CRISPR/Cas9

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

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

New image

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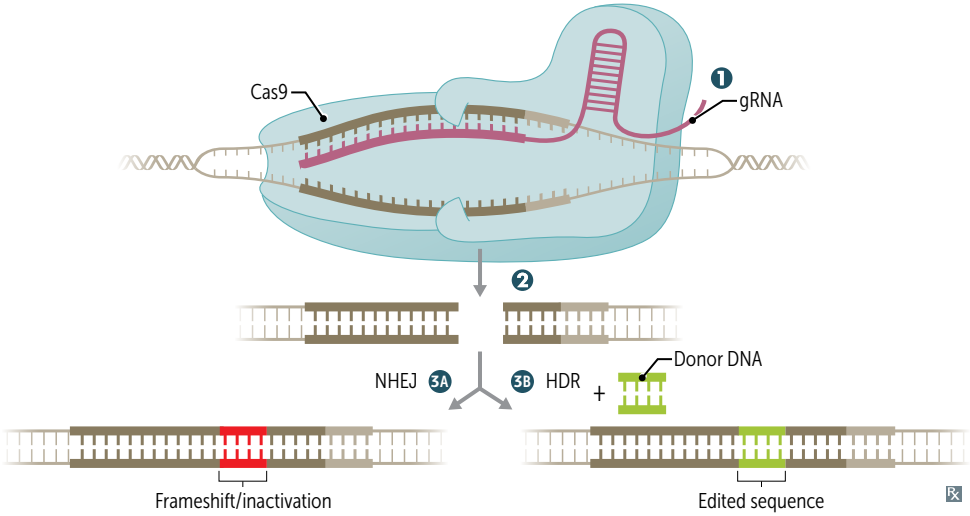
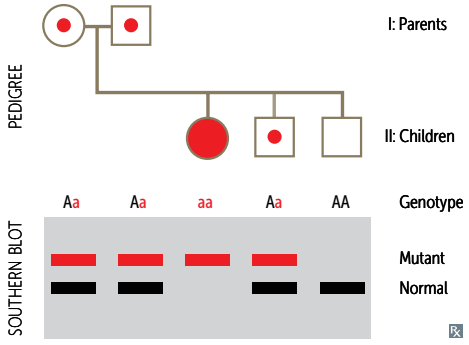


Blotting procedures

Southern blot	1. **DNA** sample is enzymatically cleaved into smaller pieces, which are separated on a gel by electrophoresis, and then transferred to a filter. 2. Filter is exposed to radiolabeled DNA probe that recognizes and anneals to its complementary strand. 3. Resulting double-stranded, labeled piece of DNA is visualized when filter is exposed to film.
Northern blot	Similar to Southern blot, except that an **RNA** sample is electrophoresed. Useful for studying mRNA levels, which are reflective of gene expression.
Western blot	Sample protein is separated via gel electrophoresis and transferred to a membrane. Labeled antibody is used to bind to relevant **protein.**
Southwestern blot	Identifies **DNA-binding proteins** (eg, c-Jun, c-Fos [leucine zipper motif]) using labeled double-stranded DNA probes.



SNoW DRoP:
Southern = DNA
Northern = RNA
Western = Protein

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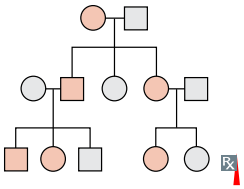
Modes of inheritance

New images

Autosomal dominant

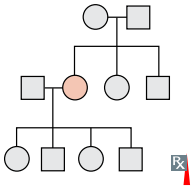


Often due to defects in structural genes. Many generations, both males and females are affected.

	A	a
a	Aa	aa
a	Aa	aa

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

Autosomal recessive



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

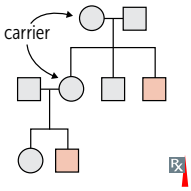
	A	a
A	AA	Aa
a	Aa	aa

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

↑ risk in consanguineous families.

Unaffected individual with affected sibling has 2/3 probability of being a carrier.

X-linked recessive



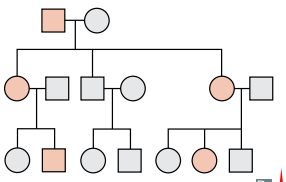
Sons of heterozygous mothers have a 50% chance of being affected. No male-to-male transmission. Skips generations.

	X	X
X	XX	XX
Y	XY	XY

	X	X
X	XX	XX
Y	XY	XY

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

X-linked dominant



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

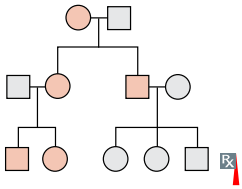
	X	X
X	XX	XX
Y	XY	XY

	X	X
X	XX	XX
Y	XY	XY

Hypophosphatemic rickets—formerly known as vitamin D–resistant rickets. Inherited disorder resulting in ↑ phosphate wasting at proximal tubule. Results in rickets-like presentation.

Other examples: fragile X syndrome, Alport syndrome.

Mitochondrial inheritance



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

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

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

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

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

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Hepatitis C therapy

Chronic HCV infection is treated with different combinations of the following drugs; none is approved as monotherapy. Developed based on understanding of HCV replication cycle. Examples of drugs are provided.

DRUG	MECHANISM	TOXICITY
NS5A inhibitors		
Ledipasvir Ombitasvir	Inhibits NS5A, a viral phosphoprotein that plays a key role in RNA replication, unknown exact mechanism.	Headache, diarrhea.
NS5B inhibitors		
Sofosbuvir Dasabuvir	Inhibits NS5B, an RNA-dependent RNA polymerase acting as a chain terminator. Prevents viral RNA replication.	Fatigue, headache.
NS3/4A inhibitors		
Grazoprevir Simeprevir	Inhibits NS3/4A, a viral protease, preventing viral replication.	Grazoprevir: Photosensitivity reactions, rash. Simeprevir: Headache, fatigue.
Alternative drugs		
Ribavirin	Inhibits synthesis of guanine nucleotides by competitively inhibiting IMP dehydrogenase. Used as adjunct in cases refractory to newer medications	Hemolytic anemia, severe teratogen.

Disinfection and sterilization

Goals include the reduction of pathogenic organism counts to safe levels (disinfection) and the inactivation of all microbes including spores (sterilization).

Autoclave	Pressurized steam at > 120°C. Sporicidal. May not reliably inactivate prions.
Alcohols	Denature proteins and disrupt cell membranes. Not sporicidal.
Chlorhexidine	Denatures proteins and disrupts cell membranes. Not sporicidal.
Chlorine	Oxidizes and denatures proteins. Sporicidal.
Ethylene oxide	Alkylating agent. Sporicidal.
Hydrogen peroxide	Free radical oxidation. Sporicidal.
Iodine and iodophors	Halogenation of DNA, RNA, and proteins. May be sporicidal.
Quaternary amines	Impair permeability of cell membranes. Not sporicidal.

Antimicrobials to avoid in pregnancy

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

SAFe Children Take Really Good Care.

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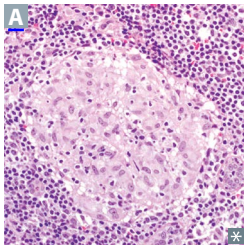
Granulomatous inflammation

A pattern of chronic inflammation. Can be induced by persistent T-cell response to certain infections (eg, TB), immune-mediated diseases, and foreign bodies. Granulomas "wall off" a resistant stimulus without completely eradicating or degrading it → persistent inflammation→ fibrosis, organ damage.

