-contraction coupling. Factors involved in excitation-contraction coupling are numbered. (1) Na^+/K^+ ATPase; (2) Na^+-Ca^{2+} exchanger; (3) voltage-gated calcium channel; (4) calcium pump in the wall of the sarcoplasmic reticulum (SR); (5) calcium release channel in the SR; (6) site of calcium interaction with troponin-tropomyosin system.

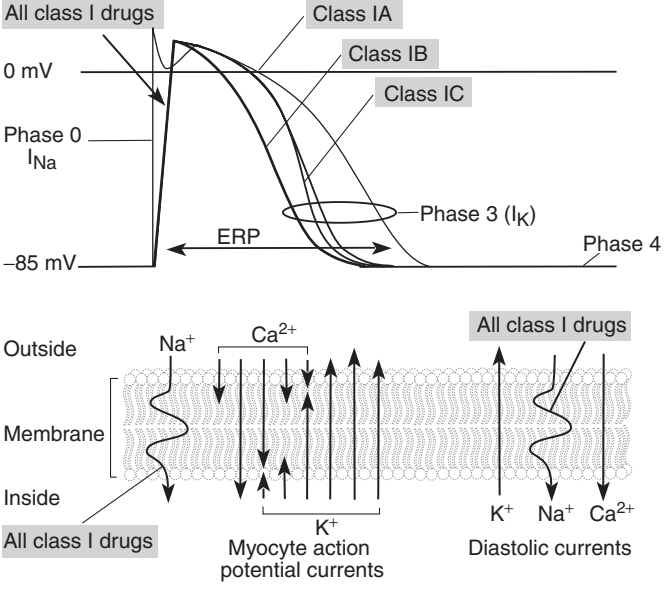
Cardiac glycosides	Digoxin—75% bioavailability, 20–40% protein bound, $t_{1/2}$ = 40 hours, urinary excretion.
Mechanism	Direct inhibition of Na^+/K^+ ATPase leads to indirect inhibition of Na^+/Ca^{2+} exchanger/antiport. ↑ $[Ca^{2+}]_i$ → positive inotropy.
Clinical use	CHF (↑ contractility); atrial fibrillation (↓ conduction at AV node and depression of SA node).
Toxicity	May cause ↑ PR, ↓ QT, scooping of ST segment, T-wave inversion of ECG. Also ↑ parasympathetic activity: nausea, vomiting, diarrhea, blurry yellow vision (think Van Gogh). Arrhythmia. Toxicities of digoxin are ↑ by renal failure (↓ excretion), hypokalemia (potentiates drug's effects), and quinidine (↓ digoxin clearance; displaces digoxin from tissue-binding sites).
Antidote	Slowly normalize K^+, lidocaine, cardiac pacer, anti-dig Fab fragments, Mg^{2+}.

Antiarrhythmics—Na^+ channel blockers (class I)

Local anesthetics. Slow or block (↓) conduction (especially in depolarized cells). ↓ slope of phase 4 depolarization and ↑ threshold for firing in abnormal pacemaker cells. Are state dependent (selectively depress tissue that is frequently depolarized, e.g., fast tachycardia).

Class IA	**Q**uinidine, **A**miodarone, **P**rocainamide, **D**iso**pyramid**e. ↑ AP duration, ↑ effective refractory period (ERP), ↑ QT interval. Affect both atrial and ventricular arrhythmias, especially reentrant and ectopic supraventricular and ventricular tachycardia. Toxicity: quinidine (cinchonism—headache, tinnitus; thrombocytopenia; torsades de pointes due to ↑ QT interval); procainamide (reversible SLE-like syndrome).	"**Q**ueen **A**my **P**roclaims **D**iso's **pyramid**."
Class **IB**	**Lid**ocaine, **Mexi**letine, **T**ocainide. ↓ AP duration. Affect ischemic or depolarized Purkinje and ventricular tissue. Useful in acute ventricular arrhythmias (especially post-MI) and in digitalis-induced arrhythmias. Toxicity: local anesthetic. CNS stimulation/depression, cardiovascular depression.	"**T**'d **B**uy **Lid**y's **Mexi**can **T**acos." Phenytoin can also fall into the IB category.
Class IC	Flecainide, encainide, propafenone. No effect on AP duration. Useful in V-tachs that progress to VF and in intractable SVT. Usually used only as last resort in refractory tachyarrhythmias. Toxicity: proarrhythmic, especially post-MI (contraindicated). Significantly prolongs refractory period in AV node.	

Hyperkalemia ↑ toxicity for all class I drugs.



(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review,* 5th ed. Stamford, CT: Appleton & Lange, 1998: 118.)

Antiarrhythmics—β-blockers (class II)

Propranolol, esmolol, metoprolol, atenolol, timolol.

Mechanism: ↓ cAMP, ↓ Ca^{2+} currents. Suppress abnormal pacemakers by ↓ slope of phase 4. AV node particularly sensitive—↑ PR interval. Esmolol very short acting.

Clinical use: V-tach, SVT, slowing ventricular rate during atrial fibrillation and atrial flutter.

Toxicity: Impotence, exacerbation of asthma, cardiovascular effects (bradycardia, AV block, CHF), CNS effects (sedation, sleep alterations). May mask the signs of hypoglycemia. Metoprolol can cause dyslipidemia.

Antiarrhythmics—K^+ channel blockers (class III)

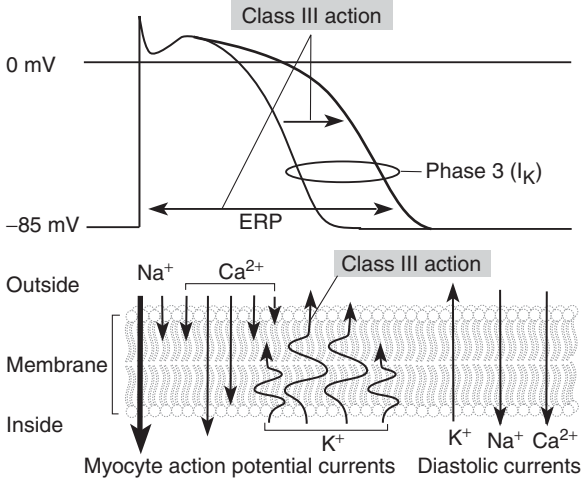
Sotalol, ibutilide, bretylium, amiodarone.

Mechanism: ↑ AP duration, ↑ ERP. Used when other antiarrhythmics fail. ↑ QT interval.

Toxicity: Sotalol—torsades de pointes, excessive β block; ibutilide—torsades; bretylium—new arrhythmias, hypotension; amiodarone—**pulmonary fibrosis,** corneal deposits, **hepatotoxicity,** skin deposits resulting in photodermatitis, neurologic effects, constipation, cardiovascular effects (bradycardia, heart block, CHF), **hypothyroidism/ hyperthyroidism.**

Remember to check **PFT**s, **LFT**s, and **TFT**s when using amiodarone.

Amiodarone is safe to use in Wolff-Parkinson-White syndrome.



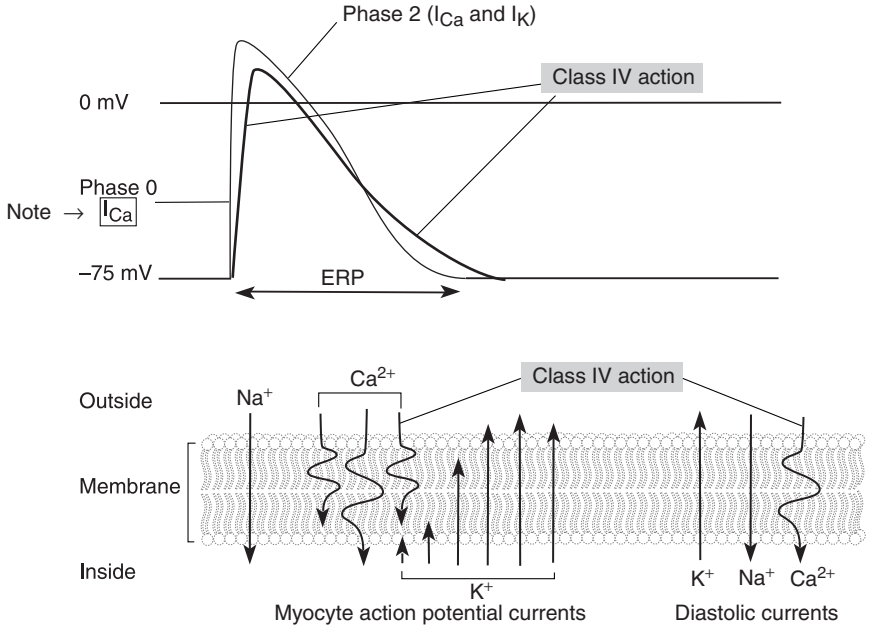
(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review,* 5th ed. Stamford, CT: Appleton & Lange, 1998: 120.)

Antiarrhythmics–Ca^{2+} channel blockers (class IV)

Verapamil, diltiazem.

Mechanism: Primarily affect AV nodal cells. ↓ conduction velocity, ↑ ERP, ↑ PR interval. Used in prevention of nodal arrhythmias (e.g., SVT).

Toxicity: Constipation, flushing, edema, CV effects (CHF, AV block, sinus node depression); torsades de pointes (bepridil).



(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review,* 5th ed. Stamford, CT: Appleton & Lange, 1998: 121.)

Other antiarrhythmics

Adenosine: ↑ K^+ out of cells → hyperpolarizing the cell. Drug of choice in diagnosing/abolishing AV nodal arrhythmias. Very short acting (~ 15 sec). Toxicity includes flushing, hypotension, chest pain.

K^+: Depresses ectopic pacemakers in hypokalemia (e.g., digoxin toxicity).

Mg^{2+}: Effective in torsades de pointes and digoxin toxicity.

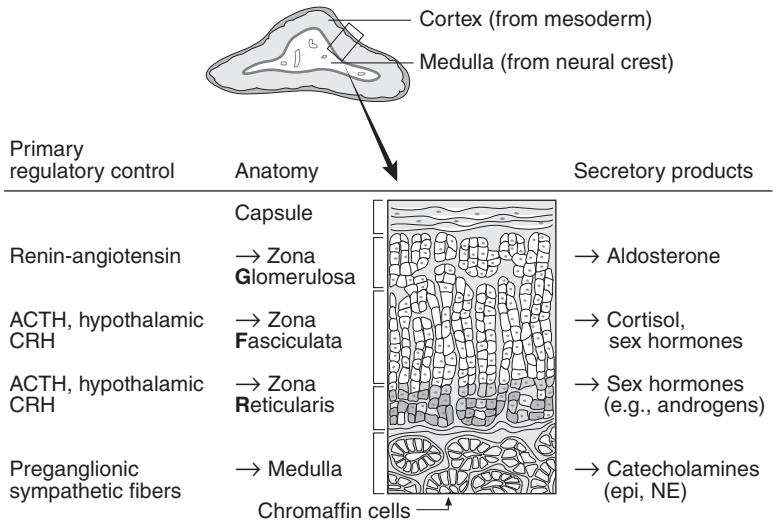
Endocrine

"Chocolate causes certain endocrine glands to secrete hormones that affect your feelings and behavior by making you happy."
—Elaine Sherman, *Book of Divine Indulgences*

- High-Yield Clinical Vignettes
- Anatomy
- Physiology
- Pathology
- Pharmacology

■ Woman presents with diffuse goiter and hyperthyroidism.	What are the expected values of TSH and thyroid hormones?	Low TSH and high thyroid hormones.
■ 48-year-old woman presents with progressive lethargy and extreme sensitivity to cold temperatures.	What is the diagnosis?	Hypothyroidism.
■ Patient with elevated serum cortisol levels undergoes a dexamethasone suppression test. 1 mg of dexamethasone does not ↓ cortisol levels, but 8 mg does.	What is the diagnosis?	Pituitary tumor.
■ 50-year-old man complains of diarrhea. On physical exam, his face is plethoric and a heart murmur is detected.	What is the diagnosis?	Carcinoid syndrome.
■ Woman of short stature presents with shortened 4th and 5th metacarpals.	What endocrine disorder comes to mind?	Albright's hereditary osteodystrophy, or pseudohypoparathyroidism.
■ Nondiabetic patient presents with hypoglycemia but low levels of C-peptide.	What is the diagnosis?	Surreptitious insulin injection.
■ Patient's MRI shows filling of sella turcica with cerebrospinal fluid.	What is the most likely clinical presentation?	Normal. Residual pituitary tissue is functional and can compensate (empty sella syndrome).
■ Patient complains of double vision, gynecomastia, and headaches.	What is the most likely diagnosis?	Prolactinoma.
■ Patient presents with hypotension and bronzed skin.	What is the most likely diagnosis?	1° adrenocortical deficiency (Addison's disease).

Adrenal cortex and medulla



GFR corresponds with **S**alt (Na^+), **S**ugar (glucocorticoids), and **S**ex (androgens).

"The deeper you go, the sweeter it gets."

Pheochromocytoma—most common tumor of the adrenal medulla in adults.

Neuroblastoma—most common in children.

Pheochromocytoma causes episodic hypertension; neuroblastoma does not.

Adrenal gland drainage

Left adrenal → left adrenal vein → left renal vein → IVC.

Right adrenal → right adrenal vein → IVC.

Same as left and right gonadal vein.

Pituitary gland

Posterior pituitary (neurohypophysis) → vasopressin and oxytocin, made in the hypothalamus and shipped to pituitary. Derived from neuroectoderm.

Anterior pituitary (adenohypophysis) → FSH, LH, ACTH, GH, TSH, melanotropin (MSH), prolactin. Derived from oral ectoderm.

α subunit—common subunit to TSH, LH, FSH, and hCG.

β subunit—determines hormone specificity.

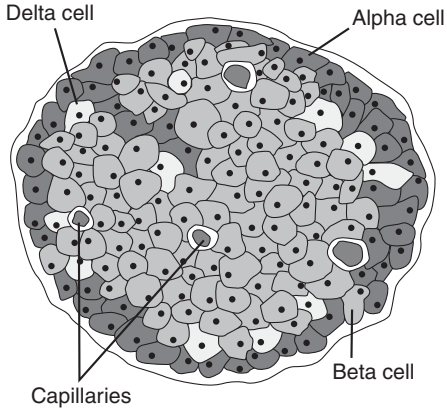
Acidophils—GH, prolactin.

B-Flat: **B**asophils—**F**SH, **L**H, **A**CTH, **T**SH.

FLAT PiG:
FSH
LH
ACTH
TSH
Prolact**i**n
GH

Endocrine pancreas cell types

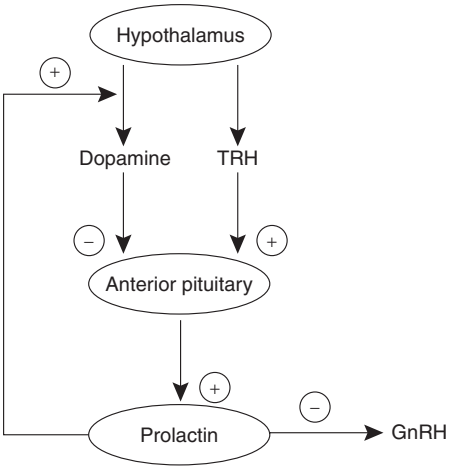
Islets of Langerhans are collections of α, β, and δ endocrine cells (most numerous in tail of pancreas). Islets arise from pancreatic buds. α = glucagon (peripheral); β = insulin (central); δ = somatostatin (interspersed).



Prolactin regulation

Prolactin ↑ dopamine synthesis and secretion from the hypothalamus. Dopamine subsequently **inhibits** prolactin secretion. Dopamine agonists (e.g., bromocriptine) therefore **inhibit** prolactin secretion, whereas dopamine antagonists (e.g., most antipsychotics) stimulate prolactin secretion. In females, prolactin inhibits GnRH synthesis and release, which inhibits ovulation. Amenorrhea is commonly seen in prolactinomas.

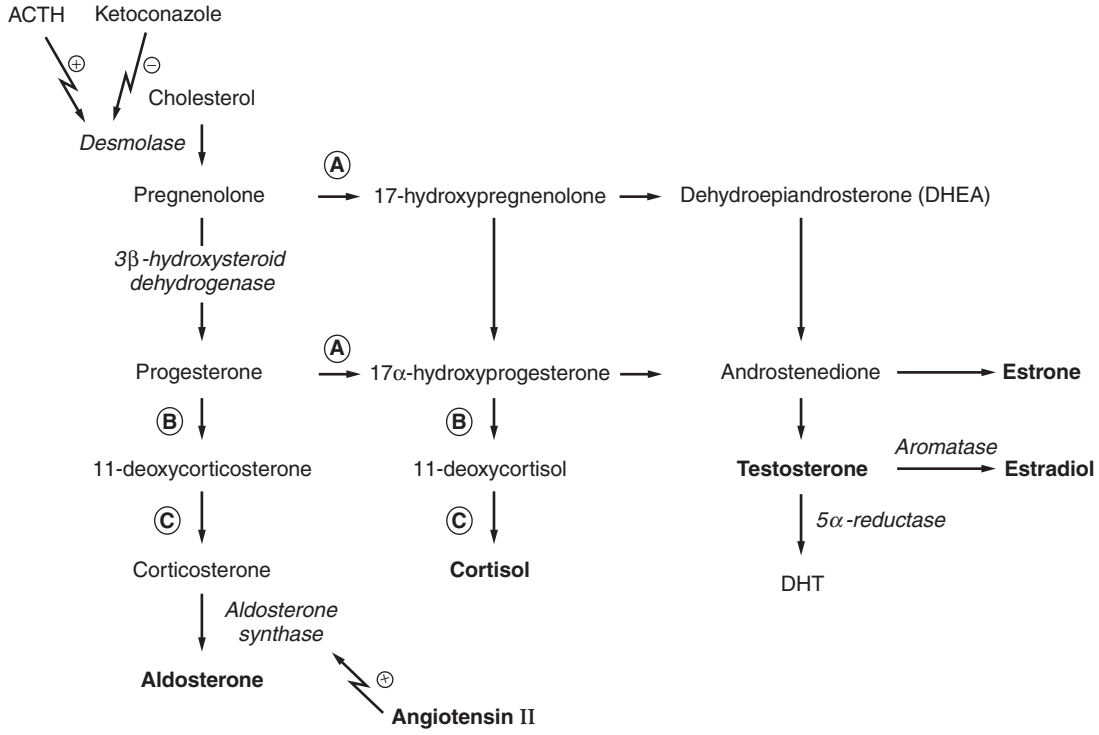
Prolactin regulation



Hypothalamic-pituitary hormone regulation

TRH—⊕ → TSH, prolactin.
Dopamine—⊖ → prolactin.
CRH—⊕ → ACTH.
GHRH—⊕ → GH.
Somatostatin—⊖ → GH, TSH.
GnRH—⊕ → FSH, LH.

Adrenal steroids



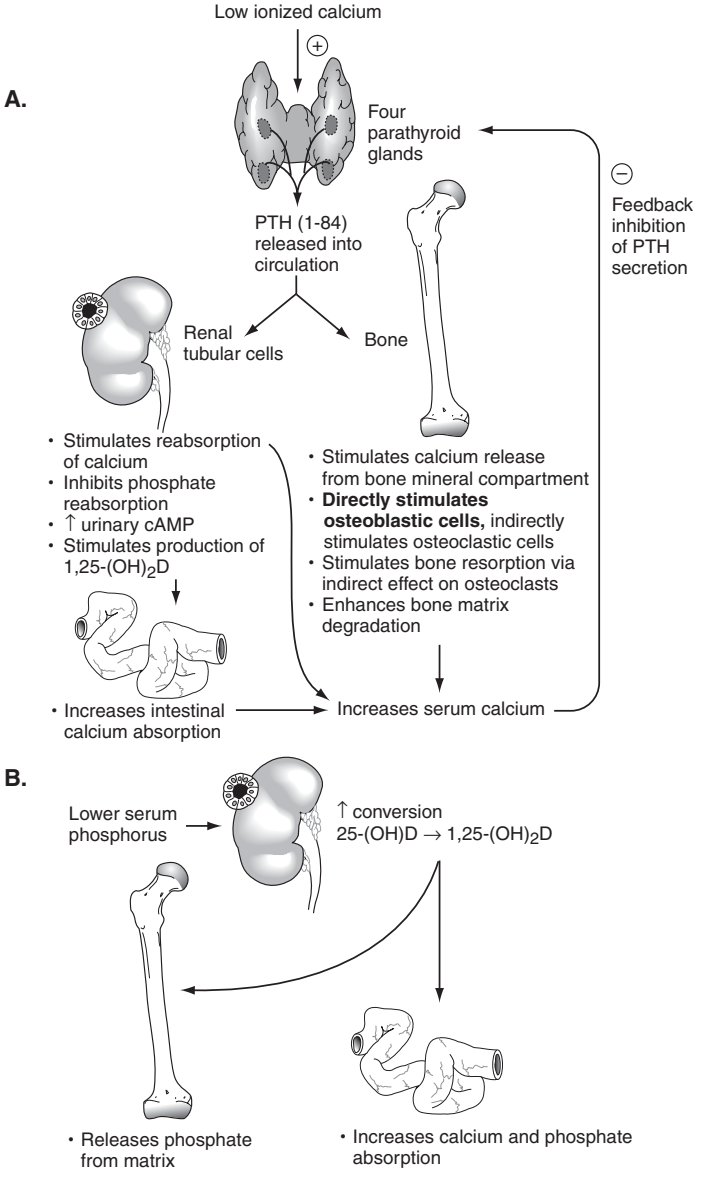
Congenital bilateral adrenal hyperplasias*

- **A** = **17α-hydroxylase deficiency.** ↓ sex hormones, ↓ cortisol, ↑ mineralocorticoids. Cx = **HYPER**tension, hypokalemia; phenotypically female but no maturation.
- **B** = **21α-hydroxylase deficiency.** Most common form. ↓ cortisol (increased ACTH), ↓ mineralocorticoids, ↑ sex hormones. Cx = masculinization, female pseudohermaphroditism, **HYPO**tension, hyperkalemia, ↑ plasma renin activity, and volume depletion. Salt wasting can lead to hypovolemic shock in the newborn.
- **C** = **11ß-hydroxylase deficiency.** ↓ cortisol, ↓ aldosterone and corticosterone, ↑ sex hormones. Cx = masculinization, **HYPER**tension (11-deoxycorticosterone is a mineralocorticoid and is secreted in excess).

*All congenital adrenal enzyme deficiencies are characterized by an enlargement of the adrenal glands due to an ↑ in ACTH stimulation because of the ↓ levels of cortisol.

PTH

Source	Chief cells of parathyroid.	
Function	1. ↑ bone resorption of calcium and phosphate 2. ↑ kidney reabsorption of calcium in distal convoluted tubule 3. ↓ kidney reabsorption of phosphate 4. ↑ 1,25-$(OH)_2$ vitamin D (calcitrol) production by stimulating kidney 1α-hydroxylase	PTH ↑ serum Ca^{2+}, ↓ serum $(PO_4)^{3-}$, ↑ urine $(PO_4)^{3-}$. PTH stimulates both osteoclasts and osteoblasts. **PTH** = **P**hosphate **T**rashing **H**ormone.
Regulation	↓ in free serum Ca^{2+} ↑ PTH secretion.	



(Adapted, with permission, from Chandrasoma P et al. *Concise Pathology,* 3rd ed. Stamford, CT: Appleton & Lange, 1998.)

Shown above are the main actions of PTH and 1,25-$(OH)_2$D in the maintenance of calcium (**A**) and phosphate (**B**) homeostasis.

Vitamin D

Source	Vitamin D_3 from sun exposure in skin. D_2 ingested from plants. Both converted to 25-OH vitamin D in liver and to 1,25-$(OH)_2$ vitamin D (active form) in kidney.	If you do not get vitamin D, you get rickets (kids) or osteomalacia (adults). 24,25-$(OH)_2$ vitamin D is an inactive form of vitamin D.
Function	1. ↑ absorption of dietary calcium 2. ↑ absorption of dietary phosphate 3. ↑ bone resorption of Ca^{2+} and $(PO_4)^{3-}$	
Regulation	↑ PTH causes ↑ 1,25-$(OH)_2$ vitamin D production. ↓ $[Ca^{2+}]$ ↑ 1,25-$(OH)_2$ vitamin D production. ↓ phosphate causes ↑ 1,25-$(OH)_2$ vitamin D production. 1,25-$(OH)_2$ vitamin D feedback inhibits its own production.	

Calcium, phosphate, and alkaline phosphatase levels

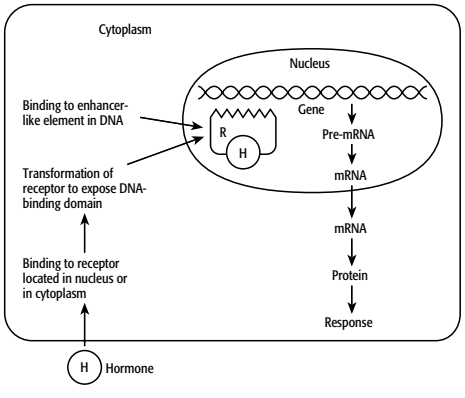
	Ca^{2+}	Phosphate	Alkaline phosphatase	PTH
Hyperparathyroidism	↑	↓	↑	↑
Paget's disease of bone	N/↑	N	↑↑↑	N
Vitamin D intoxication	↑	↑	N/↑	↓
Osteomalacia	↓	↓	↑	↑
Osteoporosis	N	N	N	N
Renal insufficiency	↓	↑	N	↑

N = no change.

Calcitonin

Source	Parafollicular cells (C cells) of thyroid.	Calcitonin opposes actions of PTH. It is probably not important in normal calcium homeostasis.
Function	↓ bone resorption of calcium.	
Regulation	↑ serum Ca^{2+} causes calcitonin secretion.	

Steroid/thyroid hormone mechanism



(Adapted, with permission, from Ganong WF. *Review of Medical Physiology,* 22th ed. New York: McGraw-Hill, 2005.)

The need for gene transcription and protein synthesis delays the onset of action of these hormones.

Steroid/thyroid hormones—
PET CAT:
Progesterone
Estrogen
Testosterone
Cortisol
Aldosterone
Thyroxine and T_3

Steroid hormones are lipophilic and relatively insoluble in plasma; therefore, they must circulate bound to specific binding globulins, which ↑ solubility and allows for ↑ delivery of steroid to the target organ. ↑ levels of sex hormone–binding globulin (SHBG) lower free testosterone → gynecomastia. ↓ SHBG raises free testosterone → hirsutism.

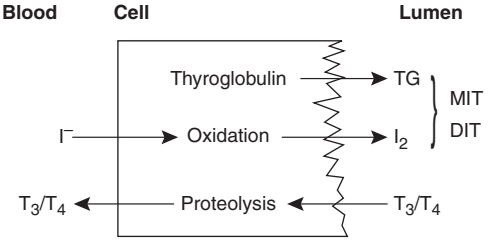
Thyroid hormones (T_3/T_4)

Iodine-containing hormones that control the body's metabolic rate.

Source: Follicles of thyroid. Most T_3 formed in blood.

Function:
1. Bone growth (synergism with GH)
2. CNS maturation
3. β-adrenergic effects (↑ CO, HR, SV, contractility)
4. ↑ basal metabolic rate via ↑ Na^+/K^+-ATPase activity = ↑ O_2 consumption, RR, ↑ body temperature
5. ↑ glycogenolysis, gluconeogenesis, lipolysis

Regulation: TRH (hypothalamus) stimulates TSH (pituitary), which stimulates follicular cells. Negative feedback by free T_3 to anterior pituitary ↓ sensitivity to TRH. TSI, like TSH, stimulates follicular cells (Graves' disease).



T_3 functions—**4 B**'s:
Brain maturation
Bone growth
Beta-adrenergic effects
BMR ↑

Thyroxine-binding globulin (TBG) binds most T_3/T_4 in blood; only free hormone is active. ↓ TBG in hepatic failure; ↑ TBG in pregnancy (estrogen ↑ TBG).

T_4 is major product.

T_4 is converted to T_3 by peripheral tissue. T_3 binds receptors with greater affinity than T_4.

Insulin-dependent organs

Skeletal muscle and adipose tissue depend on insulin for ↑ glucose uptake (GLUT-4).

Brain and RBCs take up glucose independent of insulin levels (GLUT-1). Brain depends on glucose for metabolism under normal circumstances and uses ketone bodies in starvation. RBCs always depend on glucose.

Cortisol

Source: Adrenal fasciculata.

Function:
1. Anti-inflammatory
2. ↑ gluconeogenesis, lipolysis, proteolysis
3. ↓ immune function
4. Maintains blood pressure
5. ↓ bone formation

Regulation: CRH (hypothalamus) stimulates ACTH release (pituitary), causing cortisol production in adrenal fasciculata.

Bound to corticosteroid-binding globulin (CBG).

Chronic stress induces prolonged secretion.

Signaling pathways of endocrine hormones

cAMP	cGMP	IP_3	Steroid receptor	Tyrosine kinase
ACTH	ANP	GnRH	Glucocorticoid	Insulin
LH	EDRF	TRH	Estrogen	IGF-1
FSH	NO	GHRH	Progesterone	FGF
TSH		ADH (V1)	Testosterone	
ADH (V2)		Oxytocin	Aldosterone	
hCG			Vitamin D	
MSH			T_3/T_4	
CRH				
PTH				
Calcitonin				
Glucagon				

► ENDOCRINE—PATHOLOGY

Cushing's syndrome

↑ cortisol due to a variety of causes.

Etiologies include:

1. Cushing's disease (1° pituitary adenoma); ↑ ACTH
2. 1° adrenal (hyperplasia/neoplasia); ↓ ACTH (see Color Image 68)
3. Ectopic ACTH production (e.g., small cell lung cancer); ↑ ACTH
4. Iatrogenic (e.g., chronic steroids); ↓ ACTH

The clinical picture includes hypertension, weight gain, moon facies, truncal obesity, buffalo hump, hyperglycemia (insulin resistance), skin changes (thinning, striae), osteoporosis, amenorrhea, and immune suppression (see Color Image 70).

Dexamethasone suppression test:

- Healthy—↓ cortisol after low dose.
- ACTH-producing pituitary tumor—↑ cortisol after low dose; ↓ cortisol after high dose.
- Ectopic ACTH-producing tumor (e.g., small cell carcinoma)—↑ cortisol after low dose; ↑ cortisol after high dose.
- Cortisol-producing tumor—↑ cortisol after low and high dose.

Hyperaldosteronism

Primary (Conn's syndrome): Caused by an aldosterone-secreting tumor, resulting in hypertension, hypokalemia, metabolic alkalosis, and **low** plasma renin. Treatment includes spironolactone, a K^+-sparing diuretic that works by acting as an aldosterone antagonist.

Secondary: Due to renal artery stenosis, chronic renal failure, CHF, cirrhosis, or nephrotic syndrome. Kidney perception of low intravascular volume results in an overactive renin-angiotensin system. Therefore, it is associated with **high** plasma renin.

Addison's disease

1° deficiency of aldosterone and cortisol due to adrenal atrophy or destruction by disease, causing hypotension (hyponatremic volume contraction) and skin hyperpigmentation (due to MSH, a by-product of ↑ ACTH production from POMC). Characterized by **A**drenal **A**trophy and **A**bsence of hormone production; involves **A**ll 3 cortical divisions. Distinguish from 2° insufficiency, which has no skin hyperpigmentation (↓ pituitary ACTH production).

Waterhouse-Friderichsen syndrome — Acute adrenocortical insufficiency; adrenal hemorrhage syndrome associated with meningococcal septicemia.

Tumors of the adrenal medulla

Pheochromocytoma	The most common tumor of the adrenal medulla in adults. Derived from chromaffin cells (arise from neural crest) (see Color Image 69). VMA in urine.	Pheochromocytomas may be associated with neurofibromatosis, MEN types II and III.
Neuroblastoma	The most common tumor of the adrenal medulla in children, but it can occur anywhere along the sympathetic chain. HVA in urine. Less likely to develop hypertension. N-*myc* oncogene.	

Sheehan's syndrome — Postpartum hypopituitarism. Caused by infarction of the pituitary gland following severe bleeding and hypoperfusion during delivery. May cause fatigue, anorexia, poor lactation, and loss of pubic and axillary hair.

Pheochromocytoma

Most of these tumors secrete epinephrine, NE, and dopamine. Urinary VMA levels and plasma catecholamines are elevated. Associated with MEN types II and III. Treated with α-antagonists, especially **phenoxybenzamine,** a nonselective, **irreversible** α-blocker.

Episodic hyperadrenergic symptoms **(5 P's):**
- **P**ressure (elevated blood pressure)
- **P**ain (headache)
- **P**erspiration
- **P**alpitations (tachycardia)
- **P**allor

Rule of 10's:
- **10%** malignant
- **10%** bilateral
- **10%** extra-adrenal
- **10%** calcify
- **10%** kids
- **10%** familial

Symptoms occur in "spells"—relapse and remit.

Multiple endocrine neoplasias (MEN)

MEN type I (Wermer's syndrome)—pancreas (e.g., Zollinger-Ellison syndrome, insulinomas, VIPomas), parathyroid, and pituitary tumors (prolactinoma). Presents with kidney stones and stomach ulcers.

MEN type II (Sipple's syndrome)—medullary carcinoma of the thyroid, pheochromocytoma, parathyroid tumor.

MEN type III (formerly MEN IIb)—medullary carcinoma of the thyroid, pheochromocytoma, and oral and intestinal ganglioneuromatosis (mucosal neuromas).

MEN I = **3 P's** (**P**ancreas, **P**ituitary, and **P**arathyroid).

MEN II = **2 P's** (**P**heochromocytoma and **P**arathyroid).

MEN III = **1 P** (**P**heochromocytoma).

All MEN syndromes have autosomal-dominant inheritance.

Associated with *ret* gene in MEN types II and III.

Hypothyroidism and hyperthyroidism

Hypothyroidism	Cold intolerance, hypoactivity, weight gain, fatigue, lethargy, ↓ appetite, constipation, weakness, ↓ reflexes, myxedema (facial/periorbital), dry, cool skin, and coarse, brittle hair.	↑ TSH (sensitive test for 1° hypothyroidism), ↓ total T_4, ↓ free T_4, ↓ T_3 uptake. **Riedel's thyroiditis**—thyroid replaced by fibrous tissue (hypothyroid).
Hyperthyroidism	Heat intolerance, hyperactivity, weight loss, chest pain/palpitations, arrhythmias, diarrhea, ↑ reflexes, warm, moist skin, and fine hair.	↓ TSH (if 1°), ↑ total T_4, ↑ free T_4, ↑ T_3 uptake.
Graves' disease	An autoimmune hyperthyroidism with thyroid-stimulating/TSH receptor antibodies. Ophthalmopathy (proptosis, EOM swelling), pretibial myxedema, diffuse goiter (see Image 120). Often presents during stress (e.g., childbirth) (see Color Image 71).	Graves' is a type II hypersensitivity.
Thyroid storm	Underlying Graves' disease with a stress-induced catecholamine surge leading to death by arrhythmia.	

Hashimoto's thyroiditis

Autoimmune disorder resulting in hypothyroidism (can have thyrotoxicosis during follicular rupture). Slow course; moderately enlarged, nontender thyroid. Lymphocytic infiltrate with germinal centers. Antimicrosomal and antithyroglobulin antibodies. Associated with Hürthle cells on histology.

Subacute thyroiditis (de Quervain's)

Self-limited hypothyroidism often following a flulike illness. Elevated ESR, jaw pain, early inflammation, and very tender thyroid gland. Histology shows granulomatous inflammation.

May be hyperthyroid early in course.
Lymphocytic subacute thyroiditis is painless.

Toxic multinodular goiter

Iodine deprivation followed by iodine restoration. Causes release of T_3 and T_4. Nodules are not malignant.
Jod-Basedow phenomenon—thyrotoxicosis if a patient with endemic goiter moves to iodine-replete area.

Thyroid cancer

1. Papillary carcinoma—most common, excellent prognosis, "ground-glass" nuclei (Orphan Annie), psammoma bodies. ↑ risk with childhood irradiation.
2. Follicular carcinoma—good prognosis, uniform follicles.
3. Medullary carcinoma—from parafollicular "C cells"; produces calcitonin, sheets of cells in amyloid stroma. MEN types II and III.
4. Undifferentiated/anaplastic—older patients; very poor prognosis.
5. Lymphoma—associated with Hashimoto's thyroiditis.

Cretinism

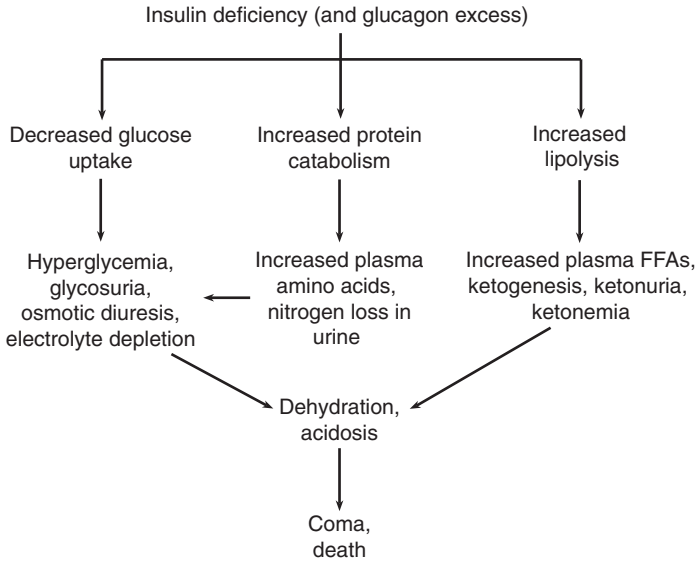
Endemic cretinism occurs wherever endemic goiter is prevalent (lack of dietary iodine); sporadic cretinism is caused by defect in T_4 formation or developmental failure in thyroid formation.
Findings: pot-bellied, pale, puffy-faced child with protruding umbilicus and protuberant tongue.

Cretin means Christlike (French *chrétien*). Those affected were considered so mentally retarded as to be incapable of sinning. Still common in China.

Acromegaly	Excess GH in adults. Findings: large tongue with deep furrows, deep voice, large hands and feet, coarse facial features, impaired glucose tolerance (insulin resistance). ↑ GH in children → gigantism. Treat medically with octreotide.	↑ GH is normal in stress, exercise, and hypoglycemia. Test with oral glucose tolerance test.
Hyperparathyroidism		
Primary	Usually an adenoma. Hypercalcemia, hypercalciuria **(renal stones),** hypophosphatemia, ↑ PTH, ↑ alkaline phosphatase, ↑ cAMP in urine. Often asymptomatic, or may present with weakness and constipation (“**groans**”**).**	“**Stones, bones, and groans.**” **Osteitis fibrosa cystica** (von Recklinghausen’s syndrome)—cystic bone spaces filled with brown fibrous tissue **(bone pain).**
Secondary	2° hyperplasia due to ↓ serum Ca^{2+}, most often in chronic renal disease. Hypocalcemia, hyperphosphatemia, ↑ alkaline phosphatase,↑ PTH.	**Renal osteodystrophy—**bone lesions due to 2° hyperparathyroidism due in turn to renal disease.
Hypoparathyroidism	Hypocalcemia, tetany. Due to accidental surgical excision (thyroid surgery), autoimmune destruction or DiGeorge syndrome. Chvostek’s sign—tap facial nerve → contraction of facial muscles. Trousseau’s sign—occlusion of brachial artery with BP cuff → carpal spasm.	**Pseudohypoparathyroidism—** autosomal-dominant kidney unresponsiveness to PTH. Hypocalcemia, shortened 4th/5th digits, short stature.
Hypercalcemia	Caused by **C**alcium ingestion (milk-alkali syndrome), **H**yperparathyroid, **H**yperthyroid, **I**atrogenic (thiazides), **M**ultiple myeloma, **P**aget’s disease, **A**ddison’s disease, **N**eoplasms, **Z**ollinger-Ellison syndrome, **E**xcess vitamin D, **E**xcess vitamin A, **S**arcoidosis.	**CHIMPANZEES.**
Pituitary adenoma	Most commonly prolactinoma—amenorrhea, galactorrhea, low libido, infertility. Bromocriptine (dopamine agonist) causes shrinkage. Can impinge on optic chiasm → bitemporal hemianopia.	

Diabetes mellitus

Acute manifestations Polydipsia, polyuria, polyphagia, weight loss, DKA (type 1), hyperosmolar coma (type 2), unopposed secretion of GH and epinephrine (exacerbating hyperglycemia).



Chronic manifestations

Nonenzymatic glycosylation:

1. Small vessel disease (diffuse thickening of basement membrane) → retinopathy (hemorrhage, exudates, microaneurysms, vessel proliferation), glaucoma, nephropathy (nodular sclerosis, progressive proteinuria, chronic renal failure, arteriosclerosis leading to hypertension, Kimmelstiel-Wilson nodules)
2. Large vessel atherosclerosis, CAD, peripheral vascular occlusive disease and gangrene, cerebrovascular disease

Osmotic damage:

1. Neuropathy (motor, sensory, and autonomic degeneration)
2. Cataracts (sorbitol accumulation)

Tests Fasting serum glucose, glucose tolerance test, HbA_{1c} (measures long-term diabetic control).

Type 1 vs. type 2 diabetes mellitus

Variable	Type 1—juvenile onset (IDDM)	Type 2—adult onset (NIDDM)
1° defect	Viral or immune destruction of β cells (see Color Image 67)	↑ resistance to insulin
Insulin necessary in treatment	Always	Sometimes
Age (exceptions commonly occur)	< 30	> 40
Association with obesity	No	Yes
Genetic predisposition	Weak, polygenic	Strong, polygenic
Association with HLA system	Yes (HLA-DR3 and 4)	No
Glucose intolerance	Severe	Mild to moderate
Ketoacidosis	Common	Rare
β-cell numbers in the islets	↓	Variable
Serum insulin level	↓	Variable
Classic symptoms of polyuria, polydipsia, thirst, weight loss	Common	Sometimes

Diabetic ketoacidosis

One of the most important complications of type 1 diabetes. Usually due to an ↑ in insulin requirements from an ↑ in stress (e.g., infection). Excess fat breakdown and ↑ ketogenesis from the ↑ in free fatty acids, which are then made into ketone bodies (β-hydroxybutyrate > acetoacetate).

Signs/symptoms	Kussmaul respirations (rapid/deep breathing), nausea/vomiting, abdominal pain, psychosis/delirium, dehydration. Fruity breath odor (due to exhaled acetone).
Labs	Hyperglycemia, ↑ H^+, ↓ HCO_3^- (anion gap metabolic acidosis), ↑ blood ketone levels, leukocytosis. Hyperkalemia, but depleted intracellular K^+ due to transcellular shift from ↓ insulin.
Complications	Life-threatening mucormycosis, *Rhizopus* infection, cerebral edema, cardiac arrhythmias, heart failure.
Treatment	Fluids, insulin, and potassium (to replete intracellular stores); glucose if necessary to prevent hypoglycemia.

Diabetes insipidus

Characterized by intense thirst and polyuria together with an inability to concentrate urine owing to lack of ADH (central DI—pituitary tumor, trauma, surgery, histiocytosis X) or to a lack of renal response to ADH (nephrogenic DI—hereditary or 2° to hypercalcemia, lithium, demeclocycline).

Diagnosis	Water deprivation test—urine osmolality doesn't ↑. Response to desmopressin distinguishes between central and nephrogenic.
Findings	Urine specific gravity < 1.006; serum osmolality > 290 mOsm/L.
Treatment	Adequate fluid intake. For central DI—intranasal desmopressin (ADH analog). For nephrogenic DI—hydrochlorothiazide, indomethacin, or amiloride.

SIADH

Syndrome of inappropriate antidiuretic hormone secretion:

1. Excessive water retention
2. Hyponatremia
3. Urine osmolarity > serum osmolarity

Very low serum sodium levels can lead to seizures (correct slowly).

Treat with demeclocycline or H_2O restriction.

Causes include:

1. Ectopic ADH (small cell lung cancer)
2. CNS disorders/head trauma
3. Pulmonary disease
4. Drugs (e.g., cyclophosphamide)

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,** and **right-sided valvular disease.** Most common tumor of appendix. ↑ 5-HIAA in urine.

Rule of 1/3s:

1/3 metastasize
1/3 present with 2nd malignancy
1/3 multiple

Derived from neuroendocrine cells of GI tract.

Treat with octreotide.

Zollinger-Ellison syndrome

Gastrin-secreting tumor of pancreas or duodenum. Causes recurrent ulcers. May be associated with MEN type I.

Diabetes drugs

Treatment strategy for type 1 DM—low-sugar diet, insulin replacement.
Treatment strategy for type 2 DM—dietary modification and exercise for weight loss; oral hypoglycemics.

Drug Classes	Action	Clinical Use	Toxicities
Insulin: Lispro (short-acting) Aspart (short-acting) NPH (intermediate) Lente (long-acting) Ultralente (long-acting)	**Bind insulin receptor** (tyrosine kinase activity). Liver: ↑ glucose stored as glycogen. Muscle: ↑ glycogen and protein synthesis, K^+ uptake. Fat: aids TG storage.	Type 1 DM. Also life-threatening hyperkalemia and stress-induced hyperglycemia.	Hypoglycemia, hypersensitivity reaction (very rare).
Sulfonylureas: First generation: Tolbutamide Chlorpropamide Second generation: Glyburide Glimepiride Glipizide	Close K^+ channel in β-cell membrane, so cell depolarizes → **triggering of insulin release** via ↑ Ca^{2+} influx.	Stimulate release of endogenous insulin in type 2 DM. Require some islet function, so useless in type 1 DM.	First generation: disulfiram-like effects. Second generation: hypoglycemia.
Biguanides: Metformin	Exact mechanism is unknown. Possibly ↓ **gluconeogenesis,** ↑ glycolysis, ↓ serum glucose levels.	Used as oral hypoglycemic. Can be used in patients without islet function.	Most grave adverse effect is lactic acidosis.
Glitazones: Pioglitazone Rosiglitazone	↑ target cell response to insulin.	Used as monotherapy in type 2 DM or combined with above agents.	Weight gain, edema. Hepatotoxicity, CV toxicity.
α-glucosidase inhibitors: Acarbose Miglitol	**Inhibit intestinal brush-border α-glucosidases.** Delayed sugar hydrolysis and glucose absorption lead to ↓ postprandial hyperglycemia.	Used as monotherapy in type 2 DM or in combination with above agents.	GI disturbances.

Orlistat

Mechanism	Alters fat metabolism by inhibiting pancreatic lipases.
Clinical use	Long-term obesity management (in conjunction with modified diet).
Toxicity	Steatorrhea, GI discomfort, reduced absorption of fat-soluble vitamins, headache.

Sibutramine

Mechanism	Sympathomimetic serotonin and norepinephrine reuptake inhibitor.
Clinical use	Short-term and long-term obesity management.
Toxicity	Hypertension and tachycardia.

Propylthiouracil, methimazole

Mechanism	Inhibit organification and coupling of thyroid hormone synthesis. Propylthiouracil also ↓ peripheral conversion of T_4 to T_3.
Clinical use	Hyperthyroidism.
Toxicity	Skin rash, agranulocytosis (rare), aplastic anemia.

Hypothalamic/pituitary drugs

Drug	Clinical use
GH	GH deficiency, Turner's syndrome
Somatostatin (octreotide)	Acromegaly, carcinoid, gastrinoma, glucagonoma
Oxytocin	Stimulates labor, uterine contractions, milk let-down; controls uterine hemorrhage
ADH (desmopressin)	Pituitary (central, not nephrogenic) DI

Levothyroxine, triiodothyronine

Mechanism	Thyroxine replacement.
Clinical use	Hypothyroidism, myxedema.
Toxicity	Tachycardia, heat intolerance, tremors, arrhythmias.

Glucocorticoids	Hydrocortisone, prednisone, triamcinolone, dexamethasone, beclomethasone.
Mechanism	↓ the production of leukotrienes and prostaglandins by inhibiting phospholipase A_2 and expression of COX-2.
Clinical use	Addison's disease, inflammation, immune suppression, asthma.
Toxicity	Iatrogenic Cushing's syndrome—buffalo hump, moon facies, truncal obesity, muscle wasting, thin skin, easy bruisability, osteoporosis, adrenocortical atrophy, peptic ulcers, diabetes (if chronic).

Gastrointestinal

"A good set of bowels is worth more to a man than any quantity of brains."
—Josh Billings

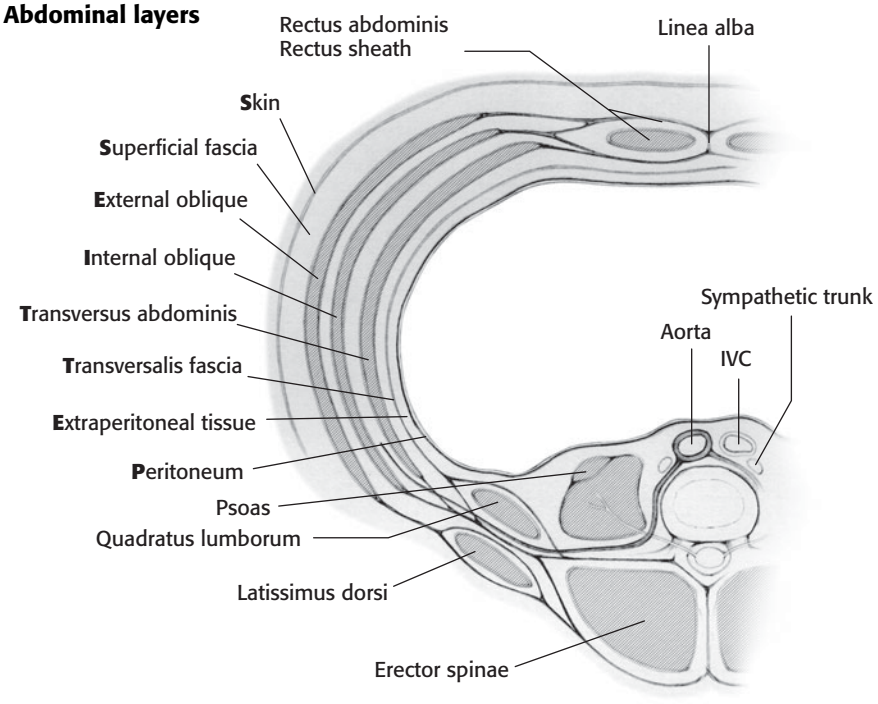
"Man should strive to have his intestines relaxed all the days of his life."
—Moses Maimonides

"The colon is the playing field for all human emotions."
—Cyrus Kapadia, MD

- High-Yield Clinical Vignettes
- Anatomy
- Physiology
- Pathology
- Pharmacology

■ Baby vomits milk when fed and has a gastric air bubble.	What kind of fistula is present?	Blind esophagus with lower segment of esophagus attached to the trachea.
■ After a stressful life event, 30-year-old man has diarrhea and blood per rectum; intestinal biopsy shows transmural inflammation.	What is the diagnosis?	Crohn's disease.
■ Young man presents with mental deterioration and tremors. He has brown pigmentation in a ring around the periphery of his cornea and altered LFTs.	What treatment should he receive?	Penicillamine for Wilson's disease.
■ 20-year-old man presents with idiopathic hyperbilirubinemia.	What is the most common cause?	Gilbert's syndrome.
■ 55-year-old man with chronic GERD presents with esophageal cancer.	What is the most likely histologic subtype?	Adenocarcinoma.
■ Woman presents with alternating bouts of painful diarrhea and constipation. Colonoscopy is normal.	What is the most likely diagnosis?	Irritable bowel syndrome.

Abdominal layers



Sally **S**truthers **E**ats **I**ndian **T**oddlers **T**o **E**nlarge **P**eritoneum.

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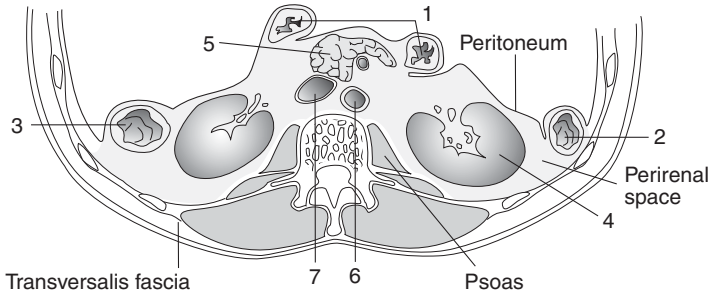
Retroperitoneal structures

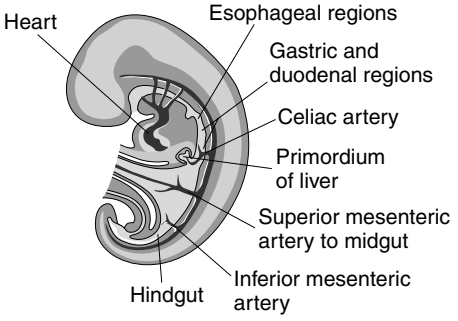


1. Duodenum (2nd, 3rd, 4th parts)
2. Descending colon
3. Ascending colon
4. Kidney and ureters
5. Pancreas (except tail)
6. Aorta
7. IVC

Adrenal glands and rectum (not shown in diagram)

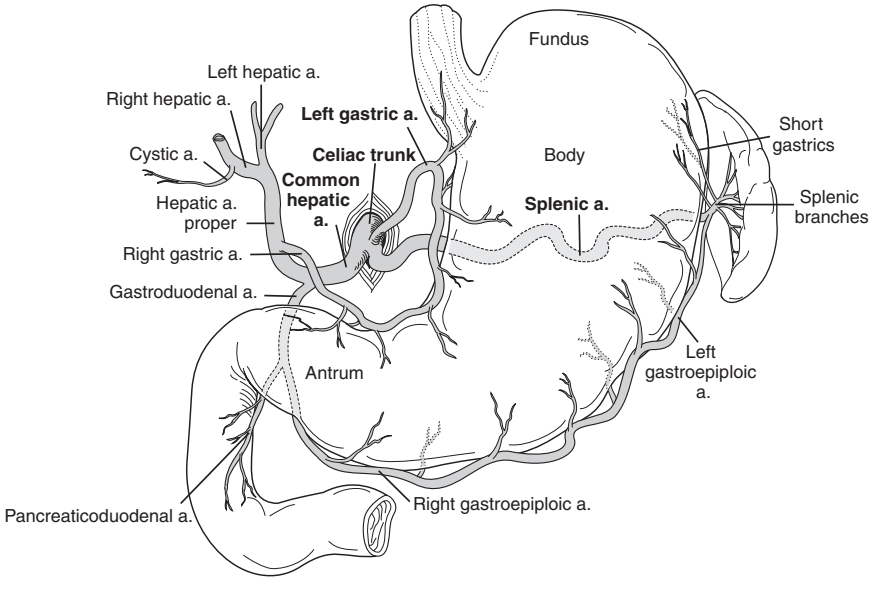
GI blood supply and innervation

Embryonic gut region	Artery	Parasympathetic innervation	Vertebral level	Structures supplied
Foregut	Celiac	Vagus	T12/L1	Stomach to proximal duodenum; liver, gallbladder, pancreas
Midgut	SMA	Vagus	L1	Distal duodenum to proximal 2/3 of transverse colon
Hindgut	IMA	Pelvic	L3	Distal 1/3 of transverse colon to upper portion of rectum; splenic flexure is a watershed region



Celiac trunk

Branches of celiac trunk: common hepatic, splenic, left gastric. These comprise 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

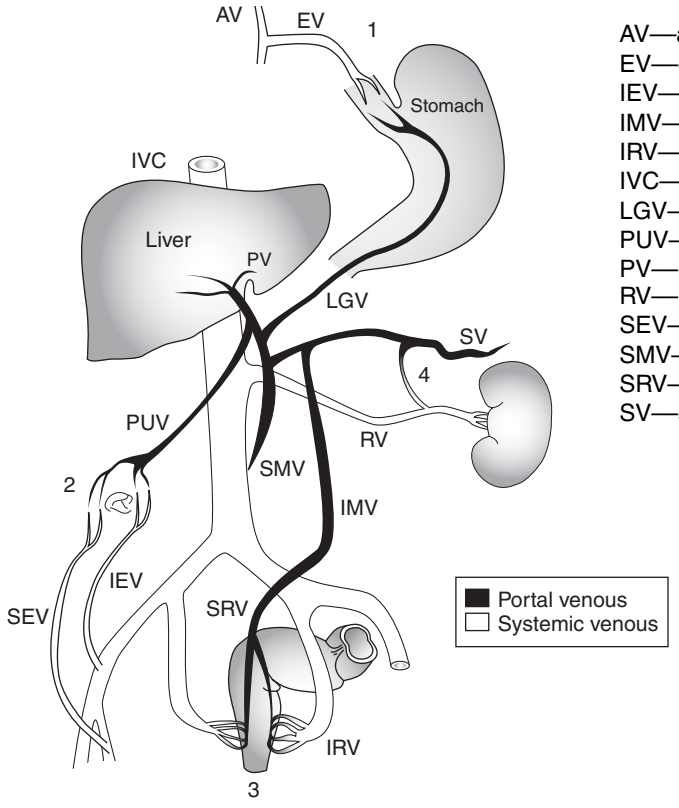
—Left and right gastrics

Collateral circulation

If the abdominal aorta is blocked, these arterial anastomoses (with origin) compensate:

1. Internal thoracic/mammary (subclavian) ↔ superior epigastric (internal thoracic) ↔ inferior epigastric (external iliac)
2. Superior pancreaticoduodenal (celiac trunk) ↔ inferior pancreaticoduodenal (SMA)
3. Middle colic (SMA) ↔ left colic (IMA)
4. Superior rectal (IMA) ↔ middle rectal (internal iliac)

Portosystemic anastomoses



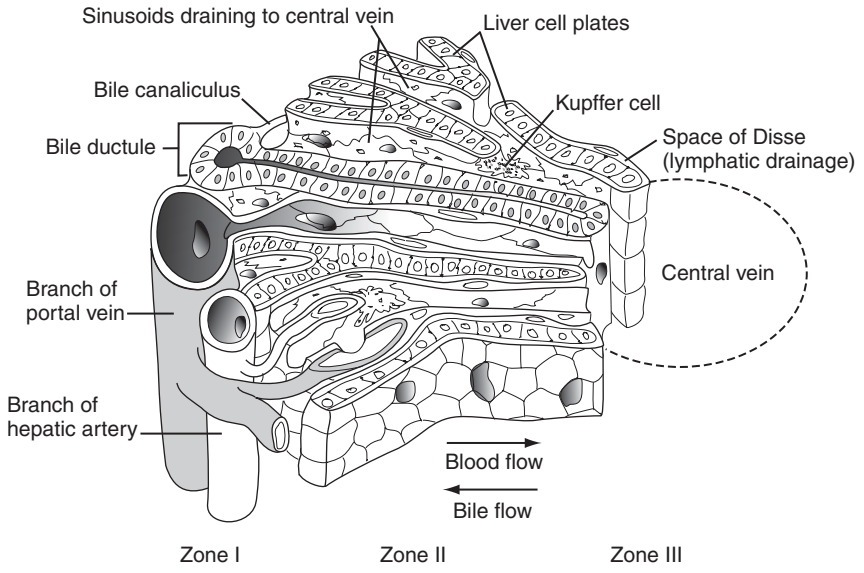
AV—azygous vein
EV—esophageal vein
IEV—inferior epigastric vein
IMV—inferior mesenteric vein
IRV—inferior rectal vein
IVC—inferior vena cava
LGV—left gastric vein
PUV—paraumbilical vein
PV—portal vein
RV—renal vein
SEV—superior epigastric vein
SMV—superior mesenteric vein
SRV—superior rectal vein
SV—splenic vein

Site of anastomosis	Clinical sign	Portal ↔ systemic
1. Esophagus	Esophageal varices	Left gastric ↔ esophageal
2. Umbilicus	Caput medusae	Paraumbilical ↔ superficial and inferior epigastric
3. Rectum	Hemorrhoids	Superior rectal ↔ middle and inferior rectal

Varices of **gut, butt,** and **caput** are commonly seen with portal hypertension.
Inserting a portocaval shunt (4) between the splenic and left renal veins relieves portal hypertension by shunting blood to the systemic circulation.

Liver anatomy

Apical surface of hepatocytes faces bile canaliculi. Basolateral surface faces sinusoids.

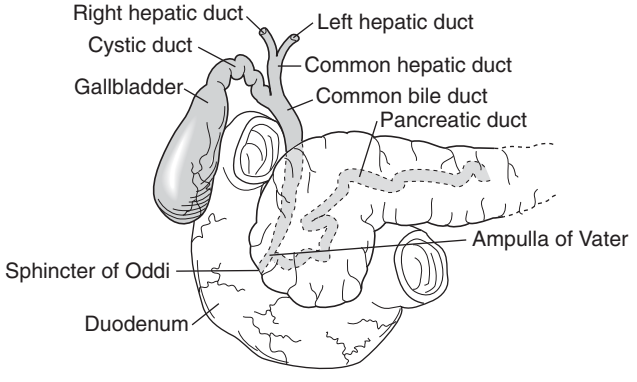


Zone I: periportal zone:
—Affected 1st by viral hepatitis
Zone II: intermediate zone.
Zone III: pericentral vein (centrilobular) zone:
—Contains P-450 system
—Affected 1st by ischemia
—Most sensitive to toxic injury
—Alcoholic hepatitis

Sinusoids of liver

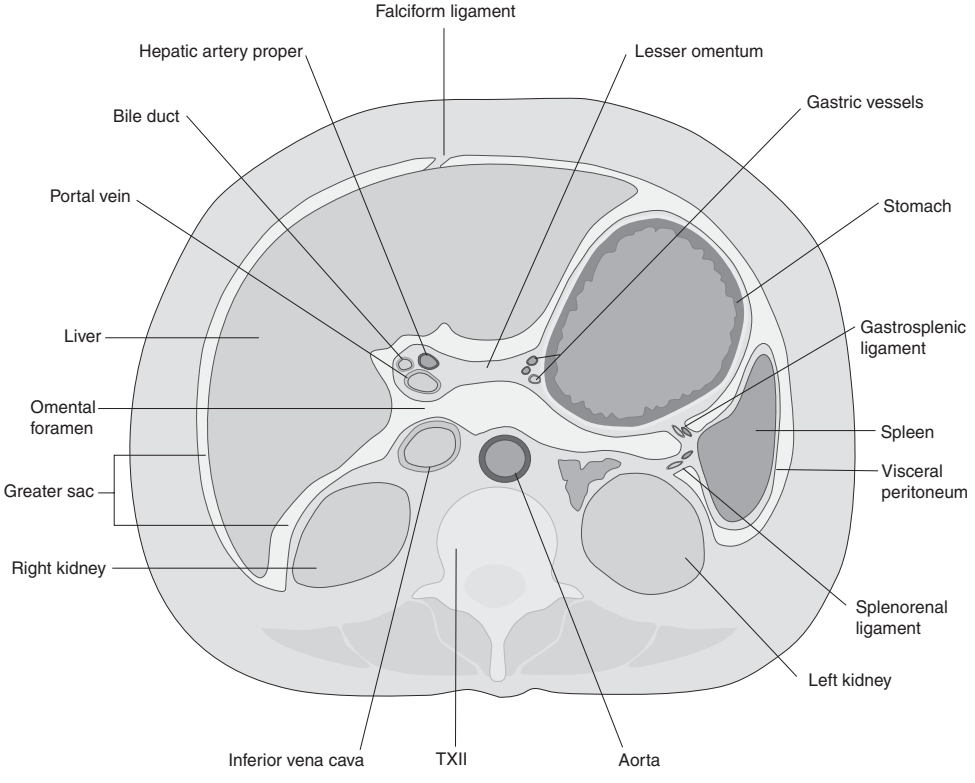
Irregular "capillaries" with fenestrated endothelium (pores 100–200 nm in diameter). No basement membrane. Allow macromolecules of plasma full access to basal surface of hepatocytes through perisinusoidal space (space of Disse).

Biliary structures



Important GI ligaments

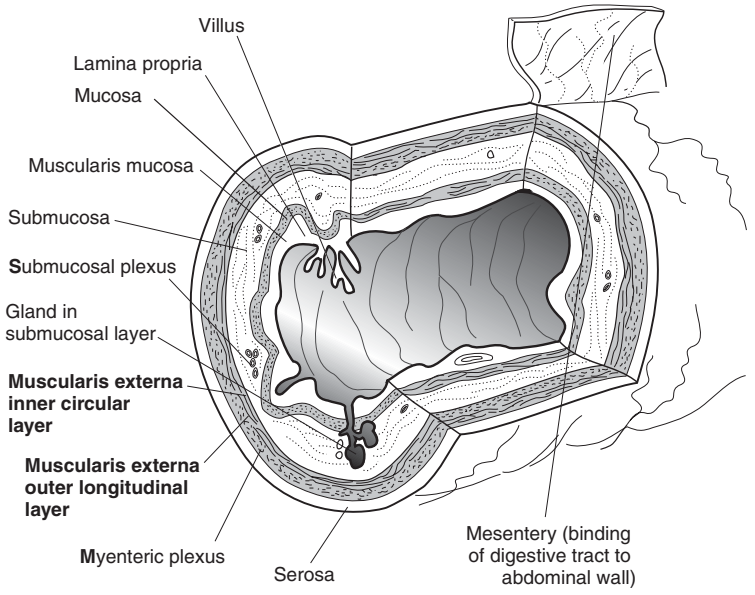
Ligament	Connects	Structures contained	Notes
Falciform	Liver to anterior abdominal wall	Ligamentum teres	Derivative of fetal umbilical vein
Hepatoduodenal	Liver to duodenum	Portal triad: hepatic artery, portal vein, common bile duct	May be compressed between thumb and index finger placed in epiploic foramen (of Winslow) to control bleeding Connects greater and lesser sacs
Gastrohepatic	Liver to lesser curvature of stomach	Gastric arteries	Separates right greater and lesser sacs May be cut during surgery to access lesser sac
Gastrocolic	Greater curvature and transverse colon	Gastroepiploic arteries	Part of greater omentum
Gastrosplenic	Greater curvature and spleen	Short gastrics	Separates left greater and lesser sacs
Splenorenal	Spleen to posterior abdominal wall	Splenic artery and vein	



Esophageal anatomy

Upper ⅓	Striated muscle.
Middle ⅓	Striated and smooth muscle.
Lower ⅓	Smooth muscle.

Digestive tract anatomy



(Adapted, with permission, from McPhee S et al. *Pathophysiology of Disease: An Introduction to Clinical Medicine,* 3rd ed. New York: McGraw-Hill, 2000: 296.)

Layers of gut wall (inside to outside):

1. **Mucosa**—epithelium (absorption), lamina propria (support), muscularis mucosa (motility)
2. **Submucosa**—includes **S**ubmucosal nerve plexus (Meissner's)
3. **Muscularis externa**—includes **M**yenteric nerve plexus (Auerbach's)
4. **Serosa/adventitia**

Frequencies of basal electric rhythm (slow waves):

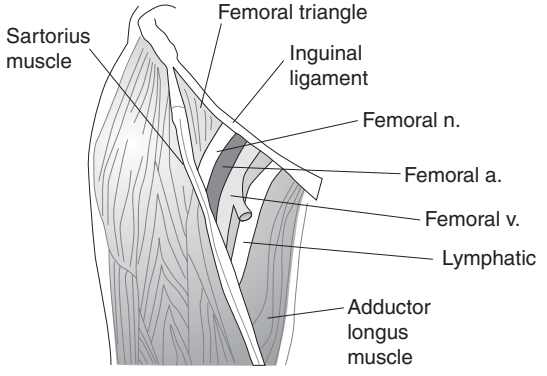
Stomach—3 waves/min
Duodenum—12 waves/min
Ileum—8–9 waves/min

Enteric nerve plexuses

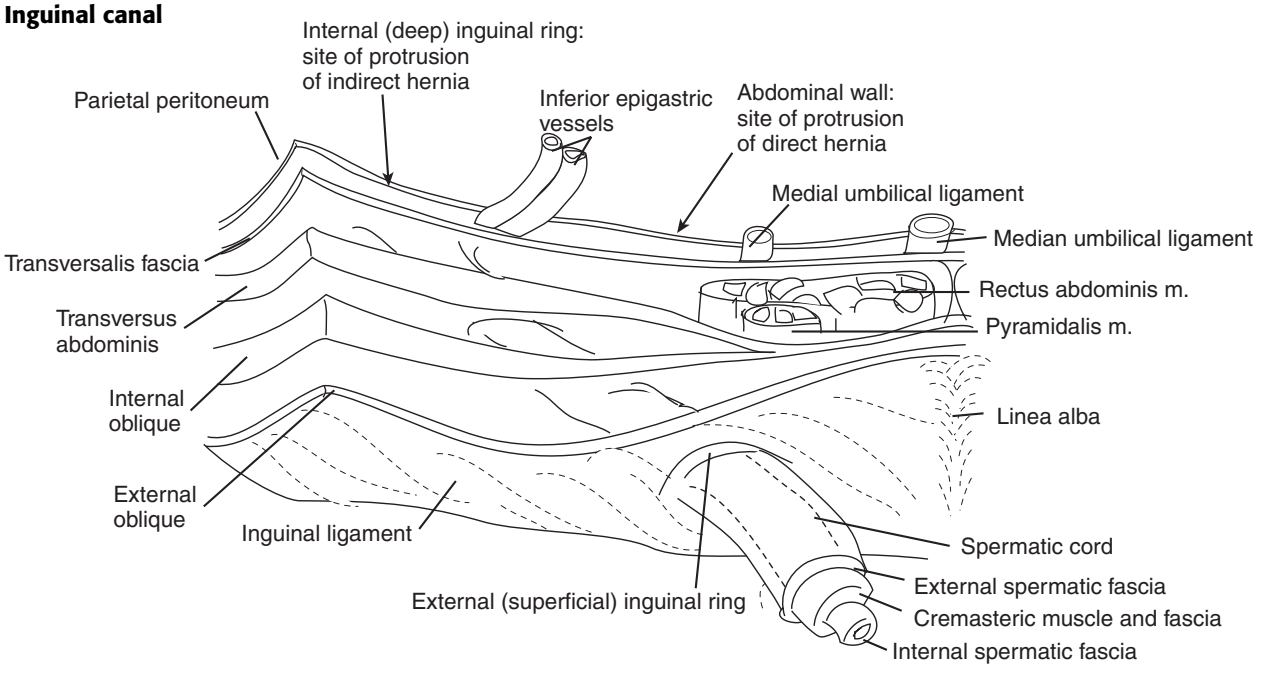
Myenteric (Auerbach's)	Coordinates **M**otility along entire gut wall. Contains cell bodies of some parasympathetic terminal effector neurons. Located between inner (circular) and outer (longitudinal) layers of smooth muscle in GI tract wall.
Submucosal (Meissner's)	Regulates local **S**ecretions, blood flow, and absorption. Contains cell bodies of some parasympathetic terminal effector neurons. Located between mucosa and inner layer of smooth muscle in GI tract wall.

Femoral region

Organization	Lateral to medial: **N**erve-**A**rtery-**V**ein-**E**mpty space-**L**ymphatics.	**NAVEL.**
Femoral triangle	Contains femoral vein, artery, nerve.	
Femoral sheath	Fascial tube 3–4 cm below inguinal ligament. Contains femoral vein, artery, and canal (deep inguinal lymph nodes) but **not** femoral nerve.	



Inguinal canal



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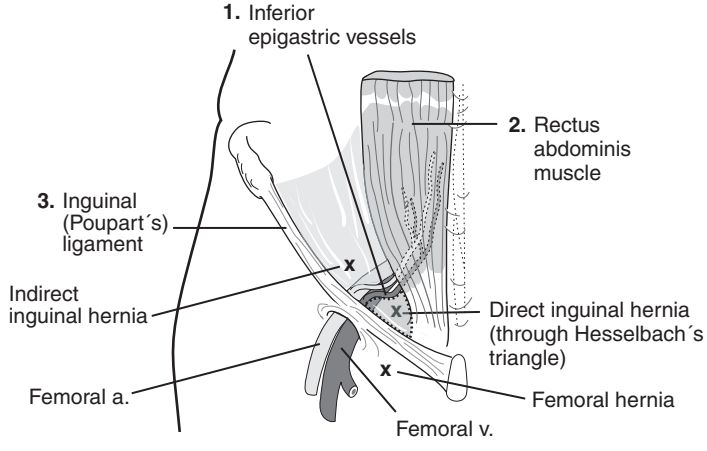
Hernias

A hernia is a protrusion of peritoneum through an opening, usually sites of weakness.

Diaphragmatic hernia	Abdominal structures enter the thorax; may occur in infants as a result of defective development of pleuroperitoneal membrane. Most commonly a **hiatal hernia**, in which stomach herniates upward through the esophageal hiatus of the diaphragm.	**Hiatal hernias—sliding** (most common): GE junction is displaced **Paraesophageal:** GE junction is normal. Cardia moves into the thorax.
Indirect inguinal hernia	Goes through the **IN**ternal (deep) inguinal ring, external (superficial) inguinal ring, and **IN**to the scrotum. Enters internal inguinal ring lateral to inferior epigastric artery. Occur in **IN**fants owing to failure of processus vaginalis to close. Much more common in males.	Follows the path of the descent of the testes. Covered by all 3 layers of spermatic fascia.
Direct inguinal hernia	Protrudes through the inguinal (Hesselbach's) triangle. Bulges directly through abdominal wall medial to inferior epigastric artery. Goes through the external (superficial) inguinal ring only. Covered by transversalis fascia. Usually in older men.	**MD**s don't **LI**e: **M**edial to inferior epigastric artery = **D**irect hernia. **L**ateral to inferior epigastric artery = **I**ndirect hernia.
Femoral hernia	Protrudes below inguinal ligament through femoral canal below and lateral to pubic tubercle. More common in women.	Leading cause of bowel incarceration.



Hesselbach's triangle:
- Inferior epigastric artery
- Lateral border of rectus abdominis
- Inguinal ligament

Peyer's patches

Unencapsulated lymphoid tissue found in lamina propria and submucosa of small intestine. Contain specialized M cells that take up antigen.
Stimulated B cells leave Peyer's patch and travel through lymph and blood to lamina propria of intestine, and differentiate into IgA-secreting plasma cells in mesenteric lymph nodes. IgA receives protective secretory component and is then transported across epithelium to gut to deal with intraluminal antigen.

Think of **IgA**, the **I**ntra-**g**ut **A**ntibody. And always say "secretory IgA."

Salivary secretion

Source: Parotid (most serous), submandibular, submaxillary, and sublingual (most mucinous) glands.

Serous on the **S**ides (parotids); **M**ucinous in the **M**iddle (sublingual).

Function:
1. α-amylase (ptyalin) begins starch digestion; inactivated by low pH on reaching stomach
2. Bicarbonate neutralizes oral bacterial acids, maintains dental health
3. Mucins (glycoproteins) lubricate food

Salivary secretion is stimulated by both sympathetic (T1–T3 superior cervical ganglion) and parasympathetic (facial, glossopharyngeal nerve) activity. Low flow rate → hypotonic. High flow rate → closer to isotonic.

CN VII runs through parotid gland. Can be damaged during surgery.

Brunner's glands

Secrete alkaline mucus to neutralize acid contents entering the duodenum from the stomach. Located in **duodenal submucosa** (the only GI submucosal glands). Hypertrophy of Brunner's glands is seen in peptic ulcer disease.

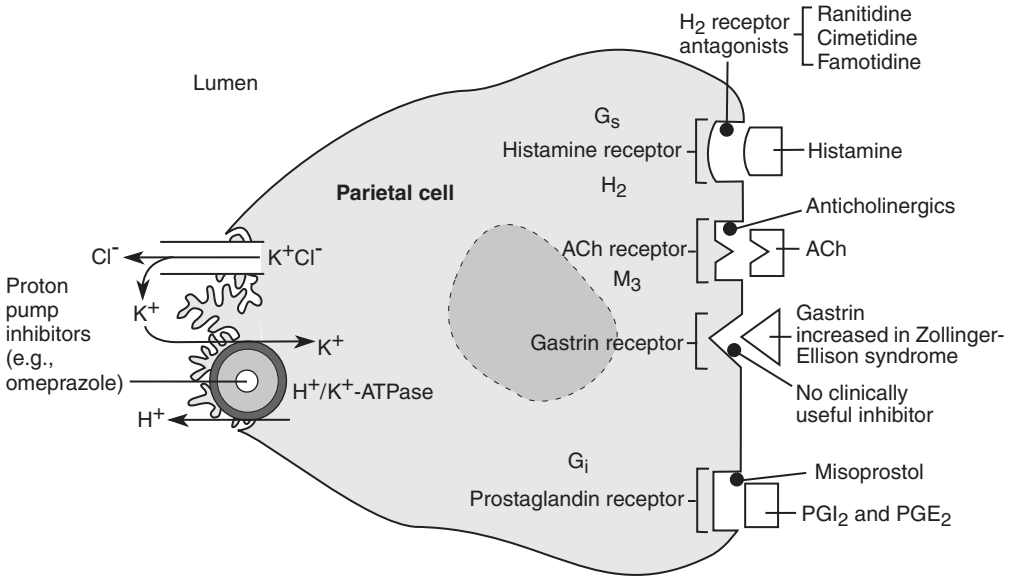
GI secretory products

Product	Source	Action	Regulation	Notes
Intrinsic factor	Parietal cells Stomach	Vitamin B_{12} binding protein (required for B_{12} uptake in terminal ileum)		Autoimmune destruction of parietal cells → chronic gastritis and pernicious anemia.
Gastric acid	Parietal cells Stomach	↓ stomach pH	↑ by histamine, ACh, gastrin ↓ by somatostatin, GIP, prostaglandin, secretin	**Gastrinoma:** gastrin-secreting tumor that causes continuous high levels of acid secretion and ulcers.
Pepsin	Chief cells Stomach	Protein digestion	↑ by vagal stimulation, local acid	Inactive pepsinogen → pepsin by H^+.
HCO_3^-	Mucosal cells Stomach Duodenum	Neutralizes acid Prevents autodigestion	↑ by secretin	HCO_3^- is trapped in mucus that covers the gastric epithelium.

GI hormones

Hormone	Source	Action	Regulation	Notes
Gastrin	G cells Antrum of stomach	↑ gastric H^+ secretion ↑ growth of gastric mucosa ↑ gastric motility	↑ by stomach distention, amino acids, peptides, vagal stimulation ↓ by stomach pH < 1.5	↑↑ in Zollinger-Ellison syndrome. Phenylalanine and tryptophan are potent stimulators.
Cholecystokinin	I cells Duodenum Jejunum	↑ pancreatic secretion ↑ gallbladder contraction ↓ gastric emptying	↑ by fatty acids, amino acids	In cholelithiasis, pain worsens after fatty food ingestion due to ↑ CCK.
Secretin	S cells Duodenum	↑ pancreatic HCO_3^- secretion ↓ gastric acid secretion ↑ bile secretion	↑ by acid, fatty acids in lumen of duodenum pancreatic enzymes to function.	↑ HCO_3^- neutralizes gastric acid in duodenum, allowing
Somatostatin	D cells Pancreatic islets GI mucosa	↓ gastric acid and pepsinogen secretion ↓ pancreatic and small intestine fluid secretion ↓ gallbladder contraction ↓ insulin and glucagon release	↑ by acid ↓ by vagal stimulation	Inhibitory hormone. Antigrowth hormone effects (digestion and absorption of substances needed for growth). Used to treat VIPoma and carcinoid tumors.
Gastric inhibitory peptide (GIP)	K cells Duodenum Jejunum	Exocrine: ↓ gastric H^+ secretion Endocrine: ↑ insulin release	↑ by fatty acids, amino acids, oral glucose	An oral glucose load is used more rapidly than the equivalent given by IV.
Vasoactive intestinal polypeptide (VIP)	Parasympathetic ganglia in sphincters, gallbladder, small intestine	↑ intestinal water and electrolyte secretion ↑ relaxation of intestinal smooth muscle and sphincters	↑ by distention and vagal stimulation ↓ by adrenergic input	**VIPoma**—non-α, non-β islet cell pancreatic tumor that secretes VIP. Copious diarrhea.
Nitric oxide		↑ smooth muscle relaxation, including lower esophageal sphincter		Loss of NO secretion is implicated in ↑ lower esophageal tone of achalasia.
Motilin	Small intestine	Produces migrating motor complexes (MMCs)	↑ in fasting state	

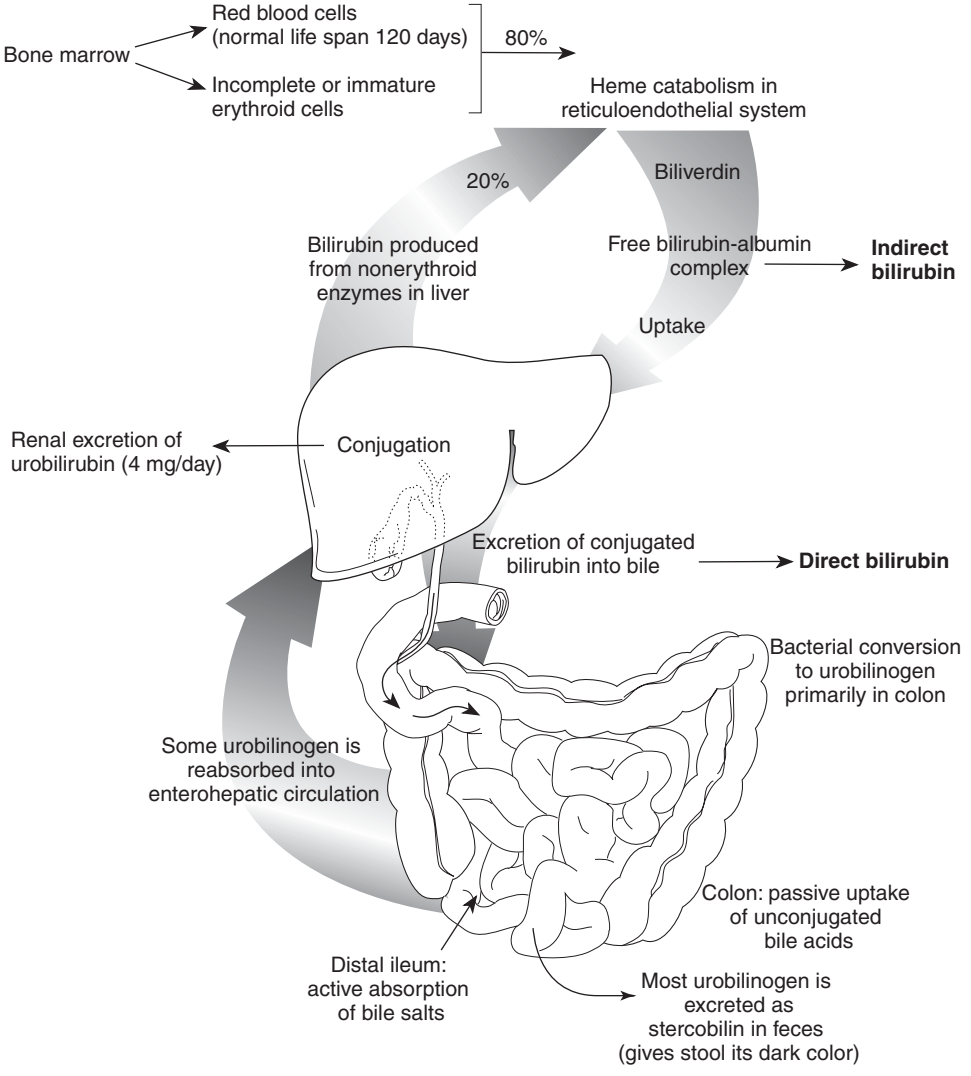
Regulation of gastric acid secretion



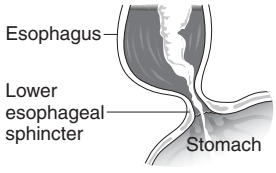
Pancreatic enzymes	α-amylase—starch digestion, secreted in active form. Lipase, phospholipase A, colipase—fat digestion. Proteases (trypsin, chymotrypsin, elastase, carboxypeptidases)—protein digestion, secreted as proenzymes also known as "zymogens." Trypsinogen is converted to active enzyme trypsin by **enterokinase/enteropeptidase,** an enzyme secreted from duodenal mucosa. Trypsin activates other proenzymes and more trypsinogen (positive feedback loop).
Carbohydrate digestion	
Salivary amylase	Starts digestion, hydrolyzes α-1,4 linkages to yield disaccharides (maltose, maltotriose, and α-limit dextrans).
Pancreatic amylase	Highest concentration in duodenal lumen, hydrolyzes starch to oligosaccharides and disaccharides.
Oligosaccharide hydrolases	At brush border of intestine, the rate-limiting step in carbohydrate digestion, produce monosaccharides from oligo- and disaccharides.
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.
Bile	Composed of bile salts (bile acids conjugated to glycine or taurine, making them water soluble), phospholipids, cholesterol, bilirubin, water, and ions. The only significant mechanism for cholesterol excretion.

Bilirubin

Product of heme metabolism; actively taken up by hepatocytes. Direct bilirubin—conjugated with glucuronic acid; water soluble. Indirect bilirubin—unconjugated; water insoluble. Jaundice (yellow skin, sclerae) results from elevated bilirubin levels.



Achalasia



Failure of relaxation of lower esophageal sphincter (LES) due to loss of **myenteric (Auerbach's) plexus.** High LES opening pressure and uncoordinated peristalsis lead to progressive dysphagia. Barium swallow shows dilated esophagus with an area of distal stenosis. Associated with an ↑ risk of esophageal carcinoma.

A-chalasia = absence of relaxation.
"Bird's beak" on barium swallow.
2° achalasia may arise from Chagas' disease.
Scleroderma (CREST syndrome) is associated with esophageal dysmotility involving low pressure proximal to LES.

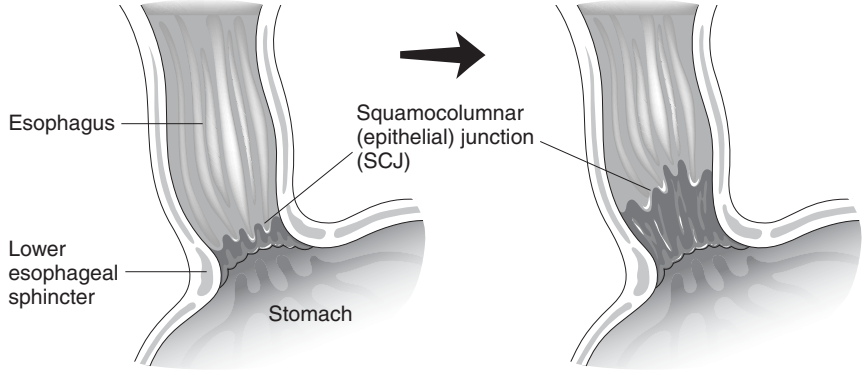
Esophageal pathologies

Gastroesophageal reflux disease (GERD)	Commonly presents as heartburn and regurgitation upon lying down.
Esophageal varices	**Painless** bleeding of submucosal veins in lower ⅓ of esophagus (see Color Image 33).
Mallory-Weiss syndrome	**Painful** mucosal lacerations at the gastroesophageal junction due to severe vomiting. Leads to hematemesis. Usually found in alcoholics and bulimics.
Boerhaave syndrome	Transmural esophageal rupture due to violent retching.
Esophageal strictures	Associated with lye ingestion.
Esophagitis	Associated with reflux, infection (HSV-1, CMV, *Candida*), or chemical ingestion.
Plummer-Vinson syndrome	Triad of: 1. Dysphagia (due to esophageal webs) 2. Glossitis 3. Iron deficiency anemia

Barrett's esophagus

Glandular metaplasia—replacement of nonkeratinized (stratified) squamous epithelium with intestinal (columnar) epithelium in the distal esophagus. Due to chronic acid reflux (GERD).

BARRett's = **B**ecomes **A**denocarcinoma, **R**esults from **R**eflux.



Esophageal cancer

Risk factors for esophageal cancer are:

Alcohol/**A**chalasia
Barrett's esophagus
Cigarettes
Diverticuli (e.g., Zenker's diverticulum)
Esophageal web (e.g., Plummer-Vinson)/ **E**sophagitis
Familial

ABCDEF.

Worldwide, squamous cell is most common.

In the United States, squamous and adenocarcinoma are equal in incidence.

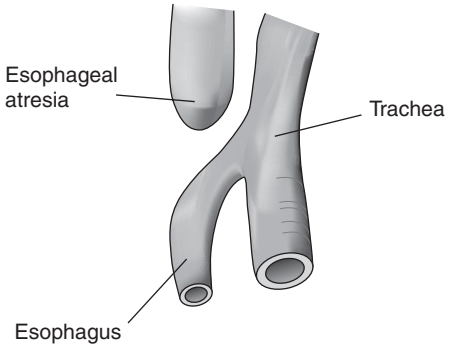
Squamous cell—upper and middle ⅓.

Adenocarcinoma—lower ⅓.

Tracheoesophageal fistula

Abnormal connection between esophagus and trachea.

Most common subtype is blind upper esophagus with lower esophagus connected to trachea. Results in cyanosis, choking and vomiting with feeding, air bubble on CXR, and polyhydramnios.



Congenital pyloric stenosis

Hypertrophy of the pylorus causes obstruction. Palpable "olive" mass in epigastric region and nonbilious projectile vomiting at ≈ 2 weeks of age. Treatment is surgical incision. Occurs in 1/600 live births, often in 1st-born males.

Malabsorption syndromes

Can cause diarrhea, steatorrhea, weight loss, weakness.

Celiac sprue	Autoantibodies to gluten (gliadin) in wheat and other grains. Proximal small bowel primarily.
Tropical sprue	Probably infectious; responds to antibiotics. Similar to celiac sprue, but can affect entire small bowel.
Whipple's disease	Infection with *Tropheryma whippelii* (gram positive); PAS-positive macrophages in intestinal lamina propria, mesenteric nodes. Arthralgias, cardiac and neurologic symptoms are common. Most often occurs in older men.
Disaccharidase deficiency	Most common is lactase deficiency → milk intolerance. Normal-appearing villi. Osmotic diarrhea.
Pancreatic insufficiency	Due to cystic fibrosis, obstructing cancer, and chronic pancreatitis. Causes malabsorption of protein, fat, vitamins A, D, E, K.

