CHAPTER 1

General Pathology

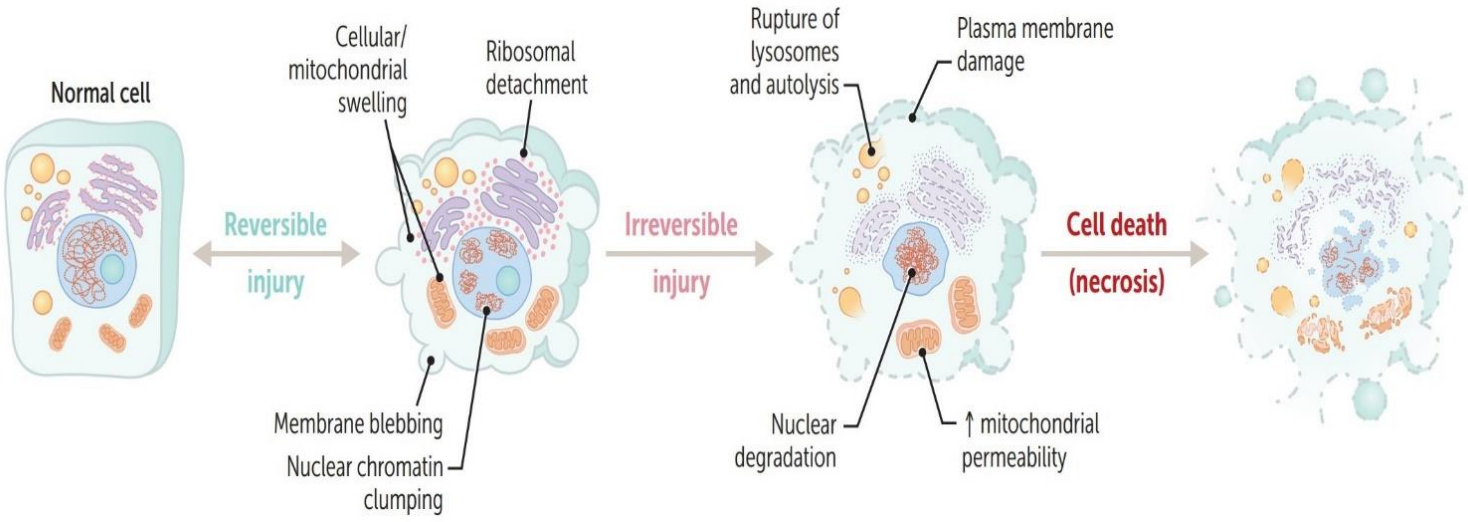
Cell injury

A. Reversible cell injury:

- ↓ ATP → ↓ activity of Ca and Na/K pumps → cellular swelling (earliest morphologic manifestation), mitochondrial swelling.
- Ribosomal/polysomal detachment → ↓ protein synthesis.
- Plasma membrane changes (blebbing).
- Nuclear changes (chromatin clumping).
- Rapid loss of function (myocardial cells are noncontractile after 1-2 minutes of ischemia).

B. Irreversible cell injury:

- Breakdown of plasma membrane → cytosolic enzymes (troponin) leak into serum, influx of Ca → activation of degradative enzymes.
- Mitochondrial damage/dysfunction → loss of electron transport chain → ↓ ATP.
- Rupture of lysosomes → autolysis.
- Nuclear degradation: pyknosis (nuclear condensation) → karyorrhexis (nuclear fragmentation caused by endonuclease-mediated cleavage) → karyolysis (nuclear dissolution).



Cell death

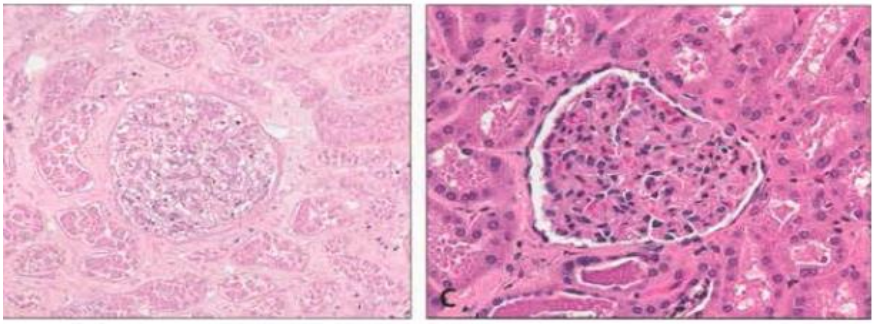
- The morphologic hallmark of cell death is loss of the nucleus, which occurs via nuclear condensation (pyknosis), fragmentation (karyorrhexis), and dissolution (karyolysis).
- The two mechanisms of cell death are necrosis and apoptosis.

Necrosis

- Death of large groups of cells followed by acute inflammation (unlike apoptosis).
- Due to some underlying pathologic process; never physiologic.
- Divided into several types based on gross features.

A. Coagulative necrosis:

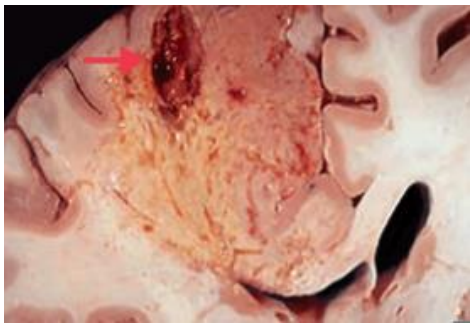
- Necrotic tissue that remains firm; cell shape and organ structure are preserved by coagulation of proteins, but the nucleus disappears.
- Characteristic of ischemic infarction of any organ except the brain.



B. Liquefactive necrosis:

- Necrotic tissue that becomes liquefied; enzymatic lysis of cells and protein results in liquefaction.
- Characteristic of:

- Brain infarction: Proteolytic enzymes from microglial cells liquefy the brain.
- Abscess: Proteolytic enzymes from neutrophils liquefy tissue.
- Pancreatitis: Proteolytic enzymes from pancreas liquefy parenchyma.

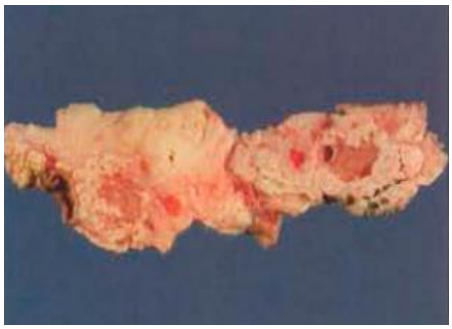


C. Caseous necrosis:

- Soft and friable necrotic tissue with "cottage cheese-like" appearance.
- Combination of coagulative and liquefactive necrosis.
- Characteristic of granulomatous inflammation due to tuberculous or fungal infection.

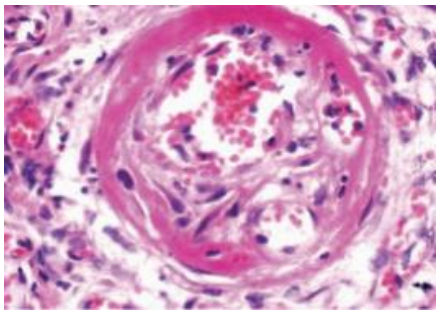
D. Fat necrosis:

- Necrotic adipose tissue with chalky-white appearance due to deposition of Calcium.
- Characteristic of trauma to fat (breast) and pancreatitis-mediated damage of peripancreatic fat.
- Fatty acids released by trauma (to breast) or lipase (pancreatitis) join with calcium via a process called saponification.
- Saponification is an example of dystrophic calcification in which calcium deposits on dead tissues. In dystrophic calcification, the necrotic tissue acts as a nidus for calcification in the setting of normal serum calcium and phosphate.



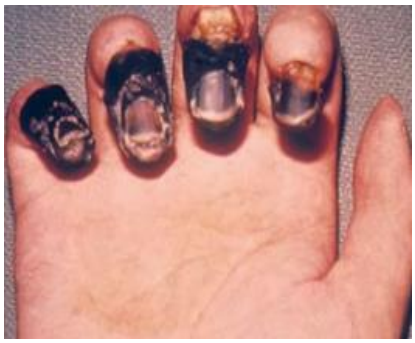
E. Fibrinoid necrosis:

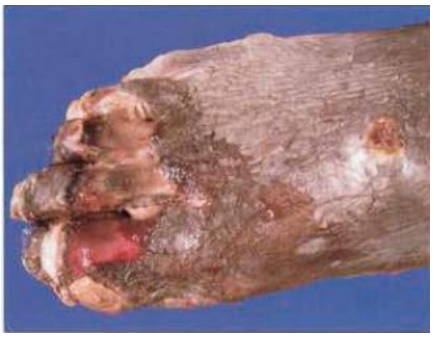
- Necrotic damage to blood vessel wall.
- Leaking of proteins (including fibrin) into vessel wall results in bright pink staining of the wall microscopically.
- Characteristic of malignant hypertension and vasculitis.



F. Gangrenous necrosis:

- Coagulative necrosis that resembles mummified tissue (dry gangrene).
- Characteristic of ischemia of lower limb and GI tract.
- If superimposed infection of dead tissues occurs, the liquefactive necrosis ensues (wet gangrene).





Apoptosis

- ATP-dependent programmed cell death.
- Intrinsic or extrinsic pathway; both pathways → activation of cytosolic proteases called caspases that mediate cellular breakdown → cell shrinkage, chromatin condensation, membrane blebbing, and formation of apoptotic bodies, which are then phagocytosed.
- Characterized by deeply eosinophilic cytoplasm and basophilic nucleus, pyknosis (nuclear shrinkage), and karyorrhexis (fragmentation caused by endonucleases cleaving at internucleosomal regions).
- DNA laddering (fragments in multiples of 180 bp) is a sensitive indicator of apoptosis.
- Cell membrane typically remains intact without significant inflammation (unlike necrosis).

A. Intrinsic (mitochondrial) pathway:

- Involved in tissue remodeling in embryogenesis.
- Occurs when a regulating factor is withdrawn from a proliferating cell population (↓ IL-2 after a completed immunologic reaction → apoptosis of proliferating effector cells).

- Also occurs after exposure to injurious stimuli (radiation, toxins, hypoxia).

- Regulated by Bcl-2 family of proteins such as BAX and BAK (proapoptotic) and Bcl-2, Bcl-xL (antiapoptotic).

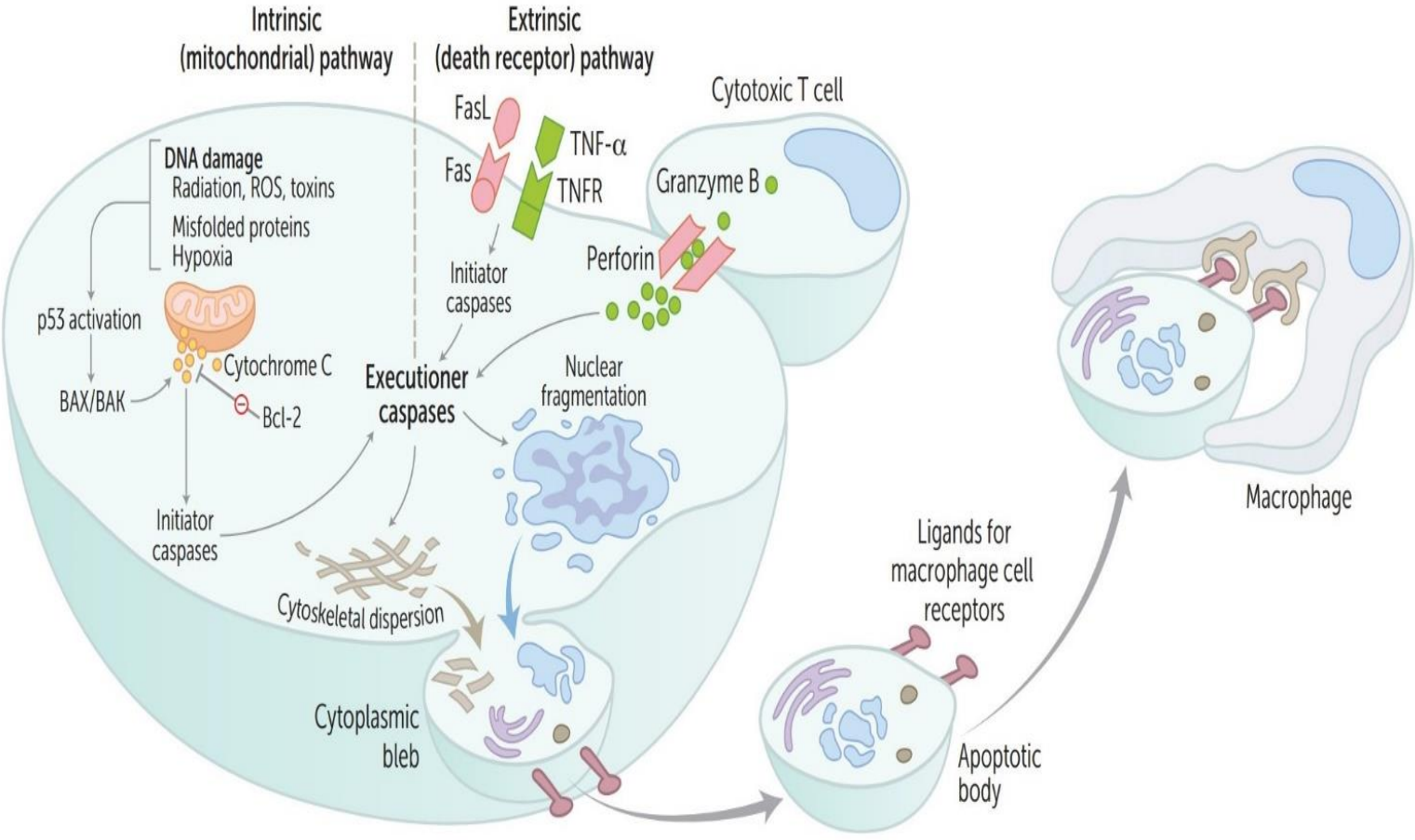
- BAX and BAK form pores in the mitochondrial membrane → release of cytochrome C from inner mitochondrial membrane into the cytoplasm → activation of caspases.

- Bcl-2 keeps the mitochondrial membrane impermeable, thereby preventing cytochrome C release. If Bcl-2 is overexpressed (follicular lymphoma t[14;18]), then APAF-1 is overly inhibited → ↓ caspase activation and tumorigenesis.

B. Extrinsic (death receptor) pathway:

- 2 pathways:
  - Ligand receptor interactions (FasL binding to Fas [CD95] or TNF-α binding to TNF).
  - Immune cell (cytotoxic T-cell release of perforin and granzyme B).

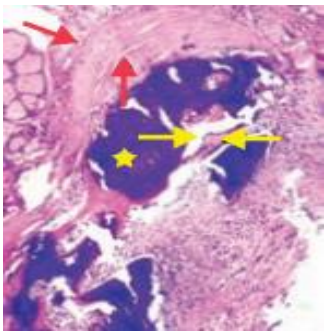
- Fas-FasL interaction is necessary in thymic medullary negative selection. Mutations in Fas ↑ numbers of circulating self-reacting lymphocytes due to failure of clonal deletion. Defective Fas-FasL interactions cause autoimmune lymphoproliferative syndrome.



Types of calcification

A. Dystrophic calcification:

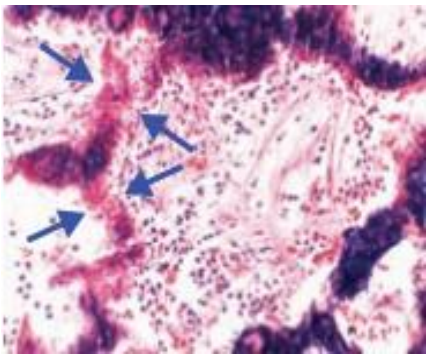
- Ca deposition in abnormal tissues 2° to injury or necrosis.
- Tends to be localized (calcific aortic stenosis).
- The figure below shows dystrophic calcification (yellow star), small bony tissue (yellow arrows), and thick fibrotic wall (red arrows).



- Seen in TB (lungs and pericardium), liquefactive necrosis of chronic abscesses, fat necrosis, infarcts, thrombi, schistosomiasis, Mönckeberg arteriolosclerosis, congenital CMV + toxoplasmosis, psammoma bodies.
- Is not directly associated with serum Ca levels (patients are usually normocalcemic).

B. Metastatic calcification:

- Widespread (diffuse, metastatic) deposition of Ca in normal tissue 2° to hypercalcemia (1° hyperparathyroidism, sarcoidosis, hypervitaminosis D) or high calcium-phosphate product levels (chronic renal failure with 2° hyperparathyroidism, long-term dialysis, calciphylaxis, warfarin).
- The figure below shows metastatic calcifications of alveolar walls in acute pneumonitis (blue arrows).



- Ca deposits predominantly in interstitial tissues of kidney, lung, and gastric mucosa (these tissues lose acid quickly; ↑ pH favors deposition).
- Patients are usually not normocalcemic.

Ischemia

- Inadequate blood supply to meet demand.
- Mechanisms include ↓ arterial perfusion (atherosclerosis), ↓ venous drainage (testicular torsion, Budd-Chiari syndrome), and shock.
- Regions most vulnerable to hypoxia/ischemia and subsequent infarction:

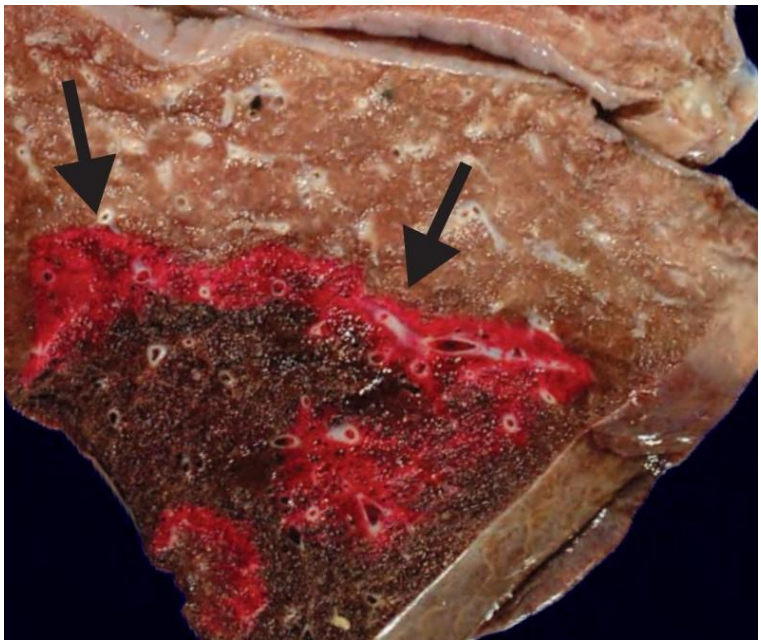
Organ	Region
Brain	ACA/MCA/PCA boundary areas
Heart	Subendocardium (LV)
Kidney	Straight segment of proximal tubule (medulla) Thick ascending limb (medulla)
Liver	Area around central vein (zone III)
Colon	Splenic flexure, rectuma

- Watershed areas (border zones) receive blood supply from most distal branches of 2 arteries with limited collateral vascularity. These areas are susceptible to ischemia from hypoperfusion.
- Neurons most vulnerable to hypoxic-ischemic insults include Purkinje cells of the cerebellum and pyramidal cells of the hippocampus and neocortex (zones 3, 5, 6).

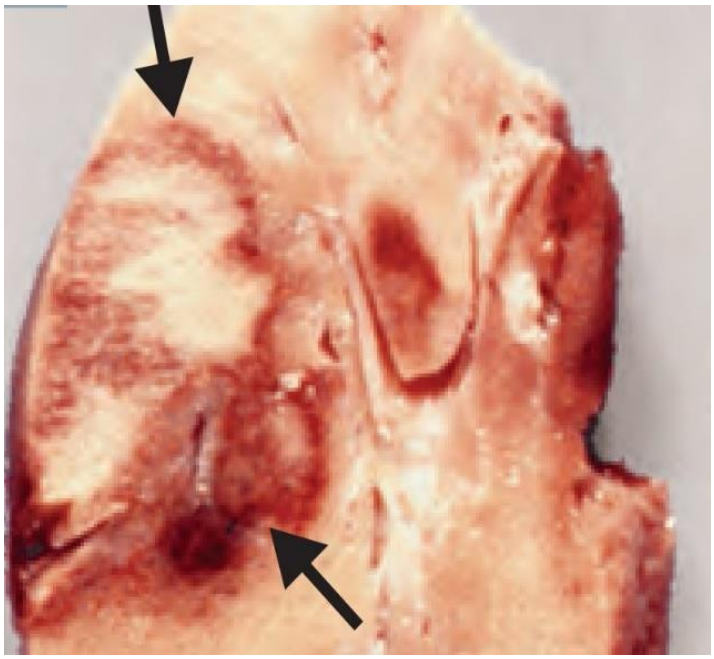
Infarcts: red vs pale

A. Red infarct:

- Occurs in venous occlusion and tissues with multiple blood supplies (liver, lung, intestine, testes), and with reperfusion (after angioplasty).
- Reperfusion injury is due to damage by free radicals. Red = reperfusion



B. Pale infarct: Occurs in solid organs with a single (endarterial) blood supply (heart, kidney).



Free radical injury

- Free radicals damage cells via membrane lipid peroxidation, protein modification, and DNA breakage.

- Initiated via radiation exposure (cancer therapy), metabolism of drugs (phase I), redox reactions, nitric oxide, transition metals, WBC (neutrophils, macrophages) oxidative burst.

- Free radicals can be eliminated by scavenging enzymes (catalase, superoxide dismutase, glutathione peroxidase), spontaneous decay, antioxidants (vitamins A, C, E), and certain metal carrier proteins (transferrin, ceruloplasmin).

- Examples:

- Oxygen toxicity: retinopathy of prematurity (abnormal vascularization), bronchopulmonary dysplasia, reperfusion injury after thrombolytic therapy.

- Drug/chemical toxicity: acetaminophen overdose (hepatotoxicity), carbon tetrachloride (converted by cytochrome P-450 into CCl3 free radical → fatty liver [cell injury → ↓ apolipoprotein synthesis → fatty change], centrilobular necrosis)

- Metal storage diseases: hemochromatosis (iron) and Wilson disease (copper)

Inflammation

- Response to eliminate initial cause of cell injury, to remove necrotic cells resulting from the original insult, and to initiate tissue repair.
- Divided into acute and chronic.
- The inflammatory response itself can be harmful to the host if the reaction is excessive (septic shock), prolonged (persistent infections such as TB), or inappropriate (autoimmune diseases such as SLE).
- Cardinal signs of inflammation:

Sign	Mechanism	Mediators
Rubor (redness), calor (warmth)	Vasodilation (relaxation of arteriolar smooth muscle) → ↑ blood flow.	Histamine, prostaglandins, bradykinin, NO.
Tumor (swelling)	Endothelial contraction/disruption (from tissue damage) → ↑ vascular permeability → leakage of protein-rich fluid from postcapillary venules into interstitial space (exudate) → ↑ interstitial oncotic pressure.	Endothelial contraction: leukotrienes (C4, D4, E4), histamine, serotonin.
Dolor (pain)	Sensitization of sensory nerve endings.	Bradykinin, PGE2, histamine.
Functio laesa (loss of function)	Cardinal signs above impair function (inability to make fist with hand that has cellulitis).	

- Systemic manifestations (acute-phase reaction):

A. Fever: Pyrogens (LPS) induce macrophages to release IL-1 and TNF → ↑ COX activity in perivascular cells of hypothalamus → ↑ PGE2 → ↑ temperature set point.

B. Leukocytosis:

- Elevation of WBC count.
- Type of cell that is predominantly elevated depends on the inciting agent or injury (bacteria → ↑ neutrophils).

C. ↑ plasma acute-phase proteins:

- Factors whose serum concentrations change significantly in response to inflammation.
- Produced by the liver in both acute and chronic inflammatory states. Notably induced by IL-6.

- Acute phase reactants [More FFiSH in the C (sea):

A. Positive (upregulated):

- Ferritin: Binds and sequesters iron to inhibit microbial iron scavenging.
- Fibrinogen: Coagulation factor; promotes endothelial repair; correlates with ESR.
- Serum amyloid A: Prolonged elevation can lead to amyloidosis.
- Hepcidin: ↓ iron absorption (by degrading ferroportin) and ↓ iron release (from macrophages) → anemia of chronic disease.
- C-reactive protein: Opsonin; fixes complement and facilitates phagocytosis. Measured clinically as a nonspecific sign of ongoing inflammation.

B. Negative (Downregulated):

- Albumin: Reduction conserves amino acids for positive reactants.
- Transferrin: Internalized by macrophages to sequester iron.

Erythrocyte sedimentation rate

- RBCs normally remain separated via ⊖ charges.
- Products of inflammation (fibrinogen) coat RBCs → ↓ ⊖ charge → ↑ RBC aggregation.
- Denser RBC aggregates fall at a faster rate within a pipette tube → ↑ ESR.
- Often co-tested with CRP (more specific marker of inflammation).