HISTOLOGY



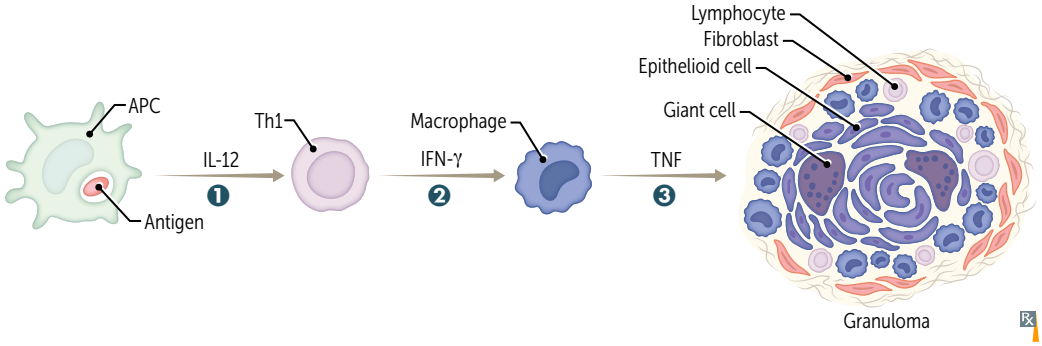
Focus of epithelioid cells (activated macrophages with abundant pink cytoplasm) surrounded by lymphocytes and multinucleated giant cells (formed by fusion of several activated macrophages).
Two types:
Caseating: associated with central necrosis. Seen with infectious etiologies (eg, TB, fungal).
Noncaseating A: no central necrosis. Seen with autoimmune diseases (eg, sarcoidosis, Crohn disease).

New images

MECHANISM

❶ APCs present antigens to CD4+ Th cells and secrete IL-12 → CD4+ Th cells differentiate into Th1 cells
❷ Th1 secretes IFN-γ → macrophage activation
❸ Macrophages ↑ cytokine secretion (eg, TNF) → formation of epithelioid macrophages and giant cells.

Anti-TNF therapy can cause sequestering granulomas to break down → disseminated disease. Always test for latent TB before starting anti-TNF therapy.
Associated with hypercalcemia due to ↑ 1α-hydroxylase-mediated vitamin D activation in macrophages.



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ETIOLOGIES

INFECTIOUS

- Bacterial: *Mycobacteria* (tuberculosis, leprosy), *Bartonella henselae* (cat scratch disease; stellate necrotizing granulomas), *Listeria monocytogenes* (granulomatosis infantiseptica), *Treponema pallidum* (3° syphilis)
- Fungal: endemic mycoses (eg, histoplasmosis)
- Parasitic: schistosomiasis

NONINFECTIOUS

- Immune-mediated: sarcoidosis, Crohn disease, 1° biliary cholangitis, subacute (de Quervain/granulomatous) thyroiditis
- Vasculitis: granulomatosis with polyangiitis (Wegener), eosinophilic granulomatosis with polyangiitis (Churg-Strauss), giant cell (temporal) arteritis, Takayasu arteritis
- Foreign material: berylliosis, talcosis, hypersensitivity pneumonitis
- Chronic granulomatous disease

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Immune evasion in cancer

Immune cells can recognize and attack tumor cells. For successful tumorigenesis, tumor cells must evade the immune system. Multiple escape mechanisms exist:

- ↓ MHC class I expression by tumor cells → cytotoxic T cells are unable to recognize tumor cells.
- Tumor cells secrete immunosuppressive factors (eg, TGF-β) and recruit regulatory T cells to down-regulate immune response.
- Tumor cells up-regulate immune checkpoint molecules, which inhibit immune response.

Immune checkpoint interactions

This fact was migrated from Hem/Onc.

Signals that modulate T cell activation and function → ↓ immune response against tumor cells. Targeted by several cancer immunotherapies. Examples include:

- Interaction between PD-1 (on T cells) and PD-L1/2 (on tumor cells or immune cells in tumor microenvironment) → T cell dysfunction (exhaustion). Inhibited by antibodies against PD-1 (eg, pembrolizumab, nivolumab) or PD-L1 (eg, atezolizumab, durvalumab, avelumab).
- CTLA-4 on T cells outcompetes CD28 for B7 on APCs → loss of T cell costimulatory signal. Inhibited by ipilimumab (anti-CTLA-4 antibody).

New Fact for 2019

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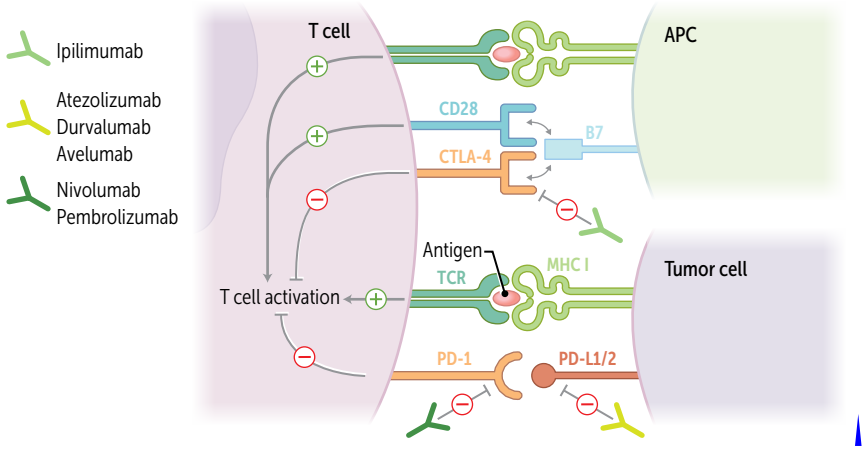
This illustration was edited in Pass 4



Cancer epidemiology

Skin cancer (basal > squamous >> melanoma) is the most common cancer (not included below).

	MEN	WOMEN	CHILDREN (AGE 0–14)	NOTES
Cancer incidence	1. Prostate 2. Lung 3. Colon/rectum	1. Breast 2. Lung 3. Colon/rectum	1. Leukemia 2. CNS 3. Neuroblastoma	Lung cancer incidence has ↓ in men, but has not changed significantly in women.
Cancer mortality	1. Lung 2. Prostate 3. Colon/rectum	1. Lung 2. Breast 3. Colon/rectum	1. Leukemia 2. CNS 3. Neuroblastoma	Cancer is the 2nd leading cause of death in the United States (heart disease is 1st).

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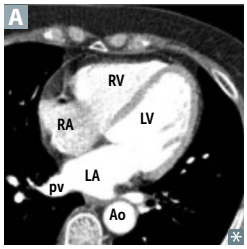
▸ CARDIOVASCULAR—ANATOMY

Anatomy of the heart



LA is the most posterior part of the heart A; enlargement can cause dysphagia (due to compression of the esophagus) or hoarseness (due to compression of the left recurrent laryngeal nerve, a branch of the vagus nerve).

RV is the most anterior part of the heart and most commonly injured in trauma.

Pericardium

Consists of 3 layers (from outer to inner):
- Fibrous pericardium
- Parietal layer of serous pericardium
- Visceral layer of serous pericardium

Pericardial cavity lies between parietal and visceral layers.

Pericardium innervated by phrenic nerve.

Pericarditis can cause referred pain to the neck, arms, or one or both shoulders (often left).

Coronary blood supply

LAD and its branches supply anterior 2/3 of interventricular septum, anterolateral papillary muscle.

LAD supplies anterior of interventricular septum, anterolateral papillary muscle, and anterior surface of LV. Most commonly occluded.