Celiac sprue	Autoimmune-mediated intolerance of gliadin (wheat) leading to steatorrhea. Associated with people of northern European descent. Findings include blunting of villi (see Color Image 32) and lymphocytes in the lamina propria. ↓ mucosal absorption that primarily affects jejunum. Serum levels of tissue transglutaminase are used for screening. Associated with dermatitis herpetiformis. Moderately ↑ risk of malignancy (most often T-cell lymphoma).	
Gastritis		
Acute gastritis (erosive)	Disruption of mucosal barrier → inflammation. Can be caused by stress, NSAIDs, alcohol, uricemia, burns (Curling's ulcer), and brain injury (Cushing's ulcer).	
Chronic gastritis (nonerosive)		
Type A (fundus/body)	**A**utoimmune disorder characterized by **A**utoantibodies to parietal cells, pernicious **A**nemia, and **A**chlorhydria.	**AB pairing—**pernicious **A**nemia affects gastric **B**ody.
Type B (antrum)	Caused by *H. pylori* infection. ↑ risk of MALT lymphoma.	*H. pylori* **B**acterium affects **A**ntrum.
Ménétrier's disease	Gastric hypertrophy with protein loss, parietal cell atrophy, and ↑ mucous cells. Precancerous.	
Stomach cancer	Almost always adenocarcinoma. Early aggressive local spread and node/liver mets. Associated with dietary nitrosamines (smoked foods), achlorhydria, chronic gastritis, type A blood. Termed linitis plastica when diffusely infiltrative (thickened, rigid appearance, "leather bottle"), signet ring cells (see Image 115), acanthosis nigricans.	Virchow's node—involvement of left supraclavicular node by mets from stomach. Krukenberg's tumor—bilateral mets to ovaries. Abundant mucus, signet ring cells.
Peptic ulcer disease		
Gastric ulcer	Pain can be greater with meals—weight loss. Often occurs in older patients. *H. pylori* infection in 70%; chronic NSAID use also implicated. Due to ↓ mucosal protection against gastric acid.	
Duodenal ulcer	Pain **D**ecreases with meals—weight gain. Almost 100% have *H. pylori* infection. Due to ↑ gastric acid secretion (e.g., Zollinger-Ellison syndrome) or ↓ mucosal protection. Hypertrophy of Brunner's glands. Tend to have clean, "punched-out" margins unlike the raised/irregular margins of carcinoma. Potential complications include bleeding, penetration into pancreas, perforation, and obstruction (not intrinsically precancerous) (see Image 114).	

Inflammatory bowel disease

	Crohn's disease	Ulcerative colitis
Possible etiology	Postinfectious.	Autoimmune.
Location	Any portion of the GI tract, usually the terminal ileum and colon. **Skip** lesions, **rec**tal sparing.	*Colitis* = colon inflammation. Continuous colonic lesions, always with rectal involvement.
Gross morphology	Transmural inflammation. **Cobblestone** mucosa, creeping **fat,** bowel wall thickening ("string sign" on barium swallow x-ray), linear ulcers, fissures, fistulas.	Mucosal and submucosal inflammation only. Friable mucosal pseudopolyps with freely hanging mesentery. "Lead pipe" appearance on imaging.
Microscopic morphology	Noncaseating **gran**ulomas and lymphoid aggregates.	Crypt abscesses and ulcers, bleeding, no granulomas.
Complications	Strictures, fistulas, perianal disease, malabsorption, nutritional depletion.	Severe stenosis, toxic megacolon, **colorectal carcinoma.**
Intestinal manifestation	Diarrhea that may or may not be bloody.	Bloody diarrhea.
Extraintestinal manifestations	Migratory polyarthritis, erythema nodosum, ankylosing spondylitis, uveitis, immunologic disorders.	Pyoderma gangrenosum, 1° sclerosing cholangitis.
Treatment	Corticosteroids.	Sulfasalazine.

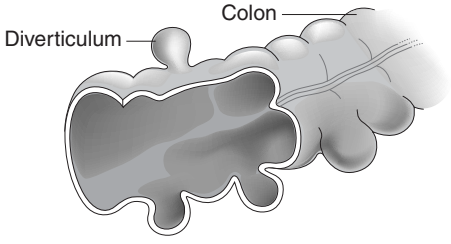
For **Crohn's,** think of a **fat gran**ny and an old **crone skipping** down a **cobblestone** road away from the **wreck** (rectal sparing) (see Images 118, 119).

Appendicitis

All age groups; most common indication for emergent abdominal surgery in children.
Initial diffuse periumbilical pain → localized pain at McBurney's point. Nausea, fever; may perforate → peritonitis.
Differential: diverticulitis (elderly), ectopic pregnancy (use β-hCG to rule out).

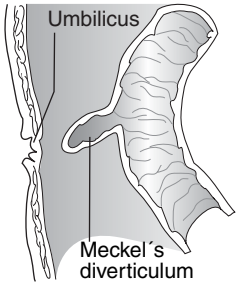
Diverticular disease

Diverticulum	Blind pouch leading off the alimentary tract that communicates with the lumen of the gut. Most diverticula (esophagus, stomach, duodenum, colon) are acquired and are termed "false" in that they lack or have an attenuated muscularis externa. Most often in sigmoid colon.	"**True**" diverticulum—all 3 gut wall layers outpouch. "**False**" diverticulum or pseudodiverticulum—only mucosa and submucosa outpouch. Occur especially where vasa recta perforate muscularis externa.
Diverticulosis	Many diverticula. Common (in ~50% of people > 60 years). Caused by ↑ intraluminal pressure and focal weakness in colonic wall. Associated with low-fiber diets. Most often in sigmoid colon.	Often asymptomatic or associated with vague discomfort and/or rectal bleeding.
Diverticulitis	Inflammation of diverticula classically causing LLQ pain, fever, leukocytosis. May perforate → peritonitis, abscess formation, or bowel stenosis (see Color Image 31). Give antibiotics.	May cause bright red rectal bleeding.



Zenker's diverticulum — False diverticulum. Herniation of mucosal tissue at junction of pharynx and esophagus. Presenting symptoms: halitosis, dysphagia, obstruction.

Meckel's diverticulum



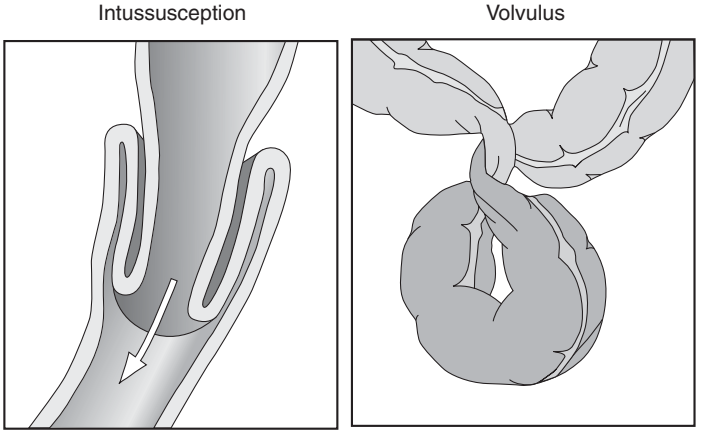
Persistence of the vitelline duct or yolk stalk. May contain ectopic acid–secreting gastric mucosa and/or pancreatic tissue. **Most common congenital anomaly of the GI tract.** Can cause bleeding, intussusception, volvulus, or obstruction near the terminal ileum. Contrast with omphalomesenteric cyst = cystic dilatation of vitelline duct.

The five **2**'s:
- **2** inches long.
- **2** feet from the ileocecal valve.
- **2**% of population.
- Commonly presents in first **2** years of life.
- May have **2** types of epithelia (gastric/pancreatic).

Intussusception and volvulus

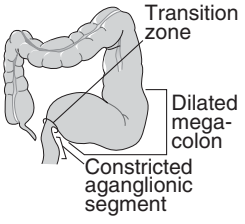
Intussusception—"telescoping" of 1 bowel segment into distal segment; can compromise blood supply (see Color Image 34). Often due to intraluminal mass. Usually in infants.

Volvulus—twisting of portion of bowel around its mesentery; can lead to obstruction and infarction. May occur at sigmoid colon, where there is redundant mesentery. Usually in elderly.



(Reproduced, with permission, from Kumar V et al. *Robbins & Cotran Pathologic Basis of Disease,* 7th ed. Atlanta: Elsevier, 2004: 856.)

Hirschsprung's disease



Congenital megacolon characterized by lack of ganglion cells/enteric nervous plexuses (Auerbach's and Meissner's plexuses) in segment on intestinal biopsy. Due to **failure of neural crest cell migration.**

Presents as chronic constipation early in life. Dilated portion of the colon proximal to the aganglionic segment, resulting in a "transition zone." Involves rectum. Usually failure to pass meconium.

Think of a giant spring that has **sprung** in the colon. Risk ↑ with Down syndrome.

Other intestinal disorders

Duodenal atresia	Causes early bilious vomiting with proximal stomach distention ("double bubble") due to failure of recanalization of small bowel. Associated with Down syndrome.
Meconium ileus	In cystic fibrosis, meconium plug obstructs intestine, preventing stool passage.
Necrotizing enterocolitis	Necrosis of intestinal mucosa and possible perforation. Colon is usually involved, but can involve entire GI tract. In neonates, more common in preemies (↓ immunity).
Ischemic colitis	Reduction in intestinal blood causes ischemia. Typically affects elderly. Consequences include sepsis, bowel infarction, and death.
Adhesion	Acute bowel obstruction, commonly from a recent surgery. Can have well-demarcated necrotic zones.
Angiodysplasia	Tortuous dilation of vessels → bleeding. Most often found in cecum and ascending colon. More common in older patients. Confirmed by angiography.

Colonic polyps

90% are benign hyperplastic hamartomas, not neoplasms. Often rectosigmoid. Sawtooth appearance. The more villous the polyp, the more likely it is to be malignant (see Color Image 30).

Colorectal cancer

Colorectal cancer (CRC)

3rd most common cancer. Most are sporadic, due to chromosomal instability (85%) or microsatellite instability (15%) (see Color Image 107).

Risk factors: colorectal villous adenomas, chronic IBD (especially ulcerative colitis, ↑ age), FAP, HNPCC, past medical or family history; screen patients > 50 years of age with stool occult blood test and colonoscopy.

"Apple core" lesion seen on barium enema x-ray.

CEA tumor marker.

Familial adenomatous polyposis (FAP)

Autosomal-dominant mutation of *APC* gene on chromosome 5q. Two-hit hypothesis.

Thousands of polyps; pancolonic; always involving the rectum.

Gardner's syndrome—FAP with osseous and soft tissue tumors, retinal hyperplasia.

Turcot's syndrome—FAP with possible brain involvement (glioblastoma).

HNPCC or Lynch syndrome

Mutations of DNA mismatch repair genes. ~80% progress to CRC. Proximal colon always involved.

Peutz-Jeghers syndrome

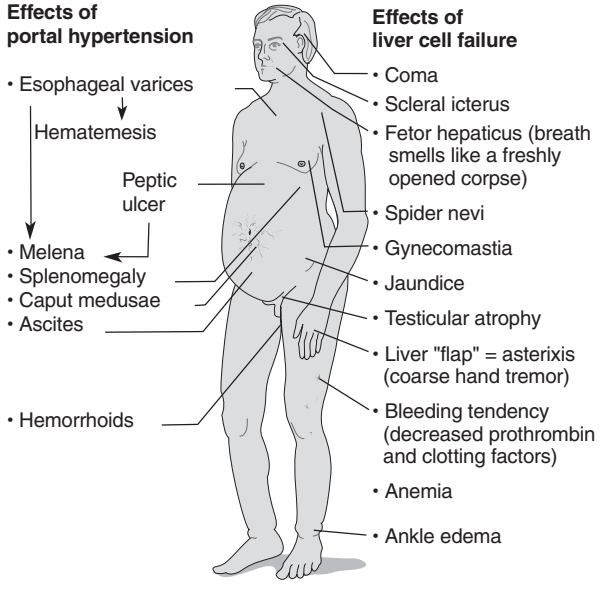
Benign polyposis syndrome. Associated with ↑ risk of CRC and other visceral malignancies (pancreas, breast, stomach, ovary).

Findings: hamartomatous polyps of colon and small intestine; hyperpigmented mouth, lips, hands, genitalia.

Carcinoid tumor

Tumor of endocrine cells. Comprise 50% of small bowel tumors. Most common site is in small intestine. "Dense core bodies" seen on EM. Often produce 5-HT (depending on location → **carcinoid syndrome**). Classic symptoms: wheezing, right-sided heart murmurs, diarrhea, flushing.

Cirrhosis and portal hypertension



(Adapted, with permission, from Chandrasoma P, Taylor CE. *Concise Pathology,* 3rd ed. Stamford, CT: Appleton & Lange, 1998: 654.)

Cirrho (Greek) = tawny yellow.

Diffuse fibrosis of liver, destroys normal architecture.

Nodular regeneration.

Micronodular—nodules < 3 mm, uniform size. Due to metabolic insult (e.g., alcohol, hemochromatosis, Wilson's disease).

Macronodular—nodules > 3 mm, varied size. Usually due to significant liver injury leading to hepatic necrosis (e.g., postinfectious or drug-induced hepatitis). ↑ risk of hepatocellular carcinoma.

Portacaval shunt between splenic vein and left renal vein may relieve portal hypertension (see Color Image 29).

Enzyme markers of GI pathology	**Serum enzyme**	**Major diagnostic use**
	Aminotransferases (AST and ALT)	Viral hepatitis Alcoholic hepatitis Myocardial infarction (AST)
	GGT (γ-glutamyl transpeptidase)	Various liver diseases
	Alkaline phosphatase	Obstructive liver disease (hepatocellular carcinoma), bone disease, bile duct disease
	Amylase	Acute pancreatitis, mumps
	Lipase	Acute pancreatitis
	Ceruloplasmin (↓)	Wilson's disease
Reye's syndrome	Rare, often fatal childhood hepatoencephalopathy. Findings: fatty liver (microvesicular fatty change), hypoglycemia, coma. Associated with viral infection (especially VZV and influenza B) that has been treated with salicylates. **Aspirin is not recommended for children** (use acetaminophen, with caution).	
Alcoholic liver disease		
Hepatic steatosis	Short-term change with moderate alcohol intake. Reversible macrovesicular fatty change upon alcohol cessation (see Color Image 28).	You're to**AST**ed with alcoholic hepatitis: **AST** > ALT (ratio usually > 1.5).
Alcoholic hepatitis	Requires sustained, long-term consumption. Swollen and necrotic hepatocytes with neutrophilic infiltration. **Mallory bodies** (intracytoplasmic eosinophilic inclusions) are present.	ALT > AST in viral hepatitis.
Alcoholic cirrhosis	Final and irreversible form. Micronodular, irregularly shrunken liver with "hobnail" appearance (see Color Image 29). Sclerosis around central vein (zone III). Has manifestations of chronic liver disease (e.g., jaundice, hypoalbuminemia).	
Hepatocellular carcinoma/hepatoma	Most common 1° malignant tumor of the liver in adults. ↑ incidence of hepatocellular carcinoma is associated with hepatitis B and C, Wilson's disease, hemochromatosis, α_1-antitrypsin deficiency, alcoholic cirrhosis, and carcinogens (e.g., aflatoxin in peanuts). Can present with tender hepatomegaly, ascites, polycythemia, and hypoglycemia.	Commonly spread by hematogenous dissemination. Elevated **α-fetoprotein.** May lead to Budd-Chiari syndrome.

Budd-Chiari syndrome

Occlusion of IVC or hepatic veins with centrilobular congestion and necrosis, leading to congestive liver disease (hepatomegaly, ascites, abdominal pain, and eventual liver failure). May develop varices and have visible abdominal and back veins. Absence of JVD. Associated with polycythemia vera, pregnancy, and hepatocellular carcinoma.

α_1-antitrypsin deficiency

Misfolded gene product protein accumulates in hepatocellular ER. ↓ elastic tissue in lungs → emphysema. PAS-positive globules in liver. Autosomal recessive.

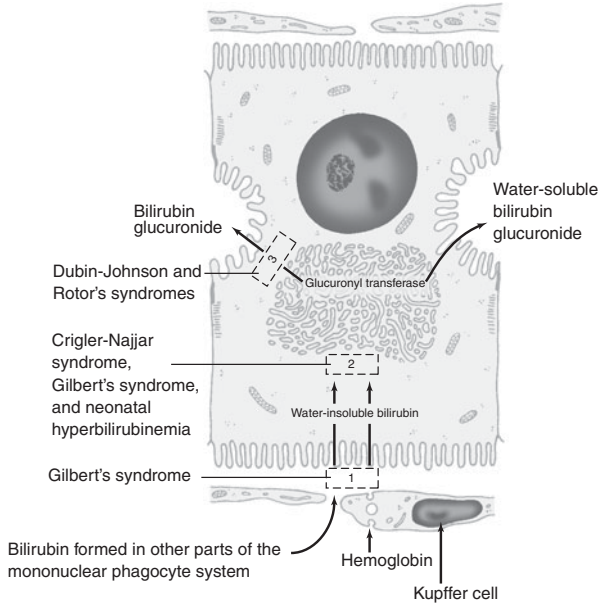
Jaundice

Normally, liver cells convert unconjugated (indirect) bilirubin into conjugated (direct) bilirubin. Direct bilirubin is water soluble and can be excreted into urine and by the liver into bile to be converted by gut bacteria to urobilinogen (some of which is reabsorbed). Some urobilinogen is also formed directly from heme metabolism.

Jaundice type	Hyperbilirubinemia	Urine bilirubin	Urine urobilinogen
Hepatocellular	Conjugated/unconjugated	↑	Normal/↓
Obstructive	Conjugated	↑	↓
Hemolytic	Unconjugated	Absent (acholuria)	↑

Hereditary hyperbilirubinemias

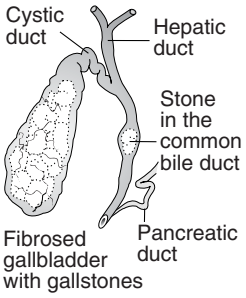
Gilbert's syndrome	Mildly ↓ UDP-glucuronyl transferase or ↓ bilirubin uptake. Asymptomatic. Elevated unconjugated bilirubin without overt hemolysis. Associated with stress.	No clinical consequences.
Crigler-Najjar syndrome, type I	Absent UDP-glucuronyl transferase. Presents early in life; patients die 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.
Dubin-Johnson syndrome	Conjugated hyperbilirubinemia due to defective liver excretion. Grossly black liver. Benign.	**Rotor's syndrome** is similar but even milder and does not cause black liver.



(Adapted, with permission, from Junqueira LC, Carneiro J, Kelley RO. *Basic Histology,* 9th ed. Stamford, CT: Appleton & Lange, 1999.)

Wilson's disease	Inadequate hepatic copper excretion and failure of copper to enter circulation as ceruloplasmin. Leads to copper accumulation, especially in liver, brain, cornea, kidneys, and joints. Also known as hepatolenticular degeneration. Wilson's disease is characterized by: **A**sterixis **B**asal ganglia degeneration (parkinsonian symptoms) **C**eruloplasmin ↓, **C**irrhosis, **C**orneal deposits (Kayser-Fleischer rings—see Color Image 51), **C**opper accumulation, **C**arcinoma (hepatocellular), **C**horeiform movements **D**ementia	Treat with penicillamine. Autosomal-recessive inheritance. **ABCD.**
Hemochromatosis	Hemosiderosis is the deposition of hemosiderin (iron); hemochromatosis is the disease caused by this iron deposition (see Color Image 26). Classic triad of micronodular **C**irrhosis, **D**iabetes mellitus, and skin pigmentation → **"bronze" diabetes.** Results in **C**HF and ↑ risk of hepatocellular carcinoma. Disease may be 1° (autosomal recessive) or 2° to chronic transfusion therapy (e.g., β-thalassemia major). ↑ ferritin, ↑ iron, ↓ TIBC → ↑ transferrin saturation.	**H**emochromatosis **C**an **C**ause **D**eposits. Total body iron may reach 50 g, enough to set off metal detectors at airports. Treat hereditary hemochromatosis with repeated phlebotomy, deferoxamine. Associated with HLA-A3.
Primary sclerosing cholangitis	Both intra- and extrahepatic. Inflammation and fibrosis of bile ducts → alternating strictures and dilation with "beading" on ERCP. Concentric "onion skin" bile duct fibrosis. ↑ ALP. Associated with ulcerative colitis. Can lead to 2° biliary cirrhosis.	
Biliary cirrhosis		
Primary	Intrahepatic, autoimmune disorder; severe obstructive jaundice, steatorrhea, pruritus, hypercholesterolemia (xanthoma). ↑ ALP, ↑ **serum mitochondrial antibodies**. Associated with scleroderma and CREST syndrome.	
Secondary	Due to extrahepatic biliary obstruction. ↑ in pressure in intrahepatic ducts → injury/fibrosis. Often complicated by ascending cholangitis (bacterial infection), bile stasis, and "bile lakes." ↑ ALP, ↑ conjugated bilirubin.	

Gallstones (cholelithiasis)



Form when solubilizing bile acids and lecithin are overwhelmed by ↑ cholesterol and/or bilirubin.

2 types of stones:

1. **Cholesterol stones** (radiolucent with 10–20% opaque due to calcifications)—80% of stones. Associated with obesity, Crohn's disease, cystic fibrosis, advanced age, clofibrate, estrogens, multiparity, rapid weight loss, and Native American origin.
2. **Pigment stones** (radiopaque)—seen in patients with chronic RBC hemolysis, alcoholic cirrhosis, advanced age, and biliary infection.

Can cause ascending cholangitis, acute pancreatitis, bile stasis, cholecystitis.

Can also → **biliary colic**—gallstones interfere with bile flow, causing bile duct contraction. May present without pain (e.g., in diabetics).

Diagnose with ultrasound. Treat with cholecystectomy.

Risk factors (**4 F's**):

1. **F**emale
2. **F**at
3. **F**ertile
4. **F**orty

Charcot's triad of cholangitis:

1. Jaundice
2. Fever
3. RUQ pain

Cholecystitis

Inflammation of gallbladder. Can be infectious (e.g., CMV, *Cryptococcus*) or due to a gallstone complication. ↑ ALP if bile duct becomes involved (e.g., ascending cholangitis).

Acute pancreatitis

Autodigestion of pancreas by pancreatic enzymes.

Causes: **G**allstones, **E**thanol, **T**rauma, **S**teroids, **M**umps, **A**utoimmune disease, **S**corpion sting, **H**ypercalcemia/**H**yperlipidemia, **D**rugs (e.g., sulfa drugs).

Clinical presentation: epigastric abdominal pain radiating to back, anorexia, nausea.

Labs: elevated amylase, lipase (higher specificity).

Can lead to DIC, ARDS (pancreatic enzymes act on lung tissue), diffuse fat necrosis, hypocalcemia (Ca^{2+} collects in pancreatic calcium soap deposits), pseudocyst formation, hemorrhage, and infection.

Chronic pancreatitis can lead to pancreatic insufficiency → steatorrhea, fat-soluble vitamin deficiency, and diabetes mellitus.

Chronic calcifying pancreatitis is strongly associated with alcoholism (see Image 142).

GET SMASHeD.

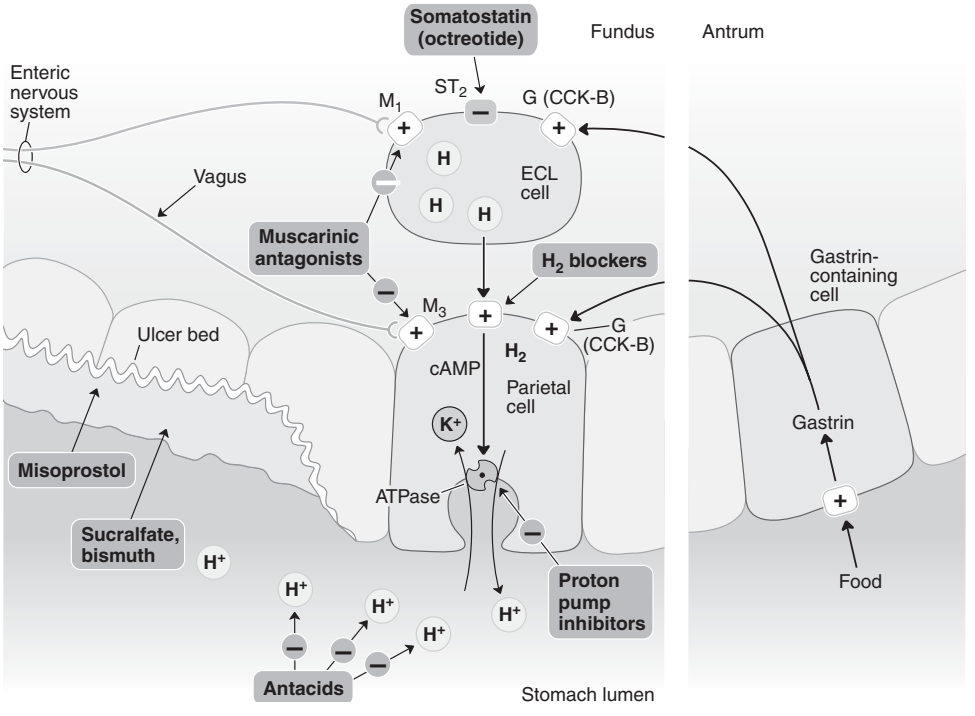
Pancreatic adenocarcinoma

Prognosis averages 6 months or less; very aggressive; usually already metastasized at presentation; tumors more common in pancreatic head (→ obstructive jaundice) (see Image 134). ↑ risk in Jewish and African-American males. CEA and CA-19-9 tumor markers. Associated with cigarettes but not EtOH.

Often presents with:

1. Abdominal pain radiating to back
2. Weight loss (due to malabsorption and anorexia)
3. Migratory thrombophlebitis—redness and tenderness on palpation of extremities (Trousseau's syndrome)
4. Obstructive jaundice with palpable gallbladder (Courvoisier's sign) (see Image 141).

GI therapy



(Adapted, with permission, from Katzung BG, Trevor AJ. *USMLE Road Map: Pharmacology*, 1st ed. New York: McGraw-Hill, 2003: 159.)

H_2 blockers	Cimeti**dine**, raniti**dine**, famoti**dine**, nizati**dine**.	Take H_2 blockers before you **DINE.**
Mechanism	Reversible block of histamine H_2 receptors → ↓ H^+ secretion by parietal cells.	
Clinical use	Peptic ulcer, gastritis, mild esophageal reflux.	
Toxicity	Cimetidine is a potent inhibitor of P-450; 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 H_2 blockers are relatively free of these effects.	
Proton pump inhibitors	Omeprazole, lansoprazole.	
Mechanism	Irreversibly inhibit H^+/K^+-ATPase in stomach parietal cells.	
Clinical use	Peptic ulcer, gastritis, esophageal reflux, Zollinger-Ellison syndrome.	
Bismuth, sucralfate		
Mechanism	Bind to ulcer base, providing physical protection, and allow HCO_3^- secretion to reestablish pH gradient in the mucous layer.	Triple therapy of *H. pylori* ulcers—**M**etronidazole, **A**moxicillin (or **T**etracycline), **B**ismuth.
Clinical use	↑ ulcer healing, traveler's diarrhea.	Can also use **P**PI—**P**lease **MA**ke **T**ummy **B**etter.
Misoprostol		
Mechanism	A PGE_1 analog. ↑ production and secretion of gastric mucous barrier, ↓ acid production.	
Clinical use	Prevention of NSAID-induced peptic ulcers; maintenance of a patent ductus arteriosus. Also used to induce labor.	
Toxicity	Diarrhea. Contraindicated in women of childbearing potential (abortifacient).	
Muscarinic antagonists	Pirenzepine, propantheline.	
Mechanism	Block M1 receptors on ECL cells (↓ histamine secretion) and M3 receptors on parietal cells (↓ H^+ secretion).	
Clinical use	Peptic ulcer.	
Toxicity	Tachycardia, dry mouth, difficulty focusing eyes.	

Antacid use

Can affect absorption, bioavailability, or urinary excretion of other drugs by altering gastric and urinary pH or by delaying gastric emptying.

Overuse can also cause the following problems:

1. **Aluminum hydroxide**—constipation and hypophosphatemia; proximal muscle weakness, osteodystrophy, seizures — Alu**minimum** amount of feces.
2. **Magnesium hydroxide**—diarrhea, hyporeflexia, hypotension, cardiac arrest — **Mg** = **M**ust **g**o to the bathroom.
3. **Calcium carbonate**—hypercalcemia, rebound acid ↑ — Can chelate and ↓ effectiveness of other drugs (e.g., tetracycline).

All can cause hypokalemia.

Infliximab

Mechanism	A monoclonal antibody to TNF, proinflammatory cytokine. — **INFLIX**imab **INFLIX** pain on TNF.
Clinical use	Crohn's disease, rheumatoid arthritis.
Toxicity	Respiratory infection, fever, hypotension.

Sulfasalazine

Mechanism	A combination of sulfapyridine (antibacterial) and mesalamine (anti-inflammatory). Activated by colonic bacteria.
Clinical use	Ulcerative colitis, Crohn's disease.
Toxicity	Malaise, nausea, sulfonamide toxicity, reversible oligospermia.

Ondansetron

Mechanism	5-HT_3 antagonist. Powerful central-acting antiemetic.
Clinical use	Control vomiting postoperatively and in patients undergoing cancer chemotherapy. — You will not vomit with **ONDANS**etron, so you can go **ON DANC**ing.
Toxicity	Headache, constipation.

Prokinetic agents

Cisapride

Mechanism	Acts through serotonin receptors to ↑ ACh release at the myenteric plexus. ↑ esophageal tone; ↑ gastric and duodenal contractility, improving transit time (including through the colon).
Toxicity	No longer used. Serious interactions (torsades des pointes) with erythromycin, ketoconazole, nefazodone, fluconazole.

Metoclopramide

Mechanism	D_2 receptor antagonist. ↑ resting tone, contractility, LES tone, motility. Does not influence colon transport time.
Clinical use	Diabetic and post-surgery gastroparesis.
Toxicity	↑ parkinsonian effects. Restlessness, drowsiness, fatigue, depression, nausea, diarrhea. Drug interaction with digoxin and diabetic agents. Contraindicated in patients with small bowel obstruction.

Hematology and Oncology

"The best blood will at some time get into a fool or a mosquito."
—Austin O'Malley

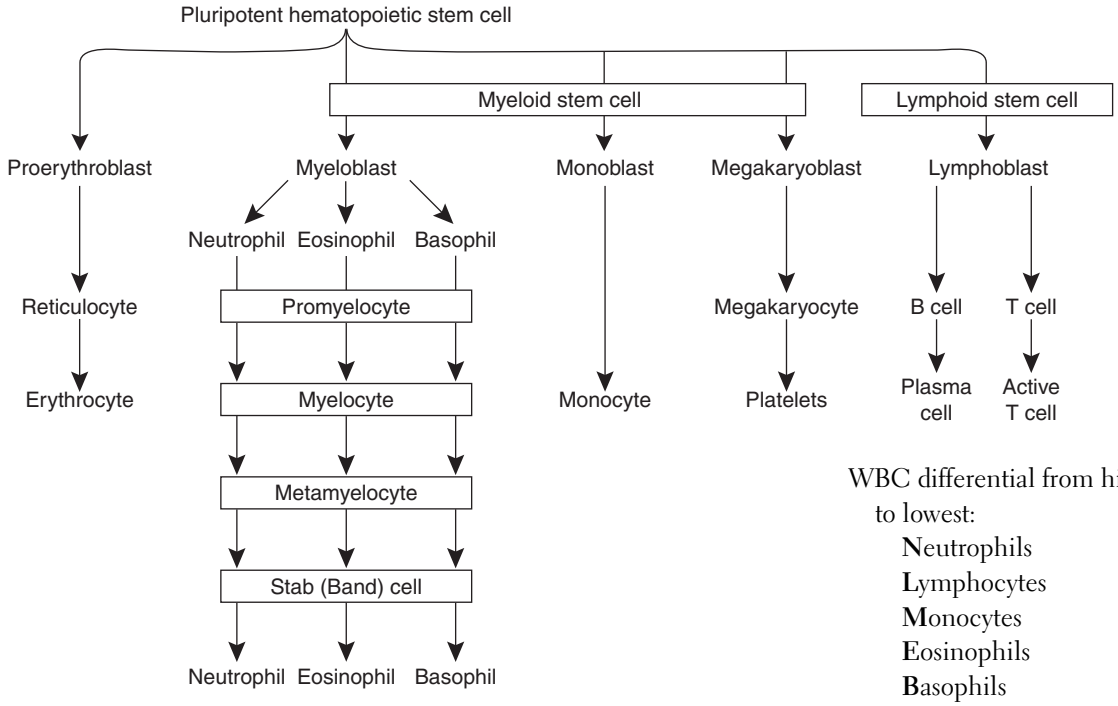
"A day without blood is like a day without sunshine."
—Joker in *Full Metal Jacket*

Study tip: When reviewing oncologic drugs, focus on mechanisms and side effects. Memorizing clinical uses is lower yield.

- High-Yield Clinical Vignettes
- Anatomy
- Physiology
- Pathology
- Pharmacology

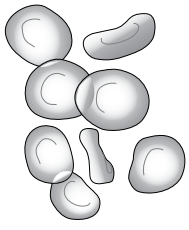
■ Child has been anemic since birth.	Splenectomy would result in ↑ hematocrit in what disease?	Spherocytosis.
■ Patient presents with fatigue, and blood tests show a macrocytic, megaloblastic anemia.	What is the danger of giving folate alone?	Corrects anemia, but neural damage progresses if the patient is B_{12} deficient.
■ Patient presents with anemia, hypercalcemia, and bone pain on palpation; bone marrow biopsy shows a slide packed with cells that have a large, round, off-center nucleus.	What is the diagnosis, and what may be found on urinalysis?	Multiple myeloma (plasma cell neoplasm); Bence Jones protein (Ig light chains).
■ AIDS patient has just been diagnosed with cancer.	What neoplasms are associated with AIDS?	B-cell lymphoma, Kaposi's sarcoma.
■ Patient with a new cancer diagnosis and a known history of CHF is being evaluated for chemotherapy.	Which chemotherapeutic agent should be avoided in this patient?	Doxorubicin (cardiotoxic).
■ Chromosome analysis reveals the presence of the Philadelphia chromosome, t(9;22).	What is the latest targeted therapy for this disease, and how does it work?	Imatinib (Gleevec) is used to treat CML; inhibitor of *bcr-abl* tyrosine kinase.
■ After a normal spontaneous vaginal delivery, a patient bleeds profusely from her vagina and later from her gums.	What abnormal lab values are noted?	↑ bleeding time, ↑ PT, ↑ PTT, and ↓ platelet count (DIC).
■ 10-year-old child presents with a chronic nonhealing ulcer on his lower leg. Imaging shows a small, calcified spleen.	What drug can improve the child's symptoms?	Hydroxyurea (↑ HbF).

Blood cell differentiation



WBC differential from highest to lowest:
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils
Neutrophils **L**ike **M**aking **E**verything **B**etter.

Erythrocyte



Anucleate, biconcave → large surface area: volume ratio → easy gas exchange (O_2 and CO_2). Source of energy—glucose (90% anaerobically degraded to lactate, 10% by HMP shunt). Survival time—120 days. Membrane contains the chloride-bicarbonate antiport important in the "physiologic chloride shift," which allows the RBC to transport CO_2 from the periphery to the lungs for elimination.

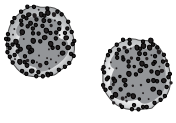
Eryth = red; *cyte* = cell.
Erythrocytosis = polycythemia = ↑ number of red cells.
Anisocytosis = varying sizes.
Poikilocytosis = varying shapes.
Reticulocyte = immature erythrocyte.

Leukocyte

Types: granulocytes (basophils, eosinophils, neutrophils) and mononuclear cells (lymphocytes, monocytes). Responsible for defense against infections. Normally 4000–10,000 per microliter.

Leuk = white; *cyte* = cell.

Basophil



Mediates allergic reaction. < 1% of all leukocytes. Bilobate nucleus. Densely basophilic granules containing heparin (anticoagulant), histamine (vasodilator) and other vasoactive amines, and leukotrienes (LTD-4). Found in the blood.

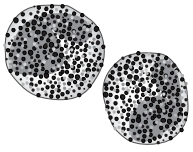
Basophilic—staining readily with **basic** stains.

Mast cell

Mediates allergic reaction. Degranulation—histamine, heparin, and eosinophil chemotactic factors. Can bind IgE to membrane. Mast cells resemble basophils structurally and functionally but are not the same cell type. Found in tissue.

Involved in type I hypersensitivity reactions. Cromolyn sodium prevents mast cell degranulation (used to treat asthma).

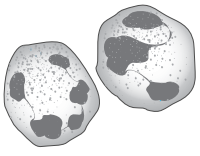
Eosinophil



1–6% of all leukocytes. Bilobate nucleus. Packed with large eosinophilic granules of uniform size. Defends against helminthic and protozoan infections (major basic protein). Highly phagocytic for antigen-antibody complexes.
Produces histaminase and arylsulfatase.

Eosin = a dye; *philic* = loving.
Causes of eosinophilia =
NAACP:
Neoplastic
Asthma
Allergic processes
Collagen vascular diseases
Parasites

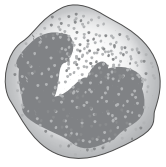
Neutrophil



Acute inflammatory response cell. 40–75% WBCs. Phagocytic. Multilobed nucleus. Large, spherical, azurophilic granules (called lysosomes) contain hydrolytic enzymes, lysozyme, myeloperoxidase, and lactoferrin.

Hypersegmented polys are seen in vitamin B_{12}/folate deficiency.

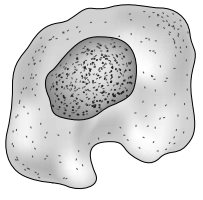
Monocyte



2–10% of leukocytes. Large. Kidney-shaped nucleus. Extensive "frosted glass" cytoplasm. Differentiates into macrophages in tissues.

Mono = one (nucleus); *cyte* = cell.

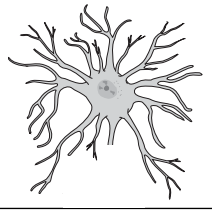
Macrophage



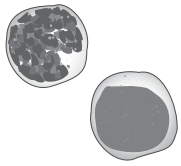
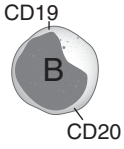
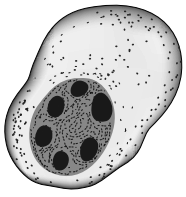
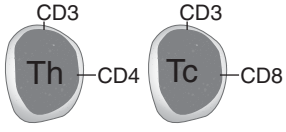
Phagocytoses bacteria, cell debris, and senescent red cells and scavenges damaged cells and tissues. Long life in tissues. Macrophages differentiate from circulating blood monocytes. Activated by γ-interferon. Can function as antigen-presenting cell (APC) via MHC II.

Macro = large; *phage* = eater.

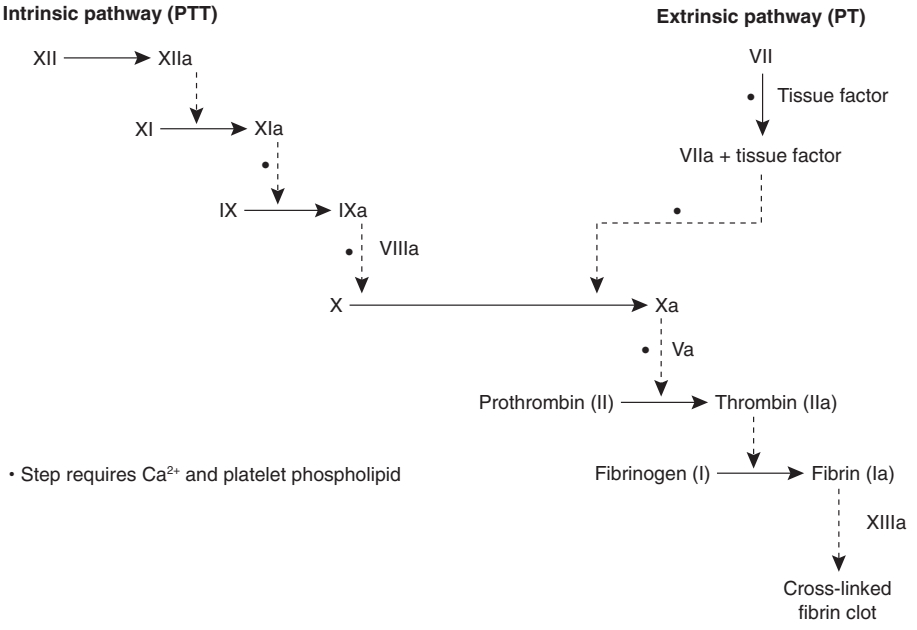
Dendritic cells



Professional APCs. Express MHC II and Fc receptor (FcR) on surface. Main inducers of 1° antibody response. Called Langerhans cells on skin.

Lymphocyte 	Round, densely staining nucleus. Small amount of pale cytoplasm. B lymphocytes produce antibodies. T lymphocytes manifest the cellular immune response as well as regulate B lymphocytes and macrophages.	
B lymphocyte 	Part of humoral immune response. Arises from stem cells in bone marrow. 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 and produce antibodies. Has memory. Can function as an APC via MHC II.	**B** = **B**one marrow.
Plasma cell 	Off-center nucleus, clock-face chromatin distribution, abundant RER and well-developed Golgi apparatus. B cells differentiate into plasma cells, which produce large amounts of antibody specific to a particular antigen.	Multiple myeloma is a plasma cell neoplasm.
T lymphocyte 	Mediates cellular immune response. Originates from stem cells in the bone marrow, but matures in the thymus. T cells differentiate into cytotoxic T cells (MHC I, CD8), helper T cells (MHC II, CD4), and suppressor T cells. The majority of circulating lymphocytes are T cells (80%).	**T** is for **T**hymus. **CD** is for **C**luster of **D**ifferentiation. **MHC** × **CD** = 8 (e.g., MHC 2 × CD4 = 8, and MHC 1 × CD8 = 8).

Coagulation cascade



Coagulation factor inhibitors and fibrinolysis

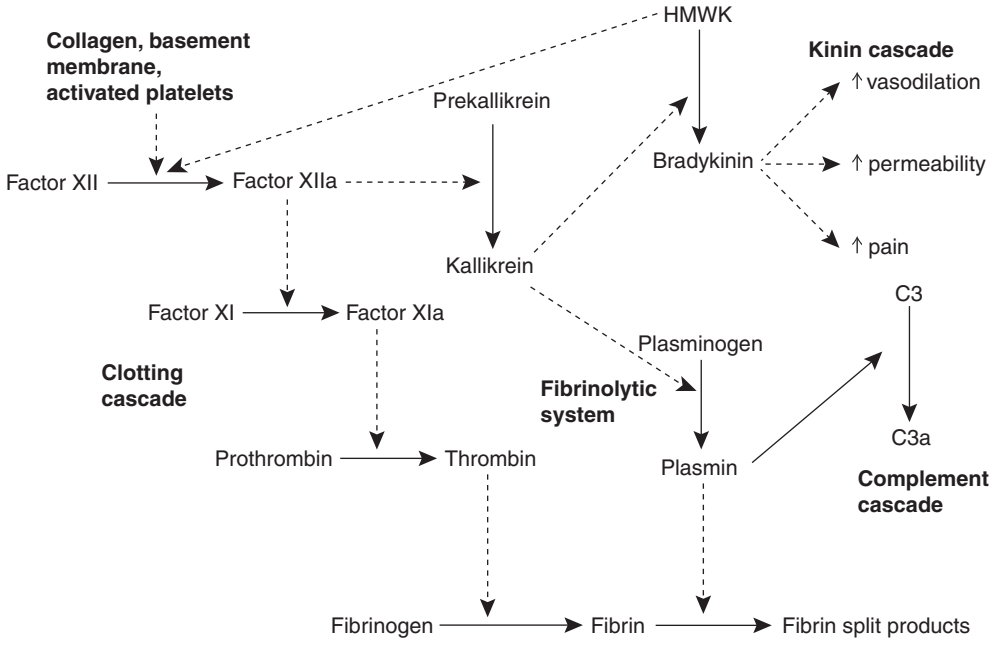
Vitamin K–dependent factors = II, VII, IX, X, protein C, and protein S. Thrombomodulin activates protein C (protein S is a cofactor for protein C activation). Activated protein C → inactivation of Va and VIIIa.

Antithrombin III—inactivates thrombin, IXa, Xa, and XIa; activated by heparin.

tPA—generates plasmin from plasminogen, which cleaves fibrin clots.

Factor V Leiden mutation causes resistance to activated protein C.

Convergence of coagulation, complement, and kinin pathways



Note: Kallikrein activates bradykinin; ACE inactivates bradykinin.

Thrombogenesis

Platelet plug formation is a temporary repair. It occurs in 3 steps:

1. Platelet adhesion to exposed basement membrane—requires vWF
2. Aggregation—regulated as follows:
   a. TXA_2 released by platelets ↑ aggregation
   b. PGI_2 (prostacyclin) and NO released by endothelial cells ↓ aggregation
3. Swelling—ADP and Ca^{2+} release to strengthen plug → fibrin deposition

► HEMATOLOGY AND ONCOLOGY—PATHOLOGY

Blood groups

A	A antigen on RBC surface and B antibody in plasma.	Rh+ blood transfusions into an Rh– individual can result in massive IgG production.
B	B antigen on RBC surface and A antibody in plasma.	
AB	A and B antigens on RBC surface; no antibodies in plasma; "universal recipient."	Incompatible blood transfusions can cause immunologic response, hemolysis, renal failure, shock, and death.
O	Neither A nor B antigen on RBC surface; both antibodies in plasma; "universal donor."	

RBC forms

Biconcave	Normal.	
Spherocytes	Hereditary spherocytosis, autoimmune hemolysis.	
Elliptocyte	Hereditary elliptocytosis.	
Macro-ovalocyte	Megaloblastic anemia (also hypersegmented PMNs), marrow failure.	
Helmet cell, schistocyte	DIC, traumatic hemolysis.	
Sickle cell	Sickle cell anemia.	
Bite cell	G6PD deficiency.	
Teardrop cell	Myeloid metaplasia with myelofibrosis.	
Acanthocyte	Spiny appearance in abetalipoproteinemia.	
Target cell	**H**bC disease, **A**splenia, **L**iver disease, **T**halassemia.	"**HALT,**" said the hunter to his **target.**
Poikilocytes	Nonuniform shapes in TTP/HUS, microvascular damage, DIC.	
Burr cell	TTP/HUS.	
Basophilic stippling	**T**halassemias, **A**nemia of chronic disease, **I**ron deficiency, **L**ead poisoning.	**TAIL.**

Anemia

Type	Etiology	Comments
Microcytic, hypochromic (MCV < 80)	Iron deficiency— ↓ serum iron, ↑ TIBC, ↓ ferritin (intracellular iron stores) (see Color Image 20). Thalassemias—target cells (see Color Image 18). Lead poisoning, sideroblastic anemias.	Vitamin B_{12} and folate deficiencies are associated with hypersegmented PMNs. Unlike folate deficiency, vitamin B_{12} deficiency (e.g., pernicious anemia) is associated with neurologic problems. ↓ serum haptoglobin and ↑ serum LDH indicate RBC hemolysis. Direct Coombs' test is used to distinguish between immune- vs. non-immune-mediated RBC hemolysis.
Macrocytic (MCV > 100)	Megaloblastic—vitamin B_{12}/folate deficiency. Drugs that block DNA synthesis (e.g., sulfa drugs, phenytoin, AZT). Marked reticulocytosis (bigger than mature RBCs).	
Normocytic, normochromic	Acute hemorrhage. Enzyme defects—G6PD deficiency (X-linked), PK deficiency (AR). RBC membrane defects (e.g., hereditary spherocytosis). Bone marrow disorders (e.g., aplastic anemia, leukemia). Hemoglobinopathies (e.g., sickle cell disease). Autoimmune hemolytic anemia. Anemia of chronic disease (ACD)— ↓ TIBC, ↑ ferritin, ↑ storage iron in marrow macrophages.	

Lab values in anemia

	Iron deficiency	Chronic disease	Pregnancy/ OCP use	Hemo-chromatosis
Serum iron	↓ (1°)	↓	—	↑ (1°)
Transferrin/ TIBC (indirectly proportional to transferrin)	↑	↓*	↑ (1°)	↓
Ferritin	↓	↑ (1°)	—	↑
% transferrin saturation (serum Fe/TIBC)	↓↓	—	↓	↑↑

*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.

Aplastic anemia

Pancytopenia characterized by severe anemia, neutropenia, and thrombocytopenia caused by failure or destruction of multipotent myeloid stem cells, with inadequate production or release of differentiated cell lines.

Causes	Radiation, benzene, chloramphenicol, alkylating agents, antimetabolites, viral agents (parvovirus B19, EBV, HIV), Fanconi's anemia, idiopathic (immune mediated, 1° stem cell defect). May follow acute hepatitis.
Symptoms	Fatigue, malaise, pallor, purpura, mucosal bleeding, petechiae, infection.
Pathologic features	Pancytopenia with normal cell morphology; hypocellular bone marrow with fatty infiltration. Diagnose with bone marrow biopsy.
Treatment	Withdrawal of offending agent, allogeneic bone marrow transplantation, RBC and platelet transfusion, G-CSF or GM-CSF.

Blood dyscrasias

Sickle cell anemia	HbS mutation is a single amino acid replacement in β chain (substitution of normal glutamic acid with valine). Low O_2 or dehydration precipitates sickling. Heterozygotes (sickle cell trait) are relatively malaria resistant (balanced polymorphism). Complications in homozygotes (sickle cell disease) include aplastic crisis (due to parvovirus B19 infection), autosplenectomy, ↑ risk of encapsulated organism infection, *Salmonella* osteomyelitis, painful crisis (vaso-occlusive), renal papillary necrosis, and splenic sequestration crisis (see Color Image 21). Therapies for sickle cell anemia include hydroxyurea (↑ HbF) and bone marrow transplantation. HbC defect is a different β-chain mutation; patients with HbC or HbSC (1 of each mutant gene) have milder disease than do HbSS patients.	8% of African-Americans carry the HbS trait; 0.2% have the disease. Sickled cells are crescent-shaped RBCs. "Crew cut" on skull x-ray due to marrow expansion from ↑ erythropoiesis (also in thalassemias). Newborns—initially asymptomatic owing to ↑ HbF and ↓ HbS.
α-thalassemia	There are 4 α-globin genes. In α-thalassemia, the α-globin chain is underproduced (as a function of number of bad genes, 1–4). There is no compensatory ↑ of any other chains. HbH (β_4-tetramers, lacks 3 α-globin genes). Hb Barts (γ_4-tetramers, lacks all 4 α-globin genes) results in hydrops fetalis and intrauterine fetal death.	α-thalassemia is prevalent in Asia and Africa. β-thalassemia is prevalent in Mediterranean populations.
β-thalassemia	In β-thalassemia minor (heterozygote), the β chain is underproduced; in β-thalassemia major (homozygote), the β chain is absent. In both cases, fetal hemoglobin production is compensatorily ↑ but is inadequate. HbS/β-thalassemia heterozygote has mild to moderate disease (see Color Image 19).	β-thalassemia major results in severe anemia requiring blood transfusions. Cardiac failure due to 2° hemochromatosis. Marrow expansion ("crew cut" on skull x-ray) → skeletal deformities.

Hemolytic anemias	↑ serum bilirubin (jaundice, pigment gallstones), ↑ reticulocytes (marrow compensating for anemia).	
Autoimmune anemia	Mostly extravascular hemolysis (accelerated RBC destruction in liver Kupffer cells and spleen). **Warm** agglutinin (Ig**G**)—chronic anemia seen in SLE, in CLL, or with certain drugs (e.g., α-methyldopa). **Cold** agglutinin (Ig**M**)—acute anemia triggered by cold; seen with *Mycoplasma pneumoniae* infections or infectious mononucleosis. Erythroblastosis fetalis—seen in newborn due to Rh or other blood antigen incompatibility → mother's antibodies attack fetal RBCs.	Autoimmune hemolytic anemias are Coombs positive. Direct Coombs' test: anti-Ig Ab added to patient's RBCs agglutinate if RBCs are coated with Ig. Indirect Coombs' test: normal RBCs added to patient's serum agglutinate if serum has anti-RBC surface Ig. **Warm** weather is **GGG**reat. **Cold** ice cream . . . **MMM**.
Hereditary spherocytosis	Intrinsic, extravascular hemolysis due to spectrin or ankyrin defect. RBCs are small and round with no central pallor → less membrane → ↑ MCHC, ↑ RDW. Howell-Jolly bodies present after splenectomy.	Coombs negative. Osmotic fragility test used to confirm.
Paroxysmal nocturnal hemoglobinuria	Intravascular hemolysis due to membrane defect → ↑ sensitivity of RBCs to the lytic activity of complement (impaired synthesis of GP I anchor in RBC membrane).	↑ urine hemosiderin.
Microangiopathic anemia	Intravascular hemolysis seen in DIC, TTP/HUS, SLE, or malignant hypertension.	Schistocytes (helmet cells) seen on blood smear.
DIC	Activation of coagulation cascade leading to microthrombi and global consumption of platelets, fibrin, and coagulation factors.	
Causes	**S**epsis (gram-negative), **T**rauma, **O**bstetric complications, acute **P**ancreatitis, **M**alignancy, **N**ephrotic syndrome, **T**ransfusion.	**STOP M**aking **N**ew **T**hrombi!
Lab findings	↑ PT, ↑ PTT, ↑ fibrin split products (D-dimers), ↓ platelet count. Helmet-shaped cells and schistocytes on blood smear.	

Bleeding disorders

Platelet abnormalities	Causes include: 1. ITP (peripheral platelet destruction, antiplatelet antibodies, ↑ megakaryocytes) 2. TTP (↑ platelet aggregation → thrombosis → schistocytes, ↑ LDH, neurologic and renal symptoms, fever) 3. DIC (schistocytes, ↑ fibrin split products) 4. Aplastic anemia 5. Drugs (e.g., immunosuppressive agents)	Microhemorrhage: mucous membrane bleeding, epistaxis, petechiae, purpura, ↑ bleeding time.
Coagulation factor defects	Coagulopathies include: 1. Hemophilia A (factor VIII deficiency) 2. Hemophilia B (factor IX deficiency) 3. von Willebrand's disease (mild; most common bleeding disorder; deficiency of von Willebrand factor → defect of platelet adhesion and ↓ factor VIII survival)	Macrohemorrhage: hemarthroses (bleeding into joints), easy bruising, ↑ PT and/or PTT.

Hemorrhagic disorders

Disorder	Platelet count	Bleeding time	PT	PTT
Thrombocytopenia	↓	↑	—	—
Hemophilia A or B	—	—	—	↑
von Willebrand's disease	—	↑	—	↑
DIC	↓	↑	↑	↑
Vitamin K deficiency	—	—	↑	↑
Bernard-Soulier disease	↓	↑	—	—
Glanzmann's thrombasthenia	—	↑	—	—

Bernard-Soulier disease = defect of platelet adhesion (↓ GP Ib).
Glanzmann's thrombasthenia = defect of platelet a**G**gregation (↓ GP IIb-IIIa).
Note: platelet count must reach a very low value (15,000–20,000/mm^3) before generalized bleeding occurs; thrombocytopenia = < 100,000/mm^3.
PT (extrinsic)—factors II, V, VII, and X.
PTT (intrinsic)—all factors except VII.

Reed-Sternberg cells Distinctive tumor giant cell seen in Hodgkin's disease (see Color Image 25); binucleate or bilobed with the 2 halves as mirror images ("owl's eyes"). Necessary but not sufficient for a diagnosis of Hodgkin's disease. Variants include lacunar cells in nodular sclerosis variant.

Lymphomas

Hodgkin's

Presence of Reed-Sternberg cells (RS cells are CD30+ and CD15+ B-cell origin)
Localized, single group of nodes; extranodal rare; contiguous spread
Constitutional ("B") signs/symptoms—low-grade fever, night sweats, weight loss
Mediastinal lymphadenopathy
50% of cases associated with EBV; bimodal distribution—young and old; more common in men except for nodular sclerosing type
Good prognosis = ↑ lymphocytes, ↓ RS

Non-Hodgkin's

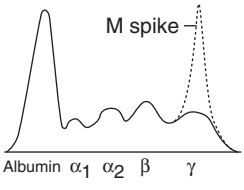
Associated with HIV and immunosuppression
Multiple, peripheral nodes; extranodal involvement common; noncontiguous spread
Majority involve B cells (except those of lymphoblastic T-cell origin)
No hypergammaglobulinemia
Fewer constitutional signs/symptoms
Peak incidence 20–40 years of age

Hodgkin's lymphoma

Type	RS	Lymphos	Prognosis	Comments
Nodular sclerosing (65–75%)	+	+++	Excellent	Most common; collagen banding; lacunar cells; women > men; primarily young adults.
Mixed cellularity (25%)	++++	+++	Intermediate	Numerous RS cells.
Lymphocyte predominant (6%)	+	++++	Excellent	< 35-year-old males.
Lymphocyte depleted (rare)	*	+	Poor	Older males with disseminated disease.

*RS high relative to lymphocytes.

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 the elderly (> 40–50 years of age). Destructive bone lesions and consequent hypercalcemia. Renal insufficiency, ↑ susceptibility to infection, and anemia. Associated with 1° amyloidosis (AL) and punched-out lytic bone lesions on x-ray. Characterized by monoclonal immunoglobulin spike (M protein) on serum protein electrophoresis and Ig light chains in urine (Bence Jones protein). Blood smear shows RBCs stacked like poker chips (rouleaux formation). Compare with Waldenström's macroglobulinemia → M spike = IgM (→ hyperviscosity symptoms); no lytic bone lesions (see Color Image 23).

If asymptomatic, called monoclonal gammopathy of undetermined significance (MGUS).

Non-Hodgkin's lymphoma

Type	Occurs in	Cell type	Genetics	Comments
Small lymphocytic lymphoma	Adults	B cells		Like CLL with focal mass; low grade.
Follicular lymphoma (small cleaved cell)	Adults	B cells	t(14;18) *bcl*-2 expression	Most common (adult). Difficult to cure; indolent course; *bcl*-2 inhibits apoptosis.
Diffuse large cell lymphoma	Usually older adults, but 20% occur in children	80% B cells 20% T cells (mature)		Aggressive, but up to 50% are curable.
Mantle cell lymphoma	Adults	B cells	t(11;14)	Poor prognosis, CD5+.
Lymphoblastic lymphoma	Most often children	T cells (immature)		Most common in children; commonly presents with ALL and mediastinal mass; very aggressive T-cell lymphoma.
Burkitt's lymphoma	Most often children	B cells	t(8;14) c-*myc* gene moves next to heavy-chain Ig gene (14)	"Starry-sky" appearance (sheets of lymphocytes with interspersed macrophages); associated with EBV; jaw lesion in endemic form in Africa; pelvis or abdomen in sporadic form (see Color Image 24).

Chromosomal translocations

Translocation	Associated disorder	
t(9;22) (**Philadelphia** chromosome)	**CML** (*bcr-abl* hybrid)	**Philadelphia** Crea**ML** cheese.
t(8;14)	Burkitt's lymphoma (c-*myc* activation)	
t(14;18)	Follicular lymphomas (*bcl*-2 activation)	
t(15;17)	M3 type of AML (responsive to all-*trans* retinoic acid)	
t(11;22)	Ewing's sarcoma	
t(11;14)	Mantle cell lymphoma	

Leukemoid reaction ↑ with left shift (e.g., 80% bands) and ↑ leukocyte alkaline phosphatase.

Leukemias

General considerations— ↑ number of circulating leukocytes in blood; bone marrow infiltrates of leukemic cells; marrow failure can cause anemia (↓ RBCs), infections (↓ mature WBCs), and hemorrhage (↓ platelets); leukemic cell infiltrates in liver, spleen, and lymph nodes are common (see Color Image 22).

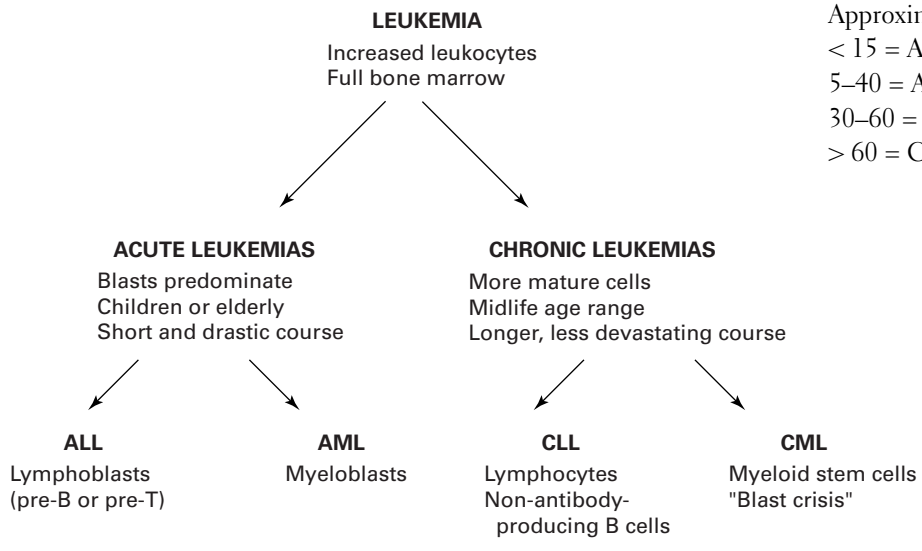
ALL — Children; lymphoblasts; TdT+ (marker of pre–T and pre–B cells); most responsive to therapy. May spread to CNS and testes.

AML — Auer rods; myeloblasts; adults.

CLL — Older adults (> 60 years of age); lymphadenopathy; hepatosplenomegaly; few symptoms; indolent course; ↑ smudge cells in peripheral blood smear; warm antibody autoimmune hemolytic anemia; very similar to SLL (small lymphocytic lymphoma).

CML — Defined by the Philadelphia chromosome (t[9;22], *bcr-abl*); myeloid stem cell proliferation; presents with ↑ neutrophils and metamyelocytes; splenomegaly; may accelerate to AML ("blast crisis"). Very low leukocyte alkaline phosphatase (vs. leukemoid reaction).

Hairy cell leukemia—mature B-cell tumor in the elderly. Cells have filamentous, hair-like projections. Stains TRAP (tartrate-resistant acid phosphatase) positive.



Approximate ages:
< 15 = ALL
5–40 = AML
30–60 = CML
> 60 = CLL

Auer bodies (rods) Auer rods are peroxidase-positive cytoplasmic inclusions in granulocytes and myeloblasts. Primarily seen in acute promyelocytic leukemia (M3). Treatment of AML M3 can release Auer rods → DIC.

Histiocytosis X Caused by Langerhans cells from the monocyte lineage that infiltrate the lung. Birbeck granules ("tennis rackets" on EM). Primarily affects young adults. Worse with smoking.

Heparin

Mechanism	Catalyzes the activation of antithrombin III, ↓ thrombin and Xa. Short half-life.
Clinical use	Immediate anticoagulation for pulmonary embolism, stroke, angina, MI, DVT. Used during pregnancy (does not cross placenta). Follow PTT.
Toxicity	Bleeding, thrombocytopenia (HIT), osteoporosis, drug-drug interactions. For rapid reversal of heparinization, use **protamine sulfate** (positively charged molecule that acts by binding negatively charged heparin).
Notes	Newer **low-molecular-weight heparins** (enoxaparin) act more on Xa, have better bioavailability and 2–4 times longer half-life. Can be administered subcutaneously and without laboratory monitoring. Not easily reversible.
	Heparin-induced thrombocytopenia (HIT)—heparin binds platelets, causing autoantibody production that destroys platelets and overactivates the remaining ones, resulting in a thrombocytopenic, hypercoagulable state.

Lepirudin, bivalirudin — Hirudin derivatives; directly inhibit thrombin. Used as an alternative to heparin for anticoagulating patients with HIT.

Warfarin (Coumadin)

Mechanism	Interferes with normal synthesis and γ-carboxylation of vitamin K–dependent clotting factors II, VII, IX, and X and protein C and S. Metabolized by the cytochrome P-450 pathway. Affects **EX**trinsic pathway and ↑ **PT.** Long half-life.	The **EX-P**a**T**riot went to **WAR**(farin).
Clinical use	Chronic anticoagulation. Not used in pregnant women (because warfarin, unlike heparin, can cross the placenta). Follow PT/INR values.	
Toxicity	Bleeding, teratogenic, skin/tissue necrosis, drug-drug interactions.	

Heparin vs. warfarin

	Heparin	Warfarin
Structure	Large anionic polymer, acidic	Small lipid-soluble molecule
Route of administration	Parenteral (IV, SC)	Oral
Site of action	Blood	Liver
Onset of action	Rapid (seconds)	Slow, limited by half-lives of normal clotting factors
Mechanism of action	Activates antithrombin III, which ↓ the action of IIa (thrombin) and Xa	Impairs the synthesis of vitamin K–dependent clotting factors II, VII, IX, and X (vitamin K antagonist)
Duration of action	Acute (hours)	Chronic (days)
Inhibits coagulation in vitro	Yes	No
Treatment of acute overdose	Protamine sulfate	IV vitamin K and fresh frozen plasma
Monitoring	PTT (intrinsic pathway)	PT/INR (extrinsic pathway)
Crosses placenta	No	Yes (teratogenic)

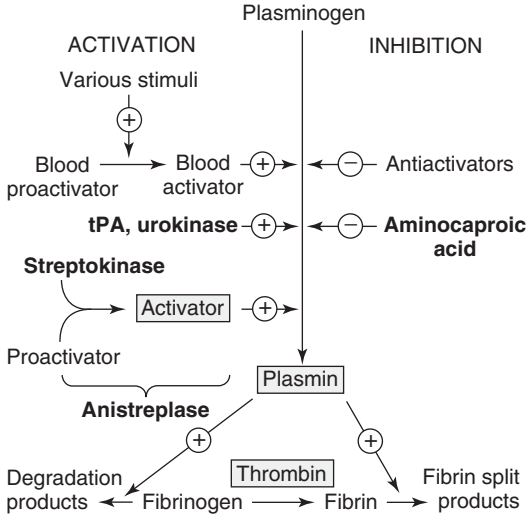
Thrombolytics

Streptokinase, urokinase, tPA (alteplase), APSAC (anistreplase).

Mechanism: Directly or indirectly aid conversion of plasminogen to plasmin, the major fibrinolytic enzyme, which cleaves thrombin and fibrin clots. ↑ PT, ↑ PTT, no change in platelet count.

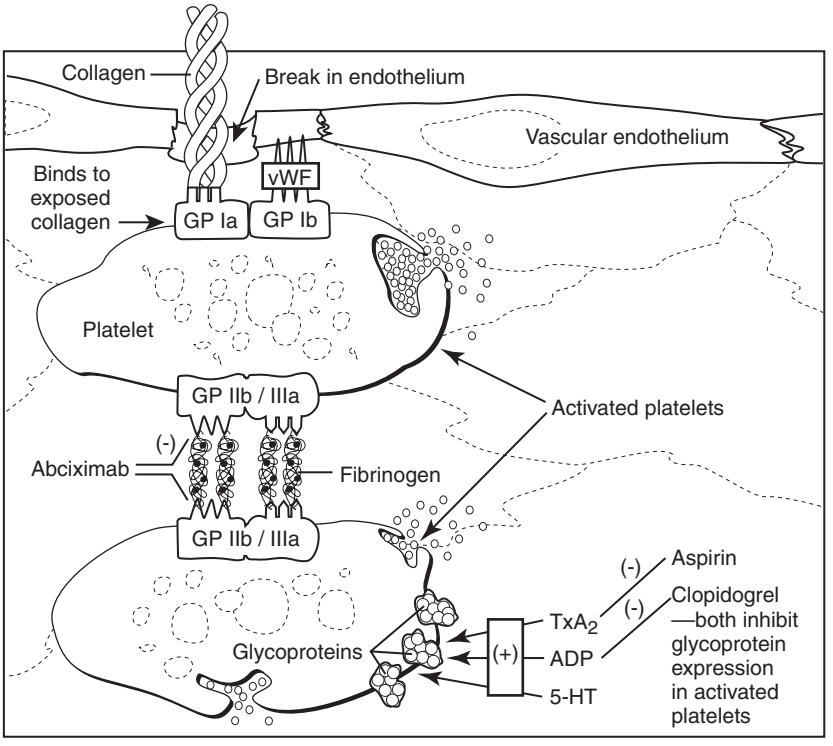
Clinical use: Early MI, early ischemic stroke.

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.



(Adapted, with permission, from Katzung BG. *Basic and Clinical Pharmacology,* 7th ed. Stamford, CT: Appleton & Lange, 1997: 550.)

Mechanism of antiplatelet interaction



Aspirin (ASA)

Mechanism	Acetylates and irreversibly inhibits cyclooxygenase (both COX-1 and COX-2) to prevent conversion of arachidonic acid to thromboxane A_2. ↑ bleeding time. No effect on PT, PTT.
Clinical use	Antipyretic, analgesic, anti-inflammatory, antiplatelet drug.
Toxicity	Gastric ulceration, bleeding, hyperventilation, Reye's syndrome, tinnitus (CN VIII).

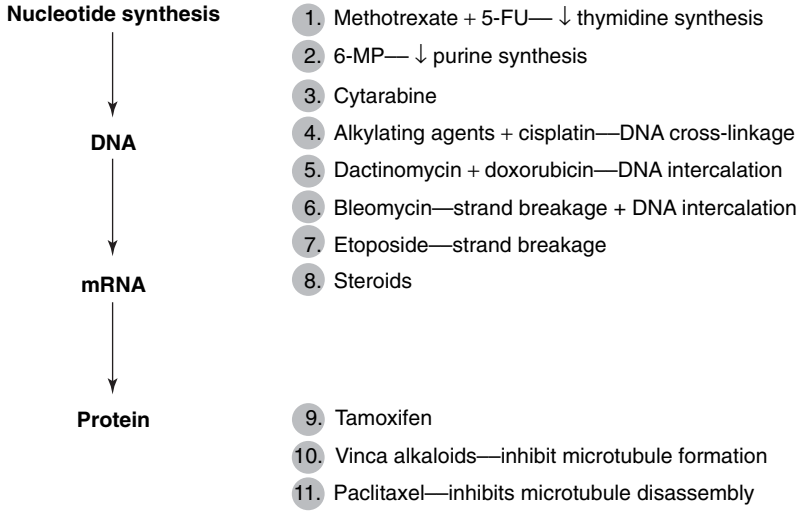
Clopidogrel, ticlopidine

Mechanism	Inhibit platelet aggregation by irreversibly blocking ADP receptors. Inhibit fibrinogen binding by preventing glycoprotein IIb/IIIa expression.
Clinical use	Acute coronary syndrome; coronary stenting. ↓ incidence or recurrence of thrombotic stroke.
Toxicity	Neutropenia (ticlopidine).

Abciximab

Mechanism	Monoclonal antibody that binds to the glycoprotein receptor IIb/IIIa on activated platelets, preventing aggregation.
Clinical use	Acute coronary syndromes, percutaneous transluminal coronary angioplasty.
Toxicity	Bleeding, thrombocytopenia.

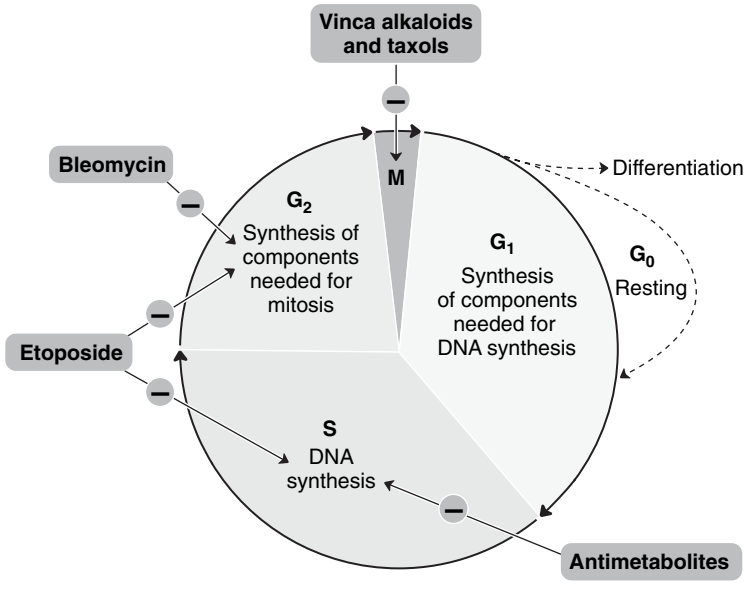
Cancer drugs—site of action



Cell cycle specific—antimetabolites (MTX, 5-FU, 6-MP), etoposide, bleomycin, vinca alkaloids, paclitaxel.

Cell cycle nonspecific—alkylating agents, antibiotics (dactinomycin, doxorubicin).

Cancer drugs—cell cycle



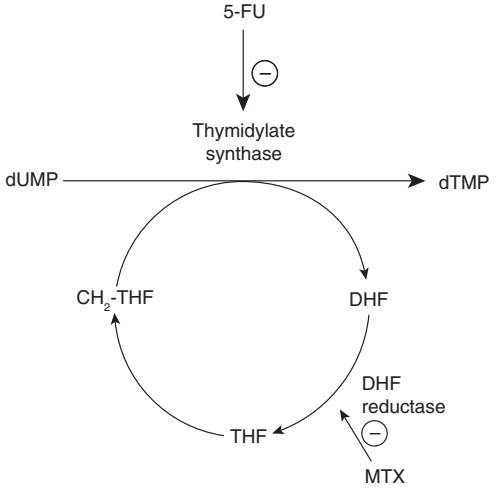
(Adapted, with permission, from Katzung BG, Trevor AJ. *USMLE Road Map: Pharmacology*, 1st ed. New York: McGraw-Hill, 2003: 133.)

Methotrexate (MTX)

Mechanism	S-phase-specific antimetabolite. Folic acid analog that inhibits dihydrofolate reductase, resulting in ↓ dTMP and therefore ↓ DNA and protein synthesis.
Clinical use	Leukemias, lymphomas, choriocarcinoma, sarcomas. Abortion, ectopic pregnancy, rheumatoid arthritis, psoriasis.
Toxicity	Myelosuppression, which is reversible with leucovorin (folinic acid) "rescue." Macrovesicular fatty change in liver. Mucositis.

5-fluorouracil (5-FU)

Mechanism	S-phase-specific antimetabolite. Pyrimidine analog bioactivated to 5F-dUMP, which covalently complexes folic acid. This complex inhibits thymidylate synthase, resulting in ↓ dTMP and same effects as MTX.
Clinical use	Colon cancer and other solid tumors, basal cell carcinoma (topical). Synergy with MTX.
Toxicity	Myelosuppression, which is NOT reversible with leucovorin; photosensitivity. Can "rescue" with thymidine.



6-mercaptopurine (6-MP)

Mechanism	Blocks de novo purine synthesis. Activated by HGPRTase.
Clinical use	Leukemias, lymphomas (not CLL or Hodgkin's).
Toxicity	Bone marrow, GI, liver. Metabolized by xanthine oxidase; thus ↑ toxicity with allopurinol.

Cytarabine (ara-C)

Mechanism	Inhibits DNA polymerase.
Clinical use	AML.
Toxicity	Leukopenia, thrombocytopenia, megaloblastic anemia.

Cyclophosphamide, ifosfamide

Mechanism	Alkylating agents; covalently x-link (interstrand) DNA at guanine N-7. Require bioactivation by liver.
Clinical use	Non-Hodgkin's lymphoma, breast and ovarian carcinomas. Also immunosuppressants.
Toxicity	Myelosuppression; hemorrhagic cystitis, which can be partially prevented with mesna.

Nitrosoureas Carmustine, lomustine, semustine, streptozocin.

Mechanism	Alkylate DNA. Require bioactivation. Cross blood-brain barrier → CNS.
Clinical use	Brain tumors (including glioblastoma multiforme).
Toxicity	CNS toxicity (dizziness, ataxia).

Cisplatin, carboplatin

Mechanism	Act like alkylating agents.
Clinical use	Testicular, bladder, ovary, and lung carcinomas.
Toxicity	Nephrotoxicity and acoustic nerve damage.

Busulfan

Mechanism	Alkylates DNA.
Clinical use	CML.
Toxicity	Pulmonary fibrosis, hyperpigmentation.

Doxorubicin (Adriamycin), daunorubicin

Mechanism	Generate free radicals and noncovalently intercalate in DNA (creating breaks in DNA strand to ↓ replication).
Clinical use	Part of the **A**BVD combination regimen for Hodgkin's and for myelomas, sarcomas, and solid tumors (breast, ovary, lung).
Toxicity	Cardiotoxicity; also myelosuppression and marked alopecia. Toxic extravasation.

Dactinomycin (actinomycin D)

Mechanism	Intercalates in DNA.	**ACT**inomycin D is used for childhood tumors (children **ACT** out).
Clinical use	Wilms' tumor, Ewing's sarcoma, rhabdomyosarcoma.	
Toxicity	Myelosuppression.	

Bleomycin

Mechanism	Induces formation of free radicals, which cause breaks in DNA strands.
Clinical use	Testicular cancer, lymphomas (part of the A**B**VD regimen for Hodgkin's).
Toxicity	Pulmonary fibrosis, skin changes, but minimal myelosuppression.

Hydroxyurea

Mechanism	Inhibits **R**ibonucleotide **R**eductase → ↓ DNA **S**ynthesis (**S**-phase specific).
Clinical use	Melanoma, CML, sickle cell disease.
Toxicity	Bone marrow suppression, GI upset.

Etoposide (VP-16)

Mechanism	G_2-phase-specific agent that inhibits topoisomerase II and ↑ DNA degradation.
Clinical use	Small cell carcinoma of the lung and prostate, testicular carcinoma.
Toxicity	Myelosuppression, GI irritation, alopecia.

Prednisone

Mechanism	May trigger apoptosis. May even work on nondividing cells.
Clinical use	Most commonly used glucocorticoid in cancer chemotherapy. Used in CLL, Hodgkin's lymphomas (part of the MOP**P** regimen). Also an immunosuppressant used in autoimmune diseases.
Toxicity	Cushing-like symptoms; immunosuppression, cataracts, acne, osteoporosis, hypertension, peptic ulcers, hyperglycemia, psychosis.

Tamoxifen, raloxifene

Mechanism	Receptor antagonists in breast, agonists in bone; block the binding of estrogen to estrogen receptor–positive cells.
Clinical use	Breast cancer. Also useful to prevent osteoporosis.
Toxicity	Tamoxifen may ↑ the risk of endometrial carcinoma via partial agonist effects; "hot flashes." Raloxifene does not cause endometrial carcinoma because it is an endometrial antagonist.

Trastuzumab (Herceptin)

Mechanism	Monoclonal antibody against HER-2 (*erb*-B2). Helps kill breast cancer cells that overexpress HER-2, possibly through antibody-dependent cytotoxicity.
Clinical use	Metastatic breast cancer.
Toxicity	Cardiotoxicity.

Imatinib (Gleevec)

Mechanism	Philadelphia chromosome *bcr-abl* tyrosine kinase inhibitor.
Clinical use	CML, GI stromal tumors.
Toxicity	Fluid retention.

Vincristine, vinblastine

Mechanism	M-phase-specific alkaloids that bind to tubulin and block polymerization of microtubules so that mitotic spindle cannot form. Microtubules are the **vines** of your cells.
Clinical use	Part of the M**O**PP (**O**ncovin [vincristine]) regimen for lymphoma, Wilms' tumor, choriocarcinoma.
Toxicity	Vincristine—neurotoxicity (areflexia, peripheral neuritis), paralytic ileus. Vin**BLAST**ine **BLAST**s **B**one marrow (suppression).

Paclitaxel, other taxols

Mechanism	M-phase-specific agents that bind to tubulin and hyperstabilize polymerized microtubules so that mitotic spindle cannot break down (anaphase cannot occur).
Clinical use	Ovarian and breast carcinomas.
Toxicity	Myelosuppression and hypersensitivity.

Musculoskeletal and Connective Tissue

- High-Yield Clinical Vignettes
- Anatomy and Physiology
- Pathology
- Pharmacology

"I just use my muscles like a conversation piece, like someone walking a cheetah down 42nd Street."

—Arnold Schwarzenegger

"There's 215 bones in the human body. That's one."

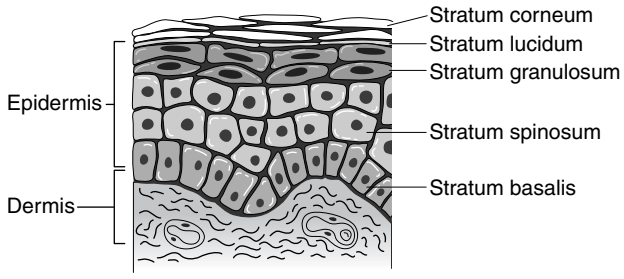
—Sarah Connor in *Terminator 2: Judgment Day*

▪ Soccer player who was kicked in the leg suffered a damaged medial meniscus.	What else is likely to have been damaged?	Anterior cruciate ligament (remember the "unhappy triad").
▪ Gymnast dislocates her shoulder anteriorly.	What nerve is most likely to have been damaged?	Axillary nerve (C5, C6).
▪ X-ray shows bilateral hilar lymphadenopathy.	What is the diagnosis?	Sarcoidosis.
▪ 25-year-old woman presents with a low-grade fever, a rash across her nose that gets worse when she is out in the sun, and widespread edema.	You are concerned about what disease?	SLE.
▪ 85-year-old man presents with acute knee pain and swelling. X-ray shows joint space without erosion.	What is the diagnosis, and what would you find on aspiration?	Pseudogout; rhomboid calcium pyrophosphate crystals.
▪ Patient describes ↓ prick sensation on the lateral aspect of her leg and foot.	A deficit in what muscular action can also be expected?	Dorsiflexion and eversion of the foot (common peroneal nerve).
▪ Elderly woman presents with arthritis, pain, numbness, and tingling over the lateral digits of her right hand. On exam, she has wasting of the thenar eminence.	What is the diagnosis?	Carpal tunnel syndrome, median nerve compression.
▪ 20-year-old dancer reports ↓ plantar flexion and ↓ sensation over the back of her thigh, calf, and lateral half of her foot.	What spinal nerve is involved?	Tibial (L4–S3).
▪ Teen falls while rollerblading and hurts his elbow. He can't feel the medial part of his palm.	Which nerve and what injury?	Ulnar nerve due to broken medial condyle.
▪ Field hockey player presents to the ER after falling on her arm during practice. X-ray shows midshaft break of the humerus.	Which nerve and which artery are most likely damaged?	The radial nerve and deep brachial artery, which run together.

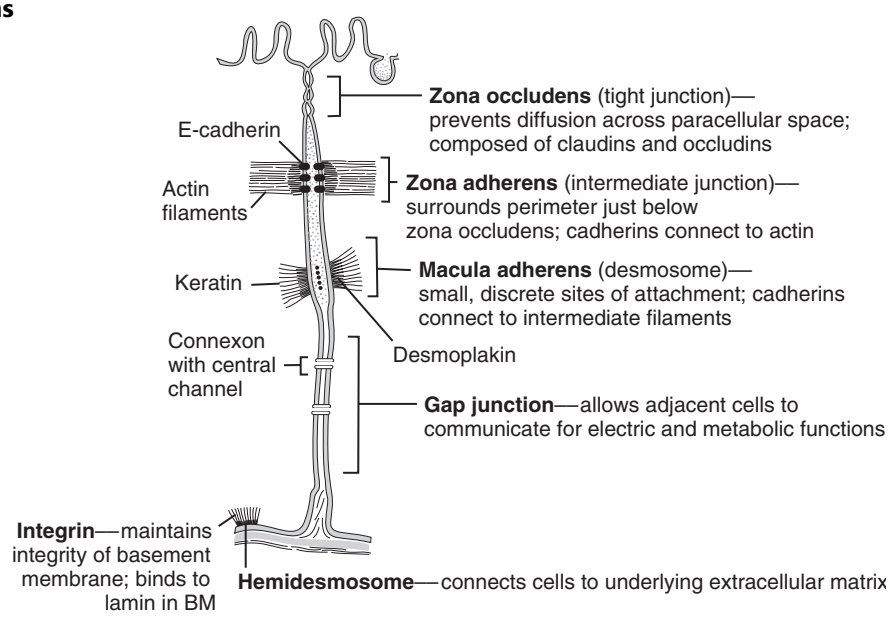
Epidermis layers

From surface to base: stratum **C**orneum, stratum **L**ucidum, stratum **G**ranulosum, stratum **S**pinosum, stratum **B**asalis.

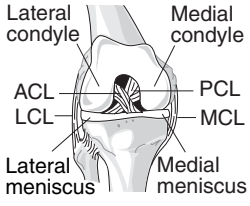
Californians **L**ike **G**irls in **S**tring **B**ikinis.



Epithelial cell junctions



Unhappy triad/ knee injury



This common football injury (caused by clipping from the lateral side) consists of damage to medial collateral ligament (MCL), medial meniscus, and anterior cruciate ligament (ACL).

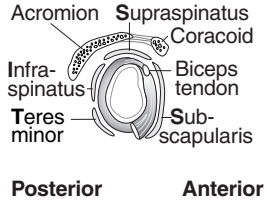
PCL = posterior cruciate ligament. LCL = lateral collateral ligament.

"Anterior" and "posterior" in ACL and PCL refer to sites of **tibial** attachment.

Positive anterior drawer sign indicates tearing of the ACL.

Abnormal passive abduction indicates a torn MCL.

Rotator cuff muscles



Shoulder muscles that form the rotator cuff:

Supraspinatus—helps deltoid abduct arm.

Infraspinatus—laterally rotates arm.

Teres minor—adducts and laterally rotates arm.

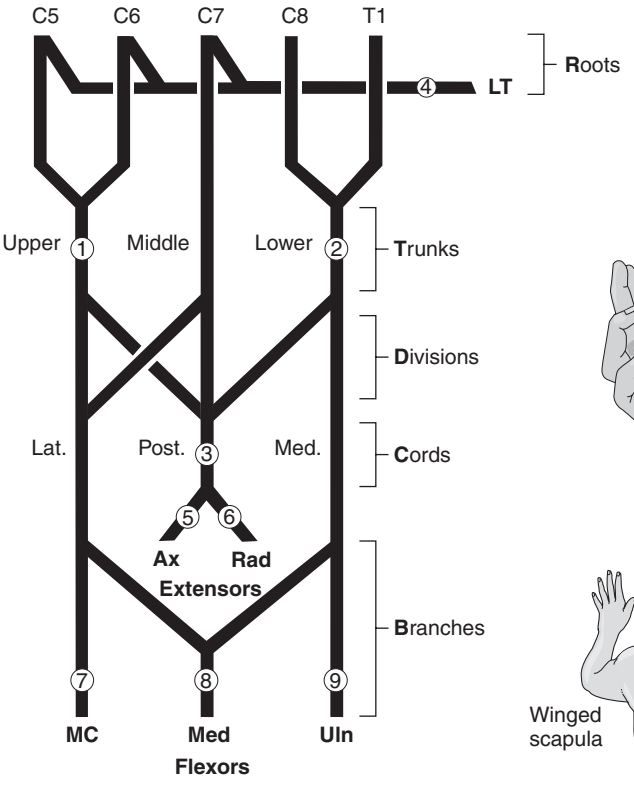
Subscapularis—medially rotates and adducts arm.

SItS (small t is for teres minor).

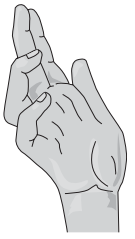
Brachial plexus

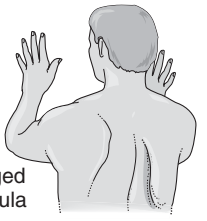
1. Waiter´s tip (Erb's palsy)
2. Claw hand (Klumpke's palsy)
3. Wrist drop
4. Winged scapula
5. Deltoid paralysis
6. Saturday night palsy (wrist drop)
7. Difficulty flexing elbow, variable sensory loss
8. ↓ thumb function, Pope´s blessing
9. Intrinsic muscles of hand, claw hand

Rad = radial nerve
Ax = axillary nerve
LT = long thoracic nerve
MC = musculocutaneous nerve
Med = median nerve
Uln = ulnar nerve



Randy
Travis
Drinks
Cold
Beer.

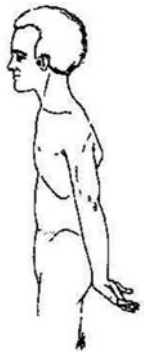




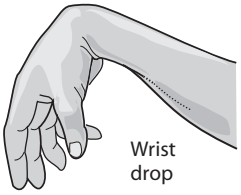
Clavicle fracture is relatively common—brachial plexus is protected from injury by subclavius muscle.

Upper extremity nerves

Common injury	Extensor/flexor	Motor deficit	Sensory deficit
Shoulder dislocation	Extensor	Can't abduct arm > 90°	
Midshaft humerus fracture	Extensor Flexor	Wrist drop Can't flex at elbow	Posterior arm and dorsal hand (excluding fingertips as well as little and ½ of ring fingers) Lateral arm
Supracondylar humerus fracture or wrist swelling/fracture (carpal tunnel syndrome)	Flexor (abduction and opposition of thumb)	Can't flex fingers; can't abduct/oppose thumb	Palmar aspect (and dorsal tips) of thumb, index, middle, and ½ of ring fingers
Fracture at medial epicondyle of humerus or wrist fracture	Flexor (adduction of thumb and both abduction and adduction of fingers)	Claw hand—can't adduct thumb; can't abduct or adduct fingers	Palmar and dorsal aspect of little finger and ½ of ring finger

Erb-Duchenne palsy 	Traction or tear of the upper trunk of the brachial plexus (C5 and C6 roots); follows blow to shoulder or trauma during delivery. Findings: limb hangs by side (paralysis of abductors), medially rotated (paralysis of lateral rotators), forearm is pronated (loss of biceps).	"Waiter's tip" owing to appearance of arm.
Thoracic outlet syndrome (Klumpke's palsy)	An embryologic defect; can compress subclavian artery and inferior trunk of brachial plexus (C8, T1), resulting in thoracic outlet syndrome: 1. Atrophy of the thenar and hypothenar eminences 2. Atrophy of the interosseous muscles 3. Sensory deficits on the medial side of the forearm and hand 4. Disappearance of the radial pulse upon moving the head toward the opposite side	

Radial nerve

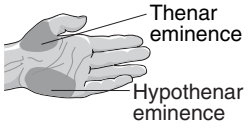


Known as the "great extensor nerve." Provides innervation of the **B**rachioradialis, **E**xtensors of the wrist and fingers, **S**upinator, and **T**riceps.

Radial nerve innervates the **BEST!**

To **SUP**inate is to move as if carrying a bowl of **SOUP.**

Hand muscles



Thenar—**O**pponens pollicis, **A**bductor pollicis brevis, **F**lexor pollicis brevis.

Hypothenar—**O**pponens digiti minimi, **A**bductor digiti minimi, **F**lexor digiti minimi.

Dorsal interosseous muscles—abduct the fingers.

Palmar interosseous muscles—adduct the fingers.

Lumbrical muscles—flex at the MP joint.