↑ ESR	↓ ESR
Most anemias **Infections** **Inflammation (giant cell [temporal] arteritis, polymyalgia rheumatica)** **Cancer (metastases, multiple myeloma)** **Renal disease (end-stage or nephrotic syndrome)** **Pregnancy**	Sickle cell anemia (altered shape) Polycythemia (↑ RBCs "dilute" aggregation factors) HF Microcytosis Hypofibrinogenemia

Exudate vs transudate

Exudate	Transudate
Cellular (cloudy)	Hypocellular (clear)
↑ protein (> 2.9 g/dL)	↓ protein (< 2.5 g/dL)
Due to: **Lymphatic obstruction (chylous)** **Inflammation/infection** **Malignancy**	Due to: ↑ hydrostatic pressure (HF, Na retention) ↓ oncotic pressure (cirrhosis, nephrotic syndrome)

- Light criteria:

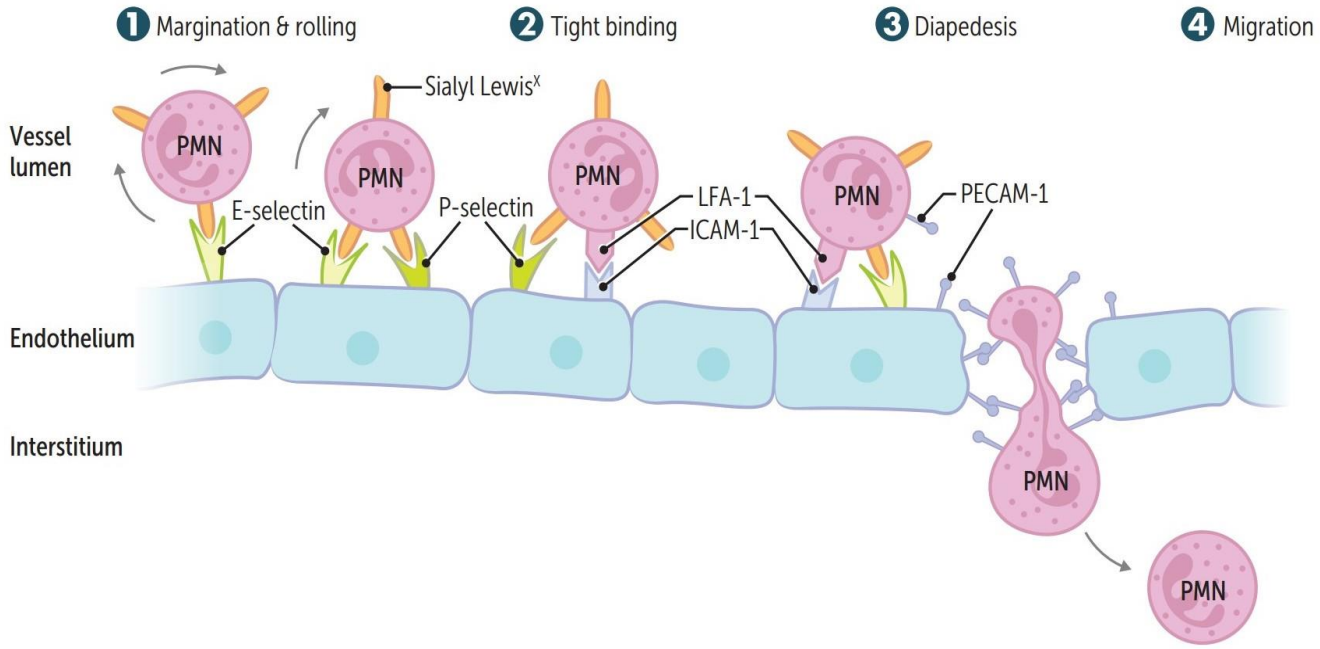
- Pleural fluid is exudative if ≥ 1 of the following criteria is met:
  - Pleural fluid protein/serum protein ratio > 0.5.
  - Pleural fluid LDH/serum LDH ratio > 0.6.
  - Pleural fluid LDH > 2⁄3 of the upper limit of normal for serum LDH.

- Exudate = Excess protein and LDH.

Leukocyte extravasation

Extravasation predominantly occurs at postcapillary venules.
WBCs exit from blood vessels at sites of tissue injury and inflammation in 4 steps:

STEP	VASCULATURE/STROMA	LEUKOCYTE
❶ Margination and rolling—defective in leukocyte adhesion deficiency type 2 (↓ Sialyl Lewis^X)	E-selectin (upregulated by TNF and IL-1)	Sialyl Lewis^X
	P-selectin (released from Weibel-Palade bodies)	Sialyl Lewis^X
	GlyCAM-1, CD34	L-selectin
❷ Tight binding (adhesion)—defective in leukocyte adhesion deficiency type 1 (↓ CD18 integrin subunit)	ICAM-1 (CD54)	CD11/18 integrins (LFA-1, Mac-1)
	VCAM-1 (CD106)	VLA-4 integrin
❸ Diapedesis (transmigration)—WBC travels between endothelial cells and exits blood vessel	PECAM-1 (CD31)	PECAM-1 (CD31)
❹ Migration—WBC travels through interstitium to site of injury or infection guided by chemotactic signals	Chemotactic factors: C5a, IL-8, LTB_4, kallikrein, platelet-activating factor	Various



Wound healing

Tissue mediators

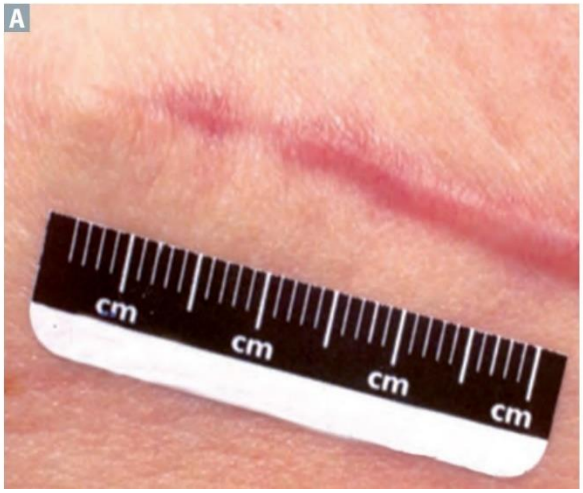
MEDIATOR	ROLE
FGF	Stimulates angiogenesis
TGF-β	Angiogenesis, fibrosis
VEGF	Stimulates angiogenesis
PDGF	Secreted by activated platelets and macrophages Induces vascular remodeling and smooth muscle cell migration Stimulates fibroblast growth for collagen synthesis
Metalloproteinases	Tissue remodeling
EGF	Stimulates cell growth via tyrosine kinases (eg, EGFR/*ErbB1*)

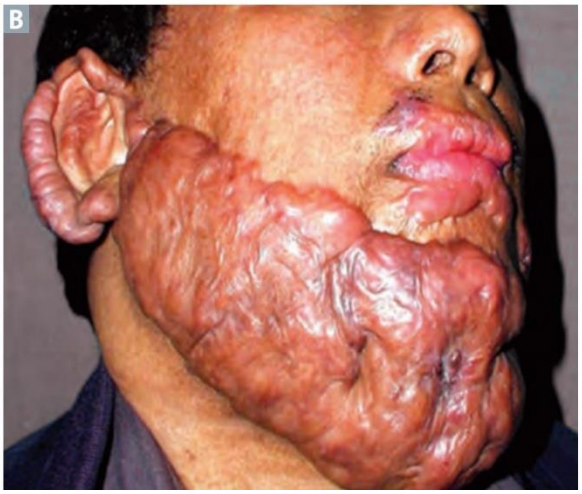
PHASE OF WOUND HEALING	EFFECTOR CELLS	CHARACTERISTICS
Inflammatory (up to 3 days after wound)	Platelets, neutrophils, macrophages	Clot formation, ↑ vessel permeability and neutrophil migration into tissue; macrophages clear debris 2 days later
Proliferative (day 3–weeks after wound)	Fibroblasts, myofibroblasts, endothelial cells, keratinocytes, macrophages	Deposition of granulation tissue and type III collagen, angiogenesis, epithelial cell proliferation, dissolution of clot, and wound contraction (mediated by myofibroblasts) Delayed second phase of wound healing in vitamin C and copper deficiency
Remodeling (1 week–6+ months after wound)	Fibroblasts	Type III collagen replaced by type I collagen, ↑ tensile strength of tissue Collagenases (require zinc to function) break down type III collagen Zinc deficiency → delayed wound healing

Scar formation

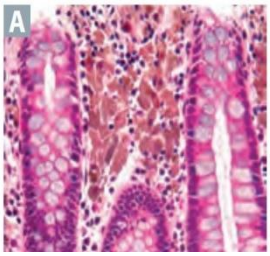
Occurs when repair cannot be accomplished by cell regeneration alone. Nonregenerated cells (2° to severe acute or chronic injury) are replaced by connective tissue. 70–80% of tensile strength regained at 3 months; little tensile strength regained thereafter. Associated with excess TGF-β.

SCAR TYPE	Hypertrophic A	Keloid B
COLLAGEN SYNTHESIS	↑ (type III collagen)	↑↑↑ (types I and III collagen)
COLLAGEN ORGANIZATION	Parallel	Disorganized
EXTENT OF SCAR	Confined to borders of original wound	Extends beyond borders of original wound with "claw-like" projections typically on earlobes, face, upper extremities
RECURRENCE	Infrequent	Frequent
PREDISPOSITION	None	↑ incidence in ethnic groups with darker skin





Lipofuscin

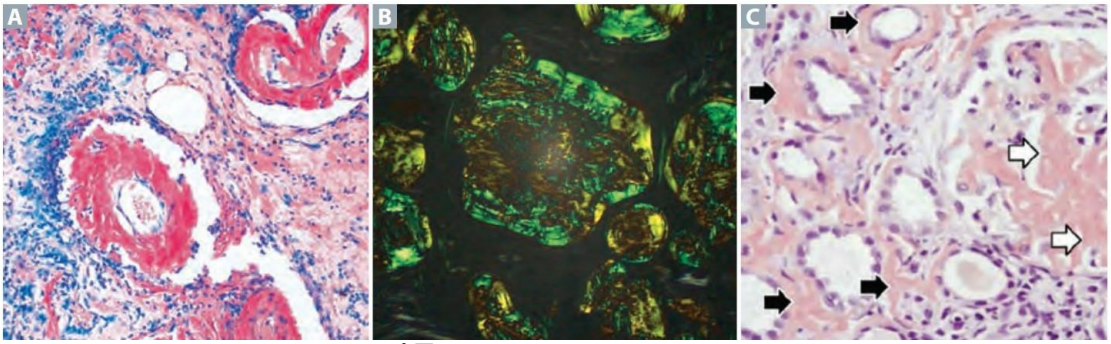


A yellow-brown "wear and tear" pigment A associated with normal aging.
Formed by oxidation and polymerization of autophagocytosed organellar membranes.
Autopsy of elderly person will reveal deposits in heart, colon, liver, kidney, eye, and other organs.

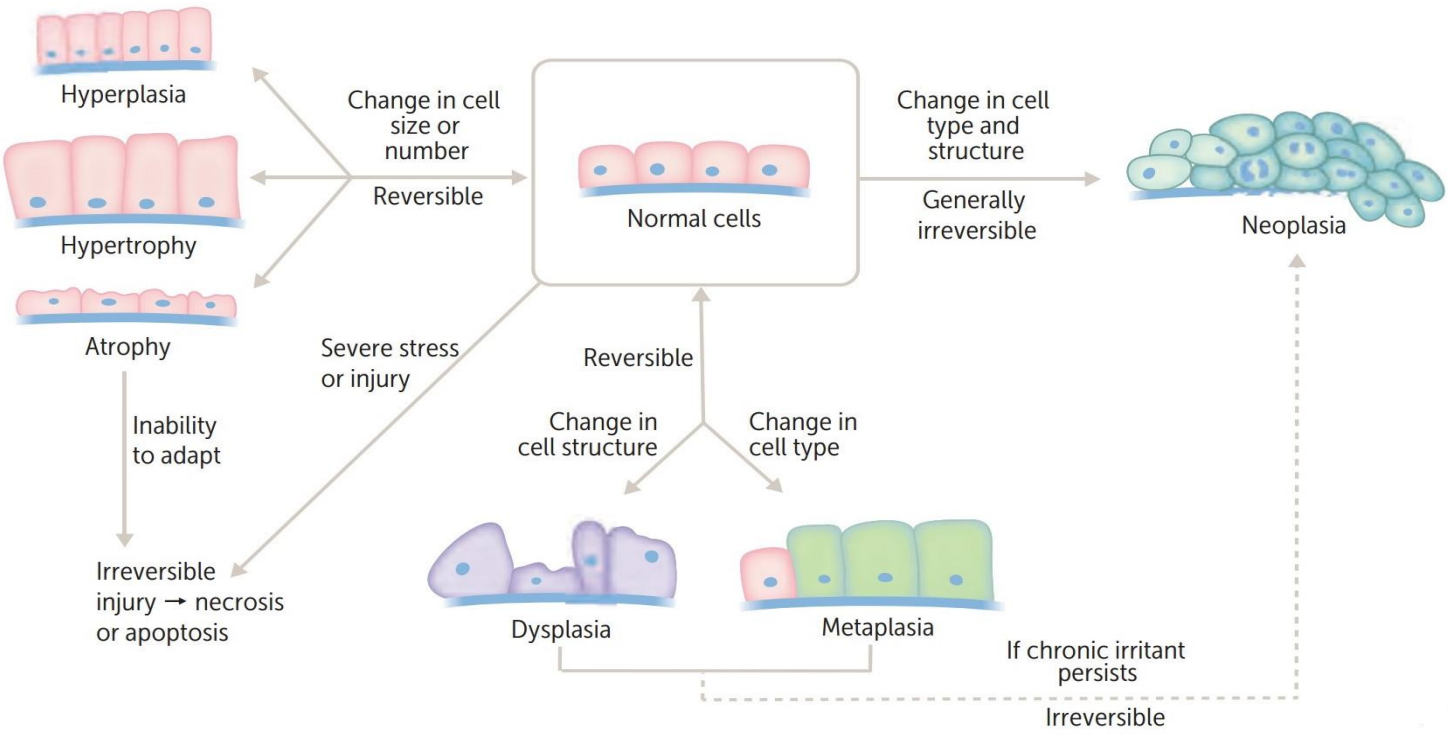
Amyloidosis

Abnormal aggregation of proteins (or their fragments) into β-pleated linear sheets → insoluble fibrils → cellular damage and apoptosis. Amyloid deposits visualized by Congo red stain A, polarized light (apple-green birefringence) B, and H&E stain (C shows deposits in glomerular mesangial areas [white arrows], tubular basement membranes [black arrows]).

COMMON TYPES	FIBRIL PROTEIN	DESCRIPTION	
Systemic			
Primary amyloidosis	AL (from Ig Light chains)	Seen in Plasma cell disorders (eg, multiple myeloma)	Manifestations include: ▪ Cardiac (eg, restrictive cardiomyopathy, arrhythmia) ▪ GI (eg, macroglossia, hepatomegaly) ▪ Renal (eg, nephrotic syndrome) ▪ Hematologic (eg, easy bruising, splenomegaly) ▪ Neurologic (eg, neuropathy) ▪ Musculoskeletal (eg, carpal tunnel syndrome)
Secondary amyloidosis	Serum Amyloid A (AA)	Seen in chronic inflammatory conditions, (eg, rheumatoid arthritis, IBD, familial Mediterranean fever, protracted infection)	
Dialysis-related amyloidosis	β_2-microglobulin	Seen in patients with ESRD and/or on long-term dialysis	
Localized			
Alzheimer disease	β-amyloid protein	Cleaved from amyloid precursor protein (APP)	
Type 2 diabetes mellitus	Islet amyloid polypeptide (IAPP)	Caused by deposition of amylin in pancreatic islets	
Medullary thyroid cancer	Calcitonin (A Cal)		
Isolated atrial amyloidosis	ANP	Common in normal aging ↑ risk of atrial fibrillation	
Systemic senile (age-related) amyloidosis	Normal (wild-type) transthyretin (TTR)	Seen predominantly in cardiac ventricles	Cardiac dysfunction more insidious than in AL amyloidosis
Hereditary			
Familial amyloid cardiomyopathy	Mutated transthyretin (ATTR)	Ventricular endomyocardium deposition → restrictive cardiomyopathy, arrhythmias	5% of African Americans are carriers of mutant allele
Familial amyloid polyneuropathies	Mutated transthyretin (ATTR)	Due to transthyretin gene mutation	

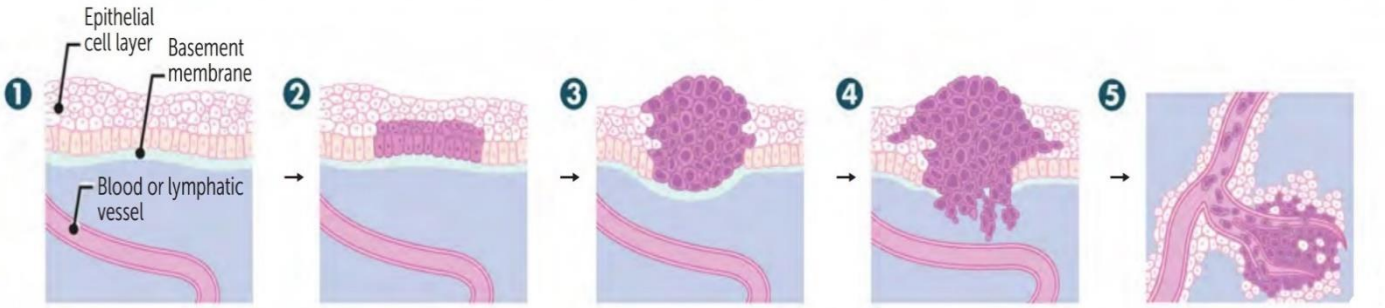


Cellular adaptations	Reversible changes that can be physiologic (eg, uterine enlargement during pregnancy) or pathologic (eg, myocardial hypertrophy 2° to systemic HTN). If stress is excessive or persistent, adaptations can progress to cell injury (eg, significant LV hypertrophy → injury to myofibrils → HF).
Hypertrophy	↑ structural proteins and organelles → ↑ in size of cells.
Hyperplasia	Controlled proliferation of stem cells and differentiated cells → ↑ in number of cells. Excessive stimulation → pathologic hyperplasia (eg, endometrial hyperplasia), which may progress to dysplasia and cancer.
Atrophy	↓ in tissue mass due to ↓ in size (↑ cytoskeleton degradation via ubiquitin-proteasome pathway and autophagy; ↓ protein synthesis) and/or number of cells (apoptosis). Causes include disuse, denervation, loss of blood supply, loss of hormonal stimulation, poor nutrition.
Metaplasia	Reprogramming of stem cells → replacement of one cell type by another that can adapt to a new stress. Usually due to exposure to an irritant, such as gastric acid (→ Barrett esophagus) or cigarette smoke (→ respiratory ciliated columnar epithelium replaced by stratified squamous epithelium). May progress to dysplasia → malignant transformation with persistent insult (eg, Barrett esophagus → esophageal adenocarcinoma). Metaplasia of connective tissue can also occur (eg, myositis ossificans, the formation of bone within muscle after trauma).
Dysplasia	Disordered, precancerous epithelial cell growth; not considered a true adaptive response. Characterized by loss of uniformity of cell size and shape (pleomorphism); loss of tissue orientation; nuclear changes (eg, ↑ nuclear:cytoplasmic ratio and clumped chromatin). Mild and moderate dysplasias (ie, do not involve entire thickness of epithelium) may regress with alleviation of inciting cause. Severe dysplasia often becomes irreversible and progresses to carcinoma in situ. Usually preceded by persistent metaplasia or pathologic hyperplasia.

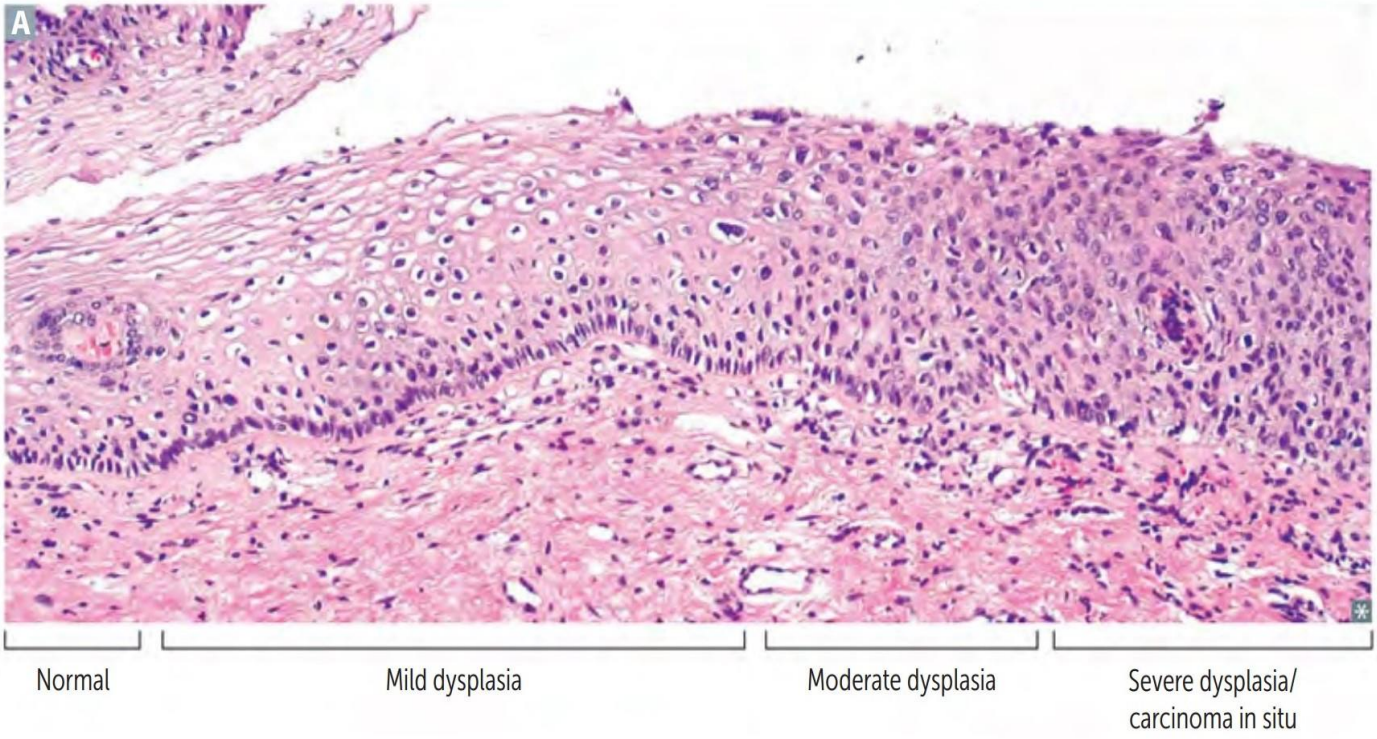


Neoplasia and neoplastic progression

Uncontrolled, monoclonal proliferation of cells. Can be benign or malignant. Any neoplastic growth has two components: parenchyma (neoplastic cells) and supporting stroma (non-neoplastic; eg, blood vessels, connective tissue).



Normal cells	1 Normal cells with basal → apical polarity. See cervical example A, which shows normal cells and spectrum of dysplasia, as discussed below.
Dysplasia	2 Loss of uniformity in cell size and shape (pleomorphism); loss of tissue orientation; nuclear changes (eg, ↑ nuclear:cytoplasmic ratio) A.
Carcinoma in situ/ preinvasive	3 Irreversible severe dysplasia that involves the entire thickness of epithelium but does not penetrate the intact basement membrane A.
Invasive carcinoma	4 Cells have invaded basement membrane using collagenases and hydrolases (metalloproteinases). Cell-cell contacts lost by inactivation of E-cadherin.
Metastasis	5 Spread to distant organ(s) via lymphatics or blood.



Tumor nomenclature

Carcinoma implies epithelial origin, whereas **sarcoma** denotes mesenchymal origin. Both terms generally imply malignancy.

Benign tumors are usually well-differentiated and well-demarcated, with low mitotic activity, no metastases, and no necrosis.

Malignant tumors (cancers) may show poor differentiation, erratic growth, local invasion, metastasis, and ↓ apoptosis.

Terms for non-neoplastic malformations include hamartoma (disorganized overgrowth of tissues in their native location, eg, Peutz-Jeghers polyps) and choristoma (normal tissue in a foreign location, eg, gastric tissue located in distal ileum in Meckel diverticulum).

CELL TYPE	BENIGN	MALIGNANT
Epithelium	Adenoma, papilloma	Adenocarcinoma, papillary carcinoma
Mesenchyme		
Blood cells		Leukemia, lymphoma
Blood vessels	Hemangioma	Angiosarcoma
Smooth muscle	Leiomyoma	Leiomyosarcoma
Striated muscle	Rhabdomyoma	Rhabdomyosarcoma
Connective tissue	Fibroma	Fibrosarcoma
Bone	Osteoma	Osteosarcoma
Fat	Lipoma	Liposarcoma
Melanocyte	Nevus/mole	Melanoma

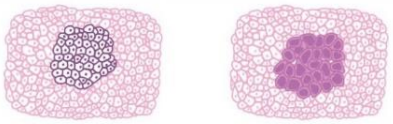
Tumor grade vs stage

Differentiation—degree to which a tumor resembles its tissue of origin. Well-differentiated tumors (often less aggressive) closely resemble their tissue of origin, whereas poorly differentiated tumors (often more aggressive) do not.

Anaplasia—complete lack of differentiation of cells in a malignant neoplasm.

Grade

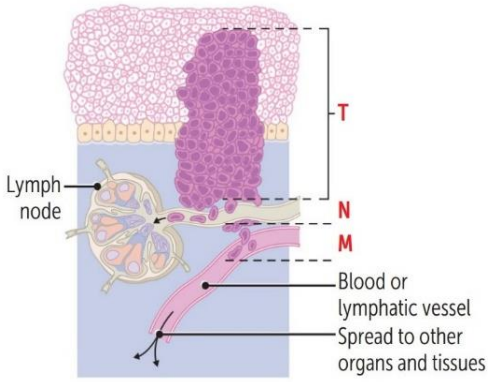
Degree of cellular differentiation and mitotic activity on histology. Ranges from low grade (well-differentiated) to high grade (poorly differentiated, undifferentiated, or anaplastic).



Stage

Degree of localization/spread based on site and size of 1° lesion, spread to regional lymph nodes, presence of metastases. Based on clinical (c) or pathologic (p) findings. Stage generally has more prognostic value than grade (eg, a high-stage yet low-grade tumor is usually worse than a low-stage yet high-grade tumor). Stage determines Survival.

TNM staging system (Stage = Spread):
T = Tumor size/invasiveness, N = Node involvement, M = Metastases, eg, cT3N1M0. Each TNM factor has independent prognostic value; N and M are often most important.



Hallmarks of cancer — Cancer is caused by (mostly acquired) DNA mutations that affect fundamental cellular processes (eg, growth, DNA repair, survival). Accumulation of mutations gives rise to hallmarks of cancer.