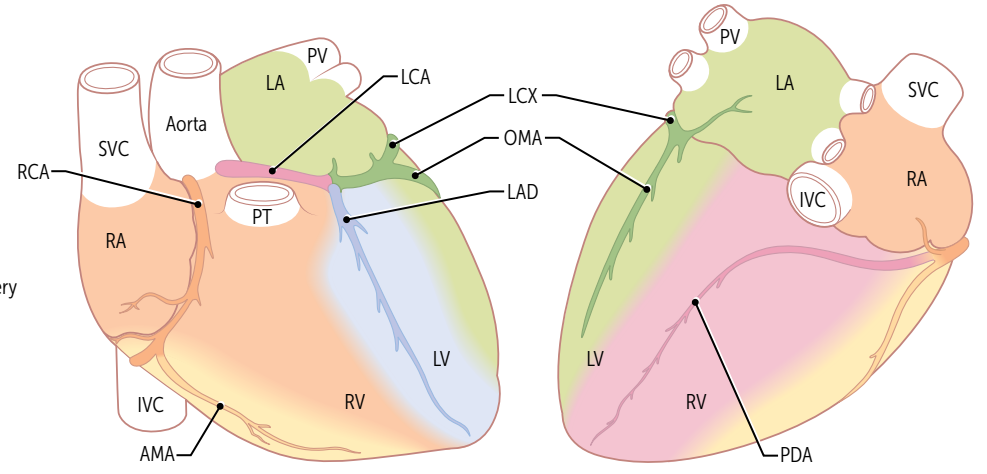
PDA supplies AV node (dependent on dominance), posterior 1/3 of interventricular septum, posterior 2/3 walls of ventricles, and posteromedial papillary muscle. Right (acute) marginal artery supplies RV.

RCA supplies SA node (blood supply independent of dominance). Infarct may cause nodal dysfunction (bradycardia or heart block).

Dominance:
- Right-dominant circulation (85%) = PDA arises from RCA.
- Left-dominant circulation (8%) = PDA arises from LCX.
- Codominant circulation (7%) = PDA arises from both LCX and RCA.

Coronary blood flow peaks in early diastole.

New image



Key:
AMA = Acute marginal artery
LAD = Left anterior descending artery
LCA = Left coronary artery
LCX = Left circumflex artery
OMA = Obtuse marginal artery
PDA = Posterior descending artery
PT = Pulmonary trunk
PV = Pulmonary vein
RCA = Right coronary artery

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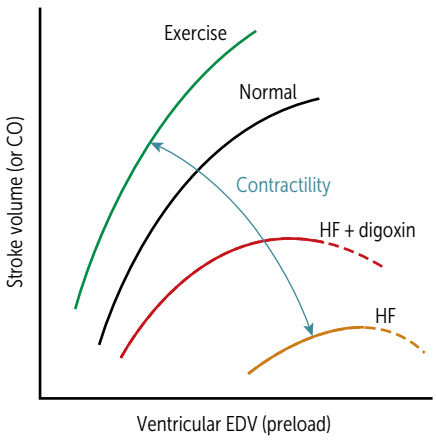
Cardiac output equations

	EQUATIONS	NOTES
Stroke volume	$SV = EDV - ESV$	
Ejection fraction	$EF = \frac{SV}{EDV} = \frac{EDV - ESV}{EDV}$	EF is an index of ventricular contractility (↓ in systolic HF; usually normal in diastolic HF).
Cardiac output	$CO = SV \times HR$ Fick principle: $CO = \frac{\text{rate of } O_2 \text{ consumption}}{(\text{arterial } O_2 \text{ content} - \text{venous } O_2 \text{ content})}$	In early stages of exercise, CO maintained by ↑ HR and ↑ SV. In later stages, CO maintained by ↑ HR only (SV plateaus). Diastole is shortened with ↑↑ HR (eg, ventricular tachycardia) → ↓ diastolic filling time → ↓ SV → ↓ CO.
Pulse pressure	$PP = SBP - DBP$	PP directly proportional to SV and inversely proportional to arterial compliance. ↑ PP in hyperthyroidism, aortic regurgitation, aortic stiffening (isolated systolic hypertension in elderly), obstructive sleep apnea (↑ sympathetic tone), anemia, exercise (transient). ↓ PP in aortic stenosis, cardiogenic shock, cardiac tamponade, advanced HF.
Mean arterial pressure	$MAP = CO \times TPR$	MAP (at resting HR) = ⅔ DBP + ⅓ SBP = DBP + ⅓ PP

Starling curve



Force of contraction is proportional to end-diastolic length of cardiac muscle fiber (preload).
↑ contractility with catecholamines, positive inotropes (eg, digoxin).
↓ contractility with loss of myocardium (eg, MI), β-blockers (acutely), non-dihydropyridine Ca^{2+} channel blockers, dilated cardiomyopathy.

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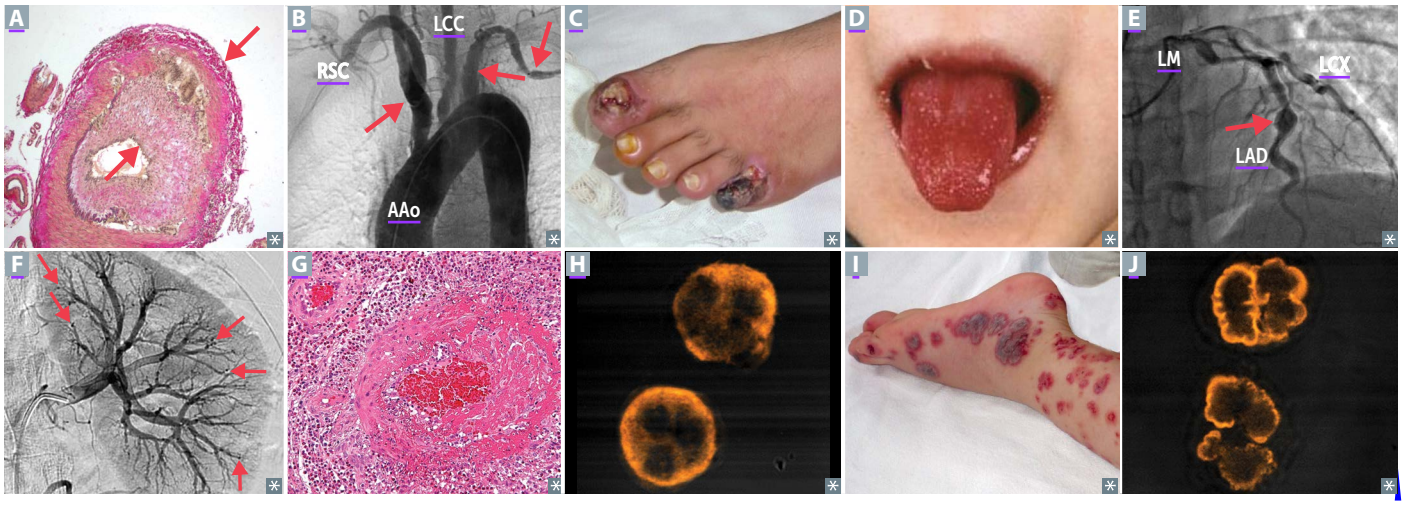
Vasculitides *(continued)*