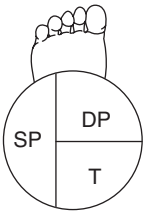
Both groups perform the same functions: **O**ppose, **A**bduct, and **F**lex (**OAF**).

DAB = **D**orsals **AB**duct.

PAD = **P**almars **AD**duct.

Lower extremity nerves

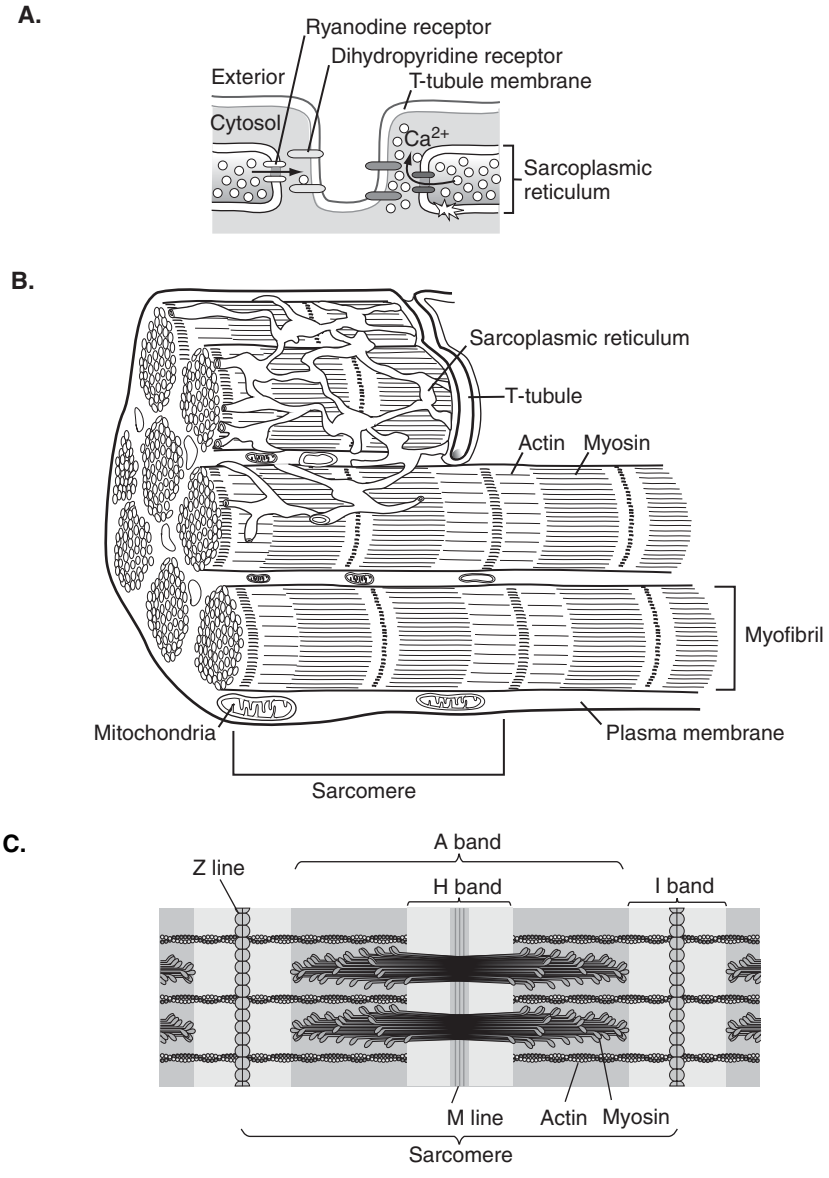
Nerve name	Cause of injury	Motor deficit	Sensory deficit
Obturator	Anterior hip dislocation	Can't adduct thigh	Medial thigh
Femoral	Pelvic fracture	Can't flex thigh or extend leg	Anterior thigh and medial leg
Common peroneal	Trauma to lateral aspect of leg or fibula neck fracture	Can't evert or dorsiflex foot; can't extend toes	Anterolateral leg and dorsal aspect of foot
Tibial	Knee trauma	Can't invert or plantarflex foot; can't flex toes	Sole of foot
Superior gluteal	Posterior hip dislocation or polio	Can't abduct thigh (positive Trendelenburg sign)	
Inferior gluteal	Posterior hip dislocation	Can't jump, climb stairs, or rise from seated position	



PED = **P**eroneal **E**verts and **D**orsiflexes; if injured, foot drop**PED.**

TIP = **T**ibial **I**nverts and **P**lantarflexes; if injured, can't stand on **TIP**toes.

Muscle conduction to contraction

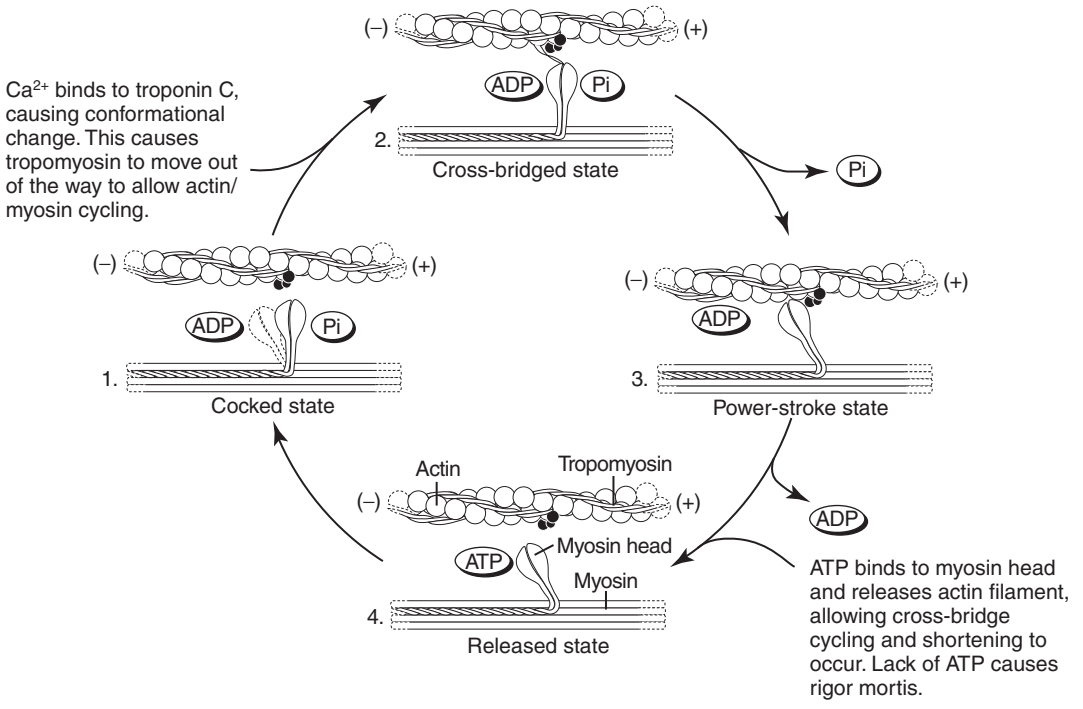


A band = length of myosin, I band = only actin, H band = only myosin,
Z line = actin attachment, M line = myosin attachment.

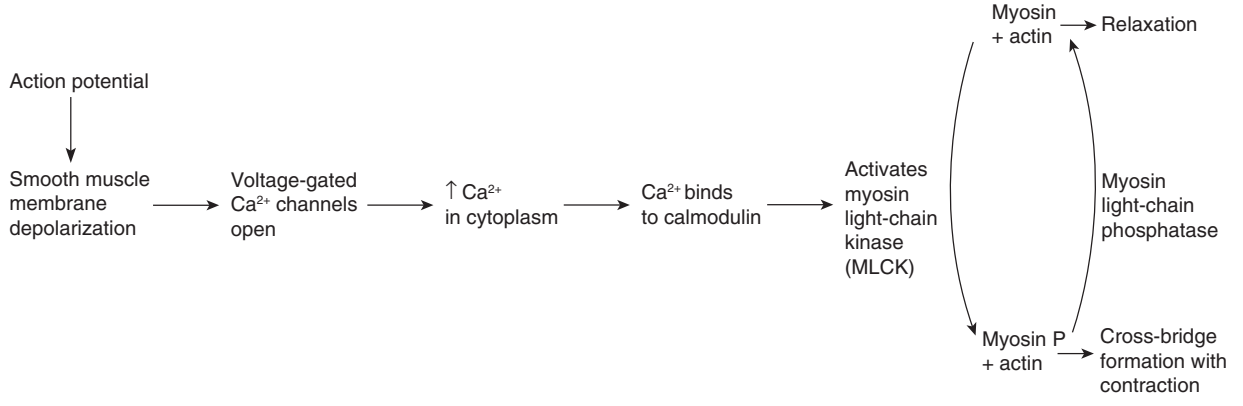
Action potential:

1. Action potential depolarization opens voltage-gated Ca^{2+} channels, inducing neurotransmitter release.
2. Postsynaptic ligand binding leads to muscle cell depolarization in the motor end plate.
3. Depolarization travels along muscle cell and down the T-tubule.
4. Depolarization of the voltage-sensitive dihydropyridine receptor, coupled to the ryanodine receptor on the sarcoplasmic reticulum, induces a conformational change causing Ca^{2+} release (calcium-induced calcium release).
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 is displaced on the actin filament (power stroke). Contraction results in H- and I band shortening, but the A band remains the same length (**A** band is **A**lways the same length).

Skeletal and cardiac muscle contraction



Smooth muscle contraction



Bone formation

Endochondral ossification	Longitudinal bone growth. Cartilaginous model of bone is first made by chondrocytes. Osteoclasts and osteoblasts later replace with woven bone and remodel to lamellar bone.	Osteoblast source—mesenchymal stem cells in periosteum.
Membranous ossification	Flat bone growth (skull, facial bones, and axial skeleton). Woven bone formed directly without cartilage. Later remodeled to lamellar bone.	

Achondroplasia

Autosomal-dominant trait. Failure of longitudinal bone growth → short limbs. Membranous ossification is not affected. Impaired cartilage maturation in growth plate caused by fibroblast growth factor receptor mutation. Normal life span and fertility.

Osteoporosis

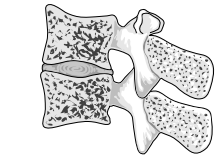
Reduction of bone mass in spite of normal bone mineralization. Sparse trabeculae.

Type I

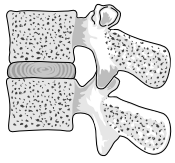
Postmenopausal; ↑ bone resorption due to ↓ estrogen levels. Estrogen replacement is controversial as prophylaxis (side effects).

Type II

Senile osteoporosis—affects men and women > 70 years.



Mild compression fracture



Normal vertebra

Vertebral crush fractures—acute back pain, loss of height, kyphosis.

Distal radius (Colles') fractures, vertebral wedge fractures.

Prophylaxis: exercise and calcium ingestion before age 30.

Treatment: estrogen and/or calcitonin; bisphosphonates or pulsatile PTH for severe cases. Glucocorticoids are contraindicated.

Osteopetrosis (marble bone disease)

Failure of normal bone resorption → thickened, dense bones. Bone defect is due to abnormal function of osteoclasts. Serum calcium, phosphate, and **alkaline phosphatase** are **normal.** ↓ marrow space leads to anemia, thrombocytopenia, infection. Genetic deficiency of carbonic anhydrase II. X-rays shows "Erlenmeyer flask" bones that flare out. Can result in cranial nerve impingement and palsies due to narrowed foramina.

Osteomalacia/rickets

Defective mineralization/calcification of osteoid → soft bones. Vitamin D deficiency in adults → ↓ calcium levels → ↑ secretion of PTH, ↓ in serum phosphate. Reversible when vitamin D is replaced. Vitamin D deficiency in childhood causes rickets.

Osteitis fibrosa cystica

Caused by hyperparathyroidism. Characterized by "brown tumors" (cystic spaces lined by osteoclasts, filled with fibrous stroma and sometimes blood). High serum calcium, low serum phosphorus, and high ALP.

Paget's disease (osteitis deformans)

Abnormal bone architecture caused by ↑ in both osteoblastic and osteoclastic activity. Possibly viral in origin. Serum calcium, phosphorus, and PTH levels are normal. ↑ **ALP.** Mosaic bone pattern; long bone chalk-stick fractures. ↑ blood flow from ↑ arteriovenous shunts may cause high-output CHF. Can lead to osteogenic sarcoma.

Hat size can be ↑; hearing loss is common due to auditory foramen narrowing.

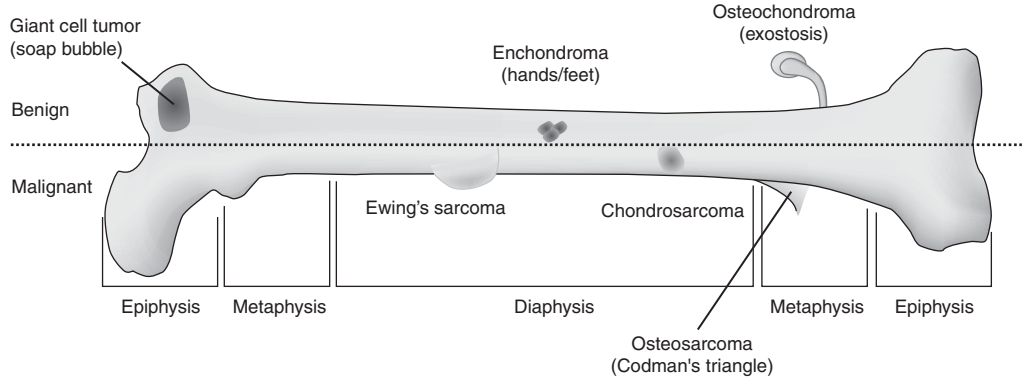
Polyostotic fibrous dysplasia	Bone is replaced by fibroblasts, collagen, and irregular bony trabeculae. Affects many bones. **McCune-Albright syndrome** is a form of polyostotic fibrous dysplasia characterized by multiple unilateral bone lesions associated with endocrine abnormalities (precocious puberty) and unilateral pigmented skin lesions (café-au-lait spots/"coast of Maine" spots).

Primary bone tumors

Benign	
Osteoma	Associated with Gardner's syndrome (FAP). New piece of bone grows on another piece of bone, often in the skull.
Osteoid osteoma	Interlacing trabeculae of woven bone surrounded by osteoblasts. < 2 cm and found in proximal tibia and femur. Most common in men < 25 years of age.
Osteoblastoma	Same morphologically as osteoid osteoma, but larger and found in vertebral column.
Giant cell tumor (osteoclastoma)	Occurs most commonly at epiphyseal end of long bones. Peak incidence 20–40 years of age. Locally aggressive benign tumor often around the distal femur, proximal tibial region (knee). Characteristic "double bubble" or "soap bubble" appearance on x-ray. Spindle-shaped cells with multinucleated giant cells.
Osteochondroma (exostosis)	Most common benign bone tumor. Mature bone with cartilaginous cap. Usually in men < 25 years of age. Commonly originates from long metaphysis. Malignant transformation to chondrosarcoma is rare.
Enchondroma	Benign cartilaginous neoplasm found in intramedullary bone. Usually distal extremities (vs. chondrosarcoma).
Malignant	
Osteosarcoma (osteogenic sarcoma)	2nd most common 1° malignant tumor of bone (after multiple myeloma). Peak incidence in men 10–20 years of age. Commonly found in the metaphysis of long bones, often around distal femur, proximal tibial region (knee). Predisposing factors include Paget's disease of bone, bone infarcts, radiation, and familial retinoblastoma. Codman's triangle or sunburst pattern (from elevation of periosteum) on x-ray. Poor prognosis.
Ewing's sarcoma	Anaplastic small blue cell malignant tumor. Most common in boys < 15. Extremely aggressive with early mets, but responsive to chemotherapy. Characteristic "**onion**-skin" appearance in bone ("going out for E**wings** and **onion** rings"). Commonly appears in diaphysis of long bones, pelvis, scapula, and ribs. 11;22 translocation.
Chondrosarcoma	Malignant cartilaginous tumor. Most common in men aged 30–60. Usually located in pelvis, spine, scapula, humerus, tibia, or femur. May be of 1° origin or from osteochondroma. Expansile glistening mass within the medullary cavity.

Primary bone tumor locations

	Benign	Malignant
Epiphysis	Giant cell tumor (osteoclastoma)	—
Metaphysis	Osteochondroma	Osteosarcoma
Diaphysis	Osteoid osteoma	Ewing's sarcoma
Intramedullary	Enchondroma	Chondrosarcoma

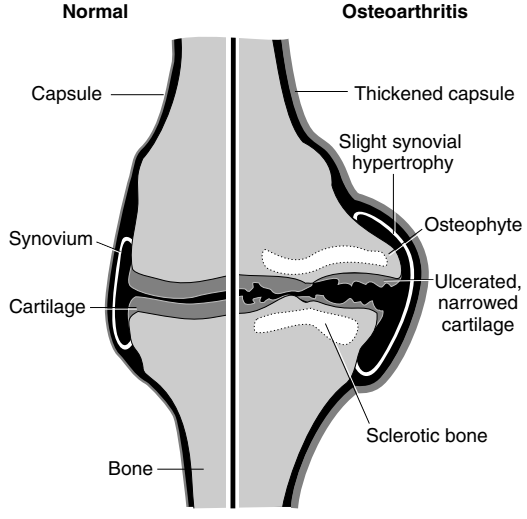


Osteoarthritis

Mechanical—wear and tear of joints leads to destruction of articular cartilage (see Image 144), subchondral cysts, sclerosis, osteophytes, eburnation, Heberden's nodes (DIP), and Bouchard's nodes (PIP).

Predisposing factors: age, obesity, joint deformity.

Classic presentation: pain in weight-bearing joints after use (e.g., at the end of the day), improving with rest. No systemic symptoms.



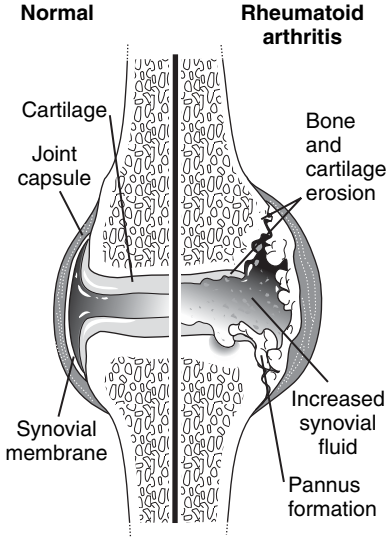
(Adapted, with permission, from Stobo J et al. *The Principles and Practice of Medicine,* 23rd ed. Stamford, CT: Appleton & Lange, 1996: 241.)

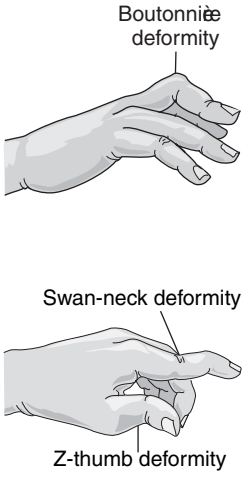
Rheumatoid arthritis

Autoimmune—inflammatory disorder affecting synovial joints, with pannus formation in joints (MCP, PIP), subcutaneous rheumatoid nodules, ulnar deviation, subluxation (see Color Image 56).

Females > males. 80% of RA patients have positive rheumatoid factor (anti-IgG antibody). Strong association with HLA-DR4.

Classic presentation: morning stiffness improving with use, symmetric joint involvement, and systemic symptoms (fever, fatigue, pleuritis, pericarditis).





Sjögren's syndrome

Classic triad:

1. Xerophthalmia (dry eyes, conjunctivitis)
2. Xerostomia (dry mouth, dysphagia)
3. Arthritis

Parotid enlargement, ↑ risk of B-cell lymphoma, dental caries. Autoantibodies to ribonucleoprotein antigens, SS-A (Ro), SS-B (La).

Predominantly affects females between 40 and 60 years of age.

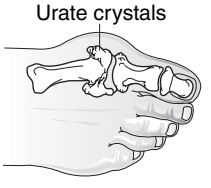
Associated with rheumatoid arthritis.

Sicca syndrome—dry eyes, dry mouth, nasal and vaginal dryness, chronic bronchitis, reflux esophagitis.

Gout

Symptoms: Asymmetric joint distribution. Joint is swollen, red, and painful. Classic manifestation is painful MTP joint of the big toe (podagra). Tophus formation (often on external ear or Achilles tendon). Acute attack tends to occur after alcohol consumption or a large meal.

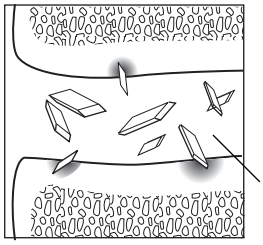
Findings: Precipitation of monosodium urate crystals into joints due to hyperuricemia, which can be caused by Lesch-Nyhan syndrome, PRPP excess, ↓ excretion of uric acid (e.g., thiazide diuretics), ↑ cell turnover, or von Gierke's disease. Crystals are needle shaped and **negatively birefringent** (see Color Image 54). More common in men.



Treatment: Allopurinol, probenecid, colchicine, and NSAIDs.

Pseudogout

Caused by deposition of calcium pyrophosphate crystals within the joint space. Forms basophilic, rhomboid crystals that are **weakly positively birefringent.** Usually affects large joints (classically the knee). > 50 years old; both sexes affected equally. No treatment.



Gout—crystals are ye**ll**ow when parallel (∥) to the light.

Pseudogout—crystals are yellow when perpendicular (⊥) to the light. **P**seudogout is **P**ositively birefringent.

Infectious arthritis

Septic	*S. aureus*, *Streptococcus*, and *Neisseria gonorrhoeae* are common. **Gonococcal arthritis** presents as a monoarticular, migratory arthritis with an asymmetrical pattern. Affected joint is swollen, red, and painful.	
Chronic	TB (from mycobacterial dissemination) and Lyme disease.	

Seronegative spondylo-arthropathies

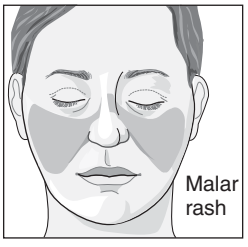
Arthritis without rheumatoid factor (no anti-IgG antibody). Strong association with HLA-B27 (gene that codes for HLA MHC I). Occurs more often in males.

Ankylosing spondylitis	Chronic inflammatory disease of spine and sacroiliac joints → ankylosis (stiff spine), uveitis, and aortic regurgitation.	Bamboo spine.
Reiter's syndrome	Classic triad: 1. Conjunctivitis and anterior uveitis 2. Urethritis 3. Arthritis	"Can't **see,** can't **pee,** can't climb a **tree.**" Post-GI or chlamydia infections.
Psoriatic arthritis	Joint pain and stiffness associated with psoriasis. Asymmetric and patchy involvement. Dactylitis ("sausage fingers") is commonly observed. "Pencil and cup" deformity on x-ray. Seen in fewer than ⅓ of patients with psoriasis.	

Systemic lupus erythematosus

90% are female and between ages 14 and 45. Most common and severe in black females. Symptoms include fever, fatigue, weight loss, nonbacterial verrucous endocarditis, hilar adenopathy, and Raynaud's phenomenon (see Color Image 52). Wire-loop lesions in kidney with immune complex deposition (with nephrotic syndrome); death from renal failure and infections. False positives on syphilis tests (RPR/VDRL) due to antiphospholipid antibodies. Lab tests detect presence of:

1. Antinuclear antibodies (ANA)—sensitive, but not specific for SLE
2. Antibodies to double-stranded DNA (anti-dsDNA)—very specific, poor prognosis
3. Anti-Smith antibodies (anti-Sm)—very specific, but not prognostic
4. Antihistone antibodies—drug-induced lupus



I'M DAMN SHARP:
- **I**mmunoglobulins (anti-dsDNA, anti-Sm, antiphospholipid)
- **M**alar rash
- **D**iscoid rash
- **A**ntinuclear antibody
- **M**ucositis (oropharyngeal ulcers)
- **N**eurologic disorders
- **S**erositis (pleuritis, pericarditis)
- **H**ematologic disorders
- **A**rthritis
- **R**enal disorders
- **P**hotosensitivity

Sarcoidosis

Characterized by immune-mediated, widespread noncaseating granulomas and elevated serum ACE levels. Common in black females.

Associated with restrictive lung disease, bilateral hilar lymphadenopathy, erythema nodosum, Bell's palsy, epithelial granulomas containing microscopic Schaumann and asteroid bodies, uveoparotitis, and hypercalcemia (due to elevated conversion of vitamin D to its active form in epithelioid macrophages) (see Color Image 104).

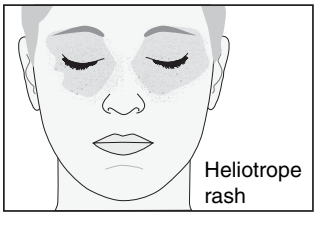
GRAIN:
- **G**ammaglobulinemia
- **R**heumatoid arthritis
- **A**CE increase
- **I**nterstitial fibrosis
- **N**oncaseating granulomas

Polymyalgia rheumatica

Symptoms	Pain and stiffness in shoulders and hips, often with fever, malaise, and weight loss. Does not cause muscular weakness. Occurs in patients > 50 years of age; associated with temporal (giant cell) arteritis.
Findings	↑ ESR, normal CK.
Treatment	Prednisone.

Polymyositis/dermatomyositis

Symptoms	**Polymyositis**—progressive symmetric proximal muscle weakness caused by CD8+ T-cell-induced injury to myofibers. Muscle biopsy with evidence of inflammation is diagnostic. **Dermatomyositis**—similar to polymyositis, but also involves heliotrope rash, "shawl and face" rash and ↑ risk of malignancy.
Findings	Labs for polymyositis/dermatomyositis show ↑ CK, ↑ aldolase, and positive ANA, anti-Jo-1.
Treatment	Steroids.



NMJ diseases	
Myasthenia gravis	Most common NMJ disorder. Autoantibodies to postsynaptic AChR cause ptosis, diplopia, and general weakness. Associated with thymoma. Symptoms worsen with muscle use. Reversal of symptoms occurs with AChE inhibitors.
Lambert-Eaton syndrome	Autoantibodies to presynaptic Ca^{2+} channel results in ↓ ACh release leading to proximal muscle weakness. Associated with paraneoplastic diseases (small cell lung cancer). Symptoms improve with muscle use. No reversal of symptoms with AChE inhibitors alone.
Mixed connective tissue disease	Raynaud's phenomenon, arthralgias, myalgias, fatigue, and esophageal hypomotility. Antibodies to U1RNP. Responds to steroids.
Scleroderma (progressive systemic sclerosis—PSS)	Excessive fibrosis and collagen deposition throughout the body. Commonly sclerosis of skin, manifesting as puffy and taut skin with absence of wrinkles (see Color Image 53). Also sclerosis of kidneys, pulmonary, cardiovascular, and GI systems. 75% female. 2 major categories: 1. Diffuse scleroderma—widespread skin involvement, rapid progression, early visceral involvement. Associated with anti-Scl-70 antibody. 2. **CREST** syndrome—**C**alcinosis, **R**aynaud's phenomenon, **E**sophageal dysmotility, **S**clerodactyly, and **T**elangiectasia. Limited skin involvement, often confined to fingers and face. More benign clinical course. Associated with **anticentromere antibody.**
Soft tissue tumors	
Lipoma	Soft, well-encapsulated fat tumor. Benign. Simple excision is usually curative.
Liposarcoma	Malignant fat tumor that can be quite large. Will recur unless adequately excised.
Rhabdomyosarcoma	Most common soft tissue tumor of childhood. Malignant. Arises from skeletal muscle, most often in head/neck.
Dermatologic terminology	
Macule	Flat discoloration < 1 cm.
Patch	Macule > 1 cm.
Papule	Elevated skin lesion < 1 cm.
Plaque	Papule > 1 cm.
Vesicle	Small fluid-containing blister.
Wheal	Transient vesicle.
Bulla	Large fluid-containing blister.
Keloid	Irregular, raised lesion resulting from scar tissue hypertrophy (follows trauma to skin, especially in African-Americans).
Pustule	Blister containing pus.
Crust	Dried exudates from a vesicle, bulla, or pustule.
Hyperkeratosis	↑ thickness of stratum corneum.
Parakeratosis	Hyperkeratosis with retention of nuclei in stratum corneum (e.g., psoriasis).
Acantholysis	Separation of epidermal cells.
Acanthosis	Epidermal hyperplasia.
Dermatitis	Inflammation of the skin.

Skin disorders

Common disorders

Verrucae	Warts. Soft, tan-colored, cauliflower-like lesions. Epidermal hyperplasia, hyperkeratosis, koilocytosis. Verruca vulgaris on hands; condyloma acuminatum on genitals (caused by HPV).
Nevocellular nevus	Common mole. Benign.
Urticaria	Hives. Intensely pruritic wheals that form after mast cell degranulation.
Ephelis	Freckle. ↑ melanin pigment.
Atopic dermatitis (eczema)	Pruritic eruption, commonly on skin flexures. Often associated with other atopic diseases (asthma, allergic rhinitis).
Allergic contact dermatitis	Type IV hypersensitivity reaction that follows exposure to allergen. Lesions occur at site of contact.
Psoriasis	Papules and plaques with silvery scaling, especially on knees and elbows (see Color Image 65). Acanthosis with parakeratotic scaling (nuclei still in stratum corneum). ↑ stratum spinosum, ↓ stratum granulosum. **Auspitz sign** (bleeding spots when scales are scraped off). Can be associated with psoriatic arthritis.
Seborrheic keratosis	Flat, greasy, pigmented squamous epithelial proliferation with keratin-filled cysts (horn cysts). Looks "pasted on." Lesions occur on head, trunk, and extremities. Common benign neoplasm of older persons.

Pigmentation disorders

Albinism	Normal melanocyte number with ↓ melanin production.
Vitiligo	Irregular areas of complete depigmentation. Caused by a ↓ in melanocytes.
Melasma	Hyperpigmentation associated with pregnancy ("mask of pregnancy") or OCP use.

Infectious disorders

Impetigo	Very superficial skin infection. Usually from *S. aureus* or *S. pyogenes*. Highly contagious. **Honey-colored crusting.**
Cellulitis	Acute, painful spreading infection of dermis and subcutaneous tissues. Usually from *S. pyogenes* or *S. aureus*.
Necrotizing fasciitis	Deeper tissue injury, usually from anaerobic bacteria and *S. pyogenes*. Results in crepitus from methane and CO_2 production. "Flesh-eating bacteria."
Staphylococcal scalded skin syndrome (SSSS)	Exotoxin destroys keratinocyte attachments in the stratum granulosum only. Characterized by fever and generalized erythematous rash with sloughing of the upper layers of the epidermis. Seen in newborns and children.
Hairy leukoplakia	White, painless plaques on the tongue that cannot be scraped off. EBV mediated. Relatively specific for HIV.

Blistering disorders

Bullous pemphigoid	Autoimmune disorder with IgG antibody against hemidesmosomes (epidermal basement membrane; antibodies are "**bullow**" the epidermis); shows linear immunofluorescence. Similar to but less severe than pemphigus vulgaris—affects skin but spares oral mucosa (see Color Image 64).
Pemphigus vulgaris	Potentially fatal autoimmune skin disorder with IgG antibody against desmosomes; shows immunofluorescence throughout epidermis. Acantholysis—intraepidermal bullae involving the skin and oral mucosa (see Color Image 63).
Dermatitis herpetiformis	Pruritic papules and vesicles. Deposits of IgA at the tips of dermal papillae. Associated with celiac disease.

Skin disorders *(continued)*

Erythema multiforme	Associated with infections, drugs, cancers, and autoimmune disease. Presents with multiple types of lesions—macules, papules, vesicles, and target lesions (red papules with a pale central area).
Stevens-Johnson syndrome	Characterized by fever, bulla formation and necrosis, sloughing of skin, and a high mortality rate. Usually associated with adverse drug reaction.
Toxic epidermal necrolysis	Characteristics similar to Stevens-Johnson syndrome, but more severe with greater epidermal involvement.

Miscellaneous disorders

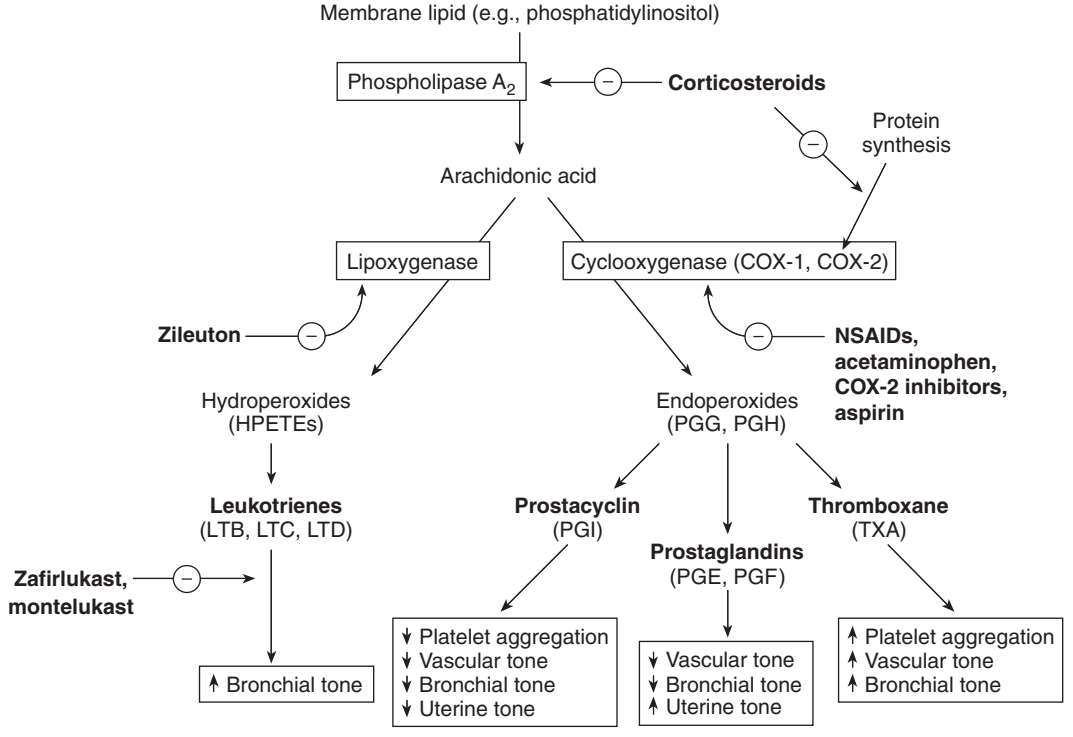
Lichen **p**lanus	**P**ruritic, **P**urple, **P**olygonal **P**apules. Sawtooth infiltrate of lymphocytes at dermal-epidermal junction.
Actinic keratosis	Premalignant lesions caused by sun exposure. Small, rough, erythematous or brownish papules. "Cutaneous horn." Risk of carcinoma is proportional to epithelial dysplasia.
Acanthosis nigricans	Hyperplasia of stratum spinosum. Associated with hyperlipidemia (e.g., from Cushing's disease, diabetes) and visceral malignancy.

Skin cancer

Squamous cell carcinoma	Very common. Associated with excessive exposure to sunlight and arsenic exposure. Commonly appear on hands and face. Locally invasive, but rarely metastasizes. Ulcerative red lesion. Histopathology: keratin "pearls" (see Color Image 60).	**Actinic keratosis** is a precursor to squamous cell carcinoma.
Basal cell carcinoma	Most common in sun-exposed areas of body. Locally invasive, but almost never metastasizes. Rolled edges with central ulceration. Gross pathology: pearly papules (see Color Image 62).	Basal cell tumors have "palisading" nuclei.
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. Dark with irregular borders (see Color Image 61).	Dysplastic nevus is a precursor to melanoma.

Arachidonic acid products

Lipoxygenase pathway yields **L**eukotrienes.	**L** for **L**ipoxygenase and **L**eukotriene.
LT**B**$_4$ is a neutrophil chemotactic agent.	Neutrophils arrive "**B4**" others.
LTC$_4$, D$_4$, and E$_4$ function in bronchoconstriction, vasoconstriction, contraction of smooth muscle, and ↑ vascular permeability.	
PGI$_2$ inhibits platelet aggregation and promotes vasodilation.	**P**latelet-**G**athering **I**nhibitor.



(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review,* 5th ed. Stamford, CT: Appleton & Lange, 1998: 150.)

NSAIDs	Ibuprofen, naproxen, indomethacin, ketorolac.
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	Renal damage, aplastic anemia, GI distress, ulcers.

COX-2 inhibitors (celecoxib)

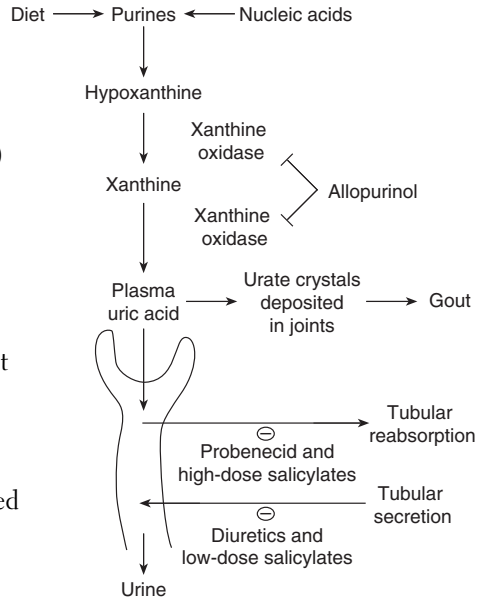
Mechanism	Reversibly inhibit specifically the cyclooxygenase (COX) isoform 2, which is found in inflammatory cells and mediates inflammation and pain; spares COX-1, which helps maintain the gastric mucosa. Thus, should not have the corrosive effects of other NSAIDs on the GI lining.
Clinical use	Rheumatoid and osteoarthritis.
Toxicity	↑ risk of thrombosis. Sulfa allergy. Less toxicity to GI mucosa (lower incidence of ulcers, bleeding).

Acetaminophen

Mechanism	Reversibly inhibits cyclooxygenase, mostly in CNS. Inactivated peripherally.
Clinical use	Antipyretic, analgesic, but lacking anti-inflammatory properties.
Toxicity	Overdose produces hepatic necrosis; acetaminophen metabolite depletes glutathione and forms toxic tissue adducts in liver. *N*-acetylcysteine is antidote—regenerates glutathione.

Gout drugs

Colchicine	Acute gout. Depolymerizes microtubules, impairing leukocyte chemotaxis and degranulation. GI side effects, especially if given orally. (Note: indomethacin is less toxic, more commonly used in acute gout.)
Probenecid	Chronic gout. Inhibits reabsorption of uric acid in PCT (also inhibits secretion of penicillin).
Allopurinol	Chronic gout. Inhibits xanthine oxidase, ↓ conversion of xanthine to uric acid. Also used in lymphoma and leukemia to prevent tumor lysis–associated urate nephropathy. Interacts with azathioprine and 6-MP.
	Probenecid and allopurinol should not be used to treat an acute episode of gout.
	Do not give salicylates.



Etanercept

Mechanism	Recombinant form of human TNF receptor that binds TNF.	Etaner**CEPT** is a TNF decoy re**CEPT**or.
Clinical use	Rheumatoid arthritis, psoriasis, ankylosing spondylitis.	

Infliximab

Mechanism	Anti-TNF antibody.	**INFLIX**imab **INFLIX** pain on TNF.
Clinical use	Crohn's disease, rheumatoid arthritis, ankylosing spondylitis.	
Toxicity	Predisposes to infections (reactivation of latent TB).	

NOTES

Neurology

- High-Yield Clinical Vignettes
- Anatomy and Physiology
- Pathology
- Pharmacology

"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."

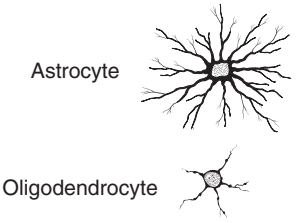
—Anonymous

▪ Patient presents with ↓ pain and temperature sensation over the lateral aspects of both arms.	What is the lesion?	Syringomyelia.
▪ Penlight in patient's right eye produces bilateral pupillary constriction. When moved to the left eye, there is paradoxical dilatation.	What is the defect?	Atrophy of the left optic nerve.
▪ Woman involved in a motor vehicle accident cannot turn her head to the left and has right shoulder droop.	What structure is damaged?	Right CN XI (runs through the jugular foramen with CN IX and X), innervating the sternocleidomastoid and trapezius muscles.
▪ Man presents with 1 wild, flailing arm.	Where is the lesion?	Contralateral subthalamic nucleus (hemiballismus).
▪ Patient with cortical lesion does not know that he has a disease.	Where is the lesion?	Right parietal lobe.
▪ Patient's tongue protrudes toward the left side, and patient exhibits a right-sided spastic paralysis.	Where is the lesion?	Left medulla, CN XII.
▪ Patient cannot blink his right eye or seal his lips.	What is the diagnosis, and which nerve is affected?	Bell's palsy; CN VII.
▪ Woman presents with headache, visual disturbance, galactorrhea, and amenorrhea.	What is the diagnosis?	Prolactinoma.
▪ 43-year-old man experiences dizziness and tinnitus. CT shows an enlarged internal acoustic meatus.	What is the diagnosis?	Schwannoma.
▪ 25-year-old woman presents with sudden monocular vision loss and slightly slurred speech. She has a history of weakness and paresthesias that have resolved.	What is the diagnosis?	Multiple sclerosis.
▪ 10-year-old child "spaces out" in class (e.g., stops talking midsentence and then continues as if nothing had happened). During spells, the child has a slight quivering of the lips.	What is the diagnosis?	Absence seizures.

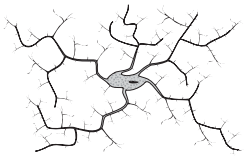
■ 23-year-old woman crashes her motorcycle. She initially feels fine, but minutes later she loses consciousness. At the ER, a CT shows an intracranial hemorrhage that does not cross suture lines.	Which bone and vessel were injured during the crash?	Middle meningeal artery and temporal bone, resulting in an epidural hematoma.
■ 38-year-old man with a history of Marfan's syndrome and hypertension presents with a severe headache. A spinal tap reveals blood in the CSF.	What is the cause of the man's head pain?	Subarachnoid hemorrhage resulting from a ruptured berry aneurysm.
■ 78-year-old man with Alzheimer's disease falls and presents 3 days later with severe headache and vomiting.	What structures were damaged by the fall?	Bridging veins, resulting in subdural hematoma.

CNS/PNS supportive cells

Astrocytes—physical support, repair, K^+ metabolism; help maintain blood-brain barrier. Astrocyte marker—GFAP.
Ependymal cells—inner lining of ventricles; make CSF.
Microglia—macrophages of the brain.
Oligodendroglia—central myelin production.
Schwann cells—peripheral myelin production.
Microglia, like **M**acrophages, originate from **M**esoderm. All other CNS/PNS supportive cells originate from ectoderm.



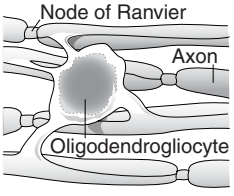
Microglia



CNS phagocytes. Mesodermal origin. Not readily discernible in Nissl stains. Have small irregular nuclei and relatively little cytoplasm.
Microglia $\xrightarrow{\text{tissue damage}}$ large ameboid phagocytic cells.

HIV-infected microglia fuse to form multinucleated giant cells in the CNS.

Oligodendroglia



Each oligodendrocyte myelinates multiple CNS axons, up to 30 each. In Nissl stains, they appear as small nuclei with dark chromatin and little cytoplasm. Predominant type of glial cell in white matter.

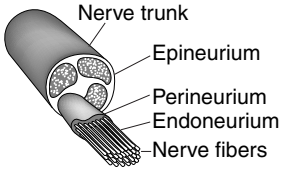
These cells are destroyed in multiple sclerosis.
Look like fried eggs on H&E staining (see Color Image 49).

Schwann cells

Each Schwann cell myelinates only 1 PNS axon. Also promote axonal regeneration. Derived from neural crest.

Acoustic neuroma is an example of a schwannoma.
Acoustic neuromas are typically located in the internal acoustic meatus (CN VIII).

Peripheral nerve layers



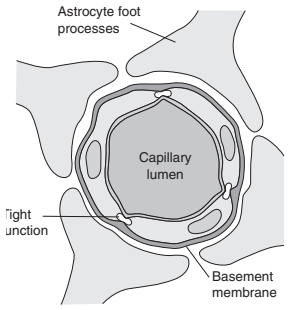
Endoneurium invests single nerve fiber.
Perineurium (permeability barrier) surrounds a fascicle of nerve fibers.
Epineurium (dense connective tissue) surrounds entire nerve (fascicles and blood vessels).

Perineurium—**P**ermeability barrier; must be rejoined in microsurgery for limb reattachment.
Endo = inner.
Peri = around.
Epi = outer.

Neurotransmitters—locations of synthesis

NE	Locus ceruleus.
Dopamine	Ventral tegmentum and SNc.
5-HT	Raphe nucleus.
ACh	Basal nucleus of Meynert.

Blood-brain barrier



Formed by 3 structures:
1. Tight junctions between nonfenestrated capillary endothelial cells
2. Basement membrane
3. Astrocyte processes

Glucose and amino acids cross slowly by carrier-mediated transport mechanism.

Nonpolar/lipid-soluble substances cross rapidly via diffusion.

A few specialized brain regions with fenestrated capillaries and no blood-brain barrier allow molecules in the blood to affect brain function (e.g., area postrema—vomiting after chemo) or neurosecretory products to enter circulation (e.g., neurohypophysis—ADH release).

Other barriers include:
1. Blood-testis barrier
2. Maternal-fetal blood barrier of placenta

Infarction destroys endothelial cell tight junctions → vasogenic edema.

Hypothalamus functions

Thirst and water balance (supraoptic nucleus).

Adenohypophysis control via releasing factors.

Neurohypophysis and median eminence release hormones synthesized in hypothalamic nuclei.

Hunger (lateral area—destruction → anorexia and starvation) and satiety (ventromedial area—destruction → hyperphagia and obesity).

Autonomic regulation (**A**nterior hypothalamus regulates p**A**rasympathetic; posterior hypothalamus regulates sympathetic) and circadian rhythms (suprachiasmatic nucleus).

Temperature regulation (posterior hypothalamus regulates heat conservation and production when cold; **A**nterior hypothalamus coordinates **C**ooling when hot).

Sexual urges and emotions (**S**eptal nucleus—destruction → rage).

The hypothalamus wears **TAN HATS.**

If you zap your **ventromedial** nucleus, you grow **ven**trally and **medial**ly.

You need **sleep** to be **charismatic** (chiasmatic).

If you zap your **P**osterior hypothalamus, you become a **P**oikilotherm (cold-blooded, like a snake).

A/C = anterior cooling.

Posterior pituitary (neurohypophysis)

Receives hypothalamic axonal projections from supraoptic (ADH) and paraventricular (oxytocin) nuclei.

Oxytocin: *oxys* = quick; *tocos* = birth.

Adenohypophysis = **A**nterior pituitary.

Thalamus

Major relay for ascending sensory information that ultimately reaches the cortex.

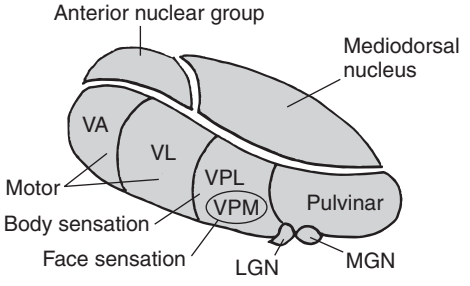
Lateral geniculate nucleus (LGN)—visual. — **L**ateral for **L**ight.

Medial geniculate nucleus (MGN)—auditory. — **M**edial for **M**usic.

Ventral posterior nucleus, lateral part (VPL)—body sensation (proprioception, pressure, pain, touch, vibration via dorsal columns, spinothalamic tract).

Ventral posterior nucleus, medial part (VPM)—facial sensation (via CN V). — You put **M**akeup on your face, and the sensory info is relayed through the VP**M**.

Ventral anterior/lateral (VA/VL) nuclei—motor. — Motor is anterior to sensation in the thalamus, just like the cortex.



Blood supply—posterior communicating, posterior cerebral, and anterior choroidal arteries.

Limbic system

Includes cingulate gyrus, hippocampus, fornix, and mammillary bodies. Responsible for **F**eeding, **F**leeing, **F**ighting, **F**eeling, and sex. — The famous **5 F's.**

Cerebellar nerves

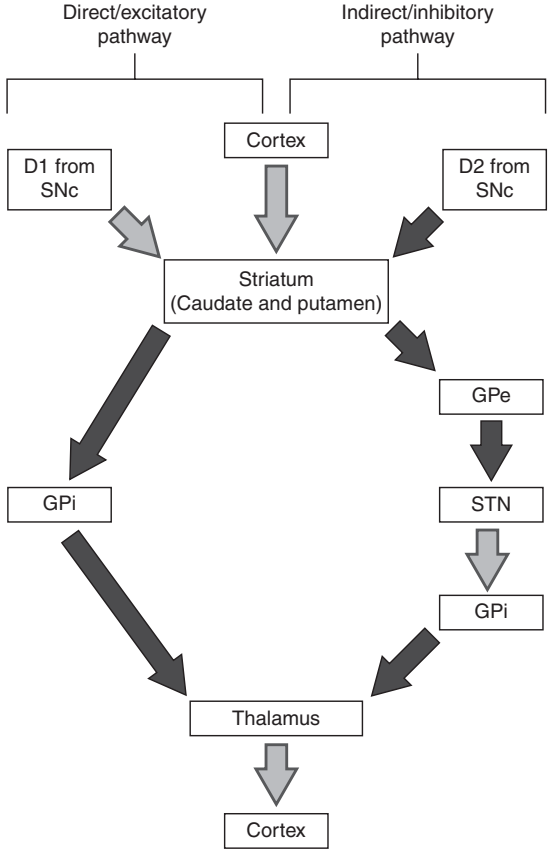
Climbing and mossy fibers—input to cerebellum.

Purkinje fibers—output of cerebellum.

Basal ganglia

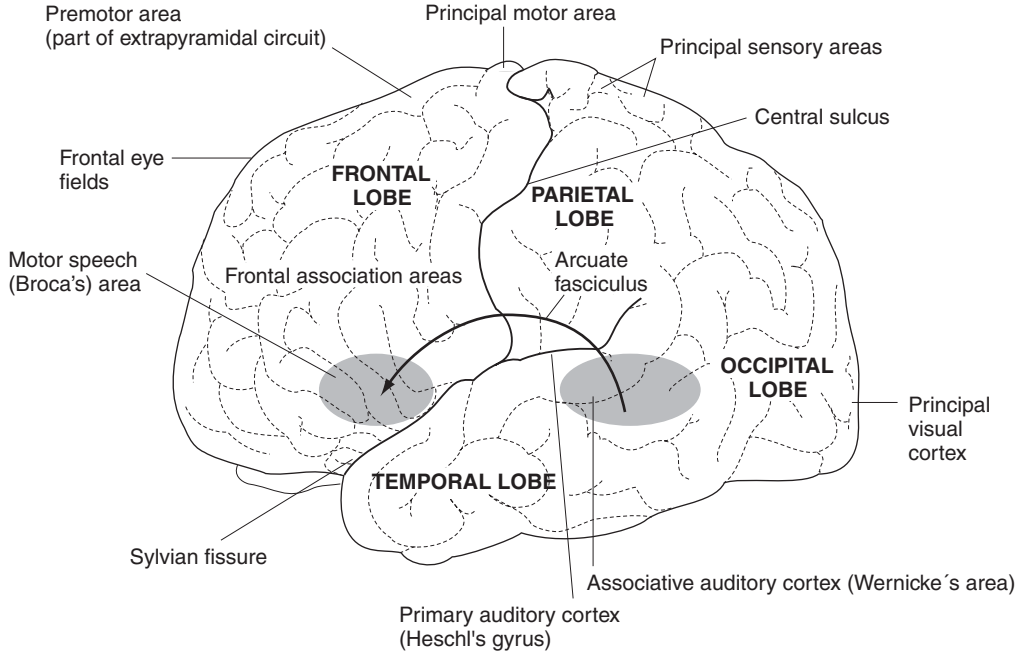
Important in voluntary movements and making postural adjustments.

■ stimulatory
■ inhibitory
SNc Substantia nigra pars compacta
GPe Globus pallidus externus
GPi Globus pallidus internus
STN Subthalamic nucleus
D1 Dopamine D1 receptor
D2 Dopamine D2 receptor



The SNc's dopamine binds to D1 receptors in the excitatory pathway, stimulating the excitatory pathway (↑ motion). Therefore, loss of dopamine in Parkinson's inhibits the excitatory pathway (↓ motion).
The SNc's dopamine binds to D2 receptors in the inhibitory pathway, inhibiting the inhibitory pathway (↑ motion). Therefore, loss of dopamine in Parkinson's excites (i.e., disinhibits) the inhibitory pathway (↓ motion).

Cerebral cortex functions



Frontal lobe functions

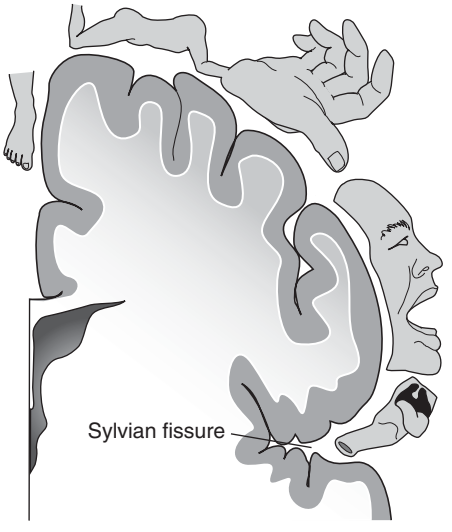
"Executive functions"—planning, inhibition, concentration, orientation, language, abstraction, judgment, motor regulation, mood. Lack of social judgment is most notable in frontal lobe lesion.

Damage = **D**isinhibition (e.g., Phineas Gage).

Homunculus

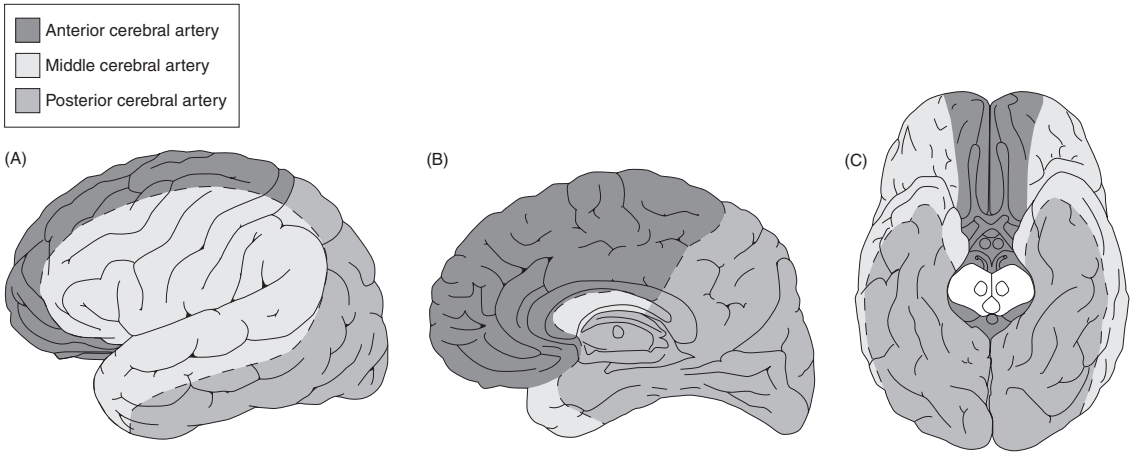
Topographical representation of sensory and motor areas in the cerebral cortex. Use to localize lesion (e.g., in blood supply) leading to specific defects.

For example, lower extremity deficit in sensation or movement indicates involvement of the anterior cerebral artery.

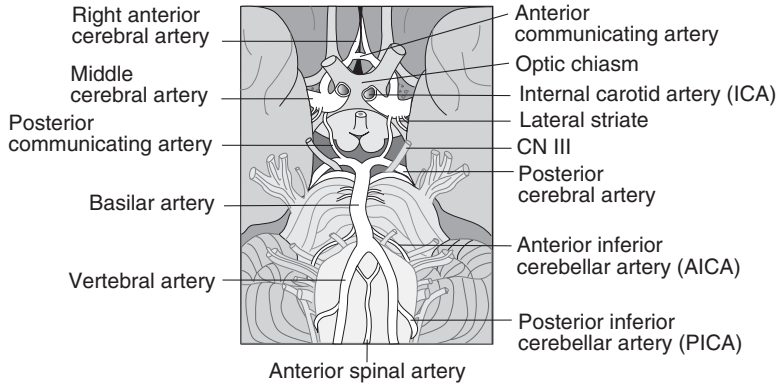


Motor homunculus

Cerebral arteries—cortical distribution



Circle of Willis



Anterior cerebral artery—supplies medial surface of the brain, leg-foot area of motor and sensory cortices.

Middle cerebral artery—supplies lateral aspect of brain, trunk-arm-face area of motor and sensory cortices, Broca's and Wernicke's speech areas.

Anterior communicating artery—most common site of circle of Willis aneurysm; lesions may cause visual field defects.

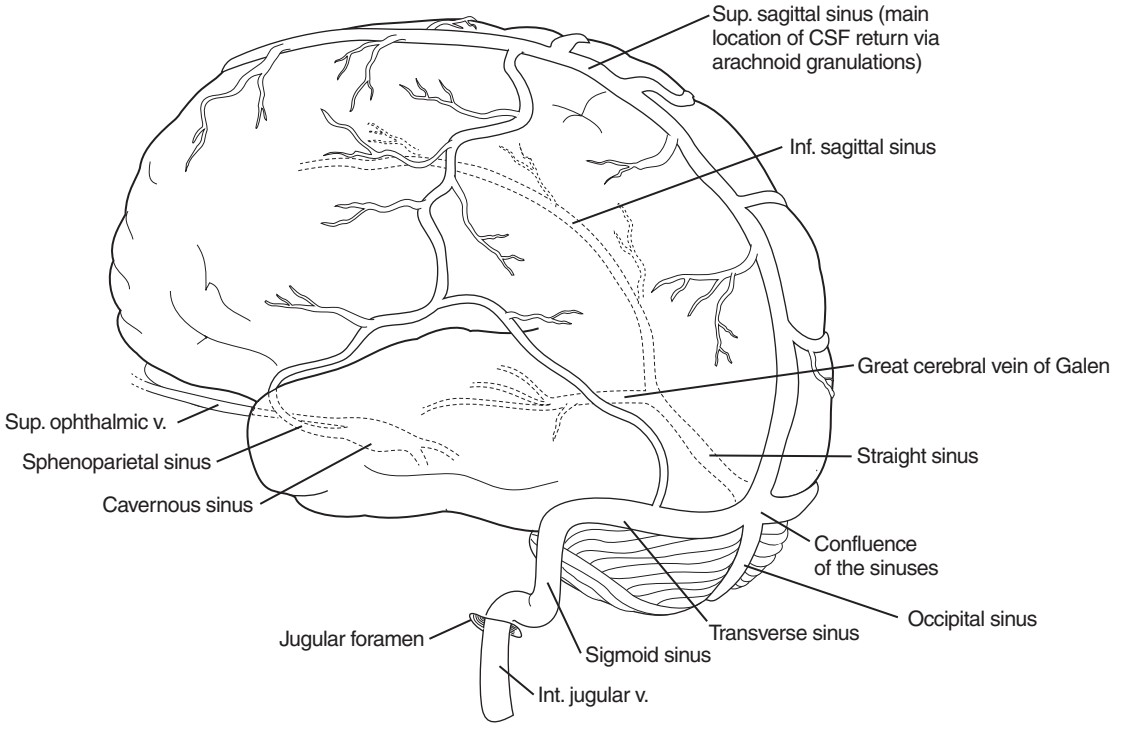
Posterior communicating artery—common area of aneurysm; causes CN III palsy.

Lateral striate—divisions of middle cerebral artery; "arteries of stroke"; supply internal capsule, caudate, putamen, globus pallidus.

In general, stroke of anterior circle → general sensory and motor dysfunction, aphasia; stroke of posterior circle → cranial nerve deficits (vertigo, visual deficits), coma, cerebellar deficits (ataxia).

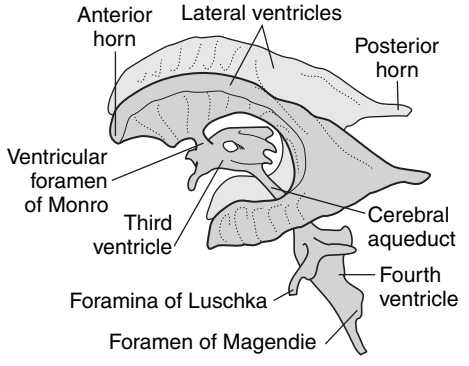
Dural venous sinuses

Venous sinuses run in the dura mater where its meningeal and periosteal layers separate. Cerebral veins → venous sinuses → internal jugular vein.



(Adapted, with permission, from White JS. *USMLE Road Map: Gross Anatomy,* 1st ed. New York: McGraw-Hill, 2003.)

Ventricular system



CSF is made by ependymal cells lining the ventricles; it is reabsorbed by venous sinus arachnoid granulations.

Hydrocephalus—accumulation of excess CSF in the ventricular system. Caused by impaired flow or reabsorption, choroid tumor, or ependymoma.

Lateral ventricle → 3rd ventricle via foramen of Monro.
3rd ventricle → 4th ventricle via cerebral aqueduct.
4th ventricle → subarachnoid space via:
Foramina of **L**uschka = **L**ateral.
Foramen of **M**agendie = **M**edial.

Spinal nerves

There are 31 spinal nerves altogether: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, 1 coccygeal.
For C1–C7, nerves exit via intervertebral foramina above the corresponding vertebra. Nerves C8 and below exit below.

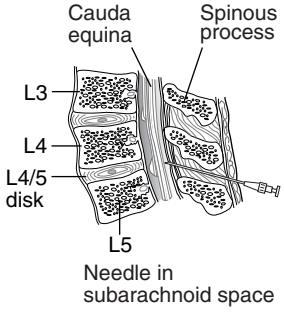
31, just like 31 flavors!
Vertebral disk herniation usually occurs between L5 and S1.

Spinal cord lower extent

In adults, spinal cord extends to lower border of L1–L2; subarachnoid space extends to lower border of S2. Lumbar puncture is usually performed in L3–L4 or L4–L5 interspaces, at level of cauda equina.

To keep the cord **alive,** keep the spinal needle between **L3 and L5.**

Lumbar puncture

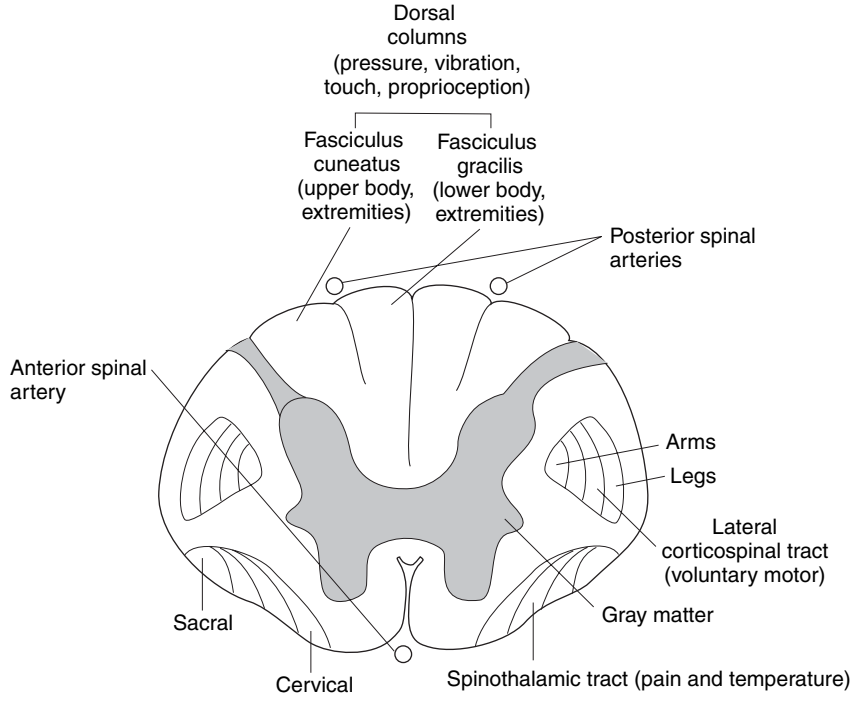


CSF obtained from lumbar subarachnoid space between L4 and L5 (at the level of iliac crests).
Structures pierced as follows:

1. Skin/superficial fascia
2. Ligaments (supraspinous, interspinous, ligamentum flavum)
3. Epidural space
4. Dura mater
5. Subdural space
6. Arachnoid
7. Subarachnoid space—CSF

Pia is not **pier**ced.

Spinal cord and associated tracts



Spinal tract anatomy and functions

Tract and function	1st-order neuron	Synapse 1	2nd-order neuron	Synapse 2	3rd-order neuron
Dorsal column—medial lemniscal pathway (ascending pressure, vibration, touch, and proprioceptive sensation)	Sensory nerve ending → cell body in dorsal root ganglion → enters spinal cord, ascends ipsilaterally in dorsal column	Nucleus cuneatus or gracilis (medulla)	Decussates in medulla → ascends contralaterally in medial lemniscus	VPL of thalamus	Sensory cortex
Spinothalamic tract (ascending pain and temperature sensation)	Sensory nerve ending (A-delta and C fibers) (cell body in dorsal root ganglion) → enters spinal cord	Ipsilateral gray matter (spinal cord)	Decussates at anterior white commissure → ascends contralaterally	VPL of thalamus	Sensory cortex
Lateral corticospinal tract (descending voluntary movement of contralateral limbs)	**Upper motor neuron:** cell body in 1° motor cortex → descends ipsilaterally until decussating at caudal medulla (pyramidal decussation)→ descends contralaterally	Cell body of anterior horn (spinal cord)	**Lower motor neuron:** Leaves spinal cord	Neuromuscular junction	

Dorsal column organization

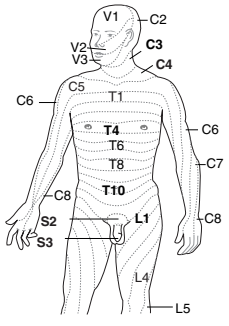
Fasciculus gracilis = legs.
Fasciculus cuneatus = arms.

Dorsal column is organized as you are, with hands at sides—arms outside and legs inside.

Clinically important landmarks

Pudendal nerve block (to relieve pain of pregnancy)—ischial spine.
Appendix—2/3 of the way from the umbilicus to the anterior superior iliac spine (McBurney's point).
Lumbar puncture—iliac crest.

Landmark dermatomes



C2 is the posterior half of a skull "cap."
C3 is a high turtleneck shirt.
C4 is a low-collar shirt.
T4 is at the nipple.
T7 is at the xiphoid process.
T10 is at the umbilicus (important for early appendicitis pain referral).
L1 is at the inguinal ligament.
L4 includes the kneecaps.
S2, S3, S4 erection and sensation of penile and anal zones.

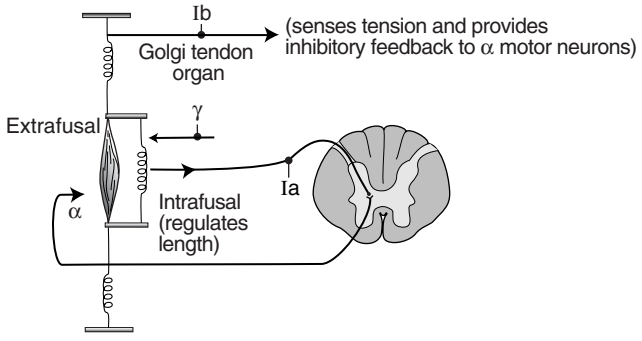
Gallbladder pain referred to the right shoulder via the phrenic nerve.
T4 at the **teat pore.**

T**10** at the belly but**TEN.**

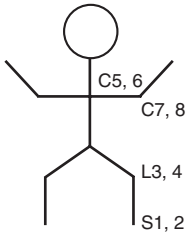
L1 is **IL** (**I**nguinal **L**igament).
Down on **L4s (all fours).**
"**S2, 3, 4** keep the penis off the floor."

Spindle muscle control

Muscle spindle	In parallel with muscle fibers. Muscle stretch → intrafusal stretch → stimulates Ia afferent→ stimulates α motor neuron → reflex muscle (extrafusal) contraction.	Muscle spindles monitor muscle length (help you pick up a heavy suitcase when you didn't know how heavy it was). Golgi **T**endon organs monitor muscle **T**ension (make you drop a heavy suitcase you've been holding too long).
Gamma loop	CNS stimulates γ motor neuron → contracts intrafusal fiber → ↑ sensitivity of reflex arc.	



Clinical reflexes



Biceps = C5 nerve root.
Triceps = C7 nerve root.
Patella = L4 nerve root.
Achilles = S1 nerve root.
Babinski—dorsiflexion of the big toe and fanning of other toes; sign of UMN lesion, but normal reflex in 1st year of life.

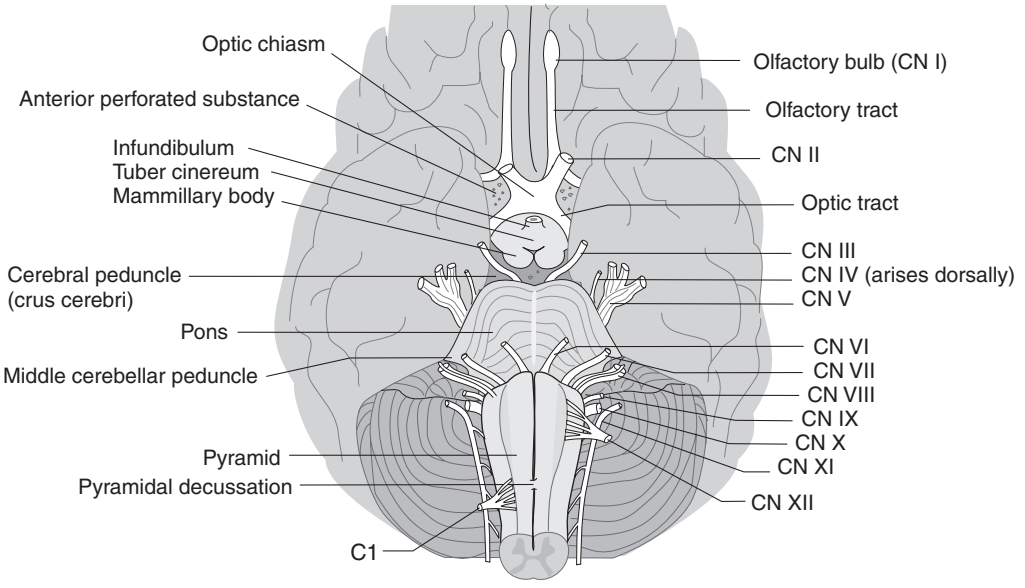
Reflexes count up in order:
S1, 2
L3, 4
C5, 6
C7, 8

Primitive reflexes

1. Moro reflex—extension of limbs when startled
2. Rooting reflex—nipple seeking
3. Palmar reflex—grasps objects in palm
4. Babinski reflex—large toe dorsiflexes with plantar stimulation

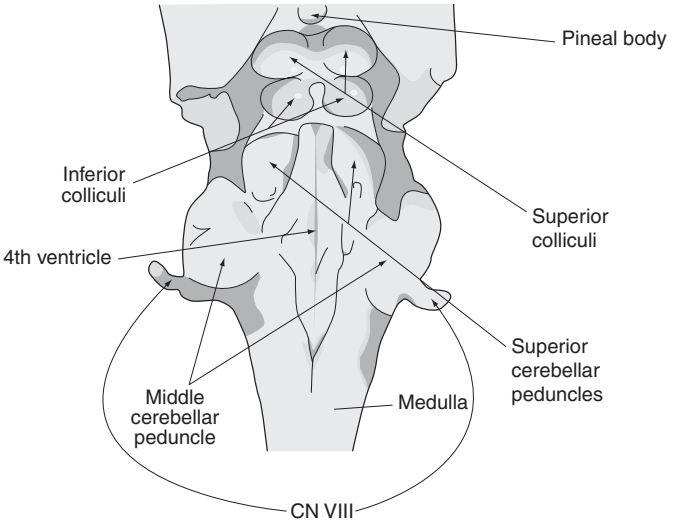
Normally disappear within 1st year. May reemerge following frontal lobe lesion.

Brain stem—ventral view



CNs that lie medially at brain stem: III, VI, XII. 3(×2) = 6(×2) = 12.

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., pinealoma).

Your eyes are **above** your ears, and the superior colliculus (visual) is **above** the inferior colliculus (auditory).

Cranial nerves

Nerve	CN	Function	Type	Mnemonic
Olfactory	I	Smell (only CN without thalamic relay to cortex)	**S**ensory	**S**ome
Optic	II	Sight	**S**ensory	**S**ay
Oculomotor	III	Eye movement, pupil constriction, accommodation, eyelid opening (levator palpebrae)	**M**otor	**M**arry
Trochlear	IV	Eye movement	**M**otor	**M**oney
Trigeminal	V	Mastication, facial sensation	**B**oth	**B**ut
Abducens	VI	Eye movement (arises from contralateral nuclei)	**M**otor	**M**y
Facial	VII	Facial movement, taste from anterior $^2/_3$ of tongue, lacrimation, salivation (submandibular and sublingual glands), eyelid closing (orbicularis oculi), stapedius muscle in ear	**B**oth	**B**rother
Vestibulocochlear	VIII	Hearing, balance	**S**ensory	**S**ays
Glossopharyngeal	IX	Taste from posterior $^1/_3$ of tongue, swallowing, salivation (parotid gland), monitoring carotid body and sinus chemo- and baroreceptors, and stylopharyngeus	**B**oth	**B**ig
Vagus	X	Taste from epiglottic region, swallowing, palate elevation, talking, coughing, thoracoabdominal viscera, monitoring aortic arch chemo- and baroreceptors	**B**oth	**B**rains
Accessory	XI	Head turning, shoulder shrugging	**M**otor	**M**atter
Hypoglossal	XII	Tongue movement	**M**otor	**M**ost

Cranial nerve nuclei

Located in tegmentum portion of brain stem (between dorsal and ventral portions).

1. Midbrain—nuclei of CN III, IV
2. Pons—nuclei of CN V, VI, VII, VIII
3. Medulla—nuclei of CN IX, X, XI, XII

Lateral nuclei = sensory.
Medial nuclei = **M**otor.

Reflexes and cranial nerves

Cranial nerve reflex	Afferent	Efferent
Corneal	V_1	VII
Lacrimation	V_1	VII
Jaw jerk	V_3 (sensory)	V_3 (motor)
Pupillary	II	III
Gag	IX	IX, X

Vagal nuclei

Nucleus **S**olitarius	Visceral **S**ensory information (e.g., taste, baroreceptors, gut distention).	VII, IX, X.
Nucleus a**M**biguus	**M**otor innervation of pharynx, larynx, and upper esophagus (e.g., swallowing, palate elevation).	IX, X, XI.
Dorsal motor nucleus	Sends autonomic (parasympathetic) fibers to heart, lungs, and upper GI.	

Cranial nerve and vessel pathways

Cribriform plate (CN I).

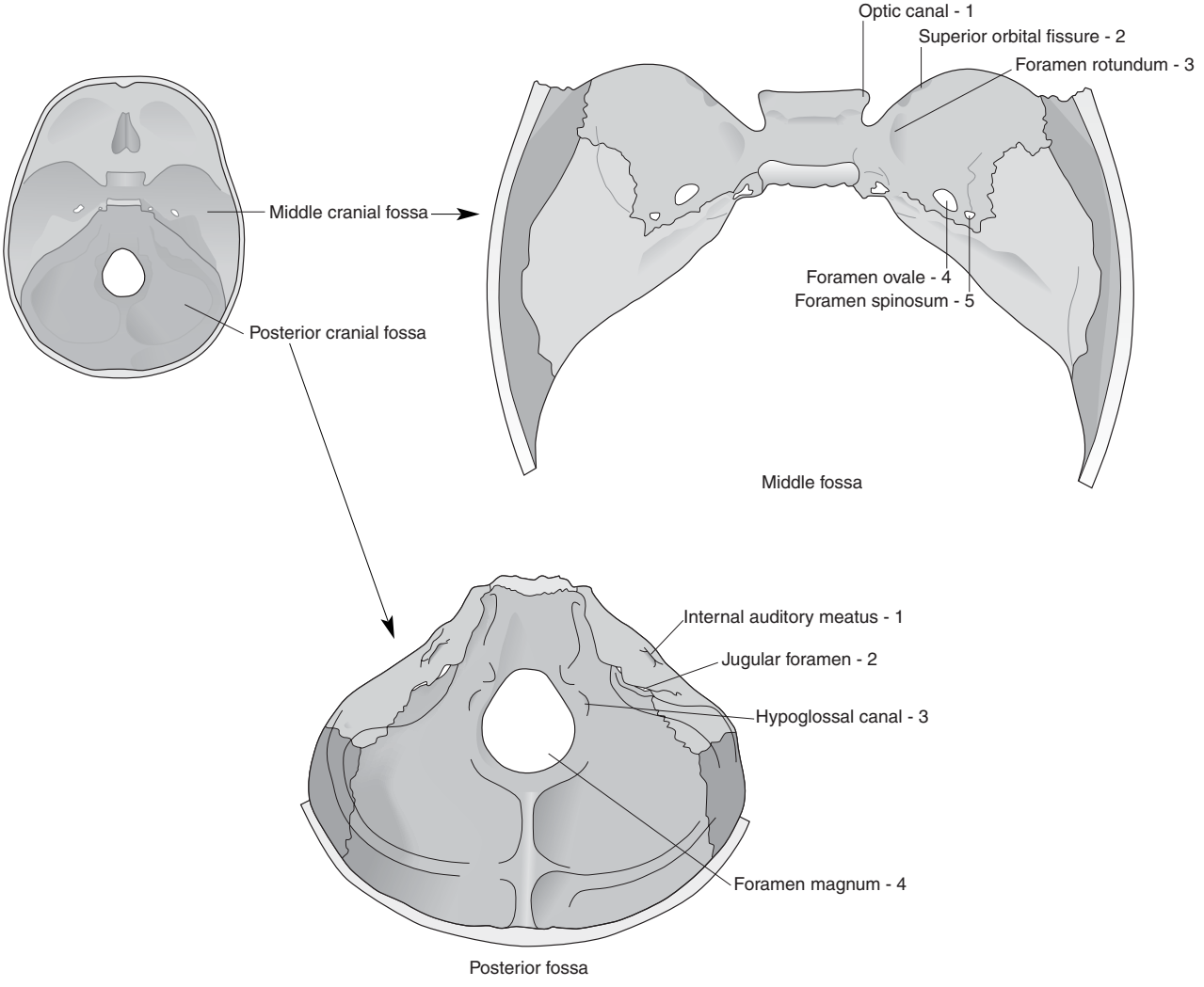
Middle cranial fossa (CN II–VI)—through sphenoid bone:

1. Optic canal (CN II, ophthalmic artery, central retinal vein)
2. **S**uperior orbital fissure (CN III, IV, V_1, VI, ophthalmic vein)
3. Foramen **R**otundum (CN V_2)
4. Foramen **O**vale (CN V_3)
5. Foramen spinosum (middle meningeal artery)

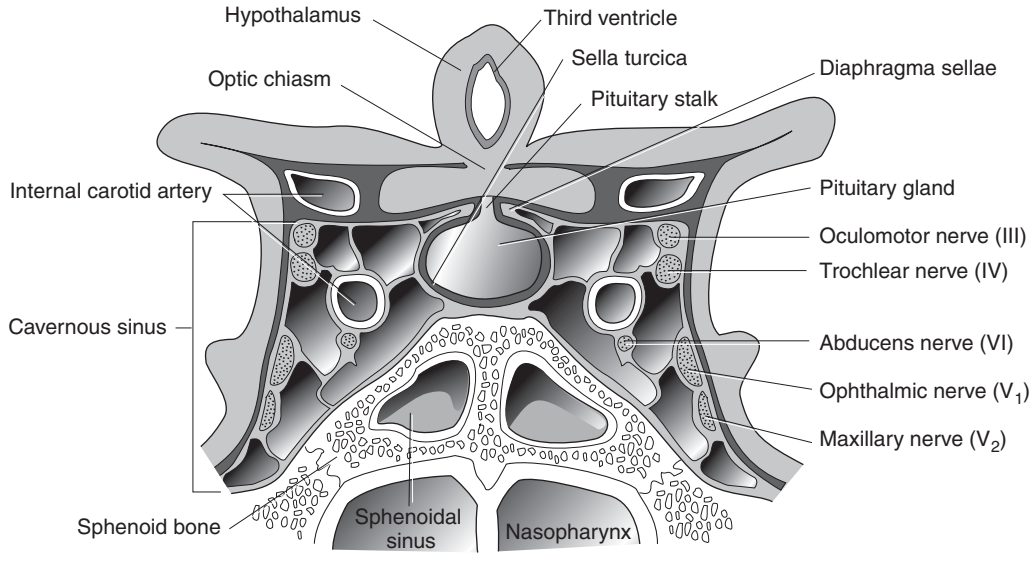
Posterior cranial fossa (CN VII–XII)—through temporal or occipital bone:

1. Internal auditory meatus (CN VII, VIII)
2. Jugular foramen (CN IX, X, XI, jugular vein)
3. Hypoglossal canal (CN XII)
4. Foramen magnum (spinal roots of CN XI, brain stem, vertebral arteries)

Divisions of CN V exit owing to **S**tanding **R**oom **O**nly.



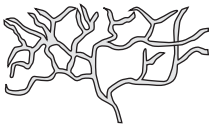
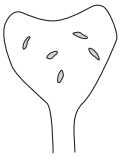
Cavernous sinus	A collection of venous sinuses on either side of the pituitary. Blood from eye and superficial cortex → cavernous sinus → internal jugular vein. CN III, IV, V_1, V_2, and VI and postganglionic sympathetic fibers en route to the orbit all pass through the cavernous sinus. Only CN VI is "free-floating." Cavernous portion of internal carotid artery is also here.	The nerves that control extraocular muscles (plus V_1 and V_2) pass through the cavernous sinus. Cavernous sinus syndrome (e.g., due to mass effect)—ophthalmoplegia, ophthalmic and maxillary sensory loss.



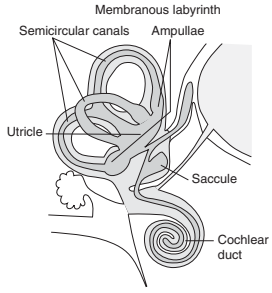
(Adapted, with permission, from Stobo J et al. *The Principles and Practice of Medicine,* 23rd ed. Stamford, CT: Appleton & Lange, 1996: 277.)

KLM sounds: kuh, la, mi	Kuh-kuh-kuh tests palate elevation (CN X—vagus). La-la-la tests tongue (CN XII—hypoglossal). Mi-mi-mi tests lips (CN VII—facial).	Say it aloud.
Mastication muscles	3 muscles close jaw: **M**asseter, te**M**poralis, **M**edial pterygoid. 1 opens: lateral pterygoid. All are innervated by the trigeminal nerve (V_3).	**M**'s **M**unch. **L**ateral **L**owers (when speaking of pterygoids with respect to jaw motion).
Muscles with *glossus*	All muscles with root *glossus* in their names (**except palatoglossus**, innervated by vagus nerve) are innervated by hypo*glossal* nerve.	*Palat*: vagus nerve. *Glossus*: hypo*glossal* nerve.
Muscles with *palat*	All muscles with root *palat* in their names (**except tensor veli palatini**, innervated by mandibular branch of CN V) are innervated by vagus nerve.	*Palat*: vagus nerve (except **TENS**or, who was too **TENSE**).

Sensory corpuscles

Receptor type	Location	Senses	
Free nerve endings (C, Aδ fibers)	All skin (some viscera)	Pain and temperature	
Meissner's corpuscles	Glabrous (hairless) skin—40% of fingertip receptors	Dynamic fine touch (e.g., manipulation)	
Pacinian corpuscles	Deep skin layers, ligaments, and joints—15% of fingertip receptors	Vibration	
Merkel's disks (cup-shaped)	Hair follicles—25% of fingertip receptors	Static touch (e.g., shapes, edges, textures)	

Inner ear



Consists of a series of tubes in the temporal bone (bony labyrinth) filled with perilymph (Na^+ rich, similar to ECF) that includes cochlea, vestibule, and semicircular canals.

Within the bony labyrinth is a 2nd series of tubes (membranous labyrinth) filled with endolymph (K^+ rich, similar to ICF) that includes cochlear duct (within the cochlea), utricle and saccule (within the vestibule), and semicircular canals. Hair cells (located within the organ of Corti) are the sensory elements in both vestibular apparatus (spatial orientation) and cochlea (hearing).

Hearing loss:

1. Conductive—negative Rinne (bone conduction > air conduction); Weber localizes to affected ear.
2. Sensorineural—positive Rinne (air conduction > bone conduction); Weber localizes to normal ear.

Peri—think outside of cell (Na^+).

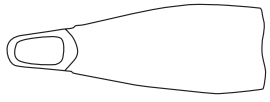
Endo—think inside of cell (K^+).

Endolymph is made by the stria vascularis.

Utricle and saccule contain maculae—detect linear acceleration.

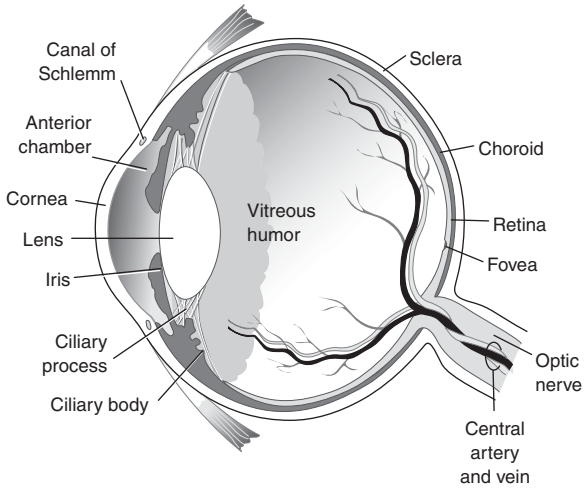
Semicircular canals contain **A**mpullae—detect **A**ngular acceleration.

Cochlear membrane = scuba flipper: narrow/stiff at the base (high frequency) and wide/flexible at the apex (low frequency).

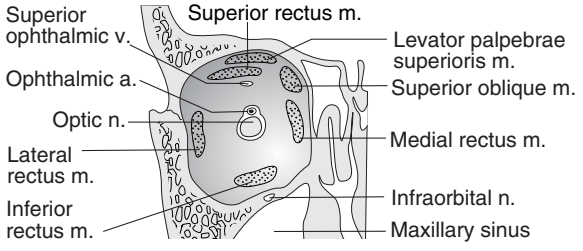


Hearing loss in the elderly—high frequency → low frequency.

Eye and retina



Extraocular muscles and nerves



(Note: inferior oblique not in plane of diagram)

CN III damage—eye looks down and out,

CN IV damage—diplopia with downward gaze.

CN VI damage—medially directed eye.

CN VI innervates the **L**ateral **R**ectus.

CN IV innervates the **S**uperior **O**blique.

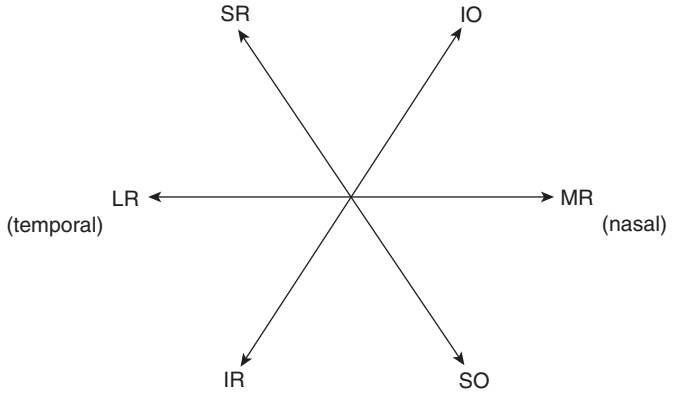
CN III innervates the **R**est.

The "chemical formula" $\mathbf{LR_6SO_4R_3}$.

The superior oblique abducts, intorts, depresses.

Testing extraocular muscles

To test the function of each muscle, have the patient look in the following directions (i.e., to test SO, have patient depress eye from adducted position):

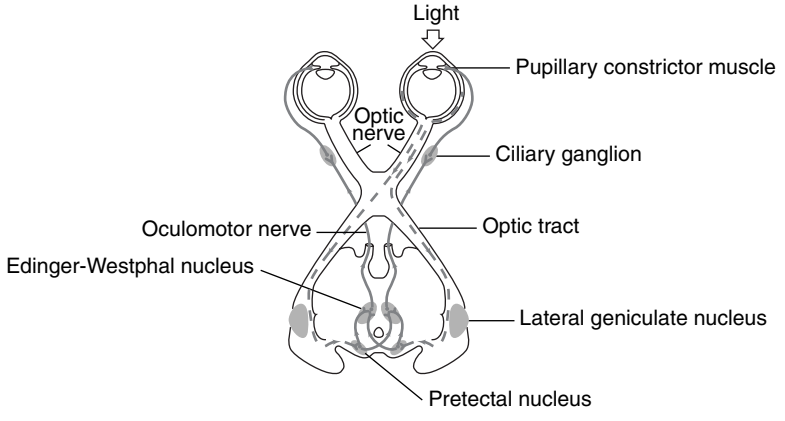


Pupillary light reflex

Light in either retina sends a signal via CN II to pretectal nuclei (dashed lines) in midbrain that activate bilateral Edinger-Westphal nuclei; pupils contract bilaterally (consensual reflex).

Note that the illumination of 1 eye results in bilateral pupillary constriction.

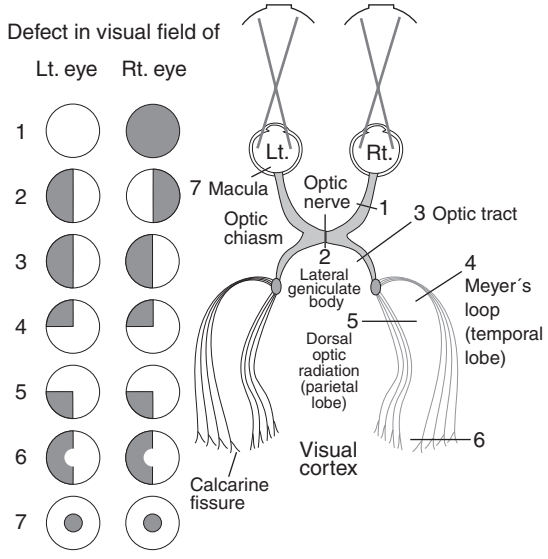
Marcus Gunn phenomenon—afferent pupillary defect (e.g., due to optic nerve damage or retinal detachment).