HALLMARK	MECHANISM
Growth signal self-sufficiency	Mutations in genes encoding: ▪ Proto-oncogenes → ↑ growth factors → autocrine loop (eg, ↑ PDGF in brain tumors) ▪ Growth factor receptors → constitutive signalling (eg, *HER2/neu* in breast cancer) ▪ Signaling molecules (eg, *RAS*) ▪ Transcription factors (eg, *MYC*) ▪ Cell cycle regulators (eg, cyclins, CDKs)
Anti-growth signal insensitivity	▪ Mutations in tumor suppressor genes (eg, *Rb*) ▪ Loss of E-cadherin function → loss of contact inhibition (eg, *NF2* mutations)
Evasion of apoptosis	Mutations in genes that regulate apoptosis (eg, *TP53*, *BCL2* → follicular B cell lymphoma).
Limitless replicative potential	Reactivation of telomerase → maintenance and lengthening of telomeres → prevention of chromosome shortening and cell aging.
Sustained angiogenesis	↑ pro-angiogenic factors (eg, VEGF) or ↓ inhibitory factors. Factors may be produced by tumor or stromal cells. Vessels can sprout from existing capillaries (neoangiogenesis) or endothelial cells are recruited from bone marrow (vasculogenesis). Vessels may be leaky and/or dilated.
Tissue invasion	Loss of E-cadherin function → loosening of intercellular junctions → metalloproteinases degrade basement membrane and ECM → cells attach to ECM proteins (eg, laminin, fibronectin) → cells migrate through degraded ECM ("locomotion") → vascular dissemination.
Metastasis	Tumor cells or emboli spread via lymphatics or blood → adhesion to endothelium → extravasation and homing. Site of metastasis can be predicted by site of primary tumor, as the target organ is often the first-encountered capillary bed ("seed and soil" theory). Some cancers show organ tropism (eg, lung cancers commonly metastasize to adrenals).
Warburg effect	Shift of glucose metabolism away from mitochondrial oxidative phosphorylation toward glycolysis.

Immune evasion in cancer

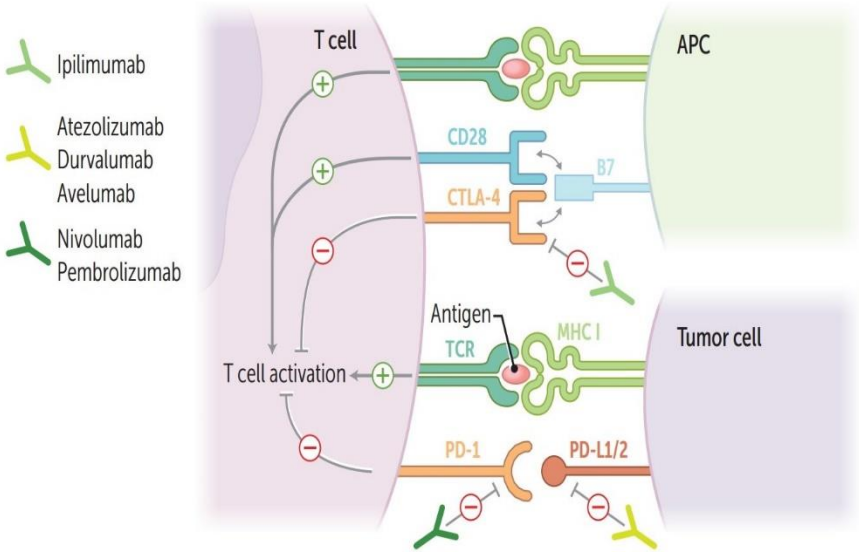
Immune cells can recognize and attack tumor cells. For successful tumorigenesis, tumor cells must evade the immune system. Multiple escape mechanisms exist:

- ↓ 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

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).



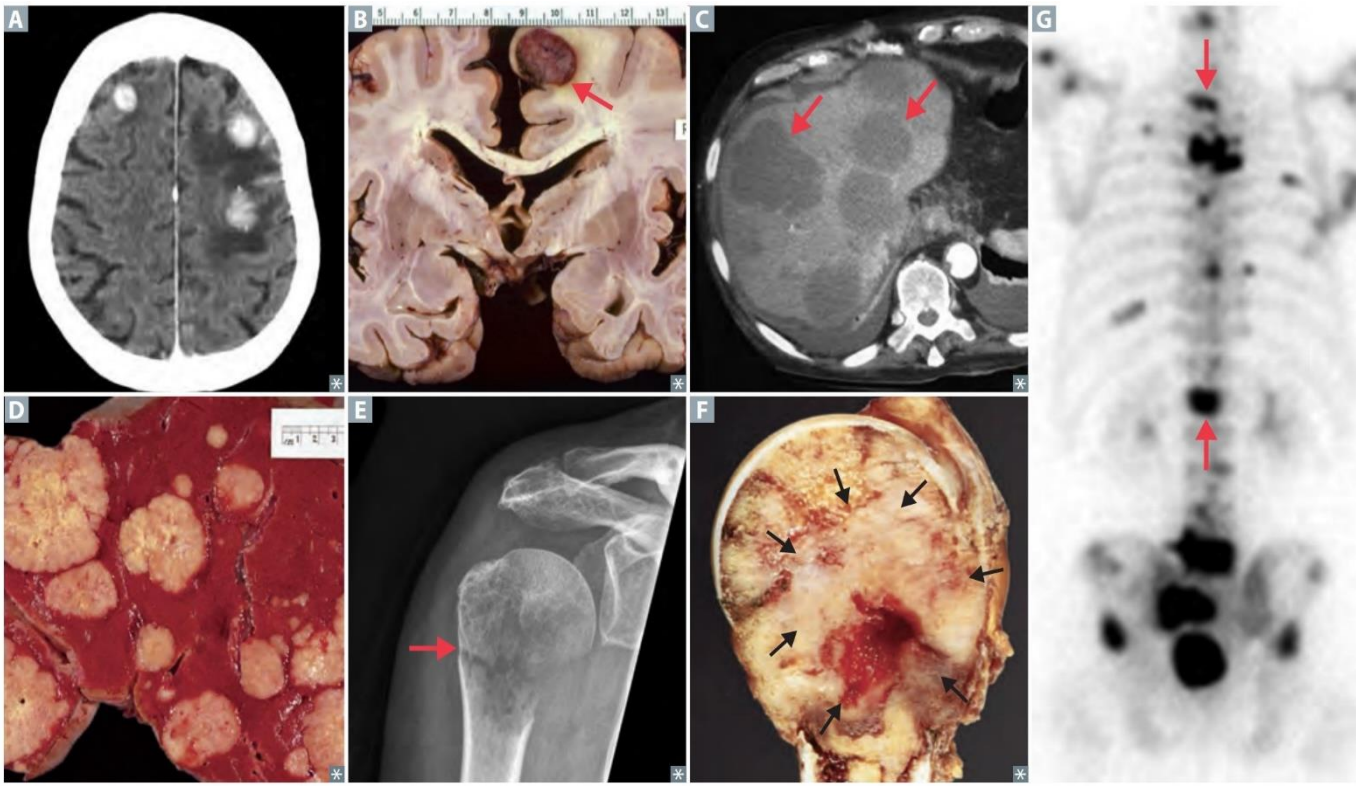
Cancer epidemiology

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).

Common metastases Most sarcomas spread hematogenously; most carcinomas spread via lymphatics. However, Four Carcinomas Route Hematogenously: Follicular thyroid carcinoma, Choriocarcinoma, Renal cell carcinoma, and Hepatocellular carcinoma.

SITE OF METASTASIS	1° TUMOR	NOTES
Brain	Lung > breast > melanoma, colon, kidney.	50% of brain tumors are from metastases A B. Commonly seen as multiple well-circumscribed tumors at gray/white matter junction.
Liver	Colon >> Stomach > Pancreas (Cancer Sometimes Penetrates liver).	Liver C D and lung are the most common sites of metastasis after the regional lymph nodes.
Bone	Prostate, Breast > Kidney, Thyroid, Lung (Painful Bones Kill The Lungs).	Bone metastasis E F >> 1° bone tumors (eg, multiple myeloma). Predilection for axial skeleton G. Bone metastasis can be: ▪ Lytic (eg, thyroid, kidney, non-small cell lung cancer) ▪ Blastic (eg, prostate, small cell lung cancer) ▪ Mixed (eg, breast)



Oncogenes — Gain of function mutation converts proto-oncogene (normal gene) to oncogene → ↑ cancer risk. Requires damage to only one allele of a proto-oncogene.

GENE	GENE PRODUCT	ASSOCIATED NEOPLASM
ALK	Receptor tyrosine Kinase	Lung Adenocarcinoma (Adenocarcinoma of the Lung Kinase)
BCR-ABL	Non-receptor tyrosine kinase	CML, ALL
BCL-2	Antiapoptotic molecule (inhibits apoptosis)	Follicular and diffuse large B Cell Lymphomas
BRAF	Serine/threonine kinase	Melanoma, non-Hodgkin lymphoma, papillary thyroid carcinoma, hairy cell leukemia
c-KIT	CytoKIne receptor	Gastrointestinal stromal tumor (GIST)
c-MYC	Transcription factor	Burkitt lymphoma
HER2/neu (c-erbB2)	Receptor tyrosine kinase	Breast and gastric carcinomas
JAK2	Tyrosine kinase	Chronic myeloproliferative disorders
KRAS	GTPase	Colon cancer, lung cancer, pancreatic cancer
MYCL1	Transcription factor	Lung tumor
N-myc (MYCN)	Transcription factor	Neuroblastoma
RET	Receptor tyrosine kinase	MEN 2A and 2B, papillary thyroid carcinoma

Tumor suppressor genes — Loss of function → ↑ cancer risk; both (two) alleles of a tumor suppressor gene must be lost for expression of disease.

GENE	GENE PRODUCT	ASSOCIATED CONDITION
APC	Negative regulator of β-catenin/WNT pathway	Colorectal cancer (associated with FAP)
BRCA1/BRCA2	DNA repair protein	Breast, ovarian, and pancreatic cancer
CDKN2A	p16, blocks G_1 → S phase	Melanoma, pancreatic cancer
DCC	DCC—Deleted in Colon Cancer	Colon cancer
SMAD4 (DPC4)	DPC—Deleted in Pancreatic Cancer	Pancreatic cancer
MEN1	Menin	Multiple Endocrine Neoplasia 1
NF1	Neurofibromin (Ras GTPase activating protein)	Neurofibromatosis type 1
NF2	Merlin (schwannomin) protein	Neurofibromatosis type 2
PTEN	Negative regulator of PI3k/AKT pathway	Breast, prostate, and endometrial cancer
Rb	Inhibits E2F; blocks G_1 → S phase	Retinoblastoma, osteosarcoma (bone cancer)
TP53	p53, activates p21, blocks G_1 → S phase	Most human cancers, Li-Fraumeni syndrome (multiple malignancies at early age, aka, SBLA cancer syndrome: Sarcoma, Breast, Leukemia, Adrenal gland)
TSC1	Hamartin protein	Tuberous sclerosis
TSC2	Tuberin protein	Tuberous sclerosis
VHL	Inhibits hypoxia-inducible factor 1a	von Hippel-Lindau disease
WT1	Transcription factor that regulates urogenital development	Wilms tumor (nephroblastoma)

Oncogenic microbes

Microbe	Associated cancer
EBV	Burkitt lymphoma, Hodgkin lymphoma, nasopharyngeal carcinoma, 1° CNS lymphoma (in immunocompromised patients)
HBV, HCV	Hepatocellular carcinoma
HHV-8	Kaposi sarcoma
HPV	Cervical and penile/anal carcinoma (types 16, 18), head and neck cancer
H pylori	Gastric adenocarcinoma and MALT lymphoma
HTLV-1	Adult T-cell leukemia/lymphoma
Liver fluke (*Clonorchis sinensis*)	Cholangiocarcinoma
Schistosoma haematobium	Squamous cell bladder cancer

Carcinogens

TOXIN	EXPOSURE	ORGAN	IMPACT
Aflatoxins (*Aspergillus*)	Stored grains and nuts	Liver	Hepatocellular carcinoma
Alkylating agents	Oncologic chemotherapy	Blood	Leukemia/lymphoma
Aromatic amines (eg, benzidine, 2-naphthylamine)	Textile industry (dyes), cigarette smoke (2-naphthylamine)	Bladder	Transitional cell carcinoma
Arsenic	Herbicides (vineyard workers), metal smelting	Liver Lung Skin	Angiosarcoma Lung cancer Squamous cell carcinoma
Asbestos	Old roofing material, shipyard workers	Lung	Bronchogenic carcinoma > mesothelioma
Cigarette smoke		Bladder Cervix Esophagus Kidney Larynx Lung Pancreas	Transitional cell carcinoma Squamous cell carcinoma Squamous cell carcinoma/ adenocarcinoma Renal cell carcinoma Squamous cell carcinoma Squamous cell and small cell carcinoma Pancreatic adenocarcinoma
Ethanol		Esophagus Liver	Squamous cell carcinoma Hepatocellular carcinoma
Ionizing radiation		Thyroid	Papillary thyroid carcinoma, leukemias
Nitrosamines	Smoked foods	Stomach	Gastric cancer
Radon	By-product of uranium decay, accumulates in basements	Lung	Lung cancer (2nd leading cause after cigarette smoke)
Vinyl chloride	Used to make PVC pipes (plumbers)	Liver	Angiosarcoma

Serum tumor markers Tumor markers should not be used as the 1° tool for cancer diagnosis or screening. They may be used to monitor tumor recurrence and response to therapy, but definitive diagnosis is made via biopsy. Some can be associated with non-neoplastic conditions.

MARKER	IMPORTANT ASSOCIATIONS	NOTES
Alkaline phosphatase	Metastases to bone or liver, Paget disease of bone, seminoma (placental ALP).	Exclude hepatic origin by checking LFTs and GGT levels.
α-fetoprotein	Hepatocellular carcinoma, Endodermal sinus (yolk sac) tumor, Mixed germ cell tumor, Ataxia-telangiectasia, Neural tube defects. (HE-MAN is the alpha male!)	Normally made by fetus. Transiently elevated in pregnancy. High levels associated with neural tube and abdominal wall defects, low levels associated with Down syndrome.
hCG	Hydatidiform moles and Choriocarcinomas (Gestational trophoblastic disease), testicular cancer, mixed germ cell tumor.	Produced by syncytiotrophoblasts of the placenta.
CA 15-3/CA 27-29	Breast cancer.	
CA 19-9	Pancreatic adenocarcinoma.	
CA 125	Ovarian cancer.	
Calcitonin	Medullary thyroid carcinoma (alone and in MEN2A, MEN2B).	
CEA	Major associations: colorectal and pancreatic cancers. Minor associations: gastric, breast, and medullary thyroid carcinomas.	Carcinoembryonic antigen. Very nonspecific.
Chromogranin	Neuroendocrine tumors.	
LDH	Testicular germ cell tumors, ovarian dysgerminoma, other cancers.	Can be used as an indicator of tumor burden.
Neuron-specific enolase	Neuroendocrine tumors (eg, small cell lung cancer, carcinoid tumor, neuroblastoma)	
PSA	Prostate cancer.	Prostate-specific antigen. Can also be elevated in BPH and prostatitis. Questionable risk/benefit for screening. Marker for recurrence after treatment.

Important immunohistochemical stains

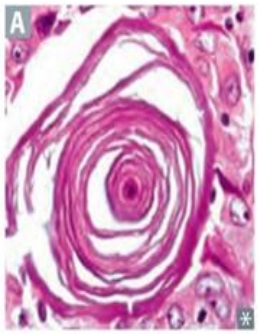
Determine primary site of origin for metastatic tumors and characterize tumors that are difficult to classify. Can have prognostic and predictive value.

STAIN	TARGET	TUMORS IDENTIFIED
Chromogranin and synaptophysin	Neuroendocrine cells	Small cell carcinoma of the lung, carcinoid tumor
Cytokeratin	Epithelial cells	Epithelial tumors (eg, squamous cell carcinoma)
DesMin	Muscle	Muscle tumors (eg, rhabdomyosarcoma)
GFAP	NeuroGlia (eg, astrocytes, Schwann cells, oligodendrocytes)	Astrocytoma, Glioblastoma
Neurofilament	Neurons	Neuronal tumors (eg, neuroblastoma)
PSA	Prostatic epithelium	Prostate cancer
S-100	Neural crest cells	Melanoma, schwannoma, Langerhans cell histiocytosis
TRAP	Tartrate-resistant acid phosphatase	Hairy cell leukemia
Vimentin	Mesenchymal tissue (eg, fibroblasts, endothelial cells, macrophages)	Mesenchymal tumors (eg, sarcoma), but also many other tumors (eg, endometrial carcinoma, renal cell carcinoma, meningioma)

P-glycoprotein

Also known as multidrug resistance protein 1 (MDR1). Classically seen in adrenocortical carcinoma but also expressed by other cancer cells (eg, colon, liver). Used to pump out toxins, including chemotherapeutic agents (one mechanism of ↓ responsiveness or resistance to chemotherapy over time).

Psammoma bodies



Laminated, concentric spherules with dystrophic calcification A, PSaMMOMa bodies are seen in:

- Papillary carcinoma of thyroid
- Somatostatinoma
- Meningioma
- Malignant Mesothelioma
- Ovarian serous papillary cystadenocarcinoma
- Prolactinoma (Milk)

Cachexia

Weight loss, muscle atrophy, and fatigue that occur in chronic disease (eg, cancer, AIDS, heart failure, COPD). Mediated by TNF-α, IFN-γ, IL-1, and IL-6.

Paraneoplastic syndromes

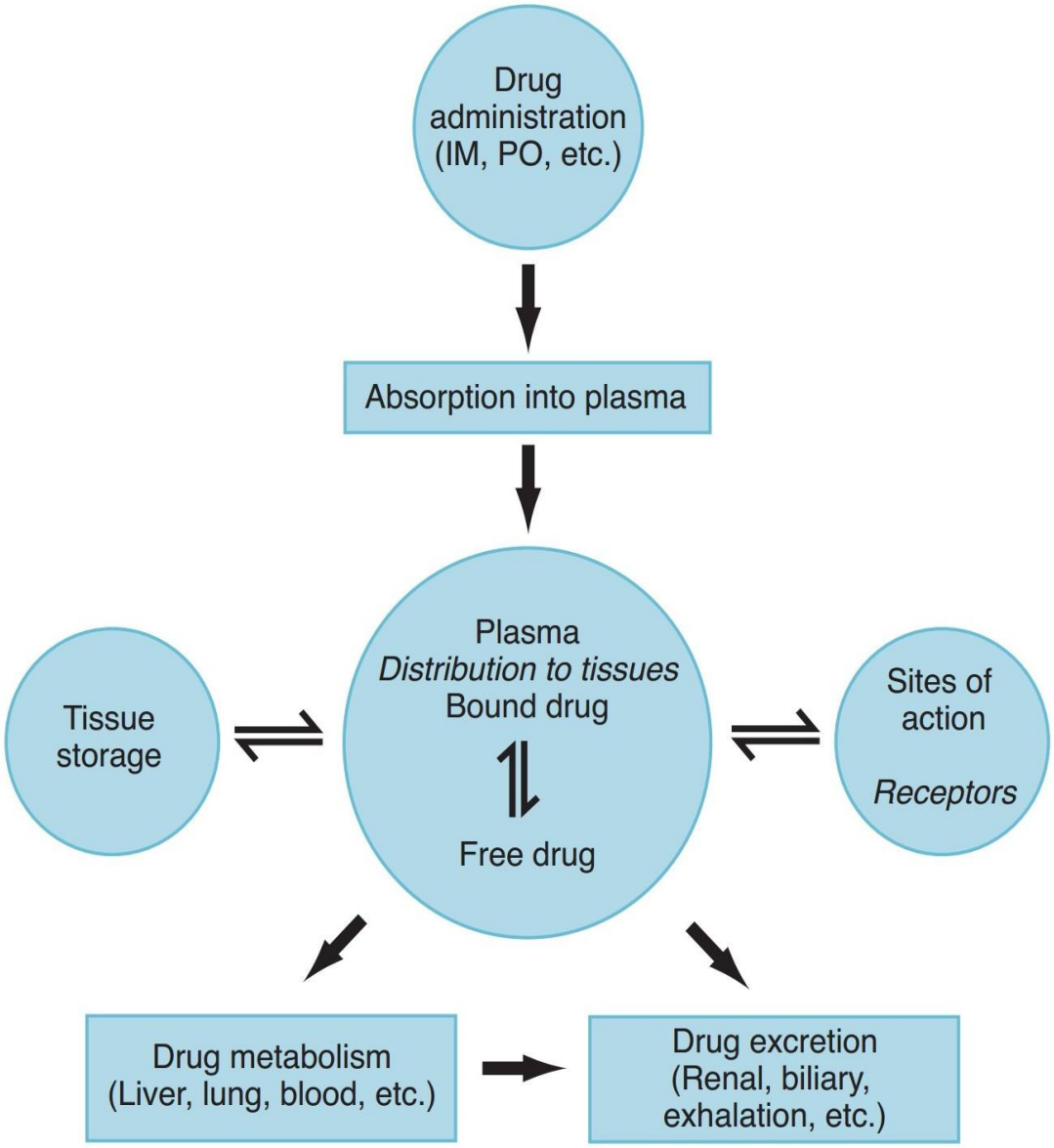
MANIFESTATION	DESCRIPTION/MECHANISM	MOST COMMONLY ASSOCIATED TUMOR(S)
Musculoskeletal and cutaneous		
Dermatomyositis	Progressive proximal muscle weakness, Gottron papules, heliotrope rash	Adenocarcinomas, especially ovarian
Acanthosis nigricans	Hyperpigmented velvety plaques in axilla and neck	Gastric adenocarcinoma and other visceral malignancies
Sign of Leser-Trélat	Sudden onset of multiple seborrheic keratoses	GI adenocarcinomas and other visceral malignancies
Hypertrophic osteoarthropathy	Abnormal proliferation of skin and bone at distal extremities → clubbing, arthralgia, joint effusions, periostosis of tubular bones	Adenocarcinoma of the lung
Endocrine		
Hypercalcemia	PTHrP	Squamous cell carcinomas of lung, head, and neck; renal, bladder, breast, and ovarian carcinomas
	↑ 1,25-$(OH)_2$ vitamin D_3 (calcitriol)	Lymphoma
Cushing syndrome	↑ ACTH	Small cell lung cancer
Hyponatremia (SIADH)	↑ ADH	
Hematologic		
Polycythemia	↑ Erythropoietin Paraneoplastic rise to high hematocrit levels	Pheochromocytoma, renal cell carcinoma, HCC, hemangioblastoma, leiomyoma
Pure red cell aplasia	Anemia with low reticulocytes	Thymoma
Good syndrome	Hypogammaglobulinemia	
Trousseau syndrome	Migratory superficial thrombophlebitis	Adenocarcinomas, especially pancreatic
Nonbacterial thrombotic (marantic) endocarditis	Deposition of sterile platelet thrombi on heart valves	
Neuromuscular		
Anti-NMDA receptor encephalitis	Psychiatric disturbance, memory deficits, seizures, dyskinesias, autonomic instability, language dysfunction	Ovarian teratoma
Opsoclonus-myoclonus ataxia syndrome	"Dancing eyes, dancing feet"	Neuroblastoma (children), small cell lung cancer (adults)
Paraneoplastic cerebellar degeneration	Antibodies against antigens in Purkinje cells	Small cell lung cancer (anti-Hu), gynecologic and breast cancers (anti-Yo), and Hodgkin lymphoma (anti-Tr)
Paraneoplastic encephalomyelitis	Antibodies against Hu antigens in neurons	Small cell lung cancer
Lambert-Eaton myasthenic syndrome	Antibodies against presynaptic (P/Q-type) Ca^{2+} channels at NMJ	
Myasthenia gravis	Antibodies against postsynaptic ACh receptors at NMJ	Thymoma

CHAPTER 2

General Pharmacology

Pharmacokinetics

- Pharmacokinetic characteristics of drug molecules concern the processes of absorption, distribution, metabolism, and excretion.



Permeation

- Drug permeation is dependent on:

A. Solubility: Ability to diffuse through lipid bilayers (lipid solubility) is important for most drugs.

B. Concentration gradient: Diffusion down a concentration gradient.

C. Surface area and vascularity:

- Important with regard to absorption of drugs into the systemic circulation.

- The larger the surface area and the greater the vascularity, the better is the absorption of the drug (stomach VS. small intestine) (IM Vs Subcutaneous).

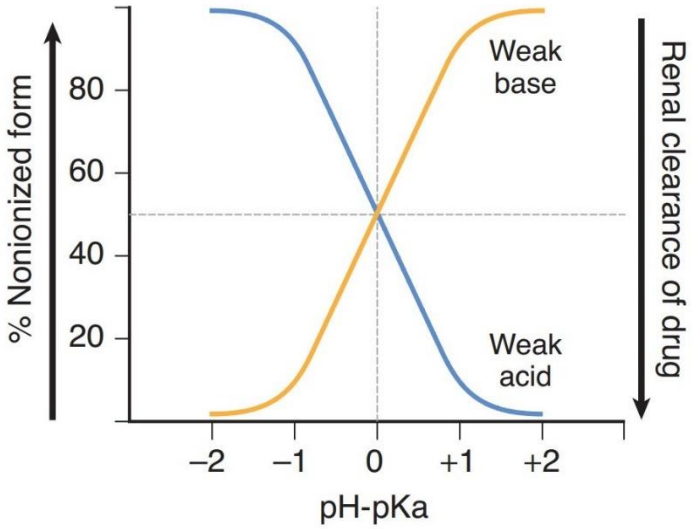
- Ionization:

- Many drugs are weak acids or weak bases and can exist in either nonionized or ionized forms in an equilibrium, depending on the pH of the environment and the pKa (the pH at which the molecule is 50% ionized and 50% nonionized).

- Only the nonionized (uncharged) form of a drug crosses biomembranes.

- The ionized form is better renally excreted because it is water soluble.

Weak Acid	R–COOH (crosses membranes)	⇌	$R–COO^- + H^+$ (better cleared)
Weak Base	$R–NH_3^+$ (better cleared)	⇌	$R–NH_2 + H^+$ (crosses membranes)



- In a nutshell:

- Weak acids: aspirin, penicillin, cephalosporin, loop and thiazide diuretics.

- Weak bases: morphine, local anesthetic, amphetamine and phencyclidine (PCP).

- For Weak Acids and Weak Bases:
  - Ionized = Water soluble.
  - Nonionized = Lipid soluble.

- **Ionization Increases Renal Clearance of Drugs:**

- Only free, unbound drug is filtered.

- Both ionized and nonionized forms of a drug are filtered.

- Only nonionized forms undergo active secretion and active or passive reabsorption.

- Ionized forms of drugs are "trapped" in the filtrate.