	EPIDEMIOLOGY/PRESENTATION	PATHOLOGY/LABS
Small-vessel vasculitis *(continued)*		
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)	Asthma, sinusitis, skin nodules or purpura, peripheral neuropathy (eg, wrist/foot drop). Can also involve heart, GI, kidneys (pauci-immune glomerulonephritis).	Granulomatous, necrotizing vasculitis with eosinophilia G. MPO-ANCA/p-ANCA, ↑ IgE level.
Granulomatosis with polyangiitis (Wegener)	Upper respiratory tract: perforation of nasal septum, chronic sinusitis, otitis media, mastoiditis. Lower respiratory tract: hemoptysis, cough, dyspnea. Renal: hematuria, red cell casts.	Triad: ▪ Focal necrotizing vasculitis ▪ Necrotizing granulomas in lung and upper airway ▪ Necrotizing glomerulonephritis PR3-ANCA/c-ANCA H (anti-proteinase 3). CXR: large nodular densities. Treat with cyclophosphamide, corticosteroids.
Immunoglobulin A vasculitis	Also known as Henoch-Schönlein purpura. Most common childhood systemic vasculitis. Often follows URI. Classic triad: ▪ Skin: palpable purpura on buttocks/legs I ▪ Arthralgias ▪ GI: abdominal pain (associated with intussusception)	Vasculitis 2° to IgA immune complex deposition. Associated with IgA nephropathy (Buerger disease).
Microscopic polyangiitis	Necrotizing vasculitis commonly involving lung, kidneys, and skin with pauci-immune glomerulonephritis and palpable purpura. Presentation similar to granulomatosis with polyangiitis but without nasopharyngeal involvement.	No granulomas. MPO-ANCA/p-ANCA J (anti-myeloperoxidase). Treat with cyclophosphamide, corticosteroids.
Mixed cryoglobulinemia	Often due to viral infections, especially HCV. Triad of palpable purpura, weakness, arthralgias. May also have peripheral neuropathy and renal disease (eg, glomerulonephritis).	Cryoglobulins are immunoglobulins that precipitate in the cold. Vasculitis due to mixed IgG and IgA immune complex deposition.



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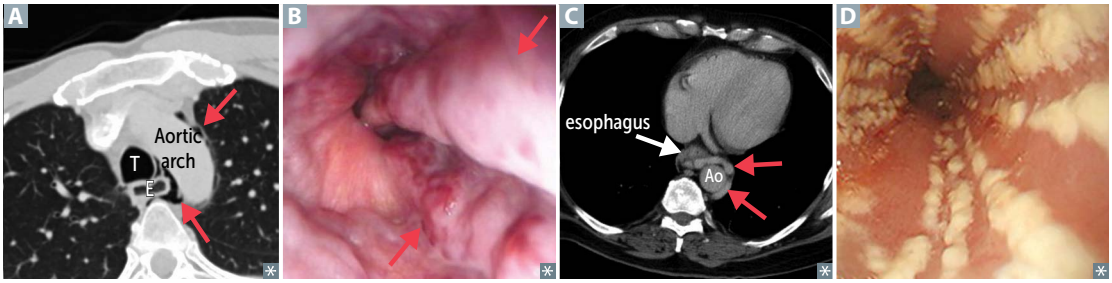
Esophageal pathologies

Diffuse esophageal spasm	Spontaneous, nonperistaltic (uncoordinated) contractions of the esophagus with normal LES pressure. Presents with dysphagia and angina-like chest pain. Barium swallow reveals "corkscrew" esophagus. Manometry is diagnostic. Treatment includes nitrates and CCBs.
Eosinophilic esophagitis	Infiltration of eosinophils in the esophagus often in atopic patients. Food allergens → dysphagia, food impaction. Esophageal rings and linear furrows often seen on endoscopy. Typically unresponsive to GERD therapy.
Esophageal perforation	Most commonly iatrogenic following esophageal instrumentation. Noniatrogenic causes include spontaneous rupture, foreign body ingestion, trauma, malignancy. May present with pneumomediastinum (arrows in A). Subcutaneous emphysema may be due to dissecting air (signs include crepitus in the neck region or chest wall). Boerhaave syndrome—transmural, usually distal esophageal rupture due to violent retching.
Esophageal strictures	Associated with caustic ingestion, acid reflux, and esophagitis.
Esophageal varices	Dilated submucosal veins (red arrows in B C) in lower ⅓ of esophagus 2° to portal hypertension. Common in cirrhotics, may be source of life-threatening hematemesis.
Esophagitis	Associated with reflux, infection in immunocompromised (*Candida*: white pseudomembrane D; HSV-1: punched-out ulcers; CMV: linear ulcers), caustic ingestion, or pill-induced esophagitis (eg, bisphosphonates, tetracycline, NSAIDs, iron, and potassium chloride).
Gastroesophageal reflux disease	Commonly presents as heartburn, regurgitation, dysphagia. May also present as chronic cough, hoarseness (laryngopharyngeal reflux). Associated with asthma. Transient decreases in LES tone.
Mallory-Weiss syndrome	Partial thickness, longitudinal lacerations of gastroesophageal junction, confined to mucosa/submucosa, due to severe vomiting. Often presents with hematemesis. Usually found in alcoholics and bulimics.
Plummer-Vinson syndrome	Triad of Dysphagia, Iron deficiency anemia, and Esophageal webs. May be associated with glossitis. Increased risk of esophageal squamous cell carcinoma ("Plumbers DIE").
Schatzki rings	Rings formed at gastroesophageal junction, typically due to chronic acid reflux. Can present with dysphagia.
Sclerodermal esophageal dysmotility	Esophageal smooth muscle atrophy → ↓ LES pressure and dysmotility → acid reflux and dysphagia → stricture, Barrett esophagus, and aspiration. Part of CREST syndrome.



New image

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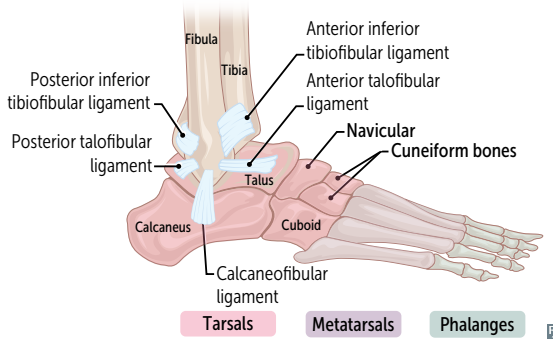
Ankle sprains

Anterior TaloFibular ligament—most common ankle sprain overall, classified as a low ankle sprain. Due to overinversion/supination of foot.
Anterior inferior tibiofibular ligament—most common high ankle sprain.
Always Tears First.



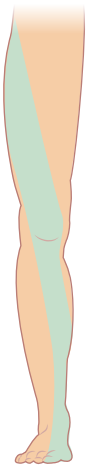
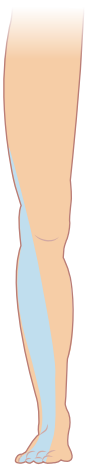
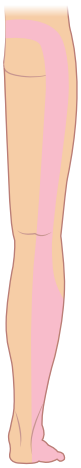
This fact was migrated.

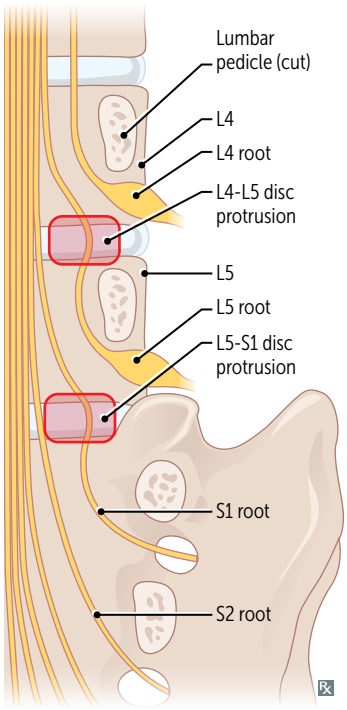
This illustration was edited in Pass 2

Signs of lumbosacral radiculopathy

Paresthesia and weakness related to specific lumbosacral spinal nerves. Intervertebral disc (nucleus pulposus) herniates posterolaterally through annulus fibrosus (outer ring) into central canal due to thin posterior longitudinal ligament and thicker anterior longitudinal ligament along midline of vertebral bodies.
Nerve affected is usually below the level of herniation.