(Adapted, with permission, from Simon RP et al. *Clinical Neurology,* 3rd ed. Stamford, CT: Appleton & Lange, 1996.)

Visual field defects

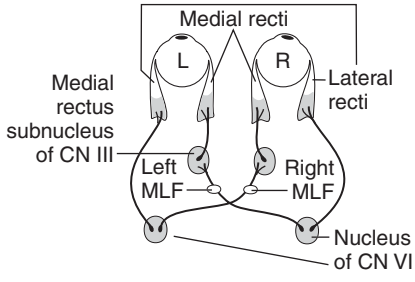
1. Right anopia
2. Bitemporal hemianopia
3. Left homonymous hemianopia
4. Left upper quadrantic anopia (right temporal lesion)
5. Left lower quadrantic anopia (right parietal lesion)
6. Left hemianopia with macular sparing
7. Central scotoma (macular degeneration)



Note: When an image hits 1° visual cortex, it is upside down and left-right reversed.

Internuclear ophthalmoplegia (MLF syndrome)

Lesion in the medial longitudinal fasciculus (MLF). Results in medial rectus palsy on attempted lateral gaze. Nystagmus in abducting eye. Convergence is normal. MLF syndrome is seen in many patients with multiple sclerosis.



MLF = **M**S.

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.

Looking to the right with left MLF damage

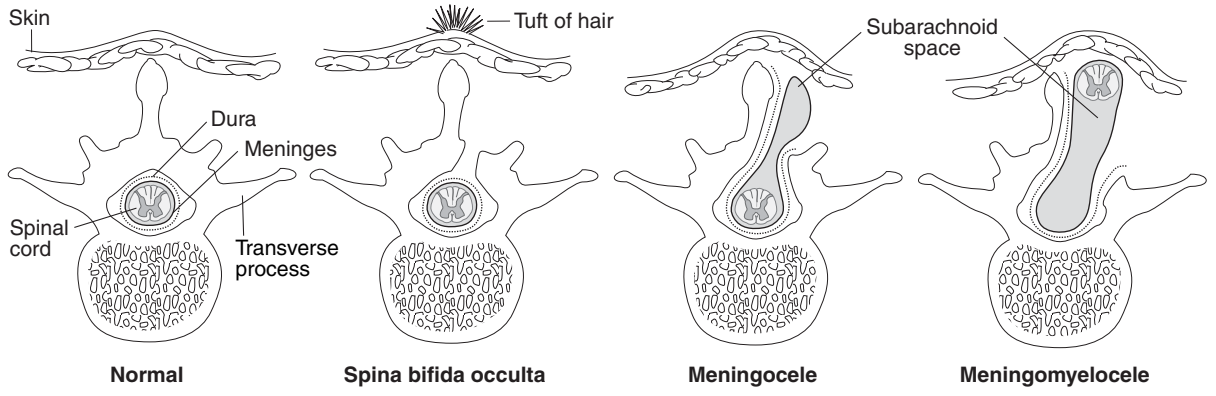
Neural tube defects

Associated with low folic acid intake during pregnancy. Elevated α-fetoprotein in amniotic fluid and maternal serum.

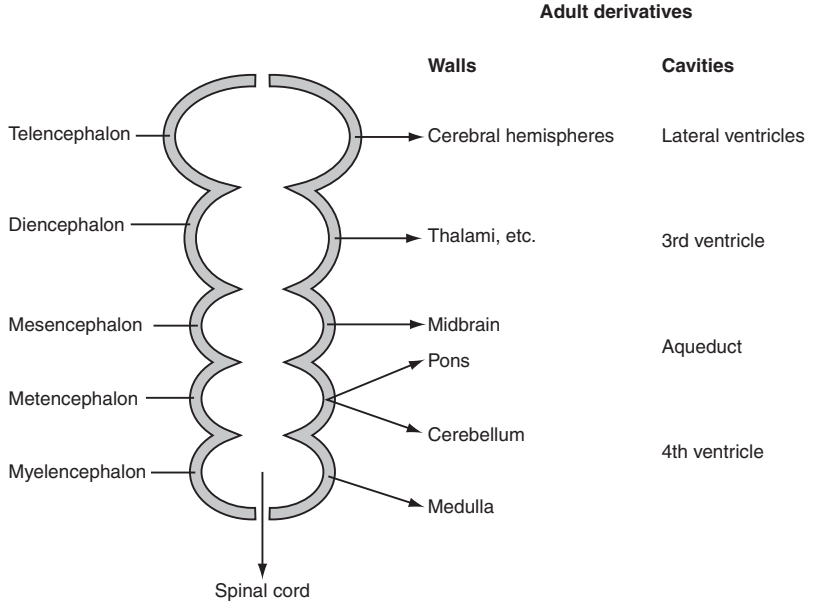
Spina bifida occulta—failure of bony spinal canal to close, but no structural herniation. Usually seen at lower vertebral levels. Dura is intact.

Meningocele—meninges herniate through spinal canal defect.

Meningomyelocele—meninges and spinal cord herniate through spinal canal defect.



Regional specification of developing brain



Forebrain anomalies

Anencephaly	Malformation of anterior end of neural tube; no brain/calvarium, elevated AFP, polyhydramnios (no swallowing center in brain).
Holoprosencephaly	↓ separation of hemispheres across midline; results in cyclopia; associated with Patau's syndrome and severe fetal alcohol syndrome.

Motor neuron signs

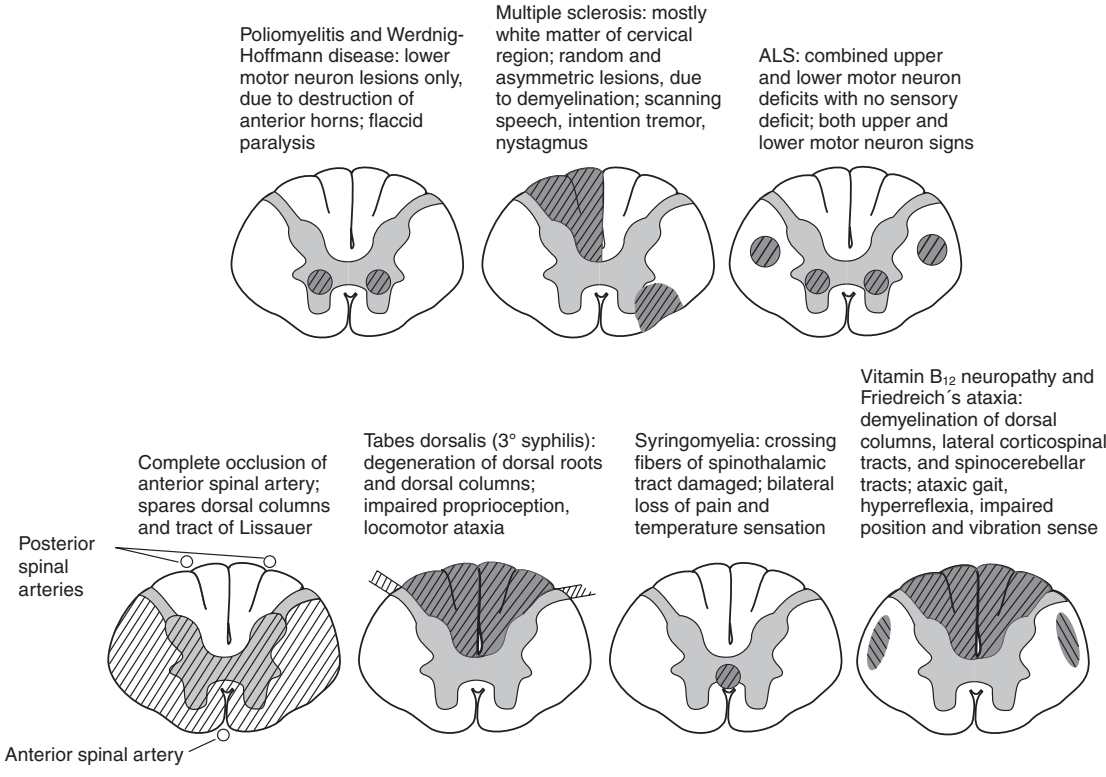
Sign	UMN lesion	LMN lesion
Weakness	+	+
Atrophy	–	+
Fasciculation	–	+
Reflexes	↑	↓
Tone	↑	↓
Babinski	+	–
Spastic paralysis	+	–

Lower MN = everything **lowered** (less muscle mass, ↓ muscle tone, ↓ reflexes, downgoing toes).

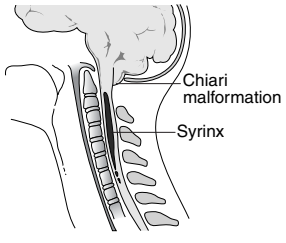
Upper MN = everything **up** (tone, DTRs, toes).

Upgoing Babinski is normal in infants.

Spinal cord lesions



Syringomyelia



Enlargement of the central canal of spinal cord.

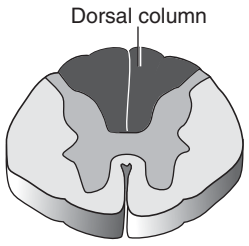
Crossing fibers of spinothalamic tract are damaged. Bilateral loss of pain and temperature sensation in upper extremities with preservation of touch sensation.

Syrinx (Greek) = tube, as in syringe.

Often presents in patients with Arnold-Chiari malformation.

Most common at C8–T1.

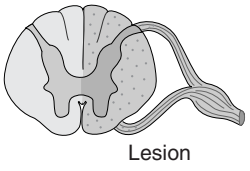
Tabes dorsalis



Degeneration of dorsal columns and dorsal roots due to 3° syphilis, resulting in impaired proprioception and locomotor ataxia. Associated with Charcot's joints, shooting (lightning) pain (see Color Image 12), Argyll Robertson pupils (reactive to accommodation but not to light), and absence of DTRs.

Argyll Robertson pupils are also known as "prostitute's pupils" because they accommodate but do not react.

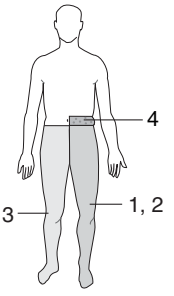
Brown-Séquard syndrome



Hemisection of spinal cord. Findings:

1. Ipsilateral UMN signs (corticospinal tract) below lesion
2. Ipsilateral loss of tactile, vibration, proprioception sense (dorsal column) below lesion
3. Contralateral pain and temperature loss (spinothalamic tract) below lesion
4. Ipsilateral loss of all sensation at level of lesion
5. LMN signs (e.g., flaccid paralysis) at level of lesion

If lesion occurs above T1, presents with Horner's syndrome.



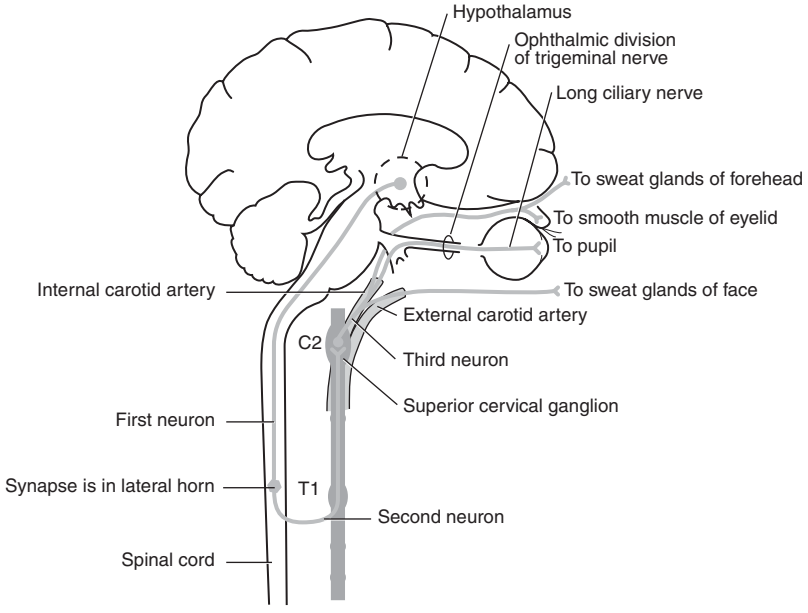
Horner's syndrome

Sympathectomy of face:

1. **P**tosis (slight drooping of eyelid)
2. **A**nhidrosis (absence of sweating) and flushing (rubor) of affected side of face
3. **M**iosis (pupil constriction)

Associated with lesion of spinal cord above T1 (e.g., Pancoast's tumor, Brown-Séquard syndrome [cord hemisection], late-stage syringomyelia).

PAM is **horny** (Horner's).



The 3-neuron oculosympathetic pathway above projects from the hypothalamus to the intermediolateral column of the spinal cord, then to the superior cervical (sympathetic) ganglion, and finally to the pupil, the smooth muscle of the eyelids, and the sweat glands of the forehead and face. Interruption of these pathways results in Horner's syndrome.

Brain lesions

Area of lesion	Consequence	
Broca's area	Motor (nonfluent/expressive) aphasia with good comprehension	**BRO**ca's is **BRO**ken speech. **W**ernicke's is **W**ordy but makes no sense.
Wernicke's area	Sensory (fluent/receptive) aphasia with poor comprehension	
Arcuate fasciculus	Conduction aphasia; poor repetition with good comprehension, fluent speech	Connects Wernicke's to Broca's area.
Amygdala (bilateral)	Klüver-Bucy syndrome (hyperorality, hypersexuality, disinhibited behavior)	
Frontal lobe	Personality changes and deficits in concentration, orientation, and judgment; may have reemergence of primitive reflexes	
Right parietal lobe	Spatial neglect syndrome (agnosia of the contralateral side of the world)	
Reticular activating system	Reduced levels of arousal and wakefulness (e.g., coma)	
Mammillary bodies (bilateral)	Wernicke-Korsakoff syndrome	
Basal ganglia	May result in tremor at rest, chorea, or athetosis	
Cerebellar hemisphere	Intention tremor, limb ataxia. Damage to the cerebellum results in ipsilateral deficits.	Cerebellar hemispheres are **laterally** located—affect **lateral** limbs.
Cerebellar vermis	Truncal ataxia, dysarthria	Vermis is **centrally** located—affects **central** body.
Subthalamic nucleus	Contralateral hemiballismus	
Hippocampus	Anterograde amnesia—can't make new memories	
Parapontine reticular formation (PPRF)	Eyes look toward side of lesion	
Frontal eye fields	Eyes look away from lesion	

Chorea	Sudden, jerky, purposeless movements. Characteristic of basal ganglia lesion (e.g., Huntington's disease).	*Chorea* = dancing (Greek). Think choral dancing or choreography.
Athetosis	Slow, writhing movements, especially of fingers. Characteristic of basal ganglia lesion.	*Athetos* = not fixed (Greek). Think snakelike.
Hemiballismus	Sudden, wild flailing of 1 arm. Characteristic of contralateral subthalamic nucleus lesion. Loss of inhibition of thalamus through globus pallidus.	Half ballistic (as in throwing a baseball).
Aphasia		
Broca's	Nonfluent aphasia with intact comprehension. Broca's area—inferior frontal gyrus.	**Bro**ca's **Bro**ken **Boca.** **W**ernicke's is **W**ordy but makes no sense.
Wernicke's	Fluent aphasia with impaired comprehension. Wernicke's area—superior temporal gyrus.	**W**ernicke's = "**W**hat?"

Degenerative diseases

Cerebral cortex	**Alzheimer's disease—**most common cause of dementia in the elderly. Associated with senile plaques (extracellular, β-amyloid core) and neurofibrillary tangles (intracellular, abnormally phosphorylated tau protein; tangles correlate with degree of dementia). Down syndrome patients are at ↑ risk of developing Alzheimer's. Familial form (10%) associated with genes on chromosomes 1, 14, 19 (*APOE4* allele), and 21 (p-*App* gene) (see Color Image 41).	Multi-infarct dementia is the 2nd most common cause of dementia in the elderly. May cause amyloid angiopathy → intracranial hemorrhage. Alzheimer's—diffuse cortical atrophy.
	Pick's disease (frontotemporal dementia)—dementia, aphasia, parkinsonian aspects; associated with Pick bodies (intracellular, aggregated tau protein).	Pick's—frontotemporal lobe atrophy.
	Lewy body dementia—parkinsonism with dementia and hallucinations. Caused by α-synuclein defect.	
	Creutzfelt-Jakob disease (CJD)—rapidly progressive (weeks to months) dementia with myoclonus, spongiform cortex; associated with prions.	
Basal ganglia and brain stem	**Huntington's disease—**autosomal-dominant inheritance, chorea, dementia. Atrophy of caudate nucleus (loss of GABAergic neurons). Triplet repeat defect causes genetic anticipation. Degeneration of caudate leads to enlarged lateral ventricles on CT.	Chromosome 4—expansion of CAG repeats. **CAG—C**audate loses **A**Ch and **G**ABA.
	Parkinson's disease—associated with Lewy bodies (composed of α-synuclein) and depigmentation of the substantia nigra pars compacta (loss of dopaminergic neurons). Rare cases have been linked to exposure to MPTP, a contaminant in illicit street drugs.	**TRAP** = **T**remor (at rest), cogwheel **R**igidity, **A**kinesia, and **P**ostural instability (you are **TRAP**ped in your body).
Spinocerebellar	**Olivopontocerebellar atrophy; Friedreich's ataxia.**	
Motor neuron	**Amyotrophic lateral sclerosis (ALS)**—associated with **both** LMN and UMN signs; no sensory deficit. Can be caused by defect in superoxide dismutase 1 (SOD1).	Commonly known as Lou Gehrig's disease.
	Werdnig-Hoffmann disease (infantile spinal muscular atrophy)—autosomal-recessive inheritance; presents at birth as a "floppy baby," tongue fasciculations; median age of death 7 months. Associated with degeneration of anterior horns. LMN involvement only.	
	Polio—follows infection with poliovirus; LMN signs. Associated with degeneration of anterior horns.	

Poliomyelitis	Caused by poliovirus, which is transmitted by the fecal-oral route. Replicates in the oropharynx and small intestine before spreading through the bloodstream to the CNS, where it leads to the destruction of cells in the anterior horn of the spinal cord, leading in turn to LMN destruction.	
Symptoms	Malaise, headache, fever, nausea, abdominal pain, sore throat. Signs of LMN lesions—muscle weakness and atrophy, fasciculations, fibrillation, and hyporeflexia.	
Findings	CSF with lymphocytic pleocytosis with slight elevation of protein (with no change in CSF glucose). Virus recovered from stool or throat.	
Demyelinating and dysmyelinating diseases	**Multiple sclerosis (MS)—**↑ prevalence with ↑ distance from the equator; periventricular plaques (areas of oligodendrocyte loss and reactive gliosis) with preservation of axons; ↑ protein (IgG) in CSF. Many patients have a relapsing-remitting course. Patients can present with optic neuritis (sudden loss of vision), MLF syndrome (internuclear ophthalmoplegia), hemiparesis, hemisensory symptoms, or bladder/bowel incontinence (see Color Image 47). **Progressive multifocal leukoencephalopathy (PML)—**associated with JC virus and seen in 2–4% of AIDS patients (reactivation of latent viral infection). **Acute disseminated (postinfectious) encephalomyelitis.** **Metachromatic leukodystrophy—**an autosomal-recessive lysosomal storage disease; arylsulfatase A deficiency. **Guillain-Barré syndrome** (see below).	Classic triad of **MS** is a **SIN:** **S**canning speech **I**ntention tremor, **I**ncontinence, **I**nternuclear ophthalmoplegia **N**ystagmus Most often affects women in their 20s and 30s; more common in whites. Treatment: β-interferon or immunosuppressant therapy.
Guillain-Barré syndrome (acute idiopathic polyneuritis)	Inflammation and demyelination of peripheral nerves and motor fibers of ventral roots (sensory effect less severe than motor), causing symmetric ascending muscle weakness beginning in distal lower extremities. Facial paralysis in 50% of cases. Autonomic function may be severely affected (e.g., cardiac irregularities, hypertension, or hypotension). Almost all patients survive; the majority recover completely after weeks to months. Findings: elevated CSF protein with normal cell count ("albuminocytologic dissociation"). Elevated protein → papilledema.	Associated with infections → autoimmune attack of peripheral myelin due to molecular mimicry (e.g., *Campylobacter jejuni* or herpesvirus infection), inoculations, and stress, but no definitive link to pathogens. Respiratory support is critical until recovery. Additional treatment: plasmapheresis, IV immune globulins.

Seizures

Partial seizures—1 area of the brain.
1. Simple partial (consciousness intact)—motor, sensory, autonomic, psychic
2. Complex partial (impaired consciousness)

Generalized seizures—diffuse.
1. Absence (petit mal)—blank stare
2. Myoclonic—quick, repetitive jerks
3. Tonic-clonic (grand mal)—alternating stiffening and movement
4. Tonic—stiffening
5. Atonic—"drop" seizures—falls to floor; commonly mistaken for fainting

Epilepsy is a disorder of recurrent seizures (febrile seizures are not epilepsy).
Partial seizures can secondarily generalize.
Causes of seizures by age:
Children—genetic, infection, trauma, congenital, metabolic.
Adults—tumors, trauma, stroke, infection.
Elderly—stroke, tumor, trauma, metabolic, infection.

Intracranial hemorrhage

Epidural hematoma	Rupture of middle meningeal artery (branch of maxillary artery), often 2° to fracture of temporal bone. Lucid interval (see Color Image 44).	CT shows "biconvex disk" not crossing suture lines.
Subdural hematoma	Rupture of bridging veins. Venous bleeding (less pressure) with delayed onset of symptoms. Seen in elderly individuals, alcoholics, blunt trauma, shaken baby (predisposing factors—brain atrophy, shaking, whiplash) (see Color Image 43).	Crescent-shaped hemorrhage that crosses suture lines.
Subarachnoid hemorrhage	Rupture of an aneurysm (usually berry aneurysm) or an AVM. Patients complain of "worst headache of my life." Bloody or yellow (xanthochromic) spinal tap.	
Parenchymal hematoma	Caused by hypertension, amyloid angiopathy, diabetes mellitus, and tumor.	

Berry aneurysms

Berry aneurysms occur at the bifurcations in the circle of Willis. Most common site is bifurcation of the anterior communicating artery. Rupture (most common complication) leads to hemorrhagic stroke/subarachnoid hemorrhage. Associated with adult polycystic kidney disease, Ehlers-Danlos syndrome, and Marfan's syndrome. Other risk factors: advanced age, hypertension, smoking, race (higher risk in blacks) (see Color Image 46).

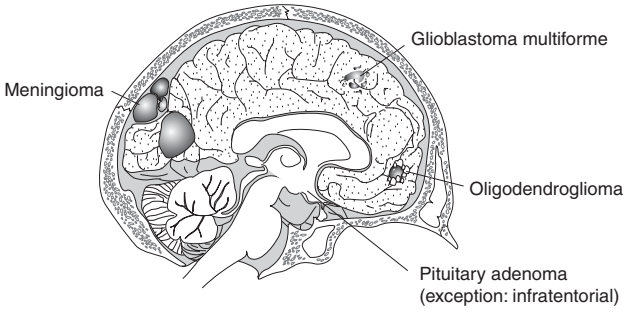
Charcot-Bouchard microaneurysms—associated with chronic hypertension; affects small vessels.

Hydrocephalus	Normal pressure (communicating) hydrocephalus—enlarged ventricles with normal opening pressure on lumbar puncture. Classic triad of dementia, gait problems, urinary incontinence. Caused by impaired absorption of CSF by arachnoid granulations. Obstructive (noncommunicating) hydrocephalus—caused by structural blockage of CSF circulation within the ventricular system (e.g., stenosis of the aqueduct of Sylvius).
Neurocutaneous disorders	Sturge-Weber syndrome—congenital disorder with port-wine stains and ipsilateral leptomeningeal angioma. Can cause glaucoma, seizures, hemiparesis, and mental retardation. Tuberous sclerosis—hamartomas in CNS, skin, organs; cardiac rhabdomyoma, renal angiomyolipoma, subependymal giant cell astrocytoma, MR, seizures, ash leaf spots, sebaceous adenoma, shagreen patch. Neurofibromatosis—café-au-lait spots, Lisch nodules (iris), neurofibromas in skin. von Hippel–Lindau disease—autosomal-dominant disorder with cavernous hemangiomas in skin, mucosa, organs; renal cell carcinoma, hemangioblastoma in retina, brain stem, cerebellum.

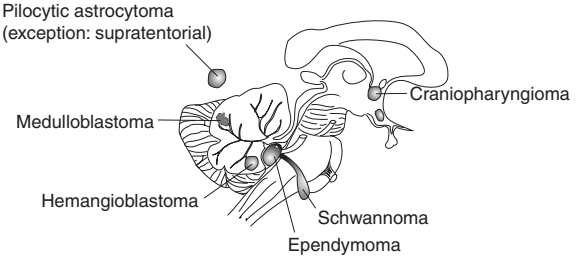
Primary brain tumors

Clinical presentation due to mass effects (e.g., seizures, dementia, focal lesions); 1° brain tumors rarely undergo metastasis. The majority of adult 1° tumors are supratentorial, while the majority of childhood 1° tumors are infratentorial. Note: half of adult brain tumors are metastases; usually present at the gray-white junction.

Adult peak incidence		
Glioblastoma multiforme (grade IV astrocytoma)	Most common 1° brain tumor. Prognosis grave; < 1-year life expectancy. Found in cerebral hemispheres. Can cross corpus callosum ("butterfly glioma") (see Color Image 48). Stain astrocytes for GFAP.	"Pseudopalisading" pleomorphic tumor cells—border central areas of necrosis and hemorrhage.
Meningioma	2nd most common 1° brain tumor. Most often occurs in convexities of hemispheres and parasagittal region. Arises from arachnoid cells external to brain. Resectable.	Spindle cells concentrically arranged in a whorled pattern; **psammoma bodies** (laminated calcifications).
Schwannoma	3rd most common 1° brain tumor. Schwann cell origin; often localized to CN VIII → acoustic schwannoma. Resectable.	Bilateral schwannoma found in neurofibromatosis type 2.
Oligodendroglioma	Relatively rare, slow growing. Most often in frontal lobes. Chicken-wire capillary pattern (see Color Image 49).	Oligodendrocytes = "fried egg" cells—round nuclei with clear cytoplasm. Often calcified in oligodendroglioma.
Pituitary adenoma	Prolactin secreting is most common form. Bitemporal hemianopia (due to pressure on optic chiasm) and hyper- or hypopituitarism are sequelae.	Rathke's pouch.
Childhood peak incidence		
Pilocytic (low-grade) astrocytoma	Usually well circumscribed. In children, most often found in posterior fossa. Benign; good prognosis.	Rosenthal fibers—eosinophilic, corkscrew fibers.
Medulloblastoma	Highly malignant cerebellar tumor. A form of primitive neuroectodermal tumor (PNET). Can compress 4th ventricle, causing hydrocephalus.	Rosettes or perivascular pseudorosette pattern of cells. Radiosensitive.
Ependymoma	Ependymal cell tumors most commonly found in 4th ventricle. Can cause hydrocephalus. Poor prognosis.	Characteristic perivascular pseudorosettes. Rod-shaped blepharoplasts (basal ciliary bodies) found near nucleus.
Hemangioblastoma	Most often cerebellar; associated with von Hippel–Lindau syndrome when found with retinal angiomas. Can produce EPO → 2° polycythemia.	Foamy cells and high vascularity are characteristic.
Craniopharyngioma	Benign childhood tumor, confused with pituitary adenoma (can also cause bitemporal hemianopia). Most common childhood supratentorial tumor.	Derived from remnants of Rathke's pouch. Calcification is common (tooth enamel–like).



Supratentorial/adult tumors



Infratentorial/childhood tumors

Posterior fossa malformations

Arnold-Chiari—small posterior fossa, downward displacement of cerebellum, medulla deformity; associated with tonsillar herniation.
Chiari I—low-lying cerebellum obstructs CSF flow and compresses medulla; cerebellar tonsils descend through foramen magnum. Frequently asymptomatic; correctable with surgery.
Chiari II—cerebellar vermis and medulla descend through foramen magnum; fatal
Dandy-Walker—large posterior fossa; absent cerebellum with cyst in its place.

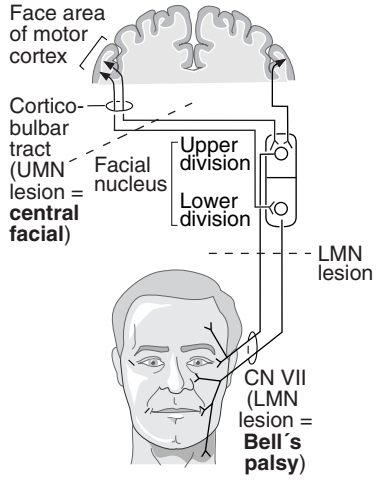
Cranial nerve and cerebellar lesions

CN XII lesion (LMN)—tongue deviates **toward** side of lesion (lick your wounds).
CN V motor lesion—jaw deviates **toward** side of lesion.
Unilateral lesion of cerebellum—patient tends to fall **toward** side of lesion.
CN X lesion—uvula deviates **away** from side of lesion.
CN XI lesion—weakness turning head to contralateral side of lesion. Shoulder droop on side of lesion.

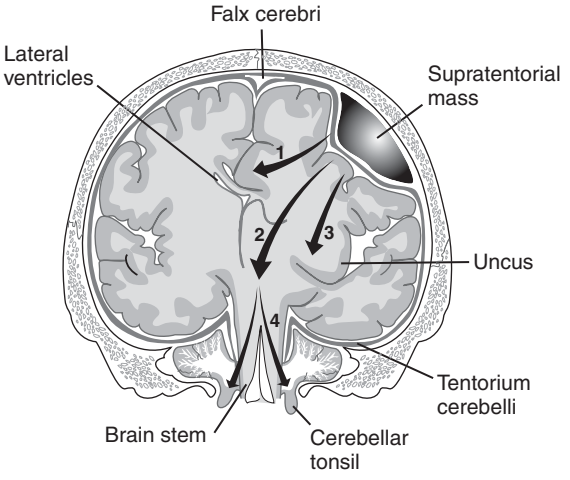
Facial lesions

UMN lesion	Lesion of motor cortex or connection between cortex and facial nucleus. Contralateral paralysis of lower face only.
LMN lesion	Ipsilateral paralysis of upper and lower face.
Bell's palsy	Complete destruction of the facial nucleus itself or its branchial efferent fibers (facial nerve proper). Peripheral ipsilateral facial paralysis with inability to close eye on involved side. Only lower face is affected, since upper face has contralateral and ipsilateral innervation by CN VII. Can occur idiopathically; gradual recovery in most cases. Seen as a complication in **A**IDS, **L**yme disease, **S**arcoidosis, **T**umors, **D**iabetes.

ALexander **Bell** with **STD:** **A**IDS, **L**yme, **S**arcoid, **T**umors, **D**iabetes.



Herniation syndromes



1. Cingulate (subfalcine) herniation under falx cerebri
2. Downward transtentorial (central) herniation
3. Uncal herniation
4. Cerebellar tonsillar herniation into the foramen magnum

Can compress anterior cerebral artery.
Coma and death result when these herniations compress the brain stem.
Uncus = medial temporal lobe.

(Adapted, with permission, from Simon RP et al. *Clinical Neurology*, 4th ed. Stamford, CT: Appleton & Lange, 1999: 314.)

Uncal herniation

Clinical signs	Cause
Ipsilateral dilated pupil/ptosis	Stretching of CN III
Contralateral homonymous hemianopia	Compression of ipsilateral posterior cerebral artery
Ipsilateral paresis	Compression of contralateral crus cerebri (Kernohan's notch); this is a "false localizing" sign
Duret hemorrhages—paramedian artery rupture	Caudal displacement of brain stem

Opioid analgesics	Morphine, fentanyl, codeine, heroin, methadone, meperidine, dextromethorphan.
Mechanism	Act as agonists at opioid receptors (mu = morphine, delta = enkephalin, kappa = dynorphin) to modulate synaptic transmission.
Clinical use	Pain, cough suppression (dextromethorphan), diarrhea (loperamide and diphenoxylate), acute pulmonary edema, maintenance programs for addicts (methadone).
Toxicity	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 naltrexone (opioid receptor antagonist).

Epilepsy drugs

	PARTIAL		GENERALIZED				
	Simple	Complex	Tonic-Clonic	Absence	Status	Mechanism	Notes
Phenytoin	✓	✓	1st line		1st line for prophylaxis	↑ Na^+ channel inactivation	
Carbamazepine	✓	✓	1st line			↑ Na^+ channel inactivation	1st line for trigeminal neuralgia
Lamotrigine	✓	✓	✓			Blocks voltage-gated Na^+ channels	
Gabapentin	✓	✓	✓			↑ GABA release	Also used for peripheral neuropathy
Topiramate	✓	✓	✓			Blocks Na^+ channels, ↑ GABA action	
Phenobarbital	✓	✓	✓			↑ $GABA_A$ action	1st line in pregnant women, children
Valproic acid	✓	✓	1st line	✓		↑ Na^+ channel inactivation, ↑ GABA concentration	Also used for myoclonic seizures
Ethosuximide				1st line		Blocks thalamic T-type Ca^{2+} channels	
Benzodiazepines (diazepam or lorazepam)					1st line for acute	↑ $GABA_A$ action	Also used for seizures of eclampsia (1st line to prevent seizures of eclampsia is $MgSO_4$)

Epilepsy drug toxicities

Benzodiazepines	Sedation, tolerance, dependence.
Carbamazepine	Diplopia, ataxia, blood dyscrasias (agranulocytosis, aplastic anemia), liver toxicity, teratogenesis, induction of cytochrome P-450.
Ethosuximide	GI distress, fatigue, headache, urticaria, Stevens-Johnson syndrome.
Phenobarbital	Sedation, tolerance, dependence, induction of cytochrome P-450.
Phenytoin	Nystagmus, diplopia, ataxia, sedation, gingival hyperplasia, hirsutism, megaloblastic anemia, teratogenesis, SLE-like syndrome, induction of cytochrome P-450.
Valproic acid	GI distress, rare but fatal hepatotoxicity (measure LFTs), neural tube defects in fetus (spina bifida), tremor, weight gain. Contraindicated in pregnancy.
Lamotrigine	Stevens-Johnson syndrome.
Gabapentin	Sedation, ataxia.
Topiramate	Sedation, mental dulling, kidney stones, weight loss.

EFGH—Ethosuximide, Fatigue, GI, Headache.

Stevens-Johnson syndrome—prodrome of malaise and fever followed by rapid onset of erythematous/purpuric macules (oral, ocular, genital). Skin lesions progress to epidermal necrosis and sloughing.

Phenytoin

Mechanism	Use-dependent blockade of Na^+ channels; inhibition of glutamate release from excitatory presynaptic neuron.
Clinical use	Tonic-clonic seizures. Also a class IB antiarrhythmic.
Toxicity	Nystagmus, ataxia, diplopia, sedation, SLE-like syndrome, induction of cytochrome P-450. Chronic use produces gingival hyperplasia in children, peripheral neuropathy, hirsutism, megaloblastic anemia (↓ folate absorption), and malignant hyperthermia (rare); teratogenic (fetal hydantoin syndrome).

Barbiturates

Phenobarbital, pentobarbital, thiopental, secobarbital.

Mechanism	Facilitate $GABA_A$ action by ↑ **duration** of Cl^- channel opening, thus ↓ neuron firing.	Barbi**DURAT**e (↑ **DURAT**ion). Contraindicated in porphyria.
Clinical use	Sedative for anxiety, seizures, insomnia, induction of anesthesia (thiopental).	
Toxicity	Dependence, additive CNS depression effects with alcohol, respiratory or cardiovascular depression (can lead to death), drug interactions owing to induction of liver microsomal enzymes (cytochrome P-450). Treat overdose with symptom management (assist respiration, ↑ BP).	

Benzodiazepines

Diazepam, lorazepam, triazolam, temazepam, oxazepam, midazolam, chlordiazepoxide, alprazolam.

Mechanism	Facilitate $GABA_A$ action by ↑ **frequency** of Cl^- channel opening. Most have long half-lives and active metabolites.	**FRE**nzodiazepines (↑ **FRE**quency). Short acting = **TOM** Thumb = **T**riazolam, **O**xazepam, **M**idazolam.
Clinical use	Anxiety, spasticity, status epilepticus (lorazepam and diazepam), detoxification (especially alcohol withdrawal–DTs), night terrors, sleepwalking.	
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 receptor).	

Anesthetics—general principles

CNS drugs must be lipid soluble (cross the blood-brain barrier) or be actively transported.

Drugs with ↓ solubility in blood = rapid induction and recovery times.

Drugs with ↑ solubility in lipids = ↑ potency = $\frac{1}{\text{MAC}}$

where MAC = minimal alveolar concentration.

Examples: N_2O has low 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	Halothane, enflurane, isoflurane, sevoflurane, methoxyflurane, nitrous oxide.
Mechanism	Mechanism unknown.
Effects	Myocardial depression, respiratory depression, nausea/emesis, ↑ cerebral blood flow (↓ cerebral metabolic demand).
Toxicity	Hepatotoxicity (halothane), nephrotoxicity (methoxyflurane), proconvulsant (enflurane), malignant hyperthermia (rare).

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 redistribution from brain. ↓ cerebral blood flow.	**B. B. K**ing on **OPIATES PROPO**ses **FOOL**ishly.
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), and amnesia.	
Arylcyclohexylamines (**K**etamine)	PCP analogs that act as dissociative anesthetics. Cardiovascular stimulants. Cause disorientation, hallucination, and bad dreams. ↑ cerebral blood flow.	
Opiates	Morphine, fentanyl used with other CNS depressants during general anesthesia.	
Propofol	Used for rapid anesthesia induction and short procedures. Less postoperative nausea than thiopental.	

Local anesthetics	Esters—procaine, cocaine, tetracaine; amides—l**I**doca**I**ne, mep**I**vaca**I**ne, bup**I**vaca**I**ne (am**I**des have 2 **I**'s in name).
Mechanism	Block Na^+ channels by binding to specific receptors on inner portion of channel. 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.
Principle	1. In infected (acidic) tissue, alkaline anesthetics are charged and cannot penetrate membrane effectively. Therefore, more anesthetic is needed in these cases. 2. 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—pain (lose first) > temperature > touch > pressure (lose last). 3. Except for cocaine, given with vasoconstrictors (usually epinephrine) to enhance local action—↓ bleeding, ↑ anesthesia by ↓ systemic concentration.
Clinical use	Minor surgical procedures, spinal anesthesia. If allergic to esters, give amides.
Toxicity	CNS excitation, severe cardiovascular toxicity (bupivacaine), hypertension, hypotension, and arrhythmias (cocaine).

Neuromuscular blocking drugs

Used for muscle paralysis in surgery or mechanical ventilation. Selective for motor (vs. autonomic) nicotinic receptor.

Depolarizing

Succinylcholine (complications include hypercalemia and hyperkalemia).

Reversal of blockade:

- Phase I (prolonged depolarization)—no antidote. Block potentiated by cholinesterase inhibitors.
- Phase II (repolarized but blocked)—antidote consists of cholinesterase inhibitors (e.g., neostigmine).

Nondepolarizing

Tubocurarine, atracurium, mivacurium, pancuronium, vecuronium, rocuronium. Competitive—compete with ACh for receptors.

Reversal of blockade—neostigmine, edrophonium, and other cholinesterase inhibitors.

Dantrolene

Used in the treatment of **malignant hyperthermia**, which is caused by the concomitant use of inhalation anesthetics (except N_2O) and succinylcholine. Also used to treat **neuroleptic malignant syndrome** (a toxicity of antipsychotic drugs).

Mechanism: prevents the release of Ca^{2+} from the sarcoplasmic reticulum of skeletal muscle.

Parkinson's disease drugs

Parkinsonism is due to loss of dopaminergic neurons and excess cholinergic activity.

Strategy	Agents	
Agonize dopamine receptors	**B**romocriptine (ergot alkaloid and partial dopamine agonist), pramipexole, ropinirole	**BALSA:**
↑ dopamine	**A**mantadine (may ↑ dopamine release); also used as an antiviral against influenza A and rubella; toxicity = ataxia	**B**romocriptine **A**mantadine
	L-dopa/carbidopa (converted to dopamine in CNS)	**L**evodopa (with carbidopa) **S**elegiline (and COMT inhibitors)
Prevent dopamine breakdown	**S**elegiline (selective MAO type B inhibitor); entacapone, tolcapone (COMT inhibitors)	**A**ntimuscarinics
Curb excess cholinergic activity	**Benz**tropine (**A**ntimuscarinic; improves tremor and rigidity but has little effect on bradykinesia)	↓ your tremor before you drive your Mercedes-**BENZ.**

For essential or familial tremors, use a β-blocker.

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.

Clinical use

Parkinsonism.

Toxicity

Arrhythmias from peripheral conversion to dopamine. Long-term use can → dyskinesia following administration, akinesia between doses. Carbidopa, a peripheral decarboxylase inhibitor, is given with L-dopa in order to ↑ the bioavailability of L-dopa in the brain and to limit peripheral side effects.

Selegiline	
Mechanism	Selectively inhibits MAO-B, thereby ↑ the availability of dopamine.
Clinical use	Adjunctive agent to L-dopa in treatment of Parkinson's disease.
Toxicity	May enhance adverse effects of L-dopa.
Sumatriptan	
Mechanism	5-HT_{1D} agonist. Causes vasoconstriction. Half-life < 2 hours.
Clinical use	Acute migraine, cluster headache attacks.
Toxicity	Coronary vasospasm, mild tingling (contraindicated in patients with CAD or Prinzmetal's angina), hypertensive emergencies.

NOTES

HIGH-YIELD PRINCIPLES IN

Psychiatry

"What a terrible thing to have lost one's mind. Or not to have a mind at all. How true that is."

—Dan Quayle

- High-Yield Clinical Vignettes
- Pathology
- Psychology
- Pharmacology

■ Person demands only the best and most famous doctor in town.	What is the personality disorder?	Narcissistic personality disorder.
■ Nurse has episodes of hypoglycemia; blood analysis reveals no elevation in C-peptide.	What is the diagnosis?	Factitious disorder; surreptitious insulin.
■ 55-year-old businessman complains of lack of successful sexual contacts with women and lack of ability to reach a full erection. Two years ago he had a heart attack.	What might be the cause of his problem?	Fear of sudden death during intercourse.
■ 15-year-old girl of normal height and weight for her age has enlarged parotid glands but no other complaints. The mother confides that she found laxatives in the daughter's closet.	What is the diagnosis?	Bulimia.
■ Man on several medications, including antidepressants and antihypertensives, has mydriasis and becomes constipated.	What is the cause of his symptoms?	TCAs (anticholinergic effects).
■ Woman on MAO inhibitor has hypertensive crisis after a meal.	What did she ingest?	Tyramine (wine or cheese).
■ 3-year-old child presents with retinal detachment.	What is the most likely diagnosis, and what must you do?	Child abuse. Report it!
■ Homeless man admitted for pneumonia complains of bugs crawling on his skin (formication).	What is the most likely diagnosis?	Delirium tremens 2° to alcohol withdrawal.
■ Vietnam veteran becomes paralyzed upon hearing airplane engines.	What is the most likely diagnosis?	PTSD.
■ Unconscious teenager is rushed to the ER. He has pinpoint pupils and is seizing.	What is the most likely diagnosis?	Opioid overdose.

Infant deprivation effects

Long-term deprivation of affection results in:
1. ↓ muscle tone
2. Poor language skills
3. Poor socialization skills
4. Lack of basic trust
5. Anaclitic depression
6. Weight loss
7. Physical illness

Severe deprivation can result in infant death.

The **4 W's: W**eak, **W**ordless, **W**anting (socially), **W**ary.
Deprived babies say **W**ah, **W**ah, **W**ah, **W**ah.
Deprivation for > 6 months can lead to irreversible changes.

Anaclitic depression

Depression in an infant attributable to continued separation from caregiver—can result in failure to thrive. Infant becomes withdrawn and unresponsive.

Regression in children

Children regress to younger behavior under conditions of stress such as physical illness, punishment, birth of a new sibling, or fatigue (e.g., bedwetting in a previously toilet-trained child when hospitalized).

Childhood and early-onset disorders

Attention-deficit hyperactivity disorder (ADHD)—limited attention span and hyperactivity. Children are emotionally labile, impulsive, and prone to accidents. Normal intelligence. Treatment: methylphenidate (Ritalin).
Conduct disorder—continued behavior violating social norms. After 18 years of age, diagnosed as antisocial personality disorder.
Oppositional defiant disorder—child is noncompliant in the absence of criminality.
Tourette's syndrome—motor/vocal tics and involuntary profanity. Associated with OCD. Onset at < 18 years of age. Treatment: haloperidol.
Separation anxiety disorder—fear of loss of attachment figure leading to factitious physical complaints to avoid going to school. Common onset at 7–8 years of age.

Pervasive developmental disorders

Autistic disorder—patients have severe communication problems and difficulty forming relationships. Characterized by repetitive behavior, unusual abilities (savants), and usually below-normal intelligence. Treatment: ↑ communication and social skills.
Asperger's disorder—a milder form of autism involving problems with social relationships and repetitive behavior. Children are of normal intelligence and lack verbal or cognitive deficits.
Rett's disorder—X-linked disorder seen only in girls (affected males die in utero). Characterized by loss of development and mental retardation appearing at approximately age 4. Stereotyped hand-wringing.
Childhood disintegrative disorder—marked regression in multiple areas of functioning after at least 2 years of apparently normal development. Significant loss of expressive or receptive language, social skills or adaptive behavior, bowel or bladder control, play, or motor skills. Onset at 2–10 years of age.

Child abuse

	Physical abuse	Sexual abuse
Evidence	Healed fractures on x-ray, cigarette burns, subdural hematomas, multiple bruises, retinal hemorrhage or detachment	Genital/anal trauma, STDs, UTIs
Abuser	Usually female and the 1° caregiver	Known to victim, usually male
Epidemiology	~3000 deaths/year in the United States	Peak incidence 9–12 years of age

Neurotransmitter changes with disease

Anxiety—↑ NE, ↓ GABA, ↓ serotonin (5-HT).
Depression—↓ NE and ↓ serotonin (5-HT).
Alzheimer's dementia—↓ **A**Ch.
Huntington's disease—↓ GABA, ↓ ACh.
Schizophrenia—↑ dopamine.
Parkinson's disease—↓ dopamine, ↑ ACh.

Orientation

Patient's ability to know who he or she is, what date and time it is, and what his or her present circumstances are.

Deficits in orientation:

1. Anosognosia—lack of awareness that one is ill
2. Autotopagnosia—inability to locate one's own body parts
3. Depersonalization—body seems unreal or dissociated

Order of loss: 1st—time; 2nd—place; last—person.

Amnesia types

*Antero*grade amnesia—inability to remember things that occurred after a CNS insult (no new memory).
Korsakoff's amnesia—classic anterograde amnesia that is caused by thiamine deficiency. Leads to bilateral destruction of the mammillary bodies. Seen in alcoholics, and associated with confabulations.
*Retro*grade amnesia—inability to remember things that occurred before a CNS insult.

Delirium

Waxing and waning level of consciousness; rapid ↓ in attention span and level of arousal—disorganized thinking, hallucinations, illusions, misperceptions, disturbance in sleep-wake cycle, cognitive dysfunction.
The most common psychiatric illness on medical and surgical floors. Often reversible. Abnormal EEG.

Deli**RIUM** = changes in senso**RIUM.**
Check for drugs with anticholinergic effects.

Dementia

Gradual ↓ in cognition—memory deficits, aphasia, apraxia, agnosia, loss of abstract thought, behavioral/personality changes, impaired judgment. Patient is alert; no change in level of consciousness.
↑ incidence with age. More often gradual onset.

De**MEM**tia is characterized by **MEM**ory loss. Commonly irreversible.
In elderly patients, depression may present like dementia (pseudodementia). Normal EEG.

Hallucination vs. illusion vs. delusion vs. loose association	Hallucinations are perceptions in the absence of external stimuli. Illusions are misinterpretations of actual external stimuli. Delusions are false beliefs not shared with other members of culture/subculture that are firmly maintained in spite of obvious proof to the contrary. Loose associations are disorders in the form of thought (the way ideas are tied together).
Dissociative fugue	Abrupt change in geographic location with inability to recall past, confusion about personal identity, or assumption of a new identity. Leads to distress or impairment. Not the result of substance abuse or general medical condition.
Hallucination types	Visual and auditory hallucinations are common in schizophrenia. Olfactory hallucination often occurs as an aura of a psychomotor epilepsy. Gustatory hallucination is rare. Tactile hallucination (e.g., formication—the sensation of ants crawling on one's skin) is common in DTs. Also seen in cocaine abusers ("cocaine bugs"). Hypna**GO**gic hallucination occurs while **GO**ing to sleep. Hypnopompic hallucination occurs while waking from sleep.
Schizophrenia	Periods of psychosis and disturbed behavior with a decline in functioning lasting > 6 months (1–6 months—schizophreniform disorder; < 1 month—brief psychotic disorder, usually stress related). Diagnosis requires 2 or more of the following (1–4 are "positive symptoms"): 1. Delusions 2. Hallucinations—often auditory 3. Disorganized thought (loose associations) 4. Disorganized or catatonic behavior 5. "Negative symptoms"—flat affect, social withdrawal, lack of motivation, lack of speech or thought Genetic factors outweigh environmental factors in the etiology of schizophrenia. Lifetime prevalence—1.5% (males = females, blacks = whites). Presents earlier in men. 5 subtypes: 1. Disorganized (with regard to speech, behavior, and affect) 2. Catatonic (automatisms) 3. Paranoid (delusions) 4. Undifferentiated (elements of all types) 5. Residual Schizoaffective disorder—schizophrenia plus a major depressive, manic, or mixed (both) episode. 2 subtypes: bipolar or depressive.

Manic episode

Distinct period of abnormally and persistently elevated, expansive, or irritable mood lasting at least 1 week.

During mood disturbance, 3 or more of the following are present:

1. **D**istractibility
2. **I**rresponsibility—seeks pleasure without regard to consequences (hedonistic)
3. **G**randiosity—inflated self-esteem
4. **F**light of ideas—racing thoughts
5. ↑ in goal-directed **A**ctivity/psychomotor **A**gitation
6. ↓ need for **S**leep
7. **T**alkativeness or pressured speech

Maniacs **DIG FAST.**

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; there are no psychotic features.

Bipolar disorder

6 separate criteria sets exist for bipolar disorders with combinations of manic (bipolar I), hypomanic (bipolar II), and depressed episodes. 1 manic or hypomanic episode defines bipolar disorder. Lithium is drug of choice.

Cyclothymic disorder is a milder form lasting at least 2 years.

Major depressive episode

Characterized by at least 5 of the following for 2 weeks, including either depressed mood or anhedonia:

1. **S**leep disturbance
2. Loss of **I**nterest (anhedonia)
3. **G**uilt or feelings of worthlessness
4. Loss of **E**nergy
5. Loss of **C**oncentration
6. Change in **A**ppetite/weight
7. **P**sychomotor retardation or agitation
8. **S**uicidal ideations
9. Depressed mood

SIG E CAPS.

SIG is short for *signatura* (Latin for "directions"). Depressed patients are **directed** to take **E**nergy **CAPS**ules.

Lifetime prevalence of major depressive episode—5–12% male, 10–25% female.

Major depressive disorder, recurrent—requires 2 or more episodes with a symptom-free interval of 2 months.

Dysthymia is a milder form of depression lasting at least 2 years.

Sleep patterns of depressed patients

Patients with depression typically have the following changes in their sleep stages:

1. ↓ slow-wave sleep
2. ↓ REM latency
3. ↑ REM early in sleep cycle
4. ↑ total REM sleep
5. Repeated nighttime awakenings
6. Early-morning awakening (important screening question)

Risk factors for suicide completion	**S**ex (male), **A**ge (teenager or elderly), **D**epression, **P**revious attempt, **E**thanol or drug use, loss of **R**ational thinking, **S**ickness (medical illness, 3 or more prescription medications), **O**rganized plan, **N**o spouse (divorced, widowed, or single, especially if childless), **S**ocial support lacking. Women try more often; men succeed more often.	**SAD PERSONS**.
Electroconvulsive therapy	Treatment option for major depressive disorder refractory to other treatment. Produces a painless seizure. Major adverse effects of ECT are disorientation, anterograde and retrograde amnesia.	
Panic disorder	Recurrent periods of intense fear and discomfort peaking in 10 minutes with 4 of the following: **P**alpitations, **P**aresthesias, **A**bdominal distress, **N**ausea, **I**ntense fear of dying or losing control, l**I**ght-headedness, **C**hest pain, **C**hills, **C**hoking, dis**C**onnectedness, **S**weating, **S**haking, **S**hortness of breath. Panic is described in context of occurrence (e.g., panic disorder with agoraphobia). High incidence during Step 1 exam.	**PANICS.**
Specific phobia	Fear that is excessive or unreasonable and interferes with normal routine. **Cued** by presence or anticipation of a specific object or situation. Person recognizes fear is excessive (insight), yet exposure provokes an anxiety response. Can treat with systematic desensitization. Examples include: 1. Gamophobia (*gam* = gamete)—fear of marriage 2. Algophobia (*alg* = pain)—fear of pain 3. Acrophobia (*acro* = height)—fear of heights 4. Agoraphobia (*agora* = open market)—fear of being in public place or situation from which escape may be difficult	
Post-traumatic stress disorder	Persistent reexperiencing of a previous traumatic event in the life of the patient as nightmares or flashbacks. Response involves intense fear, helplessness, or horror. Leads to avoidance of stimuli associated with the trauma and persistently ↑ arousal. **Disturbance lasts > 1 month** and causes distress or social/occupational impairment. PTSD often follows acute stress disorder, which lasts up to 2–4 weeks.	
Other anxiety disorders	**Adjustment disorder—**emotional symptoms (anxiety, depression) causing impairment following an identifiable psychosocial stressor (e.g., divorce, moving) and lasting < 6 months. **Generalized anxiety disorder—**uncontrollable anxiety for at least 6 months that is unrelated to a specific person, situation, or event. Sleep disturbance, fatigue, and difficulty concentrating are common.	
Malingering	Patient consciously fakes or claims to have a disorder in order to attain a specific 2° gain (e.g., avoiding work, obtaining drugs). Complaints cease after gain (vs. factitious disorder).	

Factitious disorder

Consciously creates symptoms in order to assume "sick role" and to get medical attention (1° gain). **Munchausen's syndrome** is manifested by a chronic history of multiple hospital admissions and willingness to receive invasive procedures. **Munchausen's syndrome by proxy** is seen when illness in a child is caused by the parent. Motivation is to assume a sick role by proxy. A form of child abuse and must be reported.

Somatoform disorders

Both illness production and motivation are unconscious drives. More common in women.

Several types:

1. **Conversion**—motor or sensory symptoms (e.g., paralysis, pseudoseizure) that suggest neurologic or physical disorder, but tests and physical exam are negative; often follows an acute stressor; patient may be unconcerned about symptoms
2. **Pain disorder**—prolonged pain that is not explained completely by illness
3. **Hypochondriasis**—preoccupation with and fear of having a serious illness in spite of medical reassurance
4. **Somatization disorder**—variety of complaints in multiple organ systems with no identifiable underlying physical findings
5. **Body dysmorphic disorder**—preoccupation with minor or imagined physical flaws; patients often seek cosmetic surgery
6. **Pseudocyesis**—false belief of being pregnant associated with objective physical signs of pregnancy

Gain: 1°, 2°, 3°

1° gain—what the symptom does for the patient's internal psychic economy.
2° gain—what the symptom gets the patient (sympathy, attention).
3° gain—what the caretaker gets (like an MD on an interesting case).

Personality

Personality trait—an enduring pattern of perceiving, relating to, and thinking about the environment and oneself that is exhibited in a wide range of important social and personal contexts.

Personality disorder—when these patterns become inflexible and maladaptive, causing impairment in social or occupational functioning or subjective distress; person is usually not aware of problem. Disordered patterns must be stable by early adulthood; not usually diagnosed in children.

Cluster A personality disorders

Odd or eccentric; cannot develop meaningful social relationships. No psychosis; genetic association with schizophrenia.

"Weird."

Types:

1. Paranoid—distrust and suspiciousness; projection is main defense mechanism
2. Schizoid—voluntary social withdrawal, limited emotional expression, content with social isolation, unlike avoidant
3. Schizotypal—interpersonal awkwardness, odd beliefs or magical thinking, eccentric appearance

Cluster B personality disorders	Dramatic, emotional, or erratic; genetic association with mood disorders and substance abuse. Types: 1. Antisocial—disregard for and violation of rights of others, criminality; males > females; conduct disorder if < 18 years 2. Borderline—unstable mood and interpersonal relationships, impulsiveness, sense of emptiness; females > males; splitting is a major defense mechanism 3. Histrionic—excessive emotionality, attention seeking, sexually provocative, overly concerned with appearance 4. Narcissistic—grandiosity, sense of entitlement; may react to criticism with rage; may demand "top" physician/best health care	"**Wild**" (**B**ad to the **B**one). Anti**SOC**ial = **SOC**iopath.
Cluster C personality disorders	Anxious or fearful; genetic association with anxiety disorders. Types: 1. Avoidant—sensitive to rejection, socially inhibited, timid, feelings of inadequacy 2. Obsessive-compulsive—preoccupation with order, perfectionism, and control 3. Dependent—submissive and clinging, excessive need to be taken care of, low self-confidence	"**Worried**" (**C**hattering teeth).
Schizo-	Keeping "schizo-" straight: **Schizoid** < **Schizotypal** (schizoid + odd thinking) < **Schizophrenic** (greater odd thinking than schizotypal) < **Schizoaffective** (schizophrenia + 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—abnormal eating habits (excessive dieting), body image distortion, and ↑ exercise. Severe weight loss, metatarsal stress fractures, amenorrhea, anemia, and electrolyte disturbances can follow. Seen primarily in adolescent girls. Commonly coexists with depression.

Bulimia nervosa—binge eating followed by self-induced vomiting or use of laxatives. Body weight is normal. Parotitis, enamel erosion, electrolyte disturbances, alkalosis, dorsal hand calluses from inducing vomiting (Russell's sign).

Substance dependence

Maladaptive pattern of substance use defined as 3 or more of the following signs in 1 year:

1. Tolerance—need more to achieve same effect
2. Withdrawal
3. Substance taken in larger amounts or over longer time than desired
4. Persistent desire or attempts to cut down
5. Significant energy spent obtaining, using, or recovering from substance
6. Important social, occupational, or recreational activities reduced because of substance use
7. Continued use in spite of knowing the problems that it causes

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Substance abuse

Maladaptive pattern leading to clinically significant impairment or distress. Symptoms have NEVER met criteria for substance dependence.

1. Recurrent use resulting in failure to fulfill major obligations at work, school, or home
2. Recurrent use in physically hazardous situations
3. Recurrent substance-related legal problems
4. Continued use in spite of persistent problems caused by use

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Withdrawal

Behavioral, physiologic, and cognitive state caused by cessation or reduction of heavy and prolonged substance use. A substance-specific syndrome with signs and symptoms often opposite to those seen in intoxication and not attributable to another medical condition.

Signs and symptoms of substance abuse

Drug	Intoxication	Withdrawal
Alcohol	Disinhibition, emotional lability, slurred speech, ataxia, coma, blackouts. Serum γ-glutamyltransferase (GGT)—sensitive indicator of alcohol use.	Tremor, tachycardia, hypertension, malaise, nausea, seizures, delirium tremens (DTs), tremulousness, agitation, hallucinations
Opioids	CNS depression, nausea and vomiting, constipation, pupillary constriction (pinpoint pupils), seizures (overdose is life-threatening).	Anxiety, insomnia, anorexia, sweating, dilated pupils, piloerection ("cold turkey"), fever, rhinorrhea, nausea, stomach cramps, diarrhea ("flulike" symptoms), yawning
Amphetamines	Psychomotor agitation, impaired judgment, pupillary dilation, hypertension, tachycardia, euphoria, prolonged wakefulness and attention, cardiac arrhythmias, delusions, hallucinations, fever.	Post-use "crash," including depression, lethargy, headache, stomach cramps, hunger, hypersomnolence
Cocaine	Euphoria, psychomotor agitation, impaired judgment, tachycardia, pupillary dilation, hypertension, hallucinations (including tactile), paranoid ideations, angina, sudden cardiac death.	Post-use "crash," including severe depression and suicidality, hypersomnolence, fatigue, malaise, severe psychological craving
PCP	Belligerence, impulsiveness, fever, psychomotor agitation, vertical and horizontal nystagmus, tachycardia, ataxia, homicidality, psychosis, delirium.	Recurrence of intoxication symptoms due to reabsorption in GI tract; sudden onset of severe, random, homicidal violence
LSD	Marked anxiety or depression, delusions, visual hallucinations, flashbacks, pupillary dilation.	
Marijuana	Euphoria, anxiety, paranoid delusions, perception of slowed time, impaired judgment, social withdrawal, ↑ appetite, dry mouth, hallucinations.	Can be detected in urine up to 1 month after last use
Barbiturates	Low safety margin, respiratory depression.	Anxiety, seizures, delirium, life-threatening cardiovascular collapse
Benzodiazepines	Greater safety margin. Amnesia, ataxia, somnolence, minor respiratory depression. Additive effects with alcohol.	Rebound anxiety, seizures, tremor, insomnia
Caffeine	Restlessness, insomnia, ↑ diuresis, muscle twitching, cardiac arrhythmias.	Headache, lethargy, depression, weight gain
Nicotine	Restlessness, insomnia, anxiety, arrhythmias.	Irritability, headache, anxiety, weight gain, craving

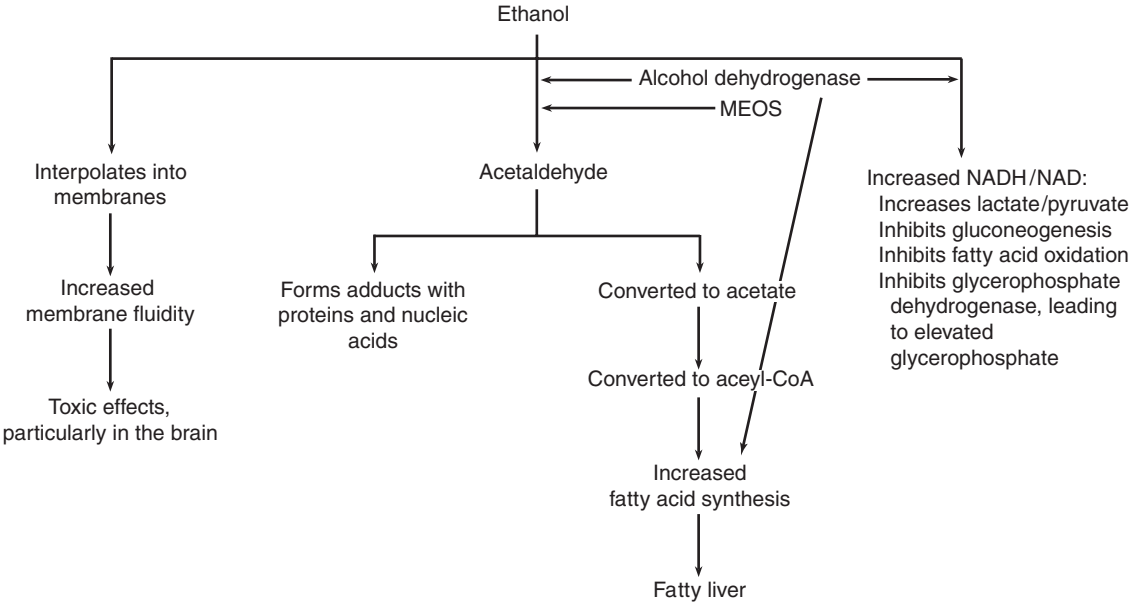
Heroin addiction

Approximately 500,000 U.S. addicts. Look for track marks (needle sticks in veins).
Users at risk for hepatitis, abscesses, overdose, hemorrhoids, AIDS, and right-sided endocarditis.
Naloxone and naltrexone competitively inhibit opioids and are used in cases of overdose.
Methadone (long-acting oral opiate) is used for heroin detoxification or long-term maintenance.

Alcoholism

Physiologic tolerance and dependence with symptoms of withdrawal (tremor, tachycardia, hypertension, malaise, nausea, DTs) when intake is interrupted. Continued drinking despite medical and social contraindications and life disruptions.

Treatment: disulfiram to condition the patient to abstain from alcohol use. Supportive treatment of other systemic manifestations. Alcoholics Anonymous and other peer support groups are helpful in sustaining abstinence.



Delirium tremens

Life-threatening alcohol withdrawal syndrome that peaks 2–5 days after last drink.

In order of appearance—autonomic system hyperactivity (tachycardia, tremors, anxiety), psychotic symptoms (hallucinations, delusions), confusion.

Treat with benzodiazepines.

Complications of alcoholism

Alcoholic cirrhosis	Micronodular cirrhosis with jaundice, hypoalbuminemia, coagulation factor deficiencies, and portal hypertension, leading to peripheral edema and ascites, encephalopathy, neurologic manifestations (e.g., asterixis, flapping tremor of the hands), and esophageal varices.
Wernicke-Korsakoff syndrome	Caused by vitamin B_1 (thiamine) deficiency; common in malnourished alcoholics. Triad of confusion, ophthalmoplegia, and ataxia (Wernicke's encephalopathy). May progress to memory loss, confabulation, personality change (Korsakoff's psychosis; irreversible). Associated with periventricular hemorrhage/necrosis, especially in mammillary bodies. Treatment: IV vitamin B_1 (thiamine).
Mallory-Weiss syndrome	Longitudinal lacerations at the gastroesophageal junction caused by excessive vomiting. Often presents with hematemesis. Associated with pain in contrast to esophageal varices.
Other	Hepatitis, pancreatitis, peripheral neuropathy, testicular atrophy, hyperestrinism.

Intelligence quotient

Stanford-Binet and Wechsler are the most famous tests of intelligence quotient (IQ).
Stanford-Binet calculates IQ as mental age/chronological age × 100.
Wechsler Adult Intelligence Scale uses 11 subtests (6 verbal, 5 performance).
Mean is defined at 100, with standard deviation of 15.
IQ < 70 (or 2 standard deviations below the mean) is one of the criteria for diagnosis of mental retardation (MR). IQ < 40—severe MR. IQ < 20—profound MR.
IQ scores are correlated with genetic factors and are highly correlated with school achievement.
Intelligence tests are objective (not projective) tests.

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).	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 reward.
Positive reinforcement—desired reward produces action (mouse presses button to get food).
Negative reinforcement—removal of aversive stimulus elicits behavior (mouse presses button to avoid shock). Do not confuse with punishment.
Punishment—application of aversive stimulus to extinguish unwanted behavior.

Reinforcement schedules	Pattern of reinforcement determines how quickly a behavior is learned or extinguished.	
Continuous	Reward received after every response. Rapidly extinguished.	Think vending machine—stop using it if it does not deliver.
Variable ratio	Reward received after random number of responses. Slowly extinguished.	Think slot machine—continue to play even if it rarely rewards.

Transference and countertransference

Transference	Patient projects feelings about formative or other important persons onto physician (e.g., psychiatrist = parent).
Countertransference	Doctor projects feelings about formative or other important persons onto patient.

Structural theory of the mind

Freud's 3 structures of the mind.

Id	Primal urges, sex, and aggression. The id "drives"; **I**nstinct. (I want it.)
Ego	Mediator between the unconscious mind and the external world. The ego "resists." (Deals with the conflict. Take it and you will get in trouble.)
Superego	Moral values, conscience; can lead to self-blame and attacks on ego. (You know you can't have it. Taking it is wrong.)

Topographic theory of the mind

Conscious—what you are aware of.
Preconscious—what you are able to make conscious with effort (e.g., your phone number).
Unconscious—what you are not aware of; the central goal of Freudian psychoanalysis is to make the patient aware of what is hidden in his/her unconscious.

Oedipus complex

Repressed sexual feelings of a child for the opposite-sex parent, accompanied by rivalry with same-sex parent. First described by Freud.

Social learning (modeling)	Behavior acquired by watching others and assimilating actions into one's own repertoire.	
Ego defenses	All ego defenses are automatic and unconscious reactions to psychological stress.	
Immature—more primitive		
Acting out	Unacceptable feelings and thoughts are expressed through actions.	Tantrums.
Dissociation	Temporary, drastic change in personality, memory, consciousness, or motor behavior to avoid emotional stress.	Extreme forms can result in multiple personalities (dissociative identity disorder).
Denial	Avoidance of awareness of some painful reality.	A common reaction in newly diagnosed AIDS and cancer patients.
Displacement	Process whereby avoided ideas and feelings are transferred to some neutral person or object (vs. projection).	Mother yells at child because she is angry at her husband.
Fixation	Partially remaining at a more childish level of development (vs. regression).	Men fixating on sports games.
Identification	Modeling behavior after another person who is more powerful (though not necessarily admired).	Abused child becomes an abuser.
Isolation	Separation of feelings from ideas and events.	Describing murder in graphic detail with no emotional response.
Projection	An unacceptable internal impulse is attributed to an external source.	A man who wants another woman thinks his wife is cheating on him.
Rationalization	Proclaiming logical reasons for actions actually performed for other reasons, usually to avoid self-blame.	After getting fired, claiming that the job was not important anyway.
Reaction formation	Process whereby a warded-off idea or feeling is replaced by an (unconsciously derived) emphasis on its opposite.	A patient with libidinous thoughts enters a monastery.
Regression	Turning back the maturational clock and going back to earlier modes of dealing with the world.	Seen in children under stress (e.g., bedwetting) and in patients on dialysis (e.g., crying).
Repression	Involuntary withholding of an idea or feeling from conscious awareness.	The basic mechanism underlying all others.
Splitting	Belief that people are either all good or all bad.	A patient says that all the nurses are cold and insensitive but that the doctors are warm and friendly.
Mature—less primitive		
Altruism	Guilty feelings alleviated by unsolicited generosity toward others.	Mafia boss makes large donation to charity.
Humor	Appreciating the amusing nature of an anxiety-provoking or adverse situation.	Nervous medical student jokes about the boards.
Sublimation	Process whereby one replaces an unacceptable wish with a course of action that is similar to the wish but does not conflict with one's value system.	Aggressive impulses used to succeed in business ventures.
Suppression	Voluntary (unlike repression) withholding of an idea or feeling from conscious awareness.	Choosing not to think about the USMLE until the week of the exam.
	Mature women wear a **SASH: S**ublimation, **A**ltruism, **S**uppression, **H**umor.	

Treatment for selected psychiatric conditions

Psychiatric condition	Drug
Alcohol withdrawal	Benzodiazepines
Anorexia/bulimia	SSRIs
Anxiety	Barbiturates
	Benzodiazepines
	Buspirone
	MAO inhibitors
ADHD	Methylphenidate (Ritalin)
	Amphetamine
Atypical depression	MAO inhibitors
Bipolar disorder	Mood stabilizers:
	Lithium
	Valproic acid
	Carbamazepine
Depression	SSRIs
	TCAs
Depression with insomnia	Trazodone
	Mirtazapine
Obsessive-compulsive disorder	SSRIs
Panic disorder	TCAs
	Buspirone
Schizophrenia	Antipsychotics
Tourette's syndrome	Antipsychotics (haloperidol)

Antipsychotics (neuroleptics)

Thioridazine, haloperidol, fluphenazine, chlorpromazine (haloperidol + "-azine"s).

Mechanism	Most antipsychotics block dopamine D_2 receptors (excess dopamine effects connected with schizophrenia).	Low potency: thioridazine, chlorpromazine—non-neurologic side effects.
Clinical use	Schizophrenia, psychosis, acute mania, Tourette's syndrome.	High potency: haloperidol, trifluoperazine—neurologic side effects.
Toxicity	Extrapyramidal system (EPS) side effects, endocrine side effects (e.g., dopamine receptor antagonism → hyperprolactinemia → galactorrhea), and side effects arising from blocking muscarinic (dry mouth, constipation), α (hypotension), and histamine (sedation) receptors.	Evolution of EPS side effects: 4 h acute dystonia 4 d akinesia 4 wk akathisia 4 mo tardive dyskinesia (often irreversible)
	Neuroleptic malignant syndrome—rigidity, myoglobinuria, autonomic instability, hyperpyrexia (treat with dantrolene and dopamine agonists).	Dystonia—muscle spasm, stiffness, oculogyric crisis.
	Tardive dyskinesia—stereotypic oral-facial movements probably due to dopamine receptor sensitization; results of long-term antipsychotic use.	Akinesia—parkinsonian symptoms. Akathisia—restlessness.

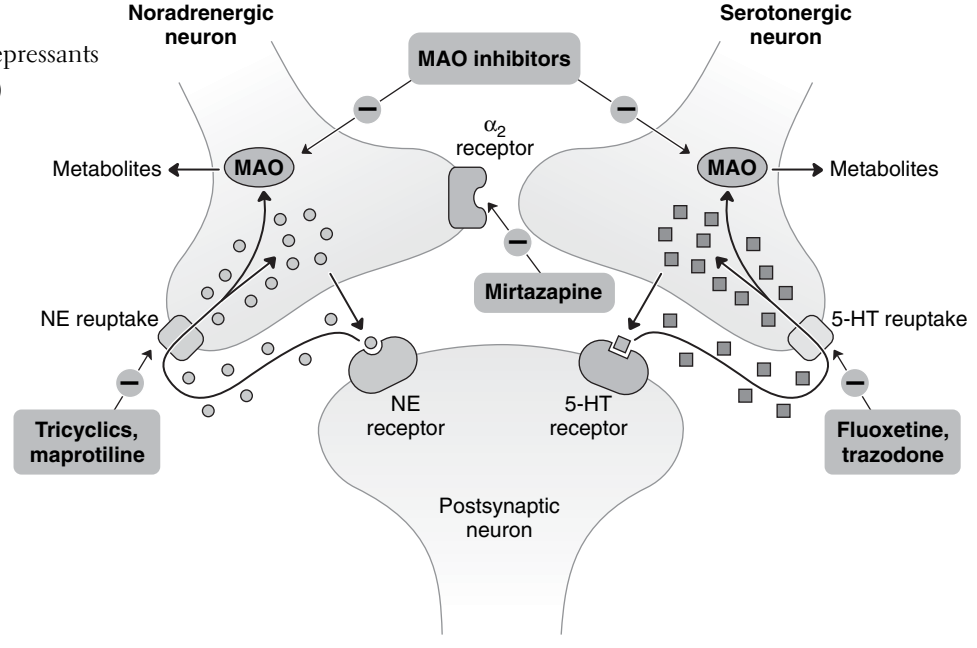
Atypical antipsychotics	**Clo**zapine, **ol**anzapine, **risper**idone, quetiapine, aripiprazole, ziprasidone.	It's not **atypical** for **old** **clo**sets to **risper.**
Mechanism	Block 5-HT_2 and dopamine receptors.	
Clinical use	Treatment of schizophrenia; useful for positive and negative symptoms. **Olanzapine** is also used for OCD, anxiety disorder, depression, mania, Tourette's syndrome.	
Toxicity	Fewer extrapyramidal and anticholinergic side effects than other antipsychotics. **Clozapine** may cause agranulocytosis (requires weekly WBC monitoring).	

Lithium		
Mechanism	Not established; possibly related to inhibition of phosphoinositol cascade.	**LMNOP:**
Clinical use	Mood stabilizer for bipolar affective disorder; blocks relapse and acute manic events.	**L**ithium side effects— **M**ovement (tremor) **N**ephrogenic diabetes insipidus
Toxicity	Tremor, hypothyroidism, polyuria (ADH antagonist causing nephrogenic diabetes insipidus), teratogenesis. Narrow therapeutic window requiring close monitoring of serum levels.	Hyp**O**thyroidism **P**regnancy problems

Buspirone	
Mechanism	Stimulates 5-HT_{1A} receptors
Clinical use	Anxiolysis for generalized anxiety disorder. Does not cause sedation or addiction. Does not interact with alcohol.

Antidepressants

1. SSRIs
2. Heterocyclic antidepressants (includes tricyclics)
3. MAOIs



(Adapted, with permission, from Katzung BG, Trevor AJ. *USMLE Road Map: Pharmacology*, 1st ed. New York: McGraw-Hill, 2003: 80.)

SSRIs	Fluoxetine, sertraline, paroxetine, citalopram.	
Mechanism	Serotonin-specific reuptake inhibitors.	It normally takes 2–3 weeks for antidepressants to have an effect.
Clinical use	Endogenous depression, OCD.	
Toxicity	Fewer than TCAs. GI distress, sexual dysfunction (anorgasmia). "Serotonin syndrome" with MAO inhibitors—hyperthermia, muscle rigidity, cardiovascular collapse.	
Tricyclic antidepressants	Imipramine, amitriptyline, desipramine, nortriptyline, clomipramine, doxepin, amoxapine.	
Mechanism	Block reuptake of NE and serotonin.	
Clinical use	Major depression, bedwetting (imipramine), OCD (clomipramine).	
Side effects	Sedation, α-blocking effects, atropine-like (anticholinergic) side effects (tachycardia, urinary retention). 3° TCAs (amitriptyline) have more anticholinergic effects than do 2° TCAs (nortriptyline). Desipramine is the least sedating.	
Toxicity	**Tri-C**'s: **C**onvulsions, **C**oma, **C**ardiotoxicity (arrhythmias); also respiratory depression, hyperpyrexia. Confusion and hallucinations in elderly due to anticholinergic side effects (use nortriptyline).	
Other antidepressants		
Bupropion (Wellbutrin)	Also used for smoking cessation. Mechanism not well known. Toxicity: stimulant effects (tachycardia, insomnia), headache, seizure in bulimic patients. Does not cause sexual side effects.	You need **BU**tane in your **VEIN**s to **MUR**der for a **MAP** of Alca**TRAZ.**
Venlafaxine	Also used in generalized anxiety disorder. Inhibits serotonin, NE, and dopamine reuptake. Toxicity: stimulant effects, sedation, nausea, constipation, ↑ BP.	
Mirtazapine	α_2 antagonist (↑ release of NE and serotonin) and potent 5-HT_2 and 5-HT_3 receptor antagonist. Toxicity: sedation, ↑ appetite, weight gain, dry mouth.	
Maprotiline	Blocks NE reuptake. Toxicity: sedation, orthostatic hypotension.	
Trazodone	Primarily inhibit serotonin reuptake. Toxicity: sedation, nausea, priapism, postural hypotension.	
Monoamine oxidase (MAO) inhibitors	Phenelzine, tranylcypromine.	
Mechanism	Nonselective MAO inhibition → ↑ levels of amine neurotransmitters.	
Clinical use	Atypical depression (i.e., with mood reactivity, sensitivity to rejection, hypersomnia), anxiety, hypochondriasis.	
Toxicity	Hypertensive crisis with tyramine ingestion (in many foods) and β-agonists; CNS stimulation. Contraindication with SSRIs or meperidine (to prevent serotonin syndrome).	
Methylphenidate (Ritalin)		
Mechanism	↑ presynaptic NE vesicular release (like amphetamines). However, the mechanism for relieving ADHD symptoms is not known.	
Clinical use	ADHD.	

NOTES

Renal

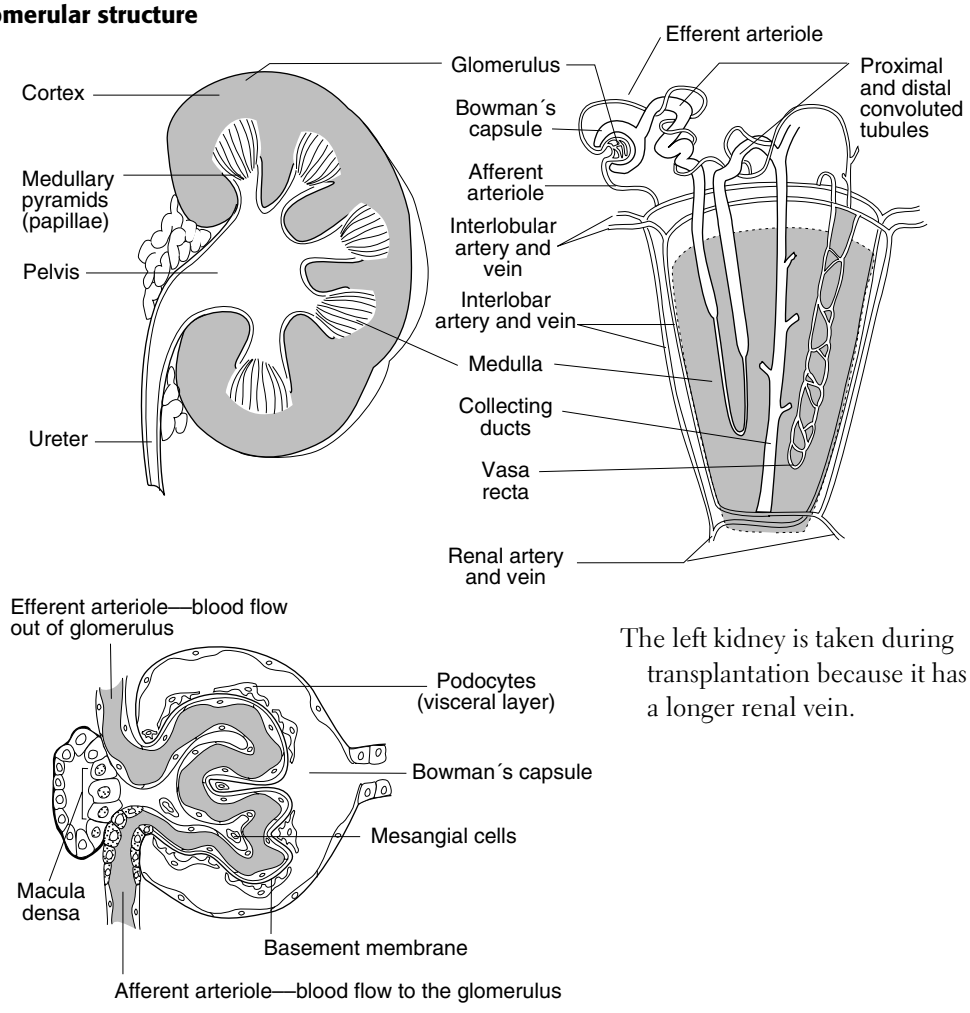
"But I know all about love already. I know precious little about kidneys."
—Aldous Huxley, *Antic Hay*

"This too shall pass. Just like a kidney stone."
—Hunter Madsen

- High-Yield Clinical Vignettes
- Anatomy
- Physiology
- Pathology
- Pharmacology

■ 3-year-old boy presents with facial edema, malaise, and proteinuria.	What is the appropriate treatment?	Steroids for minimal change disease.
■ Woman presents with UTI positive for *Proteus vulgaris*.	What type of kidney stone is she at risk for?	Ammonium magnesium phosphate (struvite).
■ Patient describes a 2-year history of acetaminophen use.	What is she at risk for?	Renal papillary necrosis.
■ X-ray film shows massively enlarged kidneys bilaterally.	What is the diagnosis?	Adult polycystic kidney disease.
■ Patient taking enalapril complains of constant coughing.	What is an appropriate alternative drug?	Losartan—angiotensin II receptor blocker.
■ Patient with CHF needs diuretic therapy but has a sulfa allergy.	What is an appropriate alternative drug?	Ethacrynic acid.
■ Patient is diagnosed with a horseshoe kidney.	What artery keeps it low in the abdomen?	IMA.
■ Patient presents with hypertension, hypokalemia, metabolic alkalosis, and low plasma renin.	What is the diagnosis, and how do you treat it?	Conn's syndrome (1° hyperaldosteronism). Treat with spironolactone.

Kidney anatomy and glomerular structure

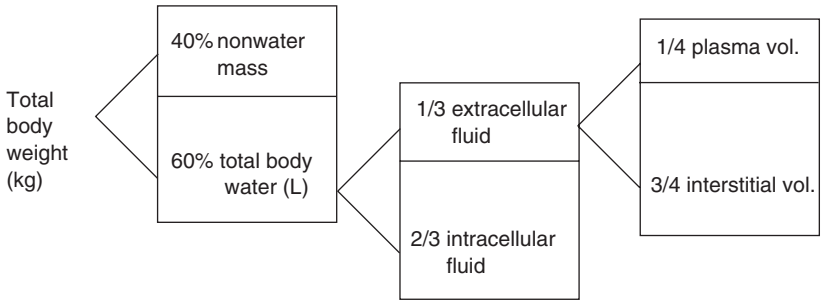


The left kidney is taken during transplantation because it has a longer renal vein.

(Adapted, with permission, from McPhee S et al. *Pathophysiology of Disease: An Introduction to Clinical Medicine,* 3rd ed. New York: McGraw-Hill, 2000: 384.)

Ureters: course	Ureters pass **under** uterine artery and **under** ductus deferens (retroperitoneal).	Water (ureters) **under** the bridge (artery, ductus deferens).

Fluid compartments



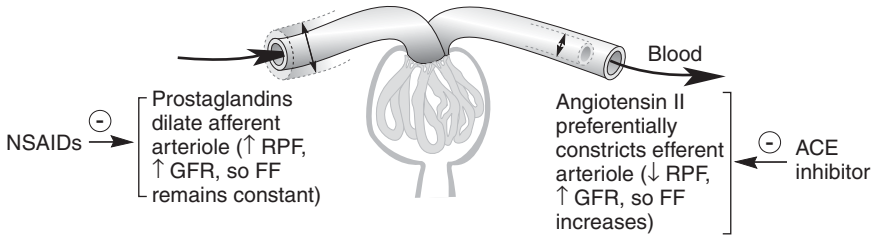
ECF: ↑ NaCl, ↓ K^+.
ICF: ↑ K^+, ↓ NaCl.
TBW – ECF = ICF.
ECF – PV = interstitial volume.
60–40–20 rule (% of body weight):
60% total body water
40% ICF
20% ECF
Plasma volume measured by radiolabeled albumin.
Extracellular volume measured by inulin.
Osmolarity = 290 mOsm.

Renal clearance	$C_x = U_x V/P_x$ = volume of plasma from which the substance is completely cleared per unit time. If C_x < GFR, then there is net tubular reabsorption of X. If C_x > GFR, then there is net tubular secretion of X. If C_x = GFR, then there is no net secretion or reabsorption.	Be familiar with calculations. C_x = clearance of X. U_x = urine concentration of X. P_x = plasma concentration of X. V = urine flow rate.
Glomerular filtration barrier	Responsible for filtration of plasma according to size and net charge. Composed of: 1. Fenestrated capillary endothelium (size barrier) 2. Fused basement membrane with heparan sulfate (negative charge barrier) 3. Epithelial layer consisting of podocyte foot processes	The charge barrier is lost in **nephrotic syndrome,** resulting in albuminuria, hypoproteinemia, generalized edema, and hyperlipidemia.
Glomerular filtration rate	Inulin can be used to calculate GFR because it is freely filtered and is neither reabsorbed nor secreted. $GFR = U_{inulin} \times V/P_{inulin} = C_{inulin}$ $= K_f [(P_{GC} - P_{BS}) - (\pi_{GC} - \pi_{BS})]$. (GC = glomerular capillary; BS = Bowman's space.) π_{BS} normally equals zero.	Creatinine clearance is an approximate measure of GFR.
Effective renal plasma flow	ERPF can be estimated using PAH because it is both filtered and actively secreted in the proximal tubule. All PAH entering the kidney is excreted. $ERPF = U_{PAH} \times V/P_{PAH} = C_{PAH}$. RBF = RPF/(1 – Hct). ERPF underestimates true RPF by ~10%.	

Filtration

Filtration fraction = GFR/RPF.
Filtered load = GFR × plasma concentration.

GFR can be estimated with creatinine.
RPF is best estimated with PAH.



Changes in renal function

Effect	RPF	GFR	FF (GFR/RPF)
Afferent arteriole constriction	↓	↓	NC
Efferent arteriole constriction	↓	↑	↑
↑ plasma protein concentration	NC	↓	↓
↓ plasma protein concentration	NC	↑	↑
Constriction of ureter	NC	↓	↓

Free water clearance

Ability to dilute urine. Given urine flow rate, urine osmolarity, and plasma osmolarity, be able to calculate free water clearance:
$C_{H_2O} = V - C_{osm}$.
V = urine flow rate; $C_{osm} = U_{osm}V/P_{osm}$.
With ADH: $C_{H_2O} < 0$.
Without ADH: $C_{H_2O} > 0$.
Isotonic urine: $C_{H_2O} = 0$.

Glucose clearance

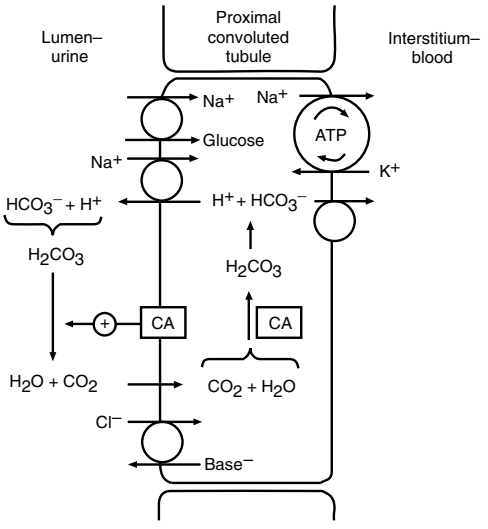
Glucose at a normal plasma level is completely reabsorbed in proximal tubule.
At plasma glucose of 200 mg/dL, glucosuria begins (threshold). At 350 mg/dL, transport mechanism is saturated (T_m).

Glucosuria is an important clinical clue to diabetes mellitus.

Amino acid clearance

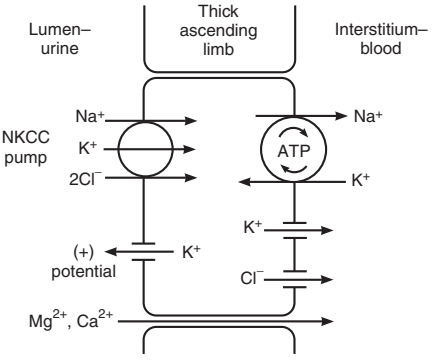
Reabsorption by at least 3 distinct carrier systems, with competitive inhibition within each group. 2° active transport occurs in proximal tubule and is saturable.

Nephron physiology

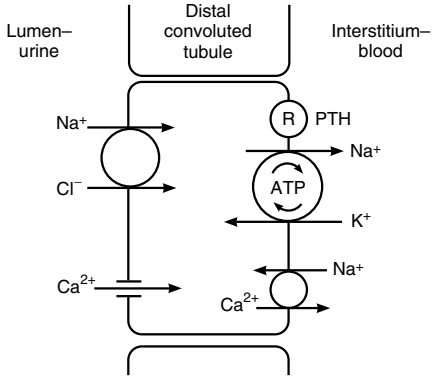


A. Early proximal convoluted tubule—"workhorse of the nephron." Contains brush border. Reabsorbs **all** of the glucose and amino acids and **most** of the bicarbonate, sodium, and water. Isotonic absorption. Secretes ammonia, which acts as a buffer for secreted H^+.