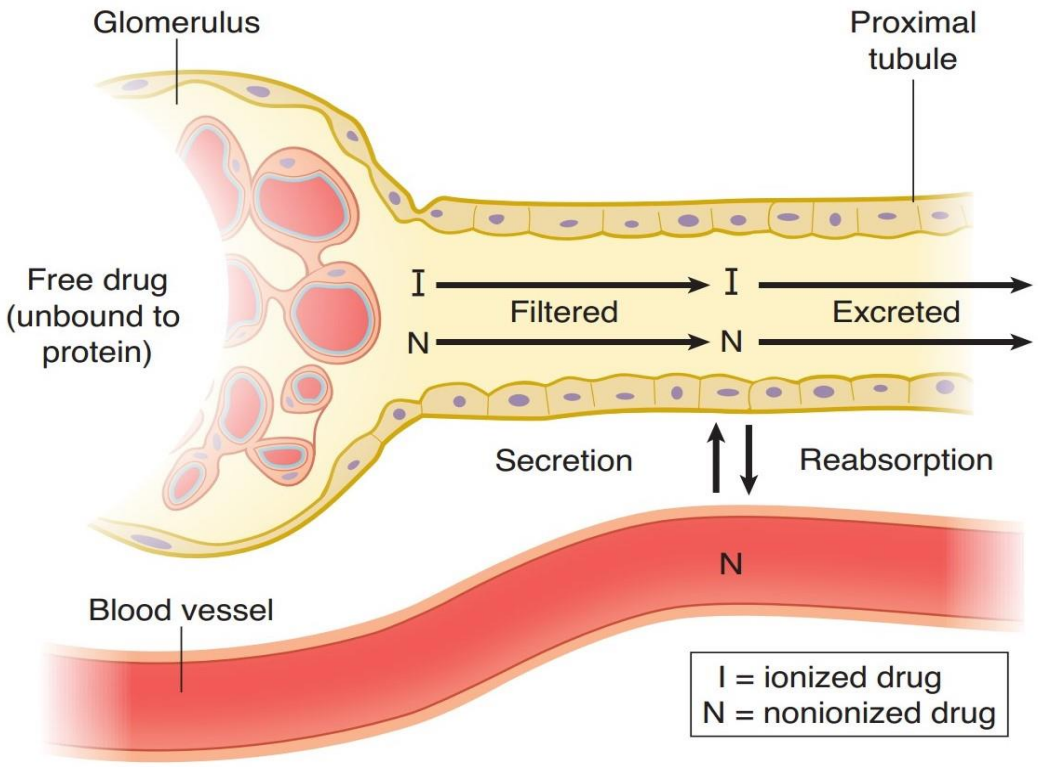
- Acidification of urine → increases ionization of weak bases (Amphetamine, PCP) → increases renal elimination.

- Alkalinization of urine → increases ionization of weak acids (Aspirin)→ increases renal elimination.

- To Change Urinary Ph:
  - Acidify: NH_4Cl, vitamin C, cranberry juice.
  - Alkalinize: $NaHCO_3$, acetazolamide.

- If you want to increase the absorption of a drug or to decrease its clearance → put it in the same Ph, but if you want to increase its clearance → put it in the opposite Ph.

- Gut bacteria metabolize lactulose to lactic acid, acidifying the fecal masses and causing ammonia (NH_3) to become ammonium (NH_4). Therefore, lactulose is useful in hepatic encephalopathy.



- Modes of Drug Transport Across a Membrane:

Mechanism	Direction	Energy required	Carrier	Saturable
Passive diffusion	Down gradient	No	No	No
Facilitated Diffusion	Down gradient	No	Yes	Yes
Active transport	Against gradient (concentration/ electrical)	Yes	Yes	Yes

Absorption

- Concerns the processes of entry of a drug into the systemic circulation from the site of its administration.
- The determinants of absorption are those described for drug permeation.
- Intravascular administration (IV) does not involve absorption, and there is no loss of drug (Bioavailability = 100%).
- With extravascular administration (per os [PO; oral], intramuscular [IM], subcutaneous [SC], inhalation), less than 100% of a dose may reach the systemic circulation because of variations in bioavailability.

Plasma Level Curves

C_{max} = maximal drug level obtained with the dose.

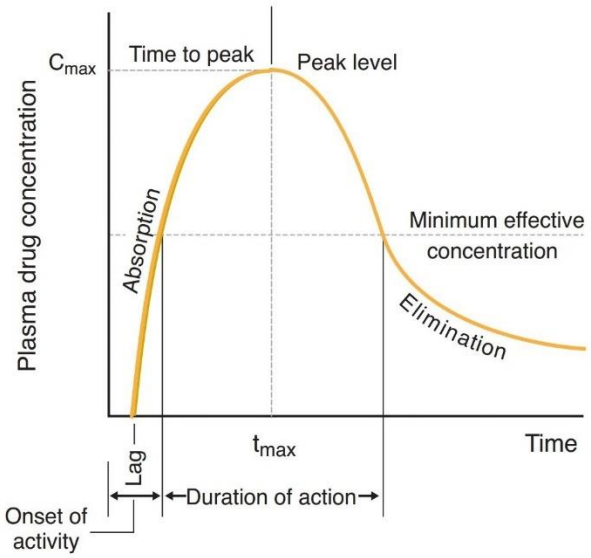
t_{max} = time at which C_{max} occurs.

Lag time = time from administration to appearance in blood.

Onset of activity = time from administration to blood level reaching minimal effective concentration (MEC).

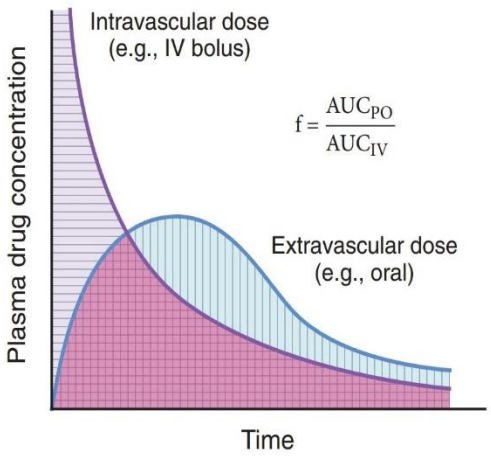
Duration of action = time plasma concentration remains greater than MEC.

Time to peak = time from administration to C_{max}.



- Bioavailability (f):

- Measure of the fraction of a dose that reaches the systemic circulation.
- By definition, intravascular doses have 100% bioavailability, f = 1.



AUC: area under the curve

PO: oral

IV: intravenous bolus

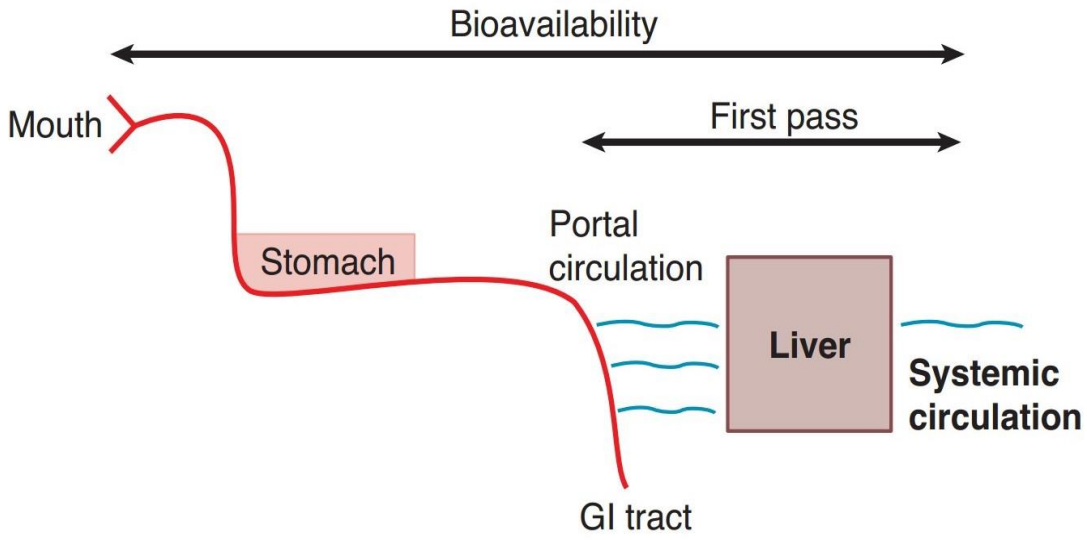
AUC_{IV}: horizontally striped area

AUC_{PO}: vertically striped area

- First-Pass Effect:

- With oral administration, drugs are absorbed into the portal circulation and initially distributed to the liver. For some drugs, their rapid hepatic metabolism decreases bioavailability (the "first-pass" effect).

- Examples:
  - Lidocaine (IV vs. PO).
  - Nitroglycerin (sublingual).



- Oral bioavailability is dependent on the absorptive properties of the drug as well as its first-pass metabolism.

- When a drug is absorbed by the GI tract after oral administration, it first enters the portal circulation before gaining access to the systemic circulation.

- If the drug is metabolized extensively by the liver (high first-pass metabolism), the amount that reaches the systemic circulation, and therefore the bioavailability, will be low.

- In order to efficiently use drugs with a high first-pass metabolism, other routes of administration are typically employed.

- For instance, nitroglycerin can be used for preventing or treating anginal pain, but because it has a very high first-pass metabolism, not enough drug reaches systemic circulation to be effective. To circumvent this shortcoming, nitroglycerin tablets are given sublingually, where they bypass the first-pass metabolism by entering the systemic circulation directly via the sublingual capillaries and arterioles.

- Long-acting isosorbide dinitrate is absorbed via the gastrointestinal tract and undergoes extensive first-pass metabolism in the liver prior to release in the systemic circulation. This leads to low bioavailability and the need for much higher doses of oral formulations as compared to sublingual nitroglycerin.

- Propranolol and lidocaine also have a very high first-pass metabolism and thus have better bioavailability through IV or subcutaneous methods.

❖ N.B:

- Rectal drug administration, such as with suppositories, partially bypasses first-pass metabolism. Recall that the rectum is drained by the superior, middle and inferior rectal veins.
- The superior rectal veins drain to the portal circulation via the inferior mesenteric vein.
- The middle and inferior rectal veins, however, drain to the systemic circulation via the internal iliac and internal pudendal veins, respectively.
- Thus, two-thirds of the venous drainage of the rectal region goes directly into the systemic circulation, thereby increasing the bioavailability of drugs that are otherwise highly cleared by the liver after oral administration.
- The amount of drug exposed to the liver within the portal blood flow is the major determinant of hepatic or first-pass metabolism.
- Oral administration subjects a drug to a large amount of first-pass metabolism, whereas IV, sublingual, and rectal administration bypasses some or all of this process and allows more drug to reach the systemic circulation.

Distribution

- The processes of distribution of a drug from the systemic circulation to organs and tissue.

- Conditions affecting distribution include:

- Many drugs bind to plasma proteins, including albumin, with an equilibrium between bound and free molecules (recall that only unbound drugs cross biomembranes).

- Competition between drugs for plasma protein-binding sites may increase the "free fraction," possibly enhancing the effects of the drug displaced.

- Example: sulfonamides and bilirubin in a neonate.

$$\underset{\text{(Active, free)}}{\text{Drug} + \text{Protein}} \rightleftharpoons \underset{\text{(Inactive, bound)}}{\text{Drug-Protein Complex}}$$

- Apparent Volume of Distribution (Vd):

- A kinetic parameter of a drug that correlates dose with plasma level at zero time.

$$Vd = \frac{Dose}{C0}$$ where C^0 = [plasma] at zero time (Initial plasma concentration).

- This relationship can be used for calculating Vd by using the dose only if one knows C^0.

- Vd is low when a high percentage of a drug is bound to plasma proteins.

- Vd is high when a high percentage of a drug is being sequestered in tissues.

- Approximate Vd Values (weight 70 kg):

- Plasma volume (3 L).

- Blood volume (5 L).

- Extracellular fluid (ECF 12-14 L).

- Total body water (TBW 40-42 L).

- Characteristics of a drug such as high molecular weight, high plasma protein binding, high charge, and hydrophilicity tend to trap the drug in the plasma compartment resulting in a low Vd.

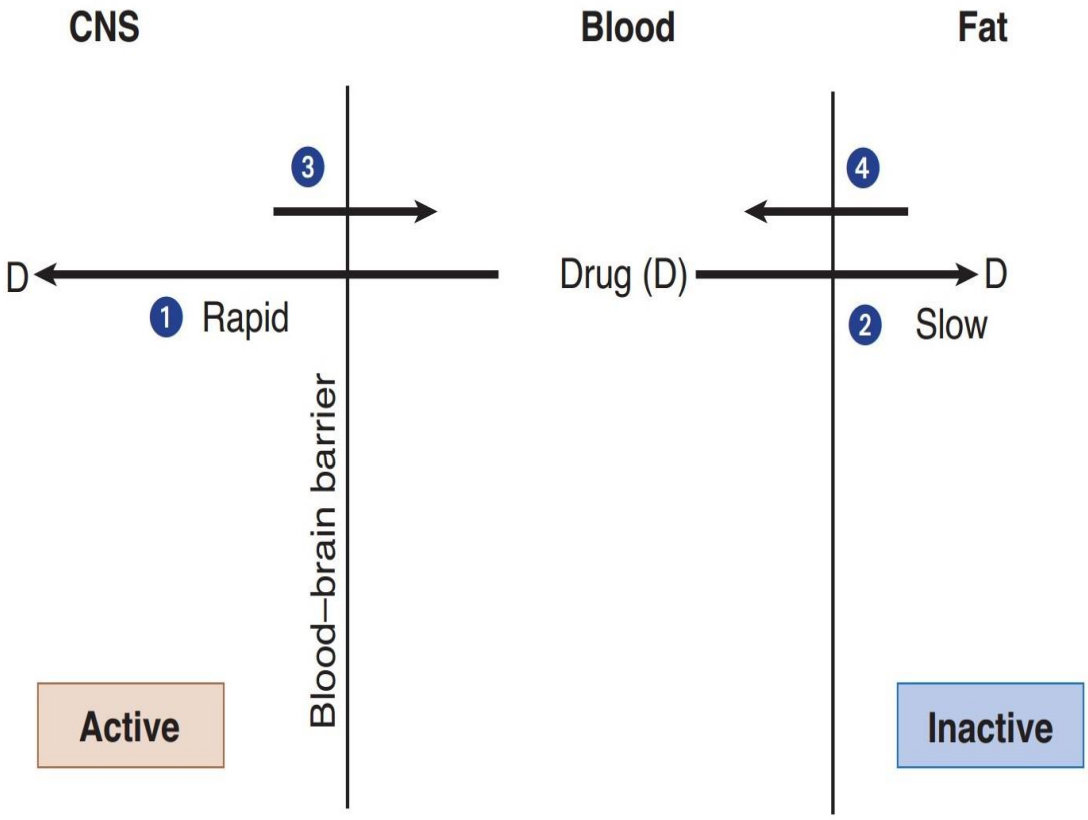
- Drugs that are avidly bound in the tissues exhibit the highest volumes of distribution, often much higher than the total body water volume (41 liters), because these drugs accumulate readily within cells thereby maintaining low plasma concentrations.

- Redistribution:

- In addition to crossing the blood-brain barrier (BBB), lipid-soluble drugs redistribute into fat tissues prior to elimination.

- In the case of CNS drugs, the duration of action of an initial dose may depend more on the redistribution rate than on the half-life.

- With a second dose, the blood/fat ratio is less; therefore, the rate of redistribution is less and the second dose has a longer duration of action.



Biotransformation

- The general principle of biotransformation is the metabolic conversion of drug molecules to more water-soluble metabolites that are more readily excreted.

- In many cases, metabolism of a drug results in its conversion to compounds that have little or no pharmacologic activity (Drug → Inactive metabolite).

- In other cases, biotransformation of an active compound may lead to the formation of metabolites that also have pharmacologic actions (Drug → Active metabolite).

- A few compounds (prodrugs) have no activity until they undergo metabolic activation (Prodrug → drug).

❖ Biotransformation Classification:

- There are two broad types of biotransformation, called phase I and phase II.

i. **Phase I:**

- Definition:
- Modification of the drug molecule via oxidation, reduction, or hydrolysis.

1. Microsomal metabolism (Cytochrome P450 isozymes):

- These are major enzyme systems involved in phase I reactions.

- General inducers: anticonvulsants (barbiturates, phenytoin, carbamazepine), antibiotics (rifampin), chronic alcohol.

- General inhibitors: antiulcer medications (cimetidine, omeprazole), antimicrobials (chloramphenicol, macrolides, ritonavir, ketoconazole), acute alcohol.

- Grapefruit juice has active components that inhibit metabolism of many drugs including statins.

2. Non-microsomal metabolism:

A. Hydrolysis:

- Phase I reaction involving addition of a water molecule with subsequent bond breakage.
- Includes esterases and amidases.

B. Monoamine oxidases:

- Metabolism of endogenous amine neurotransmitters (dopamine, norepinephrine, and serotonin)
- Metabolism of exogenous compounds (tyramine)

C. Alcohol metabolism:

- Alcohols are metabolized to aldehydes and then to acids by dehydrogenases.
- Genetic polymorphisms exist

ii. Phase II:

- Definition:

- Conjugation with endogenous compounds via the activity of transferases.

- May follow phase I or occur directly.

- Types of conjugation:

A. Glucuronidation:

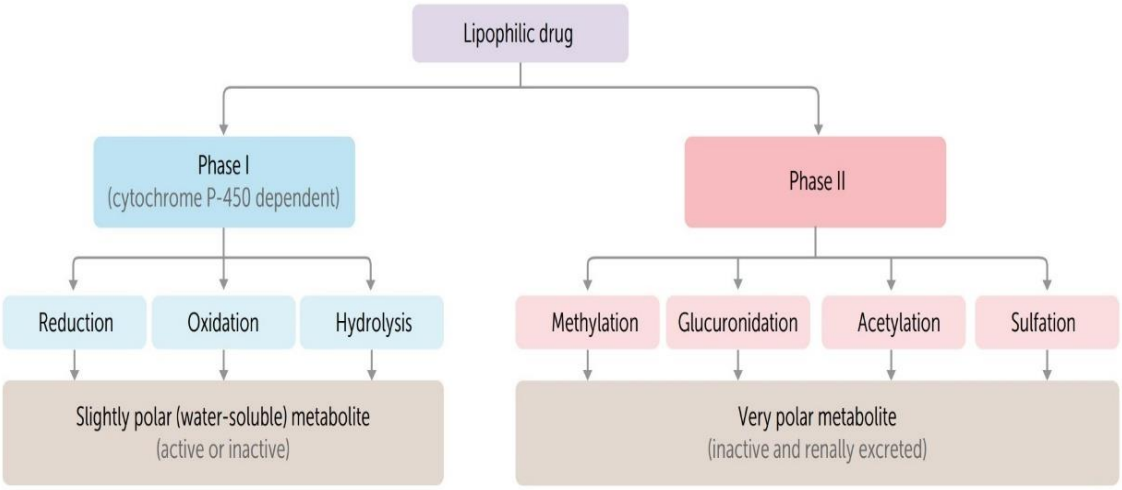
- Inducible.
- Reduced activity in neonates.
- Examples: morphine and chloramphenicol.

B. Acetylation:

- Genotypic variations (fast and slow metabolizers).
- Drug-induced SLE by slow acetylators with hydralazine > procainamide > isoniazid (INH)

C. Glutathione (GSH) conjugation: Depletion of GSH in the liver is associated with acetaminophen hepatotoxicity.

Geriatric patients lose phase I first. Patients who are slow acetylators have ↑ side effects from certain drugs because of ↓ rate of metabolism (eg, isoniazid).



Cytochrome P450 (CYP450)	
Inducers	**Inhibitors**
Carbamazepine Barbiturates Phenytoin Rifampin Griseofulvin St John's wort Modafinil Cyclophosphamide	Amiodarone Cimetidine Fluoroquinolones Clarithromycin Azole antifungals Grapefruit juice Isoniazid Ritonavir (protease inhibitors)

Elimination

- Concerns the processes involved in the elimination of drugs from the body (and/ or plasma) and their kinetic characteristics.

- The major modes of drug elimination are:

- Biotransformation to inactive metabolites.
- Excretion via the kidney.
- Excretion via other modes, including the bile duct, lungs, and sweat.

- $t_{1/2}$: Time to eliminate 50% of a given amount (or to decrease plasma level to 50% of a former level) is called the elimination half-life.

A. Zero-Order Elimination Rate:

- A constant amount of drug is eliminated per unit time; for example, if 80 mg is administered and 10 mg is eliminated every 4 h, the time course of drug elimination is:

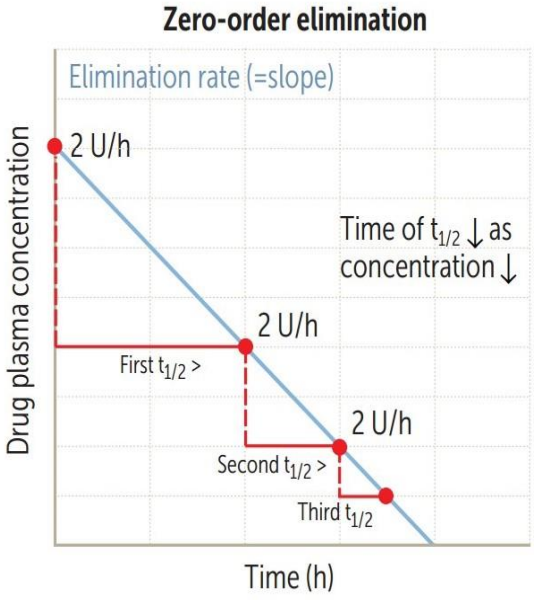
$$80\ \text{mg} \xrightarrow{4\ \text{h}} 70\ \text{mg} \xrightarrow{4\ \text{h}} 60\ \text{mg} \xrightarrow{4\ \text{h}} 50\ \text{mg} \xrightarrow{4\ \text{h}} 40\ \text{mg}$$

- Rate of elimination is independent of plasma concentration (or amount in the body).

- Drugs with zero-order elimination have no fixed half-life ($t_{1/2}$ is a variable).

- Drugs with zero-order elimination include ethanol (except low blood levels), phenytoin (high therapeutic doses), and salicylates (toxic doses).

- High risk of drug accumulation.



B. First-Order Elimination Rate:

- A constant fraction of the drug is eliminated per unit time. Graphically, first-order elimination follows an exponential decay versus time.

- For example, if 80 mg of a drug is administered and its elimination half-life = 4 h, the time course of its elimination is:

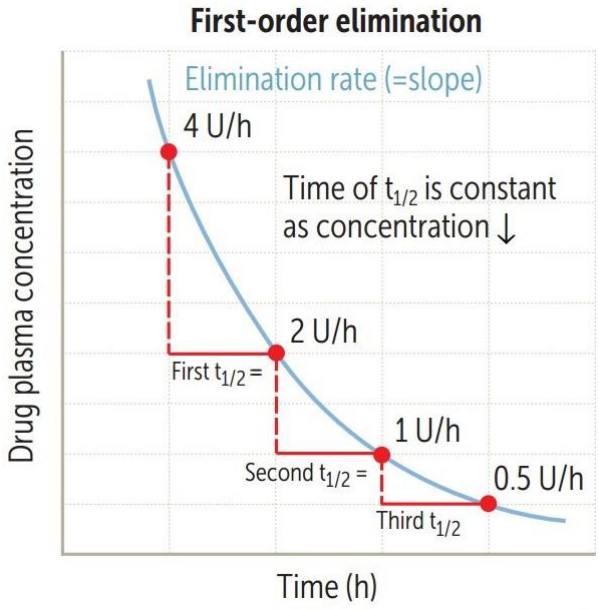
$$80\ \text{mg} \xrightarrow{4\ \text{h}} 40\ \text{mg} \xrightarrow{4\ \text{h}} 20\ \text{mg} \xrightarrow{4\ \text{h}} 10\ \text{mg} \xrightarrow{4\ \text{h}} 5\ \text{mg}$$

- Rate of elimination is directly proportional to plasma level (or the amount present). The higher the amount, the more rapid the elimination.

- Most drugs follow first-order elimination rates.

- $t_{1/2}$ is a constant.

- Low risk of drug accumulation.



- Elimination Kinetics:

- Most drugs follow first order: rate falls as plasma level falls.

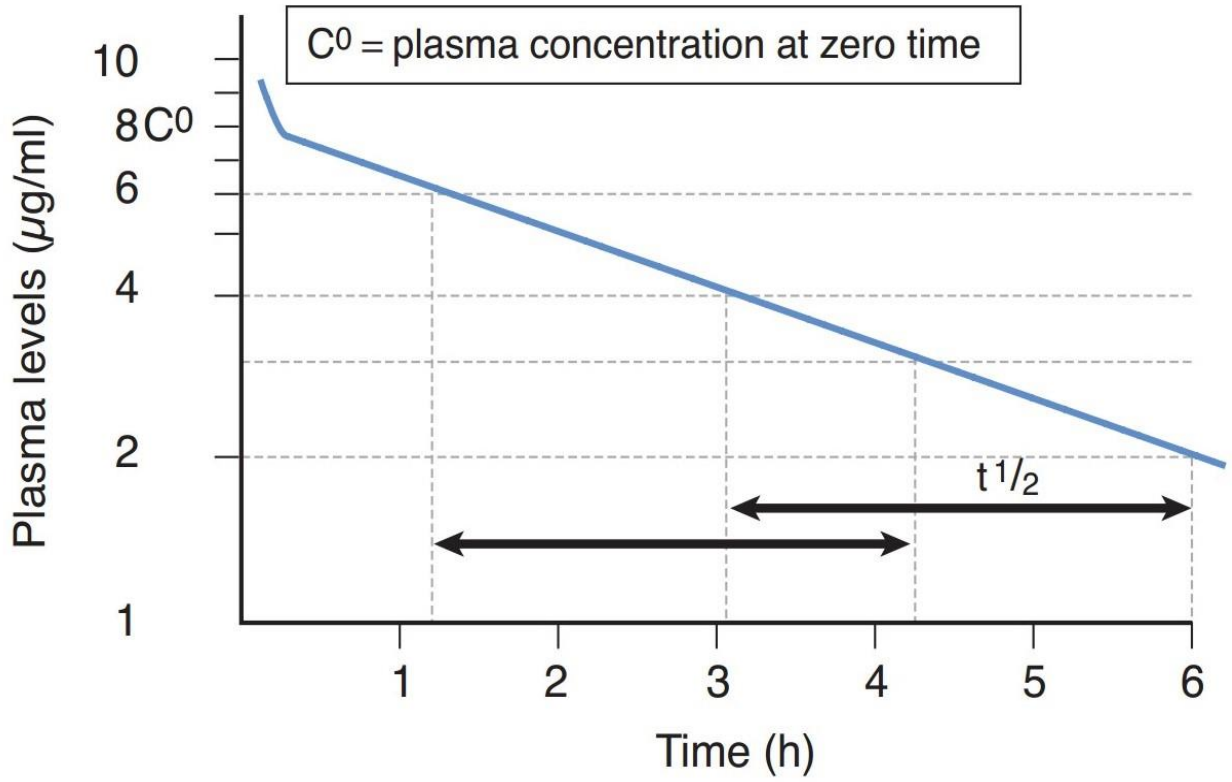
- Zero order is due to saturation of elimination mechanisms; drug metabolizing reactions have reached V_{max}.