This illustration was edited in Pass 3

Disc level herniation	L3-L4	L4-L5	L5-S1
Nerve root affected	L4	L5	S1
Dermatome affected			
Clinical findings	Weakness of knee extension ↓ patellar reflex	Weakness of dorsiflexion Difficulty in heel walking	Weakness of plantar flexion Difficulty in toe walking ↓ Achilles reflex



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New image

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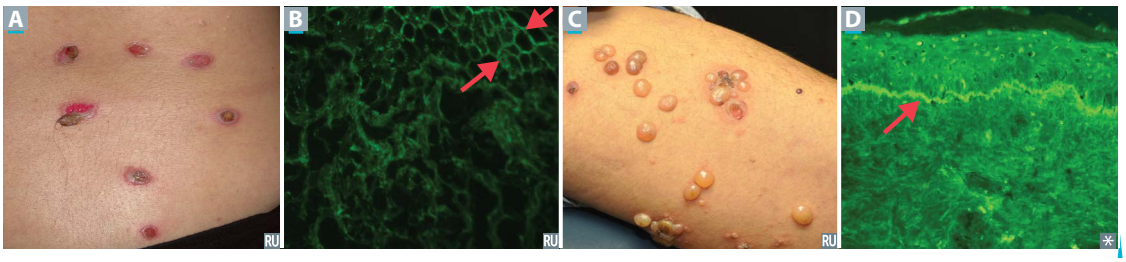
Autoimmune blistering skin disorders

This is a new fact.

	Pemphigus vulgaris	Bullous pemphigoid
PATHOPHYSIOLOGY	Potentially fatal. Most commonly seen in older adults. Type II hypersensitivity reaction. IgG antibodies against desmoglein-1 and/or desmoglein-3 (component of desmosomes, which connect keratinocytes in the stratum spinosum).	Less severe than pemphigus vulgaris. Most commonly seen in older adults. Type II hypersensitivity reaction. IgG antibodies against hemidesmosomes (epidermal basement membrane; antibodies are "bullow" the epidermis).
GROSS MORPHOLOGY	Flaccid intraepidermal bullae A caused by acantholysis (separation of keratinocytes, "row of tombstones" on H&E stain); oral mucosa is involved. Nikolsky sign ⊕.	Tense blisters C containing eosinophils; oral mucosa spared. Nikolsky sign ⊖.
IMMUNOFLUORESCENCE	Reticular pattern around epidermal cells B.	Linear pattern at epidermal-dermal junction D.



Other blistering skin disorders

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Dermatitis herpetiformis	Pruritic papules, vesicles, and bullae (often found on elbows, knees, buttocks) A. Deposits of IgA at tips of dermal papillae. Associated with celiac disease. Treatment: dapsone, gluten-free diet.
Erythema multiforme	Associated with infections (eg, *Mycoplasma pneumoniae*, HSV), drugs (eg, sulfa drugs, β-lactams, phenytoin). Presents with multiple types of lesions—macules, papules, vesicles, target lesions (look like targets with multiple rings and dusky center showing epithelial disruption) B.
Stevens-Johnson syndrome	Characterized by fever, bullae formation and necrosis, sloughing of skin at dermal-epidermal junction (⊕ Nikolsky), high mortality rate. Typically mucous membranes are involved C D. Targetoid skin lesions may appear, as seen in erythema multiforme. Usually associated with adverse drug reaction. Toxic epidermal necrolysis (TEN) E F is more severe form of SJS involving > 30% body surface area. 10–30% involvement denotes SJS-TEN.

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Homunculus

Topographic representation of motor (shown) and sensory areas in the cerebral cortex. Distorted appearance is due to certain body regions being more richly innervated and thus having ↑ cortical representation.

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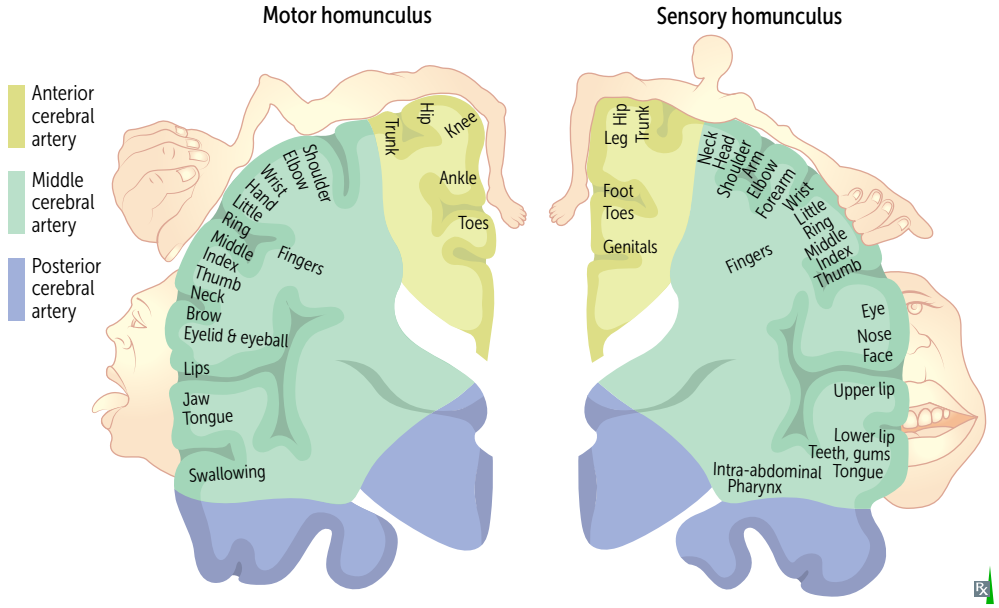

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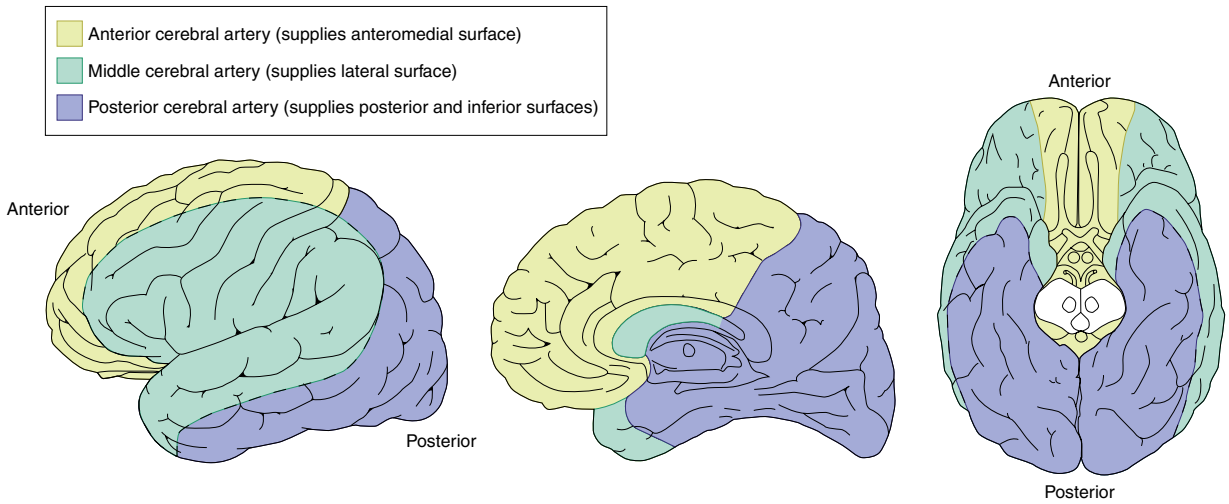
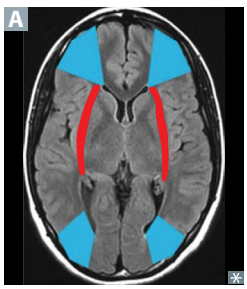
Cerebral arteries—cortical distribution



Watershed zones



Between anterior and middle cerebral arteries and posterior and middle cerebral arteries (cortical border zones) (blue areas in A); or may also occur between the superficial and deep vascular territories of the middle cerebral artery (internal border zones) (red areas in A).