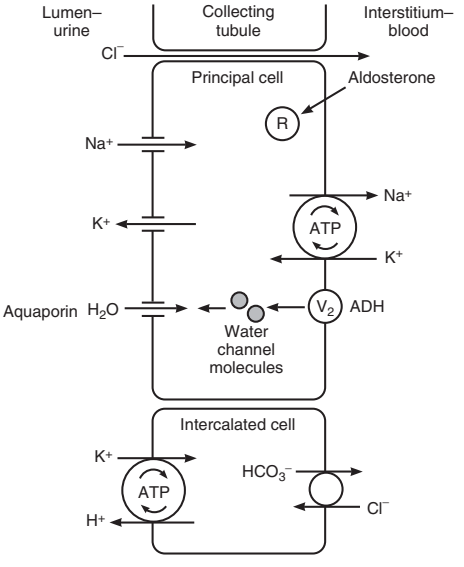
B. Thin descending loop of Henle—passively reabsorbs water via medullary hypertonicity (impermeable to sodium). Makes urine hypertonic.



C. Thick ascending loop of Henle—actively reabsorbs Na^+, K^+, and Cl^- and indirectly induces the reabsorption of Mg^{2+} and Ca^{2+}. Impermeable to H_2O. Diluting segment. Makes urine hypotonic.



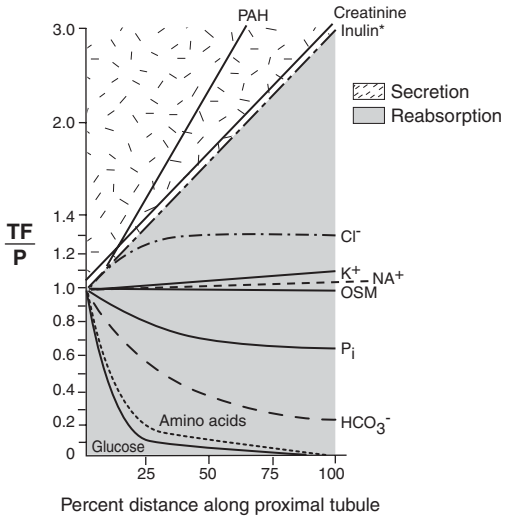
D. Early distal convoluted tubule—actively reabsorbs Na^+, Cl^-. Reabsorption of Ca^{2+} is under the control of PTH. Diluting segment. Makes urine hypotonic.



E. Collecting tubules—reabsorb Na^+ in exchange for secreting K^+ or H^+ (regulated by aldosterone). Reabsorption of water is regulated by ADH (vasopressin). Osmolarity of medulla can reach 1200 mOsm/L H_2O.

Relative concentrations along renal tubule

$$\frac{TF}{P} = \frac{[\text{Tubular fluid}]}{[\text{Plasma}]}$$



* Neither secreted nor reabsorbed; concentration increases as water is reabsorbed.

(Adapted, with permission, from Ganong WF. *Review of Medical Physiology,* 22nd ed. New York: McGraw-Hill, 2005.)

Renin-angiotensin system

Mechanism

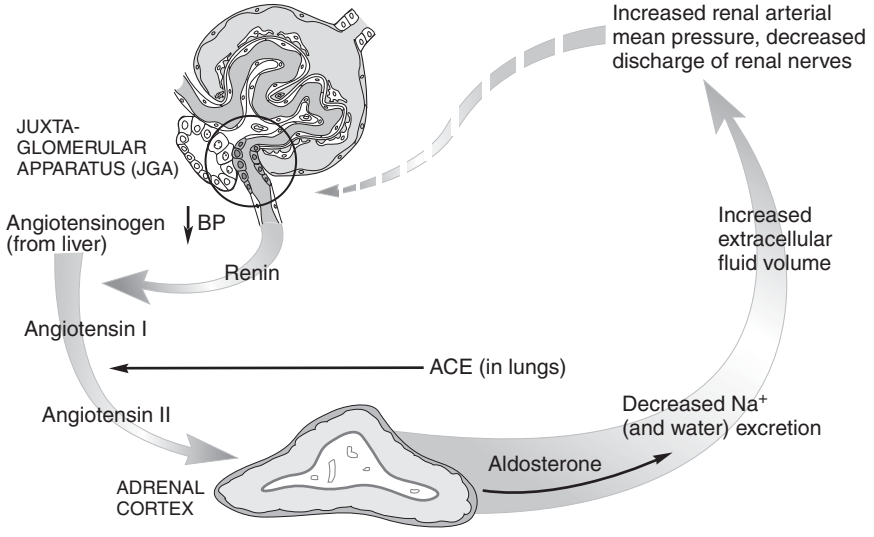
Renin is released by the kidneys upon sensing ↓ BP and cleaves angiotensinogen (from the liver) to angiotensin I. Angiotensin I is then cleaved by angiotensin-converting enzyme (ACE), primarily in the lung capillaries, to angiotensin II.

Actions of angiotensin II

1. Potent vasoconstriction
2. Release of aldosterone from adrenal cortex
3. Release of ADH from posterior pituitary
4. Stimulates hypothalamus → ↑ thirst

Overall, angiotensin II serves to ↑ intravascular volume and ↑ BP.

ANP released from atria may act as a "check" on the renin-angiotensin system (e.g., in heart failure). ↓ renin and ↑ GFR.



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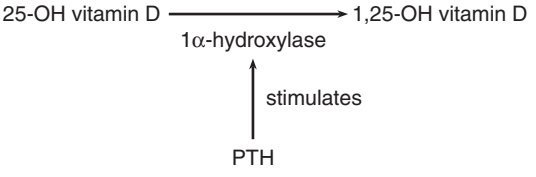
Juxtaglomerular apparatus (JGA)

JGA—JG cells (modified smooth muscle of afferent arteriole) and macula densa (Na^+ sensor, part of the distal convoluted tubule). JG cells secrete renin (leading to ↑ angiotensin II and aldosterone levels) in response to ↓ renal blood pressure, ↓ Na^+ delivery to distal tubule, and ↑ sympathetic tone.

JGA defends glomerular filtration rate via the renin-angiotensin system.
Juxta = close by.

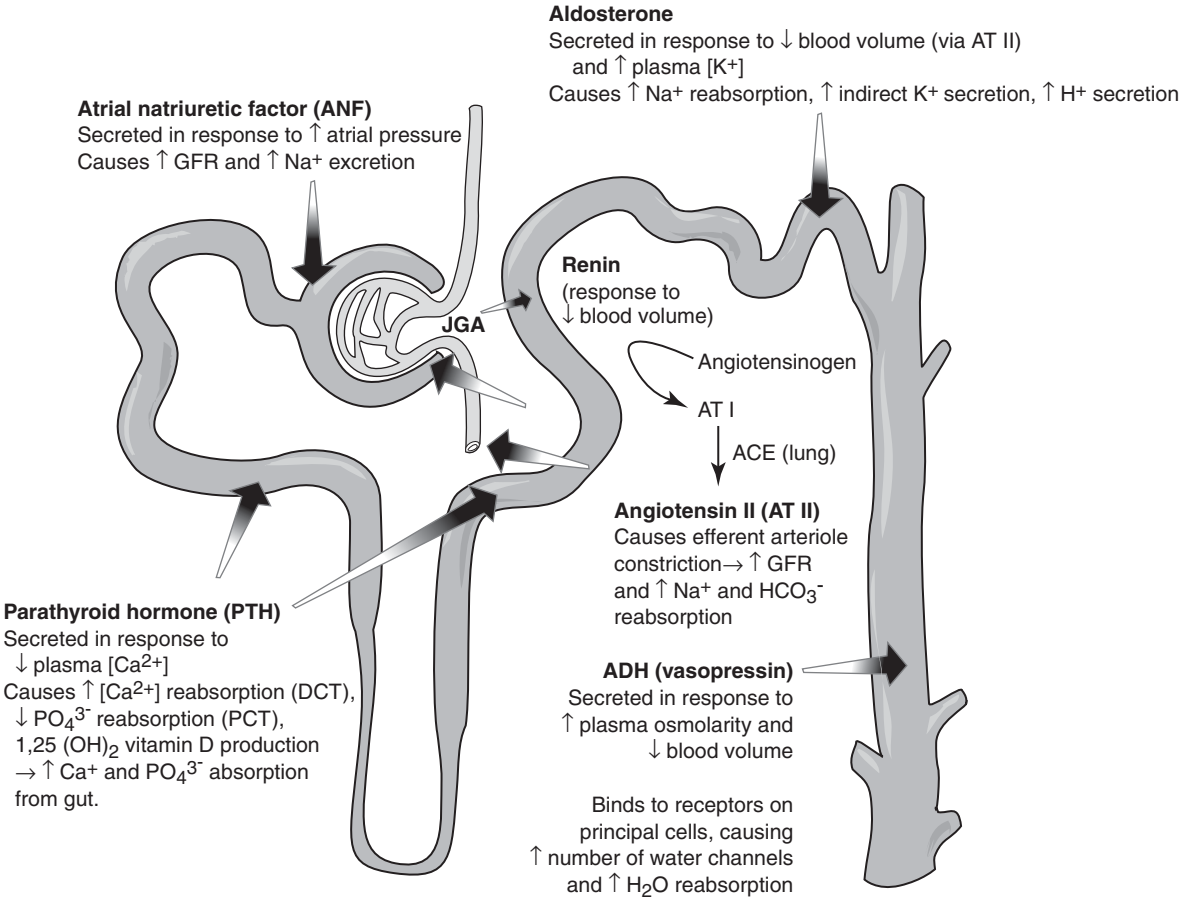
Kidney endocrine functions

1. Endothelial cells of peritubular capillaries secrete erythropoietin in response to hypoxia
2. Conversion of 25-OH vitamin D to 1,25-$(OH)_2$ vitamin D by 1α-hydroxylase, which is activated by PTH
3. JG cells secrete renin in response to ↓ renal arterial pressure and ↑ renal sympathetic discharge (β_1 effect)
4. Secretion of prostaglandins that vasodilate the afferent arterioles to ↑ GFR



NSAIDs can cause acute renal failure in high vasoconstrictive states by inhibiting the renal production of prostaglandins, which keep the afferent arterioles vasodilated to maintain GFR.

Hormones acting on kidney



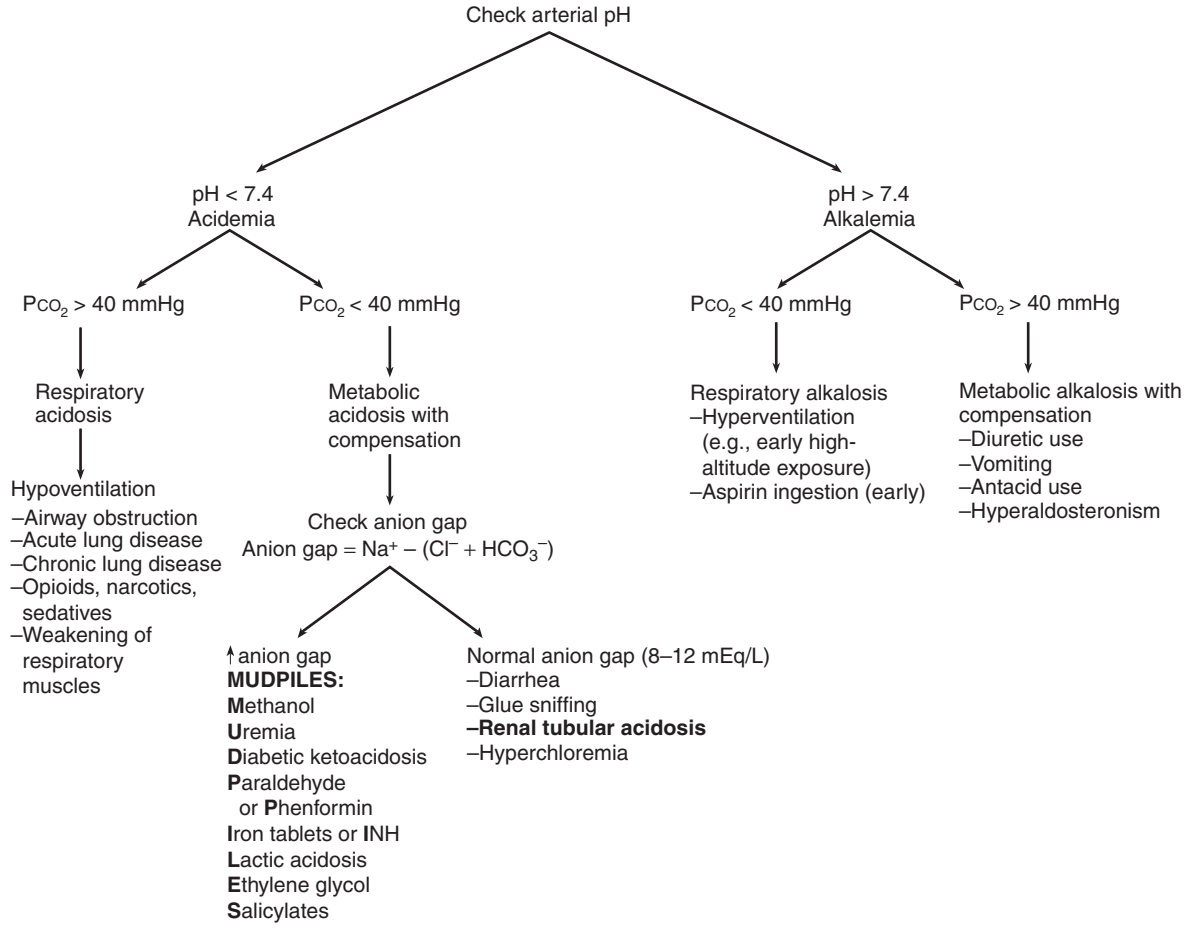
Acid-base physiology

	pH	P_{CO_2}	$[HCO_3^-]$	Compensatory response
Metabolic acidosis	↓	↓	**↓**	Hyperventilation
Metabolic alkalosis	↑	↑	**↑**	Hypoventilation
Respiratory acidosis	↓	**↑**	↑	↑ renal $[HCO_3^-]$ reabsorption
Respiratory alkalosis	↑	**↓**	↓	↓ renal $[HCO_3^-]$ reabsorption

Henderson-Hasselbalch equation: $pH = pKa + \log \frac{[HCO_3^-]}{0.03\ P_{CO_2}}$

Key: **↑ ↓** = 1° disturbance; ↓ ↑ = compensatory response.

Acidosis/alkalosis



Renal tubular acidosis

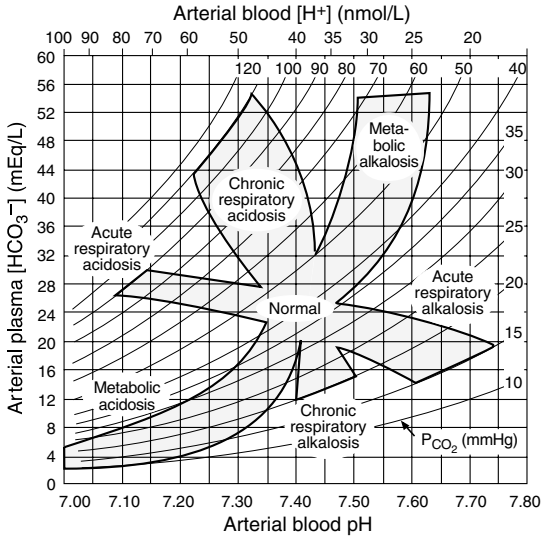
Type 1	Defect in H^+ pump → failure to acidify urine.
Type 2	Renal loss of bicarbonate.
Type 4	Hypoaldosteronism → hypokalemia → inhibition of ammonia excretion.

Acid-base compensations

The following formulas give appropriate compensations for a single disorder. If the formula does not match the actual values, suspect a mixed disorder.

Metabolic acidosis	Winter's formula: $P_{CO_2} = 1.5\ (HCO_3^-) + 8 \pm 2$.
Metabolic alkalosis	P_{CO_2} ↑ 0.7 mmHg for every ↑ 1 mEq/L HCO_3^-.
Respiratory acidosis	Acute— ↑ 1 mEq/L HCO_3^- for every ↑ 10 mmHg P_{CO_2}.
	Chronic— ↑ 3.5 mEq/L HCO_3^- for every ↑ 10 mmHg P_{CO_2}.
Respiratory alkalosis	Acute— ↓ 2 mEq/L HCO_3^- for every ↓ 10 mmHg P_{CO_2}.
	Chronic— ↓ 5 mEq/L HCO_3^- for every ↓ 10 mmHg P_{CO_2}.

Acid-base nomogram



(Adapted, with permission, from Ganong WF. *Review of Medical Physiology,* 22nd ed. New York: McGraw-Hill, 2005: 734.)

► RENAL—PATHOLOGY

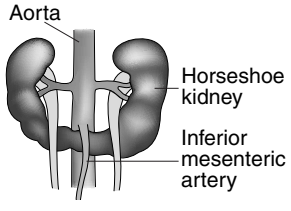
Potter's syndrome

Bilateral renal agenesis → oligohydramnios → limb deformities, facial deformities, pulmonary hypoplasia. Caused by malformation of ureteric bud.

Babies with **P**otter's can't "**P**ee" 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. Kidney functions normally.



Casts

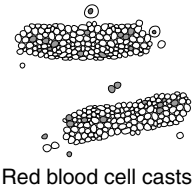
Casts in urine:

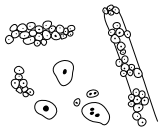
- RBC casts—glomerular inflammation (nephritic syndromes), ischemia, or malignant hypertension.
- WBC casts—tubulointerstitial disease, acute pyelonephritis, glomerular disorders.
- Granular ("muddy brown") casts—acute tubular necrosis.
- Waxy casts—advanced renal disease/CRF.
- Hyaline casts—nonspecific.

Presence of casts indicates that hematuria/pyuria is of renal origin.

Bladder cancer → RBCs, no casts.

Acute cystitis → WBCs, no casts.


Red blood cell casts


White blood cell casts

Hyaline casts

Granular casts

Glomerular pathology

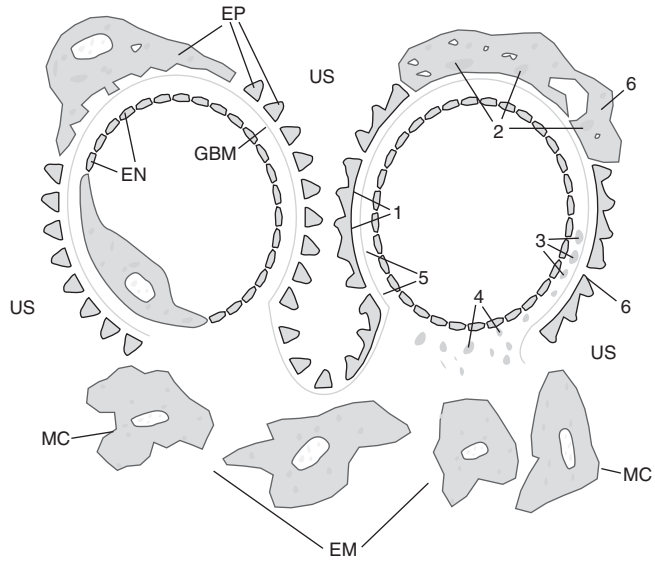
NephrItic syndrome—hematuria, hypertension, oliguria, azotemia.	**I** = **i**nflammation.
1. **Acute poststreptococcal glomerulonephritis—**LM: glomeruli enlarged and hypercellular, neutrophils, "lumpy-bumpy." EM: subepithelial humps. IF: granular pattern.	Most frequently seen in children. Peripheral and periorbital edema. Resolves spontaneously.
2. **Membranoproliferative glomerulonephritis—**EM: subendothelial humps, "tram track."	Slowly progresses to renal failure.
3. **Rapidly progressive (crescentic) glomerulonephritis—**LM and IF: crescent-moon shape.	Rapid course to renal failure. Number of crescents indicates prognosis.
4. **Goodpasture's syndrome (type II hypersensitivity)—**IF: linear pattern, anti-GBM antibodies.	Hemoptysis, hematuria.
5. **IgA nephropathy (Berger's disease)—**IF and EM: mesangial deposits of IgA.	Mild disease. Often postinfectious. Common cause of recurrent hematuria in young patients.
6. **Alport's syndrome—**split basement membrane.	Collagen IV mutation. Nerve deafness and ocular disorders.
NephrOtic syndrome—massive proteinuria (frothy urine), hypoalbuminemia, peripheral and periorbital edema, hyperlipidemia.	**O** = pr**O**teinuria.
1. **Membranous glomerulonephritis—**LM: diffuse capillary and basement membrane thickening. IF: granular pattern. EM: "spike and dome."	Most common cause of adult nephrotic syndrome.
2. **Minimal change disease (lipoid nephrosis)—**LM: normal glomeruli. EM: foot process effacement (see Color Image 93).	Most common cause of childhood nephrotic syndrome. Responds well to steroids.
3. **Focal segmental glomerular sclerosis—**LM: segmental sclerosis and hyalinosis.	More severe disease in HIV patients.
4. **Diabetic nephropathy—**LM: Kimmelstiel-Wilson nodular lesions, basement membrane thickening (see Color Image 95).	
5. **SLE** (5 patterns of renal involvement)—LM: In membranous glomerulonephritis pattern, wire-loop lesion with subepithelial deposits.	
6. **Amyloidosis—**IF: Congo red stain, apple-green birefringence.	Associated with multiple myeloma, chronic conditions, TB, rheumatoid arthritis.

(LM = light microscopy; EM = electron microscopy; IF = immunofluorescence)

Glomerular histopathology

EP = epithelium with foot processes
US = urinary space
GBM = glomerular basement membrane
EN = fenestrated endothelium
MC = mesangial cells
EM = extracellular matrix

1 = subepithelial deposits (membranous nephropathy)
2 = large irregular subepithelial deposits or "humps" (acute glomerulonephritis)
3 = subendothelial deposits in lupus glomerulonephritis
4 = mesangial deposits (IgA nephropathy)
5 = antibody binding to GBM—smooth linear pattern on immunofluorescence (Goodpasture's)
6 = effacement of epithelial foot processes (common in all forms of glomerular injury with proteinuria)



Kidney stones	Can lead to severe complications, such as hydronephrosis and pyelonephritis. 4 major types:	
Calcium	Most common kidney stones (75–85%). Calcium oxalate (see Color Image 97), calcium phosphate, or both. Conditions that cause hypercalcemia (cancer, ↑ PTH, ↑ vitamin D, milk-alkali syndrome) can lead to hypercalciuria and stones. Tend to recur.	Radiopaque. Oxalate crystals can result from antifreeze or vitamin C abuse.
Ammonium magnesium phosphate (**struvite**)	2nd most common kidney stone. Caused by infection with urease-positive bugs (*Proteus vulgaris*, *Staphylococcus*, *Klebsiella*). Can form **staghorn calculi** that can be a nidus for UTIs.	Radiopaque or radiolucent. Worsened by alkaluria.
Uric acid	Strong association with hyperuricemia (e.g., gout). Often seen as a result of diseases with ↑ cell turnover, such as leukemia and myeloproliferative disorders.	I can't see **U** on x-ray or CT.
Cystine	Most often 2° to cystinuria. Hexagonal shape.	Faintly radiopaque. Treat with alkalinization of urine.
Renal cell carcinoma	Most common renal malignancy. Invades IVC and spreads hematogenously. Most common in men ages 50–70. ↑ incidence with smoking and obesity. Associated with von Hippel–Lindau and gene deletion in chromosome 3. Originates in renal tubule cells → polygonal clear cells. Manifests clinically with hematuria, palpable mass, 2° polycythemia, flank pain, fever, and weight loss. Associated with paraneoplastic syndromes (ectopic EPO, ACTH, PTHrP, and prolactin) (see Color Image 98).	
Wilms' tumor	Most common renal malignancy of early childhood (ages 2–4). Presents with huge, palpable flank mass, hemihypertrophy. Contains embryonic glomerular structures. Deletion of tumor suppression gene *WT1* on chromosome 11. Can be part of **WAGR** complex: **W**ilms' tumor, **A**niridia, **G**enitourinary malformation, and mental-motor **R**etardation.	

Transitional cell carcinoma

Most common tumor of urinary tract system (can occur in renal calyces, renal pelvis, ureters, and bladder). Painless hematuria is suggestive of bladder cancer. Associated with problems in your **P**ee **SAC: P**henacetin, **S**moking, **A**niline dyes, and **C**yclophosphamide (see Color Image 90).

Pyelonephritis

Acute: Affects cortex with relative sparing of glomeruli/vessels. White cell casts in urine are pathognomonic (see Color Image 89A). Presents with fever, CVA tenderness.

Chronic: Coarse, asymmetric corticomedullary scarring, blunted calyx. Tubules can contain eosinophilic casts (thyroidization of kidney) (see Color Image 89B).

Diffuse cortical necrosis

Acute generalized infarction of cortices of both kidneys. Likely due to a combination of vasospasm and DIC. Associated with obstetric catastrophes (e.g., abruptio placentae) and septic shock.

Drug-induced interstitial nephritis

Acute interstitial renal inflammation. Fever, rash, eosinophilia, hematuria 2 weeks after administration. Drugs (e.g., penicillin derivatives, NSAIDs, diuretics) act as haptens inducing hypersensitivity.

Acute tubular necrosis

Most common cause of acute renal failure. Reversible, but fatal if left untreated. Associated with renal ischemia (e.g., shock), crush injury (myoglobulinuria), toxins. Death most often occurs during initial oliguric phase. Recovery in 2–3 weeks.

Loss of cell polarity, epithelial cell detachment, necrosis, granular ("muddy brown") casts. Three stages: inciting event → maintenance (low urine) → recovery.

Renal papillary necrosis

Associated with:

1. Diabetes mellitus
2. Acute pyelonephritis
3. Chronic phenacetin use (acetaminophen is phenacetin derivative)
4. Sickle cell anemia

Acute renal failure

Abrupt decline in renal function with ↑ creatinine and ↑ BUN over a period of several days.

1. Prerenal azotemia—↓ RBF (e.g., hypotension) → ↓ GFR. Na^+/H_2O and urea retained by kidney.
2. Intrinsic renal—generally due to acute tubular necrosis or ischemia/toxins. Patchy necrosis leads to debris obstructing tubule and fluid backflow across necrotic tubule → ↓ GFR. Urine has epithelial/granular casts.
3. Postrenal—outflow obstruction (stones, BPH, neoplasia). Develops only with bilateral obstruction.

Variable	Prerenal	Renal	Postrenal
Urine osmolality	**> 500**	< 350	< 350
Urine Na	**< 10**	> 20	> 40
Fe_{Na}	**< 1%**	> 2%	> 4%
BUN/Cr ratio	> 20	**< 15**	> 15

Consequences of renal failure

Failure to make urine and excrete nitrogenous wastes.

Uremia—clinical syndrome marked by ↑ BUN and ↑ creatinine and associated symptoms.

Consequences:

1. Anemia (failure of erythropoietin production)
2. Renal osteodystrophy (failure of active vitamin D production)
3. Hyperkalemia, which can lead to cardiac arrhythmias
4. Metabolic acidosis due to ↓ acid secretion and ↓ generation of HCO_3^-
5. Uremic encephalopathy
6. Sodium and H_2O excess → CHF and pulmonary edema
7. Chronic pyelonephritis
8. Hypertension

2 forms of renal failure—acute renal failure (often due to acute tubular necrosis) and chronic renal failure (e.g., due to hypertension and diabetes).

Fanconi's syndrome

Defect in proximal tubule transport of amino acids, glucose, phosphate, uric acid, protein, and electrolytes. Complications include rickets, osteomalacia, hypokalemia, metabolic acidosis.

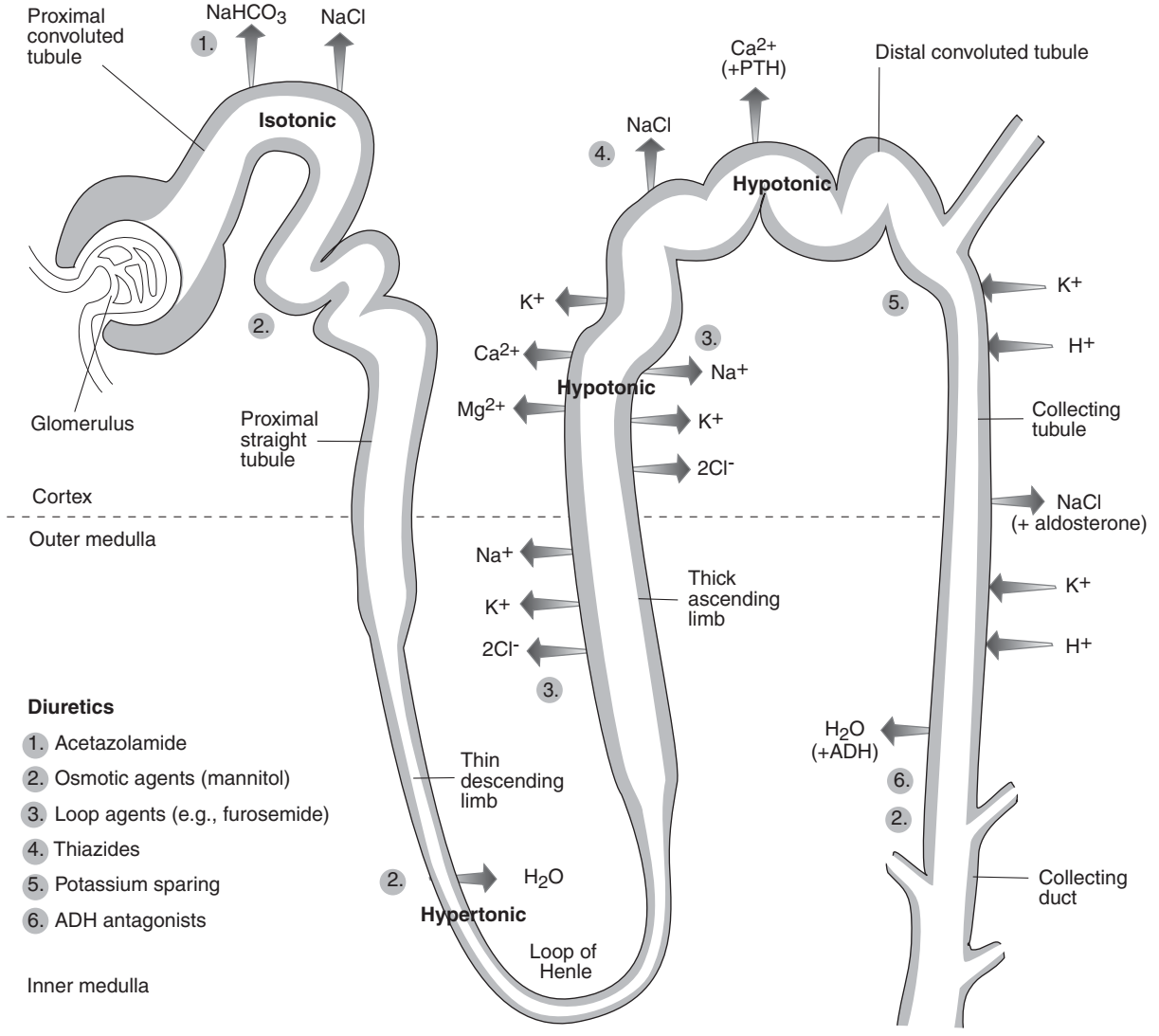
Cysts

Adult polycystic kidney disease	Multiple, large, bilateral cysts that ultimately destroy the parenchyma. Presents with flank pain, hematuria, hypertension, urinary infection, progressive renal failure. Autosomal-dominant mutation in *APKD1*. Death from uremia or hypertension. Associated with polycystic liver disease, berry aneurysms, mitral valve prolapse.
Infantile polycystic kidney disease	Infantile presentation in parenchyma. Autosomal recessive. Associated with hepatic cysts and fibrosis.
Dialysis cysts	Cortical and medullary cysts resulting from long-standing dialysis.
Simple cysts	Benign, incidental finding. Cortex only.
Medullary cystic disease	Medullary cysts. Ultrasound shows small kidney. Poor prognosis.
Medullary sponge disease	Collecting duct cysts. Good prognosis.

Electrolyte disturbances

Electrolyte	Low serum concentration	High serum concentration
Na^+	Disorientation, stupor, coma	Neurologic: irritability, delirium, coma
Cl^-	2° to metabolic alkalosis, hypokalemia, hypovolemia, ↑ aldosterone	2° to non–anion gap acidosis
K^+	U waves on ECG, flattened T waves, arrhythmias, paralysis	Peaked T waves, wide QRS, arrhythmias
Ca^{2+}	Tetany, neuromuscular irritability	Delirium, renal stones, abdominal pain, not necessarily calciuria
Mg^{2+}	Neuromuscular irritability, arrhythmias	Delirium, ↓ DTRs, cardiopulmonary arrest
PO_4^{2-}	Low-mineral ion product causes bone loss, osteomalacia	High-mineral ion product causes metastatic calcification, renal stones, met calcifications

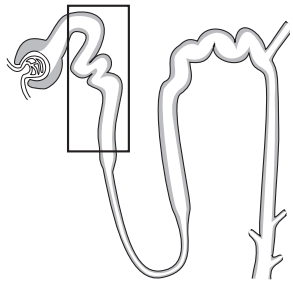
Diuretics: site of action



(Adapted, with permission, from Katzung BG. *Basic and Clinical Pharmacology,* 7th ed. Stamford, CT: Appleton & Lange, 1997: 243.)

Mannitol

Mechanism	Osmotic diuretic, ↑ tubular fluid osmolarity, producing ↑ urine flow.
Clinical use	Shock, drug overdose, ↓ intracranial/intraocular pressure.
Toxicity	Pulmonary edema, dehydration. Contraindicated in anuria, CHF.



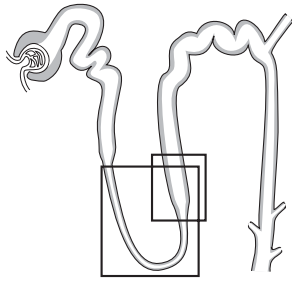
Acetazolamide

Mechanism	Carbonic anhydrase inhibitor. Causes self-limited $NaHCO_3$ diuresis and reduction in total-body HCO_3^- stores.
Clinical use	Glaucoma, urinary alkalinization, metabolic alkalosis, altitude sickness.
Toxicity	Hyperchloremic metabolic acidosis, neuropathy, NH_3 toxicity, sulfa allergy.

ACIDazolamide causes **ACID**osis.

Furosemide

Mechanism	Sulfonamide loop diuretic. Inhibits cotransport system (Na^+, K^+, 2 Cl^-) of thick ascending limb of loop of Henle. Abolishes hypertonicity of medulla, preventing concentration of urine. ↑ Ca^{2+} excretion. **L**oops **L**ose calcium.
Clinical use	Edematous states (CHF, cirrhosis, nephrotic syndrome, pulmonary edema), hypertension, hypercalcemia.
Toxicity	**O**totoxicity, **H**ypokalemia, **D**ehydration, **A**llergy (sulfa), **N**ephritis (interstitial), **G**out.



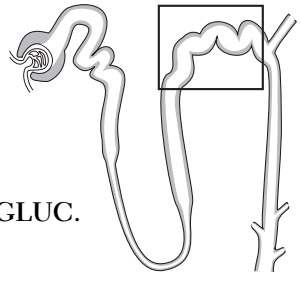
OH DANG!

Ethacrynic 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 be used in hyperuricemia, acute gout (never used to treat gout).

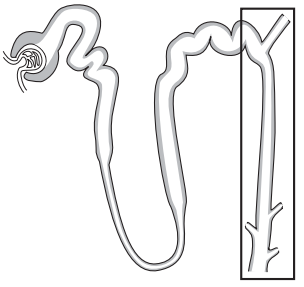
Hydrochlorothiazide

Mechanism	Thiazide diuretic. Inhibits NaCl reabsorption in early distal tubule, reducing diluting capacity of the nephron. ↓ Ca^{2+} excretion.
Clinical use	Hypertension, CHF, idiopathic hypercalciuria, nephrogenic diabetes insipidus.
Toxicity	Hypokalemic metabolic alkalosis, hyponatremia, hyper**G**lycemia, hyper**L**ipidemia, hyper**U**ricemia, and hyper**C**alcemia. Sulfa allergy.



Hyper**GLUC**.

K^+-sparing diuretics — **S**pironolactone, **T**riamterene, **A**miloride, eplerenone. The K^+ **STA**ys.



- Mechanism: Spironolactone is a competitive aldosterone receptor antagonist in the cortical collecting tubule. Triamterene and amiloride act at the same part of the tubule by blocking Na^+ channels in the CCT.
- Clinical use: Hyperaldosteronism, K^+ depletion, CHF.
- Toxicity: Hyperkalemia, endocrine effects (e.g., spironolactone causes gynecomastia, antiandrogen effects).

Diuretics: electrolyte changes

Urine NaCl	↑ (all diuretics—carbonic anhydrase inhibitors, loop diuretics, thiazides, K^+-sparing diuretics).
Urine K^+	↑ (all except K^+-sparing diuretics).
Blood pH	↓ (acidemia)—carbonic anhydrase inhibitors, K^+-sparing diuretics; ↑ (alkalemia)—loop diuretics, thiazides.
Urine Ca^+	↑ loop diuretics, ↓ thiazides.

ACE inhibitors — Captopril, enalapril, lisinopril.

- Mechanism: Inhibit angiotensin-converting enzyme, reducing levels of angiotensin II and preventing inactivation of bradykinin, a potent vasodilator. **Renin release is** ↑ due to loss of feedback inhibition.
- Clinical use: Hypertension, CHF, diabetic renal disease.
- Toxicity: **C**ough, **A**ngioedema, **P**roteinuria, **T**aste changes, hyp**O**tension, **P**regnancy problems (fetal renal damage), **R**ash, **I**ncreased renin, **L**ower angiotensin II. Also **hyperkalemia.** Avoid with bilateral renal artery stenosis.

Losartan is an angiotensin II receptor antagonist. It is **not** an ACE inhibitor and does not cause cough.

CAPTOPRIL.

Reproductive

"Artificial insemination is when the farmer does it to the cow instead of the bull."

—Student essay

- High-Yield Clinical Vignettes
- Anatomy
- Physiology
- Pathology
- Pharmacology

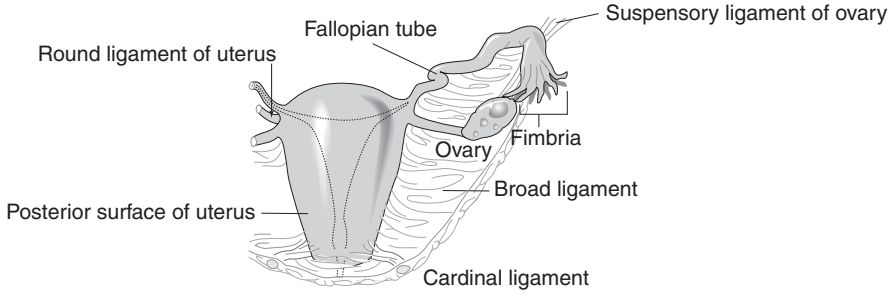
■ 24-year-old man develops testicular cancer.	Metastatic spread first occurs to what site?	Para-aortic lymph nodes (recall descent of testes during development).
■ Woman with a previous cesarean section has a scar in her lower uterus close to the opening of the os.	What is she at ↑ risk for?	Placenta previa.
■ Obese woman presents with hirsutism and ↑ levels of serum testosterone.	What is the diagnosis?	Polycystic ovarian syndrome.
■ Pregnant woman at 16 weeks of gestation presents with an atypically large abdomen.	What is the diagnosis?	High hCG; hydatidiform mole.
■ 55-year-old postmenopausal woman is on tamoxifen therapy.	What is she at ↑ risk of acquiring?	Endometrial carcinoma.

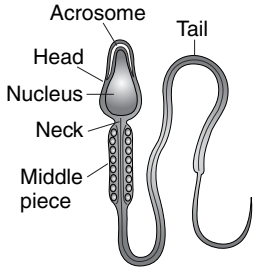
Gonadal drainage

Venous drainage	Left ovary/testis → left gonadal vein → left renal vein → IVC. Right ovary/testis → right gonadal vein → IVC.	Just as the left adrenal vein makes an extra stop at the left renal vein before the IVC.
Lymphatic drainage	Ovaries/testes → para-aortic lymph nodes.	

Ligaments of the uterus

Suspensory ligament of ovaries	Contains the ovarian vessels.	
Transverse cervical (cardinal) ligament	Contains the uterine vessels.	
Round ligament of uterus	Contains no important structures. Travels through the inguinal canal and attaches distally to the labia majora.	**Round** like the number of structures it carries: **0.**
Broad ligament	Contains the round ligaments of the uterus and ovaries and the fallopian tubes.	

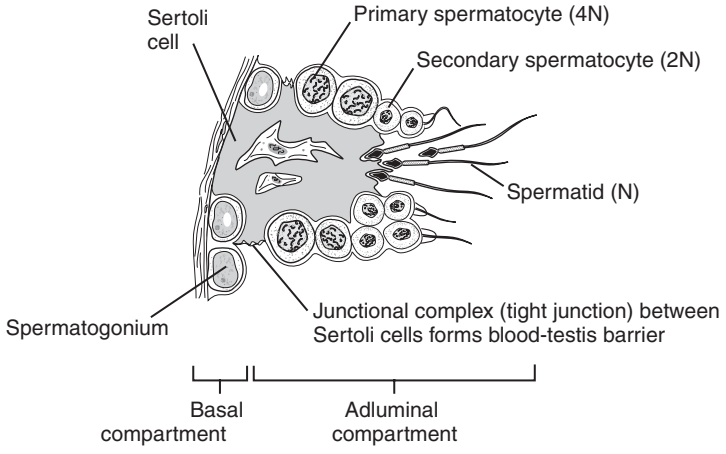


Autonomic innervation of the male sexual response	Erection is mediated by the **P**arasympathetic nervous system. Nitric oxide is vasodilator. Emission is mediated by the **S**ympathetic nervous system. Ejaculation is mediated by visceral and somatic nerves.	**P**oint and **S**hoot.
Derivation of sperm parts	Acrosome is derived from the Golgi apparatus and flagellum (tail) from one of the centrioles. **M**iddle piece (neck) has **M**itochondria. **F**eeds on **F**ructose.	

Sperm development

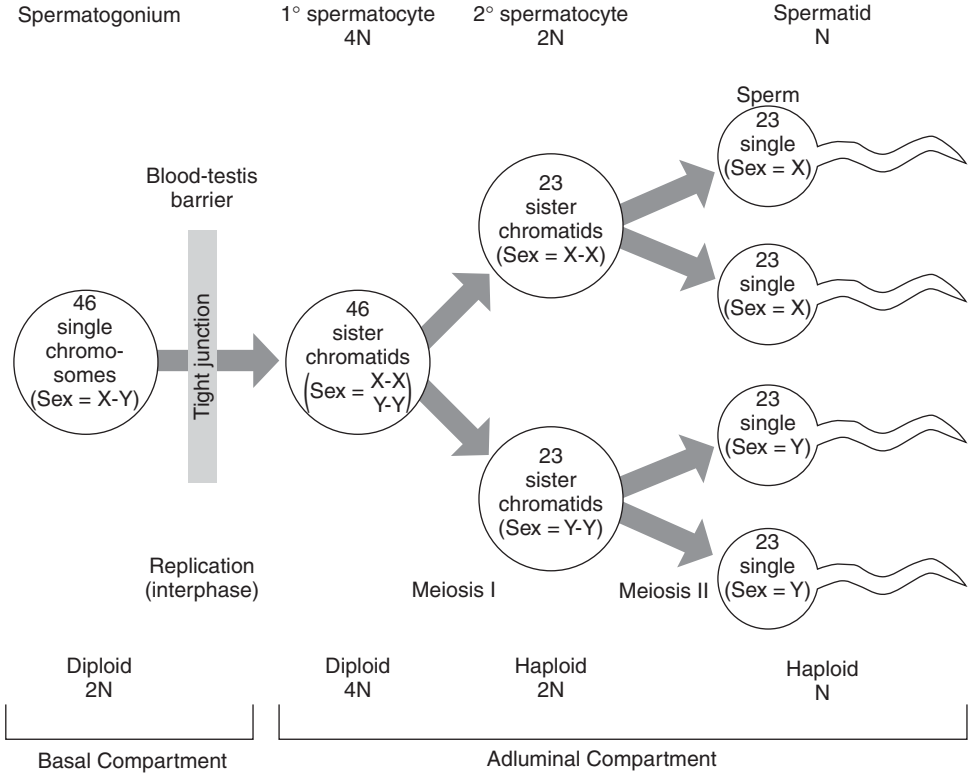
Spermatogenesis begins at puberty with spermatogonia (type A and type B). Full development takes 2 months. **S**permatogenesis occurs in **S**eminiferous tubules.

Blood-testis barrier is a physical barrier in the testis between the tissues responsible for spermatogenesis and the bloodstream (to avoid autoimmune response).

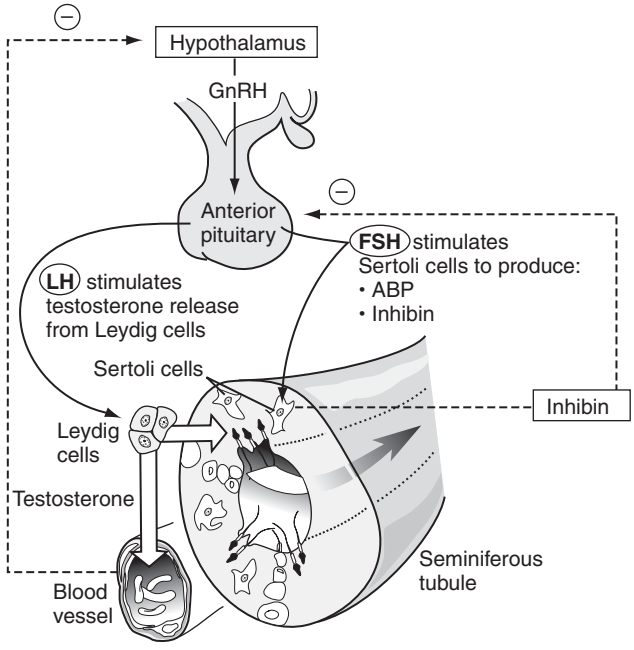


SEVEN UP:
Seminiferous tubules
Epididymis
Vas deferens
Ejaculatory ducts
(**N**othing)
Urethra
Penis

Sertoli cells
Support **S**perm
Synthesis.



Male spermatogenesis



PRODUCTS	FUNCTIONS OF PRODUCTS
Androgen-binding protein (ABP)	Ensures that testosterone in seminiferous tubule is high
Inhibin	Inhibits FSH
Testosterone	Differentiates male genitalia, has anabolic effects on protein metabolism, maintains gametogenesis, maintains libido, inhibits GnRH, and fuses epiphyseal plates in bone

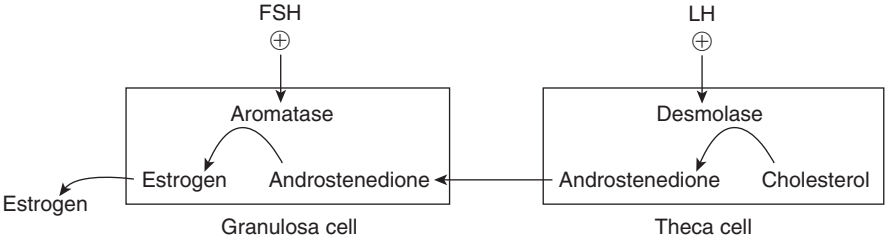
FSH → **S**ertoli cells → **S**perm production
LH → **L**eydig cell → testosterone

Androgens — Testosterone, dihydrotestosterone (DHT), androstenedione.

Source	DHT and testosterone (testis), androstenedione (adrenal).	Potency—DHT > testosterone > androstenedione.
Targets	Prostate, seminal vesicles, epididymis, liver, muscle, brain, skin.	Testosterone is converted to DHT by the enzyme 5α-reductase, which is inhibited by finasteride.
Function	1. Differentiation of wolffian duct system into internal gonadal structures 2. 2° sexual characteristics and growth spurt during puberty, close epiphyseal plates 3. Required for normal spermatogenesis 4. Anabolic effects— ↑ muscle size, ↑ RBC production 5. ↑ libido	Testosterone and androstenedione are converted to estrogen in adipose tissue and Sertoli cells by enzyme aromatase.

Estrogen

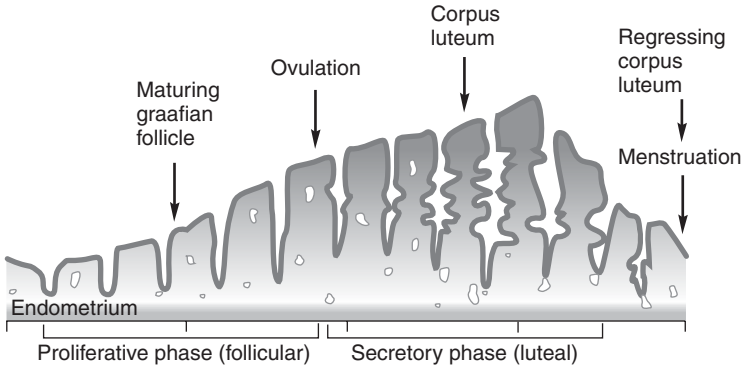
Source	Ovary (17β-estradiol), placenta (estriol), blood (aromatization).	Potency—estradiol > estrone > estriol.
Function	1. Growth of follicle 2. Endometrial proliferation 3. Development of genitalia 4. Stromal development of breast 5. Female fat distribution 6. Hepatic synthesis of transport proteins (↑ synthesis of sex hormone–binding globulin) 7. Feedback inhibition of FSH and LH 8. LH surge (estrogen negative feedback on LH secretion switches to positive from negative just before LH surge) 9. ↑ myometrial excitability 10. ↑ HDL, ↓ LDL	Pregnancy: 50-fold ↑ in estradiol and estrone 1000-fold ↑ in estriol (indicator of fetal well-being)



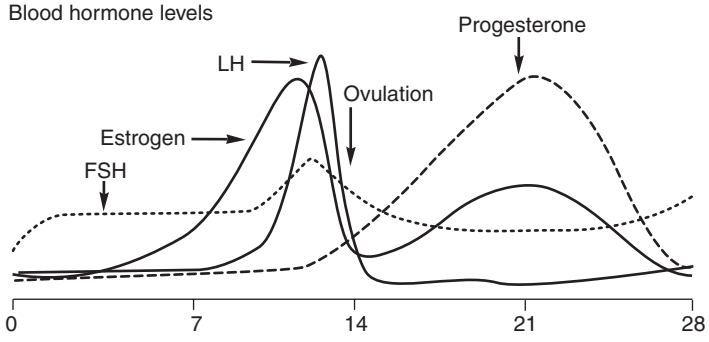
Progesterone

Source	Corpus luteum, placenta, adrenal cortex, testes.	Elevation of progesterone is indicative of ovulation.
Function	1. Stimulation of endometrial glandular secretions and spiral artery development 2. Maintenance of pregnancy 3. ↓ myometrial excitability 4. Production of thick cervical mucus, which inhibits sperm entry into the uterus 5. ↑ body temperature 6. Inhibition of gonadotropins (LH, FSH) 7. Uterine smooth muscle relaxation (preventing contractions)	**P**rogesterone **P**repares for **P**regnancy.

Menstrual cycle



Follicular growth is fastest during 2nd week of proliferative phase.
Estrogen stimulates endometrial proliferation.
Progesterone maintains endometrium to support implantation.
↓ progesterone leads to ↓ fertility.
Follicular phase can vary in length. Luteal phase is usually a constant 14 days. Ovulation day = menstruation day 14.



Estrogen
↓
LH
↓
Ovulate
↓
Progesterone (from corpus luteum)
↓
Period

Ovulation

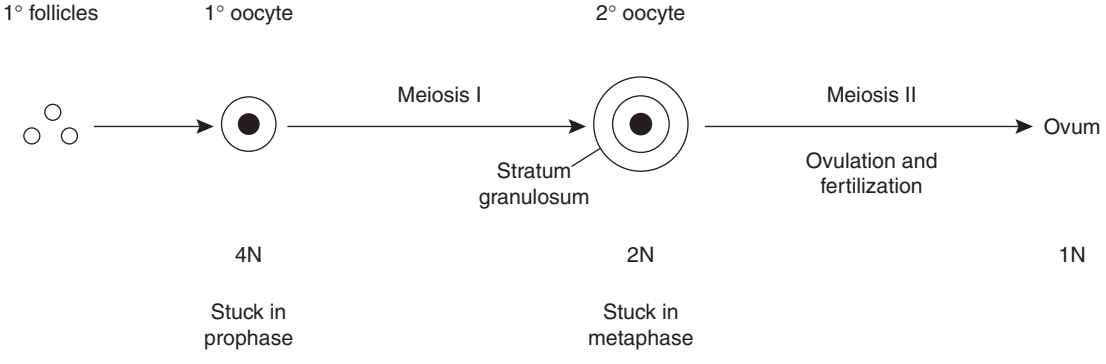
Estrogen surge day before ovulation.
Stimulates LH, inhibits FSH.
LH surge causes ovulation (rupture of follicle).
↑ temperature (progesterone induced).
Ferning of cervical mucosa.
Oral contraceptives prevent estrogen surge, LH surge → ovulation does not occur.

Mittelschmerz—blood from ruptured follicle causes peritoneal irritation that can mimic appendicitis.

Meiosis and ovulation

1° oocytes begin meiosis I during fetal life and complete meiosis I just prior to ovulation.
Meiosis I is arrested in pr**O**phase for years until **O**vulation (1° oocytes).
Meiosis II is arrested in **MET**aphase until fertilization (2° oocytes).

An egg **MET** a sperm.



► REPRODUCTIVE—PHYSIOLOGY *(continued)*

Pregnancy

Fertilization most commonly occurs in upper end of oviduct. Occurs within 1 day after ovulation.

Implantation occurs 6 days after fertilization. Trophoblasts secrete β-hCG, which is detectable in blood 1 week after conception and on home test in urine 2 weeks after conception.

↑ estrogen, progesterone, oxytocin, and prolactin at term (hCG peak is in 1st trimester).

Lactation—during pregnancy, estrogen inhibits prolactin and inhibits lactation. After labor, the ↓ in maternal estrogen induces lactation. Suckling is required to maintain milk production, since ↑ nerve stimulation ↑ oxytocin.

hCG

Source: Syncytiotrophoblast of placenta.

Function:
1. Maintains the corpus luteum (and thus progesterone) for the 1st trimester by acting like LH (otherwise no luteal cell stimulation, and abortion results). In the 2nd and 3rd trimester, the placenta synthesizes its own estriol and progesterone and the corpus luteum degenerates.
2. Used to detect pregnancy because it appears early in the urine (see above).
3. Elevated hCG in women with hydatidiform moles or choriocarcinoma.

Menopause

Cessation of estrogen production with age-linked decline in number of ovarian follicles. Average age of onset is 51 years (earlier in smokers).

Hormonal changes: ↓ estrogen, ↑↑ FSH, ↑ LH (no surge), ↑ GnRH.

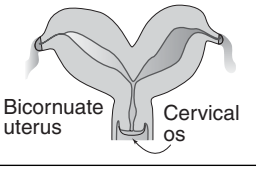
Menopause causes **HAVOC:** **H**ot flashes, **A**trophy of the **V**agina, **O**steoporosis, **C**oronary artery disease.

Early menopause can indicate premature ovarian failure.

► REPRODUCTIVE—PATHOLOGY

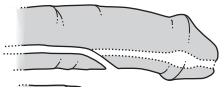
Bicornuate uterus

Results from incomplete fusion of the paramesonephric ducts. Associated with urinary tract abnormalities and infertility.



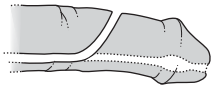
Congenital penile abnormalities

Hypospadias



Hypospadias—abnormal opening of penile urethra on inferior (ventral) side of penis due to failure of urethral folds to close.

Epispadias



Epispadias—abnormal opening of penile urethra on superior (dorsal) side of penis due to faulty positioning of genital tubercle.

Hypospadias is more common than epispadias. Fix hypospadias to prevent UTIs.

Hypo is **below.**

Exstrophy of the bladder is associated with **E**pispadias.

When you have **E**pispadias, you hit your **E**ye when you p**EE**.

Sex chromosome disorders		
Klinefelter's syndrome [male] (XXY), 1:850	Testicular atrophy, eunuchoid body shape, tall, long extremities, gynecomastia, female hair distribution. Presence of inactivated X chromosome (Barr body) (see Image 108). Common cause of hypogonadism seen in infertility workup.	Dysgenesis of seminiferous tubules → ↓ inhibin → ↑ FSH. Abnormal Leydig cell function → ↓ testosterone → ↑ LH → ↑ estrogen.
Turner's syndrome [female] **(XO)**, 1:3000	Short stature, ovarian dysgenesis (streak ovary), webbing of neck, preductal coarctation of the aorta, most common cause of 1° amenorrhea. No Barr body (see Image 109).	"Hugs and kisses" **(XO)** from Tina **Turner** (female). ↓ estrogen leads to ↑ LH and FSH.
Double Y males [male] (XYY), 1:1000	Phenotypically normal, very tall, severe acne, antisocial behavior (seen in 1–2% of XYY males). Normal fertility.	Observed with ↑ frequency among inmates of penal institutions.
Pseudo-hermaphroditism	Disagreement between the phenotypic (external genitalia) and gonadal (testes vs. ovaries) sex.	
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 (i.e., 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).	
True hermaphrodite (46,XX or 47,XXY)	Both ovary and testicular tissue present; ambiguous genitalia. Very rare.	
Androgen insensitivity syndrome (46,XY)	Defect in androgen receptor resulting in normal-appearing female; female external genitalia with rudimentary vagina; uterus and uterine tubes generally absent; develops testes (often found in labia majora; surgically removed to prevent malignancy). Levels of testosterone, estrogen, and LH are all high.	
5α-reductase deficiency	Unable to convert testosterone to DHT. Ambiguous genitalia until puberty, when ↑ testosterone causes masculinization of genitalia. Testosterone/estrogen levels are normal; LH is normal or ↑. "Penis at 12" (when testosterone production begins at puberty, it stimulates growth of external male genitalia).	

Hydatidiform mole

A pathologic ovum ("empty egg"—ovum with no DNA) resulting in cystic swelling of chorionic villi and proliferation of chorionic epithelium (trophoblast). Most common precursor of choriocarcinoma. High β-hCG. "Honeycombed uterus," "cluster of grapes" appearance. Genotype of a **complete** mole is 46,XX and is **completely** paternal in origin (no maternal chromosomes).

Complete moles have no associated fetus and commonly lead to an abnormally enlarged uterus. **PART**ial mole is made up of 3 or more **PARTS** (triploid or tetraploid); may contain fetal **PARTS.** Partial moles are less likely to be associated with excessive uterine size (see Color Image 74). Moles can lead to uterine rupture. Treat with dilatation and curettage and methotrexate. Monitor β-hCG.

Complete—2 sperm + empty egg.
Partial—2 sperm + 1 egg.

Pregnancy-induced hypertension (preeclampsia-eclampsia)

Preeclampsia is the triad of hypertension, proteinuria, and edema; eclampsia is the addition of seizures to the triad. Affects 7% of pregnant women from 20 weeks' gestation to 6 weeks postpartum (before 20 weeks suggests molar pregnancy). ↑ incidence in patients with preexisting hypertension, diabetes, chronic renal disease, and autoimmune disorders. Etiology involves placental ischemia (lack of trophoblastic invasion of spiral arteries in myometrium). Can be associated with HELLP syndrome (**H**emolysis, **E**levated **L**FTs, **L**ow **P**latelets). Mortality due to cerebral hemorrhage and ARDS.

Clinical features: Headache, blurred vision, abdominal pain, edema of face and extremities, altered mentation, hyperreflexia; lab findings may include thrombocytopenia, hyperuricemia.

Treatment: Delivery of fetus as soon as viable. Otherwise bed rest, salt restriction, and monitoring and treatment of hypertension. For eclampsia, a medical emergency, IV magnesium sulfate and diazepam.

Pregnancy complications

Abruptio placentae—premature detachment of placenta from implantation site. **Painful** uterine bleeding (usually during 3rd trimester). Fetal death. May be associated with DIC. ↑ risk with smoking, hypertension, cocaine use.

Painful bleeding.

Placenta accreta—defective decidual layer allows placenta to attach directly to myometrium. Predisposed by prior C-section or inflammation. May have massive hemorrhage after delivery.

Massive bleeding.

Placenta previa—attachment of placenta to lower uterine segment. May occlude internal os. **Painless** bleeding in any trimester. Prior C-section predisposes.

Painless bleeding.

Ectopic pregnancy—most often in fallopian tubes, predisposed by salpingitis (PID). Suspect with ↑ hCG and sudden lower abdominal pain; confirm with ultrasound. Often clinically mistaken for appendicitis.

Pain without bleeding.

Amniotic fluid abnormalities	
Polyhydramnios	> 1.5–2 L of amniotic fluid; associated with esophageal/duodenal atresia, causing inability to swallow amniotic fluid, and with anencephaly.
Oligohydramnios	< 0.5 L of amniotic fluid; associated with bilateral renal agenesis or posterior urethral valves (in males) and resultant inability to excrete urine. Can give rise to Potter's syndrome.
Cervical pathology	
Dysplasia and carcinoma in situ	Disordered epithelial growth; begins at basal layer of squamo-columnar junction and extends outward. Classified as CIN 1, CIN 2, or CIN 3 (carcinoma in situ), depending on extent of dysplasia. Associated with HPV **16, 18.** Vaccine—Gardasil (tetravalent). May progress slowly to invasive carcinoma.
Invasive carcinoma	Often squamous cell carcinoma. Pap smear can catch cervical dysplasia (koilocytes) before it progresses to invasive carcinoma. Lateral invasion can block ureters, causing renal failure.
Uterine pathology	
Endometriosis	Non-neoplastic endometrial glands/stroma in abnormal locations outside the uterus. Characterized by cyclic bleeding (menstrual type) from ectopic endometrial tissue resulting in blood-filled "chocolate cysts." In ovary or on peritoneum. Manifests clinically as severe menstrual-related pain. Often results in infertility (see Color Image 77). Can be due to retrograde menstrual flow.
Adenomyosis	Endometriosis within the myometrium.
Endometrial hyperplasia	Abnormal endometrial gland proliferation usually caused by excess estrogen stimulation. ↑ risk for endometrial carcinoma. Most commonly manifests clinically as postmenopausal vaginal bleeding. Risk factors include anovulatory cycles, hormone replacement therapy, polycystic ovarian syndrome, and granulosa cell tumor.
Endometrial carcinoma	Most common gynecologic malignancy. Peak age 55–65 years of age. Clinically presents with vaginal bleeding. Typically preceded by endometrial hyperplasia. Risk factors include prolonged use of estrogen without progestins, obesity, diabetes, hypertension, nulliparity, and late menopause. Prognosis correlates with degree of myometrial invasion.
Leiomyoma (fibroid)	Most common of all tumors in females. Often presents with multiple tumors with well-demarcated borders. ↑ incidence in blacks. Benign smooth muscle tumor; malignant transformation is rare. Estrogen sensitive—tumor size ↑ with pregnancy and ↓ with menopause. Peak occurrence in women 20–40 years of age. May be asymptomatic or may cause abnormal uterine bleeding. Severe bleeding may lead to iron deficiency anemia. Does not progress to leiomyosarcoma (see Image 129). Whorled pattern of smooth muscle bundles.
Leiomyosarcoma	Bulky, irregularly shaped tumor with areas of necrosis and hemorrhage, typically arising de novo (not from leiomyoma). ↑ incidence in blacks. Highly aggressive tumor with tendency to recur. May protrude from cervix and bleed.
Gynecological tumor epidemiology	Incidence—endometrial > ovarian > cervical. Worst prognosis—ovarian > cervical > endometrial.

Polycystic ovarian syndrome

↑ LH, ↓ FSH, ↑ testosterone. ↑ LH production leads to anovulation, hyperandrogenism due to deranged steroid synthesis. Enlarged, bilateral cystic ovaries manifest clinically with amenorrhea, infertility, obesity, and hirsutism. Associated with insulin resistance. ↑ risk of endometrial cancer. Treat with weight loss, OCPs, gonadotropin analogs, clomiphene, or surgery.

Ovarian cysts

1. Follicular cyst—distention of unruptured graafian follicle. May be associated with hyperestrinism and endometrial hyperplasia.
2. Corpus luteum cyst—hemorrhage into persistent corpus luteum. Menstrual irregularity.
3. Theca-lutein cyst—often bilateral/multiple. Due to gonadotropin stimulation. Associated with choriocarcinoma and moles.
4. "Chocolate cyst"—blood-containing cyst from ovarian endometriosis. Varies with menstrual cycle.

Ovarian germ cell tumors

Type	Characteristics	Tumor markers
Dysgerminoma	Malignant, equivalent to male seminoma. Sheets of uniform cells.	hCG.
Choriocarcinoma	Rare but malignant; can develop during pregnancy in mother or baby. Large, hyperchromatic syncytiotrophoblastic cells. ↑ frequency of theca-lutein cysts.	hCG.
Yolk sac (endodermal sinus tumor)	Aggressive malignancy in ovaries (testes in boys) and sacrococcygeal area of young children.	AFP.
Teratoma	90% of ovarian germ cell tumors (see Images 130, 131). Contain cells from 2 or 3 germ layers. Mature teratoma ("dermoid cyst")—most frequent benign ovarian tumor. Immature teratoma—aggressively malignant. Struma ovarii—contains functional thyroid tissue. Can present as hyperthyroidism.	

Ovarian non–germ cell tumors	1. Serous cystadenoma—20% of ovarian tumors. Frequently bilateral, lined with fallopian tube–like epithelium. Benign. 2. Serous cystadenocarcinoma—50% ovarian tumors, malignant and frequently bilateral. 3. Mucinous cystadenoma—multilocular cyst lined by mucus-secreting epithelium. Benign. 4. Mucinous cystadenocarcinoma—malignant. Pseudomyxoma peritonei—intraperitoneal accumulation of mucinous material from ovarian or appendiceal tumor. 5. **B**renner tumor—**B**enign. Looks like **B**ladder. 6. Fibromas—bundles of spindle-shaped fibroblasts. Meigs' syndrome—triad of ovarian fibroma, ascites, and hydrothorax. Pulling sensation in groin. 7. Granulosa cell tumor—secretes estrogen → precocious puberty (kids). Can cause endometrial hyperplasia or carcinoma in adults. Call-Exner bodies—small follicles filled with eosinophilic secretions. 8. Krukenberg tumor—GI malignancy that metastasizes to ovaries, causing a mucin-secreting signet cell adenocarcinoma.	↑ CA-125 is general ovarian cancer marker. Risk factors—BRCA-1, HNPCC.
Vaginal carcinoma	1. Squamous cell carcinoma—2° to cervical SCC. 2. Clear cell adenocarcinoma—exposure to DES. 3. Sarcoma botryoides (rhabdomyosarcoma variant)—affects girls < 4 years of age; spindle-shaped tumor cells that are desmin positive.	

Breast tumors

Type	Characteristics
Benign tumors	1. Fibroadenoma—most common tumor < 25 years. Small, mobile, firm mass with sharp edges. ↑ size and tenderness with pregnancy. Not a precursor to breast cancer. 2. Intraductal papilloma—tumor of lactiferous ducts; presents with serous or bloody nipple discharge. 3. Phyllodes tumor—large, bulky mass of connective tissue and cysts. Tumor may have "leaflike" projections. Some may be malignant (cystosarcoma phyllodes).
Malignant tumors (carcinoma)	Common postmenopause. Arise from mammary duct epithelium or lobular glands. Overexpression of estrogen/progesterone receptors or *erb*-B2 (HER-2, an EGF receptor) is common; affects therapy and prognosis (give tamoxifen for ER/PR-positive tumors). Axillary lymph node involvement is the single most important prognostic factor. Histologic types: 1. **Noninvasive:** Ductal carcinoma in situ (DCIS)—early malignancy without basement membrane penetration. 2. **Invasive** (in descending order of incidence): a. Invasive ductal, no specific type (76%)—firm, fibrous mass. Worst and most invasive. Common. b. Invasive lobular (8%)—often multiple, bilateral, orderly rows of cells. c. Medullary (1.2%–10%)—fleshy, cellular, lymphocytic infiltrate. Good prognosis. d. Comedocarcinoma (1.6%)—ductal, caseous necrosis. e. Inflammatory—lymphatic involvement; red, swollen; peau d'orange (breast skin resembles orange peel). f. Paget's disease of the breast—eczematous patches on nipple. Paget cells—large cells with clear halo; suggest underlying carcinoma. Also seen on vulva. Risk factors: gender, age, early 1st menarche (< 12 years old), delayed 1st pregnancy (> 30 years old), late menopause (> 50 years old), family history of 1st-degree relative with breast cancer at a young age. Risk is NOT increased by fibroadenoma or nonhyperplastic cysts.

Common breast conditions

Fibrocystic disease	Most common cause of "breast lumps" from age 25 to menopause. Presents with diffuse breast pain and multiple lesions, often bilateral. Usually does not indicate ↑ risk of carcinoma. Histologic types: 1. Fibrosis—hyperplasia of breast stroma. 2. Cystic—fluid filled, blue dome. 3. Sclerosing—↑ acini and intralobular fibrosis. 4. Epithelial hyperplasia—↑ in number of epithelial cell layers in terminal duct lobule. ↑ risk of carcinoma with atypical cells. Occurs in women > 30 years of age.	
Acute mastitis	Breast abscess; during breast-feeding, ↑ risk of bacterial infection through cracks in the nipple; *S. aureus* is the most common pathogen.	
Fat necrosis	A benign painless lump; forms as a result of injury to breast tissue.	
Gynecomastia	Results from hyperestrogenism (cirrhosis, testicular tumor, puberty, old age), Klinefelter's syndrome, or drugs (estrogen, marijuana, heroin, psychoactive drugs, **S**pironolactone, **D**igitalis, **C**imetidine, **A**lcohol, **K**etoconazole).	**S**ome **D**rugs **C**reate **A**wesome **K**nockers.

Prostate pathology

Prostatitis—dysuria, frequency, urgency, low back pain. Acute: bacterial (e.g., *E. coli*); chronic: bacterial or abacterial (most common).

Benign prostatic hyperplasia (not hypertrophy)

Common in men > 50 years of age. May be due to an age-related ↑ in estradiol with possible sensitization of the prostate to the growth-promoting effects of DHT. Characterized by a nodular enlargement of the periurethral (lateral and middle) lobes of the prostate gland, compressing the urethra into a vertical slit. Often presents with ↑ frequency of urination, nocturia, difficulty starting and stopping the stream of urine, and dysuria. May lead to distention and hypertrophy of the bladder, hydronephrosis, and UTIs. Not considered a premalignant lesion. ↑ free prostate-specific antigen (PSA).

Prostatic adenocarcinoma

Common in men > 50 years of age. Arises most often from the posterior lobe (peripheral zone) of the prostate gland and is most frequently diagnosed by digital rectal examination (hard nodule) and prostate biopsy. 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 an ↑ in serum alkaline phosphatase and PSA.

Cryptorchidism

Undescended testis (one or both); lack of spermatogenesis due to ↑ body temperature; associated with ↑ risk of germ cell tumors. Prematurity ↑ the risk of cryptorchidism.

Testicular germ cell tumors	~95% of all testicular tumors.
Seminoma	Malignant; painless testicular enlargement; most common testicular tumor, mostly affecting males age 15–35. Large cells in lobules with watery cytoplasm and a "fried egg" appearance. Radiosensitive. Late metastasis, excellent prognosis.
Embryonal carcinoma	Malignant; painful; worse prognosis than seminoma. Often glandular/papillary morphology. Can differentiate to other tumors.
Yolk sac (endodermal sinus) tumor	Analogous to ovarian yolk sac tumor. Schiller-Duval bodies, primitive glomeruli (↑ AFP).
Choriocarcinoma	Malignant, ↑ hCG.
Teratoma	Unlike in females, mature teratoma in males is most often malignant.
Testicular non–germ cell tumors	5% of all testicular tumors. Mostly benign.
Leydig cell	Benign, contains Reinke crystals; usually androgen producing, gynecomastia in men, precocious puberty in boys.
Sertoli cell	Benign, androblastoma from sex cord stroma.
Testicular lymphoma	Most common testicular cancer in older men.
Tunica vaginalis lesions	Lesions in the serous covering of testis—present as testicular masses that can be transilluminated (vs. testicular tumors). 1. Varicocele—dilated vein in pampiniform plexus; can cause infertility; "bag of worms" 2. Hydrocele—↑ fluid 2° to incomplete fusion of processus vaginalis 3. Spermatocele—dilated epididymal duct
Penile pathology	
Carcinoma in situ	
Erythroplasia of Queyrat	Red velvety plaques, usually involving the glans; otherwise similar to Bowen's disease.
Bowenoid papulosis	Multiple papular lesions; affects younger age group than other subtypes; usually does not become invasive.
Bowen's disease	Gray, solitary, crusty plaque, usually on the shaft of the penis or on the scrotum; peak incidence in 5th decade of life; progresses to invasive SCC in < 10% of cases.
Squamous cell carcinoma (SCC)	Rare in circumcised men; uncommon in the United States and Europe, more common in Asia, Africa, and South America. Commonly associated with HPV.
Peyronie's disease	Bent penis due to acquired fibrous tissue formation.

Antiandrogens	Testosterone $\xrightarrow{5\alpha\text{-reductase}}$ DHT (more potent).	
Finasteride (Propecia)	A 5α-reductase inhibitor (↓ conversion of testosterone to dihydrotestosterone). Useful in BPH. Also promotes hair growth—used to treat male-pattern baldness.	To prevent male-pattern hair growth, give a drug that will encourage female breast growth.
Flutamide	A nonsteroidal competitive inhibitor of androgens at the testosterone receptor. Used in prostate carcinoma.	Ketoconazole and spironolactone are used in the treatment of polycystic ovarian syndrome to prevent hirsutism. Both have side effects of gynecomastia and amenorrhea.
Ketoconazole	Inhibits steroid synthesis.	
Spironolactone	Inhibits steroid binding.	
Leuprolide		
Mechanism	GnRH analog with agonist properties when used in pulsatile fashion; antagonist properties when used in continuous fashion.	**Leu**prolide can be used in **lieu** of GnRH.
Clinical use	Infertility (pulsatile), prostate cancer (continuous—use with flutamide), uterine fibroids.	
Toxicity	Antiandrogen, nausea, vomiting.	
Sildenafil, vardenafil		
Mechanism	Inhibit cGMP phosphodiesterase, causing ↑ cGMP, smooth muscle relaxation in the corpus cavernosum, ↑ blood flow, and penile erection.	Sildena**fil** and varidena**fil** **fill** the penis.
Clinical use	Treatment of erectile dysfunction.	
Toxicity	Headache, flushing, dyspepsia, impaired blue-green color vision. Risk of life-threatening hypotension in patients taking nitrates.	
Mifepristone (RU-486)		
Mechanism	Competitive inhibitor of progestins at progesterone receptors.	
Clinical use	Termination of pregnancy. Administered with misoprostol (PGE_1).	
Toxicity	Heavy bleeding, GI effects (nausea, vomiting, anorexia), abdominal pain.	

	Advantages	Disadvantages
Oral contraception (synthetic progestins, estrogen)	Reliable (< 1% failure) ↓ risk of endometrial and ovarian cancer ↓ incidence of ectopic pregnancy ↓ pelvic infections Regulation of menses	Taken daily No protection against STDs ↑ triglycerides Depression, weight gain, nausea, hypertension Hypercoagulable state

Hormone replacement therapy (HRT)	Used for relief or prevention of menopausal symptoms (e.g., hot flashes, vaginal atrophy) and osteoporosis (due to diminished estrogen levels). Unopposed estrogen replacement therapy (ERT) ↑ the risk of endometrial cancer, so progesterone is added. Possible ↑ CV risk.

Dinoprostone — PGE_2 analog causing cervical dilation and uterine contraction, inducing labor.

Ritodrine/terbutaline — β_2-agonists that relax the uterus.

Anastrozole — Aromatase inhibitor used in postmenopausal women with breast cancer.

Testosterone (methyltestosterone)

Mechanism	Agonist at androgen receptors.
Clinical use	Treat hypogonadism and promote development of 2° sex characteristics; stimulation of anabolism to promote recovery after burn or injury; treat ER-positive breast cancer (exemestane).
Toxicity	Causes masculinization in females; reduces intratesticular testosterone in males by inhibiting Leydig cells; leads to gonadal atrophy. Premature closure of epiphyseal plates. ↑ LDL, ↓ HDL.

Estrogens (ethinyl estradiol, DES, mestranol)

Mechanism	Bind estrogen receptors.
Clinical use	Hypogonadism or ovarian failure, menstrual abnormalities, HRT in postmenopausal women; use in men with androgen-dependent prostate cancer.
Toxicity	↑ 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-positive breast cancer.

Progestins

Mechanism	Bind progesterone receptors, reduce growth, and ↑ vascularization of endometrium.
Clinical use	Used in oral contraceptives and in the treatment of endometrial cancer and abnormal uterine bleeding.

Estrogen partial agonists (selective estrogen receptor modulators—SERMs)

Clomiphene	Partial agonist at estrogen receptors in pituitary gland. Prevents normal feedback inhibition and ↑ release of LH and FSH from pituitary, which stimulates ovulation. Used to treat infertility and PCOS. May cause hot flashes, ovarian enlargement, multiple simultaneous pregnancies, and visual disturbances.
Tamoxifen	Antagonist on breast tissue; used to treat and prevent recurrence of ER-positive breast cancer.
Raloxifene	Agonist on bone; reduces reabsorption of bone; used to treat osteoporosis.

Respiratory

"There's so much pollution in the air now that if it weren't for our lungs, there'd be no place to put it all."

—Robert Orben

"Mars is essentially in the same orbit. Somewhat the same distance from the Sun, which is very important. We have seen pictures where there are canals, we believe, and water. If there is water, that means there is oxygen. If there is oxygen, that means we can breathe."

—Former Vice President Dan Quayle

- High-Yield Clinical Vignettes
- Anatomy
- Physiology
- Pathology
- Pharmacology

■ Patient exhibits an extended expiratory phase.	What is the disease process?	Obstructive lung disease.
■ Tall, thin male teenager has abrupt-onset dyspnea and left-sided chest pain. There is hyperresonant percussion on the affected side, and breath sounds are diminished.	What is the diagnosis?	Spontaneous pneumothorax.
■ Young man is concerned about his wife's inability to conceive and her recurrent URIs. She has dextrocardia.	Which of her proteins is defective?	Dynein (Kartagener's).
■ The following lung volumes are obtained from an elderly smoker: FRC 5.0 L, IRV 1.5 L, IC 2.0 L, VC 3.5 L.	What is his TLC?	7.0 L.
■ Preterm infant has difficulty breathing. An x-ray reveals ↑ lung densities.	What is the diagnosis, and what could have prevented this condition?	Neonatal respiratory distress syndrome; administration of maternal steroids before birth to ↑ surfactant production.
■ 25-year-old comatose man on ventilatory support following an automobile accident develops fever and dies. Autopsy reveals a pus-filled cavity in his right lung.	What is the likely etiology?	Aspiration of infective material leading to lung abscess.
■ 52-year-old woman undergoing menopause is chronically tired.	What is the most likely diagnosis, and what changes have occurred in her oxygen content and saturation?	Anemia due to chronic blood loss. ↓ oxygen content; oxygen saturation unchanged.
■ Patient is shown to have hypoxia despite a normal chest x-ray.	What is the cause of the hypoxia, and what disease process does it mimic?	Pulmonary embolism. May be mistaken for an MI.
■ Patient is shown to have hypoxia and has an abnormal chest x-ray showing an enlarged heart.	What is the most likely cause of the hypoxia?	CHF.

Respiratory tree

Conducting zone	Consists of nose, pharynx, trachea, bronchi, bronchioles, and terminal bronchioles. Cartilage is present only in the trachea and bronchi. Brings air in and out. Warms, humidifies, filters air. Anatomic dead space. Walls of conducting airways contain smooth muscle.
Respiratory zone	Consists of respiratory bronchioles, alveolar ducts, and alveoli. Participates in gas exchange.

Pneumocytes

Pseudocolumnar ciliated cells extend to the respiratory bronchioles; goblet cells extend only to the terminal bronchioles.

Type I cells (97% of alveolar surfaces) line the alveoli. Squamous; thin for optimal gas diffusion.

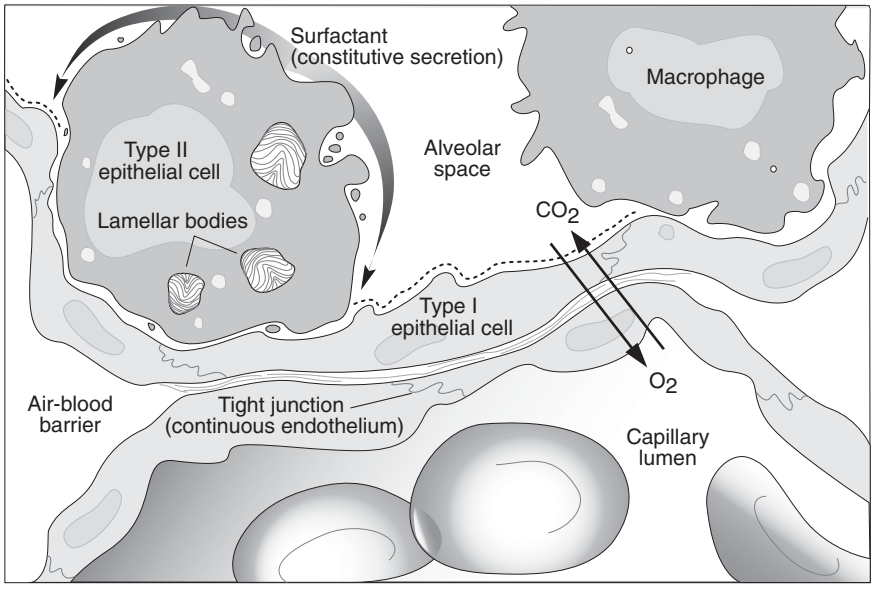
Type II cells (3%) secrete pulmonary surfactant (dipalmitoyl phosphatidylcholine), which ↓ the alveolar surface tension. Cuboidal and clustered. Also serve as precursors to type I cells and other type II cells. Type II cells proliferate during lung damage.

Clara cells—nonciliated; columnar with secretory granules. Secrete component of surfactant; degrade toxins; act as reserve cells.

Mucus secretions are swept out of the lungs toward the mouth by ciliated cells.

A lecithin-to-sphingomyelin ratio of > 2.0 in amniotic fluid is indicative of fetal lung maturity.

Gas exchange barrier



Bronchopulmonary segments

Each bronchopulmonary segment has a 3° (segmental) bronchus and 2 arteries (bronchial and pulmonary) in the center; veins and lymphatics drain along the borders.

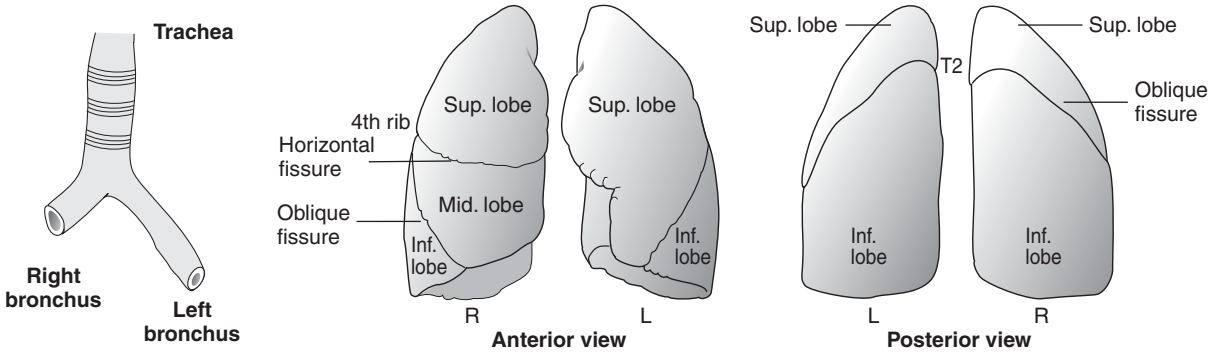
Pulmonary arteries carry deoxygenated blood from the right side of the heart. Elastic walls maintain pulmonary arterial pressure at relatively constant levels throughout cardiac cycle.

Arteries run with **A**irways.

Lung relations

Right lung has 3 lobes; **L**eft has 2 lobes and **L**ingula (homologue of right middle lobe). Right lung is more common site for inhaled foreign body because the right main stem bronchus is wider and more vertical than the left.

Instead of a middle lobe, the left lung has a space occupied by the heart. The relation of the pulmonary artery to the bronchus at each lung hilus is described by **RALS—R**ight **A**nterior; **L**eft **S**uperior.



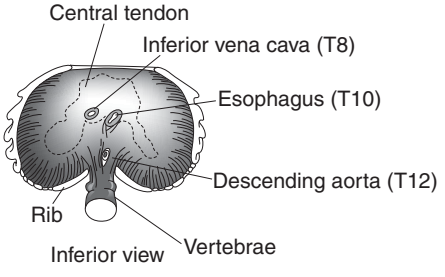
Diaphragm structures

Structures perforating diaphragm:
- At T8: IVC.
- At T**10**: esophagus, vagus (2 trunks).
- At T**12**: aorta (red), thoracic duct (white), azygous vein (blue).

Diaphragm is innervated by **C3, 4,** and **5** (phrenic nerve). Pain from the diaphragm can be referred to the shoulder.

Number of letters = T level:
- **T8**: vena cava
- **T10**: (o)esophagus
- **T12**: aortic hiatus

"**C3, 4, 5** keeps the diaphragm alive."



Muscles of respiration

Quiet breathing:
- Inspiration—diaphragm.
- Expiration—passive.

Exercise:
- Inspiration—external intercostals, scalene muscles, sternomastoids.
- Expiration—rectus abdominis, internal and external obliques, transversus abdominis, internal intercostals.

Important lung products

1. Surfactant—produced by type II pneumocytes, ↓ alveolar surface tension, ↑ compliance, ↓ work of inspiration
2. Prostaglandins
3. Histamine ↑ bronchoconstriction
4. Angiotensin-converting enzyme (ACE)—angiotensin I → angiotensin II; inactivates bradykinin (ACE inhibitors ↑ bradykinin and cause cough, angioedema)
5. Kallikrein—activates bradykinin

Surfactant—dipalmitoyl phosphatidylcholine (lecithin) deficient in neonatal RDS.

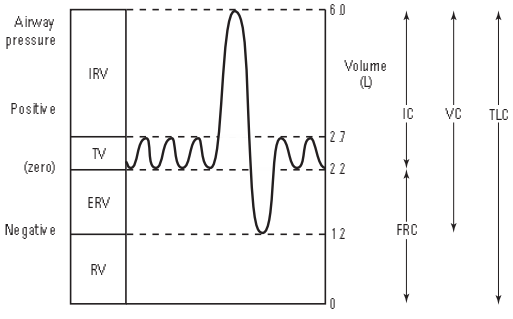
Collapsing pressure = $\frac{2\ (\text{tension})}{\text{radius}}$

Lung volumes

1. Residual volume (RV)—air in lung after maximal expiration
2. Expiratory reserve volume (ERV)—air that can still be breathed out after normal expiration
3. Tidal volume (TV)—air that moves into lung with each quiet inspiration, typically 500 mL
4. Inspiratory reserve volume (IRV)—air in excess of tidal volume that moves into lung on maximum inspiration
5. Vital capacity (VC)—TV + IRV + ERV
6. Functional residual capacity (FRC)—RV + ERV (volume in lungs after normal expiration)
7. Inspiratory capacity (IC)—IRV + TV
8. Total lung capacity—TLC = IRV + TV + ERV + RV

Vital capacity is everything but the residual volume.

A capacity is a sum of ≥ 2 volumes.



Determination of physiologic dead space

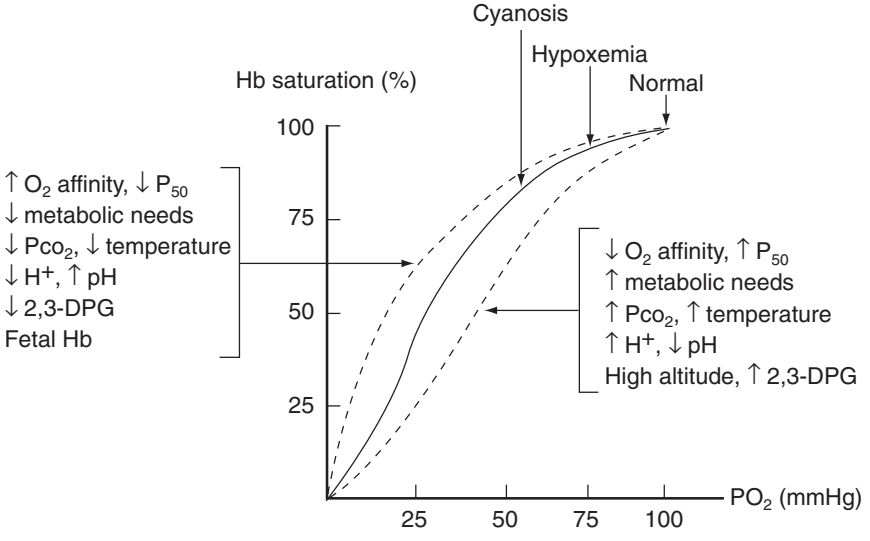
$$V_D = V_T \times \frac{(PaCO_2 - PeCO_2)}{PaCO_2}$$

V_D = physiologic dead space = anatomical dead space of conducting airways plus functional dead space in alveoli. Volume of inspired air that does not take part in gas exchange.

V_T = tidal volume.

$PaCO_2$ = arterial PCO_2, $PeCO_2$ = expired air PCO_2.

Oxygen-hemoglobin dissociation curve



Sigmoidal shape due to positive cooperativity, i.e., hemoglobin can bind 4 oxygen molecules and has higher affinity for each subsequent oxygen molecule bound.

When curve shifts to the right, ↓ affinity of hemoglobin for O_2 (facilitates unloading of O_2 to tissue).

An ↑ in all factors (except pH) causes a shift of the curve to the right.

A ↓ in all factors (except pH) causes a shift of the curve to the left.

Fetal Hb has a higher affinity for oxygen than adult Hb, so its dissociation curve is shifted left.