Zero order → elimination rate is constant; $t_{1/2}$ is a variable

First order → elimination rate is variable; $t_{1/2}$ is a constant

- Graphic Analysis:

- Example of a graphic analysis of $t_{1/2}$:



- The elimination half-life ($t_{1/2}$) and the theoretical plasma concentration at zero time (C^0) can be estimated from the graphic relationship between plasma concentrations and time.

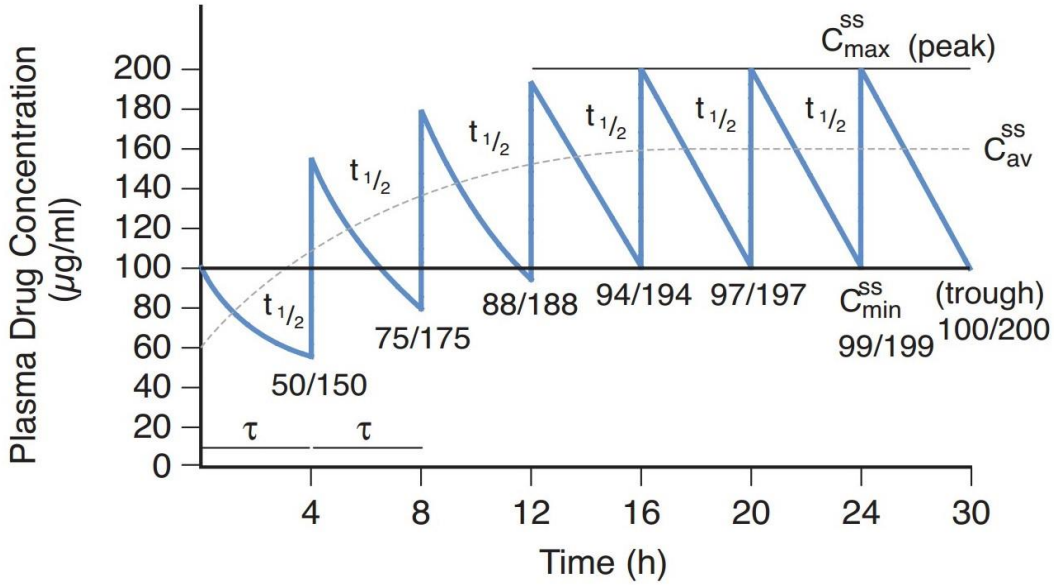
- Steady state: Steady state is reached either when rate in = rate out or when values associated with a dosing interval are the same as those in the succeeding interval.

- Plateau Principle:

- The time to reach steady state is dependent only on the elimination half-life of a drug and is independent of dose size and frequency of administration, assuming the drug is eliminated by first-order kinetics.

- The Figure below shows plasma levels (solid lines) achieved following the IV bolus.

- Administration of 100 units of a drug at intervals equivalent to every half-life $t_{1/2}$ = 4 h. With such intermittent dosing, plasma levels oscillate through peaks and troughs, with averages shown in the diagram by the dashed line.



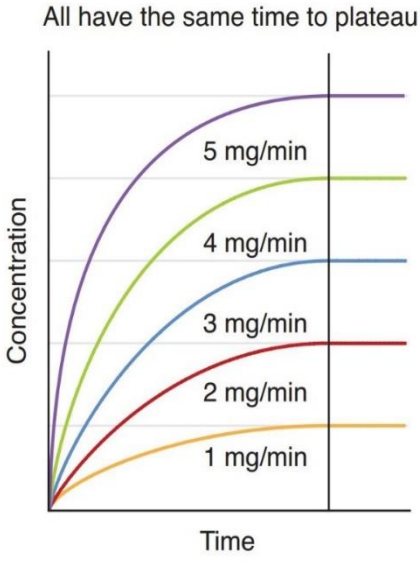
- Time and Steady State:

- 50% = 1 × half-life
- 90% = 3.3 × half-life
- 95% = 4–5 × half-life
- 100% = >7 × half-life

- Note: Although it takes > 7 $t_{1/2}$ to reach mathematical steady state, by convention clinical steady state is accepted to be reached at 4–5 $t_{1/2}$.

- Rate of Infusion:

- The Figure below shows the increases in plasma levels of the same drug infused at five different rates. Regardless of the rate of infusion, it takes the same amount of time to reach steady state.



- Rate of infusion does determine plasma level at steady state. If the rate of infusion is doubled, then the plasma level of the drug at steady state is doubled.

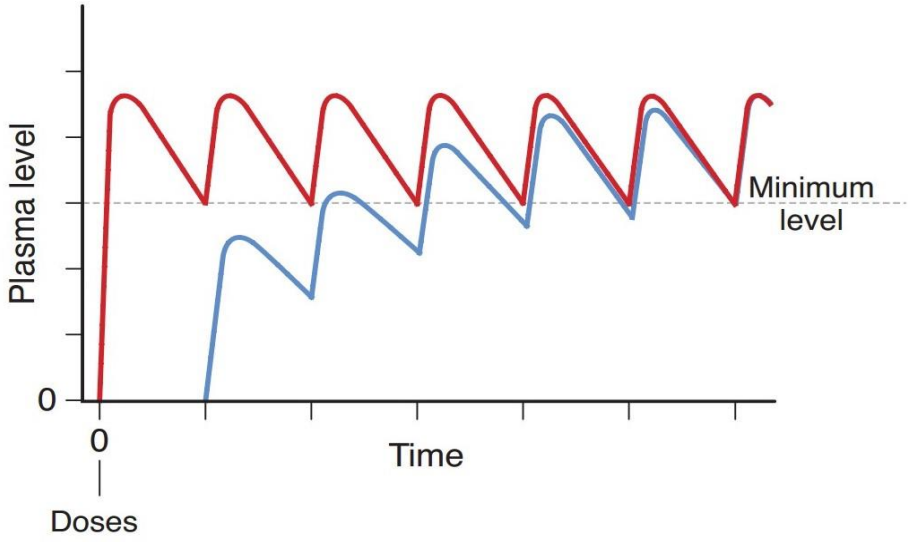
- Effect of Loading Dose:

- It takes 4-5 half-lives to achieve steady state.

- In some situations, it may be necessary to give a higher dose (loading dose) to more rapidly achieve effective blood levels (C_p).

- Such loading doses are often one time only and are estimated to put into the body the amount of drug that should be there at a steady state.

- The loading dose equation can be used to calculate the amount of drug in the body at any time by knowing the V_d and the plasma concentration.



C^0 = conc. at time zero

Cl = clearance

C_p = conc. in plasma

C^{ss} = steady state conc.

D = dose

f = bioavailability

τ = dosing interval

Single-Dose Equations

Volume of distribution $(V_d) = \frac{D}{C^0}$

Half-life $(t_{1/2}) = 0.7 \times \frac{V_d}{Cl}$

Multiple Dose or (Infusion Rate) Equations

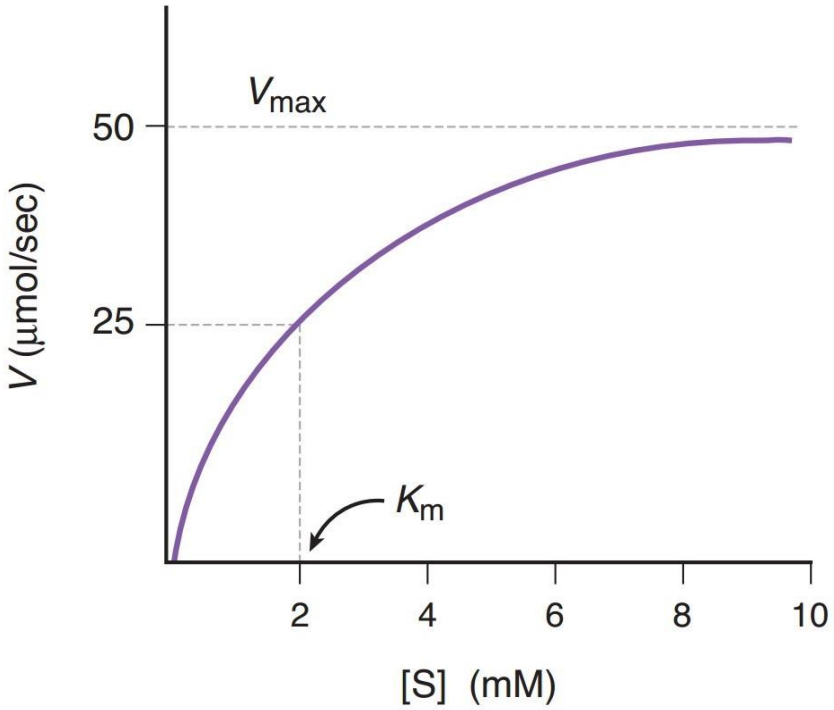
Infusion rate $(k_0) = Cl \times C^{ss}$

Loading dose $(LD) = \frac{V_d \times C_p}{f}$

Maintenance dose $(MD) = \frac{Cl \times C^{ss} \times \tau}{f}$

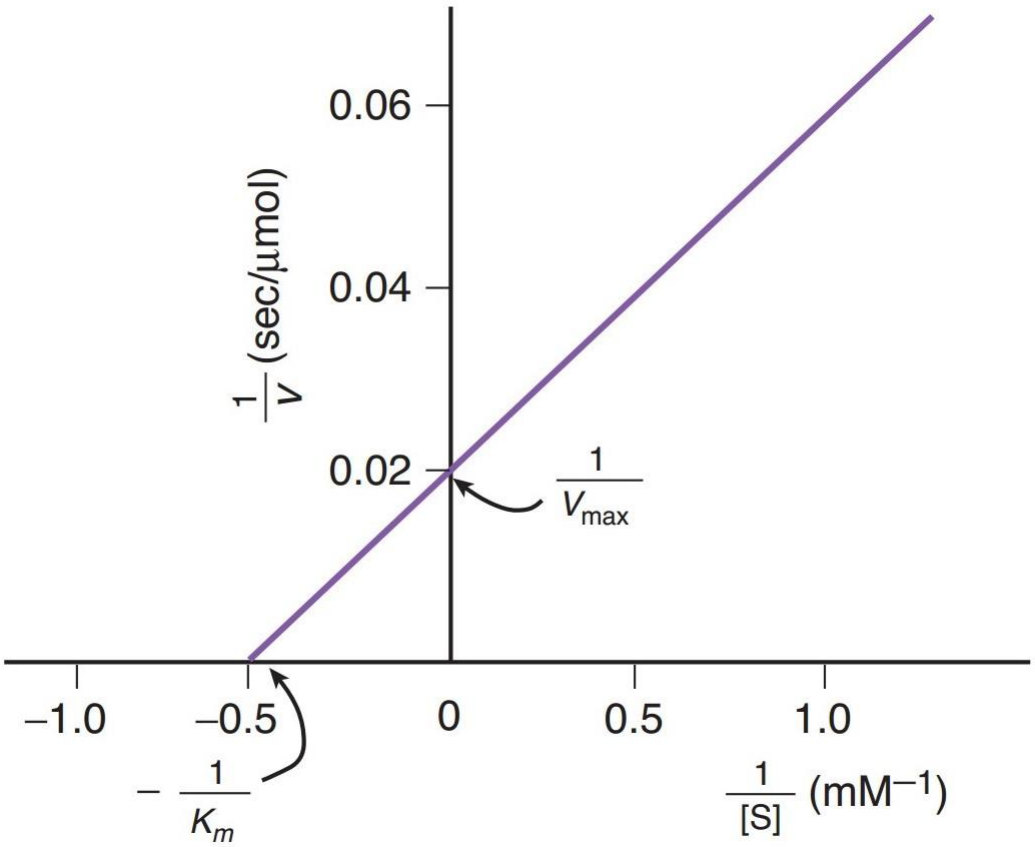
Michaelis-Menten Equation

- The Michaelis-Menten equation describes how the rate of the reaction, V, depends on the concentration of both the enzyme [E] and the substrate [S], which forms product [P].
- V_{max} is the maximum rate possible to achieve with a given amount of enzyme.
- The only way to increase Vmax is by increasing the [E]. In the cell, this can be accomplished by inducing the expression of the gene encoding the enzyme.
- The other constant in the equation, Km is often used to compare enzymes. K_m is the substrate concentration required to produce half the maximum velocity.
- Under certain conditions, K_m is a measure of the affinity of the enzyme for its substrate. When comparing two enzymes, the one with the higher Km has a lower affinity for its substrate.
- The K_m value is an intrinsic property of the enzyme-substrate system and cannot be altered by changing [S] or [E].



Lineweaver-Burk Equation

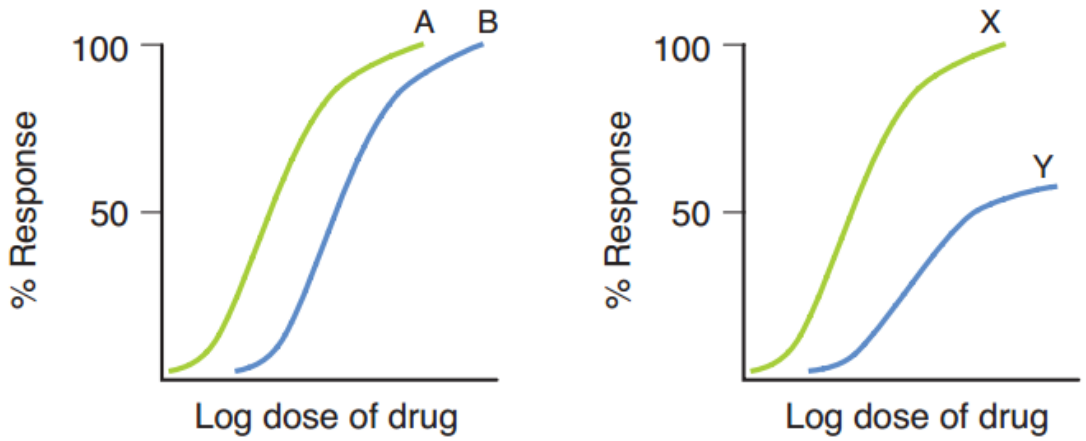
- The Lineweaver-Burk equation is a reciprocal form of the Michaelis-Menten equation. The same data graphed yield a straight line, as shown below.
- The actual data are represented by the portion of the graph to the right of the y-axis, but the line is extrapolated into the left quadrant to determine its intercept with the x-axis.
- The intercept of the line with the x-axis gives the value of $-1/K_m$.
- The intercept of the line with the y-axis gives the value of $1/V_{max}$.
- If the x-intercept shifts to the right → ↑ K_m → ↓ affinity. For example: $-\frac{1}{Km}$: -2 → 1, this means Km → .5 → 1.
- If the y-intercept shifts to the downward → ↑ V_{max} → ↑ reaction rate. For example: $\frac{1}{Vmax}$: 2 → 1, this means V_{max} → .5 → 1.



Pharmacodynamics

- Pharmacodynamics relates to drugs binding to receptors and their effects.
- Agonist: A drug is called an agonist when binding to the receptor results in a response.
- Antagonist: A drug is called an antagonist when binding to the receptor is not associated with a response. The drug has an effect only by preventing an agonist from binding to the receptor.
- Affinity: ability of drug to bind to receptor, shown by the proximity of the curve to the y axis (if the curves are parallel); the nearer the y axis, the greater the affinity.
- Potency: shows relative doses of two or more agonists to produce the same magnitude of effect, again shown by the proximity of the respective curves to the y axis (if the curves do not cross).
- Efficacy: a measure of how well a drug produces a response (effectiveness), shown by the maximal height reached by the curve.
- Graded (quantitative) dose-response (D-R) Curves:

- Plots of dose (or log dose) versus response for drugs (agonists) that activate receptors can reveal information about affinity, potency, and efficacy of these agonists.

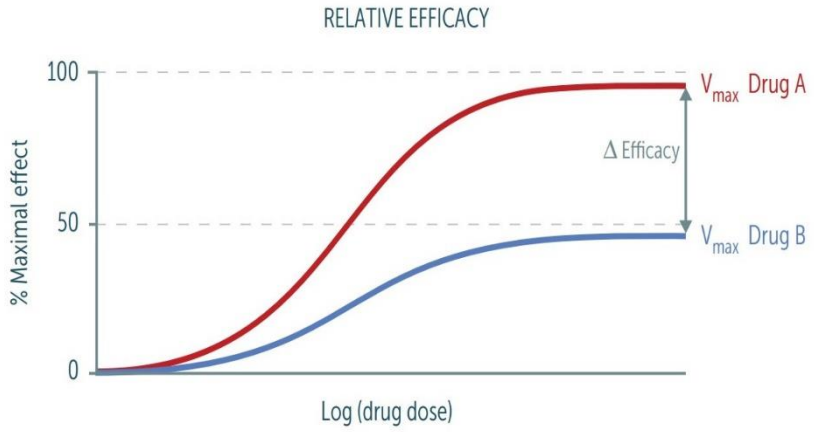


- It may be seen from the log dose-response curves that:

1. When two drugs interact with the same receptor (same pharmacologic mechanism), the D-R curves will have parallel slopes. Drugs A and B have the same mechanism; drugs X and Y do not.
2. Affinity can be compared only when two drugs bind to the same receptor. Drug A has a greater affinity than drug B.
3. In terms of potency, drug A has greater potency than drug B, and X is more potent than Y.
4. In terms of efficacy, drugs A and B are equivalent. Drug X has greater efficacy than drug Y.

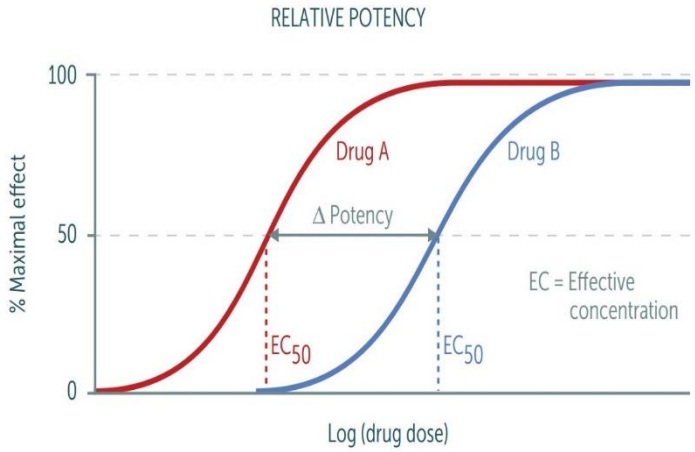
Efficacy

Maximal effect a drug can produce. Represented by the y-value (V_{max}). ↑ y-value = ↑ V_{max} = ↑ efficacy. Unrelated to potency (ie, efficacious drugs can have high or low potency). Partial agonists have less efficacy than full agonists.



Potency

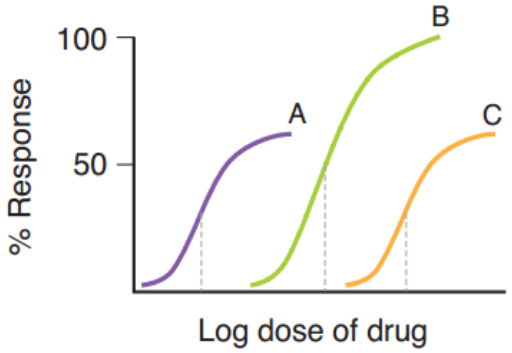
Amount of drug needed for a given effect. Represented by the x-value (EC_{50}). Left shifting = ↓ EC_{50} = ↑ potency = ↓ drug needed. Unrelated to efficacy (ie, potent drugs can have high or low efficacy).



- **Full and Partial Agonists:**

- Full agonists produce a maximal response (they have maximal efficacy).

- Partial agonists are incapable of eliciting a maximal response and are less effective than full agonists.

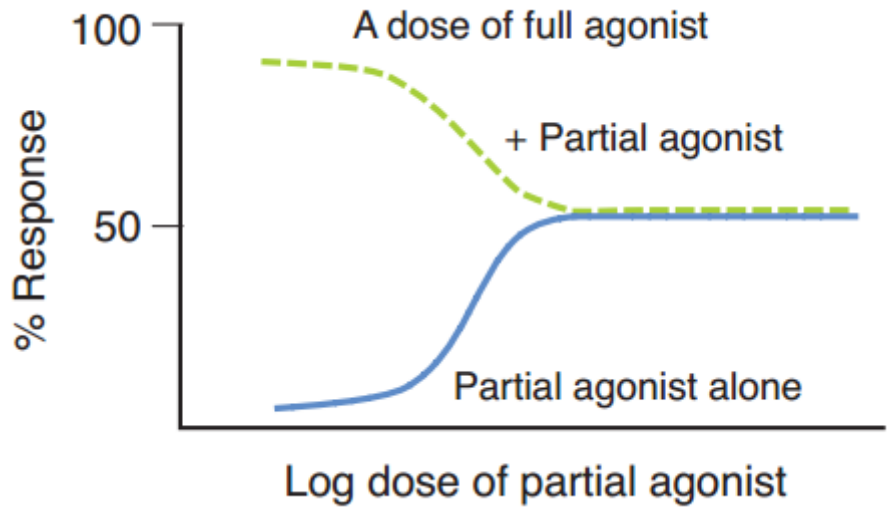


- **Duality of Partial Agonists:**

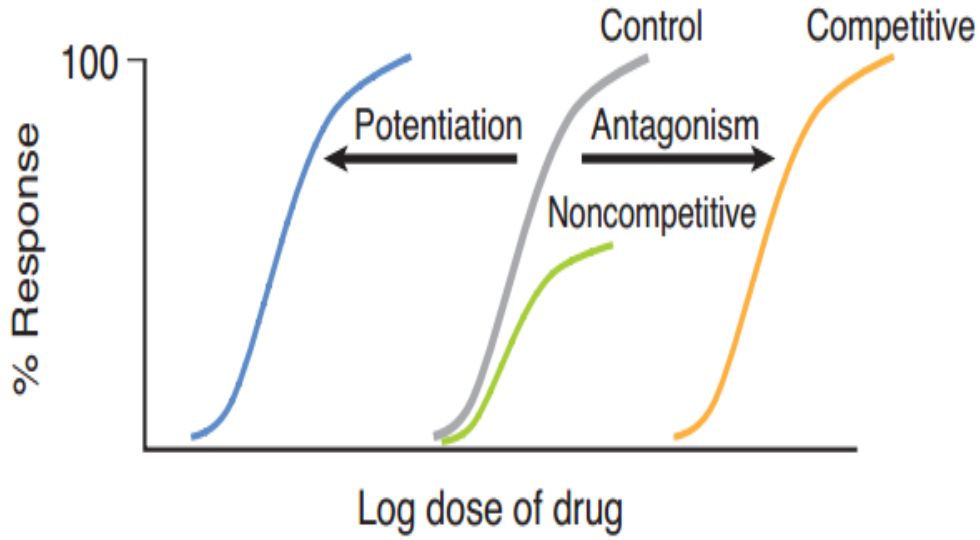
- In the Figure below, the lower curve represents effects of a partial agonist when used alone: its ceiling effect = 50% of maximal in this example.

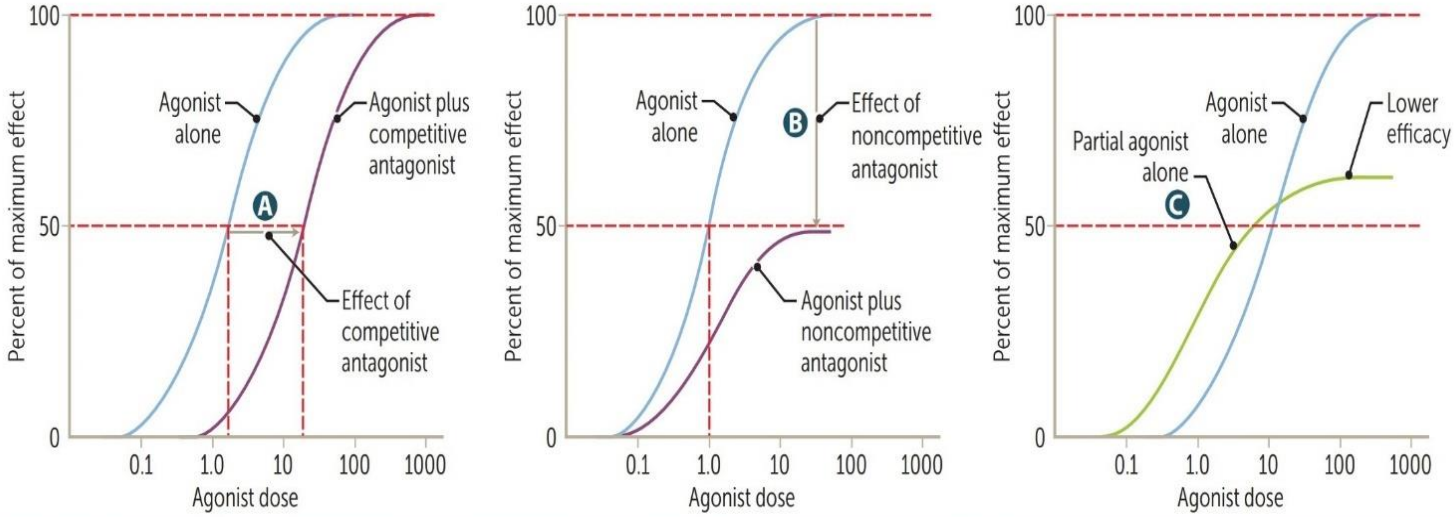
- The upper curve shows the effect of increasing doses of the partial agonist on the maximal response (100%) achieved in the presence of or by pretreatment with a full agonist.