Infarct due to severe hypotension → proximal upper and lower extremity weakness ("man-in-the-barrel syndrome"), higher order visual dysfunction (if posterior cerebral/middle cerebral cortical border zone stroke).

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Cranial nerve reflexes

REFLEX	AFFERENT	EFFERENT
Corneal	V_1 ophthalmic (nasociliary branch)	Bilateral VII (temporal branch—orbicularis oculi)
Lacrimation	V_1 (loss of reflex does not preclude emotional tears)	VII
Jaw jerk	V_3 (sensory—muscle spindle from masseter)	V_3 (motor—masseter)
Pupillary	II	III
Gag	IX	X

Mastication muscles

3 muscles close jaw: **M**asseter, te**M**poralis, **M**edial pterygoid. 1 opens: **L**ateral pterygoid. All are innervated by trigeminal nerve (V_3).

M's **M**unch.
Lateral **L**owers (when speaking of pterygoids with respect to jaw motion).
"It takes more muscle to keep your mouth shut."

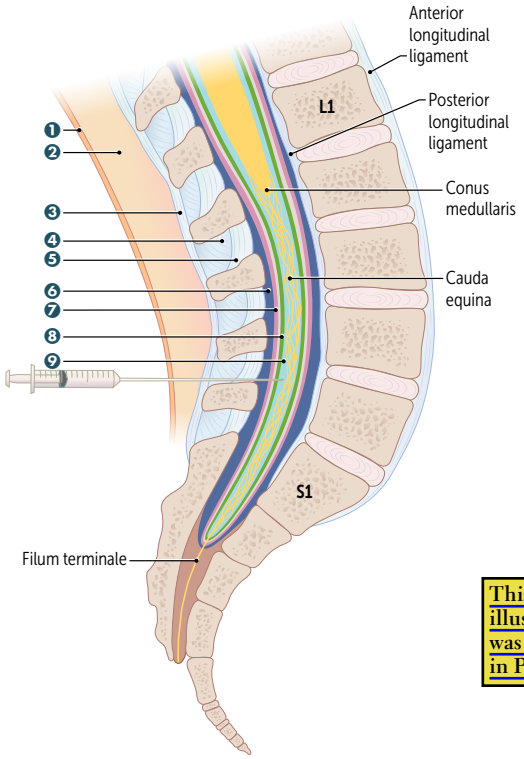
Spinal nerves

There are 31 pairs of spinal nerves: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, 1 coccygeal.
Nerves C1–C7 exit above the corresponding vertebrae. C8 spinal nerve exits below C7 and above T1. All other nerves exit below (eg, C3 exits above the 3rd cervical vertebra; L2 exits below the 2nd lumbar vertebra).

Spinal cord—lower extent

In adults, spinal cord ends at lower border of L1–L2 vertebrae. **S**ubarachnoid **S**pace (which contains the CSF) extends to lower border of **S2** vertebra. Lumbar puncture is usually performed between L3–L4 or L4–L5 (level of cauda equina).
Goal of lumbar puncture is to obtain sample of CSF without damaging spinal cord. To **keep** the cord **alive**, keep the spinal needle between **L3** and **L5**.
Needle passes through:

1. skin
2. fascia and fat
3. supraspinous ligament
4. interspinous ligament
5. ligamentum flavum
6. epidural space
   (epidural anesthesia needle stops here)
7. dura mater
8. arachnoid mater
9. subarachnoid space
   (CSF collection occurs here)



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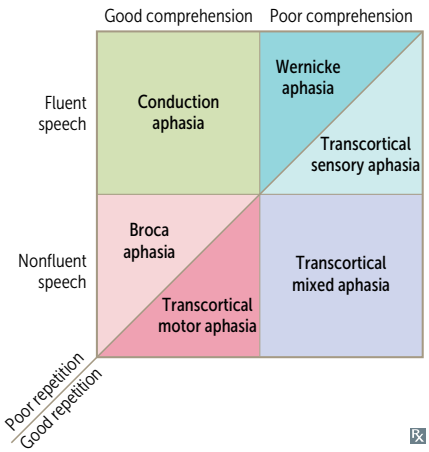
Aphasia

Aphasia—higher-order language deficit (inability to understand/produce/use language appropriately); caused by pathology in dominant cerebral hemisphere (usually left).

Dysarthria—motor inability to produce speech (movement deficit).



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TYPE	COMMENTS
Broca (expressive)	Broca area in inferior frontal gyrus of frontal lobe. Patient appears frustrated, insight intact. Broca = Broken Boca (*boca* = mouth in Spanish).
Wernicke (receptive)	Wernicke area in superior temporal gyrus of temporal lobe. Patients do not have insight. Wernicke is a Word salad and makes no sense.
Conduction	Can be caused by damage to arCuate fasciculus.
Global	Arcuate fasciculus; Broca and Wernicke areas affected.
Transcortical motor	Affects frontal lobe around Broca area, but Broca area is spared.
Transcortical sensory	Affects temporal lobe around Wernicke area, but Wernicke area is spared.
Transcortical mixed	Broca and Wernicke areas and arcuate fasciculus remain intact; surrounding watershed areas affected.

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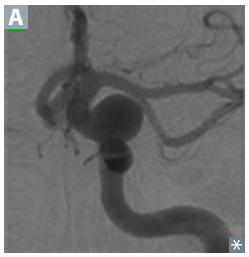
Aneurysms

Abnormal dilation of an artery due to weakening of vessel wall.

Saccular aneurysm



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Also known as berry aneurysm A. Occurs at bifurcations in the circle of Willis. Most common site is junction of ACom and ACA. Associated with ADPKD, Ehlers-Danlos syndrome. Other risk factors: advanced age, hypertension, smoking, race (↑ risk in African-Americans).

Usually clinically silent until rupture (most common complication) → subarachnoid hemorrhage ("worst headache of my life" or "thunderclap headache") → focal neurologic deficits. Can also cause symptoms via direct compression of surrounding structures by growing aneurysm.

- ACom—compression → bitemporal hemianopia (compression of optic chiasm); visual acuity deficits; rupture → ischemia in ACA distribution → contralateral lower extremity hemiparesis, sensory deficits.
- MCA—rupture → ischemia in MCA distribution → contralateral upper extremity and lower facial hemiparesis, sensory deficits.
- PCom—compression → ipsilateral CN III palsy → mydriasis ("blown pupil"); may also see ptosis, "down and out" eye.

Charcot-Bouchard microaneurysm

Common, associated with chronic hypertension; affects small vessels (eg, lenticulostriate arteries in basal ganglia, thalamus) and can cause hemorrhagic intraparenchymal strokes. Not visible on angiography.

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Seizures

Characterized by synchronized, high-frequency neuronal firing. Variety of forms.

Partial (focal) seizures

Affect single area of the brain. Most commonly originate in medial temporal lobe. Types:

- Simple partial (consciousness intact)—motor, sensory, autonomic, psychic
- Complex partial (impaired consciousness, automatisms)

Generalized seizures

Diffuse. Types:

- Absence (petit mal)—3 Hz spike-and-wave discharges, no postictal confusion, blank stare
- Myoclonic—quick, repetitive jerks
- Tonic-clonic (grand mal)—alternating stiffening and movement, postictal confusion, urinary incontinence, tongue biting
- Tonic—stiffening
- Atonic—"drop" seizures (falls to floor); commonly mistaken for fainting

Epilepsy—a disorder of recurrent, unprovoked seizures (febrile seizures are not epilepsy).