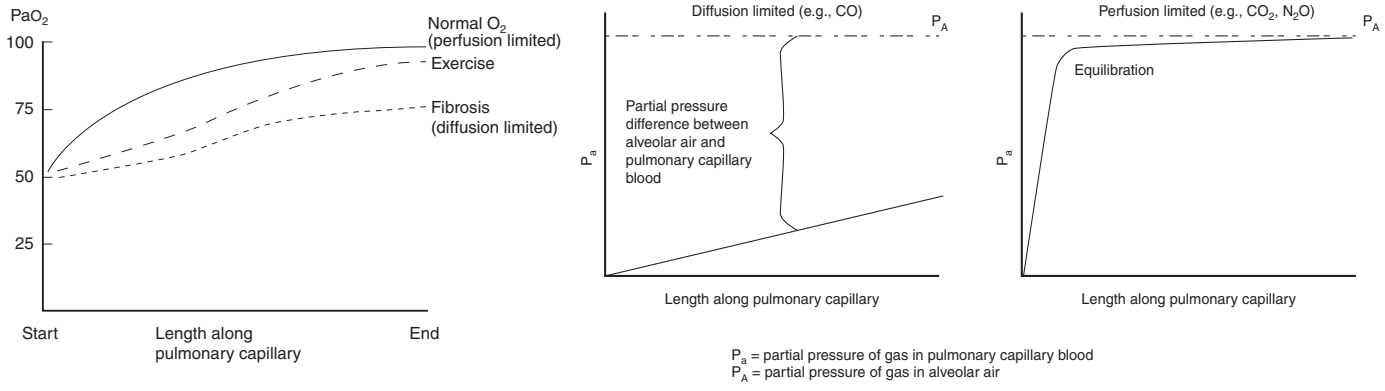
Right shift—**CADET** face **right**:
CO_2
Acid/**A**ltitude
DPG (2,3-DPG)
Exercise
Temperature

Pulmonary circulation

Normally a low-resistance, high-compliance system. P_{O_2} and P_{CO_2} exert opposite effects on pulmonary and systemic circulation. A ↓ in Pa_{O_2} causes a hypoxic vasoconstriction that shifts blood away from poorly ventilated regions of lung to well-ventilated regions of lung.

1. Perfusion limited—O_2 (normal health), CO_2, N_2O. Gas equilibrates early along the length of the capillary. Diffusion can be ↑ only if blood flow ↑.
2. Diffusion limited—O_2 (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).



CO poisoning

CO has 50 times greater affinity for hemoglobin than does oxygen. Causes ↓ oxygen-binding capacity with a left shift in the oxygen-hemoglobin dissociation curve. ↓ oxygen unloading in tissues.

Pulmonary hypertension

Normal pulmonary artery pressure = 10–14 mmHg; pulmonary hypertension ≥ 25 mmHg or > 35 mmHg during exercise.

1°—unknown etiology; poor prognosis.

2°—usually caused by COPD; can also be caused by L → R shunt.

Pulmonary vascular resistance (PVR)

$$PVR = \frac{P_{\text{pulm artery}} - P_{\text{L atrium}}}{\text{Cardiac output}}$$

Remember: $\Delta P = Q \times R$, so $R = \Delta P / Q$.

$R = 8\eta l / \pi r^4$

$P_{\text{pulm artery}}$ = pressure in pulmonary artery.

$P_{\text{L atrium}}$ = pulmonary wedge pressure.

η = the viscosity of inspired air;
l = airway length;
r = airway radius.

Oxygen content of blood

O_2 content = (O_2 binding capacity × % saturation) + dissolved O_2.
Normally 1 g Hb can bind 1.34 mL O_2; normal Hb amount in blood is 15 g/dL.
Cyanosis results when Hb is < 5 g/dL.
O_2 binding capacity ≈ 20.1 mL O_2 / dL.
O_2 content of arterial blood ↓ as Hb falls, but O_2 saturation and arterial P_{O_2} do not.
Arterial P_{O_2} ↓ with chronic lung disease because physiologic shunt ↓ O_2 extraction ratio.
Oxygen delivery to tissues = cardiac output × oxygen content of blood.

Alveolar gas equation

$$P_{AO_2} = P_{IO_2} - \frac{P_{ACO_2}}{R}$$

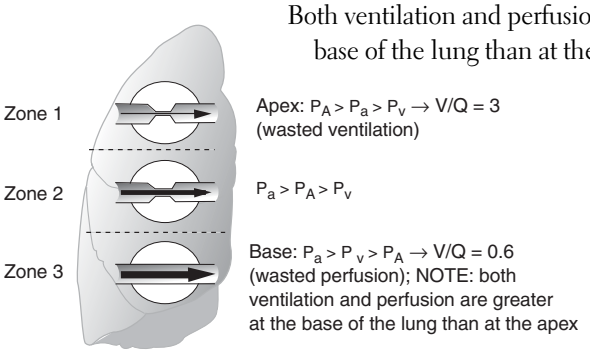
Can normally be approximated:
$P_{AO_2} = 150 - P_{aCO_2} / 0.8$

P_{AO_2} = alveolar P_{O_2} (mmHg).
P_{IO_2} = P_{O_2} in inspired air (mmHg).
P_{ACO_2} = alveolar P_{CO_2} (mmHg).
R = respiratory quotient.
A-a gradient = $P_{AO_2} - P_{aO_2}$ = 10–15 mmHg.
↑ A-a gradient may occur in hypoxemia; causes include shunting, V/Q mismatch, fibrosis (diffusion block).

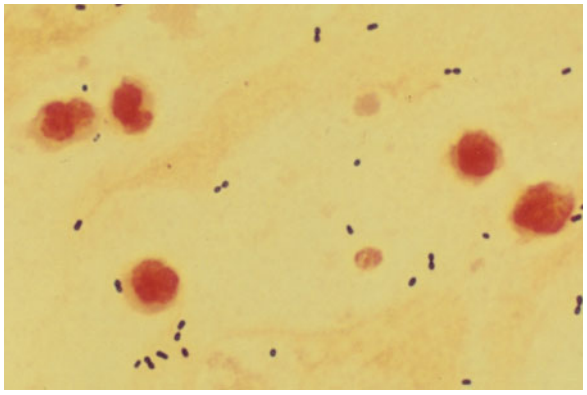
V/Q mismatch

Ideally, ventilation is matched to perfusion (i.e., V/Q = 1) in order for adequate gas exchange to occur.
Lung zones:
1. Apex of the lung—V/Q = 3 (wasted ventilation)
2. Base of the lung—V/Q = 0.6 (wasted perfusion)

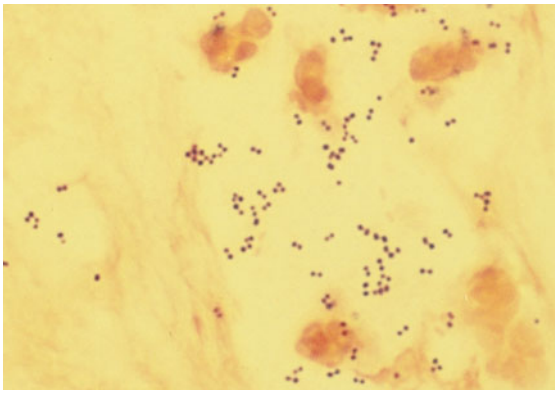
Both ventilation and perfusion are greater at the base of the lung than at the apex of the lung.



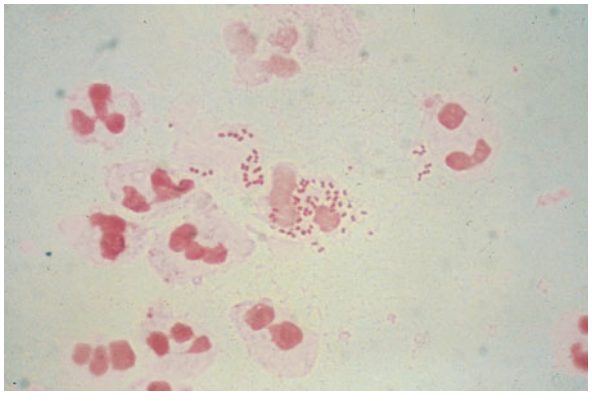
With exercise (↑ cardiac output), there is vasodilation of apical capillaries, resulting in a V/Q ratio that approaches 1.
Certain organisms that thrive in high O_2 (e.g., TB) flourish in the apex.
V/Q → 0 = airway obstruction (shunt). In shunt, 100% O_2 does not improve P_{O_2}.
V/Q → ∞ = blood flow obstruction (physiologic dead space). Assuming < 100% dead space, 100% O_2 improves P_{O_2}.



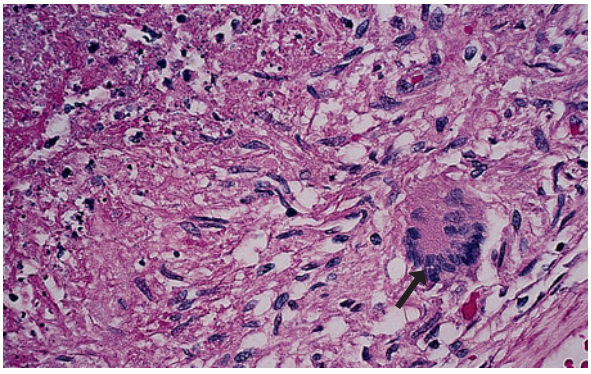
Color Image 1. ***Streptococcus pneumoniae.*** Sputum sample from a patient with pneumonia shows gram-positive diplococci.



Color Image 3. ***Staphylococcus aureus.*** Sputum sample from another patient with pneumonia shows gram-positive cocci in clusters.



Color Image 4. ***Neisseria gonorrhoeae.*** Gram stain shows multiple gram-negative diplococci within polymorphonuclear leukocytes as well as in the extracellular areas of a smear from a urethral discharge. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 906.)



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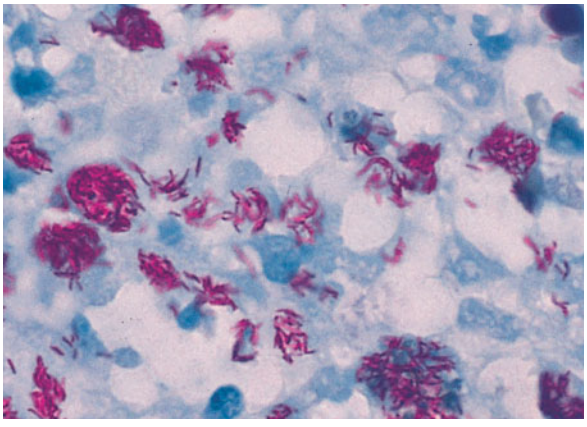

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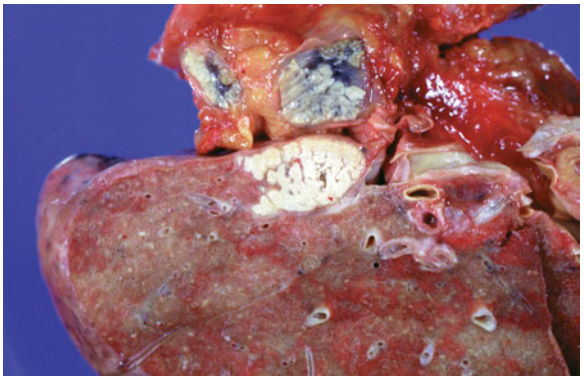
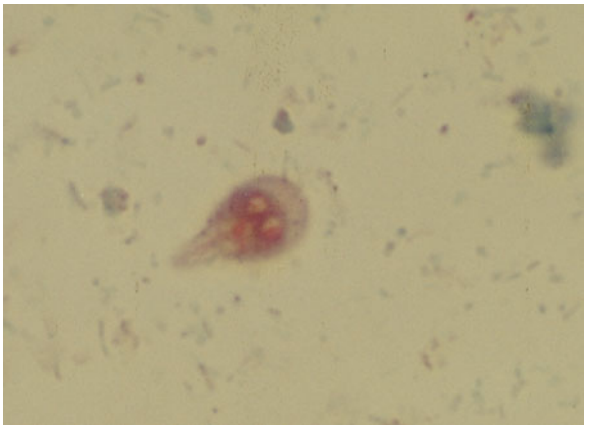


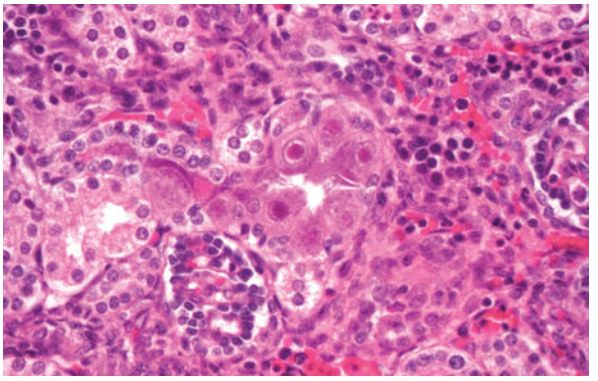
C

Color Image 2. ***Mycobacterium tuberculosis*** **(A)** is characterized by caseating granulomas containing Langhans' giant cells, which have a "horseshoe" pattern of nuclei (see arrow). Organisms **(B)** are identified by their red color on acid-fast staining ("red snappers"). **Miliary tuberculosis (C)** is seen here with large caseous lesions at the left medial upper lobe and miliary lesions in the surrounding hilar node. This life-threatening infection is caused by blood-borne dissemination of *Mycobacterium tuberculosis* to many organs from a quiescent site of infection.*

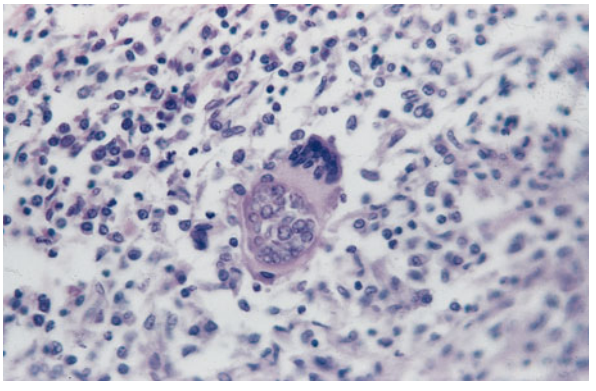
*Reproduced courtesy of the Pathology Education Instructional Resource Digital Library (http://peir.net) at the University of Alabama, Birmingham.



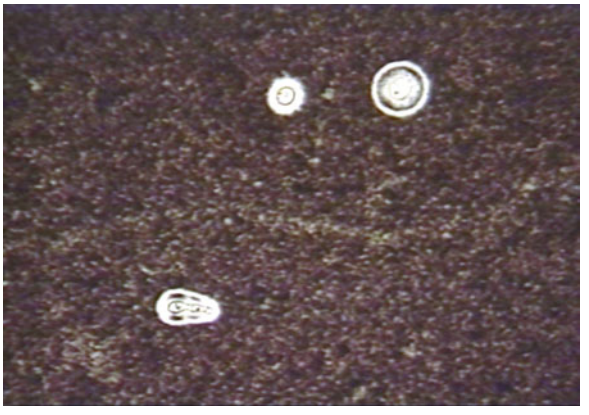
Color Image 5. *Giardia lamblia*, small intestine, microscopic. The trophozoite has a classic pear shape, with double nuclei giving an "owl's-eye" appearance.



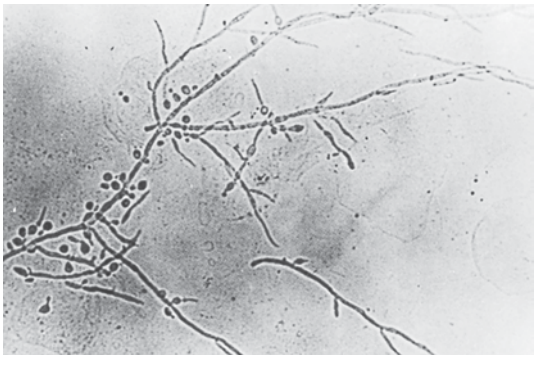
Color Image 6. Cytomegalovirus (CMV). Renal tubular cells in a neonate with congenital CMV infection show prominent Cowdry type A nuclear inclusions resembling owls' eyes. (Reproduced, with permission, from USMLERx.com.)



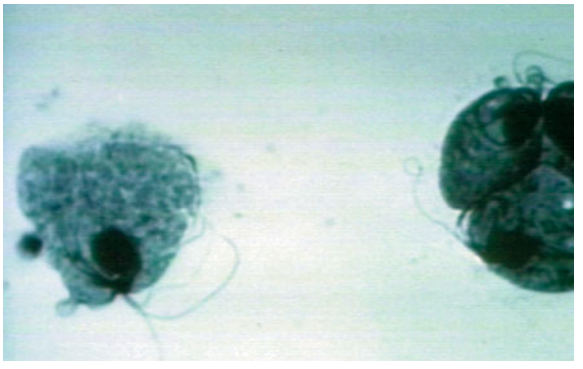
Color Image 7. Coccidioidomycosis. Endospores within a spherule in infected lung parenchyma. Initial infection usually resolves spontaneously, but when immunity is compromised, dissemination to almost any organ can occur. Endemic in the southwestern United States.



Color Image 8. *Cryptococcus neoformans*. The polysaccharide capsule is visible by India ink preparation in CSF from an AIDS patient with meningoencephalitis.*

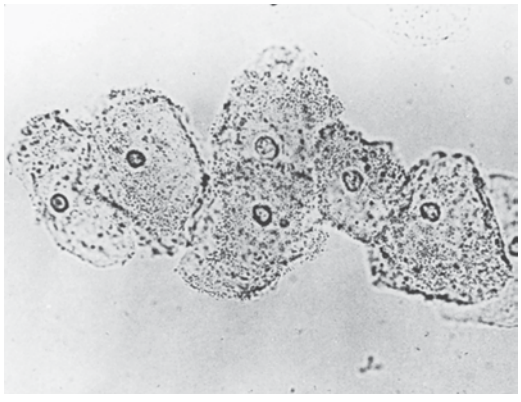


Color Image 9. *Candida albicans*. KOH preparation showing branched and budding *C. albicans*. (Reproduced, with permission, from DeCherney AH. *Current Obstetric and Gynecologic Diagnosis and Treatment*, 9th ed. New York: McGraw-Hill, 2003: 652.)

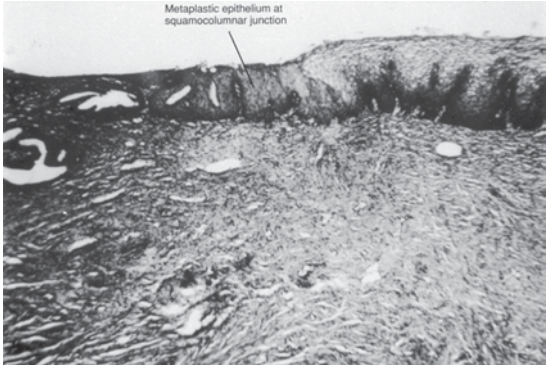


Color Image 10. *Trichomonas vaginalis* demonstrating trophozoites with flagellae.*

Color Image 11. Herpes genitalis. Ulcerating vesicles associated with HSV-2. (Reproduced, with permission, from DeCherney AH. *Current Obstetric and Gynecologic Diagnosis and Treatment*, 9th ed. New York: McGraw-Hill, 2003: 664.)

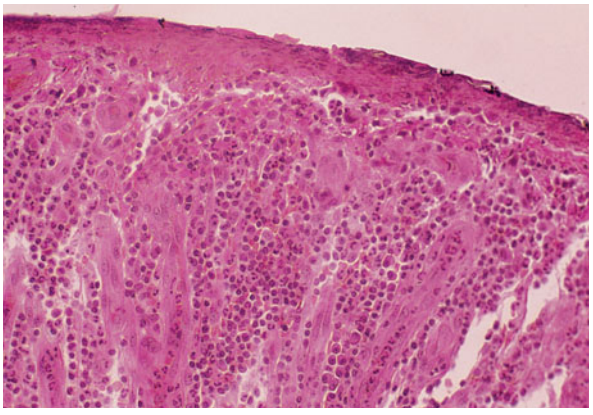


Color Image 13. Bacterial vaginosis. Saline wet mount of clue cells. Note the absence of inflammatory cells. (Reproduced, with permission, from DeCherney AH. *Current Obstetric and Gynecologic Diagnosis and Treatment*, 9th ed. New York: McGraw-Hill, 2003: 653.)



Color Image 14. Human papillomavirus. Metaplastic epithelium at the cervical squamocolumnar junction, associated with HPV. (Reproduced, with permission, from DeCherney AH. *Current Obstetric and Gynecologic Diagnosis and Treatment*, 9th ed. New York: McGraw-Hill, 2003: 683.)

A



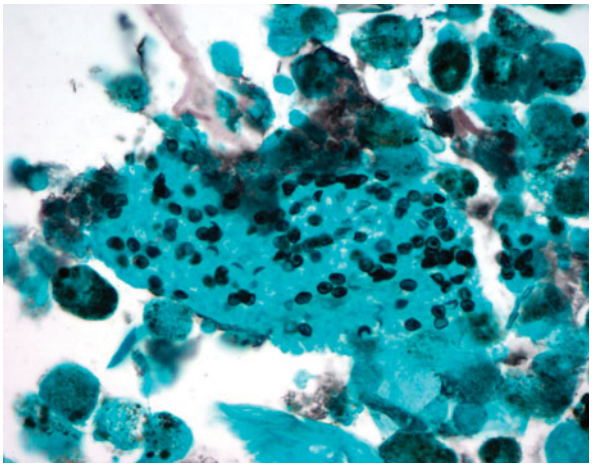
B

C

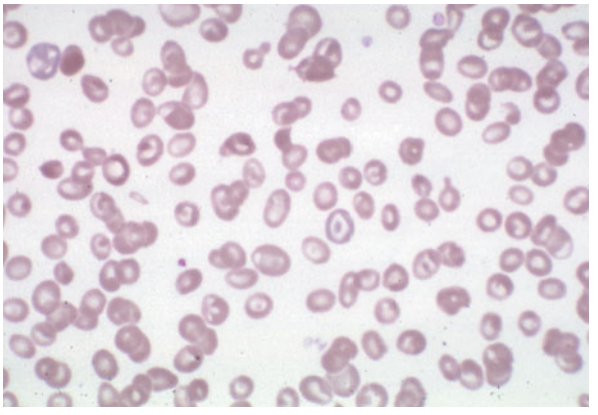
Color Image 12. Syphilis. (A) Chancre associated with primary syphilis. These ulcerative lesions are painless. **(B) Primary syphilis.** A dense infiltrate of plasma cells and dilated blood vessels can be seen. There is epidermal ulceration with crust; neutrophils are present within the predominantly plasmacytic infiltrate. **(C) Tabes dorsalis** resulting from progressive syphilis infection, thoracic spinal cord. Note degeneration of the dorsal columns and dorsal roots.* (Image B reproduced, with permission, from Hurwitz RM et al. *Pathology of the Skin: Atlas of Clinical-Pathological Correlation*, 2nd ed. Stamford, CT: Appleton & Lange, 1998.)

Color Image 15. Herpes zoster. Reactivation of virus spreads along the dermatomal distribution of infected nerves and can occur many years after initial infection. It is considered benign unless it affects an immunocompromised host or is a reinfection of the V_1 branch of the trigeminal nerve with eye/cornea involvement.*

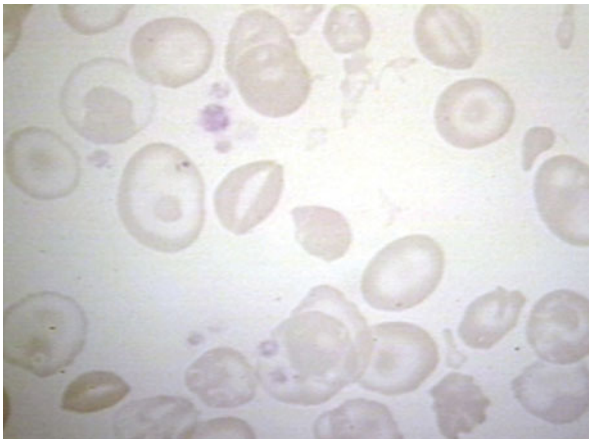
Color Image 16. Coxsackie exanthem (hand-foot-mouth disease). Diffuse eruptive vesiculopapules are seen on the hand of a three-year-old child. (Reproduced, with permission, from Hurwitz RM et al. *Pathology of the Skin: Atlas of Clinical-Pathological Correlation*, 2nd ed. Stamford, CT: Appleton & Lange, 1998.)



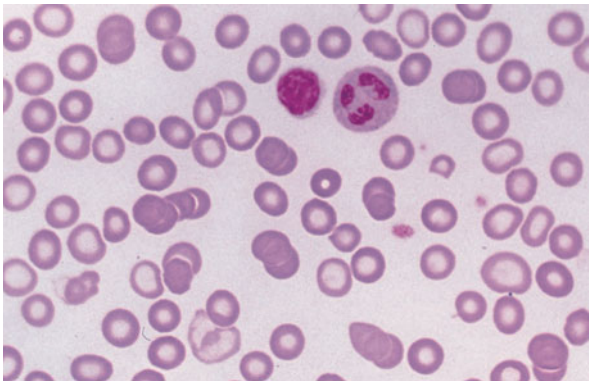
Color Image 17. *Pneumocystis carinii*. Special silver stain of lung epithelium shows numerous small, disk-shaped organisms. (Reproduced, with permission, from USMLERx.com.)



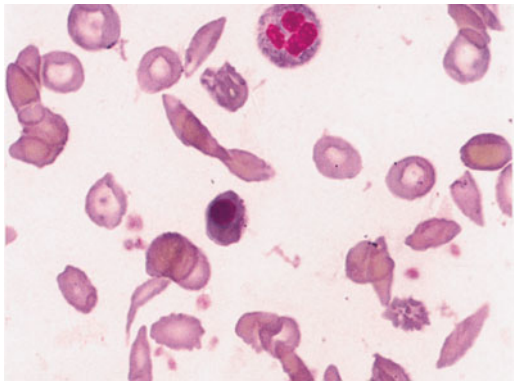
Color Image 18. Target cells. Due to an increase in surface area–to-volume ratio from iron deficiency anemia (decreased cell volume) or in obstructive liver disease (increased cell membrane).*



Color Image 19. Thalassemia major. A blood dyscrasia caused by a defect in β-chain synthesis in hemoglobin. Note the presence of target cells.*



Color Image 20. Iron deficiency anemia. Microcytosis and hypochromia can be seen.



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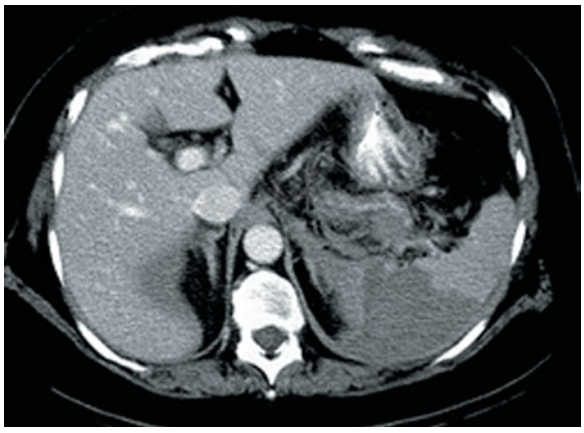
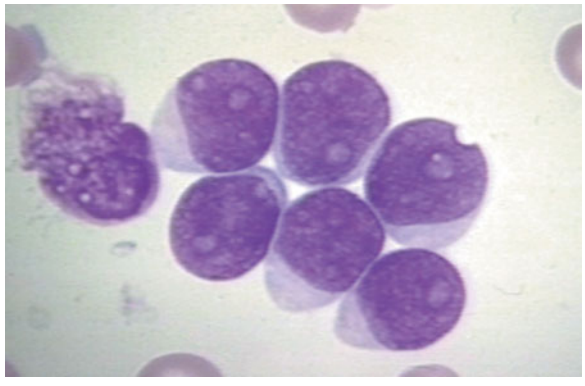


B

Color Image 21. Sickle cell anemia. (A) Sickle cell peripheral blood smear. Note the sickled cells as well as anisocytosis, poikilocytosis, and nucleated RBCs. **(B) Splenic infarction.** The splenic artery lacks collateral supply, making the spleen particularly susceptible to ischemic damage. Coagulative necrosis has occurred in a wedge shape along the pattern of vascular supply. Individual sickle cells cause generalized splenic infarcts that result in autosplenectomy by adolescence.*



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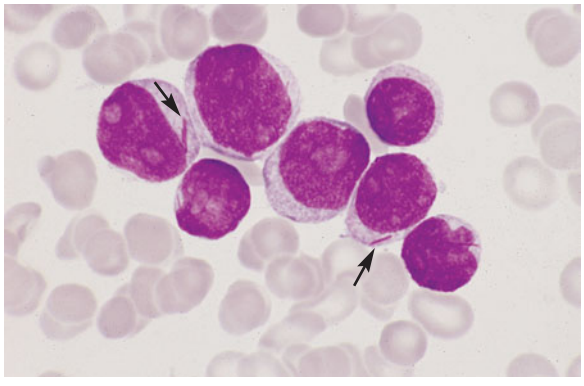

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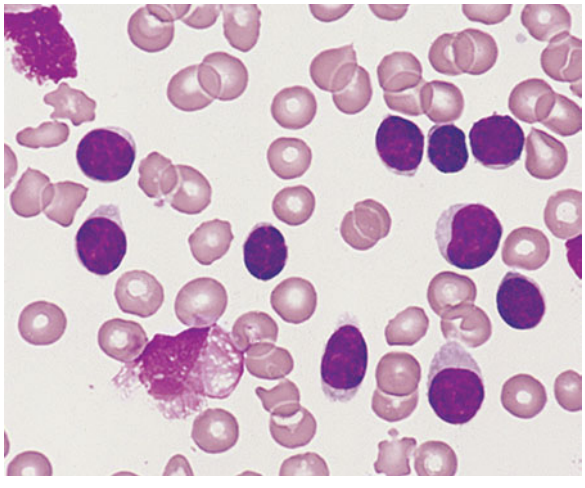

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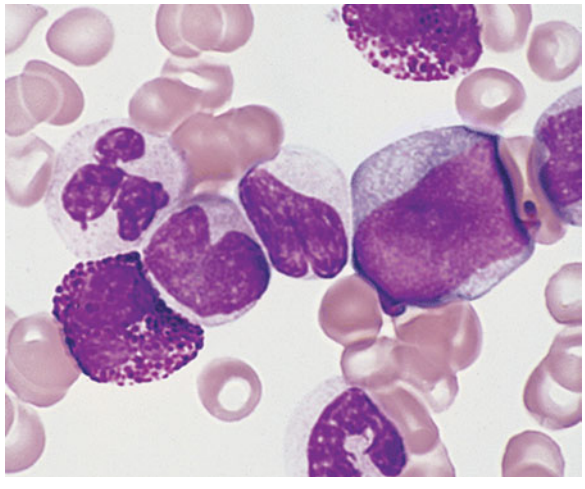
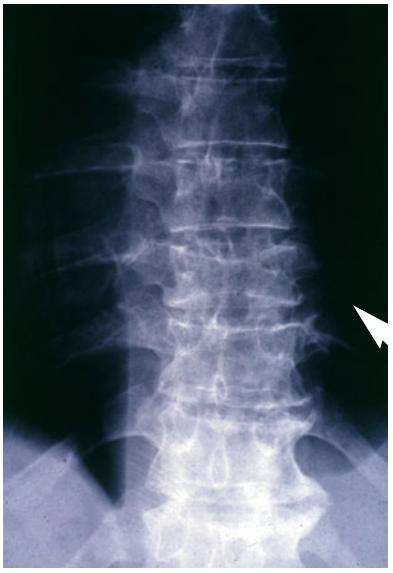


D

Color Image 22. Leukemia. (A) Acute lymphocytic leukemia, peripheral blood smear. Affects children less than 10 years of age. **(B) Acute myelocytic leukemia** with Auer rods (arrows), peripheral blood smear. Affects adolescents to young adults. **(C) Chronic lymphocytic leukemia,** peripheral blood smear. In CLL, the lymphocytes are excessively fragile. These lymphocytes are easily destroyed during slide preparation, forming "smudge cells." Affects individuals older than 60 years of age. **(D) Chronic myeloid leukemia,** peripheral blood smear. Promyelocytes and myelocytes are seen adjacent to a vascular structure. Affects individuals from 30 to 60 years of age.*



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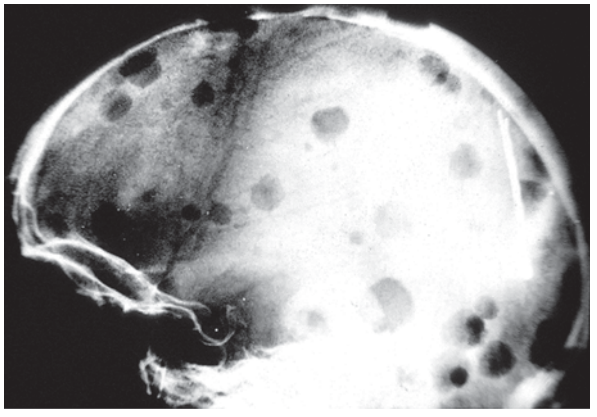

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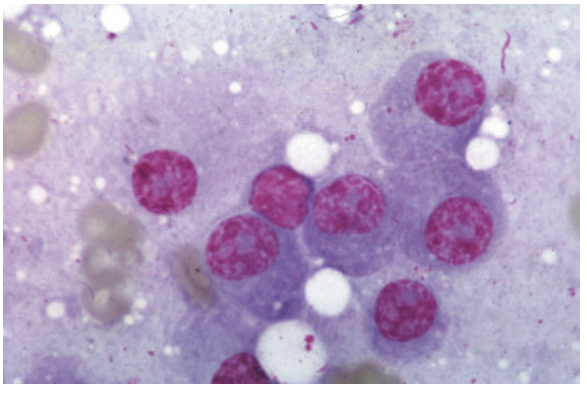
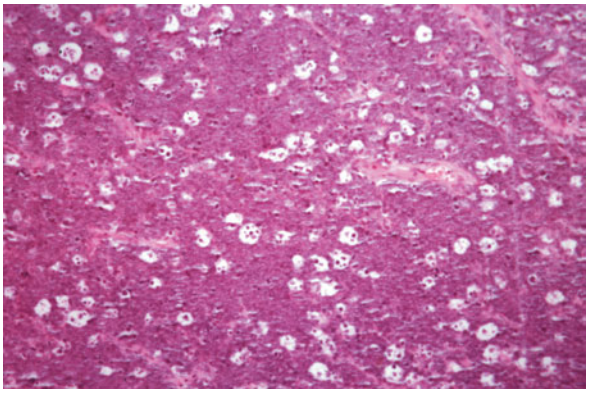
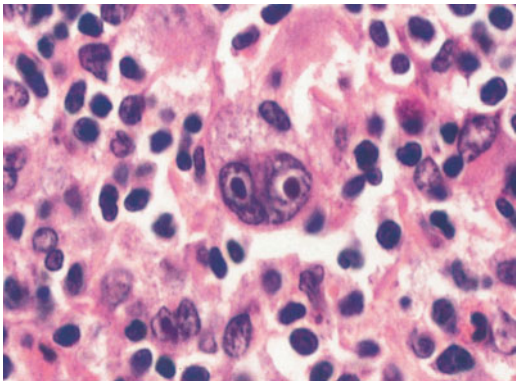


C

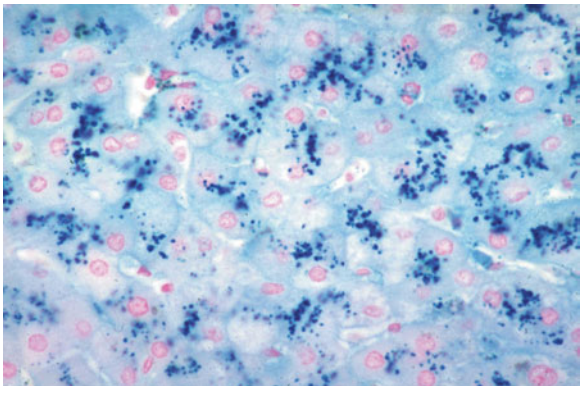
Color Image 23. Multiple myeloma. **(A)** X-ray shows numerous punched-out lytic lesions (lucent areas) typical of multiple myeloma. Note the generalized osteopenia and multiple compression fractures (arrow). **(B)** Classic bone lytic lesions seen in multiple myeloma. **(C)** Smears from a patient with multiple myeloma display an abundance of plasma cells. RBCs will often be seen in rouleaux formation, stacked like poker chips. Multiple myeloma is associated with hypercalcemia, lytic bone lesions, and renal insufficiency due to Bence Jones (light-chain) proteinuria.*



Color Image 24. Burkitt's lymphoma. The classic "starry-sky" appearance from macrophage ingestion of tumor cells can be seen.*

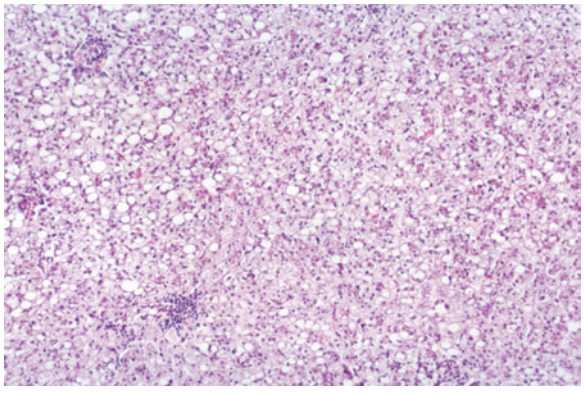


Color Image 25. Hodgkin's disease (Reed-Sternberg cells). Binucleate RS cells displaying prominent inclusion-like nucleoli surrounded by lymphocytes and other reacting inflammatory cells. The RS cell is a necessary but insufficient pathologic finding for the diagnosis of Hodgkin's disease.



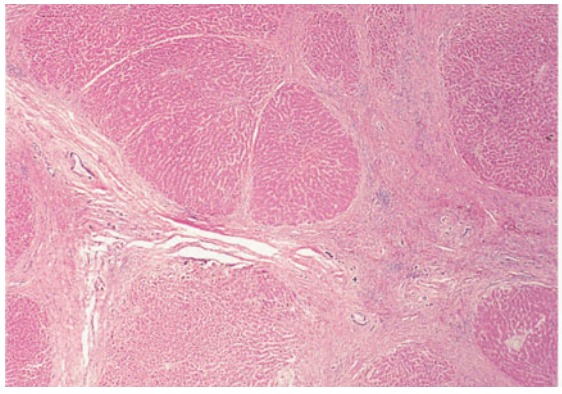
Color Image 26. Hemochromatosis with cirrhosis. Prussian blue iron stain shows hemosiderin in the liver parenchyma. Such deposition occurs throughout the body, causing organ damage and the characteristic darkening of the skin.*

Color Image 27. Metastatic carcinoma to the liver. The most common primary sites are the breast, colon, and lung. Primary tumors of the liver are less common than metastatic disease.*



Color Image 28. Fatty metamorphosis (macrovesicular steatosis) of the liver, microscopic. Early reversible change associated with alcohol consumption can be seen; there are abundant fat-filled vacuoles, but as yet there is no inflammation due to fibrosis of more serious alcoholic liver damage.*

A



B

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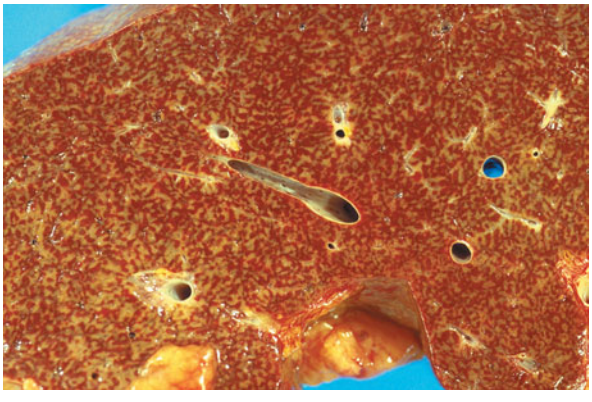
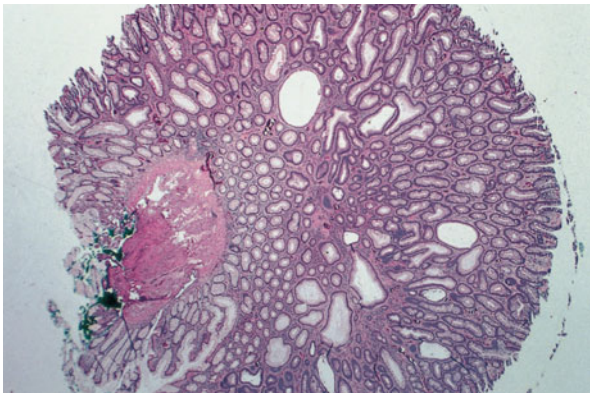
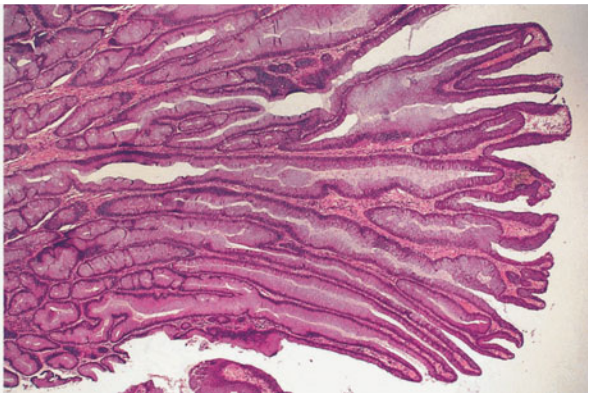


D

Color Image 29. Cirrhosis. (A) Micronodular cirrhosis of the liver, gross, from an alcoholic patient. The liver is approximately normal in size with a fine, granular appearance. Later stages of disease result in an irregularly shrunken liver with larger nodules, giving it a "hobnail" appearance. **(B) Cirrhosis,** microscopic. Regenerative lesions are surrounded by fibrotic bands of collagen ("bridging fibrosis"), forming the characteristic nodularity. **(C)** Gross natural color with macronodularity that is difficult to see. Hepatitis B surface antigen and core antigen negative. **(D)** Chronic passive biliary congestion gives the liver a "nutmeg" appearance.*

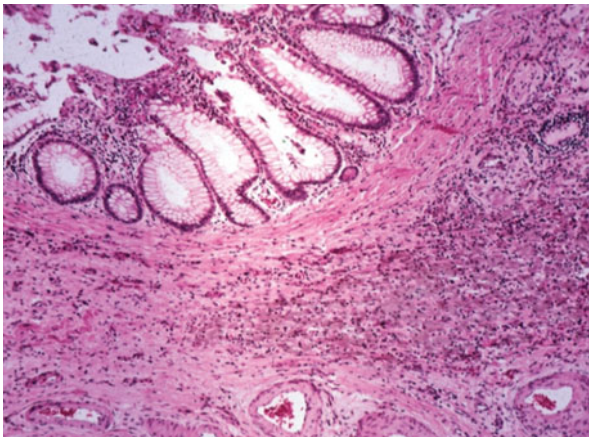


A

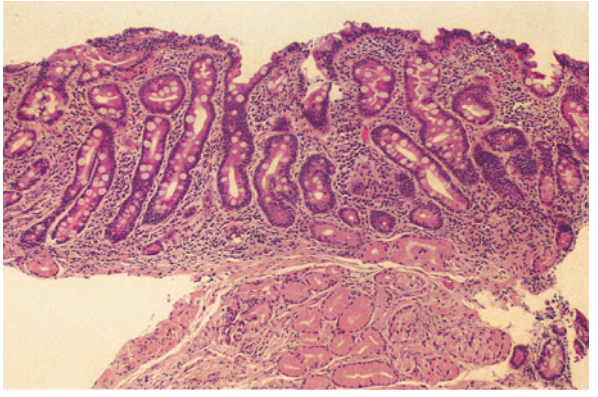


B

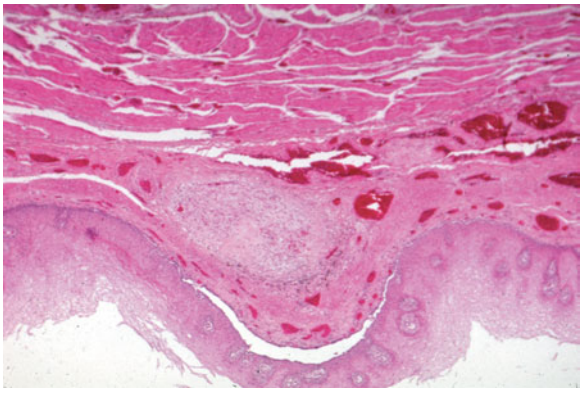
Color Image 30. Colonic polyps. Tubular adenomas (A) are smaller and rounded in morphology and have less malignant potential than do **villous adenomas (B),** which are composed of long, fingerlike projections.



Color Image 31. Diverticulitis. Inflammation of the diverticula typically causes LLQ pain and can progress to perforation, peritonitis, abscess formation, or bowel stenosis. Note the presence of macrophages. Gut lumen is seen at the top of the photo.*



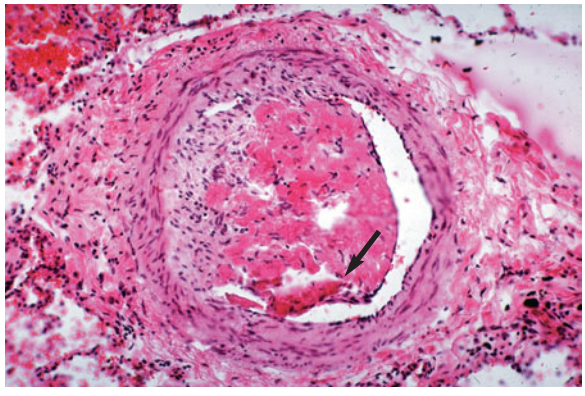
Color Image 32. Celiac sprue (gluten-sensitive enteropathy). Histology shows blunting of villi and crypt hyperplasia.



Color Image 33. Sclerosed **esophageal varix.** Overlying esophageal mucosa is generally normal.*

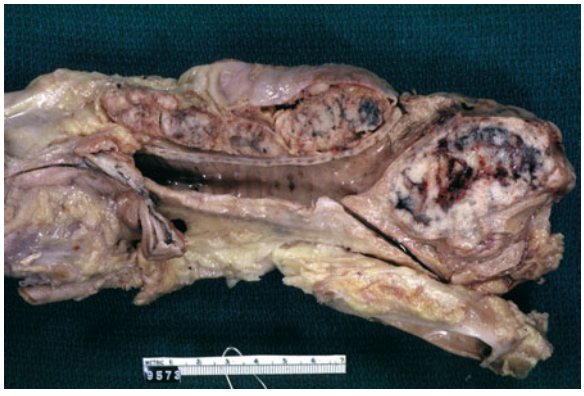
Color Image 34. Intussusception of infant gut, gross.*

A

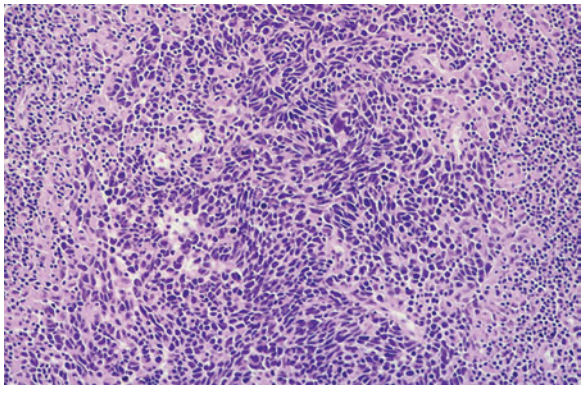


B

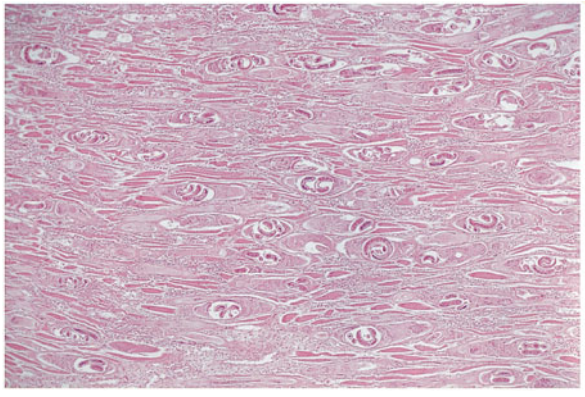
Color Image 35. Pulmonary emboli. (A) Pulmonary thromboembolus (arrow), gross. Most often arises from deep venous thrombosis. **(B) Pulmonary thromboembolus** in a small muscular pulmonary artery. The interdigitating areas of pale pink and red within the organizing embolus form the "lines of Zahn" (arrow) characteristic of a thrombus. These lines represent layers of red cells, platelets, and fibrin that are laid down in the vessel as the thrombus forms.*



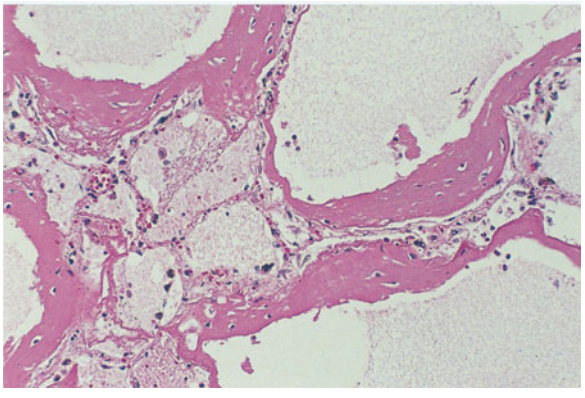
Color Image 36. Squamous cell carcinoma of the lung, gross, from a patient with a long smoking history. This tumor arises from the bronchial epithelium and is centrally located.*



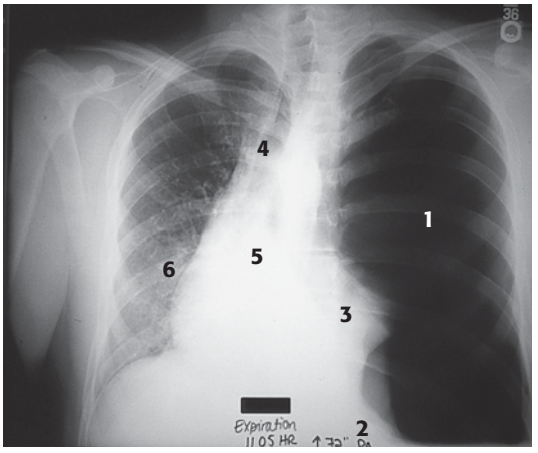
Color Image 37. Small (oat) cell carcinoma in a pulmonary hilar lymph node. Almost all of these tumors are related to tobacco smoking. They can arise anywhere in the lung, most often near the hilum, and quickly spread along the bronchi.*



Color Image 38. *Taenia solium*, the pig tapeworm, infesting porcine myocardium. When humans ingest this meat, the larvae attach to the wall of the small intestine and mature to adult worms.

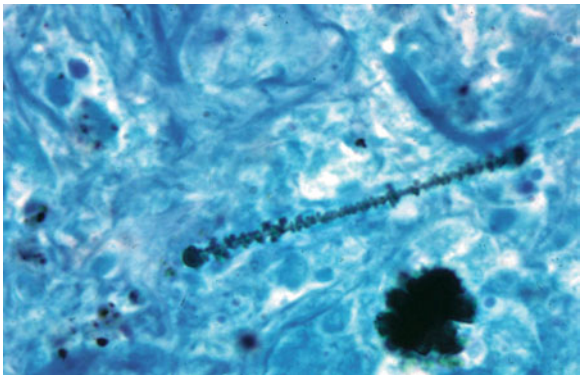


Color Image 39. Acute respiratory distress syndrome (ARDS). Persistent inflammation leads to poor pulmonary compliance and edema; note both alveolar fluid and hyaline membranes.

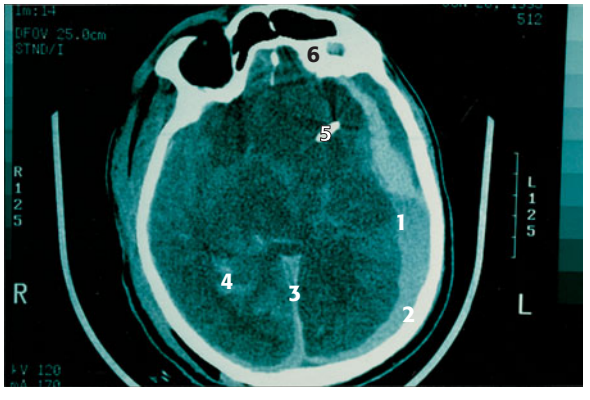


Color Image 40. Tension pneumothorax. Note these features:

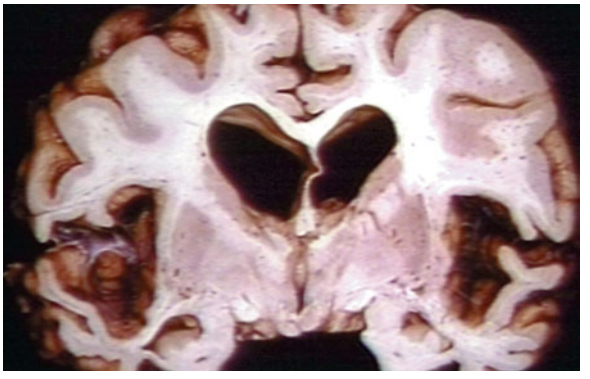
1—Hyperlucent lung field
2—Hyperexpansion lowers diaphragm
3—Collapsed lung
4—Deviation of trachea
5—Mediastinal shift
6—Compression of opposite lung



Color Image 42. Asbestosis. Ferruginous bodies (asbestos bodies with Prussian blue iron stain) in the lung, microscopic. Inhaled asbestos fibers are ingested by macrophages.*



Color Image 43. Subdural hemorrhage. Note the hyperdense extra-axial blood on the left side. Concomitant subarachnoid hemorrhage. 1—subdural blood, layering; 2—skull; 3—falx; 4—subarachnoid blood; 5—shunt catheter; 6—frontal sinus.



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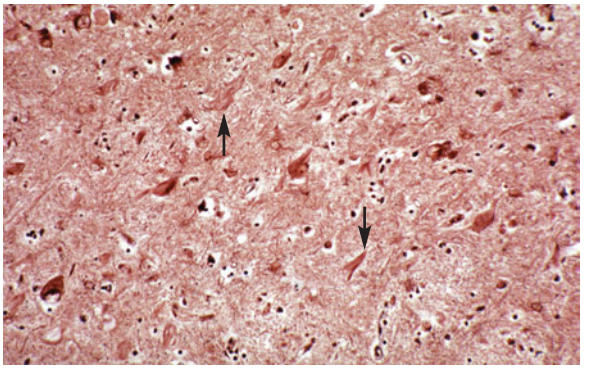

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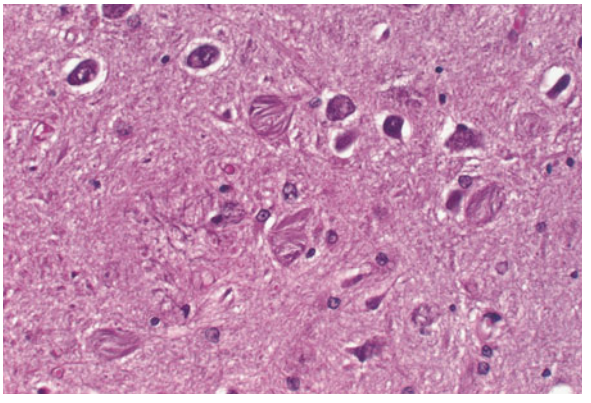
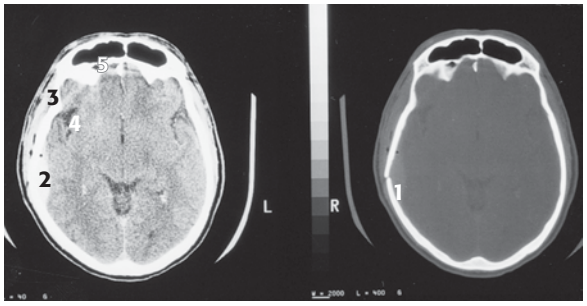
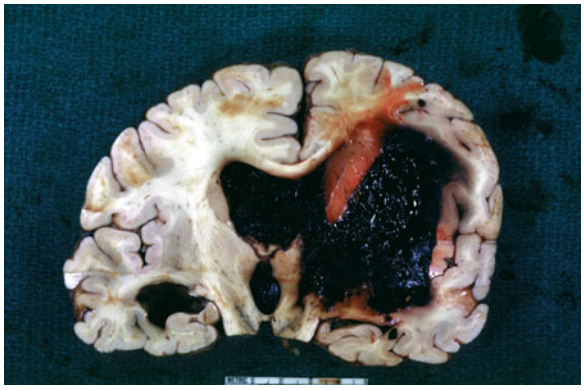


C

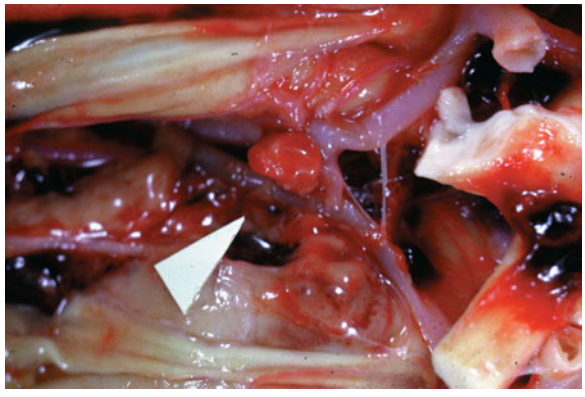
Color Image 41. Alzheimer's disease. Key histologic features include "senile plaques" **(A),** a coronal section showing atrophy, especially of the temporal lobes **(B),** and focal masses of interwoven neuronal processes around an amyloid core (neurofibrillary tangles, arrow). The remnants of neuronal degeneration **(C)** are also associated with Alzheimer's disease, the most common cause of dementia in older persons.*



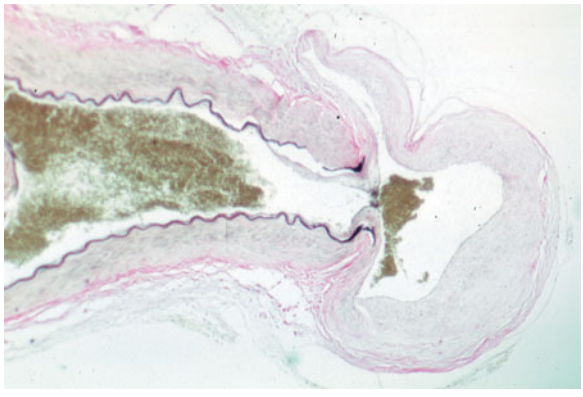
Color Image 44. Epidural hematoma from skull fracture. Note the lens-shaped (biconvex) dense blood next to the fracture. 1—skull fracture; 2—hematoma in epidural space; 3—temporalis muscle; 4—Sylvian fissure; 5—frontal sinus.



Color Image 45. Brain with **hypertensive hemorrhage** in the region of the basal ganglia, gross.*

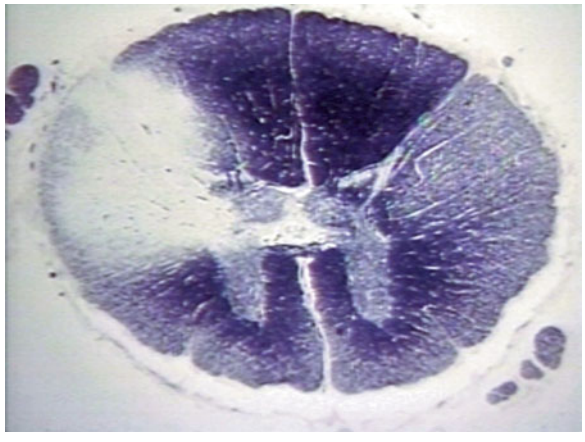


A



B

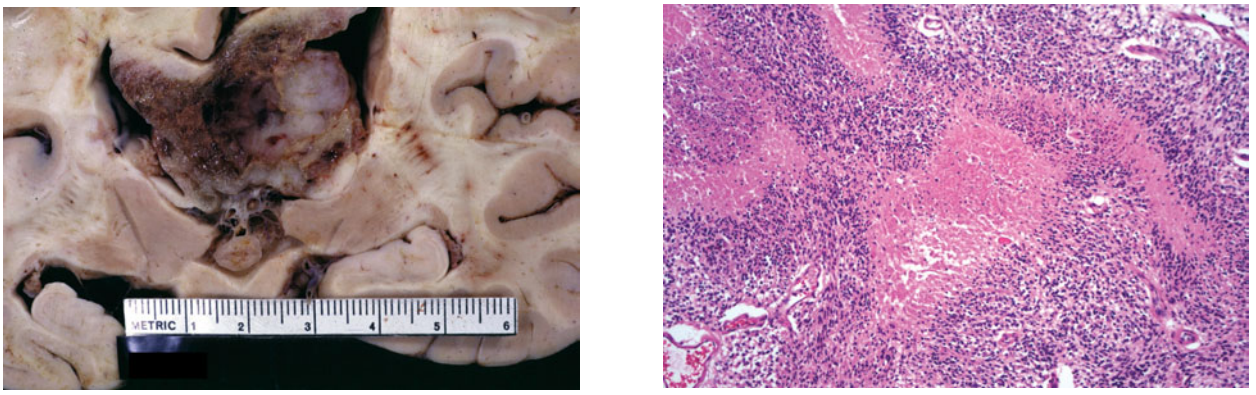
Color Image 46. Berry aneurysm (A) located on the anterior cerebral artery. The small, saclike structure can easily rupture during periods of hypertension or stress. The histologic section **(B)** at the origin of the aneurysm shows lack of internal elastic lamina.*



A

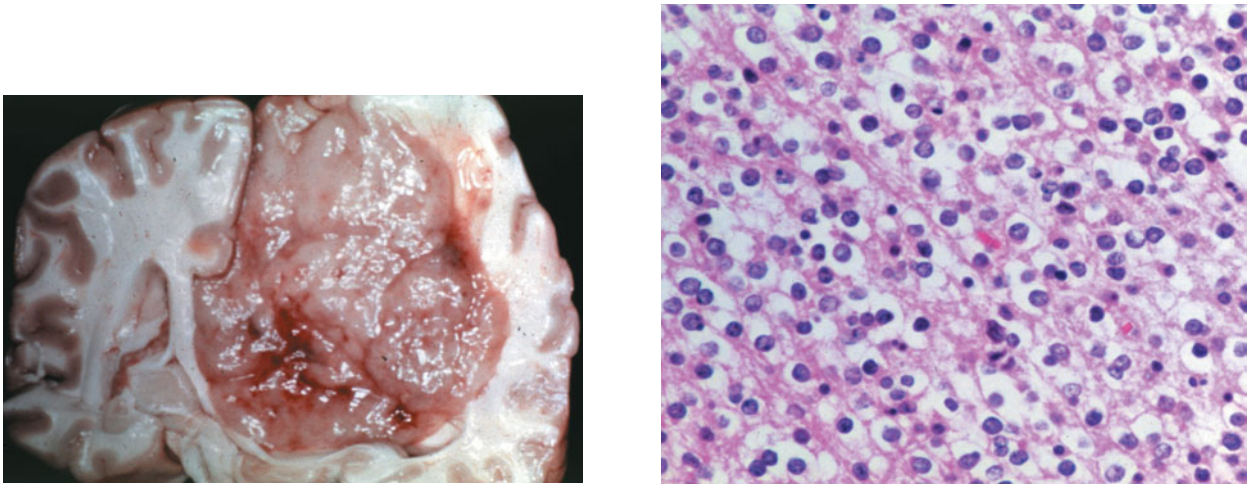
B

Color Image 47. Multiple sclerosis. (A) Lumbar spinal cord with mostly random and asymmetric white-matter lesions. **(B)** Brain with periventricular white-matter plaques of demyelination, gross. Demyelination occurs in a bilateral asymmetric distribution. Classic clinical findings are nystagmus, scanning speech, and intention tremor.*



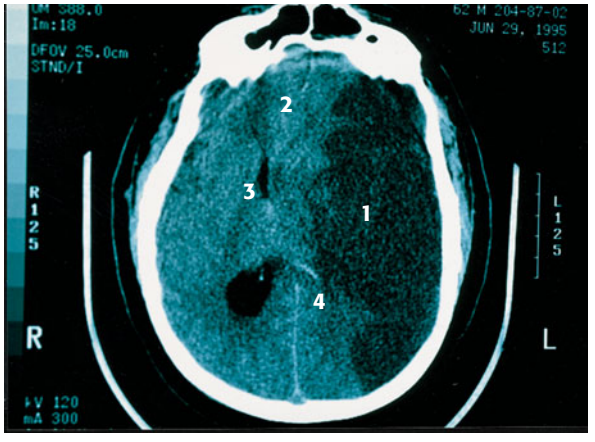
A B

Color Image 48. Glioblastoma multiforme (A) extending across the midline of the cerebral cortex, gross.* **(B)** Histology shows necrosis with surrounding pseudopalisading of malignant tumor cells. (Image B reproduced, with permission, from USMLERx.com.)

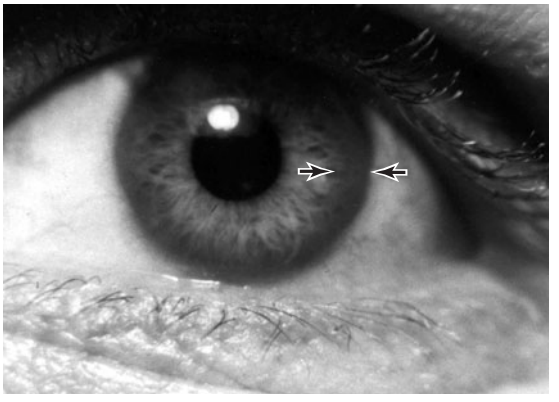


A B

Color Image 49. Oligodendroglioma. (A) Gross natural-color coronal section of cerebral hemisphere with a large lesion of the left parieto-occipital white matter. **(B)** Classic "fried egg" appearance with perinuclear halos and "chicken-wire" capillary pattern.*



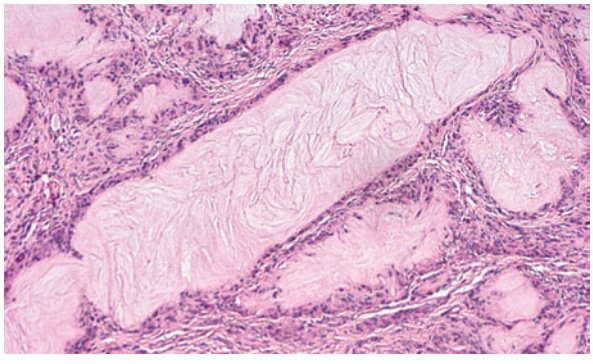
Color Image 50. Left middle cerebral artery stroke. Large left MCA territory stroke with edema and mass effect but no visible hemorrhage. The patient experienced deficits in speech and in the right side of the face and upper extremities. 1—ischemic brain parenchyma; 2—subtle midline shift to the right; 3—the right frontal horn of the lateral ventricle; 4—the left lateral ventricles obliterated by edema.



Color Image 51. Kayser-Fleischer ring in Wilson's disease. This corneal ring (between arrows) was golden brown and contrasted clearly against a gray-blue iris. Note that the darkness of the ring increases as the outer border (limbus) of the cornea is approached (right arrow). (Photo courtesy of Hoyt, WF.)

Color Image 52. Acute systemic lupus erythematosus. Bright red, sharply defined erythema is seen with slight edema and minimal scaling in a "butterfly pattern" on the face (the typical "malar rash"). Note also that the patient is female and young. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 385.)

Color Image 53. Scleroderma. The progressive "tightening" of the skin has contracted the fingers and eliminated creases over the knuckles. Fibrosis is widespread and may also involve the esophagus (dysphagia), lung (restrictive disease), and small vessels of the kidney (hypertension).



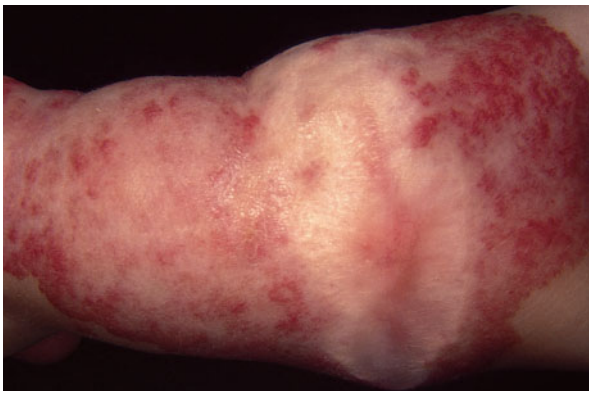
A

B

Color Image 54. Gout. (A) Tophi within joints consist of aggregates of urate crystals surrounded by an inflammatory reaction consisting of macrophages, lymphocytes, and giant cells. **(B)** Tophi affect the proximal interphalangeal (PIP) joints, knees, and elbows, growing like tubers from the bones.* (Image A reproduced, with permission, from USMLERx.com.)

Color Image 55. Erythema multiforme, captopril induced. Erythematous macules, papules, vesicles, bullae, and erosions are seen. (Reproduced, with permission, from Hurwitz RM et al. *Pathology of the Skin: Atlas of Clinical-Pathological Correlation*, 2nd ed. Stamford, CT: Appleton & Lange, 1998.)

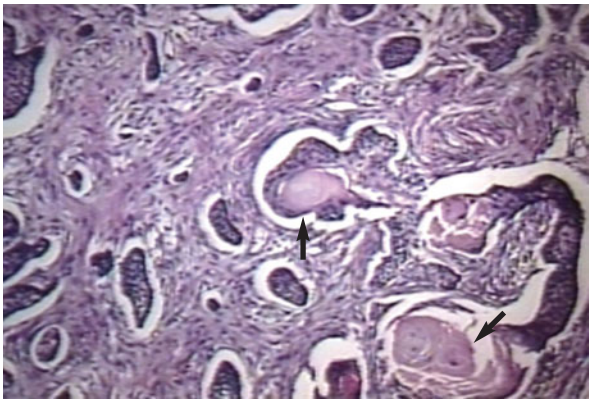
Color Image 56. Rheumatoid arthritis. Note the swan-neck deformities of the digits and severe, symmetric involvement of the PIP joints.



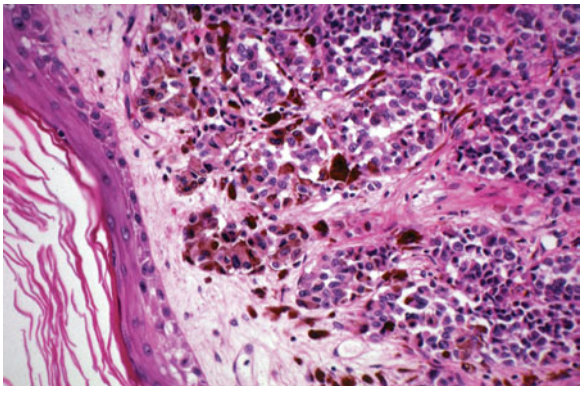
Color Image 57. Arteriovenous malformation. The markedly enlarged and distorted arm of a six-month-old boy with confluent erythematous papules and nodules. (Reproduced, with permission, from Hurwitz RM et al. *Pathology of the Skin: Atlas of Clinical-Pathological Correlation*, 2nd ed. Stamford, CT: Appleton & Lange, 1998.)

Color Image 58. Capillary malformation, port-wine type. Irregular purple patches and plaques are seen on the neck and chest of the mother, and pink patches are seen on the cheek, lip, chin, neck, and chest of the daughter. Both lesions were present at birth. (Reproduced, with permission, from Hurwitz RM et al. *Pathology of the Skin: Atlas of Clinical-Pathological Correlation*, 2nd ed. Stamford, CT: Appleton & Lange, 1998.)

Color Image 59. Scabies. Adult female mite with egg containing embryo within the epidermis. (Reproduced, with permission, from Hurwitz RM et al. *Pathology of the Skin: Atlas of Clinical-Pathological Correlation*, 2nd ed. Stamford, CT: Appleton & Lange, 1998.)



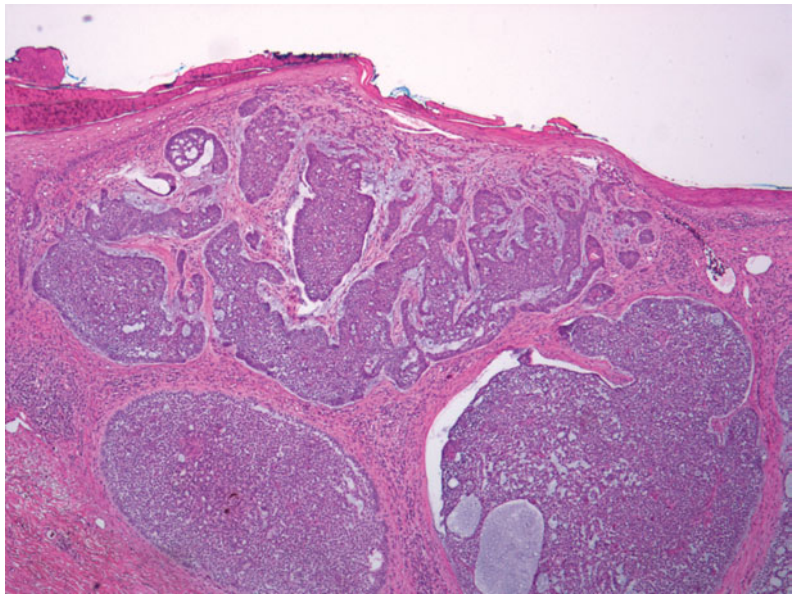
Color Image 60. Squamous cell carcinoma. Malignant skin tumor involving the epidermal skin layer. Note the presence of keratin pearls (arrows).*



A

B

Color Image 61. Malignant melanoma. (A) Lesion just beneath the epidermis with pigmented and nonpigmented cells. The tumor cells are usually polyhedral but may be spindle shaped, dendritic, or ballooned or may resemble oat cells. Many but by no means all melanomas make melanin. Large nucleoli are common.* **(B)** A multicolored tan, red, and dark brown irregular plaque on the abdomen. The depth of the lesion is a prognostic indicator. (Image B reproduced, with permission, from Hurwitz RM et al. *Pathology of the Skin: Atlas of Clinical-Pathological Correlation*, 2nd ed. Stamford, CT: Appleton & Lange, 1998.)



Color Image 62. Basal cell carcinoma. Nests of basaloid cells are present within the dermis with peripheral palisading and prominent retraction artifacts. (Reproduced, with permission, from USMLERx.com.)

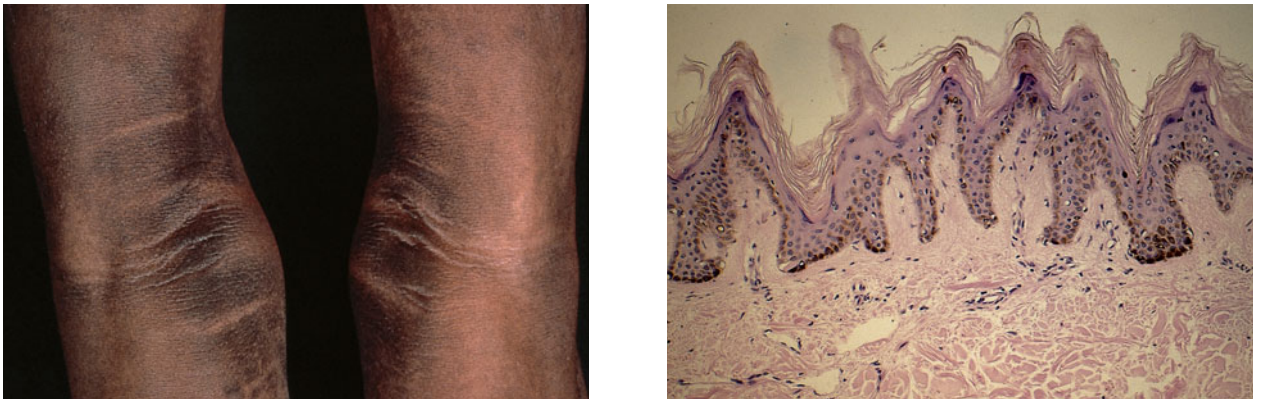
A

B

Color Image 63. Pemphigus vulgaris. (A) Numerous crusted, denuded, and weepy erythematous plaques are seen on the chest, breast, abdomen, and arms. **(B)** Vesicles on the gingiva. (Reproduced, with permission, from Hurwitz RM et al. *Pathology of the Skin: Atlas of Clinical-Pathological Correlation*, 2nd ed. Stamford, CT: Appleton & Lange, 1998.)

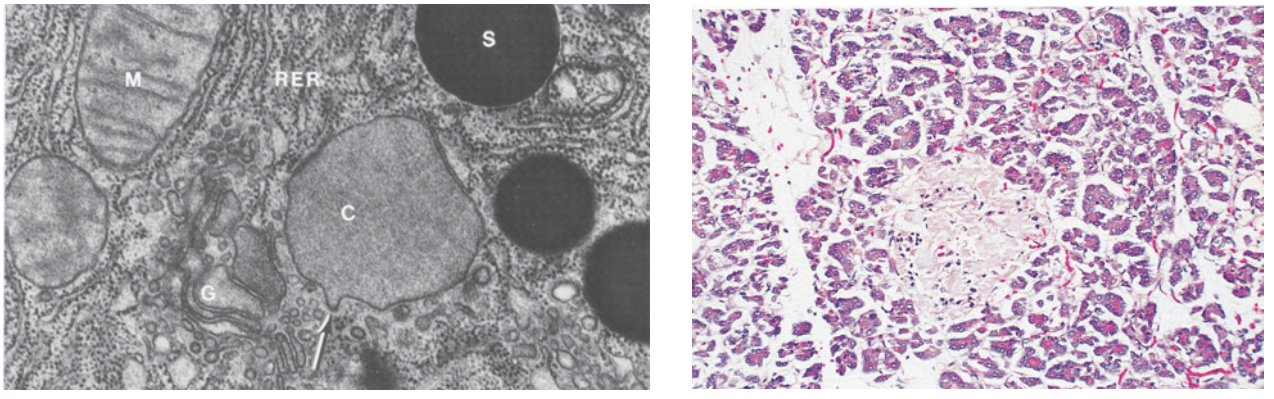
Color Image 64. Bullous pemphigoid. Erythematous plaques contiguous with large bullae. (Reproduced, with permission, from Hurwitz RM et al. *Pathology of the Skin: Atlas of Clinical-Pathological Correlation*, 2nd ed. Stamford, CT: Appleton & Lange, 1998.)

Color Image 65. Psoriasis, fully developed plaque. (Reproduced, with permission, from Hurwitz RM et al. *Pathology of the Skin: Atlas of Clinical-Pathological Correlation*, 2nd ed. Stamford, CT: Appleton & Lange, 1998.)



A **B**

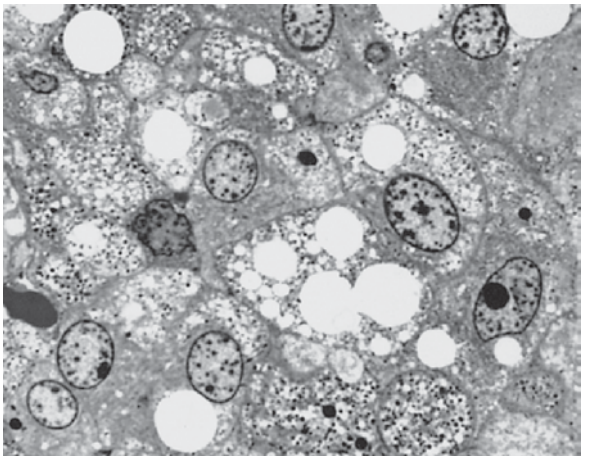
Color Image 66. Acanthosis nigricans. (A) Extensive hyperpigmented plaques on the arms in a patient with congenital lipodystrophy. This is an unusual distribution for acanthosis nigricans. **(B)** Hyperkeratosis and papillomatosis. (Reproduced, with permission, from Hurwitz RM et al. *Pathology of the Skin: Atlas of Clinical-Pathological Correlation*, 2nd ed. Stamford, CT: Appleton & Lange, 1998.)



A **B**

Color Image 67. Pancreas. (A) Pancreatic acinar cell (EM). A condensing vacuole (C) is receiving secretory product (arrow) from the Golgi complex (G). M—mitochondrion; RER—rough endoplasmic reticulum; S—mature condensed secretory zymogen granules. **(B)** Pancreatic islet cells in **diabetes mellitus type 1.** In patients with diabetes mellitus type 1, autoantibodies against β cells cause a chronic inflammation until, over time, islet cells are entirely replaced by amyloid.

Color Image 68. Adrenocortical adenoma, gross. Cause of hypercortisolism (Cushing's syndrome) or hyperaldosteronism (Conn's syndrome).*

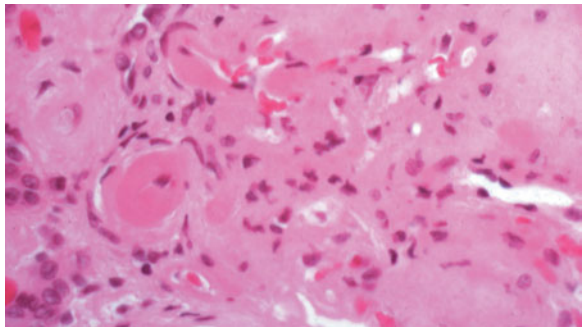


Color Image 69. Pheochromocytoma. The tumor cells have numerous vacuolar spaces within the cytoplasm (pseudoacini). Most of the punctate blue-black granules of variable density are dense-core neurosecretory granules.*

A

B

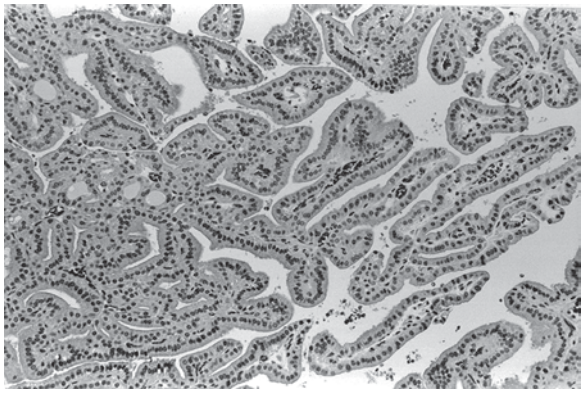
Color Image 70. Cushing's disease. The clinical picture includes (**A**) moon facies and buffalo hump and (**B**) truncal obesity and abdominal striae.



Color Image 72. Arteriolar sclerosis showing masses of hyaline material in glomerular afferent and efferent arterioles and in the glomerulus. From a type 1 diabetic patient.*

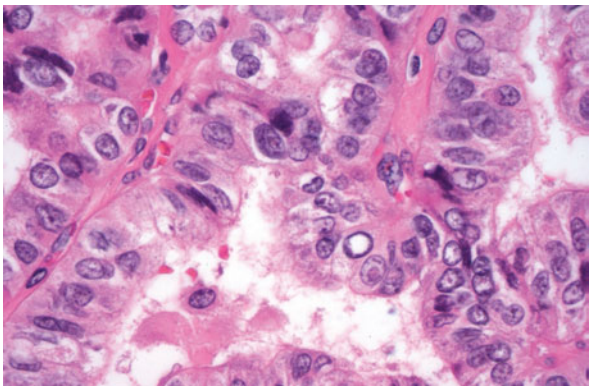
A

B

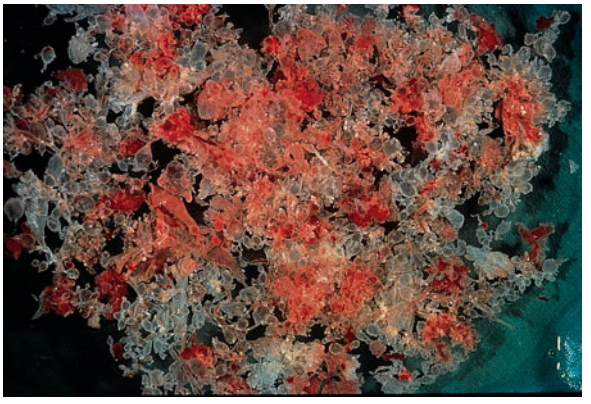


C

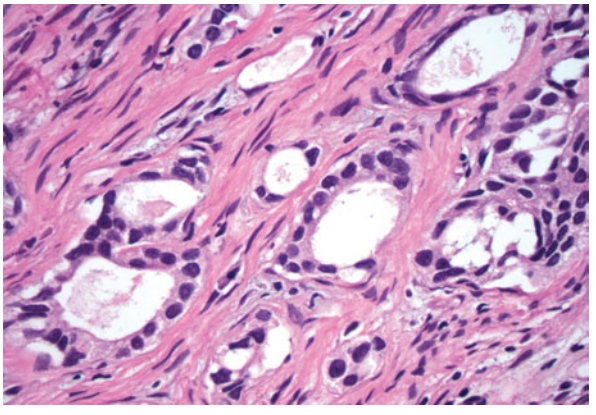
Color Image 71. Graves' disease. (**A**) Exophthalmos in a patient with proptosis and periorbital edema. (**B**) CT shows extraocular muscle enlargement at the orbital apex. (**C**) Stimulation of follicular cells by TSH causes the normal uniform architecture to be replaced by hyperplastic papillary, involuted borders, and decreased colloid. Typical medical therapy is propylthiouracil, which inhibits the production of thyroid hormone as well as peripheral conversion of T_4 to T_3.*



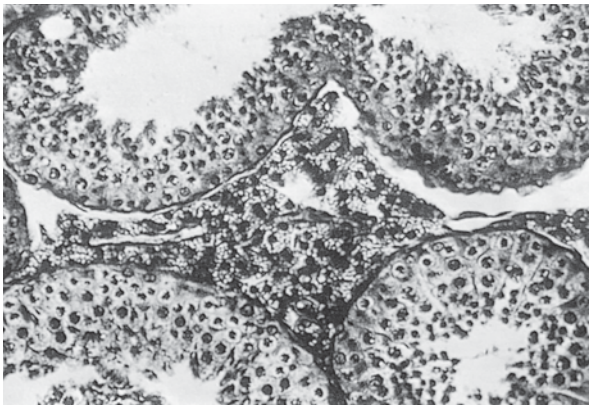
Color Image 73. Papillary carcinoma. The image shows the papillary architecture and classic nuclear features that are key in making the diagnosis, including ground-glass or "Orphan Annie eye" chromatin, nuclear grooves, and intranuclear pseudoinclusions. Psammoma bodies are not seen here but are often present. (Reproduced, with permission, from USMLERx.com.)



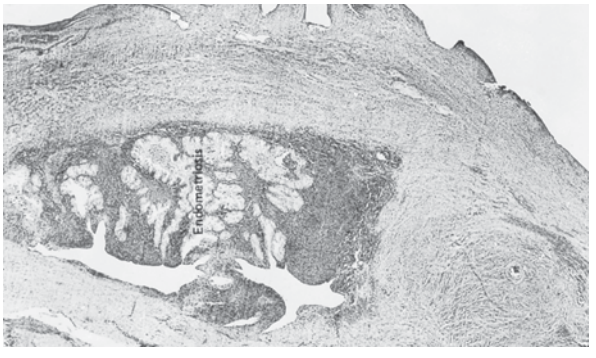
Color Image 74. Hydatidiform mole. The characteristic gross appearance is a "bunch of grapes." Hydatidiform moles are the most common precursors of choriocarcinoma. Complete moles usually display a 46,XX diploid pattern with all the chromosomes derived from the sperm. In partial moles, the karyotype is triploid or tetraploid, and fetal parts may be present.



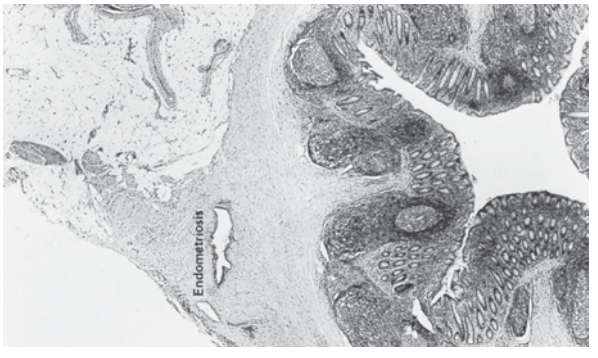
Color Image 75. Prostatic adenocarcinoma. Histology shows infiltrating glands lined by a single layer of cuboidal epithelium with enlarged nuclei and visible nucleoli. Note the absence of the outer basal layer that is usually present in normal glands. (Reproduced, with permission, from USMLERx.com.)



Color Image 76. Seminiferous tubules. Sertoli cells play a supportive and protective role in spermatogenesis. Note cells in various stages of differentiation, with spermatogonia near the basal lamina and more mature forms near the lumen.

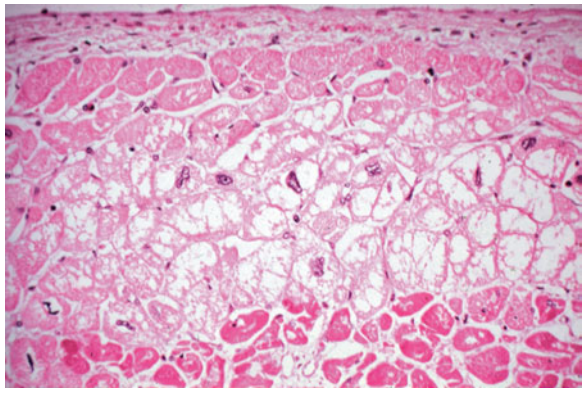


A

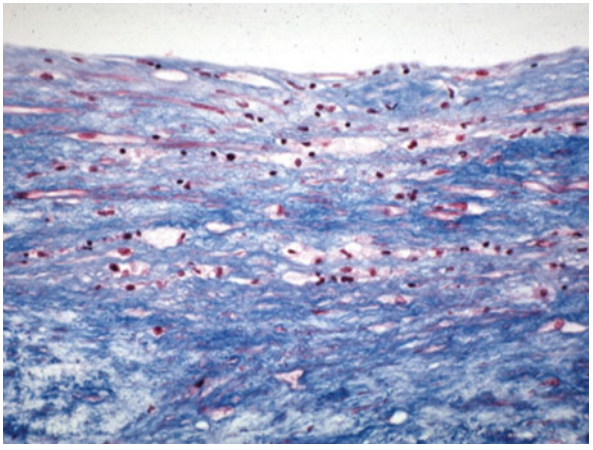


B

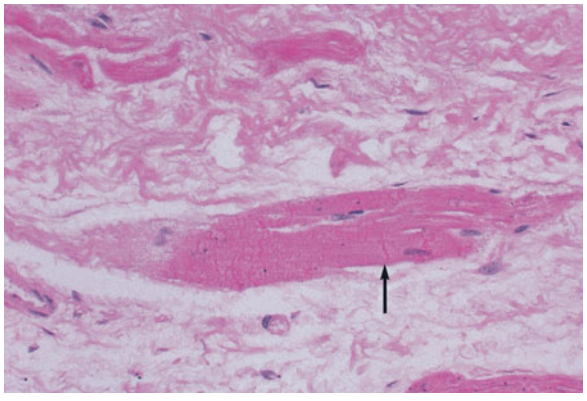
Color Image 77. Histologic appearance of endometriosis. (A) Endometriosis of the ovary. **(B)** Endometriosis of the cervix. (Reproduced, with permission, from DeCherney AH. *Current Obstetric and Gynecologic Diagnosis and Treatment*, 9th ed. New York: McGraw-Hill, 2003.)