- As the partial agonist displaces the full agonist from the receptor, the response is reduced (the partial agonist is acting as an antagonist).

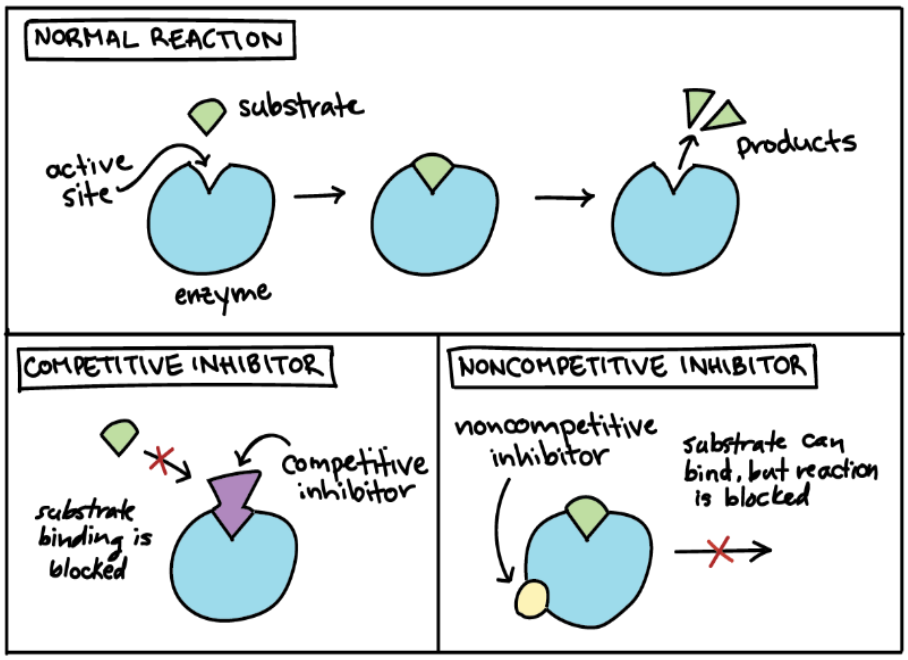


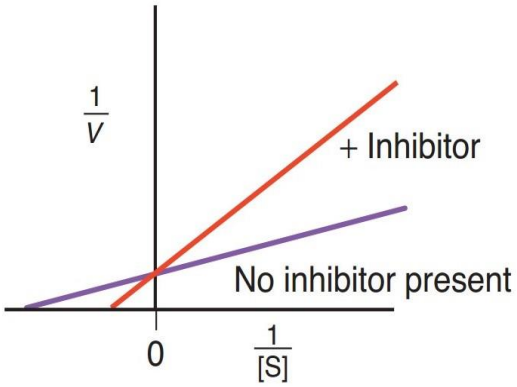
- **Antagonism and Potentiation:**



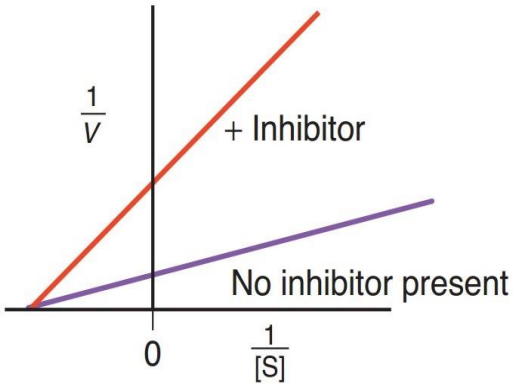


AGONIST WITH	POTENCY	EFFICACY	REMARKS	EXAMPLE
A Competitive antagonist	↓	No change	**Can** be overcome by ↑ agonist concentration	Diazepam (agonist) + flumazenil (competitive antagonist) on $GABA_A$ receptor.
B Noncompetitive antagonist	No change	↓	**Cannot** be overcome by ↑ agonist concentration	Norepinephrine (agonist) + phenoxybenzamine (noncompetitive antagonist) on α-receptors.
C Partial agonist (alone)	Independent	↓	Acts at same site as full agonist	Morphine (full agonist) vs buprenorphine (partial agonist) at opioid μ-receptors.

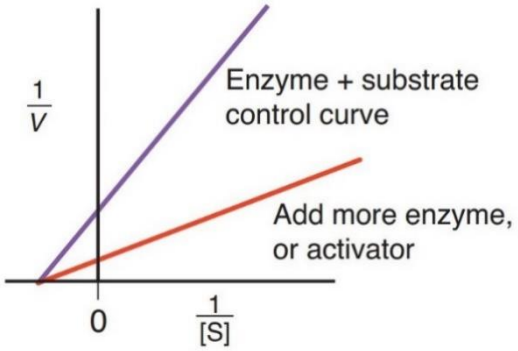




Lineweaver-Burk Plot
of Competitive Inhibition



Lineweaver-Burk Plot
of Noncompetitive Inhibition



Lineweaver-Burk Plot Showing the Addition
of More Enzyme or the Addition of an Activator

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

A. Pharmacologic antagonism (same receptor):

1. Competitive antagonists:

- Cause a parallel shift to the right in the D-R curve for agonists.
- Can be reversed by ↑ the dose of the agonist drug.
- Appears to ↓ the potency of the agonist.

2. Noncompetitive antagonists:

- Cause a nonparallel shift to the right.
- Can be only partially reversed by ↑ the dose of the agonist.
- Appear to ↓ the efficacy of the agonist.

B. Physiologic antagonism (different receptor):

- Two agonists with opposing action antagonize each other.
- Example: a vasoconstrictor with a vasodilator.

C. Chemical antagonism:

- Formation of a complex between effector drug and another compound.
- Example: protamine binds to heparin to reverse its actions.

D. Potentiation:

- Causes a parallel shift to the left to the D-R curve.
- Appears to ↑ the potency of the agonist.

▪ Toxicity and the Therapeutic Index (TI):

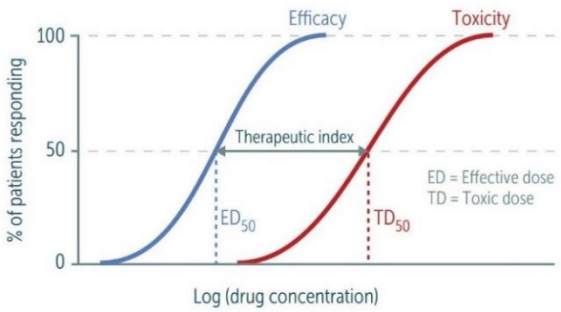
- Comparisons between ED_{50} (median effective dose) and TD_{50} (median toxic dose) values permit evaluation of the relative safety of a drug (the therapeutic index), as would comparison between ED50 and the lethal median dose (LD50) if the latter is known.

Measurement of drug safety.

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

Therapeutic window—dosage range that can safely and effectively treat disease.

TITE: Therapeutic Index = TD_{50} / ED_{50}.
Safer drugs have higher TI values. Drugs with lower TI values frequently require monitoring (eg, Warfarin, Theophylline, Digoxin, Antiepileptic drugs, Lithium; Warning! These Drugs Are Lethal!).
LD_{50} (lethal median dose) often replaces TD_{50} in animal studies.



Types of drug interactions

TERM	DEFINITION	EXAMPLE
Additive	Effect of substances A and B together is equal to the sum of their individual effects	Aspirin and acetaminophen "2 + 2 = 4"
Permissive	Presence of substance A is required for the full effects of substance B	Cortisol on catecholamine responsiveness
Synergistic	Effect of substances A and B together is greater than the sum of their individual effects	Clopidogrel with aspirin "2 + 2 > 4"
Potentiation	Similar to synergism, but drug B with no therapeutic action enhances the therapeutic action of drug A	Carbidopa only blocks enzyme to prevent peripheral conversion of levodopa "2 + 0 > 2"
Antagonistic	Effect of substances A and B together is less than the sum of their individual effects	Ethanol antidote for methanol toxicity "2 + 2 < 4"
Tachyphylactic	Acute decrease in response to a drug after initial/repeated administration	Nitrates, niacin, phenylephrine, LSD, MDMA

❖ N.B:

- Vasoconstriction by α-adrenergic agonists is prominent in the vessels of the nasal mucosa, making these medications effective decongestants.
- Phenylephrine, xylometazoline, and oxymetazoline are used as topical preparations for the treatment of allergic rhinitis and common cold associated congestion and rhinitis.
- These medications, however, are characterized by rapidly declining effect after a few days of use. This phenomenon is called tachyphylaxis.
- It occurs because of decreased production of endogenous norepinephrine from the nerve terminals due to a negative feedback mechanism, resulting in relative vasodilation (removal of normal vasoconstrictive tone) and subsequent edema and congestion. This leads to exacerbation of the nasal congestion symptoms.
- Rebound rhinorrhea is associated with the use of topical decongestants for > 3 days. The use of adrenergic agonists should be stopped to allow the restoration of normal norepinephrine feedback pathways.

The Autonomic Nervous System

- **Anatomy of the ANS:**

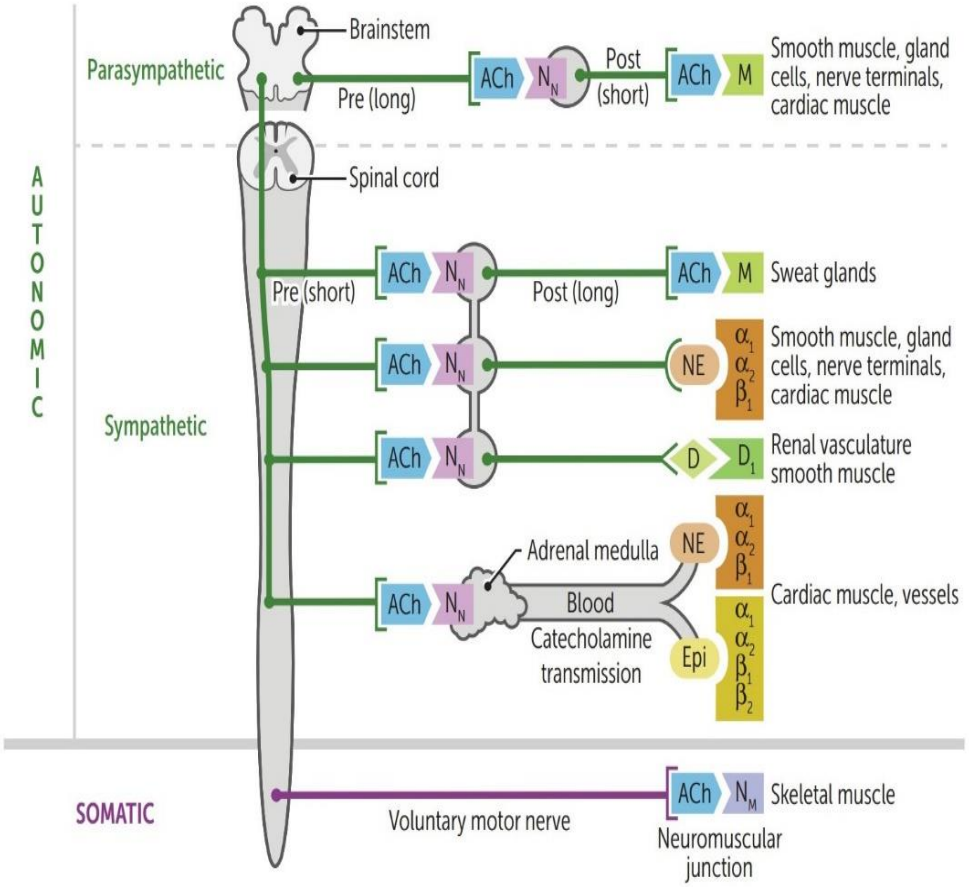
- The ANS is the major involuntary portion of the nervous system and is responsible for automatic, unconscious bodily functions, such as control of heart rate and blood pressure and both gastrointestinal and genitourinary functions.

- The ANS is divided into two major subcategories: the parasympathetic autonomic nervous system (PANS) and the sympathetic autonomic nervous system (SANS).

- **Location of ANS Ganglia:**

- Both the PANS and SANS have relay stations, or ganglia, between the CNS and the end organ, but the somatic system does not.

- An important anatomic difference between the SANS and PANS is that the ganglia of the former lie in two paravertebral chains adjacent to the vertebral column, whereas most of the ganglia of the PANS system are located in the organs innervated.



Pelvic splanchnic nerves and CNs III, VII, IX and X are part of the parasympathetic nervous system.
Adrenal medulla is directly innervated by preganglionic sympathetic fibers.
Sweat glands are part of the sympathetic pathway but are innervated by cholinergic fibers (sympathetic nervous system results in a "chold" sweat).

- The Figure above highlights the major features of the ANS and the somatic systems and also shows the location of the major receptor types. These are:

- N_N: Nicotinic receptors are located on cell bodies in ganglia of both PANS and SANS and in the adrenal medulla.

- N_M: Nicotinic receptors are located on the skeletal muscle motor end plate innervated by somatic motor nerves.

- M_{1-3}: Muscarinic receptors are located on all organs and tissues innervated by postganglionic nerves of the PANS and on thermoregulatory sweat glands innervated by the SANS.

- Neurotransmitters:

- Acetylcholine (ACh) is the neurotransmitter at both nicotinic and muscarinic receptors in tissues that are innervated.

- Note that all direct transmission from the CNS (preganglionic and motor) uses ACh, but postganglionic transmission in the SANS system may use one of the organ-specific transmitters described below.

- Norepinephrine (NE) is the neurotransmitter at most adrenoceptors in organs, as well as in cardiac and smooth muscle.

- Dopamine (DA) activates D_1 receptors, causing vasodilation in renal and mesenteric vascular beds.

- Epinephrine (E, from adrenal medulla) activates most adrenoceptors and is transported in the blood.

- ACh receptors:

- Nicotinic ACh receptors: N_N (found in autonomic ganglia, adrenal medulla) and N_M (found in neuromuscular junction of skeletal muscle).

- Muscarinic ACh receptors:
  - G-protein–coupled receptors that usually act through 2nd messengers.

  - 5 subtypes: M_{1-5} found in heart, smooth muscle, brain, exocrine glands, and on sweat glands (cholinergic sympathetic).

❖ N.B:

1. Adrenal medulla is directly innervated by preganglionic sympathetic fibers.

2. Sweat glands are part of the sympathetic pathway but are innervated by cholinergic fibers (sympathetic nervous system results in a "chold" sweat).

Drug Receptors Linked Via Coupling Proteins to Intracellular Effectors

- Many receptor systems are coupled via GTP-binding proteins (G-proteins) to adenylyl cyclase, the enzyme that converts ATP to cAMP, a second messenger that promotes protein phosphorylation by activating protein kinase A.

- Protein kinase A serves to phosphorylate a set of tissue-specific substrate enzymes or transcription factors (CREB), thereby affecting their activity.

A. G_s proteins:

- Binding of agonists to receptors linked to Gs proteins increases cAMP production.

- Such receptors include those for catecholamines (beta), dopamine (D_1), glucagon, histamine (H_2), prostacyclin, and some serotonin subtypes.

B. G_i proteins:

- Binding of agonists to receptors linked to Gi proteins decreases cAMP production.

- Such receptors include adrenoreceptors (α_2), ACh (M_2), dopamine (D_2 subtypes), and several opioid and serotonin subtypes.

C. G_q proteins:

- Other receptor systems are coupled via GTP-binding proteins (Gq), which activate phospholipase C.

- Activation of this enzyme releases the second messengers inositol triphosphate (IP_3) and diacylglycerol (DAG) from the membrane phospholipid phosphatidylinositol bisphosphate (PIP_2).

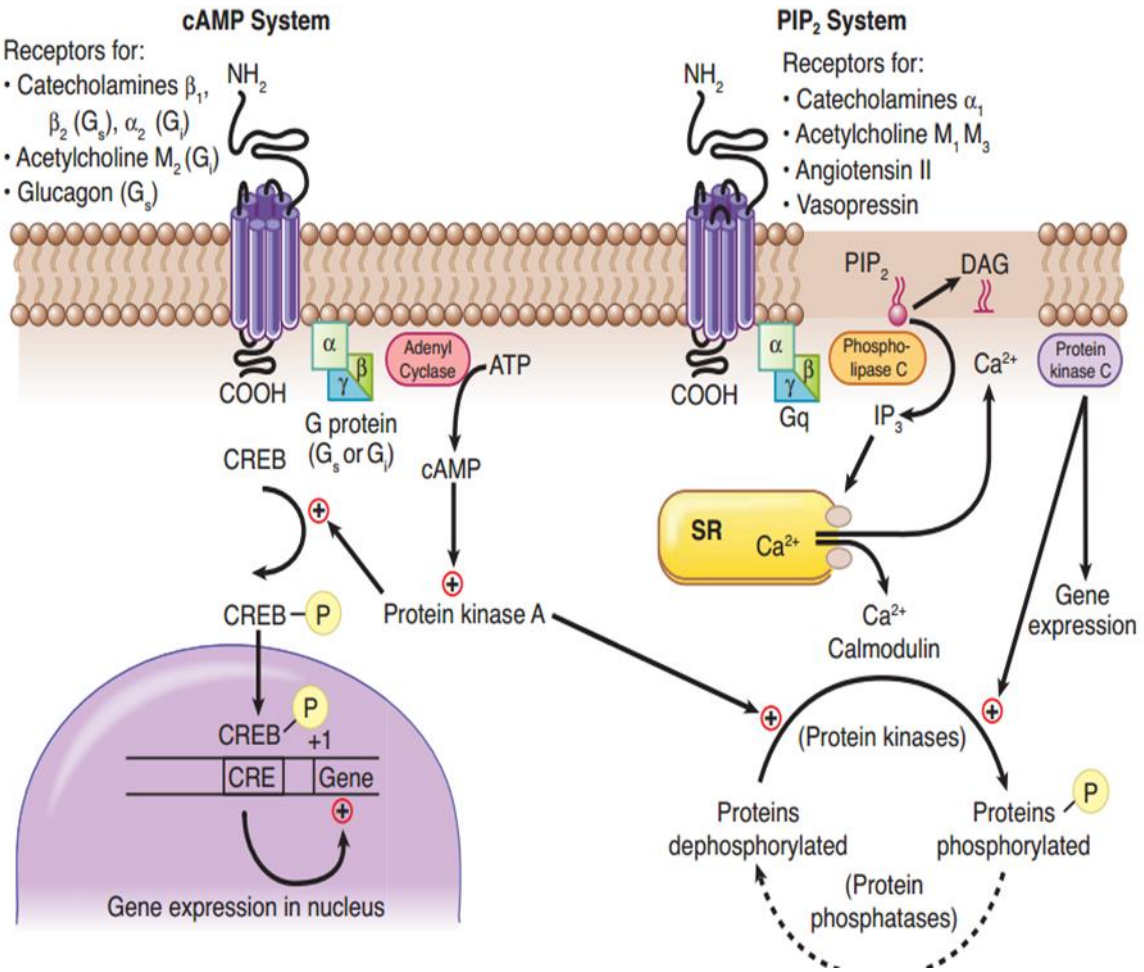
- The IP_3 induces release of Ca from the sarcoplasmic reticulum (SR), which, together with DAG, activates protein kinase C.

- The protein kinase C serves then to phosphorylate a set of tissue-specific substrate enzymes, usually not phosphorylated by protein kinase A, and thereby affects their activity.

- β_1, β_2, β_3, D_1: G_s activation of adenylyl cyclase.

- M_2, α_2, D_2: G_i inhibition of adenylyl cyclase.

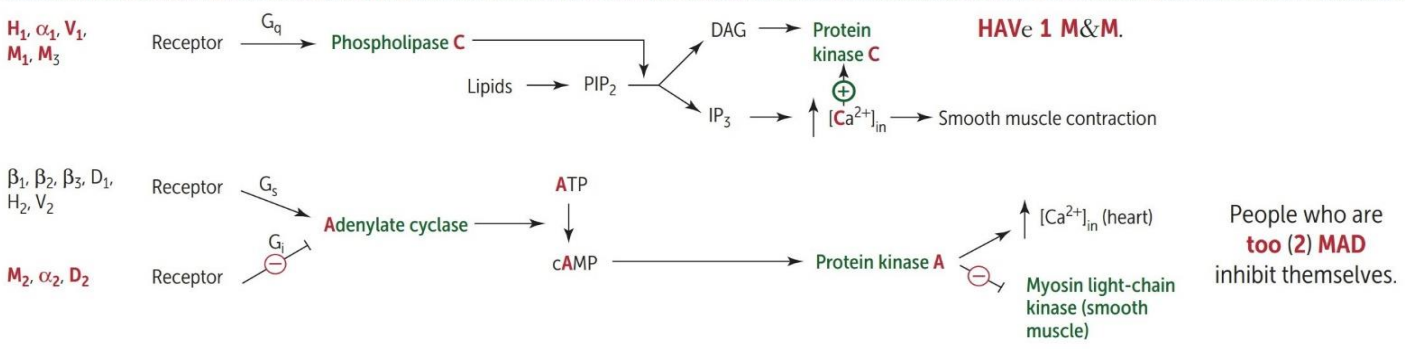
- M_1, M_3, α_1: G_q activation of phospholipase C.


cAMP System
Receptors for:
• Catecholamines β1, β2 (Gs), α2 (Gi)
• Acetylcholine M2 (Gi)
• Glucagon (Gs)
NH2
COOH
α
β
γ
G protein (Gs or Gi)
Adenyl Cyclase
ATP
cAMP
CREB
CREB – P
Protein kinase A
CREB
P
+1
CRE
Gene
Gene expression in nucleus
PIP2 System
Receptors for:
• Catecholamines α1
• Acetylcholine M1 M3
• Angiotensin II
• Vasopressin
NH2
COOH
Gq
PIP2
DAG
Phospho-lipase C
IP3
Ca2+
Protein kinase C
SR
Ca2+
Ca2+
Calmodulin
Gene expression
(Protein kinases)
Proteins dephosphorylated
Proteins phosphorylated
P
(Protein phosphatases)

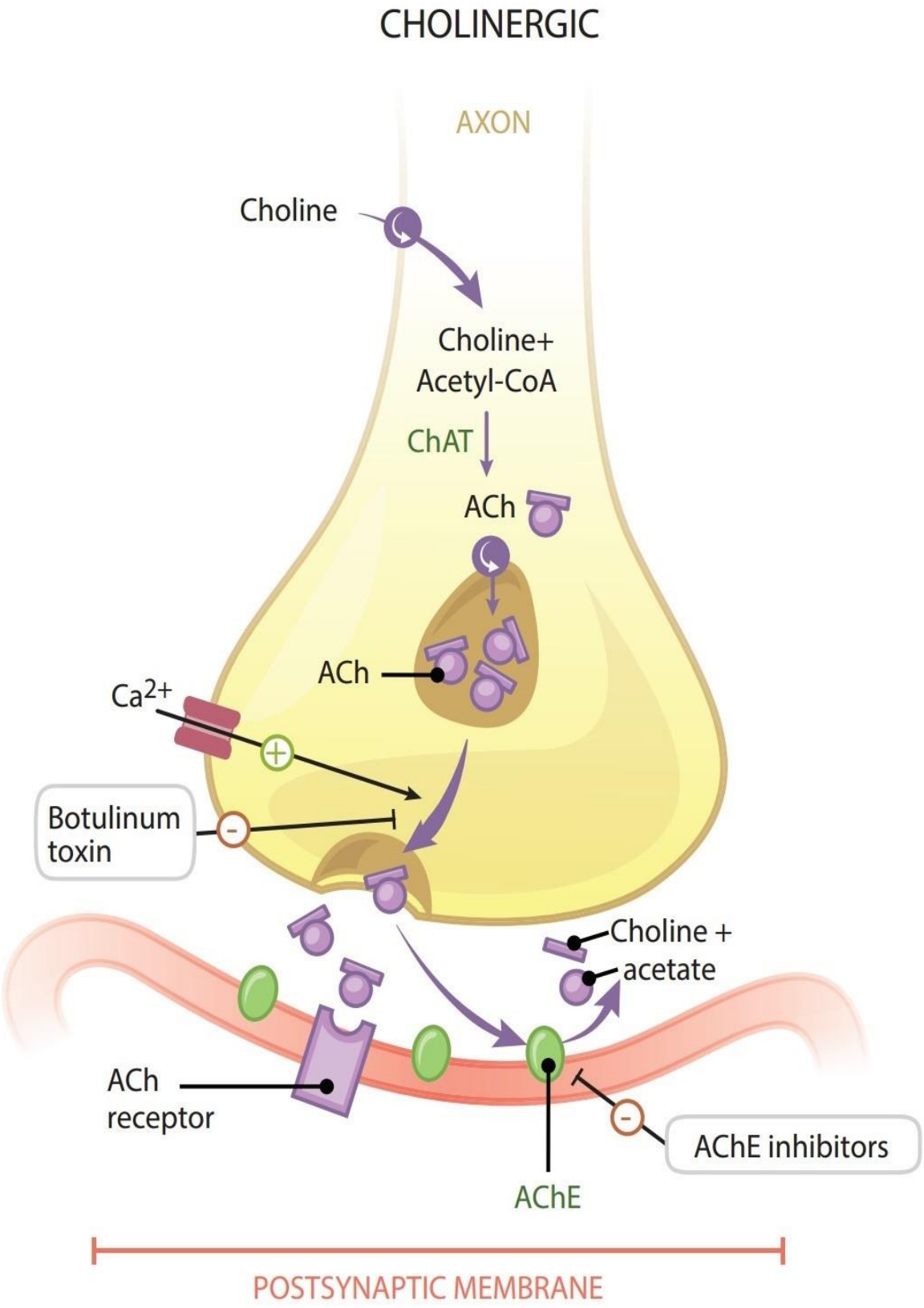
G-protein–linked second messengers

RECEPTOR	G-PROTEIN CLASS	MAJOR FUNCTIONS
Adrenergic		
α_1	q	↑ vascular smooth muscle contraction, ↑ pupillary dilator muscle contraction (mydriasis), ↑ intestinal and bladder sphincter muscle contraction
α_2	i	↓ sympathetic (adrenergic) outflow, ↓ insulin release, ↓ lipolysis, ↑ platelet aggregation, ↓ aqueous humor production
β_1	s	↑ heart rate, ↑ contractility (one heart), ↑ renin release, ↑ lipolysis
β_2	s	Vasodilation, bronchodilation (two lungs), ↑ lipolysis, ↑ insulin release, ↑ glycogenolysis, ↓ uterine tone (tocolysis), ↑ aqueous humor production, ↑ cellular K^+ uptake
β_3	s	↑ lipolysis, ↑ thermogenesis in skeletal muscle, ↑ bladder relaxation
Cholinergic		
M_1	q	Mediates higher cognitive functions, stimulates enteric nervous system
M_2	i	↓ heart rate and contractility of atria
M_3	q	↑ exocrine gland secretions (eg, lacrimal, sweat, salivary, gastric acid), ↑ gut peristalsis, ↑ bladder contraction, bronchoconstriction, ↑ pupillary sphincter muscle contraction (miosis), ciliary muscle contraction (accommodation), ↑ insulin release, endothelium-mediated vasodilation
Dopamine		
D_1	s	Relaxes renal vascular smooth muscle, activates direct pathway of striatum
D_2	i	Modulates transmitter release, especially in brain, inhibits indirect pathway of striatum
Histamine		
H_1	q	↑ nasal and bronchial mucus production, ↑ vascular permeability, bronchoconstriction, pruritus, pain
H_2	s	↑ gastric acid secretion
Vasopressin		
V_1	q	↑ vascular smooth muscle contraction
V_2	s	↑ H_2O permeability and reabsorption via upregulating aquaporin-2 in collecting twobules (tubules) of kidney, ↑ release of vWF

"After qisses (kisses), you get a qiq (kick) out of siq (sick) sqs (super qinky sex)."