Status epilepticus—continuous (≥ 5 min) or recurring seizures that may result in brain injury.

Causes of seizures by age:

- Children—genetic, infection (febrile), trauma, congenital, metabolic
- Adults—tumor, trauma, stroke, infection
- Elderly—stroke, tumor, trauma, metabolic, infection

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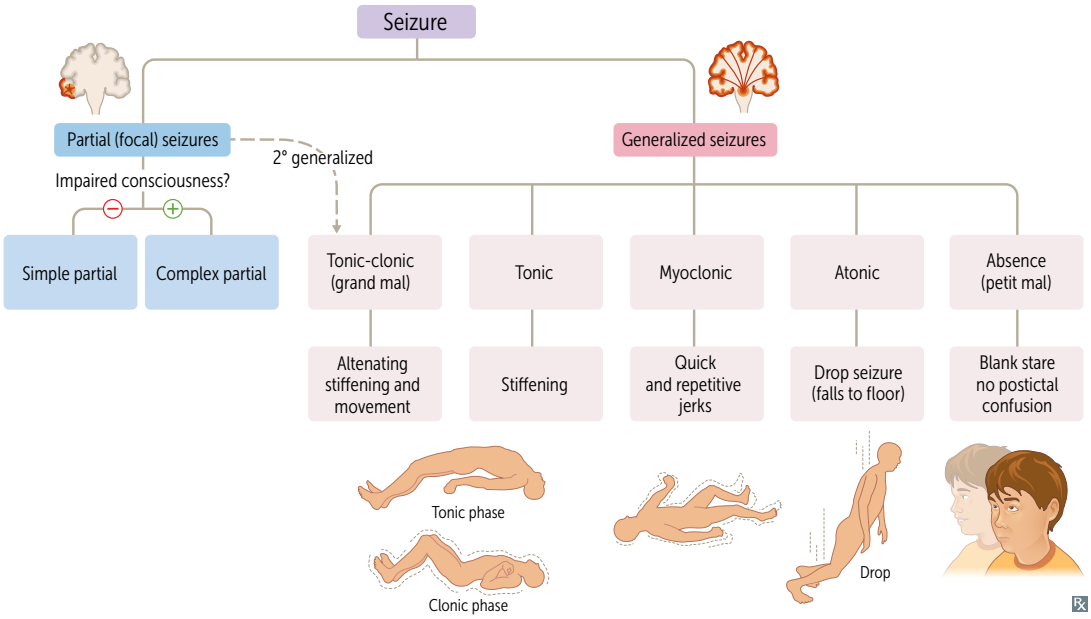

Fever vs heat stroke

New fact

	Fever	Heat stroke
PATHOPHYSIOLOGY	Cytokine activation during inflammation (eg, infection)	Inability of body to dissipate heat (eg, exertion)
TEMPERATURE	Usually < 40 °C	Usually > 40 °C
COMPLICATIONS	Febrile seizure (benign, usually self-limiting)	CNS dysfunction (eg, confusion), end-organ damage, acute respiratory distress syndrome, rhabdomyolysis
MANAGEMENT	Acetaminophen or ibuprofen for comfort (does not prevent future febrile seizures), antibiotic therapy if indicated	Rapid external cooling, rehydration and electrolyte correction

Crowdproofer feedback. This fact seems out of place here.

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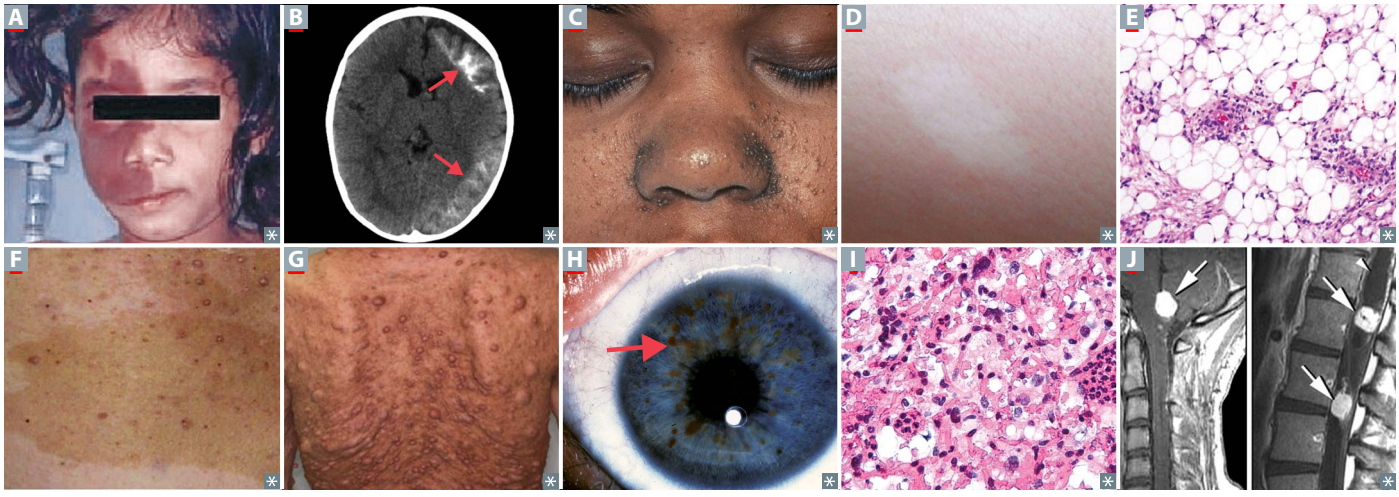
Neurocutaneous disorders

DISORDER	GENETICS	PRESENTATION	NOTES
Sturge-Weber syndrome	Congenital nonhereditary anomaly of neural crest derivatives. Somatic mosaicism of an activating mutation in one copy of the *GNAQ* gene.	Affects capillary-sized blood vessels → port-wine stain A (nevus flammeus or non-neoplastic birthmark) in CN V_1/V_2 distribution; ipsilateral leptomeningeal angioma B → seizures/epilepsy; intellectual disability; episcleral hemangioma → ↑ IOP → early-onset glaucoma.	Also known as encephalotrigeminal angiomatosis. SSTURGGE-Weber: Sporadic, port-wine Stain, Tram track calcifications (opposing gyri), Unilateral, intellectual disability (Retardation), Glaucoma, *GNAQ* gene, Epilepsy.
Tuberous sclerosis	AD, variable expression. *TSC1* mutation on chromosome 9 or *TSC2* mutation on chromosome 16, Tumor suppressor genes.	Hamartomas in CNS and skin, Angiofibromas C, Mitral regurgitation, Ash-leaf spots D, cardiac Rhabdomyoma, (Tuberous sclerosis), autosomal dOminant; Mental retardation (intellectual disability), renal Angiomyolipoma E, Seizures, Shagreen patches.	HAMARTOMASS. ↑ incidence of subependymal giant cell astrocytomas and ungual fibromas.
Neurofibromatosis type I	AD, 100% penetrance. Mutation in *NF1* tumor suppressor gene on chromosome 17 (encodes neurofibromin, a negative RAS regulator)	Café-au-lait spots F, Intellectual disability, Cutaneous neurofibromas G, Lisch nodules (pigmented iris hamartomas H), Optic gliomas, Pheochromocytomas, Seizures/focal neurologic Signs (often from meningioma), bone lesions (eg, sphenoid dysplasia).	Also known as von Recklinghausen disease. 17 letters in "von Recklinghausen." CICLOPSS.
Neurofibromatosis type II	AD, Mutation in *NF2* tumor suppressor gene on chromosome 22.	Bilateral vestibular schwannomas, juvenile cataracts, meningiomas, ependymomas.	NF2 affects 2 ears, 2 eyes, and 2 parts of the brain.
von Hippel-Lindau disease	AD, Deletion of *VHL* gene on chromosome 3p. pVHL ubiquitinates hypoxia-inducible factor 1a.	Hemangioblastomas (high vascularity with hyperchromatic nuclei I) in retina, brain stem, cerebellum, spine J; Angiomatosis; bilateral Renal cell carcinomas; Pheochromocytomas.	Numerous tumors, benign and malignant. VHL = 3 letters. HARP.