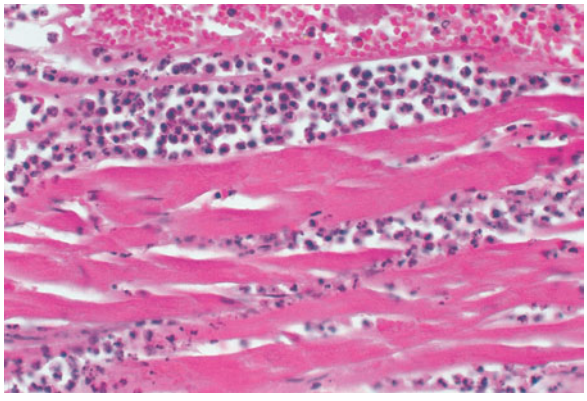
Color Image 78. Endocardial chronic ischemia. Microscopic example of myocytolysis and coagulation necrosis beneath the endocardium.*



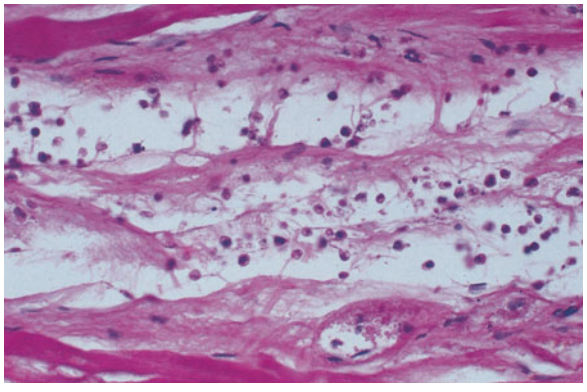
Color Image 79. Atherosclerosis. Aorta with fibrous intimal thickening and foam cells dispersed throughout smooth muscle cells, micro.*



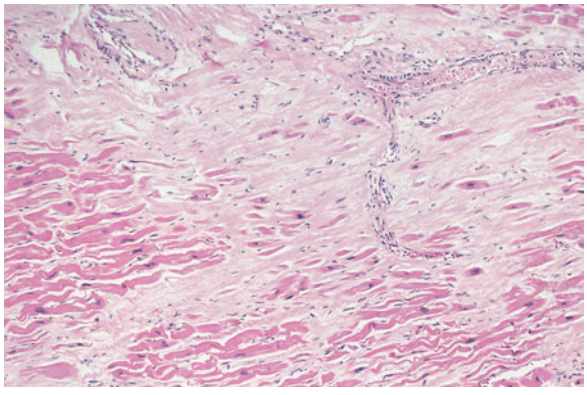
A



B

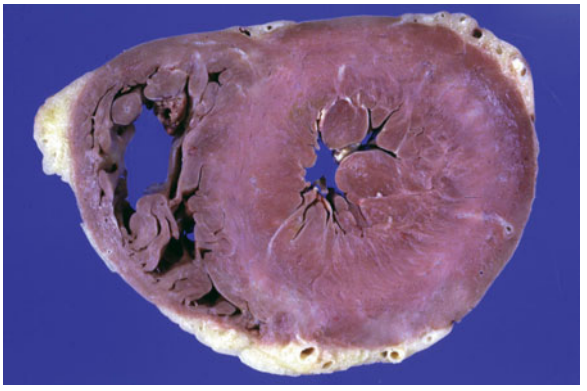


C

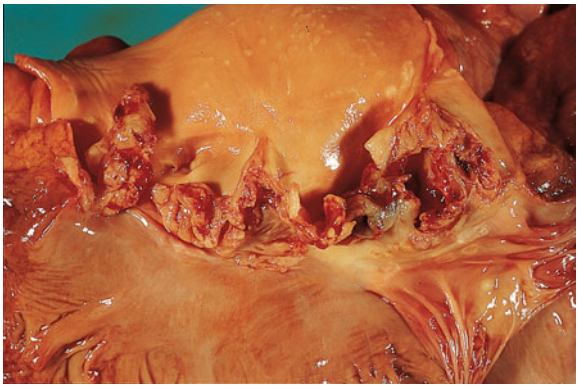


D

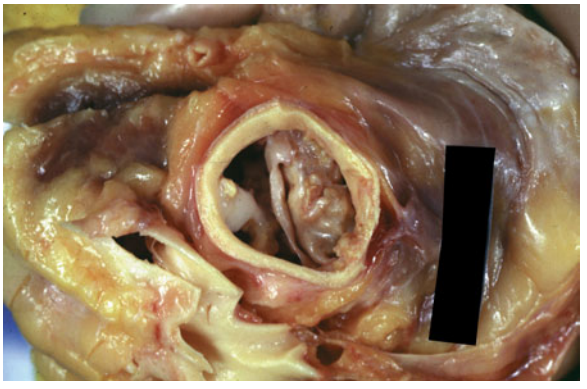
Color Image 80. Evolution of a myocardial infarction. Contraction band necrosis (arrow) is the first visible change, occurring in one to two hours (**A**). In the first three days, neutrophilic infiltration and coagulation necrosis occur (**B**). By three to seven days, neutrophils have been replaced by macrophages, and clearing of myocyte debris has begun (**C**). Within weeks, granulation and scarring occur (**D**).



Color Image 81. Heart with marked concentric **left ventricular hypertrophy** from hypertension, gross.*

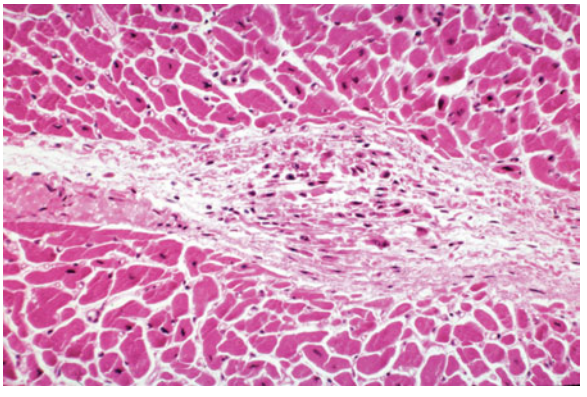


Color Image 82. Acute bacterial endocarditis. Virulent organisms (e.g., *Staphylococcus aureus*) infect previously normal valves, causing marked damage (here, in the aortic valve) and potentially giving rise to septic emboli.

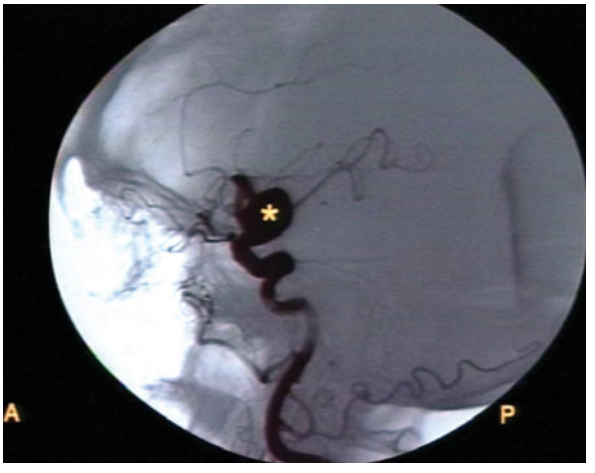


Color Image 83. Calcified **bicuspid aortic valve** showing false raphe. The abnormal architecture of the valve makes its leaflets susceptible to otherwise ordinary hemodynamic stresses, which ultimately leads to valvular thickening, calcification, increased rigidity, and stenosis.*

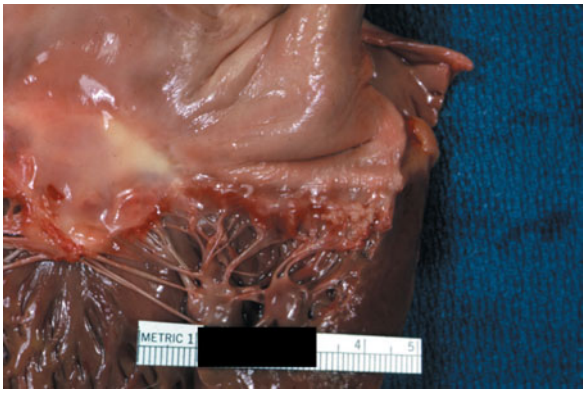
Color Image 84. Aortic dissection with a blood clot compressing the aortic lumen. A tear in the intima allowed blood to surge through the muscular layer to the adventitia (may lead to sudden death from hemothorax). Risk factors are hypertension, Marfan's syndrome, pregnancy, Ehlers-Danlos syndrome, and trauma.*



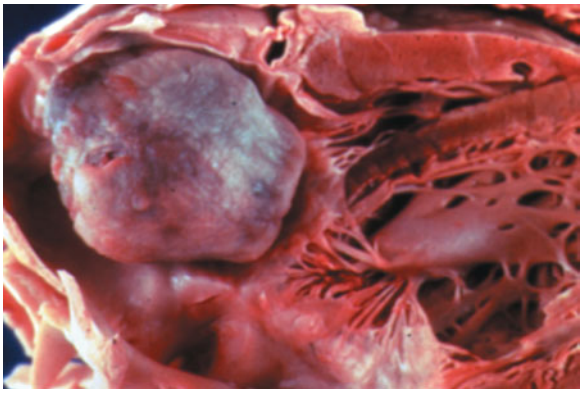
Color Image 85. The **Aschoff body,** an area of fibrinoid necrosis surrounded by mononuclear and multinucleated giant cells, is pathognomonic for **rheumatic heart disease.** The mitral valve is most commonly affected.*



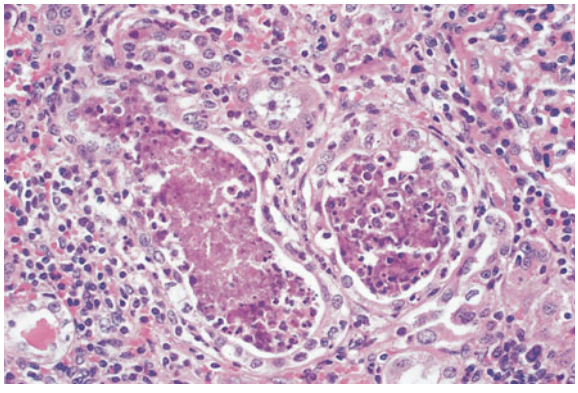
Color Image 86. Carotid angiogram showing aneurysm. Note the path of the internal carotid artery through the neck and its major branches (ophthalmic artery, anterior cerebral artery, middle cerebral artery). The aneurysm is inferior to the terminal branches in this angiogram.*



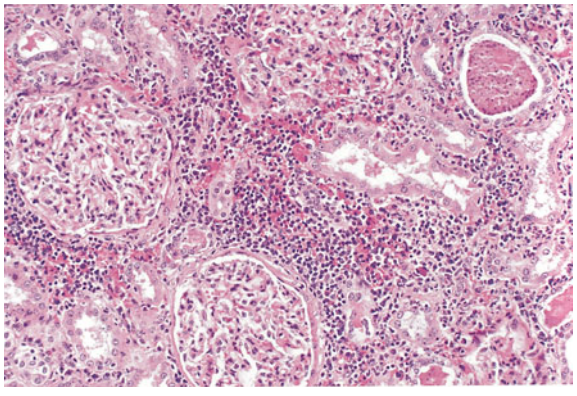
Color Image 87. Bacterial endocarditis of the mitral valve. Vegetations can embolize and infect distant organ systems.*



Color Image 88. Left atrial myxoma. The most common primary cardiac tumor; known to produce VEGF (vascular endothelial growth factor).*

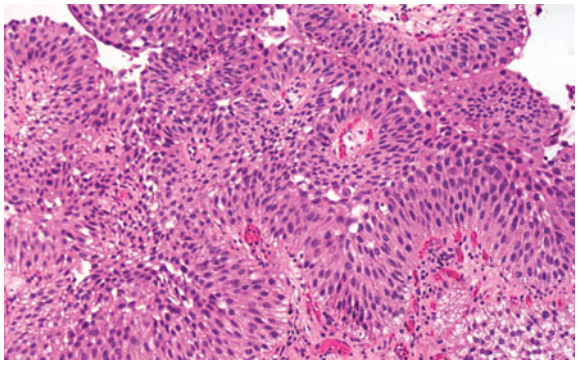


A



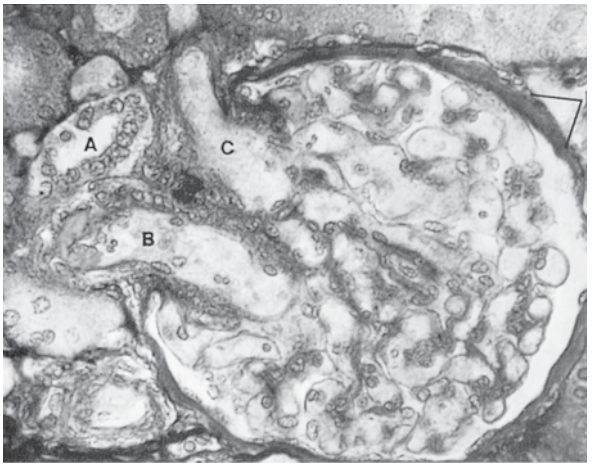
B

Color Image 89. Acute pyelonephritis (A) is characterized by neutrophilic infiltration and abscess formation within the renal interstitium. Abscesses may rupture, introducing collections of white cells to the tubular lumen. In contrast, **chronic pyelonephritis (B)** has a lymphocytic invasion with fibrosis.

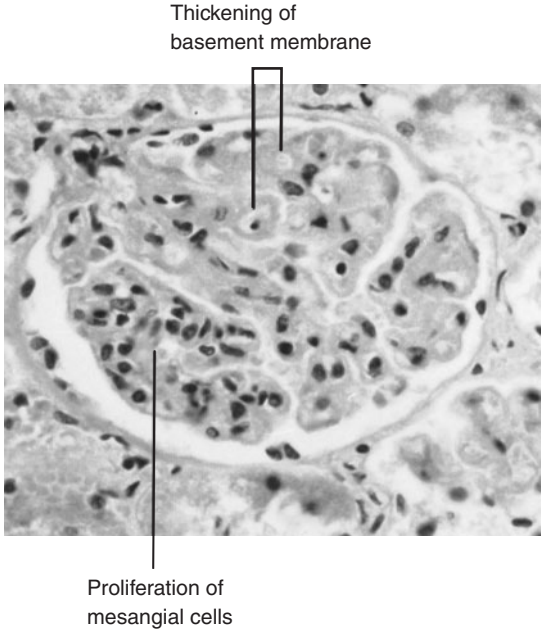


Color Image 90. Transitional cell carcinoma. The image shows a papillary growth lined by transitional epithelium with mild nuclear atypia and pleomorphism. (Reproduced, with permission, from USMLERx.com.)

Color Image 91. Lupus erythematosus, kidneys. Enlarged, very pale kidneys with "flea bite" or ectasia from a patient with nephrotic syndrome or subacute glomerulonephritis as a result of lupus erythematosus.*

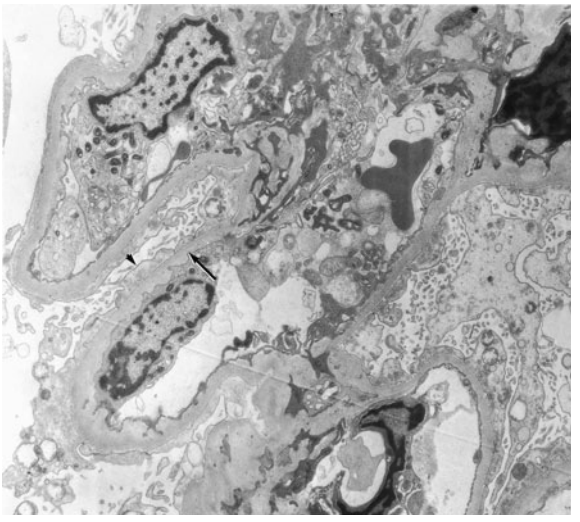


Color Image 92. Normal glomerulus, microscopic, with (**A**) macula densa and (**B**) afferent and (**C**) efferent arterioles.

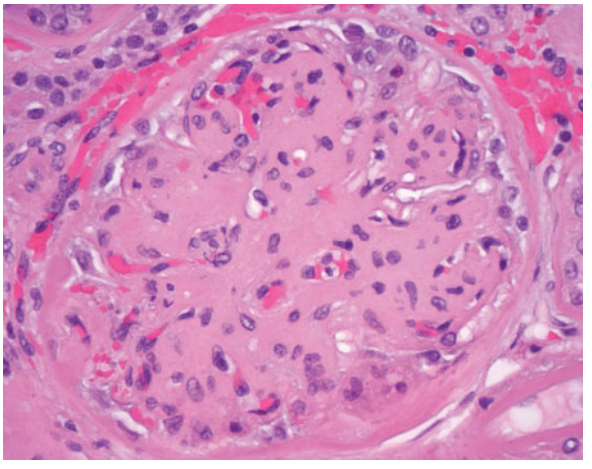


Color Image 94. Systemic lupus erythematosus, kidney pathology. In the membranous glomerulonephritic pattern, "wire-loop" thickening occurs as a result of subendothelial immune complex deposition.

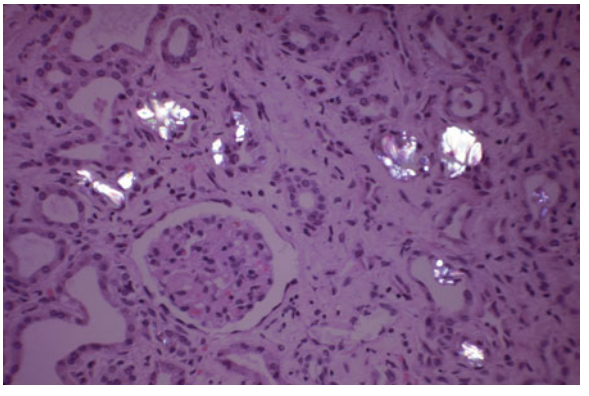
Color Image 96. Polycystic kidney disease. Abdominal CT shows multiple cysts in both kidneys. PKD is an autosomal-dominant disease and is often associated with aneurysm formation in the brain. The disease occurs bilaterally and presents with flank pain and hematuria.*



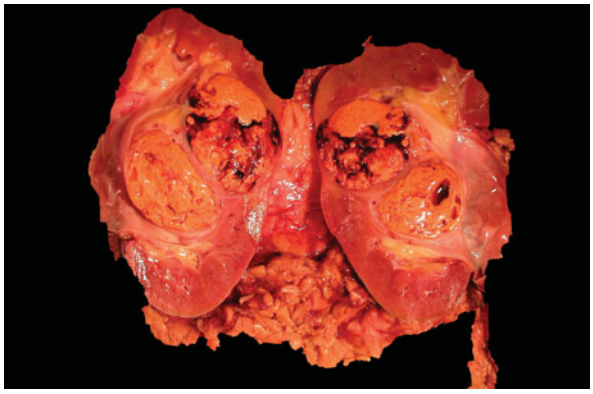
Color Image 93. Minimal change disease (lipoid nephrosis) shows normal glomeruli on light microscopy but effacement of foot processes on EM (arrowhead). The full arrow points to a normal foot process. Treatment consists of corticosteroids.



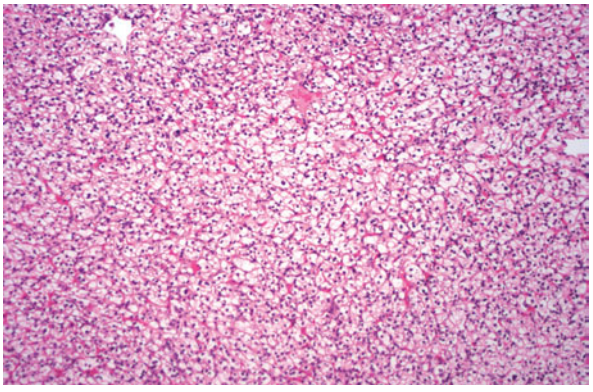
Color Image 95. Diabetic glomerulosclerosis. Nodular diabetic glomerulosclerosis is also known as Kimmelstiel-Wilson syndrome and is characterized by acellular ovoid nodules in the periphery of the glomerulus. (Reproduced, with permission, from USMLERx.com.)



Color Image 97. Calcium oxalate crystals in the kidney, viewed with partially crossed polarizers. Tubular failure in oxalate nephropathy can result from vitamin C or antifreeze abuse.*

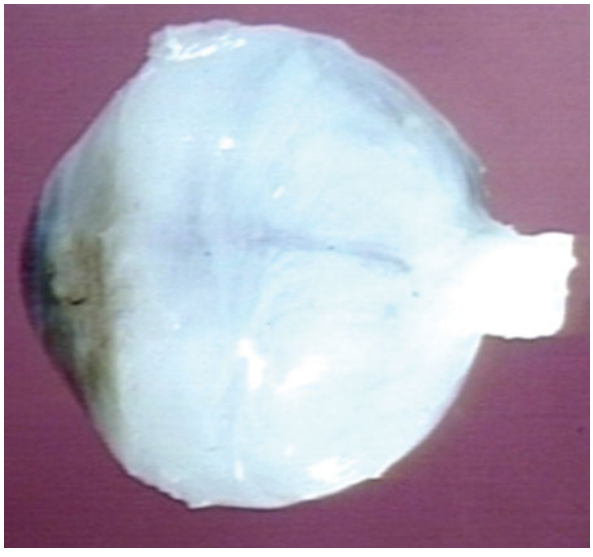


A



B

Color Image 98. Renal cell carcinoma. (**A**) Gross. The kidney has been bivalved, revealing a nodular, golden-yellow tumor in the midkidney with areas of hemorrhage and necrosis. (**B**) Histology shows polygonal cells with small nuclei and abundant clear cytoplasm with a rich, delicate branching vasculature. (Reproduced, with permission, from USMLERx.com.)

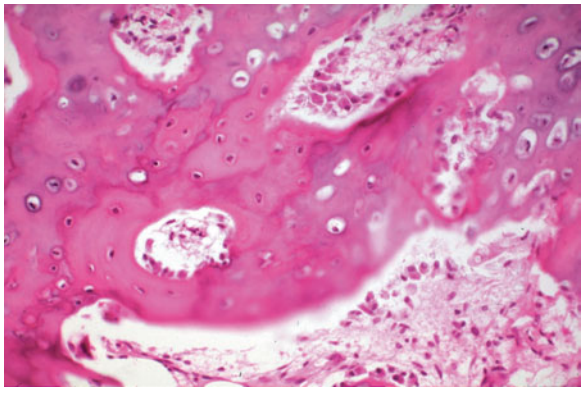


A

B

Color Image 99. Osteogenesis imperfecta. (**A**) Blue sclera caused by translucency of connective tissue over the choroid. The optic nerve is on the right side of the image. (**B**) Abnormal collagen synthesis results from a variety of gene mutations and causes brittle bones and connective tissue malformations.*

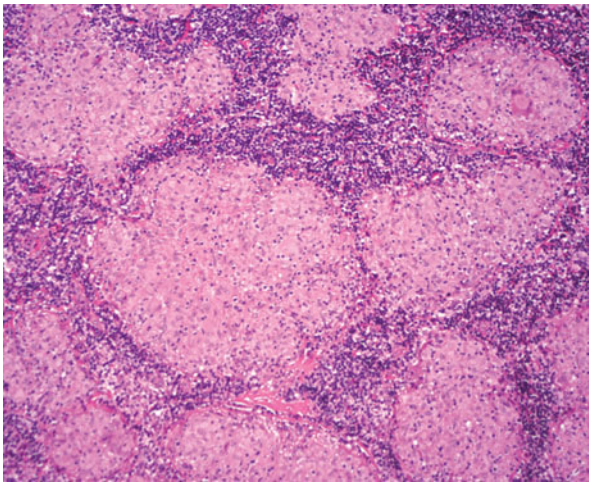
Color Image 100. Foot gangrene. The first four toes and adjacent skin are dry, shrunken, and blackened with superficial necrosis and peeling of the skin. A well-defined line of demarcation separates the black region from the viable skin.*



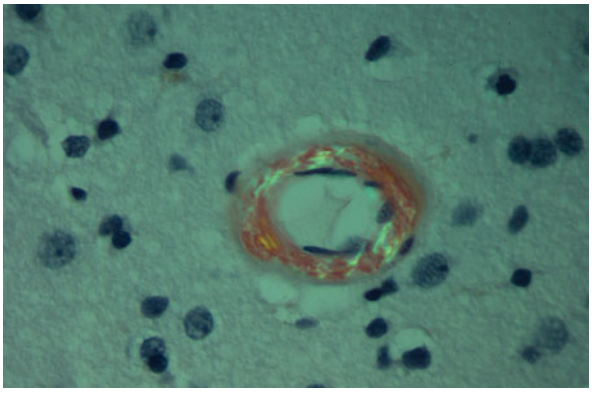
Color Image 101. Bone fracture. New bone formation with osteoblasts.*

Color Image 102. Meningomyelocele. A neural tube defect in which the meninges and spinal cord herniate through the spinal canal; gross image of infant's lower back.*

Color Image 103. Omphalocele in a newborn. Note that the defect is midline and is covered by peritoneum, as opposed to gastroschisis, which is not covered by peritoneum and is often not midline.*

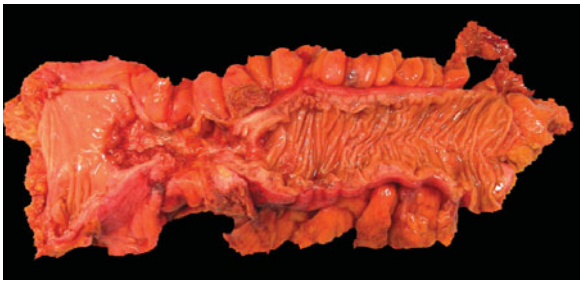


Color Image 104. Sarcoidosis. Numerous tightly formed granulomas are seen on histology of a lymph node in a patient with sarcoidosis. (Reproduced, with permission, from USMLERx.com.)



Color Image 105. Amyloidosis. Congo red stain demonstrates amyloid deposits in the artery wall that show apple-green birefringence under polarized light. (Reproduced, with permission, from USMLERx.com.)

Color Image 106. Raynaud's disease. The left hand exhibits a distal cyanosis compared to the right hand; it is seen especially well in the nail beds. Unilateral episodes such as this one may occur after contact with a cold object. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 403.)



Color Image 107. Colon cancer. Note the circumferential tumor with heaped-up edges and central ulceration. (Reproduced, with permission, from USMLERx.com.)

Image 108. Klinefelter's syndrome (XXY). Phenotype includes a female fat distribution with male external genitalia.

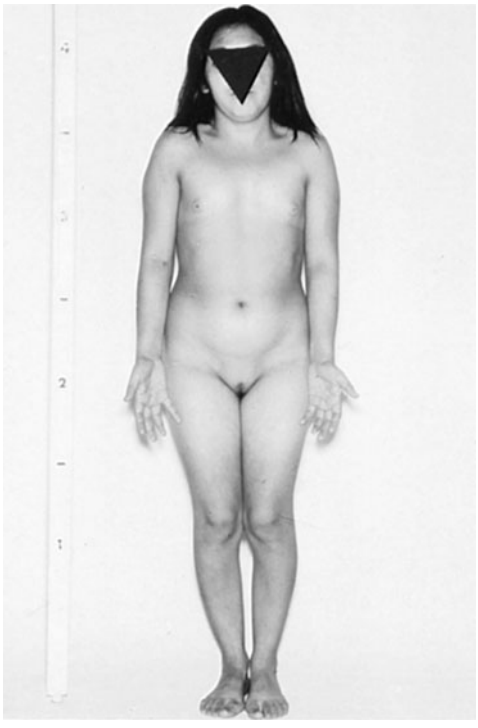


Image 109. Turner's syndrome (XO). Phenotype includes short stature, webbing of the neck, and poorly developed secondary sex characteristics.

Image 110. Marfan's syndrome. Patients are tall with very long extremities. The joints are hyperextensible, with slim bone structure and wiry muscles.*

Image 111. Simian crease. A characteristic feature of Down syndrome (trisomy 21). The palm has a single transverse crease instead of the normal two creases.*

Image 112. Hydatid cyst. Echinococcus eggs develop into larvae in the intestine, penetrate the intestinal wall, and disseminate throughout the body. The larvae form hydatid cysts in the liver and, less commonly, in the lungs, kidney, and brain. (Reproduced, with permission, from USMLERx.com.)

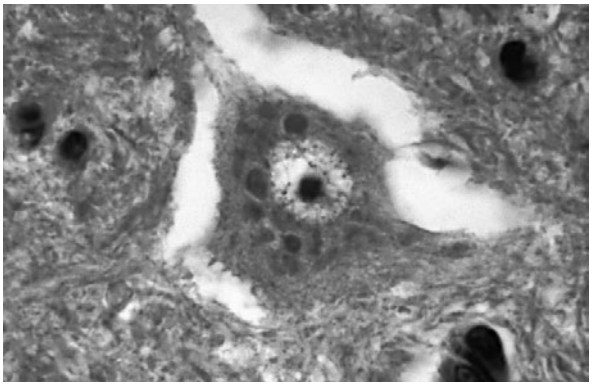


Image 113. Negri bodies are pathognomonic inclusions in the cytoplasm of neurons infected by the rabies virus. (Reproduced, with permission, from the Centers for Disease Control and Prevention, Atlanta, GA.)

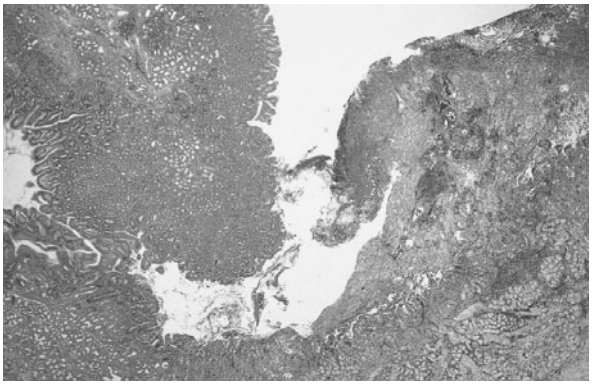


Image 114. Duodenal ulcer. The epithelium is ulcerated, and the lamina propria is infiltrated with inflammatory cells. Necrotic debris is present in the ulcer crater.

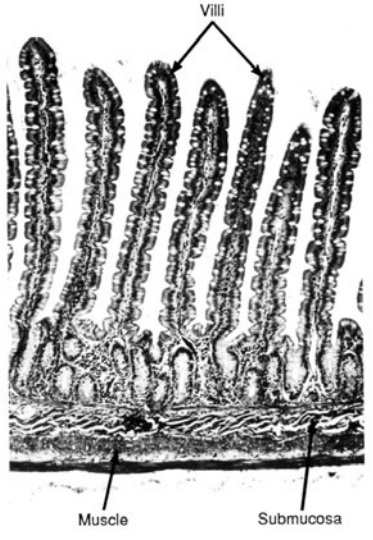


Image 116. Photomicrograph of the **small intestine.**

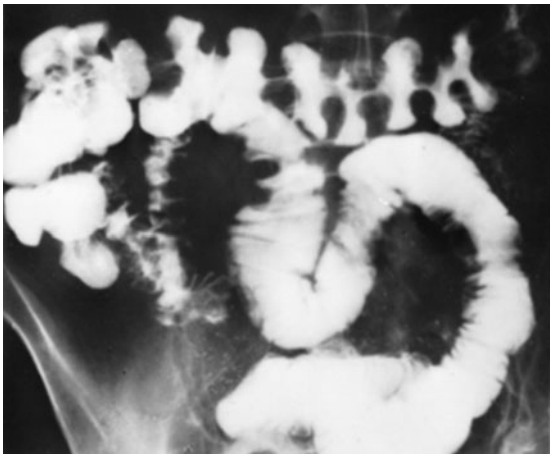


Image 118. Crohn's disease. Barium x-ray showing spicules, edema, and ulcers. (Reproduced, with permission, from Le T et al. *First Aid for the Wards,* 3rd ed. New York: McGraw-Hill, 2006: 399.)

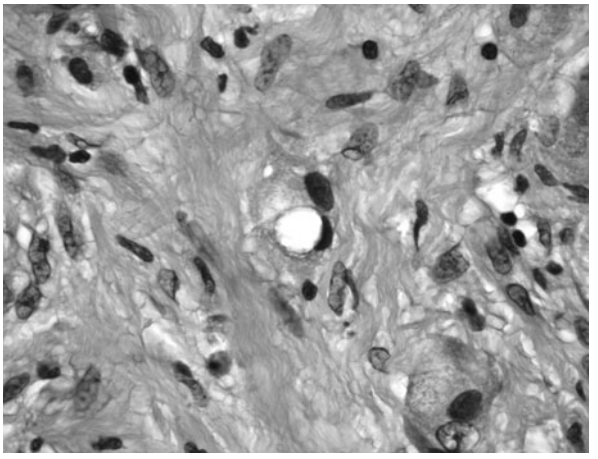


Image 115. Signet ring cell. Mucin expands the cytoplasm and pushes the nucleus to the periphery, creating the appearance of a signet ring. The diffuse type of gastric carcinoma is composed of widely infiltrative signet ring cells. (Reproduced, with permission, from USMLERx.com.)

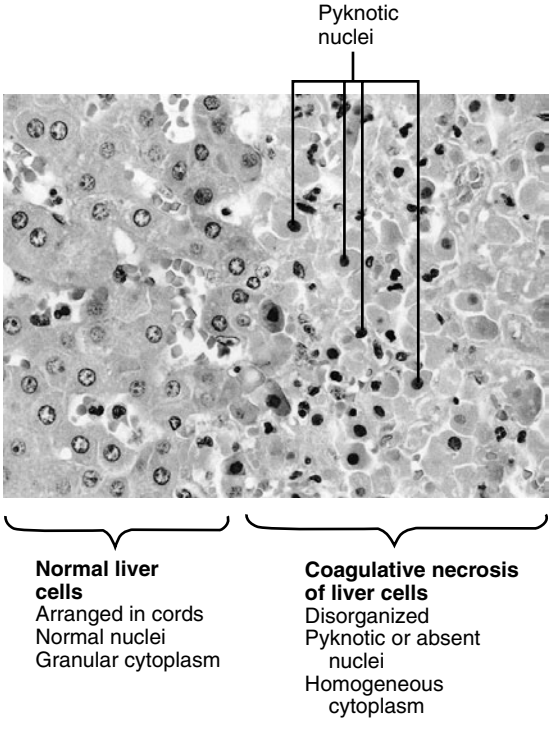
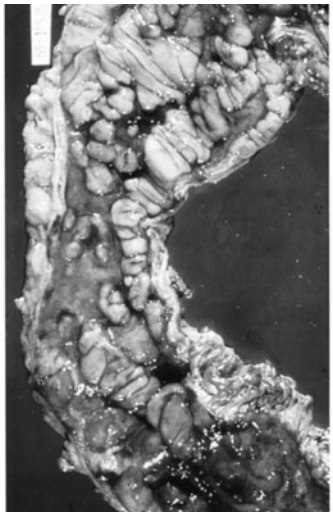
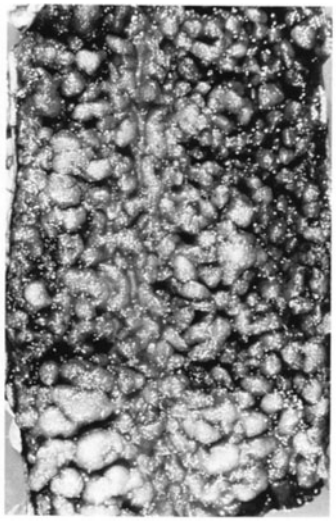


Image 117. Coagulative necrosis of hepatocytes.



A



B

Image 119. Inflammatory bowel disease. In **Crohn's disease (A),** the juxtaposition of ulcerated and normal mucosa gives a "cobblestone" appearance. In acute **ulcerative colitis (B),** the intestinal mucosa is inflamed and edematous and has a pseudopolypoid appearance. Chronically, ulcerative colitis has a more atrophic appearance.

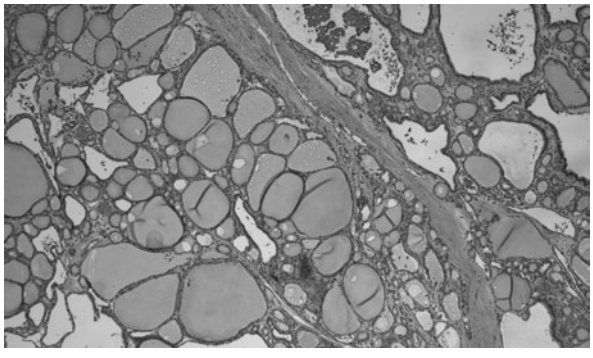


Image 120. Multinodular goiter with hyperplasia and subsequent involution of the thyroid gland. The image shows follicles distended with colloid and lined by a flattened epithelium with areas of fibrosis and hemorrhage. (Reproduced, with permission, from USMLERx.com.)

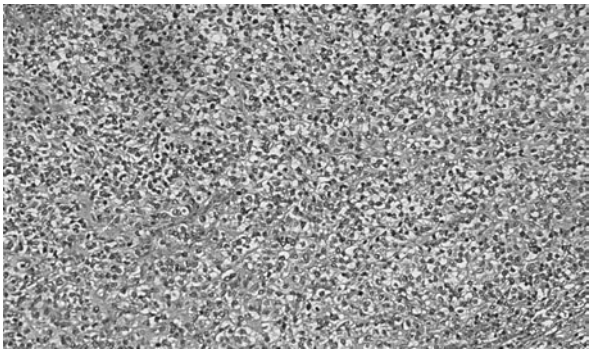
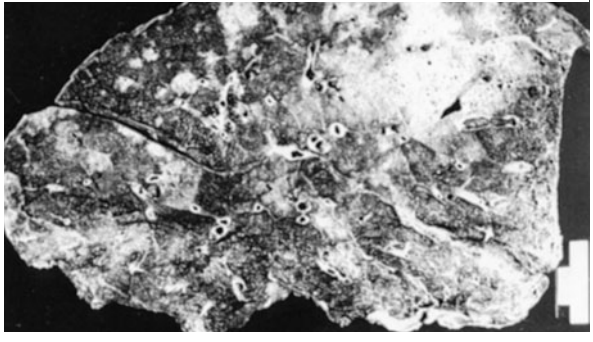
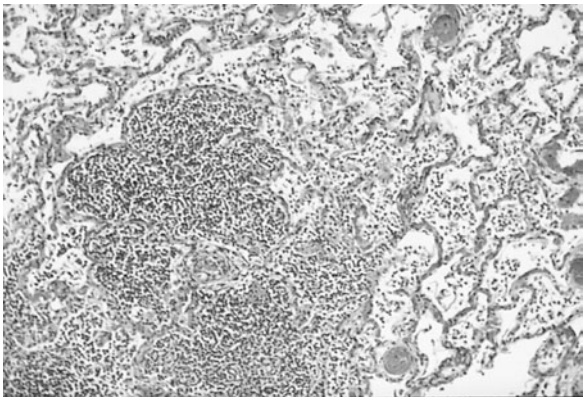


Image 121. Ewing's sarcoma. This malignant tumor of bone occurs in children and is characterized by the (11;22) translocation that results in the fusion gene EWS-FLI1. The tumor is composed of sheets of uniform small, round cells. (Reproduced, with permission, from USMLERx.com.)



A



B

Image 122. Bronchopneumonia. **(A)** Gross. Note the large area of consolidation at the base plus multiple small areas of consolidation (pale) involving bronchioles and surrounding alveolar sacs throughout the lung. **(B)** Bronchopneumonia with neutrophils in alveolar spaces, microscopic.

Image 123. Small bowel obstruction on supine abdominal x-ray. Note dilated loops of small bowel in a ladder-like pattern. Air-fluid levels may be seen if an upright x-ray is done. (Reproduced, with permission, from Le T et al. *First Aid for the Wards*, 3rd ed. New York: McGraw-Hill, 2006: 392.)

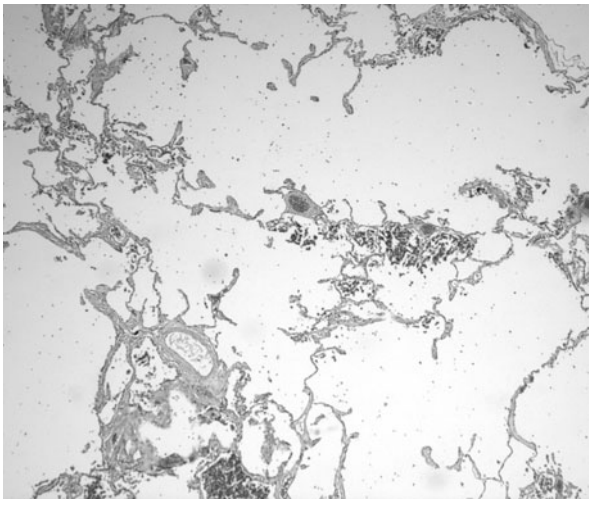


Image 124. Emphysema. Note the abnormal permanent enlargement of the airspaces distal to the terminal bronchiole. On microscopy, enlarged alveoli are seen separated by thin septa, some of which appear to float within the alveolar spaces. (Reproduced, with permission, from USMLERx.com.)

Image 125. Squamous cell carcinoma in the right lower lobe. (Reproduced, with permission, from Le T et al. *First Aid for the Wards*, 3rd ed. New York: McGraw-Hill, 2006: 133.)

A

B

Image 126. Compare the diffuse, patchy bilateral infiltrates of "atypical" **interstitial pneumonia (A)** with the localized, dense lesion of **lobar pneumonia (B)**.

Image 127. Pulmonary edema. Posteroanterior chest x-ray in a man with acute pulmonary edema due to left ventricular failure. Note the bat's-wing density, cardiac enlargement, increased size of upper lobe vessels, and pulmonary venous congestion. (Reproduced, with permission, from McPhee SJ et al. *Pathophysiology of Disease: An Introduction to Clinical Medicine*, 4th ed. New York: McGraw-Hill, 2002.)

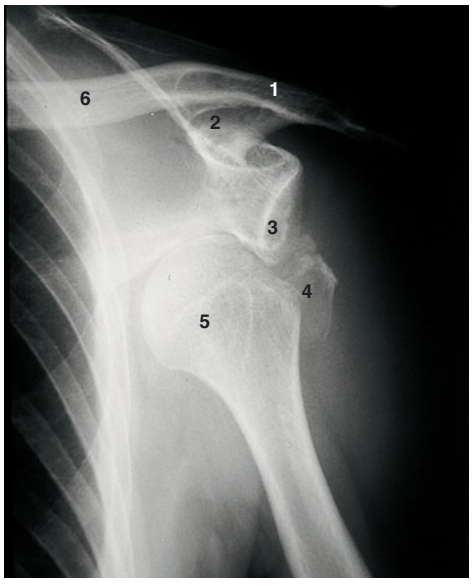
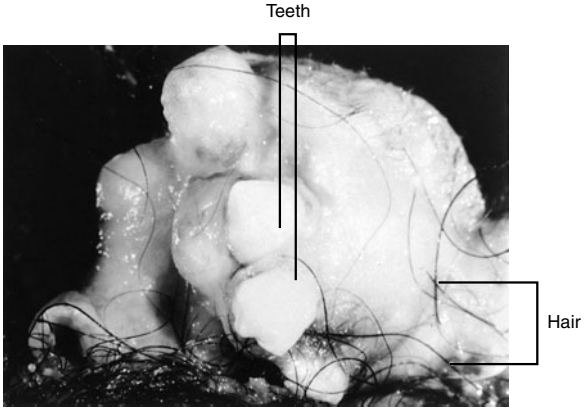
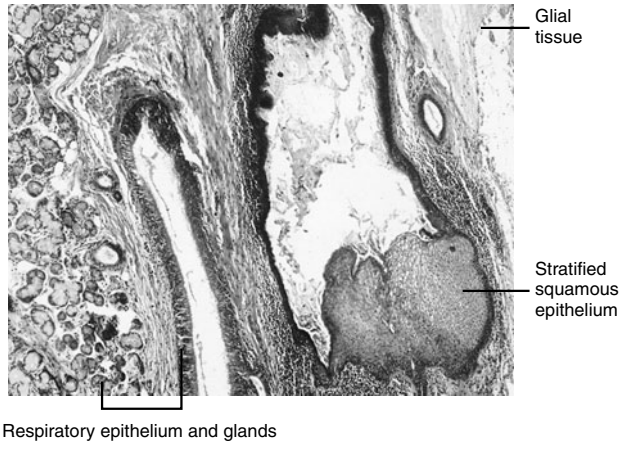


Image 128. Anterior shoulder dislocation. Note the humeral head inferior and medial to the glenoid fossa and fracture fragments from the greater tuberosity.

1—Acromion
2—Coracoid
3—Glenoid fossa
4—Fracture fragments
5—Humeral head
6—Clavicle

Image 129. Multiple **leiomyomas** (fibroids) of the uterus. A common benign uterine tumor. Fibroids beneath the endometrium may present with vaginal bleeding; they also develop subserosally or within the myometrium.





Images 130 and 131. Teratoma (benign) of the ovary containing teeth and hair—an incidental finding during abdominal surgery. In females, teratomas are generally benign, whereas in males they account for roughly 30% of testicular tumors.

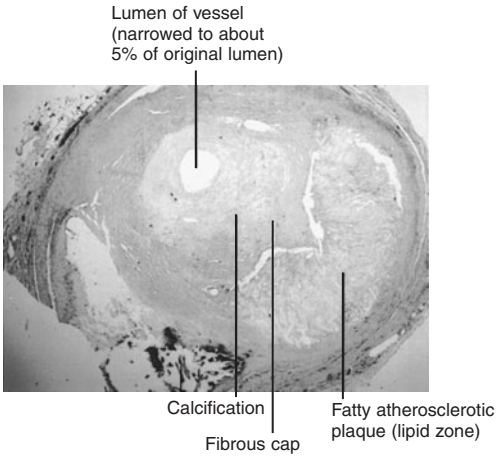


Image 132. Atherosclerosis in a coronary vessel. Calcified plaques have narrowed the lumen of the artery, increasing the risk for occlusion—i.e., myocardial infarction.

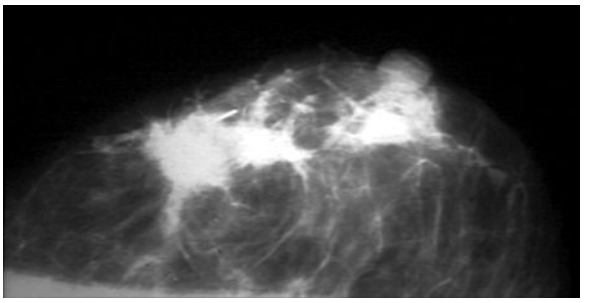


Image 133. Breast mammogram diagnostic of breast cancer. The upper half of the breast shows a dense, irregularly shaped mass with long, branching tentacles extending toward the nipple. Numerous tiny calcium deposits looking like grains of sand (microcalcifications) are seen both in the mass and in the surrounding tissue.*

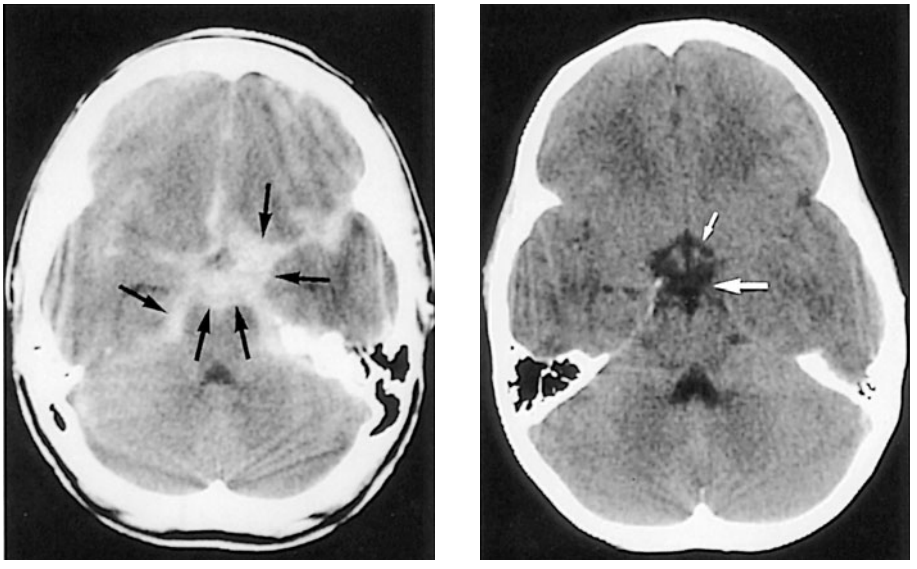


Image 134. Subarachnoid hemorrhage. CT scan with contrast reveals blood in the subarachnoid space at the base of the brain.

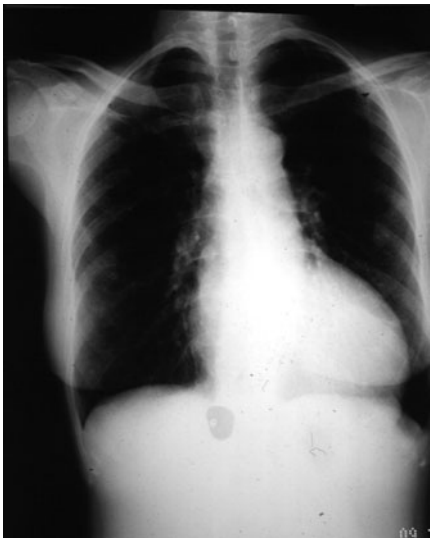


Image 135. Left ventricular hypertrophy (mediastinum wider than 50% of the width of the chest) from aortic valve stenosis.*

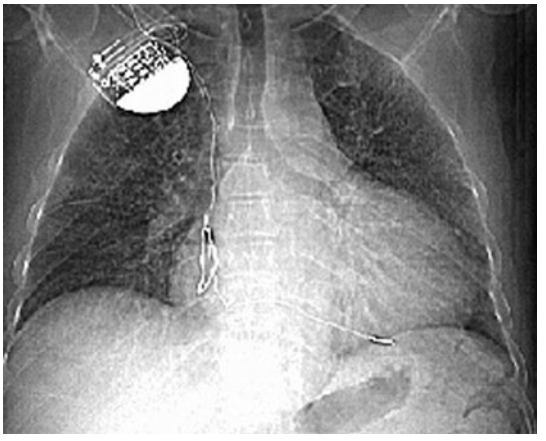


Image 136. Amiodarone toxicity. Diffuse interstitial bilateral pulmonary markings in a reticular nodular pattern, most prominent in the lung bases and posteriorly, are evidence of pulmonary fibrosis.*

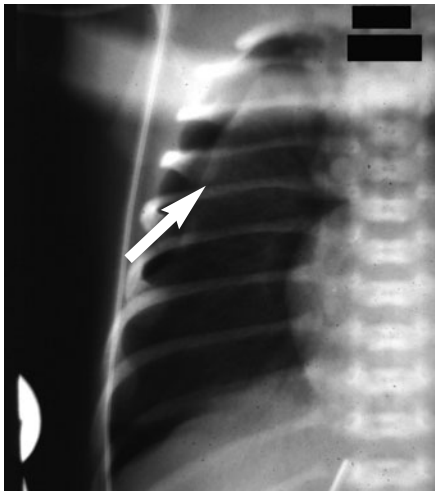


Image 137. Pneumothorax. The right lung is collapsed; the apparent straight line off the rightmost edge of the pleural space indicated by the arrow shows the edge of the collapsed lung.*

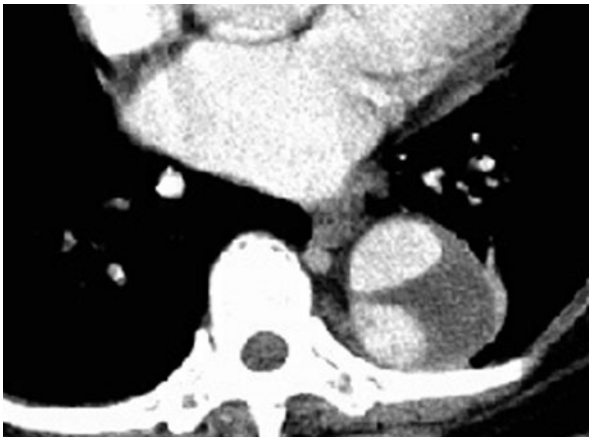


Image 138. Descending aortic dissection. Presents with severe chest pain. Type A is proximal to the subclavian artery and type B distal to the subclavian.*

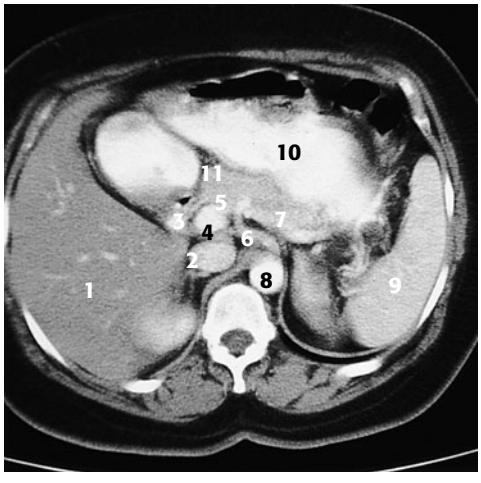


Image 139. CT of the abdomen with contrast—normal anatomy.

1—Liver
2—IVC
3—Portal vein
4—Hepatic artery
5—Gastroduodenal artery
6—Celiac trunk
7—Splenic vein
8—Aorta
9—Spleen
10—Stomach
11—Pancreas

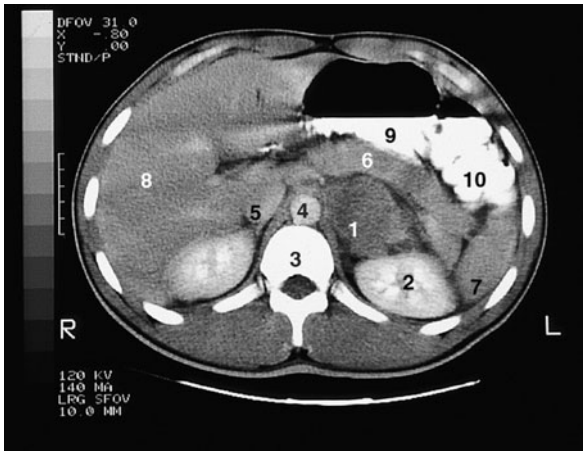


Image 140. Left adrenal mass.

1—Large left adrenal mass
2—Kidney
3—Vertebral body
4—Aorta
5—IVC
6—Pancreas
7—Spleen
8—Liver
9—Stomach with air and contrast
10—Colon–splenic flexure

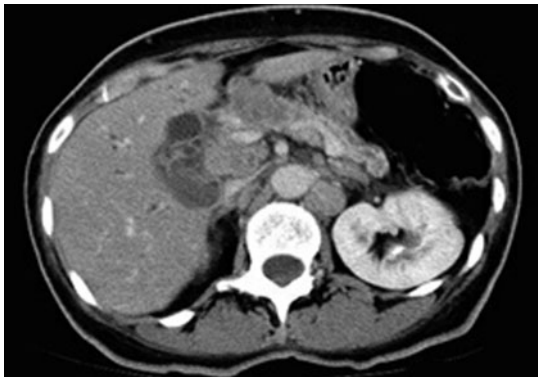


Image 141. Pancreatic adenocarcinoma. A large, heterogeneously enhancing mass is visible at the neck of the pancreas, compressing the common bile duct, portal vein, splenic vein, superior mesenteric vein, and IVC. No liver metastases are apparent.*

Image 142. Acute pancreatitis, typically from alcohol abuse or gallstone obstruction of the pancreatic duct. No evidence of necrosis or fluid collection is seen.*

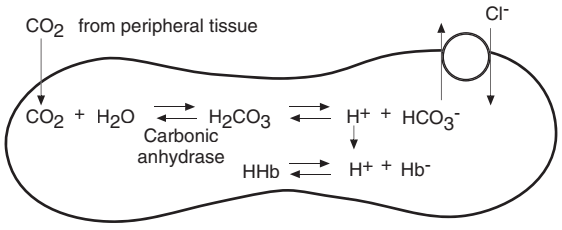
Image 143. Chronic pancreatitis precipitated by large duct stones. A small fatty infiltrate is visible to the left of the liver. Mild central biliary dilatation and a prominent common bile duct are also seen.*

Image 144. Osteoarthritis. Increased fibrosis of the joint and a decreased amount of cartilage are apparent.*

CO_2 transport

Carbon dioxide is transported from tissues to the lungs in 3 forms:

1. **Bicarbonate (90%)**



In lungs, oxygenation of Hb promotes dissociation of H^+ from Hb. This shifts equilibrium toward CO_2 formation; therefore, CO_2 is released from RBCs (Haldane effect).

In peripheral tissue, ↑ H^+ from tissue metabolism shifts curve to right, unloading O_2 (Bohr effect).

2. Bound to hemoglobin as carbaminohemoglobin (5%)
3. Dissolved CO_2 (5%)

(Adapted, with permission, from Ganong WF. *Review of Medical Physiology,* 22nd ed. New York: McGraw-Hill, 2005: 670.)

Response to high altitude

1. Acute ↑ in ventilation
2. Chronic ↑ in ventilation
3. ↑ erythropoietin → ↑ hematocrit and hemoglobin (chronic hypoxia)
4. ↑ 2,3-DPG (binds to hemoglobin so that hemoglobin releases more O_2)
5. Cellular changes (↑ mitochondria)
6. ↑ renal excretion of bicarbonate (e.g., can augment by use of acetazolamide) to compensate for the respiratory alkalosis
7. Chronic hypoxic pulmonary vasoconstriction results in RVH

Obstructive lung disease (COPD)

Obstruction of air flow resulting in air trapping in the lungs. Airways close prematurely at high lung volumes, resulting in ↑ RV and ↓ FVC. PFTs: ↓↓ FEV_1, ↓ FVC → ↓ FEV_1/FVC ratio (hallmark), V/Q mismatch.

Type	Pathology	Other
Chronic **B**ronchitis ("**B**lue **B**loater")	Hypertrophy of mucus-secreting glands in the bronchioles → Reid index = gland depth / total thickness of bronchial wall; in COPD, Reid index > 50%.	Productive cough for > 3 consecutive months in ≥ 2 years. Disease of small airways. Findings—wheezing, crackles, cyanosis.
Emphysema ("pink puffer," barrel-shaped chest)	Enlargement of air spaces and ↓ recoil resulting from destruction of alveolar walls. Centriacinar—caused by smoking. Panacinar—α_1-antitrypsin deficiency (also liver cirrhosis). Paraseptal emphysema—associated with bullae → can rupture → spontaneous pneumothorax; often in young, otherwise healthy males.	↑ elastase activity. ↑ lung compliance due to loss of elastic fibers. Exhale through pursed lips to ↑ airway pressure and prevent airway collapse during exhalation. Findings—dyspnea, ↓ breath sounds, tachycardia, ↓ I/E ratio.
Asthma	Bronchial hyperresponsiveness causes reversible bronchoconstriction. Smooth muscle hypertrophy and Curschmann's spirals (shed epithelium from mucous plugs).	Can be triggered by viral URIs, allergens, and stress. Findings: cough, wheezing, dyspnea, tachypnea, hypoxemia, ↓ I/E ratio, pulsus paradoxus, mucus plugging.
Bronchiectasis	Chronic necrotizing infection of bronchi → permanently dilated airways, purulent sputum, recurrent infections, hemoptysis.	Associated with bronchial obstruction, CF, poor ciliary motility, Kartagener's syndrome. Can develop aspergillosis.

Restrictive lung disease

Restricted lung expansion causes ↓ lung volumes (↓ FVC and TLC). PFTs—FEV_1/FVC ratio > 80%.

Types:

1. Poor breathing mechanics (extrapulmonary, peripheral hypoventilation):
   a. Poor muscular effort—polio, myasthenia gravis
   b. Poor structural apparatus—scoliosis, morbid obesity
2. Interstitial lung diseases (pulmonary, lowered diffusing capacity):
   a. Adult respiratory distress syndrome (ARDS)
   b. Neonatal respiratory distress syndrome (hyaline membrane disease)
   c. Pneumoconioses (coal miner's silicosis, asbestosis)
   d. Sarcoidosis
   e. Idiopathic pulmonary fibrosis (repeated cycles of lung injury and wound healing with ↑ collagen)
   f. Goodpasture's syndrome
   g. Wegener's granulomatosis
   h. Eosinophilic granuloma (histiocytosis X)
   i. Drug toxicity (bleomycin, busulfan, amiodarone)

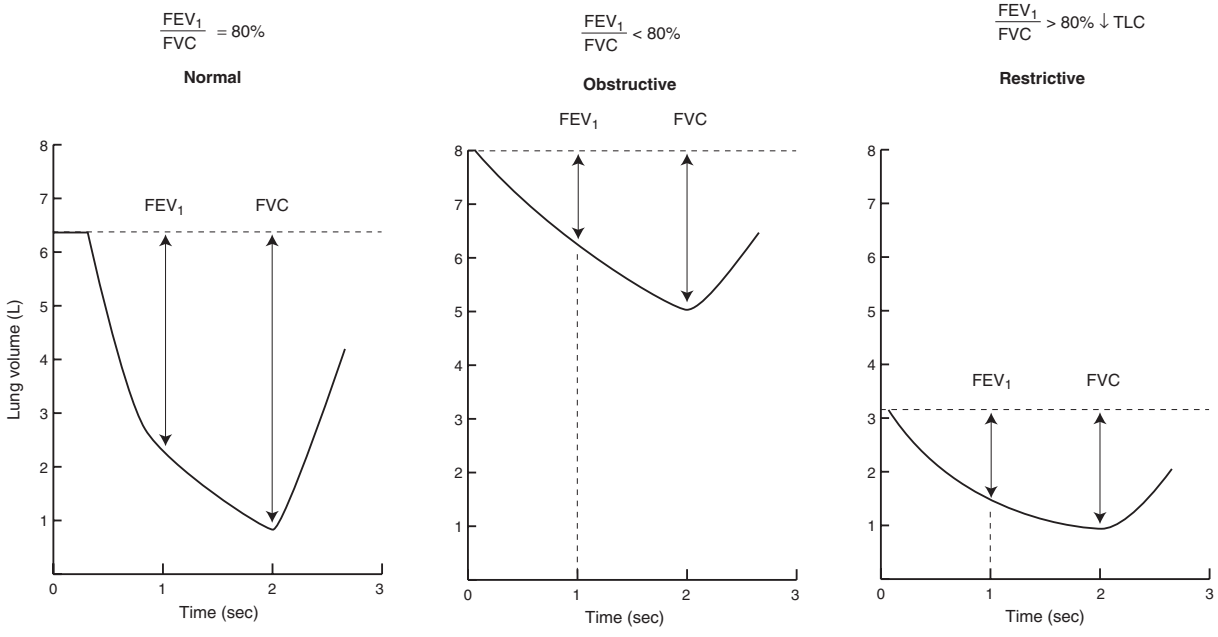
Neonatal respiratory distress syndrome

Surfactant deficiency leading to ↑ surface tension, resulting in alveolar collapse. Surfactant is made by type II pneumocytes most abundantly after 35th week of gestation. The lecithin-to-sphingomyelin ratio in the amniotic fluid, a measure of lung maturity, is usually < 1.5 in neonatal respiratory distress syndrome.
Surfactant—dipalmitoyl phosphatidylcholine.
Treatment: maternal steroids before birth; artificial surfactant for infant.

Adult respiratory distress syndrome (ARDS)

May be caused by trauma, sepsis, shock, gastric aspiration, uremia, acute pancreatitis, or amniotic fluid embolism. Diffuse alveolar damage → ↑ alveolar capillary permeability → protein-rich leakage into alveoli. Results in formation of intra-alveolar hyaline membrane. Initial damage due to neutrophilic substances toxic to alveolar wall, activation of coagulation cascade, or oxygen-derived free radicals (see Color Image 39).

Obstructive vs. restrictive lung disease



Note: Obstructive lung volumes > normal (↑ TLC, ↑ FRC, ↑ RV); restrictive lung volumes < normal. In both obstructive and restrictive, FEV_1 and FVC are reduced, but in obstructive, FEV_1 is more dramatically reduced, resulting in a ↓ FEV_1/FVC ratio.

Sleep apnea

Person stops breathing for at least 10 seconds repeatedly during sleep.
Central sleep apnea—no respiratory effort.
Obstructive sleep apnea—respiratory effort against airway obstruction.
Associated with obesity, loud snoring, systemic/pulmonary hypertension, arrhythmias, and possibly sudden death.
Individuals may become chronically tired.
Treatment: weight loss, CPAP, surgery.

Asbestosis

Diffuse pulmonary interstitial fibrosis caused by inhaled asbestos fibers. ↑ risk of pleural mesothelioma and bronchogenic carcinoma. Long latency. Ferruginous bodies in lung (asbestos fibers coated with hemosiderin). Ivory-white pleural plaques (see Color Image 42).
Mainly affects lower lobes. Other pneumoconioses affect upper lobes (e.g., coal worker's lung).

Asbestosis and smoking greatly ↑ risk of bronchogenic cancer (smoking not additive with mesothelioma).
Seen in shipbuilders, roofers, and plumbers.

Lung—physical findings

Abnormality	Breath Sounds	Resonance	Fremitus	Tracheal Deviation
Bronchial obstruction	Absent/↓ over affected area	↓	↓	Toward side of lesion
Pleural effusion	↓ over effusion	Dullness	↓	—
Pneumonia (lobar)	May have bronchial breath sounds over lesion	Dullness	↑	—
Pneumothorax	↓	Hyperresonant	Absent	Away from side of lesion (see Color Image 40)

Lung cancer

Lung cancer is the leading cause of cancer death.
Presentation: cough, hemoptysis, bronchial obstruction, wheezing, pneumonic "coin" lesion on x-ray film.

SPHERE of complications:
Superior vena cava syndrome
Pancoast's tumor
Horner's syndrome
Endocrine (paraneoplastic)
Recurrent laryngeal symptoms (hoarseness)
Effusions (pleural or pericardial)

Type	Location	Characteristics	Histology
Squamous cell carcinoma (**S**quamous **S**entral **S**moking)	**C**entral	Hilar mass arising from bronchus; **C**avitation; **C**learly linked to **S**moking; parathyroid-like activity → PTHrP (see Color Image 36, Image 125).	Keratin pearls and intercellular bridges.
Adenocarcinoma: Bronchial Bronchioloalveolar	Peripheral	Develops in site of prior pulmonary inflammation or injury (most common lung cancer in nonsmokers and females). Not linked to smoking.	Both types: Clara cells → type II pneumocytes; multiple densities on x-ray of chest.
Small cell (oat cell) carcinoma	Central	Undifferentiated → very aggressive; often associated with ectopic production of ACTH or ADH; may lead to Lambert-Eaton syndrome (autoantibodies against calcium channels). Responsive to chemotherapy.	Neoplasm of neuroendocrine Kulchitsky cells → small dark blue cells (see Color Image 37).
Large cell carcinoma	Peripheral	Highly anaplastic undifferentiated tumor; poor prognosis; less tendency to metastasize and less responsive to chemotherapy. Removed surgically.	Pleomorphic giant cells with leukocyte fragments in cytoplasm.
Carcinoid tumor	—	Secretes serotonin, can cause carcinoid syndrome (flushing, diarrhea, wheezing, salivation).	—
Metastases	—	Very common. Brain (epilepsy), bone (pathologic fracture), and liver (jaundice, hepatomegaly).	—

Pancoast's tumor

Carcinoma that occurs in apex of lung and may affect cervical sympathetic plexus, causing Horner's syndrome.

Horner's syndrome—ptosis, miosis, anhidrosis.

Pneumonia

Type	Organism(s)	Characteristics
Lobar	Pneumococcus most frequently	Intra-alveolar exudate → consolidation; may involve entire lung
Bronchopneumonia	*S. aureus*, *H. flu*, *Klebsiella*, *S. pyogenes*	Acute inflammatory infiltrates from bronchioles into adjacent alveoli; patchy distribution involving ≥ 1 lobes (see Image 122).
Interstitial (atypical) pneumonia	Viruses (RSV, adenoviruses), *Mycoplasma*, *Legionella*, *Chlamydia*	Diffuse patchy inflammation localized to interstitial areas at alveolar walls; distribution involving ≥ 1 lobes (see Image 126).

Lung abscess — Localized collection of pus within parenchyma, usually resulting from bronchial obstruction (e.g., cancer) or aspiration of gastric contents (especially in patients predisposed to loss of consciousness, e.g., alcoholics or epileptics). Often due to *S. aureus* or anaerobes.

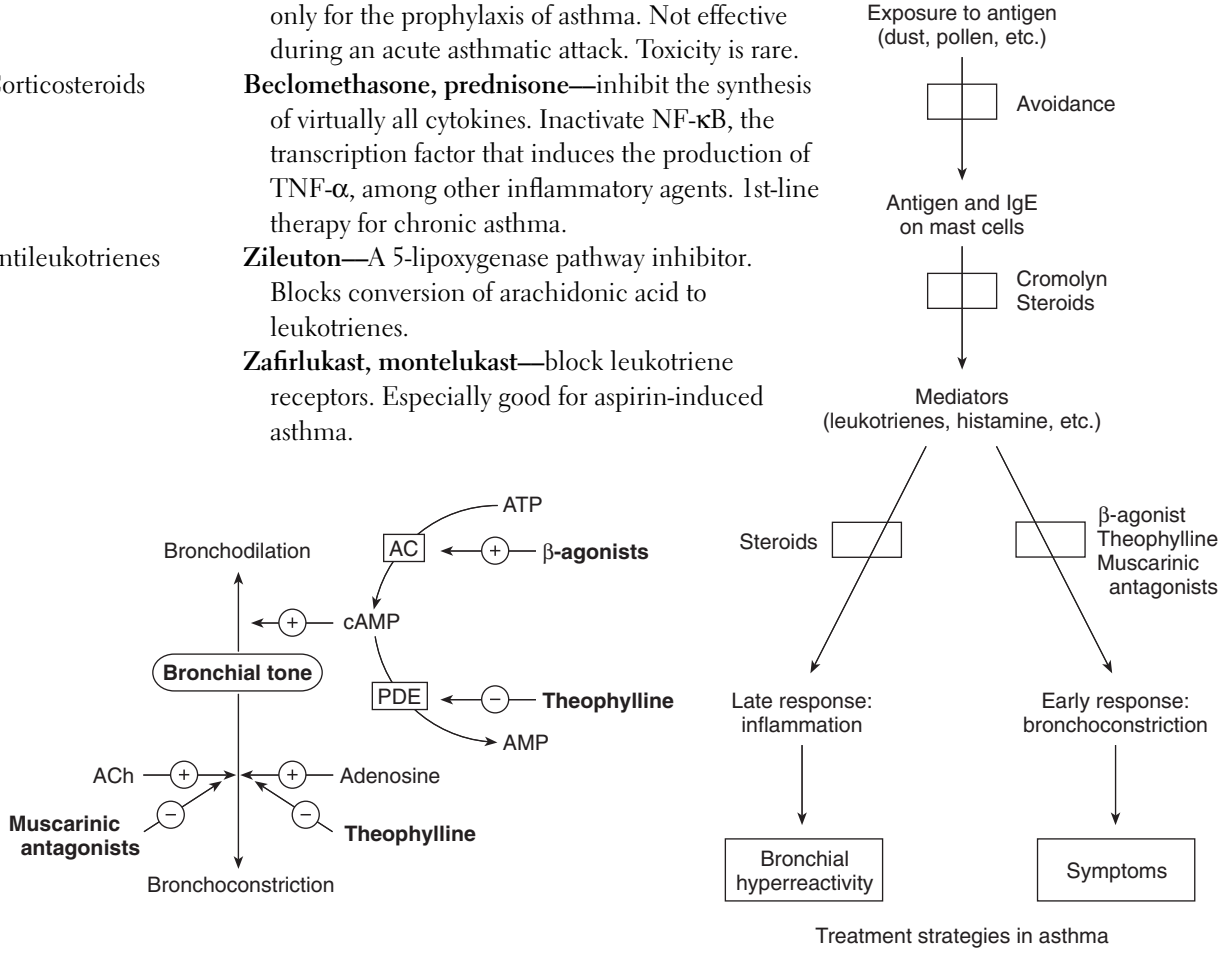
Pleural effusions

Transudate	↓ protein content. Due to CHF, nephrotic syndrome, or hepatic cirrhosis.
Exudate	↑ protein content, cloudy. Due to malignancy, pneumonia, collagen vascular disease, trauma.
Lymphatic	Milky fluid; ↑ triglycerides.

H_1 blockers	Reversible inhibitors of H_1 histamine receptors.
1st generation	Diphenhydramine, dimenhydrinate, chlorpheniramine.
Clinical uses	Allergy, motion sickness, sleep aid.
Toxicity	Sedation, antimuscarinic, anti-α-adrenergic.
2nd generation	Loratadine, fexofenadine, desloratadine, cetirizine.
Clinical uses	Allergy.
Toxicity	Far less sedating than 1st generation because of ↓ entry into CNS.

Asthma drugs

Nonspecific β-agonists	**Isoproterenol—**relaxes bronchial smooth muscle (β_2). Adverse effect is tachycardia (β_1).
β_2-agonists	**Albuterol—**relaxes bronchial smooth muscle (β_2). Use during acute exacerbation.
	Salmeterol—long-acting agent for prophylaxis. Adverse effects are tremor and arrhythmia.
Methylxanthines	**Theophylline—**likely causes bronchodilation by inhibiting phosphodiesterase, thereby ↓ cAMP hydrolysis. Usage is limited because of narrow therapeutic index (cardiotoxicity, neurotoxicity); metabolized by P-450.
Muscarinic antagonists	**Ipratropium—**competitive block of muscarinic receptors, preventing bronchoconstriction. Also used for COPD.
Cromolyn	Prevents release of mediators from mast cells. Effective only for the prophylaxis of asthma. Not effective during an acute asthmatic attack. Toxicity is rare.
Corticosteroids	**Beclomethasone, prednisone—**inhibit the synthesis of virtually all cytokines. Inactivate NF-κB, the transcription factor that induces the production of TNF-α, among other inflammatory agents. 1st-line therapy for chronic asthma.
Antileukotrienes	**Zileuton—**A 5-lipoxygenase pathway inhibitor. Blocks conversion of arachidonic acid to leukotrienes.
	Zafirlukast, montelukast—block leukotriene receptors. Especially good for aspirin-induced asthma.



Treatment strategies in asthma

(Adapted, with permission, from Katzung BG, Trevor AJ. *Pharmacology: Examination & Board Review,* 5th ed. Stamford, CT: Appleton & Lange, 1998: 159 and 161.)

Expectorants

Guaifenesin (Robitussin)	Removes excess sputum but large doses necessary; does not suppress cough reflex.
N-acetylcysteine	Mucolytic → can loosen mucous plugs in CF patients. Also used as an antidote for acetaminophen overdose.

Rapid Review

The following tables represent a collection of high-yield associations of diseases, "buzzwords," findings, and associated pathologies that may be useful for quick review right before the exam.

- Classic Findings
- Most Common Associations
- Equation Review

► CLASSIC FINDINGS

Disease/Finding	Association
Actinic keratosis	Often precedes squamous cell carcinoma
Addison's disease	1° adrenocortical deficiency
Albright's syndrome	Polyostotic fibrous dysplasia, precocious puberty, café-au-lait spots, short stature, young girls
Albuminocytologic dissociation	Guillain-Barré (↑ protein in CSF with only modest ↑ in cell count)
Alport's syndrome	Hereditary nephritis with nerve deafness
Anti–basement membrane antibodies	Goodpasture's syndrome
Anticentromere antibodies	Scleroderma (CREST)
Anti-double-stranded DNA antibodies (ANA antibodies)	SLE (type III hypersensitivity)
Anti–epithelial cell antibodies	Pemphigus vulgaris
Antigliadin antibodies	Celiac disease
Antihistone antibodies	Drug-induced SLE
Anti-IgG antibodies	Rheumatoid arthritis
Antimitochondrial antibodies	1° biliary cirrhosis
Antineutrophil antibodies	Vasculitis
Antiplatelet antibodies	Idiopathic thrombocytopenic purpura
Arachnodactyly	Marfan's syndrome
Argyll Robertson pupil	Neurosyphilis
Arnold-Chiari malformation	Cerebellar tonsillar herniation
Aschoff bodies	Rheumatic fever
Atrophy of the mammillary bodies	Wernicke's encephalopathy
Auer rods	Acute myelogenous leukemia (especially the promyelocytic type)
Autosplenectomy	Sickle cell anemia
Babinski's sign	UMN lesion
Baker's cyst in popliteal fossa	Rheumatoid arthritis
"Bamboo spine" on x-ray	Ankylosing spondylitis
Bartter's syndrome	Hyperreninemia
Basophilic stippling of RBCs	Lead poisoning
Becker's muscular dystrophy	Defective dystrophin; less severe than Duchenne's
Bell's palsy	LMN CN VII palsy
Bence Jones proteins	Multiple myeloma (kappa or lambda Ig light chains in urine), Waldenström's macroglobulinemia (IgM)

Berger's disease	IgA nephropathy
Bernard-Soulier disease	Defect in platelet adhesion
Bilateral hilar adenopathy, uveitis	Sarcoidosis
Birbeck granules on EM	Histiocytosis X (eosinophilic granuloma)
Bloody tap on LP	Subarachnoid hemorrhage
"Blue bloater"	Chronic bronchitis
Blue-domed cysts	Fibrocystic change of the breast
Blue sclera	Osteogenesis imperfecta
Boot-shaped heart on x-ray	Tetralogy of Fallot; RVH
Bouchard's nodes	Osteoarthritis (PIP swelling 2° to osteophytes)
Boutonnière deformity	Rheumatoid arthritis
Branching rods in oral infection	*Actinomyces israelii*
"Brown tumor" of bone	Hemorrhage causes brown color of osteolytic cysts: 1. Hyperparathyroidism 2. Osteitis fibrosa cystica (von Recklinghausen's disease)
Bruton's disease	X-linked agammaglobulinemia
Budd-Chiari syndrome	Posthepatic venous thrombosis
Buerger's disease	Small/medium-artery vasculitis
Burkitt's lymphoma	8:14 translocation; associated with EBV; "starry sky" appearance on histology
Burton's lines	Lead poisoning
c-ANCA, p-ANCA	Wegener's granulomatosis, microscopic polyangiitis
Café-au-lait spots on skin	Neurofibromatosis
Caisson disease	Gas emboli
Calf pseudohypertrophy	Duchenne's muscular dystrophy
Call-Exner bodies	Granulosa-theca cell tumor of the ovary
Cardiomegaly with apical atrophy	Chagas' disease
Cerebriform nuclei	Mycosis fungoides (cutaneous T-cell lymphoma)
Chagas' disease	Trypanosome infection
Chancre	1° syphilis (not painful)
Chancroid	*Haemophilus ducreyi* (painful)
Charcot's triad	Multiple sclerosis (nystagmus, intention tremor, scanning speech), cholangitis (jaundice, RUQ pain, fever)
Charcot-Leyden crystals	Bronchial asthma (eosinophil membranes)
Chédiak-Higashi disease	Phagocyte deficiency

Cherry-red spot on macula	Tay-Sachs, Niemann-Pick disease, central retinal artery occlusion
Cheyne-Stokes respirations	Central apnea in CHF and ↑ intracranial pressure
"Chocolate cysts"	Endometriosis (frequently involves both ovaries)
Chronic atrophic gastritis	Predisposition to gastric carcinoma
Chvostek's sign	Hypocalcemia (facial muscle spasm upon tapping)
Clear cell adenocarcinoma of the vagina	DES exposure in utero
Clue cells	*Gardnerella* vaginitis
Codman's triangle on x-ray	Osteosarcoma
Cold agglutinins	*Mycoplasma pneumoniae,* infectious mononucleosis
Cold intolerance	Hypothyroidism
Condylomata lata	2° syphilis
Continuous machinery murmur	Patent ductus arteriosus
Cori's disease	Debranching enzyme deficiency
Cotton-wool spots	Chronic hypertension
Cough, conjunctivitis, coryza + fever	Measles
Councilman bodies	Toxic or viral hepatitis
Cowdry type A bodies	Herpesvirus
Crescents in Bowman's capsule	Rapidly progressive crescentic glomerulonephritis
Crigler-Najjar syndrome	Congenital unconjugated hyperbilirubinemia
Curling's ulcer	Acute gastric ulcer associated with severe burns
Currant-jelly sputum	*Klebsiella*
Curschmann's spirals	Bronchial asthma (whorled mucous plugs)
Cushing's ulcer	Acute gastric ulcer associated with CNS injury
D-dimers	DIC
Depigmentation of neurons in substantia nigra	Parkinson's disease (basal ganglia disorder—rigidity, resting tremor, bradykinesia)
Dermatitis, dementia, diarrhea	Pellagra (niacin, vitamin B_3 deficiency)
Diabetes insipidus + exophthalmos + lesions of skull	Hand-Schüller-Christian disease
Dog or cat bite	*Pasteurella multocida*
Donovan bodies	Granuloma inguinale
Dressler's syndrome	Post-MI fibrinous pericarditis

Dubin-Johnson syndrome	Congenital conjugated hyperbilirubinemia (black liver)
Duchenne's muscular dystrophy	Deleted dystrophin gene (X-linked recessive)
Eburnation	Osteoarthritis (polished, ivory-like appearance of bone)
Edwards' syndrome	Trisomy 18 associated with rocker-bottom feet, low-set ears, heart disease
Eisenmenger's complex	Late cyanosis shunt (uncorrected L $\rightarrow$ R shunt becomes R $\rightarrow$ L shunt)
Elastic skin	Ehlers-Danlos syndrome
Erb-Duchenne palsy	Superior trunk (C5–C6) brachial plexus injury ("waiter's tip")
Erythema chronicum migrans	Lyme disease
Fanconi's syndrome	Proximal tubular reabsorption defect
"Fat, female, forty, and fertile"	Acute cholecystitis
Fatty liver	Alcoholism
Ferruginous bodies	Asbestosis
Gardner's syndrome	Colon polyps with osteomas and soft tissue tumors
Gaucher's disease	Glucocerebrosidase deficiency
Ghon focus	1° TB
Gilbert's syndrome	Benign congenital unconjugated hyperbilirubinemia
Glanzmann's thrombasthenia	Defect in platelet aggregation
Goodpasture's syndrome	Autoantibodies against alveolar and glomerular basement membrane proteins
Gowers' maneuver	Duchenne's (use of patient's arms to help legs pick self off the floor)
Guillain-Barré syndrome	Idiopathic polyneuritis
"Hair-on-end" (crew-cut) appearance on x-ray	β-thalassemia, sickle cell anemia (extramedullary hematopoiesis)
Hand-Schüller-Christian disease	Chronic progressive histiocytosis
HbF	Thalassemia major
HbS	Sickle cell anemia
hCG elevated	Choriocarcinoma, hydatidiform mole (occurs with and without embryo)
Heberden's nodes	Osteoarthritis (DIP swelling 2° to osteophytes)
Heinz bodies	G6PD deficiency
Henoch-Schönlein purpura	Hypersensitivity vasculitis associated with hemorrhagic urticaria and URIs
Heterophil antibodies	Infectious mononucleosis (EBV)
High-output cardiac failure (dilated cardiomyopathy)	Wet beriberi (thiamine, vitamin B_1 deficiency)
HLA-B27	Reiter's syndrome, ankylosing spondylitis
HLA-DR3 or -DR4	Diabetes mellitus type 1 (caused by autoimmune destruction of β cells)
Homer Wright rosettes	Neuroblastoma
Honeycomb lung on x-ray	Interstitial fibrosis

Horner's syndrome	Ptosis, miosis, and anhidrosis
Howell-Jolly bodies	Splenectomy (or nonfunctional spleen)
Huntington's disease	Caudate degeneration (autosomal dominant)
Hyperphagia + hypersexuality + hyperorality + hyperdocility	Klüver-Bucy syndrome (amygdala)
Hyperpigmentation of skin	1° adrenal insufficiency (Addison's disease)
Hypersegmented neutrophils	Macrocytic anemia
Hypertension + hypokalemia	Conn's syndrome
Hypochromic microcytosis	Iron deficiency anemia, lead poisoning
Increased α-fetoprotein in amniotic fluid/maternal serum	Anencephaly, spina bifida (neural tube defects)
Increased uric acid levels	Gout, Lesch-Nyhan syndrome, myeloproliferative disorders, loop and thiazide diuretics
Intussusception	Adenovirus (causes hyperplasia of Peyer's patches)
Janeway lesions	Endocarditis
Jarisch-Herxheimer reaction	Syphilis––overaggressive treatment of an asymptomatic patient that causes symptoms due to rapid lysis
Job's syndrome	Neutrophil chemotaxis abnormality
Kaposi's sarcoma	AIDS in MSM (men who have sex with men)
Kartagener's syndrome	Dynein defect
Kayser-Fleischer rings	Wilson's disease
Keratin pearls	Squamous cell carcinoma
Kimmelstiel-Wilson nodules	Diabetic nephropathy
Klüver-Bucy syndrome	Bilateral amygdala lesions
Koilocytes	HPV
Koplik spots	Measles
Krukenberg tumor	Gastric adenocarcinoma with ovarian metastases
Kussmaul hyperpnea	Diabetic ketoacidosis
Lens dislocation + aortic dissection + joint hyperflexibility	Marfan's syndrome (fibrillin deficit)
Lesch-Nyhan syndrome	HGPRT deficiency
Lewy bodies	Parkinson's disease
Libman-Sacks disease	Endocarditis associated with SLE
Lines of Zahn	Arterial thrombus
Lisch nodules	Neurofibromatosis (von Recklinghausen's disease)

Low serum ceruloplasmin	Wilson's disease
Lucid interval	Epidural hematoma
"Lumpy-bumpy" appearance of glomeruli on immunofluorescence	Poststreptococcal glomerulonephritis
Lytic bone lesions on x-ray	Multiple myeloma
Mallory bodies	Alcoholic liver disease
Mallory-Weiss syndrome	Esophagogastric lacerations
McArdle's disease	Muscle phosphorylase deficiency
McBurney's sign	Appendicitis
MLF syndrome (INO)	Multiple sclerosis
Monoclonal antibody spike	Multiple myeloma (called the M protein; usually IgG or IgA), MGUS (monoclonal gammopathy of undetermined significance), Waldenström's (M protein = IgM) macroglobulinemia
Myxedema	Hypothyroidism
Necrotizing vasculitis (lungs) and necrotizing glomerulonephritis	Wegener's and Goodpasture's (hemoptysis and glomerular disease)
Needle-shaped, negatively birefringent crystals	Gout
Negri bodies	Rabies
Nephritis + cataracts + hearing loss	Alport's syndrome
Neurofibrillary tangles	Alzheimer's disease
Niemann-Pick disease	Sphingomyelinase deficiency
No lactation postpartum	Sheehan's syndrome (pituitary infarction)
Nutmeg liver	CHF
Occupational exposure to asbestos	Malignant mesothelioma
"Orphan Annie" nuclei	Papillary carcinoma of the thyroid
Osler's nodes	Endocarditis
Owl's eye	CMV
Painless jaundice	Pancreatic cancer (head)
Palpable purpura on legs and buttocks	Henoch-Schönlein purpura
Pancoast's tumor	Bronchogenic apical tumor associated with Horner's syndrome
Pannus	Rheumatoid arthritis
Parkinson's disease	Nigrostriatal dopamine depletion
Periosteal elevation on x-ray	Pyogenic osteomyelitis
Peutz-Jeghers syndrome	Benign polyposis
Peyronie's disease	Penile fibrosis

Philadelphia chromosome (*bcr-abl*)	CML (may sometimes be associated with AML)
Pick bodies	Pick's disease
Pick's disease	Progressive dementia, similar to Alzheimer's
"Pink puffer"	Emphysema (centroacinar [smoking], panacinar [α_1-antitrypsin deficiency])
Plummer-Vinson syndrome	Esophageal webs with iron deficiency anemia
Podagra	Gout (MP joint of hallux)
Podocyte fusion	Minimal change disease
Polyneuropathy, cardiac pathology, and edema	Dry beriberi (thiamine, vitamin B_1 deficiency)
Polyneuropathy preceded by GI or respiratory infection	Guillain-Barré syndrome
Pompe's disease	Lysosomal glucosidase deficiency associated with cardiomegaly
Port-wine stain	Hemangioma
Positive anterior "drawer sign"	Anterior cruciate ligament injury
Pott's disease	Vertebral tuberculosis
Pseudopalisade tumor cell arrangement	Glioblastoma multiforme
Pseudorosettes	Ewing's sarcoma
Ptosis, miosis, anhidrosis	Horner's syndrome (Pancoast's tumor)
Rash on palms and soles	2° syphilis, Rocky Mountain spotted fever
Raynaud's syndrome	Recurrent vasospasm in extremities
RBC casts in urine	Acute glomerulonephritis
Recurrent pulmonary *Pseudomonas* and *S. aureus* infections	Cystic fibrosis
Red urine in the morning	Paroxysmal nocturnal hemoglobinuria
Reed-Sternberg cells	Hodgkin's lymphoma
Reid index (increased)	Chronic bronchitis
Reinke crystals	Leydig cell tumor
Reiter's syndrome	Urethritis, conjunctivitis, arthritis
Renal cell carcinoma + cavernous hemangiomas + adenomas	von Hippel–Lindau disease
Renal epithelial casts in urine	Acute toxic/viral nephrosis
Rhomboid crystals, positively birefringent	Pseudogout