Cholinergic Pharmacology



- Choline is accumulated in cholinergic presynaptic nerve endings via an active transport mechanism.
- Choline uptake is inhibited by hemicholinium.
- Ach is synthesized from choline and acetyl-CoA via choline acetyltransferase (ChAT) and accumulates in synaptic vesicles.
- Presynaptic membrane depolarization opens voltage-dependent Ca channels, and the influx of this ion causes fusion of the synaptic vesicle membranes with the presynaptic membrane, leading to exocytosis of ACh.
- Vesamicol: Inhibits vesicular acetylcholine transporter (VAT) preventing the storage of acetylcholine.
- Botulinum toxin interacts with synaptobrevin and other proteins to prevent ACh release and is used in blepharospasm, strabismus/hyperhydrosis, dystonia, and cosmetics.
- Some cholinergic nerve endings have presynaptic autoreceptors for Ach that on activation may elicit a negative feedback of transmitter release.
- Inactivation via acetylcholinesterase (AChE) is the major mechanism of termination of postjunctional actions of ACh.
- AChE is a target for inhibitory drugs (indirect-acting cholinomimetics).
- Postjunctional receptors (N and M) activated by ACh are major targets for both activating drugs (direct-acting cholinomimetics) and blocking agents.

Cholinomimetic agents Watch for exacerbation of COPD, asthma, and peptic ulcers in susceptible patients.

DRUG	ACTION	APPLICATIONS
Direct agonists		
Bethanechol	Activates bladder smooth muscle; resistant to AChE. No nicotinic activity. "Bethany, call me to activate your bladder."	Urinary retention.
Carbachol	Carbon copy of acetylcholine (but resistant to AChE).	Constricts pupil and relieves intraocular pressure in open-angle glaucoma.
Methacholine	Stimulates muscarinic receptors in airway when inhaled.	Challenge test for diagnosis of asthma.
Pilocarpine	Contracts ciliary muscle of eye (open-angle glaucoma), pupillary sphincter (closed-angle glaucoma); resistant to AChE, can cross blood-brain barrier (tertiary amine). "You cry, drool, and sweat on your 'pilow.'"	Potent stimulator of sweat, tears, and saliva Open-angle and closed-angle glaucoma, xerostomia (Sjögren syndrome).

Indirect agonists (anticholinesterases)		
Donepezil, rivastigmine, galantamine	↑ ACh.	1st line for Alzheimer disease (Dona Riva dances at the gala).
Edrophonium	↑ ACh.	Historically used to diagnose myasthenia gravis; replaced by anti-AChR Ab (anti-acetylcholine receptor antibody) test.
Neostigmine	↑ ACh. Neo CNS = No CNS penetration (quaternary amine).	Postoperative and neurogenic ileus and urinary retention, myasthenia gravis, reversal of neuromuscular junction blockade (postoperative).
Physostigmine	↑ ACh. Phreely (freely) crosses blood-brain barrier → CNS (tertiary amine).	Antidote for anticholinergic toxicity; physostigmine "phyxes" atropine overdose.
Pyridostigmine	↑ ACh; ↑ muscle strength. Used with glycopyrrolate, hyoscyamine, or propantheline to control pyridostigmine side effects. Pyridostigmine gets rid of myasthenia gravis.	Myasthenia gravis (long acting); does not penetrate CNS (quaternary amine).
Anticholinesterase poisoning	Often due to organophosphates (eg, parathion) that irreversibly inhibit AChE. Organophosphates commonly used as insecticides; poisoning usually seen in farmers.	
Muscarinic effects	Diarrhea, Urination, Miosis, Bronchospasm, Bradycardia, Emesis, Lacrimation, Sweating, Salivation.	DUMBBELSS. Reversed by atropine, a competitive inhibitor. Atropine can cross BBB to relieve CNS symptoms.
Nicotinic effects	Neuromuscular blockade (mechanism similar to succinylcholine).	Reversed by pralidoxime, regenerates AChE via dephosphorylation if given early. Pralidoxime (quaternary amine) does not readily cross BBB.
CNS effects	Respiratory depression, lethargy, seizures, coma.	

Muscarinic antagonists

DRUGS	ORGAN SYSTEMS	APPLICATIONS
Atropine, homatropine, tropicamide	Eye	Produce mydriasis and cycloplegia.
Benztropine, trihexyphenidyl	CNS	Parkinson disease ("park my Benz"). Acute dystonia.
Glycopyrrolate	GI, respiratory	Parenteral: preoperative use to reduce airway secretions. Oral: drooling, peptic ulcer.
Hyoscyamine, dicyclomine	GI	Antispasmodics for irritable bowel syndrome.
Ipratropium, tiotropium	Respiratory	COPD, asthma ("I pray I can breathe soon!").
Oxybutynin, solifenacin, tolterodine	Genitourinary	Reduce bladder spasms and urge urinary incontinence (overactive bladder).
Scopolamine	CNS	Motion sickness.

Atropine

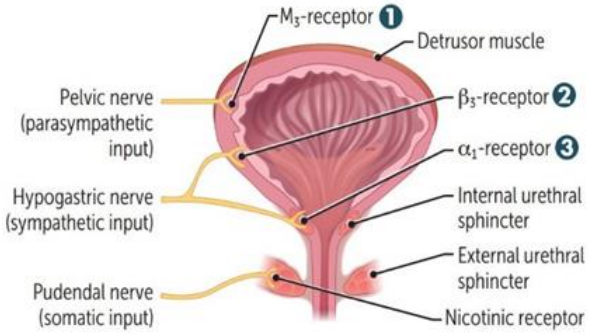
Muscarinic antagonist. Used to treat bradycardia and for ophthalmic applications.

ORGAN SYSTEM	ACTION	NOTES
Eye	↑ pupil dilation, cycloplegia	Blocks muscarinic effects (DUMBBELSS) of anticholinesterases, but not the nicotinic effects.
Airway	Bronchodilation, ↓ secretions	
Stomach	↓ acid secretion	
Gut	↓ motility	
Bladder	↓ urgency in cystitis	
ADVERSE EFFECTS	↑ body temperature (due to ↓ sweating); ↑ HR; dry mouth; dry, flushed skin; cycloplegia; constipation; disorientation Can cause acute angle-closure glaucoma in elderly (due to mydriasis), urinary retention in men with prostatic hyperplasia, and hyperthermia in infants.	Side effects: Hot as a hare Fast as a fiddle Dry as a bone Red as a beet Blind as a bat Mad as a hatter Full as a flask Jimson weed (*Datura*) → gardener's pupil (mydriasis due to plant alkaloids)

Micturition control

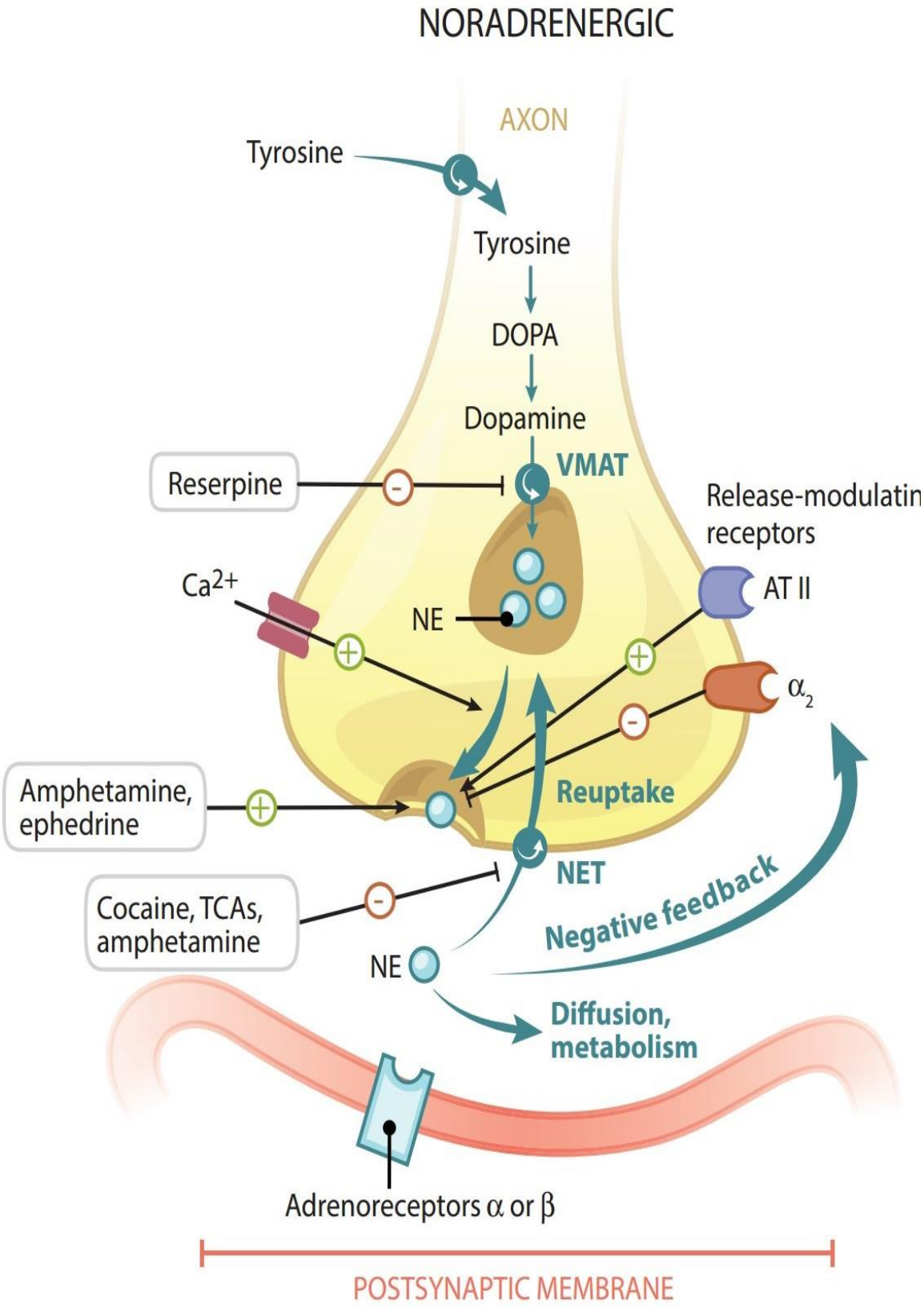
Micturition center in pons regulates involuntary bladder function via coordination of sympathetic and parasympathetic nervous systems.

- ⊕ sympathetic → ↑ urinary retention
- ⊕ parasympathetic → ↑ urine voiding. Some autonomic drugs act on smooth muscle receptors to treat bladder dysfunction.



DRUGS	MECHANISM	USE
❶ **Muscarinic antagonists** (eg, oxybutynin)	⊖ M_3 receptor → relaxation of detrusor smooth muscle → ↓ detrusor overactivity	Urgency incontinence
❶ **Muscarinic agonists** (eg, bethanechol)	⊕ M_3 receptor → contraction of detrusor smooth muscle → ↑ bladder emptying	Urinary retention
❷ **Sympathomimetics** (eg, mirabegron)	⊕ β_3 receptor → relaxation of detrusor smooth muscle → ↑ bladder capacity	Urgency incontinence
❸ **α_1-blockers** (eg, tamsulosin)	⊖ α_1-receptor → relaxation of smooth muscle (bladder neck, prostate) → ↓ urinary obstruction	BPH

Adrenergic pharmacology



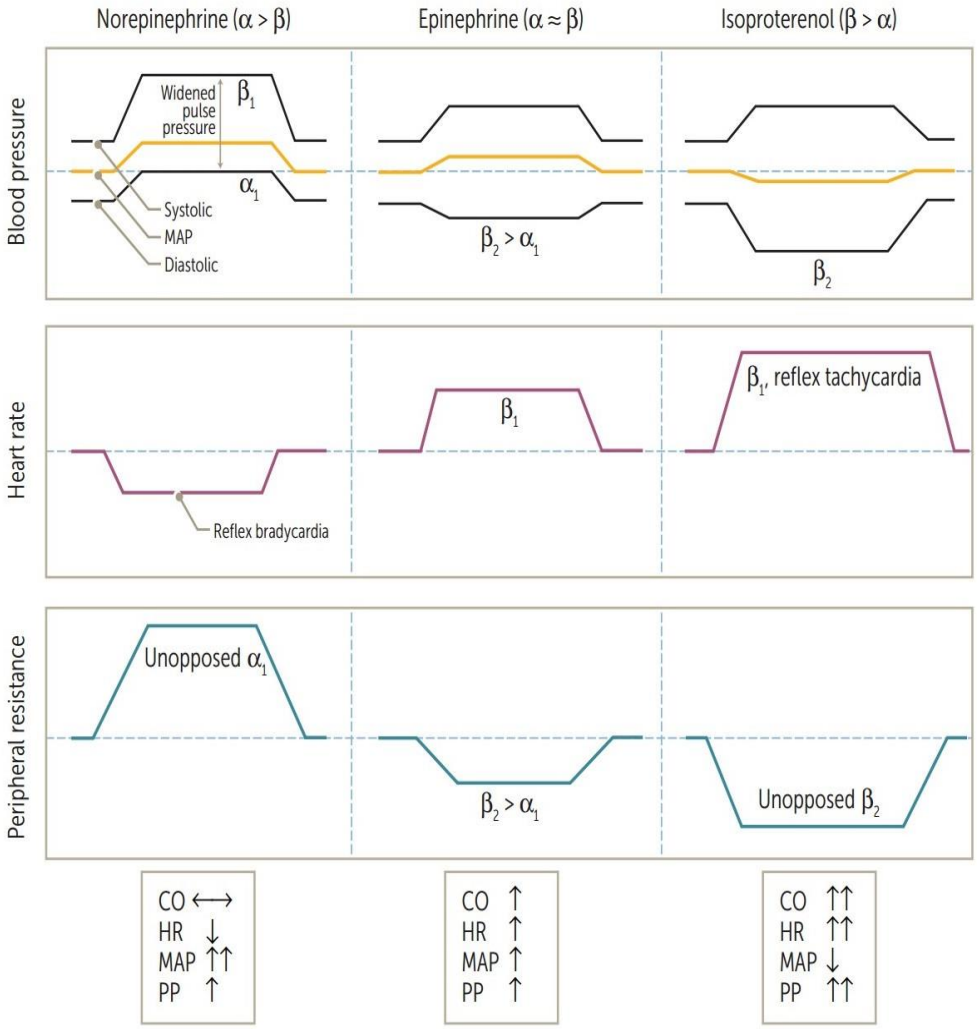
- Tyrosine is actively transported into nerve endings and is converted to dihydroxyphenylalanine (DOPA) via tyrosine hydroxylase. This step is rate limiting in the synthesis of NE.
- DOPA is converted to dopamine (DA) via DOPA decarboxylase.
- DA is taken up into storage vesicles where it is metabolized to NE via DA beta hydroxylase.
- Presynaptic membrane depolarization opens voltage-dependent Ca channels. Influx of this ion causes fusion of the synaptic granular membranes, with the presynaptic membrane leading to NE exocytosis into the neuroeffector junction.
- NE then activates post-junctional receptors, leading to tissue-specific responses depending on the adrenoceptor subtype activated.
- Termination of NE actions is mainly due to removal from the neuroeffector junction back into the sympathetic nerve ending via NE reuptake transporter system.
- Metabolism of NE is by catechol-O-methyltransferase (COMT) in the synapse or MAO-A in the prejunctional nerve terminal.
- At some sympathetic nerve endings, the NE released may activate prejunctional alpha adrenoceptors involved in feedback regulation, which results in decreased release of the neurotransmitter.

Sympathomimetics

DRUG	ACTION	HEMODYNAMIC CHANGES	APPLICATIONS
Direct sympathomimetics			
Albuterol, salmeterol, terbutaline	$\beta_2 > \beta_1$	↑ HR (little effect)	Albuterol for Acute asthma/COPD. Salmeterol for Serial (long-term) asthma/COPD. Terbutaline for acute bronchospasm in asthma and tocolysis.
Dobutamine	$\beta_1 > \beta_2, \alpha$	↔/↓ BP, ↑ HR, ↑ CO	Heart failure (HF), cardiogenic shock (inotropic > chronotropic), cardiac stress testing.
Dopamine	$D_1 = D_2 > \beta > \alpha$	↑ BP (high dose), ↑ HR, ↑ CO	Unstable bradycardia, HF, shock; inotropic and chronotropic effects at lower doses due to β effects; vasoconstriction at high doses due to α effects.
Epinephrine	$\beta > \alpha$	↑ BP (high dose), ↑ HR, ↑ CO	Anaphylaxis, asthma, open-angle glaucoma; α effects predominate at high doses. Significantly stronger effect at β_2-receptor than norepinephrine.
Fenoldopam	D_1	↓ BP (vasodilation), ↑ HR, ↑ CO	Postoperative hypertension, hypertensive crisis. Vasodilator (coronary, peripheral, renal, and splanchnic). Promotes natriuresis. Can cause hypotension and tachycardia.
Isoproterenol	$\beta_1 = \beta_2$	↓ BP (vasodilation), ↑ HR, ↑ CO	Electrophysiologic evaluation of tachyarrhythmias. Can worsen ischemia. Has negligible α effect.
Midodrine	α_1	↑ BP (vasoconstriction), ↓ HR, ↔/↓ CO	Autonomic insufficiency and postural hypotension. May exacerbate supine hypertension.
Mirabegron	β_3		Urinary urgency or incontinence or overactive bladder. Think "mirab3gron."
Norepinephrine	$\alpha_1 > \alpha_2 > \beta_1$	↑ BP, ↑ HR, ↔/↑ CO	Hypotension, septic shock.
Phenylephrine	$\alpha_1 > \alpha_2$	↑ BP (vasoconstriction), ↓ HR, ↔/↓ CO	Hypotension (vasoconstrictor), ocular procedures (mydriatic), rhinitis (decongestant), ischemic priapism.
Indirect sympathomimetics			
Amphetamine	Indirect general agonist, reuptake inhibitor, also releases stored catecholamines		Narcolepsy, obesity, ADHD.
Cocaine	Indirect general agonist, reuptake inhibitor		Causes vasoconstriction and local anesthesia. Caution when giving β-blockers if cocaine intoxication is suspected (can lead to unopposed α_1 activation → extreme hypertension, coronary vasospasm).
Ephedrine	Indirect general agonist, releases stored catecholamines		Nasal decongestion (pseudoephedrine), urinary incontinence, hypotension.

Norepinephrine vs isoproterenol

NE ↑ systolic and diastolic pressures as a result of α_1-mediated vasoconstriction → ↑ mean arterial pressure → reflex bradycardia. However, isoproterenol (rarely used) has little α effect but causes β_2-mediated vasodilation, resulting in ↓ mean arterial pressure and ↑ heart rate through β_1 and reflex activity.



Sympatholytics (α_2-agonists)

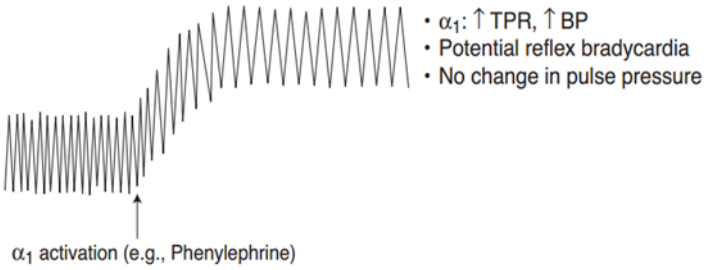
DRUG	APPLICATIONS	ADVERSE EFFECTS
Clonidine, guanfacine	Hypertensive urgency (limited situations), ADHD, Tourette syndrome, symptom control in opioid withdrawal	CNS depression, bradycardia, hypotension, respiratory depression, miosis, rebound hypertension with abrupt cessation
α-methyldopa	Hypertension in pregnancy	Direct Coombs ⊕ hemolysis, drug-induced lupus, hyperprolactinemia
Tizanidine	Relief of spasticity	Hypotension, weakness, xerostomia

- <u>Differentiation of high-dose epinephrine versus norepinephrine</u>:

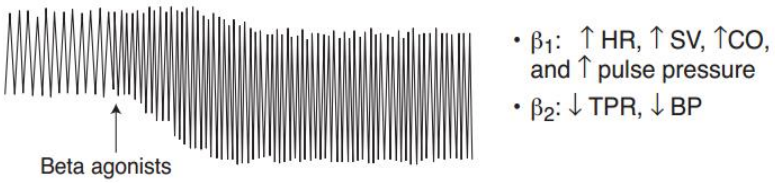
- Epinephrine reversal: Use of α1 blocker to reverse hypertension to hypotension in a patient receiving too much epinephrine

- Hypertension was due to predominant α1 tone on the vasculature

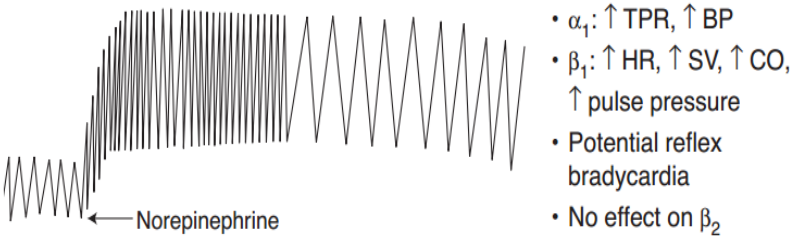
- Hypotension results from unmasking β2 receptors



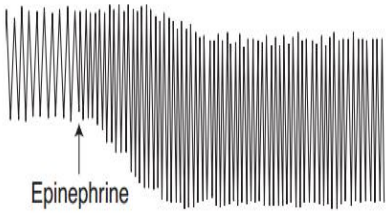
Effect of Alpha Activators on Heart Rate and Blood Pressure



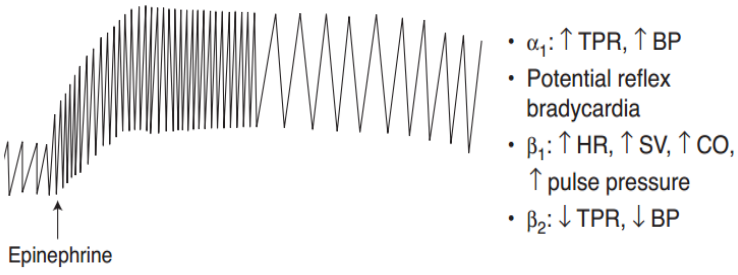
Effect of Beta Receptor Activation on Heart Rate and Blood Pressure



Effect of Norepinephrine on Heart Rate and Blood Pressure



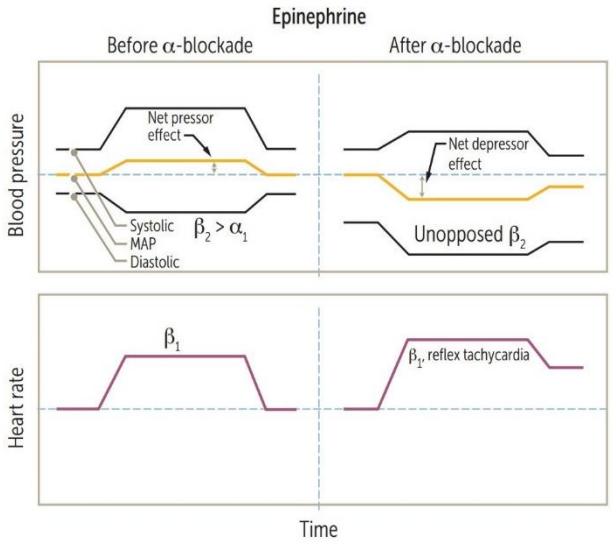
Effect of Low-dose Epinephrine on Heart Rate and Blood Pressure



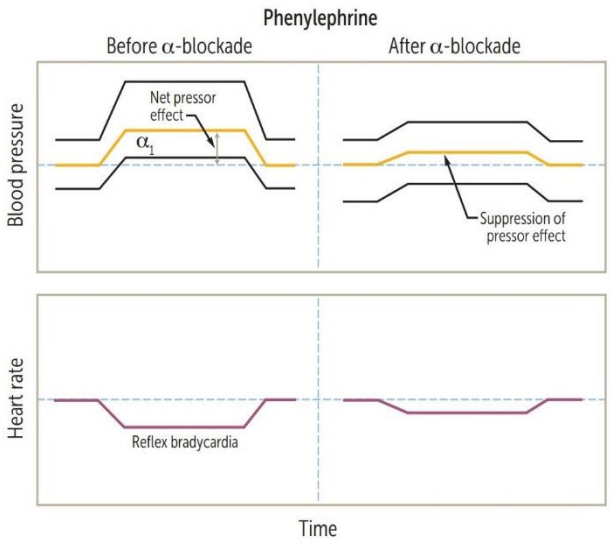
Effect of High-dose Epinephrine Is Similar to Norepinephrine

α-blockers

DRUG	APPLICATIONS	ADVERSE EFFECTS
Nonselective		
Phenoxybenzamine	Irreversible. Pheochromocytoma (used preoperatively) to prevent catecholamine (hypertensive) crisis	Orthostatic hypotension, reflex tachycardia
Phentolamine	Reversible. Given to patients on MAO inhibitors who eat tyramine-containing foods and for severe cocaine-induced hypertension (2nd line)	
α_1 selective (-osin ending)		
Prazosin, terazosin, doxazosin, tamsulosin	Urinary symptoms of BPH; PTSD (prazosin); hypertension (except tamsulosin)	1st-dose orthostatic hypotension, dizziness, headache
α_2 selective		
Mirtazapine	Depression	Sedation, ↑ serum cholesterol, ↑ appetite



Epinephrine response exhibits reversal of mean arterial pressure from a net increase (the α response) to a net decrease (the β_2 response).