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Renovascular disease	Renal impairment due to ischemia from renal artery stenosis or microvascular disease. ↓ renal perfusion (one or both kidneys) → ↑ renin → ↑ angiotensin → HTN. Main causes of renal artery stenosis: ▪ Atherosclerotic plaques—proximal 1/3rd of renal artery, usually in older males, smokers. ▪ Fibromuscular dysplasia—distal 2/3rd of renal artery or segmental branches, usually young or middle-aged females. Clinically, patients can have refractory HTN with negative family history of HTN, asymmetric renal size, epigastric/flank bruits.	Most common cause of 2° HTN in adults. Other large vessels are often involved.

Renal cyst disorders

Autosomal dominant polycystic kidney disease	Numerous cysts in cortex and medulla A causing bilateral enlarged kidneys ultimately destroy kidney parenchyma. Presents with flank pain, hematuria, hypertension, urinary infection, progressive renal failure in ~ 50% of individuals. Mutation in *PKD1* (85% of cases, chromosome 16) or *PKD2* (15% of cases, chromosome 4). Complications include chronic kidney disease and hypertension (caused by ↑ renin production). Associated with berry aneurysms, mitral valve prolapse, benign hepatic cysts, diverticulosis. Treatment: If hypertension or proteinuria develops, treat with ACE inhibitors or ARBs.
Autosomal recessive polycystic kidney disease	Cystic dilation of collecting ducts B. Often presents in infancy. Associated with congenital hepatic fibrosis. Significant oliguric renal failure in utero can lead to Potter sequence. Concerns beyond neonatal period include systemic hypertension, progressive renal insufficiency, and portal hypertension from congenital hepatic fibrosis.
Autosomal dominant tubulointerstitial kidney disease	Also known as medullary cystic kidney disease. Causes tubulointerstitial fibrosis and progressive renal insufficiency with inability to concentrate urine. Medullary cysts usually not visualized; smaller kidneys on ultrasound. Poor prognosis.
Simple vs complex renal cysts	Simple cysts are filled with ultrafiltrate (anechoic on ultrasound C). Very common and account for majority of all renal masses. Found incidentally and typically asymptomatic. Complex cysts, including those that are septated, enhanced, or have solid components on imaging require follow-up or removal due to risk of renal cell carcinoma.

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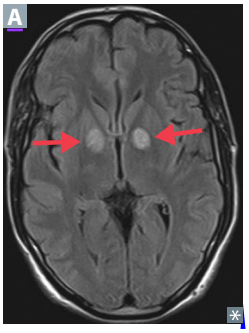
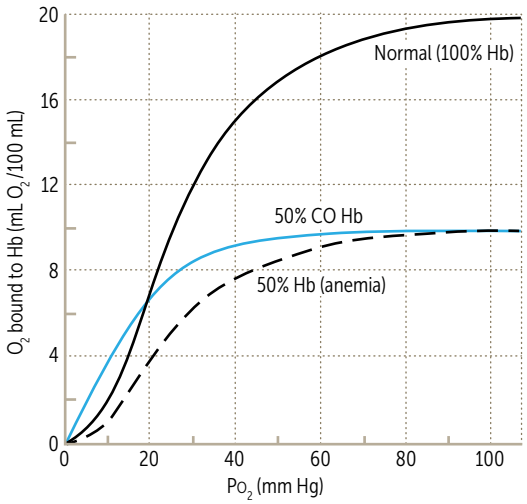
Cyanide vs carbon monoxide poisoning

Both inhibit aerobic metabolism via inhibition of complex IV (cytochrome c oxidase) → hypoxia unresponsive to supplemental O_2 and ↑ anaerobic metabolism.
Both can lead to pink or cherry red skin (usually postmortem finding), seizures, and coma.

	Cyanide	Carbon monoxide
SOURCE	Byproduct of synthetic product combustion, ingestion of amygdalin (cyanogenic glucoside found in apricot seeds) or cyanide.	Odorless gas from fires, car exhaust, or gas heaters.
TREATMENT	Hydroxocobalamin (forms cyanocobalamin) or induced methemoglobinemia with nitrites and sodium thiosulfate.	100% O_2, hyperbaric O_2.
SIGNS/SYMPTOMS 	Breath has bitter almond odor; cardiovascular collapse.	Headache, dizziness. Multiple individuals may be involved (eg, family with similar symptoms in winter). Classically associated with bilateral globus pallidus lesions on MRI A, although rarely seen with cyanide toxicity as well.
EFFECT ON OXYGEN-HEMOGLOBIN DISSOCIATION CURVE	Curve normal; oxygen saturation may appear normal initially.	↓ oxygen-binding capacity with left shift in curve, ↓ O_2 unloading in tissues. Binds competitively to Hb with 200× greater affinity than O_2 to form carboxyhemoglobin.



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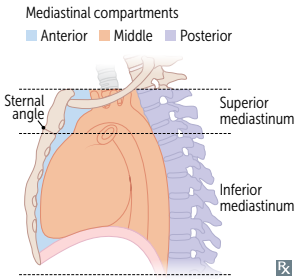
Mediastinal pathology

Normal mediastinum contains heart, thymus, lymph nodes, esophagus, and aorta. Divided into compartments.

Mediastinal masses



Some pathologies (eg, lymphoma, lung cancer, abscess) can occur in any compartment, but there are common associations:

- Anterior—4Ts: Thyroid, Thymic neoplasm, Teratoma, "Terrible" lymphoma.
- Middle—esophageal carcinoma, metastases, hiatal hernia, bronchogenic cysts.
- Posterior—neurogenic tumor (eg, neurofibroma), multiple myeloma.

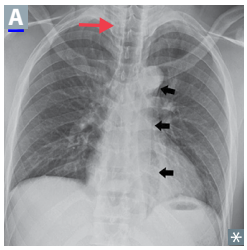
Mediastinitis

Inflammation of tissues in the mediastinum. Commonly due to postoperative complications of cardiothoracic procedures (pathology ≤ 14 days), esophageal perforation, or contiguous spread of odontogenic/retropharyngeal infection.

Chronic mediastinitis—also known as fibrosing mediastinitis; due to ↑ formation of connective tissue in mediastinum. *Histoplasma capsulatum* is common cause.

Clinical features: fever, tachycardia, leukocytosis, chest pain, and (especially with cardiac procedures) sternal wound drainage.

Pneumomediastinum



Presence of gas (usually air) in the mediastinum (black arrows show air around the aorta, red arrow shows air dissecting into the neck A). Can either be spontaneous (due to rupture of pulmonary bleb) or 2° (eg, trauma, iatrogenic, Boerhaave syndrome).

Ruptured alveoli allow tracking of air into the mediastinum via peribronchial and perivascular sheaths.

Clinical features: chest pain, dyspnea, voice change, subcutaneous emphysema, ⊕ Hamman sign (crepitus on cardiac auscultation).

Can be associated with pneumothoraces.

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