Rib notching	Coarctation of aorta
Roth's spots in retina	Endocarditis
Rotor's syndrome	Congenital conjugated hyperbilirubinemia
Rouleaux formation (RBCs)	Multiple myeloma
S3	Left-to-right shunt (VSD, PDA, ASD), mitral regurgitation, LV failure (CHF)
S4	Aortic stenosis, hypertrophic subaortic stenosis
Schiller-Duval bodies	Yolk sac tumor
Senile plaques	Alzheimer's disease
Sézary syndrome	Cutaneous T-cell lymphoma
Sheehan's syndrome	Postpartum pituitary necrosis
Shwartzman reaction	*Neisseria meningitidis*
Signet-ring cells	Gastric carcinoma
Simian crease	Down syndrome
Sipple's syndrome	MEN type IIa
Sjögren's syndrome	Dry eyes, dry mouth, arthritis
Skip lesions	Crohn's
Slapped cheeks	Erythema infectiosum (fifth disease)
Smith antigen	SLE
"Smudge cell"	CLL
Soap bubble on x-ray	Giant cell tumor of bone
Spike and dome on EM	Membranous glomerulonephritis
Spitz nevus	Benign juvenile melanoma
Splinter hemorrhages in fingernails	Endocarditis
Starry-sky pattern	Burkitt's lymphoma
"Strawberry tongue"	Scarlet fever
Streaky ovaries	Turner's syndrome
String sign on x-ray	Crohn's disease
Subepithelial humps on EM	Poststreptococcal glomerulonephritis
Suboccipital lymphadenopathy	Rubella
Sulfur granules	*Actinomyces israelii*
Swollen gums, bruising, poor wound healing, anemia	Scurvy (ascorbic acid, vitamin C deficiency)––vitamin C is necessary for hydroxylation of proline and lysine in collagen synthesis
Systolic ejection murmur (crescendo-decrescendo)	Aortic valve stenosis

t(8;14)	Burkitt's lymphoma (c-*myc* activation)
t(9;22)	Philadelphia chromosome, CML (*bcr-abl* hybrid)
t(14;18)	Follicular lymphomas (*bcl*-2 activation)
Tabes dorsalis	3° syphilis
Tendon xanthomas (classically Achilles)	Familial hypercholesterolemia
Thumb sign on lateral x-ray	Epiglottitis (*Haemophilus influenzae*)
Thyroidization of kidney	Chronic bacterial pyelonephritis
Tophi	Gout
"Tram-track" appearance on LM	Membranoproliferative glomerulonephritis
Trousseau's sign	Visceral cancer, pancreatic adenocarcinoma (migratory thrombophlebitis), hypocalcemia (carpal spasm)
Virchow's node	Left supraclavicular node enlargement from metastatic carcinoma of the stomach
Virchow's triad	Pulmonary embolism (triad = blood stasis, endothelial damage, hypercoagulation)
von Recklinghausen's disease	Neurofibromatosis with café-au-lait spots
von Recklinghausen's disease of bone	Osteitis fibrosa cystica ("brown tumor")
Wallenberg's syndrome	PICA thrombosis
Waterhouse-Friderichsen syndrome	Adrenal hemorrhage associated with meningococcemia
Waxy casts	Chronic end-stage renal disease
WBC casts in urine	Acute pyelonephritis
WBCs in urine	Acute cystitis
Wermer's syndrome	MEN type I
Whipple's disease	Malabsorption syndrome caused by *Tropheryma whippelii*
Wilson's disease	Hepatolenticular degeneration
"Wire loop" appearance on LM	Lupus nephropathy
"Worst headache of my life"	Berry aneurysm––associated with adult polycystic kidney disease
Xanthochromia (CSF)	Subarachnoid hemorrhage
Xerostomia + arthritis + keratoconjunctivitis sicca	Sjögren's syndrome
Zenker's diverticulum	Upper GI diverticulum
Zollinger-Ellison syndrome	Gastrin-secreting tumor associated with ulcers

Most Common …	
Bacteremia/pneumonia (IVDA)	*S. aureus*
Bacteria associated with cancer	*H. pylori*
Bacteria found in GI tract	*Bacteroides* (2nd most common is *E. coli*)
Brain tumor (adults)	Mets > astrocytoma (including glioblastoma multiforme) > meningioma > schwannoma
Brain tumor (kids)	Medulloblastoma (cerebellum)
Brain tumor––supratentorial (kids)	Craniopharyngioma
Breast cancer	Infiltrating ductal carcinoma (in the United States, 1 in 9 women will develop breast cancer)
Breast mass	Fibrocystic change (in postmenopausal women, carcinoma is the most common)
Breast tumor (benign)	Fibroadenoma
Bug in debilitated, hospitalized pneumonia patient	*Klebsiella*
Cardiac 1° tumor (adults)	Myxoma (4:1 left to right atrium; "ball and valve")
Cardiac 1° tumor (kids)	Rhabdomyoma
Cardiac tumor (adults)	Mets
Cardiomyopathy	Dilated cardiomyopathy
Chromosomal disorder	Down syndrome (associated with ALL, Alzheimer's dementia, and endocardial cushion defects)
Chronic arrhythmia	Atrial fibrillation (associated with high risk of emboli)
Congenital cardiac anomaly	VSD
Constrictive pericarditis	Tuberculosis
Coronary artery involved in thrombosis	LAD > RCA > LCA
Cyanosis (early; less common)	Tetralogy of Fallot, transposition of great vessels, truncus arteriosus
Cyanosis (late; more common)	VSD, ASD, PDA (close with indomethacin; open with misoprostol)
Demyelinating disease	Multiple sclerosis
Dietary deficit	Iron
Epiglottitis	*Haemophilus influenzae* type B
Esophageal cancer	Squamous cell carcinoma
Gene involved in cancer	p53 tumor suppressor gene
Group affected by cystic fibrosis	Caucasians (fat-soluble vitamin deficiencies, mucous plugs/lung infections)
Gynecologic malignancy	Endometrial carcinoma
Heart murmur	Mitral valve prolapse

Heart valve in bacterial endocarditis	Mitral
Heart valve in bacterial endocarditis in IVDA	Tricuspid
Heart valve (rheumatic fever)	Mitral valve (aortic is 2nd)
Helminth infection (U.S.)	*Enterobius vermicularis* (*Ascaris lumbricoides* is 2nd most common)
Hereditary bleeding disorder	von Willebrand's
Kidney stones	Calcium = radiopaque (2nd most common is ammonium = radiopaque; formed by urease-positive organisms such as *Proteus vulgaris* or *Staphylococcus*)
Liver disease	Alcoholic liver disease
Location of brain tumors (adults)	Supratentorial
Location of brain tumors (kids)	Infratentorial
Lysosomal storage disease	Gaucher's disease
Male cancer	Prostatic carcinoma
Malignancy associated with noninfectious fever	Hodgkin's disease
Malignant skin tumor	Basal cell carcinoma (rarely metastasizes)
Mets to bone	Breast, lung, thyroid, testes, prostate, kidney
Mets to brain	Lung, breast, skin (melanoma), kidney (renal cell carcinoma), GI
Mets to liver	Colon, gastric, pancreatic, breast, and lung carcinomas
Motor neuron disease	ALS
Neoplasm (kids)	ALL (2nd most common is cerebellar medulloblastoma)
Nephrotic syndrome	Membranous glomerulonephritis
Obstruction of male urinary tract	BPH
Opportunistic infection in AIDS	*Pneumocystis carinii* pneumonia
Organ receiving mets	Adrenal glands (due to rich blood supply)
Organ sending mets	Lung > breast, stomach
Ovarian tumor (benign)	Serous cystadenoma
Ovarian tumor (malignant)	Serous cystadenocarcinoma
Pancreatic tumor	Adenocarcinoma (head of pancreas)
Patient with ALL/CLL/AML/CML	ALL—child, CLL—adult > 60, AML—adult > 60, CML—adult 35–50
Patient with Hodgkin's	Young male (except nodular sclerosis type—female)
Patient with minimal change disease	Young child
Patient with Reiter's	Male
Pituitary tumor	Prolactinoma (2nd—somatotropic "acidophilic" adenoma)

Preventable cancer	Lung cancer
Primary bone tumor (adults)	Multiple myeloma
Primary hyperparathyroidism	Adenomas (followed by hyperplasia, then carcinoma)
Primary liver tumor	Hepatoma
Renal tumor	Renal cell carcinoma––associated with von Hippel–Lindau and acquired polycystic kidney disease; paraneoplastic syndromes (erythropoietin, renin, PTH, ACTH)
Secondary hyperparathyroidism	Hypocalcemia of chronic renal failure
Sexually transmitted disease	*Chlamydia*
Site of diverticula	Sigmoid colon
Site of metastasis	Regional lymph nodes
Site of metastasis (2nd most common)	Liver
Sites of atherosclerosis	Abdominal aorta > coronary > popliteal > carotid
Skin cancer	Basal cell carcinoma
Stomach cancer	Adenocarcinoma
Testicular tumor	Seminoma
Thyroid cancer	Papillary carcinoma
Tracheoesophageal fistula	Lower esophagus joins trachea/upper esophagus––blind pouch
Tumor in men	Prostate carcinoma
Tumor in women	Leiomyoma (estrogen dependent)
Tumor of infancy	Hemangioma
Tumor of the adrenal medulla (adults)	Pheochromocytoma (benign)
Tumor of the adrenal medulla (kids)	Neuroblastoma (malignant)
Type of Hodgkin's	Nodular sclerosis (vs. mixed cellularity, lymphocytic predominance, lymphocytic depletion)
Type of non-Hodgkin's	Follicular, small cleaved
Type of pituitary adenoma	Prolactinoma
Vasculitis	Temporal arteritis (risk of ipsilateral blindness due to thrombosis of ophthalmic artery)
Viral encephalitis	HSV
Vitamin deficiency (U.S.)	Folic acid (pregnant women are at high risk; body stores only 3- to 4-month supply)

Most Frequent Cause of …	
Addison's	Autoimmune (infection is the 2nd most common cause)
Aneurysm, dissecting	Hypertension
Aortic aneurysm, abdominal and descending aorta	Atherosclerosis
Aortic aneurysm, ascending	3° syphilis
Bacterial meningitis (adults)	*Streptococcus pneumoniae*
Bacterial meningitis (elderly)	*S. pneumoniae*
Bacterial meningitis (kids)	*S. pneumoniae* or *Neisseria meningitidis*
Bacterial meningitis (newborns)	Group B streptococcus
Cancer associated with AIDS	Kaposi's sarcoma
Congenital adrenal hyperplasia	21-hydroxylase deficiency
Cretinism	Iodine deficit/hypothyroidism
Cushing's syndrome	Corticosteroid therapy (2nd most common cause is excess ACTH secretion by pituitary)
Death in CML	Blast crisis
Death in SLE	Lupus nephropathy
Dementia	Alzheimer's (2nd most common is multi-infarct)
DIC	Gram-negative sepsis, obstetric complications, cancer, burn trauma
Ejection click	Aortic/pulmonic stenosis
Food poisoning	*S. aureus*
Glomerulonephritis (adults)	IgA nephropathy (Berger's disease)
Hematoma––epidural	Rupture of middle meningeal artery (arterial bleeding is fast)
Hematoma––subdural	Rupture of bridging veins (trauma; venous bleeding is slow)
Hemochromatosis	Multiple blood transfusions (can result in CHF and ↑ risk of hepatocellular carcinoma)
Hepatic cirrhosis	EtOH
Hepatocellular carcinoma	Cirrhotic liver (often associated with hepatitis B and C)
Holosystolic murmur	VSD, tricuspid regurgitation, mitral regurgitation
Hypertension, 2°	Renal disease
Hypoparathyroidism	Thyroidectomy
Hypopituitarism	Adenoma
Infection in blood transfusion	Hepatitis C
Infection in burn victims	*Pseudomonas*

Leukemia (adults)	AML
"Machine-like" murmur	PDA
Mental retardation	Down syndrome (fragile X is the 2nd most common cause)
MI	Atherosclerosis
Mitral valve stenosis	Rheumatic heart disease
Myocarditis	Coxsackie B
Nephrotic syndrome (adults)	Membranous glomerulonephritis
Nephrotic syndrome (kids)	Minimal change disease (associated with infections/vaccinations; treat with corticosteroids)
Opening snap	Mitral stenosis
Osteomyelitis	*S. aureus*
Osteomyelitis in patients with sickle cell disease	*Salmonella*
Osteomyelitis with IVDA	*Pseudomonas*
Pancreatitis (acute)	EtOH and gallstones
Pancreatitis (chronic)	EtOH (adults), cystic fibrosis (kids)
Peau d'orange	Carcinoma of the breast
PID	*Neisseria gonorrhoeae* (monoarticular arthritis)
Pneumonia, hospital-acquired	*Klebsiella*
Pneumonia in cystic fibrosis, burn infection	*Pseudomonas aeruginosa*
Preventable blindness	*Chlamydia*
Primary amenorrhea	Turner's (XO)
Primary hyperaldosteronism	Adenoma of adrenal cortex
Primary hyperparathyroidism	Adenoma
Pulmonary hypertension	COPD
Right heart failure due to a pulmonary cause	Cor pulmonale
Right-sided heart failure	Left-sided heart failure
Sheehan's syndrome	Postpartum pituitary infarction 2° to hemorrhage
SIADH	Small cell carcinoma of the lung
UTI	*E. coli*
UTI (young women)	*E. coli* and *Staphylococcus saprophyticus*

Topic	Equation	Page
Sensitivity	$\text{Sensitivity} = \frac{a}{a+c}$	65
Specificity	$\text{Specificity} = \frac{d}{b+d}$	65
Positive predictive value	$\text{PPV} = \frac{a}{a+b}$	65
Negative predictive value	$\text{NPV} = \frac{d}{c+d}$	65
Relative risk	$\text{RR} = \frac{\left[\frac{a}{a+b}\right]}{\left[\frac{c}{c+d}\right]}$	66
Attributable risk	$\text{AR} = \left[\frac{a}{a+b}\right] - \left[\frac{c}{c+d}\right]$	66
Hardy-Weinberg equilibrium	$p^2 + 2pq + q^2 = 1$ $p + q = 1$	115
Henderson-Hasselbalch equation	$\text{pH} = \text{pKa} + \log \frac{[HCO_3^-]}{0.03\ P_{CO_2}}$	427
Volume of distribution	$V_d = \frac{\text{amount of drug in the body}}{\text{plasma drug concentration}}$	221
Clearance	$\text{CL} = \frac{\text{rate of elimination of drug}}{\text{plasma drug concentration}}$	221
Half-life	$t_{1/2} = \frac{0.7 \times V_d}{\text{CL}}$	221
Loading dose	$\text{LD} = C_p \times \frac{V_d}{F}$	222
Maintenance dose	$\text{MD} = C_p \times \frac{\text{CL}}{F}$	222
Cardiac output	$\text{CO} = \frac{\text{rate of } O_2 \text{ consumption}}{\text{arterial } O_2 \text{ content} - \text{venous } O_2 \text{ content}}$	244
Cardiac output	CO = stroke volume × heart rate	244
Mean arterial pressure	MAP = cardiac output × total peripheral resistance	244
Mean arterial pressure	MAP = ⅓ systolic + ⅔ diastolic	244
Stroke volume	SV = end diastolic volume − end systolic volume	244
Ejection fraction	$\text{EF} = \frac{\text{stroke volume}}{\text{end diastolic volume}} \times 100$	245
Resistance	$R = \frac{\text{driving pressure}}{\text{flow}} = \frac{8\eta\ (\text{viscosity}) \times \text{length}}{\pi r^4}$	246
Net filtration pressure	$P_{net} = \left[(P_c - P_i) - (\pi_c - \pi_i)\right]$	255

Glomerular filtration rate	$GFR = U_{inulin} \times \frac{V}{P_{inulin}} = C_{inulin}$	422
Glomerular filtration rate	$GFR = K_f [(P_{GC} - P_{BS}) - (\pi_{GC} - \pi_{BS})]$	422
Effective renal plasma flow	$ERPF = U_{PAH} \times \frac{V}{P_{PAH}} = C_{PAH}$	422
Renal blood flow	$RBF = \frac{RPF}{1 - Hct}$	422
Filtration fraction	$FF = \frac{GFR}{RPF}$	423
Free water clearance	$C_{H_2O} = V - C_{osm}$	423
Physiologic dead space	$V_D = V_T \times \frac{(Paco_2 - Peco_2)}{Paco_2}$	459

NOTES

SECTION IV

Top-Rated Review Resources

- How to Use the Database
- Internet Sites
- Comprehensive
- Anatomy and Embryology
- Behavioral Science
- Biochemistry
- Cell Biology and Histology
- Microbiology and Immunology
- Pathology
- Pharmacology
- Physiology
- Commercial Review Courses
- Publisher Contacts

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► HOW TO USE THE DATABASE

This section is a database of top-rated basic science review books, sample examination books, software, Web sites, and commercial review courses that have been marketed to medical students studying for the USMLE Step 1. At the end of the section is a list of publishers and independent bookstores with addresses and phone numbers. For each recommended resource, we list the **Title** of the book, the **First Author** (or editor), the **Series Name** (where applicable), the **Current Publisher**, the **Copyright Year**, the **Number of Pages**, the **ISBN Code**, the **Approximate List Price**, the **Format** of the resource, and the **Number of Test Questions**. The entries for most books also include **Summary Comments** that describe their style and overall utility for studying. Finally, each recommended resource receives a **Rating**. Recommended resources are sorted into a comprehensive section as well as into sections corresponding to eight traditional basic medical science disciplines (anatomy and embryology, behavioral science, biochemistry, cell biology and histology, microbiology and immunology, pathology, pharmacology, and physiology). Within each section, books are arranged first by Rating and then alphabetically by First Author within each Rating group.

For the 2008 edition of *First Aid for the® USMLE Step 1*, the database of rated review books has been reorganized and updated with the addition of many new books and software and with the removal of some older, outdated items. A letter rating scale with six different grades reflects the detailed student evaluations for **Rated Resources.** Each rated resource receives a rating as follows:

A+	Excellent for boards review.
A A–	Very good for boards review; choose among the group.
B+ B	Good, but use only after exhausting better sources.
B–	Fair, but there are many better books in the discipline; or low-yield subject material.

The Rating is meant to reflect the overall usefulness of the resource in helping medical students prepare for the USMLE Step 1 examination. 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 examination

Please note that ratings do not reflect the quality of the resources for purposes other than reviewing for the USMLE Step 1 examination. Many books with lower ratings are well written and informative but are not ideal for boards preparation. We have not listed or commented on general textbooks available in the basic sciences.

Evaluations are based on the cumulative results of formal and informal surveys of thousands of medical students at many medical schools across the country. The summary comments and overall ratings represent a consensus opinion, but there may have been a broad range of opinion or limited student feedback on any particular resource.

Please note that the data listed are subject to change in that:

- 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. xv, 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-based tutorials, commercial review courses, and World Wide Web sites.

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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 the publisher. Please note that *USMLERx* and the *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.

A

WebPath: The Internet Pathology Laboratory — ***Free*** — Review/1000 q

KLATT

http://library.med.utah.edu/WebPath/webpath.html

Features a wealth of outstanding gross and microscopic illustrations, clinical vignette questions, and case studies. Contains many classic, high-quality illustrations. Includes 8 general pathology exams and 11 system-based exams with approximately 1000 questions. Also includes 170 questions associated with images. Questions reflect current boards format and difficulty level but are typically shorter. A WebPath CD-ROM is available for $60.00 and features the online Web site plan supplemented with additional illustrations, topics, tutorials, and radiology.

A

USMLEWorld Qbank — ***$90 for 1 month;*** — Test/2000 q

USMLEWORLD — ***$175 for 3 months***

www.usmleworld.com

A new high-quality USMLE question bank. Very well constructed questions. Excellent, detailed explanations with figures and tables. Questions tend to be more difficult than those on the actual exam. Features a number of test customization and analysis options. Web program does not allow other application windows to be open for studying. Reasonably priced. Compare closely to Kaplan and USMLERx.

A–

Kaplan Qbank — ***$199 for 1 month;*** — Test/2350 q

KAPLAN — ***$279 for 3 months***

www.kaplanmedical.com

A high-quality but expensive question bank providing tailored boards-format exams. Test content and performance feedback are organized by organ system and discipline. Questions are similar in style and content to those on the actual exam but are somewhat reliant on buzzwords. Includes well-written, detailed explanations. Additional Qbanks for physiology and clinical vignettes are available. Compare closely to USMLERx and USMLEWorld.

A–

USMLERx Step 1 Qmax — ***$69 for 1 month;*** — Test/2600+ q

MEDIQ LEARNING — ***$129 for 3 months***

LE

www.usmlerx.com

A well-priced question bank that closely simulates the USMLE. Question length and level of difficulty are similar to those of the actual exam. Explanations are to the point and feature high-yield facts from *First Aid for the USMLE Step 1*. Provides many helpful test selection options and detailed performance analyses. Overall, an excellent resource for high-yield questions with useful test analysis options.

B+

USMLE Steps 123 Step 1 Question Bank — ***$99 for 1 month; $199 for 3 months*** — Test/2500+ q

ELSEVIER

www.studentconsult.com/usmle

A solid question bank that can be divided according to discipline and subject area. Includes both practice and test modes. Question length, difficulty, and test interface (FRED) are similar to those of the actual exam. Offers concise explanations with links to StudentConsult and FirstConsult content. Users can see cumulative results over time and compared to other test takers. Overall, a good source of practice questions, with a number of subscription periods available. Limited student feedback.

B+

The Pathology Guy — ***Free*** — Review

FRIEDLANDER

www.pathguy.com

A free Web site containing extensive but poorly organized information on a variety of fundamental concepts in pathology. An excellent collection of high-yield facts can be found in "Ed's Pathology Review for USMLE," which is buried at the end of each pathology topic page. Philosophical and religious digressions can impede a rapid review of the site.

B+

Digital Anatomist Interactive Atlases — ***Free*** — Review

UNIVERSITY OF WASHINGTON

www9.biostr.washington.edu/da.html

A good site containing an interactive neuroanatomy course along with a three-dimensional atlas of the brain, thorax, and knee. Atlases have computer-generated images along with cadaver dissections. Each atlas also has a useful quiz in which users identify structures in the slide images. An excellent source for reviewing neuro images.

B

The Whole Brain Atlas — ***Free*** — Review

JOHNSON

www.med.harvard.edu/AANLIB/home.html

A collection of high-quality brain MR and CT images with views of normal, aging, and diseased brains (CVA, degenerative, neoplastic, and inflammatory diseases). The interface is technologically impressive but complex. Guided tours and image correlations to cases are especially useful. Although not all of the images are particularly high yield for the boards, this is an excellent introduction to neuroimaging.

B

Lippincott's 350-Question Practice Test for USMLE Step 1 — ***Free*** — Test/350 q

LIPPINCOTT WILLIAMS & WILKINS

www.lww.com/medstudent/usmle

Previously Blackwell's Step 1 Online Q&A. A full-length, seven-block, 350-question practice exam in a format similar to that of the real exam. Questions come with explanations related to the selected answer only. Users can bookmark questions and can take the test all at once or by section.

B–

USMLEasy — ***$99 for 1 month; $199 for 3 months*** — Test/2800 q

MCGRAW-HILL

www.usmleasy.com

An Internet-based question bank based on the PreTest series. Requires an online subscription. Some questions are more obscure than those appearing on the actual exam. Users can track questions completed as well as customize tests. Presented in boards format. Useful as a supplemental review after other resources have been exhausted.

B–

Active Learning Centre — ***Free*** — Test/100 q

TURCHIN

www.med.jhu.edu/medcenter/quiz/home.cgi

A quiz engine site based on a large database with an extensive list of bugs, drugs, and vaccines. Questions test the basic characteristics of each element in the database in a multiple-choice, matching, or essay format that the user selects. Questions are not boards style but are useful for learning the memory-intensive subjects of microbiology and pharmacology.

A

First Aid Cases for the USMLE Step 1 ***$39.95*** Review

LE

McGraw-Hill, 2006, 334 pages, ISBN 0071464107

A series of cases organized into the same sections as *First Aid for the USMLE Step 1*. Provides 9–45 cases per general principle or organ system. Each case includes a paragraph-long clinical vignette followed by questions and detailed explanations. Many cases include images that are highly relevant to boards review. Overall, a good supplemental USMLE review resource that provides just the right amount of depth.

A–

Kaplan's USMLE Step 1 Home Study Program ***$499.00*** Review

Kaplan, 2006, 1900 pages, ISBN 0X63410105

Includes two general-principle review books along with two organ system–based review books, all of which are lengthy and comprehensive. Useful only if started early, possibly with coursework. Excellent as a reference for studying. Expensive for the amount of material. Books can be purchased by calling 1-800-KAP-ITEM or by visiting www.kaptest.com.

A–

USMLE Q&A for the USMLE Step 1 ***$39.95*** Test/1000 q

LE

McGraw-Hill, 2006, 416 pages, ISBN 0071481729

A great resource for review questions drawn from the USMLE Step 1 Qmax. Offers 1000 questions organized according to subject along with one full-length examination consisting of 350 questions. Questions are similar to those of the actual exam in both complexity and length. Explanations are brief but adequate.

A–

medEssentials ***6 months for $129;*** Review

MANLEY ***12 months for $189;***

Kaplan, 2006, 500 pages, ISBN BK5023A ***25 months for $279***

A comprehensive review book with great tables and figures. Divided into general principles and organ systems. Contains some high-yield color images in the back. Too detailed in some parts. Comes with a monthly subscription to online interactive exercises that are of limited value. Limited student feedback.

A–

Step-Up: A High-Yield, Systems-Based Review for the USMLE Step 1

$39.95 Review

MEHTA

Lippincott Williams & Wilkins, 2006, 448 pages, ISBN 078178090X

An organ system–based review text that is useful for integrating the basic sciences covered in Step 1. Composed primarily of outlines, charts, tables, and diagrams. The appendix includes 38 clinical cases and an alphabetical section on pharmacology. The previous edition contained some errors. The organ system format appeals to many students and serves as a good contrast to other review sources. Includes useful "quick hit" facts. Limited feedback on the new edition.

A–

Deja Review: USMLE Step 1

$22.95 Review

NAHEEDY

McGraw-Hill, 2006, 192 pages, ISBN 0071447903

A review book featuring questions and answers in a two-column, quiz-yourself format, divided according to discipline. Includes a section at the end with high-yield clinical vignettes. Has a few mistakes throughout, but still a great last-second review before the exam. Compare with the Recall series. Limited student feedback.

A–

USMLE Step 1 Recall Audio

$37.95 Audio—MP3

REINHEIMER

Lippincott Williams & Wilkins, 2007, ISBN 0781765544

Downloads accessed at http://thepoint.lww.com/audio. Offers the same content as that of the corresponding text. The use of two different voices allows listeners to distinguish questions from answers. Content contains some errors, but overall a useful review resource that can be used during downtime.

B+

USMLE Step 1 Secrets

$39.95 Review

BROWN

Elsevier, 2004, 324 pages, ISBN 1560535709

Clarifies difficult concepts in a concise, easy-to-read manner. Complements other boards study material, with a focus on understanding preclinical fundamentals rather than on rote memorization. Easy-to-read style allows for rapid review during downtime. Good integration of information.

B+

Medical Boards—Step 1 Made Ridiculously Simple

$29.95 Review

CARL

MedMaster, 2007, 351 pages, ISBN 0940780712

Quick and easy reading. The table and chart format is organized by subject, but some charts are poorly labeled. Reviews are mixed. Consider as an adjunct. Compare with *Crashing the Boards: USMLE Step 1*. Limited feedback on the recent edition.

B+

Blueprints Step 1 Q&A

$34.95 Test/350 q

CLEMENT

Lippincott Williams & Wilkins, 2003, 184 pages, ISBN 140510323X

Contains one full-length exam of 350 questions written by students. Good for practicing the multistep questions common on the actual exam. Questions are at times easier than those on the actual test. A good supplemental source for practice questions on high-yield facts.

B+

Lange Outline Review: USMLE Step 1

$39.95 Review

GOLDBERG

McGraw-Hill, 2006, 364 pages, ISBN 0071451919

A comprehensive outline review of basic science topics. Includes essential facts, diseases, and disorders. Also offers a bulleted treatment of major abnormal processes by system. Includes black-and-white images of pathology and histology throughout.

B+

Lange Practice Tests USMLE Step 1

$42.95 Review/650 q

GOLDBERG

McGraw-Hill, 2005, 240 pages, ISBN 007144615X

A good resource for review questions consisting of 13 blocks of 50 questions with explanations. Less lengthy and challenging than the actual USMLE questions.

B+

Rapid Review for USMLE Step 1

$34.95 Review/1400 q

GOLJAN

Elsevier, 2002, 314 pages + CD-ROM, ISBN 0323008410

Outline format with high-yield marginal notes, figures, and tables that highlight key content. Narrative clinical boxes illustrate clinical relevance. Practice exams provide USMLE-style questions of mixed quality. The CD-ROM includes the questions from the book, but the user cannot omit previously used questions from practice sessions.

B+

Lange Q&A: USMLE Step 1

$41.95 Review/1100+ q

KING

McGraw-Hill, 2005, 528 pages, ISBN 0071445781

A large source of review questions. Offers more than 1100 questions organized according to subject along with three sections of comprehensive practice exams. Slightly less challenging than the actual USMLE questions.

B+

PreTest Clinical Vignettes for the USMLE Step 1

$29.95 Test/400 q

MCGRAW-HILL

McGraw-Hill, 2007, 416 pages, ISBN 0071471847

Clinical vignette–style questions with detailed explanations, organized as eight blocks of 50 questions covering basic sciences. Serves as a good self-evaluation tool, but questions may not mirror those on the actual exam.

B+

USMLE Step 1 Recall: Buzzwords for the Boards

$40.95 Review

REINHEIMER

Lippincott Williams & Wilkins, 2007, 467 pages, ISBN 0781778735

Quizzes on main topics and key points presented in a two-column question-and-answer format. Good for self-testing, group study, and quick review. Useful as a change of pace. Covers many important clinical features, but not comprehensive or tightly organized. Sometimes focuses on obscure details and memorization rather than on the comprehension and integration that the USMLE emphasizes. Compare with the Deja Review series.

B+

Underground Clinical Vignettes: Step 1 Bundle

$159.95 Review

SWANSON

Lippincott Williams & Wilkins, 2007, 9 volumes, ISBN 0781763622

Bundle includes nine books. Designed for easy quizzing with a group. Case-based vignettes provide a good review supplement. Best when started early with coursework or when used in conjunction with another primary review source.

B

Gold Standard Prep Set for USMLE Step 1

$309.00 Review

KNOUSE

Gold Standard, 2004

A set of 55 CDs covering USMLE Step 1 material in more than 70 hours. Limited but positive feedback on an updated and expanded set of CDs. Used by some students as a way to review while driving, while working out, and during downtime. Contains some inaccuracies. Available only by mail order through the company's Web site, www.boardprep.net.

B

NMS Review for USMLE Step 1

$44.95 Test/850 q

LAZO

Lippincott Williams & Wilkins, 2005, 480 pages + CD-ROM, ISBN 0781779219

A text that includes a CD-ROM and serves as a good source of practice questions and answers. Some questions are too picky or difficult. Annotated explanations are well written but are sometimes unnecessarily detailed. Organized as 17 practice exams. The six pages of color plates are helpful. The CD-ROM attempts to simulate the CBT format but is disorganized.

B

Kaplan's USMLE Step 1 Qbook

$44.95 Test/850 q

MANLEY

Kaplan, 2006, 464 pages, ISBN 1419551493

Consists of seventeen 50-question exams organized by the traditional basic science disciplines. Offers good USMLE-style questions with clear, detailed explanations, but lacks the classic images typically seen on the exam. Also includes a guide on test-taking strategies. Comparable to the First Aid and NMS question reviews.

B

USMLE Step 1 Recall PDA: Buzzwords for the Boards

$37.95 PDA

REINHEIMER

Lippincott Williams & Wilkins, 2004, ISBN 0781754216

The PDA version of the book of the same name. Useful for quick review.

B

PreTest Physical Diagnosis

$25.95 Test/500 q

RETEGUIZ

McGraw-Hill, 2006, 434 pages, ISBN 0071455515

A collection of clinical vignettes organized by body system, presented in a style similar to that of other books in the PreTest series. May be beyond the scope of Step 1, but could also be used in the clinical years of medical school. Limited student feedback.

B–

Exam Master Step 1

$149.00 Test/8000 q

EXAM MASTER

Exam Master Corporation, 2004, ISBN 158129087X

Windows/Mac-based testing software with access to up to 8000 Step 1 questions. Interface and exam setup can be difficult. Questions are of mixed quality and can be relatively simple or very obscure. Offers the ability to hide multiple-choice options.

B–

Cracking the Boards: USMLE Step 1

$34.95 Review/400 q

STEIN

Random House, 2000, 832 pages, ISBN 0375761632

A comprehensive text review based on the USMLE content outline, written by past and present medical students. The style is wordy and broad but offers few details. The organ-based format appeals to some students. Includes many labeled illustrations, charts, and photos.

A–

High-Yield Embryology — *$25.95* — Review

DUDEK

Lippincott Williams & Wilkins, 2006, 208 pages,
ISBN 0781768721

A very good, concise review of embryology for the USMLE. Offers excellent organization with clinical correlations. Includes a high-yield list of embryologic origins of tissues. No index or questions.

A–

High-Yield Neuroanatomy — *$25.95* — Review

FIX

Lippincott Williams & Wilkins, 2005, 178 pages,
ISBN 0781758998

A clean, easy-to-read outline format. Offers straightforward text with excellent diagrams and illustrations. The first several chapters are particularly good. Compare with *Clinical Neuroanatomy Made Ridiculously Simple*. No index.

A–

Case Files: Gross Anatomy — *$29.95* — Review

TOY

McGraw-Hill, 2005, 345 pages, ISBN 0071437797

A resource that offers both gross anatomy basics and clinical cases covering several high-yield anatomy topics. Also features a concise discussion of anatomy essentials. Diagrams are sparse but high yield.

A–

USMLE Road Map: Gross Anatomy — *$25.95* — Review/100 q

WHITE

McGraw-Hill, 2005, 240 pages, ISBN 0071445161

An outline treatment of gross anatomy with clinical correlations throughout. Also features high-yield facts in boldface along with numerous high-yield charts and figures. Clinical problems with explanations are given at the end of each chapter. An especially effective chart format is used throughout, with clearly labeled illustrations of basic anatomy. Good integration of facts.

A–

USMLE Road Map: Neuroscience — *$24.95* — Review/80 q

WHITE

McGraw-Hill, 2004, 208 pages, ISBN 0071422870

An outline review of basic anatomy and physiology with clinical correlations throughout. Also features high-yield facts in boldface along with numerous high-yield charts and figures. Clinical problems with explanations are given at the end of each chapter.

B+

Elsevier's Integrated Anatomy and Embryology

$34.95 Book

BOGART

Elsevier, 2007, 378 pages, ISBN 1416031650

Part of the new Integrated series that focuses on core knowledge in a specific basic science discipline while linking that information to related concepts from other disciplines. Case-based and USMLE-style questions at the end of each chapter allow readers to gauge their comprehension of the material. Includes online access. Best if used during coursework. Limited student feedback.

B+

High-Yield Gross Anatomy

$26.95 Review

DUDEK

Lippincott Williams & Wilkins, 2007, 190 pages, ISBN 0781770157

An excellent, concise review with clinical correlations. Contains well-labeled, high-yield radiologic images. May be useful to supplement with an atlas. No index.

B+

Clinical Neuroanatomy Made Ridiculously Simple

$19.95 Review/Few q

GOLDBERG

MedMaster, 2007, 96 pages + CD-ROM, ISBN 0940780577

An easy-to-read, memorable, and simplified format with clever hand-drawn diagrams. Offers a quick, high-yield review of clinical neuroanatomy. Good emphasis on clinically relevant pathways, cranial nerves, and neurologic diseases. Includes a CD-ROM that offers CT and MRI images as well as a tutorial on neurologic localization. Compare with *High-Yield Neuroanatomy*.

B+

Crash Course: Anatomy

$29.95 Review

GRANGER

Elsevier, 2006, 225 pages, ISBN 0323043194

Part of the Crash Course review series for basic sciences, integrating clinical topics. Offers two-color illustrations, handy study tools, and USMLE review questions. Includes online access. Provides a solid review of anatomy for Step 1. Best if started early.

B+

Rapid Review: Gross and Developmental Anatomy

$34.95 Review/350 q

MOORE

Elsevier, 2006, 400 pages, ISBN 0323045510

A detailed treatment of basic anatomy and embryology, presented in an outline format similar to that of other books in the series. At times more detailed than necessary for boards review. Contains high-yield charts and figures throughout. Two 50-question tests with extensive explanations are included, with 250 additional questions online.

B+

Underground Clinical Vignettes: Anatomy ***$22.95*** Review/20 q

SWANSON

Lippincott Williams & Wilkins, 2007, 224 pages,
ISBN 0781764750

Concise clinical cases illustrating approximately 100 frequently tested diseases with an anatomic basis. Also includes 20 additional boards-style questions. Cardinal signs, symptoms, and buzzwords are highlighted. A useful source for isolating important anatomy concepts to concentrate on for Step 1.

B+

Deja Review: Neuroscience ***$22.95*** Review

TREMBLAY

McGraw-Hill, 2006, 250 pages, ISBN 0071474625

A review book featuring questions and answers in a two-column, quiz-yourself format similar to that of the Recall series. Provides a sound review in a format that differs from straight text. A perfect length for USMLE neurophysiology and anatomy review.

B

Neuroscience at a Glance ***$34.95*** Review

BARKER

Blackwell Science, 2003, 132 pages, ISBN 1405111240

A high-yield treatment of basic principles in neuroscience using figures only, with one topic presented on each page. Includes a highly effective appendix of pathways. Most useful when used in conjunction with a neuroscience course. Limited student feedback.

B

Platinum Vignettes: Anatomy & Embryology ***$26.95*** Review

BROCHERT

Elsevier, 2003, 110 pages, ISBN 1560535814

Fifty clinical case scenarios presented in a user-friendly format, with questions appearing on the front of each page and answers printed on the back. Similar in style to other books in the Platinum Vignettes series; may be of benefit for students who wish to self-quiz. Relatively few cases are presented considering that both anatomy and embryology are covered. Expensive for the amount of material covered.

B

Gray's Anatomy Flash Cards ***$34.95*** Flash cards

DRAKE

Elsevier, 2005, 320 pages, ISBN 0443069107

The front of each card offers detailed anatomical illustrations, while the back of each card identifies the structures in each illustration along with systemically and clinically relevant information. Includes some radiology review cards and clinical question cards that are good for boards review. Overall, may be too detailed for USMLE preparation. Includes online access.

B

BRS Embryology ***$36.95*** Review/500 q

DUDEK

Lippincott Williams & Wilkins, 2007, 304 pages,
ISBN 0781771161

An outline-based review of embryology that is typical of the BRS series. Offers a good but overly detailed review of important embryology. A discussion of congenital malformations is included at the end of each chapter along with relevant questions. The comprehensive exam at the end of the book is high yield.

B

BRS Neuroanatomy ***$36.95*** Review/500 q

FIX

Lippincott Williams & Wilkins, 2007, 480 pages,
ISBN 0781772451

An updated text that covers the anatomy and embryology of the nervous system. Complete but too lengthy for USMLE review; requires time commitment. Compare with *High-Yield Neuroanatomy* by the same author.

B

Clemente's Anatomy Flash Cards ***$36.95*** Review

GEST

Lippincott Williams & Wilkins, 2007, 700 pages,
ISBN 0781765269

Organized by region, with 350 full-color illustrations. Based on Clemente's *Anatomy: A Regional Atlas of the Human Body*, 5th edition. Labels are designed for self-testing, with numbers on the front of each card and answers on the back. Tables on the back of the cards provide additional information about bones, muscles, nerves, arteries, veins, ligaments, topographic features, lymphatics, and organs. Great for use during coursework, but too detailed for boards review.

B

Clinical Anatomy Made Ridiculously Simple ***$29.95*** Review

GOLDBERG

MedMaster, 2007, 187 pages, ISBN 0940780798

An easy-to-read text offering simple diagrams along with numerous mnemonics and amusing associations. Incomplete. The humorous style has variable appeal to students, so browse before buying. Offers good coverage of selected topics. Best if used during coursework.

B

Clinical Anatomy Flash Cards

$36.95 Review

GOULD

Lippincott Williams & Wilkins, 2007, 696 pages,
ISBN 0781765099

Based on Moore and Dalley's *Clinically Oriented Anatomy*, 5th edition, and Agur and Dalley's *Grant's Atlas of Anatomy*, 11th edition. Organized by region, with 450 full-color illustrations offering realistic anatomic renderings from Grant's Atlas. Cards feature clinically relevant descriptions of structures, concise versions of the text's clinical "Blue Boxes," and correlating images. Great for use during coursework, but too detailed for boards review.

B

Netter's Anatomy Flash Cards

$34.95 Flash cards

HANSEN

Elsevier, 2006, 324 cards, ISBN 1416039740

A series of 324 flash cards featuring illustrations from Netter's *Atlas of Human Anatomy*, 4th edition. Cards are hole-punched and include a metal ring for easy portability. Includes access to www.netteranatomy.com, where cards can be viewed online. Great for use during coursework, but too detailed for boards review.

B

Netter's Clinical Anatomy

$48.95 Review

HANSEN

Elsevier, 2005, 600 pages, ISBN 192900771X

A review book that includes many of the famous Netter's anatomy and embryology images along with short descriptions. It also offers helpful clinical correlation pages for many of the common diseases. Definitely a wonderful anatomy reference text during boards studying, but too long and detailed to be used as a primary review source.

B

Crash Course: Nervous System

$29.95 Review

MIHAILOFF

Elsevier, 2005, 272 pages, ISBN 0323034438

Part of the Crash Course review series for basic sciences, integrating clinical topics. Offers two-color illustrations, handy study tools, and USMLE review questions. Includes online access. A good overall review of neuroscience with integration of multiple areas.

B

Elsevier's Integrated Neuroscience — ***$34.95*** — Book

NOLTE

Elsevier, 2007, 336 pages, ISBN 0323034098

Part of the new Integrated series that focuses on core knowledge in a specific basic science discipline while linking that information to related concepts from other disciplines. Case-based and USMLE-style questions at the end of each chapter allow readers to gauge their comprehension of the material. Includes online access. Best if used during coursework. Limited student feedback.

B

PreTest Neuroscience — ***$25.95*** — Test/500 q

SIEGEL

McGraw-Hill, 2007, 384 pages, ISBN 0071471804

Similar to other books in the PreTest series. Features a question-and-answer format that is not necessarily in USMLE style. Black-and-white images are referenced to questions throughout. Includes a brief high-yield section. Improved 2007 edition.

B

BRS Gross Anatomy Flash Cards — ***$31.99*** — Flash cards

SWANSON

Lippincott Williams & Wilkins, 2005, 254 pages, ISBN 0781756545

High-yield anatomy clinical cases presented in flash-card format. Anatomy basics are generally excluded. A useful, boards-relevant resource for students who like to study with flash cards and are reasonably well versed in anatomy.

B

Blueprints Notes & Cases: Neuroscience — ***$28.95*** — Review

WECHSLER

Lippincott Williams & Wilkins, 2003, 240 pages, ISBN 1405103493

High-yield cases followed by a discussion and tables, presented in a format similar to that of other books in the Blueprints series. Offers important gross neuroanatomy and neurophysiology facts, but diagrams must be improved if the book is to be considered sufficiently comprehensive for boards review.

B

Rapid Review: Neuroscience — ***$34.95*** — Book

WEYHENMEYER & GALLMAN

Elsevier, 2006, 304 pages, ISBN 0323022618

A detailed treatment of neuroscience, presented in an outline format similar to that of other books in the series. Should be started early given its extensive treatment of a relatively narrow topic. Contains high-yield charts and figures throughout. Two 50-question tests with extensive explanations are included, with 250 additional questions online.

B–

Anatomy Recall — ***$34.95*** — Review

ANTEVIL

Lippincott Williams & Wilkins, 2005, 384 pages,
ISBN 078179885X

Presented in question-and-answer format. Good for quick review, but too detailed for boards review.

B–

BRS Gross Anatomy — ***$36.95*** — Review/500 q

CHUNG

Lippincott Williams & Wilkins, 2007, 544 pages,
ISBN 0781771749

A detailed, lengthy text in outline format with illustrations and tables. Better for coursework than for quick boards review, especially for a lower-yield subject. Features a good clinical correlation section.

B–

Netter's Neuroscience Flash Cards — ***$34.95*** — Flash cards

FELTEN

Elsevier, 2005, 235 cards, ISBN 1929007647

Color codes identify corresponding sections from the atlas for easy cross-referencing and review. Explanatory comments are given on the back of each card along with integrative clinical points. Great for coursework, but too detailed for boards review.

B–

Manter and Gatz's Essentials of Clinical Neuroanatomy and Neurophysiology — ***$33.95*** — Review

GILMAN

F. A. Davis, 2002, 281 pages, ISBN 0803607725

A well-organized discussion of neuroanatomy, neurophysiology, and neuropharmacology presented with illustrations and images. Too dense for boards review.

B–

Biotest Study Aids: Histology and Neural Anatomy — ***$25.95*** — Review/2000 q

PAPKA

Biotest, Inc., 2004, 427 pages, ISBN 1893720136

A comprehensive outline review. Lacks illustrations and includes a large number of low-quality questions with no explanations, but answers are cross-referenced to the text. Consider using with coursework. Limited student feedback.

B–

Clinical Anatomy: An Illustrated Review ***$39.95*** Review/500 q

SNELL

Lippincott Williams & Wilkins, 2003, 294 pages,
ISBN 0781743168

A well-organized summary of Snell's major book. Includes excellent diagrams and tables. Questions incorporate radiographs, CT scans, and MRIs. Does not cover neuroanatomy or embryology. Neither the text nor the questions are as clinical as the title implies. Only some answers have explanations, and most are too short.

B–

Imaging Atlas of Human Anatomy ***$49.95*** Text

WEIR

Elsevier, 2003, 224 pages, ISBN 0723432112

An atlas of diagnostic images for all major systems, including MRIs, CT scans, and brief explanations of diagnostic methods. Useful primarily as an imaging reference for boards review.

A

High-Yield Behavioral Science — *$26.95* — Review

FADEM

Lippincott Williams & Wilkins, 2001, 144 pages,
ISBN 0781730848

A clear, concise, quick review of behavioral science. Offers a logical presentation with crammable charts, graphs, and tables. Features a short but adequate statistics chapter. No index.

A–

BRS Behavioral Science — *$36.95* — Review/500 q

FADEM

Lippincott Williams & Wilkins, 2004, 296 pages,
ISBN 0781757274

An easy-to-read outline format with boldfacing of key terms. Offers good, detailed coverage of high-yield topics. The text is lengthy and gives more information than may be needed for the USMLE. Includes excellent tables and charts as well as a short but complete statistics chapter. Offers great coverage of ethics and patient communication topics. Also features good review questions, including a 100-question comprehensive exam at the end of the book.

A–

Deja Review: Behavioral Science — *$22.95* — Review

STANFORD

McGraw-Hill, 2007, 200 pages, ISBN 0071468684

A review book featuring questions and answers in a two-column, quiz-yourself format similar to that of the Recall series. Provides a sound review in a format that differs from straight text. Allows a more interactive review of some hard-to-memorize details needed for USMLE behavioral science questions.

A–

Rapid Review: Behavioral Science — *$34.95* — Review/350 q

STEVENS

Elsevier, 2006, 352 pages, ISBN 0323045715

A quick outline format covering basic topics in behavioral science, human development, and biostatistics, presented in a format similar to that of other books in the Rapid Review series. Two 50-question multiple-choice tests are included with explanations. Somewhat more detailed on specific disorders, but not sufficient as a sole biostatistics review. The CD-ROM contains additional questions. Compare with *High-Yield Behavioral Science*. Limited student feedback.

A–

Underground Clinical Vignettes: Behavioral Science

$22.95 Review/20 q

SWANSON

Lippincott Williams & Wilkins, 2007, 224 pages,
ISBN 0781764645

Concise clinical cases illustrating commonly tested diseases in behavioral science. Cardinal signs, symptoms, and buzzwords are highlighted. Useful for picking out important points in this very broad subject. Use as a supplement to other review sources. Also includes 20 additional boards-style questions.

B+

Behavioral Sciences and Outpatient Medicine for the Boards and Wards

$19.95 Review

AYALA

Lippincott Williams & Wilkins, 2001, 112 pages,
ISBN 0632045787

Presented in a clear and informative format similar to that of other books in the Boards and Wards series. Covers some low-yield topics.

B+

Platinum Vignettes: Behavioral Science & Biostatistics

$26.95 Review

BROCHERT

Elsevier, 2003, 100 pages, ISBN 1560535768

A series of cases followed by explanations and discussions on the subsequent page, presented in a format similar to that of other books in the Platinum Vignettes series. In contrast to *Underground Clinical Vignettes: Behavioral Science*, the Platinum Vignettes series includes vignettes for biostatistics; however, there are only half as many cases. Expensive for the amount of material.

B+

High-Yield Brain and Behavior

$29.95 Review

FADEM

Lippincott Williams & Wilkins, 2007, 256 pages,
ISBN 0781792282

Part of the new High-Yield Systems series that covers embryology, gross anatomy, radiology, histology, physiology, microbiology, and pharmacology as they relate to the nervous system. Written by the same author as the High-Yield and BRS Behavioral Science texts. Overall, provides a good review of neuroscience and behavioral science.

B+

High-Yield Biostatistics ***$26.95*** Review

GLASER

Lippincott Williams & Wilkins, 2004, 128 pages,
ISBN 078179644X

A well-written text, but some explanations are confusing. Offers extensive coverage for a low-yield topic. Includes good review questions and tables. For the motivated student; not for last-minute cramming. Suitable as a course companion. Best used in conjunction with a behavioral science resource.

B+

Blueprints Notes & Cases: Behavioral Science and Epidemiology ***$29.95*** Review/184 q

NEUGROSCHL

Lippincott Williams & Wilkins, 2003, 224 pages,
ISBN 1405103558

A case-oriented approach to behavioral science, presented as part of the Blueprints Notes & Cases series. Includes the HPI, a basic science review and discussion, key points, and questions. The 8.5″ × 11″ layout may feel overwhelming to some, but the font size is conducive to easy review. A good way to master the intangibles of behavioral science, but slightly more detailed than warranted for boards review.

B

PreTest Behavioral Science ***$24.95*** Test/500 q

EBERT

McGraw-Hill, 2001, 300 pages, ISBN 0071374701

Contains detailed answers cross-referenced with other resources along with good test questions. Requires time commitment. Includes a brief high-yield section. Need updating.

B

Kaplan USMLE Medical Ethics ***$39.00*** Review

FISCHER

Kaplan, 2007, 208 pages, ISBN 1419542091

Includes 100 cases, each followed by a single multiple-choice question with detailed explanations. The first part of the book is primarily in text format. Also offers guidelines on how the USMLE requires test takers to think about ethics and medicolegal questions. Too long for review of a low-yield subject area, but its 100 cases could be a useful resource.

B

Behavioral Science Made Ridiculously Simple ***$16.95*** Review

SIERLES

MedMaster, 1998, 171 pages, ISBN 0940780348

Easy reading, and reasonably high yield for the amount of material. Includes medical sociology along with strong coverage of psychopathology with illustrative examples. No biostatistics. Sometimes offers too much detail on low-yield topics.

B

Rapid Review: Behavioral Science ***$34.95*** Review/350 q

STEVENS

Elsevier, 2006, 320 pages, ISBN 0323045715

Similar in style to other books in the Rapid Review series, providing a good review of a broad subject. Includes 100 questions and explanations along with an additional 250 questions online. Limited student feedback.

B–

Epidemiology & Biostatistics Secrets ***$39.95*** Review

NORDNESS

Elsevier, 2005, 288 pages, ISBN 0323034063

Presents information in a format similar to that of other Secrets books. A useful resource for a notably hard-to-study topic, with case questions and discussions. Comes with Student Consult online access and extras. Too long and detailed for boards review, but a useful reference for biostatistics.

A–

Lippincott's Illustrated Reviews: Biochemistry — *$52.95* — Review/250 q

CHAMPE

Lippincott Williams & Wilkins, 2007, 528 pages, ISBN 0781769604

An excellent book that offers good clinical correlations as well as highly effective color diagrams. Offers a comprehensive review of biochemistry, including some low-yield topics. The new edition also features high-yield chapter summaries and a "big picture" chapter at the end of the book that highlights the most important concepts. Requires time commitment; skim high-yield diagrams to maximize USMLE review. Best used with coursework.

A–

Deja Review: Biochemistry — *$22.95* — Review

MANZOUL

McGraw-Hill, 2007, 200 pages, ISBN 0071474633

A review book featuring questions and answers in a two-column, quiz-yourself format similar to that of the Recall series. Provides a sound review in a format that differs from straight text. Includes a helpful chapter on molecular biology. Limited student feedback.

A–

Rapid Review: Biochemistry — *$34.95* — Review/350 q

PELLEY

Elsevier, 2006, 320 pages, ISBN 0323044379

A quick outline format covering basic topics in biochemistry, presented in a format similar to that of other books in the Rapid Review series. High-yield disease correlation boxes are useful for review. Excellent tables and high-yield figures are featured throughout. Also includes two 50-question multiple-choice tests with explanations plus 250 questions online.

A–

BRS Biochemistry and Molecular Biology Flash Cards — *$29.95* — Review

SWANSON

Lippincott Williams & Wilkins, 2006, 512 pages, ISBN 0781779022

Flash cards covering a range of topics in biochemistry and molecular biology. Although not comprehensive, they provide a good source of review for these topics.

A– ***Underground Clinical Vignettes: Biochemistry*** ***$22.95*** Review/20 q

SWANSON

Lippincott Williams & Wilkins, 2007, 256 pages,
ISBN 0781764726

Concise clinical cases illustrating approximately 100 frequently tested diseases with a biochemical basis. Cardinal signs, symptoms, and buzzwords are highlighted. Also includes 20 additional boards-style questions. A nice review of "take-home" points for biochemistry, and a useful supplement to other sources of review.

B+ ***Crash Course: Metabolism and Nutrition*** ***$29.95*** Book

CLARK

Elsevier, 2005, 256 pages, ISBN 1416031170

Part of the Crash Course review series for basic sciences, integrating clinical topics. Offers two-color illustrations, handy study tools, and USMLE review questions. Includes online access. Although lengthy, it provides a clear and concise review of biochemistry for Step 1. Best if started early.

B+ ***Elsevier's Integrated Biochemistry*** ***$34.95*** Book

PELLEY

Elsevier, 2006, 300 pages, ISBN 0323034101

Part of the new Integrated series that focuses on core knowledge in a specific basic science discipline while linking that information to related concepts from other disciplines. Case-based and USMLE-style questions at the end of each chapter allow readers to gauge their comprehension of the material. Includes online access. Best if used during coursework. Limited student feedback.

B+ ***High-Yield Biochemistry*** ***$26.95*** Review

WILCOX

Lippincott Williams & Wilkins, 2003, 107 pages,
ISBN 0781743141

A concise and crammable text in outline format with good clinical correlations at the end of each chapter. Features many diagrams and tables. Good as a study supplement.

B ***Clinical Biochemistry*** ***$51.95*** Review

GAW

Churchill Livingstone, 2004, 180 pages, ISBN 0443072698

Biochemistry and physiology presented in a clinical framework. Visually pleasing. Focuses on adult medicine; skimpy on inherited disorders, genetics, and molecular biochemistry. Case studies are included throughout, but no standard question-and-answer exercises are given. Best if used during a biochemistry course.

B

Clinical Biochemistry Made Ridiculously Simple ***$22.95*** Review

GOLDBERG

MedMaster, 2004, 93 pages + foldout, ISBN 0940780305

A conceptual approach to clinical biochemistry, presented with humor. The casual style does not appeal to all students. Mnemonics tend to be somewhat complicated. Offers a good overview and integration of all metabolic pathways. Includes a 23-page clinical review that is very high yield and crammable. Also contains a unique foldout "road map" of metabolism. For students with a firm biochemistry background.

B

PreTest Biochemistry & Genetics ***$25.95*** Test/500 q

INGRAM-SMITH

McGraw-Hill, 2007, 432 pages, ISBN 0071471839

Difficult questions with detailed, referenced explanations. Best for motivated students who use it along with a review book. Contains some questions on biochemical disorders and metabolism but no clinical vignettes. Features a useful high-yield-facts section at the front of the book.

B

Case Files: Biochemistry ***$29.95*** Review

TOY

McGraw-Hill, 2005, 450 pages, ISBN 0071437819

A text that is divided into clinical cases followed by clinical correlations, a discussion, and take-home pearls, presented in a format similar to others in the Case Files series. A few questions accompany each case. The black-and-white figures are sometimes too small to read, but the clinical correlations make biochemistry concepts easier to remember. Too lengthy for rapid review; best for students who enjoy problem-based learning.

A–

High-Yield Cell and Molecular Biology ***$26.95*** Review

DUDEK

Lippincott Williams & Wilkins, 2006, 254 pages,
ISBN 078176887X

Cellular and molecular biology presented in an outline format, with good diagrams and clinical correlations. The new, recently published edition is brief but complete. Includes descriptions of laboratory techniques and genetic disorders. No questions or vignettes.

A–

Deja Review: Histology & Medical Cell Biology ***$22.95*** Review

GRISSON

McGraw-Hill, 2006, 200 pages, ISBN 0323034101

Features questions and answers in a two-column, quiz-yourself format similar to that of the Recall series. Provides a sound review in a format that differs from straight text.

B+

Crash Course: Cell Biology and Genetics ***$29.95*** Review

LAMB

Elsevier, 2006, 250 pages, ISBN 0323044948

Part of the Crash Course review series for basic sciences, integrating clinical topics. Offers two-color illustrations, handy study tools, and USMLE review questions. Includes online access. Too much coverage for a limited subject.

B

Elsevier's Integrated Genetics ***$34.95*** Book

ADLISON

Elsevier, 2007, 336 pages, ISBN 0323043291

Part of the new Integrated series that focuses on core knowledge in a specific basic science discipline while linking that information to related concepts from other disciplines. Case-based and USMLE-style questions at the end of each chapter allow readers to gauge their comprehension of the material. Includes online access. Best if used during coursework. Limited student feedback.

B

Rapid Review: Histology and Cell Biology ***$34.95*** Review/350 q

BURNS

Elsevier, 2006, 336 pages, ISBN 0323044255

Similar to other books in the Rapid Review series. Features an outline of basic concepts with numerous charts, but histology images are very limited. Two 50-question multiple-choice tests are presented with explanations, along with 250 questions online.

B

High-Yield Histology

$26.95 Review

DUDEK

Lippincott Williams & Wilkins, 2004, 288 pages,
ISBN 0781747635

A quick and easy review of a relatively low-yield subject. Tables include some high-yield information. Contains good pictures. The appendix features classic electron micrographs. Too lengthy for USMLE review.

B

BRS Cell Biology and Histology

$37.95 Review/500 q

GARTNER

Lippincott Williams & Wilkins, 2006, 384 pages + CD-ROM,
ISBN 0781785774

An outline format that is useful for looking up cell biology and histology information, presented in a style that is typical of the BRS series. Can be used alone for cell biology review, but does not include enough histology images to be considered comprehensive. Includes a CD-ROM with questions.

B

PreTest Anatomy, Histology, & Cell Biology

$25.95 Test/500 q

KLEIN

McGraw-Hill, 2007, 576 pages, ISBN 0071471855

Difficult questions with detailed answers as well as some illustrations. Requires extensive time commitment. Includes a high-yield section that highlights clinically relevant relationships and lessons.

B

Wheater's Functional Histology

$72.95 Text

YOUNG

Elsevier, 2006, 448 pages, ISBN 044306850X

A color atlas with illustrations of normal histology and accompanying text. Useful as a text for coursework. Skim through the photomicrographs for USMLE review. Image captions provide an excellent source for the review of basic cell biology.

B–

Elsevier's Integrated Histology

$34.95 Book

TELSER

Elsevier, 2007, 336 pages, ISBN 0323033881

Part of the new Integrated series that focuses on core knowledge in a specific basic science discipline while linking that information to related concepts from other disciplines. Case-based and USMLE-style questions at the end of each chapter allow readers to gauge their comprehension of the material. Includes online access. Best if used during coursework. Limited student feedback.

A

Clinical Microbiology Made Ridiculously Simple ***$32.95*** Review

GLADWIN

MedMaster, 2007, 392 pages, ISBN 094078081X

A very good chart-based review of microbiology that includes clever and humorous mnemonics. The best of this series. The text is easy to read, and an excellent antibiotic review is useful for pharmacology as well. The style of the series does not appeal to everyone. Requires a supplemental source for immunology. Excellent if you have limited time or are "burning out."

A–

Basic Immunology ***$61.95*** Review

ABBAS

Elsevier, 2006, 336 pages, ISBN 1416029745

A text that includes colorful diagrams, images, and tables that students will find useful for quick review. Also offers abundant text as well as a lengthy glossary for those who wish to delve into the topic further. Features online access.

A–

Deja Review: Microbiology & Immunology ***$22.95*** Review

CHEN

McGraw-Hill, 2006, 250 pages, ISBN 0071468668

Features questions and answers in a two-column, quiz-yourself format similar to that of the Recall series. Provides a sound review in a format that differs from straight text. A great resource once a primary review of microbiology has already been done. Limited student feedback.

A–

Microcards ***$34.95*** Flash cards

HARPAVAT

Lippincott Williams & Wilkins, 2007, 300 pages, ISBN 0781769248

A highly useful resource for students who like to use flash cards for review. Some cards include excellent flow charts of important classes of bacteria or viruses. Most of the other cards include the bacterium or virus, clinical presentation, pathobiology, diagnosis, treatment, and important quick facts. Recommended for initial use with coursework.

A–

High-Yield Immunology

$26.95 Review

JOHNSON

Lippincott Williams & Wilkins, 2005, 112 pages, ISBN 0781774691

A review book presented in a format typical of the High-Yield series. Accurately covers high-yield details within the topic in proportion to the boards' coverage of immunology. Good for quick review. The new edition includes many improvements.

A–

Review of Medical Microbiology and Immunology

$41.95 Review/654 q

LEVINSON

McGraw-Hill, 2006, 580 pages, ISBN 0071460314

A clear, concise text with excellent diagrams and tables. Includes an excellent immunology section. The "Summary of Medically Important Organisms" is highly crammable. Requires time commitment. Can be detailed and dense; best if started early with the course. Covers all topics, including some that are low yield. Includes good practice questions and a comprehensive exam, but questions have letter answers only. Compare with *Lippincott's Illustrated Reviews: Microbiology.*

A–

Review of Medical Microbiology

$36.95 Test/550 q

MURRAY

Elsevier, 2005, 176 pages, ISBN 0323033253

USMLE-style questions divided into bacteriology, virology, mycology, and parasitology. Contains high-quality color images for many questions and detailed answer explanations for each. Questions are similar to those on the boards and provide a nice review. Supplements Murray's *Medical Microbiology* textbook.

A–

Crash Course: Immunology

$29.95 Review

NOVAK

Elsevier, 2006, 144 pages, ISBN 1416030077

Part of the Crash Course review series for basic sciences, integrating clinical topics. Offers two-color illustrations, handy study tools, and USMLE review questions. Includes online access. Good length and detail for boards review.

A–

Medical Microbiology and Immunology Flashcards — ***$34.95*** — Flash cards

ROSENTHAL

Elsevier, 2005, 414 pages, ISBN 032303392X

Flash cards covering the most commonly asked-about bugs. Features full-color images of a microscopic view of each bug and its clinical presentation on one side, with the other side offering relevant bug information in conjunction with a short case. Well-organized information, and comes in a nice carrying case. Also comes with StudentConsult online access and extras. A little too much emphasis is placed on "trigger words" relating to each bug.

A–

Underground Clinical Vignettes: Microbiology Vol. I: Virology, Immunology, Parasitology, Mycology — ***$22.95*** — Review/20 q

SWANSON

Lippincott Williams & Wilkins, 2007, 224 pages, ISBN 078176470X

Concise clinical cases illustrating frequently tested diseases in microbiology and immunology (100 cases in each volume). Cardinal signs, symptoms, and buzzwords are highlighted. Also includes 20 additional boards-style questions. Use as a supplement to other sources of review.

A–

Underground Clinical Vignettes: Microbiology Vol. II: Bacteriology — ***$22.95*** — Review/20 q

SWANSON

Lippincott Williams & Wilkins, 2007, 224 pages, ISBN 0781764718

Concise clinical cases illustrating frequently tested diseases in bacteriology (100 cases in each volume). Cardinal signs, symptoms, and buzzwords are highlighted. Also includes 20 additional boards-style questions. Use as a supplement to other sources of review.

B+

Elsevier's Integrated Immunology and Microbiology — ***$34.95*** — Book

ACTOR

Elsevier, 2006, 336 pages, ISBN 032303389X

Part of the new Integrated series that focuses on core knowledge in a specific basic science discipline while linking that information to related concepts from other disciplines. Case-based and USMLE-style questions at the end of each chapter allow users to gauge their comprehension of the material. Includes online access. Best if used during coursework. Limited student feedback.

B+

Concise Medical Immunology

$39.95 Review

DOAN

Lippincott Williams & Wilkins, 2005, 256 pages, ISBN 078175741X

A concise text with useful diagrams, illustrations, and tables. Good for students who need extra immunology review or wish to study the subject thoroughly for the boards. End-of-chapter multiple-choice questions help reinforce key concepts.

B+

Bugcards: The Complete Microbiology Review Flash Cards for Class, the Boards, and the Wards

$26.50 Flash cards

LEVINE

BL Publishing, 2004, 150 pages, ISBN 0967165539

High-quality flash cards designed for rapid class and USMLE microbiology review. Cards cover all medically relevant bacteria, viruses, fungi, and parasites and include important buzzwords, mnemonics, and clinical vignettes to aid in recall. Unique "disease process cards" summarize all organisms for a particular disease (e.g., UTI, pneumonia).

B+

Review of Immunology

$32.95 Test/500 q

LICHTMAN

Elsevier, 2005, 192 pages, ISBN 0721603432

Complements Abbas's *Cellular and Molecular Immunology* and *Basic Immunology* textbooks. Contains 500 USMLE-style questions with full-color illustrations along with explanations of all answers. A good resource for questions in a lower-yield area. Limited student feedback.

B+

Case Studies in Immunology: Clinical Companion

$49.95 Review

ROSEN

Garland Science, 2007, 328 pages, ISBN 0815341458

Originally designed as a clinical companion to Janeway's *Immunobiology*, this text provides an excellent synopsis of the major disorders of immunity in a clinical vignette format. Integrates basic and clinical sciences. Excellent images, illustrations, questions, and discussion.

B+

Rapid Review: Microbiology and Immunology

$34.95 Review/350 q

ROSENTHAL

Elsevier, 2006, 368 pages, ISBN 0323044263

Similar to other books in the Rapid Review series. Contains a significant number of excellent tables and figures. Two 50-question tests with extensive explanations complement the topics covered in the review, along with 250 questions online. Limited student feedback.

B+

Case Files: Microbiology — *$29.95* — Review

TOY

McGraw-Hill, 2005, 430 pages, ISBN 0071445749

Fifty clinical microbiology cases reviewed in an interactive learning format. Each case is followed by a clinical correlation, a discussion with boldfaced buzzwords, and questions. Cases are useful for boards review, since key ideas can be readily associated with the appropriate clinical scenario.

B

Microbiology and Immunology for the Boards and Wards — *$24.95* — Review/100 q

AYALA

Lippincott Williams & Wilkins, 2005, 256 pages, ISBN 1405104686

Similar in style to other books in the Boards and Wards series. Includes many high-yield tables and buzzwords. Some parts are too detailed for USMLE review. Limited student feedback.

B

Blueprints Notes & Cases: Microbiology and Immunology — *$29.95* — Review

GANDHI

Lippincott Williams & Wilkins, 2003, 224 pages, ISBN 1405103477

Fifty-eight succinct clinical cases covering boards-relevant microbiology and immunology facts. Charts, tables, illustrations, and useful "thumbnails" are included in the discussion section to facilitate rapid synthesis of key concepts. Best used during microbiology coursework. For students proficient in immunology.

B

Lippincott's Illustrated Reviews: Microbiology — *$37.95* — Review/Few q

HARVEY

Lippincott Williams & Wilkins, 2006, 432 pages, ISBN 0781782155

A comprehensive, highly illustrated review of microbiology similar in style to Champe's *Lippincott's Illustrated Reviews: Biochemistry*. Includes a 50-page color section with more than 150 clinical and laboratory photographs. Compare with Levinson's *Review of Medical Microbiology and Immunology*.

APPENDIX

Abbreviations and Symbols

Abbreviation	Meaning
1°	primary
2°	secondary
3°	tertiary
AA	amino acid
AAMC	Association of American Medical Colleges
aa-tRNA	aminoacyl-tRNA
Ab	antibody
ABP	androgen-binding protein
ACC	acetyl-CoA carboxylase
Ac-CoA	acetylcoenzyme A
ACD	anemia of chronic disease
ACE	angiotensin-converting enzyme
ACh	acetylcholine
AChE	acetylcholinesterase
AChR	acetylcholine receptor
ACL	anterior cruciate ligament
ACTH	adrenocorticotropic hormone
ADA	adenosine deaminase, Americans with Disabilities Act
ADH	antidiuretic hormone
ADHD	attention-deficit hyperactivity disorder
ADP	adenosine diphosphate
AFP	α-fetoprotein
Ag	antigen
AICA	anterior inferior cerebellar artery
AIDS	acquired immunodeficiency syndrome
AL	amyloidosis
ALA	aminolevulinic acid
ALL	acute lymphocytic leukemia
ALP	alkaline phosphatase
ALS	amyotrophic lateral sclerosis
ALT	alanine transaminase
AML	acute myelocytic leukemia
AMP	adenosine monophosphate
ANA	antinuclear antibody
ANCA	antineutrophil cytoplasmic antibody
ANOVA	analysis of variance
ANP	atrial natriuretic peptide
ANS	autonomic nervous system
AOA	American Osteopathic Association
AP	action potential
APC	antigen-presenting cell
APKD	adult polycystic kidney disease
APRT	adenine phosphoribosyltransferase
APSAC	anistreplase
aPTT	activated partial thromboplastin time
AR	attributable risk, autosomal recessive
ARC	Appalachian Regional Commission
ARDS	adult respiratory distress syndrome
Arg	arginine
ASA	acetylsalicylic acid
ASD	atrial septal defect
ASO	antistreptolysin O
Asp	aspartic acid
AST	aspartate transaminase
AT	angiotensin
ATCase	aspartate transcarbamoylase
ATP	adenosine triphosphate
ATPase	adenosine triphosphatase
AV	atrioventricular, azygous vein
AVM	arteriovenous malformation
AZT	azidothymidine
BAL	British anti-Lewisite [dimercaprol]
BM	basement membrane
BMI	body-mass index
BMR	basal metabolic rate
BP	bisphosphate, blood pressure
BPG	bisphosphoglycerate
BPH	benign prostatic hyperplasia
BUN	blood urea nitrogen
CAD	coronary artery disease
cAMP	cyclic adenosine monophosphate
c-ANCA	cytoplasmic antineutrophil cytoplasmic antibody
CBG	corticosteroid-binding globulin
Cbl	cobalamin
CBSSA	Comprehensive Basic Science Self-Assessment
CBT	computer-based testing
CCK	cholecystokinin
CCl_4	carbon tetrachloride
CCS	computer-based case simulation
CCT	cortical collecting tubule
CD	cluster of differentiation
CDK	cyclin-dependent kinase
CE	cholesterol ester
CEA	carcinoembryonic antigen

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Abbreviation	Meaning
CETP	cholesterol-ester transfer protein
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
CFX	circumflex [artery]
cGMP	cyclic guanosine monophosphate
CGN	*cis*-Golgi network
ChAT	choline acetyltransferase
CHF	congestive heart failure
CI	confidence interval
CIN	candidate identification number, cervical intraepithelial neoplasia
CJD	Creutzfeldt-Jakob disease
CK	clinical knowledge
CK-MB	creatine kinase, MB fraction
CL	clearance
CLL	chronic lymphocytic leukemia
CML	chronic myeloid leukemia
CMV	cytomegalovirus
CN	cranial nerve, cyanide
CNS	central nervous system
CO	cardiac output
CoA	coenzyme A
COGME	Council on Graduate Medical Education
COMLEX	Comprehensive Osteopathic Medical Licensing Examination
COMT	catechol-*O*-methyltransferase
COP	coat protein
COPD	chronic obstructive pulmonary disease
CoQ	coenzyme Q
COX	cyclooxygenase
C_p	plasma concentration
CPAP	continuous positive airway pressure
CPK	creatine phosphokinase
CRC	colorectal cancer
CRF	chronic renal failure
CRH	corticotropin-releasing hormone
CS	clinical skills
CSF	cerebrospinal fluid, colony-stimulating factor
CT	computed tomography
CVA	cerebrovascular accident, costovertebral angle
Cx	complication
CXR	chest x-ray
Cys	cysteine
d4T	didehydrodeoxythymidine [stavudine]
DAF	decay-accelerating factor
DAG	diacylglycerol
dATP	deoxyadenosine triphosphate
DCIS	ductal carcinoma in situ
ddC	dideoxycytidine
ddI	didanosine
DES	diethylstilbestrol
DHAP	dihydroxyacetone phosphate
DHB	dihydrobiopterin
DHEA	dehydroepiandrosterone
DHF	dihydrofolic acid
DHS	Department of Homeland Security
DHT	dihydrotestosterone
DI	diabetes insipidus
DIC	disseminated intravascular coagulation
DIP	distal interphalangeal [joint]
DIT	diiodotyrosine
DKA	diabetic ketoacidosis
DNA	deoxyribonucleic acid
2,4-DNP	2,4-dinitrophenol
DO	doctor of osteopathy
2,3-DPG	2,3-diphosphoglycerate
DPM	doctor of podiatric medicine
DPPC	dipalmitoyl phosphatidylcholine
DS	double stranded
dsDNA	double-stranded deoxyribonucleic acid
dsRNA	double-stranded ribonucleic acid
dTMP	deoxythymidine monophosphate
DTR	deep tendon reflex
DTs	delirium tremens
dTTP	deoxythymidine triphosphate
dUMP	deoxyuridine monophosphate
DVT	deep venous thrombosis
EBV	Epstein-Barr virus
EC_{50}	median effective concentration
ECF	extracellular fluid
ECFMG	Educational Commission for Foreign Medical Graduates
ECG	electrocardiogram
ECL	enterochromaffin-like [cell]
ECT	electroconvulsive therapy
ED_{50}	median effective dose
EDRF	endothelium-derived relaxing factor
EDTA	ethylenediamine tetra-acetic acid
EDV	end-diastolic volume
EEG	electroencephalogram
EF	ejection fraction, elongation factor
EGF	epidermal growth factor
eIF	eukaryotic initiation factor
ELISA	enzyme-linked immunosorbent assay
EM	electron micrograph, electron microscopic, electron microscopy
EOM	extraocular muscle
epi	epinephrine
EPO	erythropoietin
EPS	extrapyramidal system
ER	endoplasmic reticulum, estrogen receptor
ERAS	Electronic Residency Application Service
ERCP	endoscopic retrograde cholangiopancreatography
ERP	effective refractory period
ERPF	effective renal plasma flow
ERT	estrogen replacement therapy
ERV	expiratory reserve volume
ESR	erythrocyte sedimentation rate
ESV	end-systolic volume

Abbreviation	Meaning
EtOH	ethyl alcohol
EV	esophageal vein
F6P	fructose-6-phosphate
FAD	oxidized flavin adenine dinucleotide
$FADH_2$	reduced flavin adenine dinucleotide
FAP	familial adenomatous polyposis
FBPase	fructose bisphosphatase
FcR	Fc receptor
5f-dUMP	5-fluorodeoxyuridine monophosphate
Fe_{Na}	excreted fraction of filtered sodium
FEV_1	forced expiratory volume in 1 second
FF	filtration fraction
FFA	free fatty acid
FGF	fibroblast growth factor
FISH	fluorescence in situ hybridization
FLEX	Federation Licensing Examination
f-met	formylmethionine
FMG	foreign medical graduate
FMN	flavin mononucleotide
FRC	functional residual capacity
FSH	follicle-stimulating hormone
FSMB	Federation of State Medical Boards
FTA-ABS	fluorescent treponemal antibody—absorbed
5-FU	5-fluorouracil
FVC	forced vital capacity
G3P	glucose-3-phosphate
G6P	glucose-6-phosphate
G6PD	glucose-6-phospate dehydrogenase
GABA	γ-aminobutyric acid
GBM	glomerular basement membrane
G-CSF	granulocyte colony-stimulating factor
GDP	guanosine diphosphate
GE	gastroesophageal
GERD	gastroesophageal reflux disease
GFAP	glial fibrillary acid protein
GFR	glomerular filtration rate
GGT	γ-glutamyl transpeptidase
GH	growth hormone
GHRH	growth hormone–releasing hormone
GI	gastrointestinal
GIP	gastric inhibitory peptide
GIST	gastrointestinal stromal tumor
Glu	glutamic acid
GLUT	glucose transporter
GM-CSF	granulocyte-macrophage colony-stimulating factor
GMP	guanosine monophosphate
GN	glomerulonephritis
GnRH	gonadotropin-releasing hormone
GP	glycogen phosphorylase, glycoprotein
GPe	globus pallidus externa
GPi	globus pallidus interna
GPI	glycosyl phosphatidylinositol
GPP	glycogen phosphorylase phosphatase
GS	glycogen synthase
GSH	reduced glutathione
GS-P	glycogen synthase phosphatase
GSSG	oxidized glutathione

Abbreviation	Meaning
GTP	guanosine triphosphate
GU	genitourinary
HAART	highly active antiretroviral therapy
HAV	hepatitis A virus
HAVAb	hepatitis A antibody
Hb	hemoglobin
HBcAb	hepatitis B core antibody
HBcAg	hepatitis B core antigen
HBeAb	hepatitis B early antibody
HBeAg	hepatitis B early antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
Hct	hematocrit
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDV	hepatitis D virus
H&E	hematoxylin and eosin
HEV	hepatitis E virus
HGPRT	hypoxanthine-guanine phosphoribosyltransferase
HHS	[Department of] Health and Human Services
HHV	human herpesvirus
5-HIAA	5-hydroxyindoleacetic acid
His	histidine
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HL	hepatic lipase
HLA	human leukocyte antigen
HMG-CoA	hydroxymethylglutaryl-coenzyme A
HMP	hexose monophosphate
HMWK	high-molecular-weight kininogen
HNPCC	hereditary nonpolyposis colorectal cancer
hnRNA	heterogeneous nuclear ribonucleic acid
HPA	hypothalamic-pituitary-adrenal [axis]
HPSA	Health Professional Shortage Area
HPV	human papillomavirus
HR	heart rate
HRT	hormone replacement therapy
HSV	herpes simplex virus
HSV-1	herpes simplex virus 1
HSV-2	herpes simplex virus 2
5-HT	5-hydroxytryptamine (serotonin)
HTLV	human T-cell leukemia virus
HUS	hemolytic-uremic syndrome
HVA	homovanillic acid
IBD	inflammatory bowel disease
IC	inspiratory capacity
ICA	internal carotid artery
ICAM	intracellular adhesion molecule
ICF	intracellular fluid
ICP	intracranial pressure
ID_{50}	median infectious dose
IDDM	insulin-dependent diabetes mellitus
IDL	intermediate-density lipoprotein

Abbreviation	Meaning
I/E	inspiratory/expiratory [ratio]
IEV	inferior epigastric vein
IF	immunofluorescence
IFN	interferon
Ig	immunoglobulin
IGF	insulin-like growth factor
IL	interleukin
Ile	isoleucine
IMA	inferior mesenteric artery
IMED	International Medical Education Directory
IMG	international medical graduate
IMP	inosine monophosphate
IMV	inferior mesenteric vein
INH	isonicotine hydrazine [isoniazid]
INR	International Normalized Ratio
IO	inferior oblique [muscle]
IP_3	inositol triphosphate
IPV	inactivated polio vaccine
IR	inferior rectus [muscle]
IRV	inferior rectal vein, inspiratory reserve volume
ITP	idiopathic thrombocytopenic purpura
IV	intravenous
IVC	inferior vena cava
JG	juxtaglomerular [cells]
JGA	juxtaglomerular apparatus
JVD	jugular venous distention
K_f	filtration constant
KOH	potassium hydroxide
KSHV	Kaposi's sarcoma–associated herpesvirus
LA	left atrial, left atrium
LAD	left anterior descending [artery]
LAF	left anterior fascicle
LCA	left coronary artery
LCAT	lecithin-cholesterol acyltransferase
LCFA	long-chain fatty acid
LCL	lateral collateral ligament
LCME	Liaison Committee on Medical Education
LCV	lymphocytic choriomeningitis virus
LD_{50}	median toxic dose
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LES	lower esophageal sphincter
Leu	leucine
LFA-1	leukocyte function–associated antigen 1
LFT	liver function test
LGN	lateral geniculate nucleus
LGV	left gastric vein
LH	luteinizing hormone
LLQ	left lower quadrant
LM	light microscopy
LMN	lower motor neuron
LOR	letter of recommendation
LPL	lipoprotein lipase
LPS	lipopolysaccharide
LR	lateral rectus [muscle]
LSE	Libman-Sacks endocarditis
LT	leukotriene
LV	left ventricle, left ventricular
Lys	lysine
MAC	membrane attack complex, minimal alveolar concentration
MALT	mucosa-associated lymphoid tissue
MAO	monoamine oxidase
MAOI	monoamine oxidase inhibitor
MAP	mean arterial pressure
MCA	middle cerebral artery
MCHC	mean corpuscular hemoglobin concentration
MCL	medial collateral ligament
MCP	metacarpophalangeal [joint]
MCV	mean corpuscular volume
MEN	multiple endocrine neoplasia
MEOS	microsomal ethanol oxidizing system
Met	methionine
MGN	medial geniculate nucleus
MGUS	monoclonal gammopathy of undetermined significance
MHC	major histocompatibility complex
MHPSA	Mental Health Professional Shortage Area
MI	myocardial infarction
MIT	monoiodotyrosine
MLCK	myosin light-chain kinase
MLF	medial longitudinal fasciculus
MMR	measles, mumps, rubella [vaccine]
6-MP	6-mercaptopurine
MPO	myeloperoxidase
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MR	medial rectus [muscle], mental retardation, mitral regurgitation
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MRSA	methicillin-resistant S. *aureus*
MS	multiple sclerosis
MSH	melanocyte-stimulating hormone
mTOR	mammalian target of rapamycin
MTP	metatarsophalangeal [joint]
MTX	methotrexate
MUA/P	Medically Underserved Area and Population
MVO_2	myocardial oxygen consumption
NAD^+	oxidized nicotinamide adenine dinucleotide
NADH	reduced nicotinamide adenine dinucleotide
$NADP^+$	oxidized nicotinamide adenine dinucleotide phosphate
NADPH	reduced nicotinamide adenine dinucleotide phosphate
NBME	National Board of Medical Examiners
NBOME	National Board of Osteopathic Medical Examiners

Abbreviation	Meaning
NBPME	National Board of Podiatric Medical Examiners
NE	norepinephrine
NF	neurofibromatosis
NH_3	ammonia
NIDDM	non-insulin-dependent diabetes mellitus
NK	natural killer [cells]
NMJ	neuromuscular junction
NO	nitric oxide
NPV	negative predictive value
NSAID	nonsteroidal anti-inflammatory drug
OAA	oxaloacetic acid
OCD	obsessive-compulsive disorder
OCP	oral contraceptive pill
OMT	osteopathic manipulative technique
OPV	oral polio vaccine
OR	odds ratio
PA	posteroanterior
PABA	para-aminobenzoic acid
PAH	para-aminohippuric acid
PALS	periarterial lymphatic sheath
p-ANCA	perinuclear antineutrophil cytoplasmic antibody
PAS	periodic acid Schiff
PBP	penicillin-binding protein
P_c	capillary pressure
PC	pyruvate carboxylase
PCL	posterior cruciate ligament
P_{CO_2}	partial pressure of carbon dioxide
PCOS	polycystic ovarian syndrome
PCP	phencyclidine hydrochloride, *Pneumocystis carinii* (now *jiroveci*) pneumonia
PCR	polymerase chain reaction
PCWP	pulmonary capillary wedge pressure
PD	posterior descending [artery]
PDA	patent ductus arteriosus
PDE	phosphodiesterase
PDH	pyruvate dehydrogenase
PE	pulmonary embolism
PEP	phosphoenolpyruvate
PFK	phosphofructokinase
PFT	pulmonary function test
PG	phosphoglycerate, prostaglandin
Phe	phenylalanine
P_i	interstitial fluid pressure
PICA	posterior inferior cerebellar artery
PID	pelvic inflammatory disease
PIP	proximal interphalangeal [joint]
PIP_2	phosphatidylinositol 4,5-bisphosphate
PK	pyruvate kinase
PKA	protein kinase A
PKD	polycystic kidney disease
PKU	phenylketonuria
PLP	pyridoxal phosphate
PML	progressive multifocal leukoencephalopathy
PMN	polymorphonuclear [leukocyte]

Abbreviation	Meaning
P_{net}	net filtration pressure
PNET	primitive neuroectodermal tumor
PNH	paroxysmal nocturnal hemoglobinuria
PNS	peripheral nervous system
P_{O_2}	partial pressure of oxygen
POMC	pro-opiomelanocortin
PPD	purified protein derivative
PPI	proton pump inhibitor
PPRF	paramedian pontine reticular formation
PPV	positive predictive value
PR	progesterone receptor
PRPP	phosphoribosylpyrophosphate
PSA	prostate-specific antigen
PSS	progressive systemic sclerosis
PT	prothrombin time
PTH	parathyroid hormone
PTHrP	parathyroid hormone–related protein
PTSD	post-traumatic stress disorder
PTT	partial thromboplastin time
PUV	paraumbilical vein
PV	plasma volume, portal vein
RA	rheumatoid arthritis, right atrium
RBC	red blood cell
RBF	renal blood flow
RCA	right coronary artery
RDS	respiratory distress syndrome
RDW	red-cell distribution width
REM	rapid eye movement
RER	rough endoplasmic reticulum
RNA	ribonucleic acid
RNP	ribonucleoprotein
RPF	renal plasma flow
RPR	rapid plasma reagin
RR	relative risk, respiratory rate
rRNA	ribosomal ribonucleic acid
RS	Reed-Sternberg [cells]
RSV	respiratory syncytial virus
RUQ	right upper quadrant
RV	renal vein, residual volume, right ventricle, right ventricular
RVH	right ventricular hypertrophy
SA	sinoatrial, subarachnoid
SAA	serum amyloid–associated [protein]
SAM	S-adenosylmethionine
SARS	severe acute respiratory syndrome
SC	subcutaneous
SCC	squamous cell carcinoma
SCID	severe combined immunodeficiency disease
SCJ	squamocolumnar junction
SD	standard deviation, subdural
SEM	standard error of the mean
SER	smooth endoplasmic reticulum
SEV	superior epigastric vein
SEVIS	Student and Exchange Visitor Information System
SEVP	Student and Exchange Visitor Program

Abbreviation	Meaning
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvate transaminase
SHBG	sex hormone–binding globulin
SIADH	syndrome of inappropriate antidiuretic hormone
SLE	systemic lupus erythematosus
SLL	small lymphocytic lymphoma
SMA	superior mesenteric artery
SMV	superior mesenteric vein
SMX	sulfamethoxazole
SNc	substantia nigra compacta
snRMP	small nuclear ribonucleoprotein
SO	superior oblique [muscle]
SOD	superoxide dismutase
SR	sarcoplasmic reticulum, superior rectus [muscle]
SRP	sponsoring residency program
SRV	superior rectal vein
SS	single stranded
SSB	single-stranded binding
ssDNA	single-stranded deoxyribonucleic acid
SSPE	subacute sclerosing panencephalitis
SSRI	selective serotonin reuptake inhibitor
ssRNA	single-stranded ribonucleic acid
SSSS	staphylococcal scalded-skin syndrome
STD	sexually transmitted disease
STN	subthalamic nucleus
SV	sinus venosus, splenic vein, stroke volume
SVC	superior vena cava
SVT	supraventricular tachycardia
$t_{1/2}$	half-life
T_3	triiodothyronine
T_4	thyroxine
TA	truncus arteriosus
TB	tuberculosis
TBG	thyroxine-binding globulin
TBW	total body weight
3TC	dideoxythiacytidine [lamivudine]
TCA	tricarboxylic acid [cycle], tricyclic antidepressant
Tc cell	cytotoxic T cell
TCR	T-cell receptor
TFT	thyroid function test
TG	triglyceride
TGA	trans-Golgi apparatus
TGF	transforming growth factor
THB	tetrahydrobiopterin
Th cell	helper T cell
THF	tetrahydrofolate
Thr	threonine
TI	therapeutic index
TIBC	total iron-binding capacity
TLC	total lung capacity
TMP-SMX	trimethoprim-sulfamethoxazole
TNF	tumor necrosis factor
TNM	tumor, node, metastases [staging]
TOEFL	Test of English as a Foreign Language
tPA	tissue plasminogen activator
TPP	thiamine pyrophosphate
TPR	total peripheral resistance
TRAP	tartrate-resistant acid phosphatase
TRH	thyrotropin-releasing hormone
tRNA	transfer ribonucleic acid
Trp	tryptophan
TSH	thyroid-stimulating hormone
TSI	thyroid-stimulating immunoglobulin
TSS	toxic shock syndrome
TSST	toxic shock syndrome toxin
TTP	thrombotic thrombocytopenic purpura
TV	tidal volume
TXA	thromboxane
UA	urinalysis
UCV	Underground Clinical Vignettes
UDP	uridine diphosphate
UMN	upper motor neuron
URI	upper respiratory infection
USDA	United States Department of Agriculture
USIA	United States Information Agency
USMLE	United States Medical Licensing Examination
UTI	urinary tract infection
UV	ultraviolet
VA	ventral anterior [nucleus], Veterans Administration
Val	valine
VC	vital capacity
V_d	volume of distribution
VDRL	Venereal Disease Research Laboratory
VF	ventricular fibrillation
VHL	von Hippel–Lindau [disease]
VIP	vasoactive intestinal peptide
VIPoma	vasoactive intestinal polypeptide-secreting tumor
VL	ventral lateral [nucleus]
VLDL	very low density lipoprotein
VMA	vanillylmandelic acid
VPL	ventral posterior nucleus, lateral
VPM	ventral posterior nucleus, medial
VPN	ventral posterior nucleus
V/Q	ventilation/perfusion [ratio]
VRE	vancomycin-resistant enterococcus
VSD	ventricular septal defect
vWF	von Willebrand factor
VZV	varicella-zoster virus
WBC	white blood cell
XR	X-linked recessive
ZDV	zidovudine [formerly AZT]

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Note: boldface indicates a First Aid fact title.

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