Phenylephrine response is suppressed but not reversed because it is a "pure" α-agonist (lacks β-agonist properties).

- <u>Tyramine:</u>

- Normally degraded by monoamine oxidase (MAO) in the gastrointestinal tract.

- Levels ↑ in patients taking MAO inhibitors who ingest tyramine-rich foods (old cheese, red wine).

- Excess tyramine enters presynaptic vesicles and displaces other neurotransmitters (NE) → ↑ active presynaptic neurotransmitters → ↑ diffusion of neurotransmitters into synaptic cleft → ↑ sympathetic stimulation.

- Classically results in a hypertensive crisis.

β-blockers Acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, esmolol, labetalol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol.

APPLICATION	ACTIONS	NOTES/EXAMPLES
Angina pectoris	↓ heart rate and contractility → ↓ O_2 consumption	
Glaucoma	↓ production of aqueous humor	Timolol
Heart failure	↓ mortality	Bisoprolol, Carvedilol, Metoprolol (β-blockers Curb Mortality)
Hypertension	↓ cardiac output, ↓ renin secretion (due to β_1-receptor blockade on JG cells)	
Hyperthyroidism/ thyroid storm	Symptom control (↓ heart rate, ↓ tremor)	Propranolol
Hypertrophic cardiomyopathy	↓ heart rate → ↑ filling time, relieving obstruction	
Myocardial infarction	↓ O_2 demand (short-term), ↓ mortality (long-term)	
Supraventricular tachycardia	↓ AV conduction velocity (class II antiarrhythmic)	Metoprolol, esmolol
Variceal bleeding	↓ hepatic venous pressure gradient and portal hypertension (prophylactic use)	Nadolol, propranolol, carvedilol
ADVERSE EFFECTS	Erectile dysfunction, cardiovascular (bradycardia, AV block, HF), CNS (seizures, sleep alterations), dyslipidemia (metoprolol), and asthma/COPD exacerbations	Use of β-blockers for acute cocaine-associated chest pain remains controversial due to unsubstantiated concern for unopposed α-adrenergic stimulation
SELECTIVITY	β_1-selective antagonists ($\beta_1 > \beta_2$)—acebutolol (partial agonist), atenolol, betaxolol, bisoprolol, esmolol, metoprolol	Selective antagonists mostly go from A to M (β_1 with 1st half of alphabet)
	Nonselective antagonists ($\beta_1 = \beta_2$)—nadolol, pindolol (partial agonist), propranolol, timolol	NonZelective antagonists mostly go from N to Z (β_2 with 2nd half of alphabet)
	Nonselective α- and β-antagonists—carvedilol, labetalol	Nonselective α- and β-antagonists have modified suffixes (instead of "-olol")
	Nebivolol combines cardiac-selective β_1-adrenergic blockade with stimulation of β_3-receptors (activate nitric oxide synthase in the vasculature and ↓ SVR)	Nebivolol increases NO

Phosphodiesterase inhibitors

Phosphodiesterase (PDE) inhibitors inhibit PDE, which catalyzes the hydrolysis of cAMP and/or cGMP, and thereby increase cAMP and/or cGMP. These inhibitors have varying specificity for PDE isoforms and thus have different clinical uses.

TYPE OF INHIBITOR	MECHANISM OF ACTION	CLINICAL USES	ADVERSE EFFECTS
Nonspecific PDE inhibitor Theophylline	↓ cAMP hydrolysis → ↑ cAMP → bronchial smooth muscle relaxation → bronchodilation	COPD/asthma (rarely used)	Cardiotoxicity (eg, tachycardia, arrhythmia), neurotoxicity (eg, headache), abdominal pain
PDE-5 inhibitors Sildenafil, vardenafil, tadalafil, avanafil	↓ hydrolysis of cGMP → ↑ cGMP → ↑ smooth muscle relaxation by enhancing NO activity → pulmonary vasodilation and ↑ blood flow in corpus cavernosum fills the penis	Erectile dysfunction Pulmonary hypertension BPH (tadalafil only)	Facial flushing, headache, dyspepsia, hypotension in patients taking nitrates; "Hot and sweaty," then Headache, Heartburn, Hypotension Sildenafil only: cyanopia (blue-tinted vision) via inhibition of PDE-6 in retina
PDE-4 inhibitor Roflumilast	↑ cAMP in neutrophils, granulocytes, and bronchial epithelium	Severe COPD	Abdominal pain, weight loss, mental disorders (eg, depression)
PDE-3 inhibitor Milrinone	In cardiomyocytes: ↑ cAMP → ↑ Ca^{2+} influx → ↑ ionotropy and chronotropy In vascular smooth muscle: ↑ cAMP → MLCK inhibition → vasodilation → ↓ preload and afterload	Acute decompensated HF with cardiogenic shock	Tachycardia, ventricular arrhythmias (thus not for chronic use), hypotension
"Platelet inhibitors" Cilostazol[a] Dipyridamole[b]	In platelets: ↑ cAMP → inhibition of platelet aggregation	Intermittent claudication Stroke or TIA prevention (with aspirin) Cardiac stress testing (dipyridamole only, due to coronary vasodilation) Prevention of coronary stent restenosis	Nausea, headache, facial flushing, hypotension, abdominal pain

[a]Cilostazol is a PDE-3 inhibitor, but due to its indications is categorized as a platelet inhibitor together with dipyridamole.
[b]Dipyridamole is a nonspecific PDE inhibitor, leading to inhibition of platelet aggregation. It also prevents adenosine reuptake by platelets → ↑ extracellular adenosine → ↑ vasodilation.

Ingested seafood toxins Toxin actions include Histamine release, Total block of Na^+ channels, or opening of Na^+ channels to Cause depolarization.

TOXIN	SOURCE	ACTION	SYMPTOMS	TREATMENT
Histamine (scombroid poisoning)	Spoiled dark-meat fish such as tuna, mahi-mahi, mackerel, and bonito	Bacterial histidine decarboxylase converts histidine to histamine Frequently misdiagnosed as fish allergy	Mimics anaphylaxis: acute burning sensation of mouth, flushing of face, erythema, urticaria, itching May progress to bronchospasm, angioedema, hypotension	Antihistamines Albuterol and epinephrine if needed
Tetrodotoxin	Pufferfish	Highly potent toxin; binds fast voltage-gated Na^+ channels in nerve tissue, preventing depolarization	Nausea, diarrhea, paresthesias, weakness, dizziness, loss of reflexes	Supportive
Ciguatoxin	Reef fish such as barracuda, snapper, and moray eel	Opens Na^+ channels, causing depolarization	Nausea, vomiting, diarrhea; perioral numbness; reversal of hot and cold sensations; bradycardia, heart block, hypotension	Supportive

Beers criteria Widely used criteria developed to reduce potentially inappropriate prescribing and harmful polypharmacy in the geriatric population. Includes > 50 medications that should be avoided in elderly patients due to ↓ efficacy and/or ↑ risk of adverse events. Examples:

- α-blockers (↑ risk of hypotension)
- Anticholinergics, antidepressants, antihistamines, opioids (↑ risk of delirium, sedation, falls, constipation, urinary retention)
- Benzodiazepines (↑ risk of delirium, sedation, falls)
- NSAIDs (↑ risk of GI bleeding, especially with concomitant anticoagulation)
- PPIs (↑ risk of *C difficile* infection)

Specific toxicity treatments

TOXIN	TREATMENT
Acetaminophen	N-acetylcysteine (replenishes glutathione)
AChE inhibitors, organophosphates	Atropine > pralidoxime
Antimuscarinic, anticholinergic agents	Physostigmine (crosses BBB), control hyperthermia
Arsenic	Dimercaprol, succimer
Benzodiazepines	Flumazenil
β-blockers	Atropine, glucagon, saline
Carbon monoxide	100% O_2, hyperbaric O_2
Copper	"Penny"cillamine (penicillamine), trientine (copper penny × 3)
Cyanide	Hydroxocobalamin, nitrites + sodium thiosulfate
Digitalis (digoxin)	Digoxin-specific antibody fragments
Heparin	Protamine sulfate
Iron (Fe)	Deferoxamine, deferasirox, deferiprone
Lead	Calcium disodium EDTA, dimercaprol, succimer, penicillamine
Mercury	Dimercaprol, succimer
Methanol, ethylene glycol (antifreeze)	Fomepizole > ethanol, dialysis
Methemoglobin	Methylene blue, vitamin C (reducing agent)
OpiOids	NalOxOne
Salicylates	$NaHCO_3$ (alkalinize urine), dialysis
TCAs	$NaHCO_3$ (stabilizes cardiac cell membrane)
Warfarin	Vitamin K (delayed effect), PCC (prothrombin complex concentrate)/FFP (immediate effect)

Drug reactions—cardiovascular

DRUG REACTION	CAUSAL AGENTS
Coronary vasospasm	Cocaine, Amphetamines, Sumatriptan, Ergot alkaloids (CASE)
Cutaneous flushing	Vancomycin, Adenosine, Niacin, Ca^{2+} channel blockers, Echinocandins, Nitrates (flushed from VANCEN [dancing]) Red man syndrome—rate-dependent infusion reaction to vancomycin causing widespread pruritic erythema due to histamine release. Manage with diphenhydramine, slower infusion rate.
Dilated cardiomyopathy	Anthracyclines (eg, Doxorubicin, Daunorubicin); prevent with Dexrazoxane
Torsades de pointes	Agents that prolong QT interval: antiArrhythmics (class IA, III), antiBiotics (eg, macrolides), anti"C"ychotics (eg, ziprasidone), antiDepressants (eg, TCAs), antiEmetics (eg, ondansetron) (ABCDE)

Drug reactions—endocrine/reproductive

DRUG REACTION	CAUSAL AGENTS	NOTES
Adrenocortical insufficiency	HPA suppression 2° to glucocorticoid withdrawal	
Diabetes insipidus	Lithium, demeclocycline	
Hot flashes	SERMs (eg, tamoxifen, clomiphene, raloxifene)	
Hyperglycemia	Tacrolimus, Protease inhibitors, Niacin, HCTZ, Corticosteroids	The People Need Hard Candies
Hyperprolactinemia	Typical antipsychotics (eg, haloperidol), atypical antipsychotics (eg, risperidone), metoclopramide, methyldopa, reserpine	Presents with hypogonadism (eg, infertility, amenorrhea, erectile dysfunction) and galactorrhea
Hyperthyroidism	Amiodarone, iodine	
Hypothyroidism	AMiodarone, SUlfonamides, Lithium	I AM SUddenly Lethargic
SIADH	Carbamazepine, Cyclophosphamide, SSRIs	Can't Concentrate Serum Sodium

Drug reactions—gastrointestinal

DRUG REACTION	CAUSAL AGENTS	NOTES
Acute cholestatic hepatitis, jaundice	Macrolides (eg, erythromycin)	
Diarrhea	Acamprosate, antidiabetic agents (acarbose, metformin, pramlintide), colchicine, cholinesterase inhibitors, lipid-lowering agents (eg, ezetimibe, orlistat), macrolides (eg, erythromycin), SSRIs, chemotherapy (eg, irinotecan)	
Focal to massive hepatic necrosis	Halothane, *Amanita phalloides* (death cap mushroom), Valproic acid, Acetaminophen	Liver "HAVAc"
Hepatitis	Rifampin, isoniazid, pyrazinamide, statins, fibrates	
Pancreatitis	Didanosine, Corticosteroids, Alcohol, Valproic acid, Azathioprine, Diuretics (eg, furosemide, HCTZ)	Drugs Causing A Violent Abdominal Distress
Pill-induced esophagitis	Bisphosphonates, ferrous sulfate, NSAIDs, potassium chloride, tetracyclines	Caustic effect minimized with upright posture and adequate water ingestion
Pseudomembranous colitis	Ampicillin, cephalosporins, clindamycin, fluoroquinolones, PPIs	Antibiotics predispose to superinfection by resistant *C difficile*

Drug reactions—hematologic

DRUG REACTION	CAUSAL AGENTS	NOTES
Agranulocytosis	Dapsone, Clozapine, Carbamazepine, Propylthiouracil, Methimazole, Colchicine, Ganciclovir	Drugs Can Cause Pretty Major Collapse of Granulocytes
Aplastic anemia	Carbamazepine, Methimazole, NSAIDs, Benzene, Chloramphenicol, Propylthiouracil	Can't Make New Blood Cells Properly
Direct Coombs ⊕ hemolytic anemia	Penicillin, methylDopa, Cephalosporins	P Diddy Coombs
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Allopurinol, anticonvulsants, antibiotics, sulfa drugs	Potentially fatal delayed hypersensitivity reaction. Latency period (2- 8 weeks), then fever, morbilliform skin rash, frequent multiorgan involvement. Treatment: withdrawal of offending drug, corticosteroids
Gray baby syndrome	Chloramphenicol	
Hemolysis in G6PD deficiency	Isoniazid, Sulfonamides, Dapsone, Primaquine, Aspirin, Ibuprofen, Nitrofurantoin	Hemolysis IS D PAIN
Megaloblastic anemia	Hydroxyurea, Phenytoin, Methotrexate, Sulfa drugs	You're having a mega blast with PMS
Thrombocytopenia	Heparin, vancomycin, linezolid, quinidine, indinavir, ganciclovir, abciximab	
Thrombotic complications	Combined oral contraceptives, hormone replacement therapy, SERMs (eg, tamoxifen)	Estrogen-mediated side effect

Drug reactions—musculoskeletal/skin/connective tissue

DRUG REACTION	CAUSAL AGENTS	NOTES
Drug-induced lupus	Methyldopa, Minocycline, Hydralazine, Isoniazid, Phenytoin, Sulfa drugs, Etanercept, Procainamide	Lupus Makes My HIPS Extremely Painful
Fat redistribution	Protease inhibitors, Glucocorticoids	Fat PiG
Gingival hyperplasia	Cyclosporine, Ca^{2+} channel blockers, Phenytoin	Can Cause Puffy gums
Hyperuricemia (gout)	Pyrazinamide, Thiazides, Furosemide, Niacin, Cyclosporine	Painful Tophi and Feet Need Care
Myopathy	Statins, fibrates, niacin, colchicine, daptomycin, hydroxychloroquine, interferon-α, penicillamine, glucocorticoids	
Osteoporosis	Corticosteroids, depot medroxyprogesterone acetate, GnRH agonists, aromatase inhibitors, anticonvulsants, heparin, PPIs	
Photosensitivity	Sulfonamides, Amiodarone, Tetracyclines, 5-FU	SAT For Photo
Rash (Stevens-Johnson syndrome)	Anti-epileptic drugs (especially lamotrigine), allopurinol, sulfa drugs, penicillin	Steven Johnson has epileptic allergy to sulfa drugs and penicillin
Teeth discoloration	Tetracyclines	Teethracyclines
Tendon/cartilage damage	Fluoroquinolones	

Drug reactions—neurologic

DRUG REACTION	CAUSAL AGENTS	NOTES
Cinchonism	Quinidine, quinine	Can present with tinnitus, hearing/vision loss, psychosis, and cognitive impairment
Parkinson-like syndrome	Antipsychotics, Reserpine, Metoclopramide	Cogwheel rigidity of ARM
Peripheral neuropathy	Isoniazid, phenytoin, platinum agents (eg, cisplatin), vincristine	
Idiopathic intracranial hypertension	Growth hormones, tetracyclines, vitamin A	
Seizures	Isoniazid, Bupropion, Imipenem/cilastatin, Tramadol, Enflurane	With seizures, I BITE my tongue
Tardive dyskinesia	Antipsychotics, metoclopramide	
Visual disturbance	Topiramate (blurred vision/diplopia, haloes), Digoxin (yellow-tinged vision), Isoniazid (optic neuritis), Vigabatrin (bilateral visual field defects), PDE-5 inhibitors (blue-tinged vision), Ethambutol (color vision changes)	These Drugs Irritate Very Precious Eyes

Drug reactions—renal/genitourinary

DRUG REACTION	CAUSAL AGENTS	NOTES
Fanconi syndrome	Cisplatin, ifosfamide, expired tetracyclines, tenofovir	
Hemorrhagic cystitis	Cyclophosphamide, ifosfamide	Prevent by coadministering with mesna
Interstitial nephritis	Diuretics (Pee), NSAIDs (Pain-free), Penicillins and cephalosporins, PPIs, rifamPin, and sulfa drugs	Remember the 5 P's

Drug reactions—respiratory

DRUG REACTION	CAUSAL AGENTS	NOTES
Dry cough	ACE inhibitors	
Pulmonary fibrosis	Methotrexate, Nitrofurantoin, Carmustine, Bleomycin, Busulfan, Amiodarone	My Nose Cannot Breathe Bad Air

Drug reactions—multiorgan

DRUG REACTION	CAUSAL AGENTS	NOTES
Antimuscarinic	Atropine, TCAs, H_1-blockers, antipsychotics	
Disulfiram-like reaction	1st-generation Sulfonylureas, Procarbazine, certain Cephalosporins, Griseofulvin, Metronidazole	Sorry Pals, Can't Go Mingle
Nephrotoxicity/ ototoxicity	Loop diuretics, Aminoglycosides, cisPlatin, Vancomycin, ampho**TER**icin B	Listen And Pee Very TERriBly Cisplatin toxicity may respond to amifostine

Drugs affecting pupil size

↑ pupil size	↓ pupil size
Anticholinergics (eg, atropine, TCAs, tropicamide, scopolamine, antihistamines)	Sympatholytics (eg, α_2-agonists)
Drugs of abuse (eg, amphetamines, cocaine, LSD), meperidine	Drugs of abuse (eg, heroin/opioids)
Sympathomimetics	Parasympathomimetics (eg, pilocarpine), organophosphates

Cytochrome P-450 interactions (selected)

Inducers (+)	Substrates	Inhibitors (–)
Modafinil	Warfarin	Sodium valproate
Chronic alcohol use	Anti-epileptics	Isoniazid
St. John's wort	Theophylline	Cimetidine
Phenytoin	OCPs	Ketoconazole
Phenobarbital		Fluconazole
Nevirapine		Acute alcohol abuse
Rifampin		Chloramphenicol
Griseofulvin		Erythromycin/clarithromycin
Carbamazepine		Sulfonamides
		Ciprofloxacin
		Omeprazole
		Metronidazole
		Amiodarone
		Ritonavir
		Grapefruit juice
Most chronic alcoholics Steal Phen-Phen and Never Refuse Greasy Carbs	War Against The OCPs	SICKFACES.COM (when I Am Really drinking Grapefruit juice)

Sulfa drugs	Sulfonamide antibiotics, Sulfasalazine, Probenecid, Furosemide, Acetazolamide, Celecoxib, Thiazides, Sulfonylureas. Patients with sulfa allergies may develop fever, urinary tract infection, Stevens-Johnson syndrome, hemolytic anemia, thrombocytopenia, agranulocytosis, acute interstitial nephritis, and urticaria (hives).	Scary Sulfa Pharm FACTS

PHARMACOLOGY—MISCELLANEOUS

Drug names

ENDING	CATEGORY	EXAMPLE
Antimicrobial		
-bendazole	Antiparasitic/antihelminthic	Mebendazole
-cillin	Transpeptidase inhibitor	Ampicillin
-conazole	Ergosterol synthesis inhibitor	Ketoconazole
-cycline	Protein synthesis inhibitor	Tetracycline
-ivir	Neuraminidase inhibitor	Oseltamivir
-navir	Protease inhibitor	Ritonavir
-ovir	Viral DNA polymerase inhibitor	Acyclovir
-tegravir	Integrase inhibitor	Elvitegravir, raltegravir
-thromycin	Macrolide antibiotic	Azithromycin
CNS		
-apine, -idone	Atypical antipsychotic	Quetiapine, risperidone
-azine	Typical antipsychotic	Thioridazine
-barbital	Barbiturate	Phenobarbital
-ipramine, -triptyline	TCA	Imipramine, amitriptyline
-triptan	5-$HT_{1B/1D}$ agonist	Sumatriptan
-zepam, -zolam	Benzodiazepine	Diazepam, alprazolam
Autonomic		
-chol	Cholinergic agonist	Bethanechol, carbachol
-olol	β-blocker	Propranolol
-stigmine	AChE inhibitor	Neostigmine
-terol	β_2-agonist	Albuterol
-zosin	α_1-blocker	Prazosin
Cardiovascular		
-afil	PDE-5 inhibitor	Sildenafil
-dipine	Dihydropyridine Ca^{2+} channel blocker	Amlodipine
-pril	ACE inhibitor	Captopril
-sartan	Angiotensin-II receptor blocker	Losartan
-xaban	Direct factor Xa inhibitor	Apixaban, edoxaban, rivaroxaban
Metabolic		
-gliflozin	SGLT-2 inhibitor	Dapagliflozin, canagliflozin
-glinide	Meglitinide	Repaglinide, nateglinide
-gliptin	DPP-4 inhibitor	Sitagliptin
-glitazone	PPAR-γ activator	Rosiglitazone
-glutide	GLP-1 analog	Liraglutide, albiglutide

Drug names *(continued)*

ENDING	CATEGORY	EXAMPLE
Other		
-dronate	Bisphosphonate	Alendronate
-prazole	Proton pump inhibitor	Omeprazole
-prost	Prostaglandin analog	Latanoprost
-sentan	Endothelin receptor antagonist	Bosentan
-tidine	H_2-antagonist	Cimetidine
-vaptan	ADH antagonist	Tolvaptan

Biologic agents

ENDING	CATEGORY	EXAMPLE
Monoclonal antibodies (-mab)—target overexpressed cell surface receptors		
-ximab	Chimeric human-mouse monoclonal antibody	Rituximab
-zumab	Humanized mouse monoclonal antibody	Bevacizumab
-umab	Human monoclonal antibody	Denosumab
Small molecule inhibitors (-ib)—target intracellular molecules		
-tinib	Tyrosine kinase inhibitor	Imatinib
-zomib	Proteasome inhibitor	Bortezomib
-ciclib	Cyclin-dependent kinase inhibitor	Palbociclib
Receptor fusion proteins (-cept)		
-cept	TNF-α antagonist	Etanercept
Interleukin receptor modulators (-kin)—agonists and antagonists of interleukin receptors		
-leukin	IL-2 agonist/analog	Aldesleukin
-kinra	Interleukin receptor antagonist	Anakinra

CHAPTER 3

Normal Lab Values

Blood | Hematologic | Cerebrospinal | Sweat, Urine, BMI

Blood, Plasma, Serum	Reference Range
Alanine aminotransferase (ALT), serum	8-40 U/L
Alkaline phosphatase, serum	
Male	30-100 U/L
Female	45-115 U/L
Amylase, serum	25-125 U/L
Aspartate aminotransferase (AST), serum	8-40 U/L
Bilirubin, serum (adult)	
Total	0.1-1.0 mg/dL
Direct	0.0-0.3 mg/dL
Calcium, serum (total)	8.4-10.2 mg/dL
Cholesterol, serum	
Total	150-240 mg/dL
HDL	30-70 mg/dL
LDL	<160 mg/dL
Cortisol, serum	
0800 h	5-23 µg/dL
1600 h	3-15 µg/dL
2000 h	50% of 0800 h
Creatine kinase, serum	
Male	25-90 U/L
Female	10-70 U/L

Blood | Hematologic | Cerebrospinal | Sweat, Urine, BMI

Creatinine, serum	0.6-1.2 mg/dL
Electrolytes, serum	
Sodium (Na^+)	136-145 mEq/L
Potassium (K^+)	3.5-5.0 mEq/L
Chloride (Cl^-)	95-105 mEq/L
Bicarbonate (HCO_3^-)	22-28 mEq/L
Magnesium (Mg^{2+})	1.5-2.0 mEq/L
Estriol, total, serum (in pregnancy)	
24-28 wks	30-170 ng/mL
28-32 wks	40-220 ng/mL
32-36 wks	60-280 ng/mL
36-40 wks	80-350 ng/mL
Ferritin, serum	
Male	15-200 ng/mL
Female	12-150 ng/mL
Follicle-stimulating hormone, serum/plasma	
Male	4-25 mIU/mL
Female	
premenopause	4-30 mIU/mL
midcycle peak	10-90 mIU/mL
postmenopause	40-250 mIU/mL
Gases, arterial blood (room air)	
pH	7.35-7.45
Pco_2	33-45 mm Hg
Po_2	75-105 mm Hg

Blood	Hematologic	Cerebrospinal	Sweat, Urine, BMI

Glucose, serum	
Fasting	70-110 mg/dL
2-h postprandial	<120 mg/dL
Growth hormone- arginine stimulation	
Fasting	<5 ng/mL
Provocative stimuli	>7 ng/mL
Immunoglobulins, serum	
IgA	76-390 mg/dL
IgE	0-380 IU/mL
IgG	650-1,500 mg/dL
IgM	40-345 mg/dL
Iron	50-170 µg/dL
Lactate dehydrogenase, serum	45-90 U/L (100-250 IU/L)
Luteinizing hormone, serum/plasma	
Male	6-23 mIU/mL
Female	
follicular phase	5-30 mIU/mL
midcycle	75-150 mIU/mL
postmenopause	30-200 mIU/mL
Osmolality, serum	275-295 mOsmol/kg H_2O
Parathyroid hormone, serum, N-terminal	10-65 pg/mL
Phosphate (alkaline), serum (p-NPP at 30° C)	20-70 U/L

Blood | Hematologic | Cerebrospinal | Sweat, Urine, BMI

N-terminal	10-65 pg/mL
Phosphate (alkaline), serum (p-NPP at 30° C)	20-70 U/L
Phosphorus (inorganic), serum	3.0-4.5 mg/dL
Prolactin, serum (hPRL)	<20 ng/mL
Proteins, serum Total (recumbent) Albumin Globulin	 6.0-7.8 g/dL 3.5-5.5 g/dL 2.3-3.5 g/dL
Thyroid-stimulating hormone (TSH), serum	0.5-5.0 µU/mL
Thyroidal iodine (^{123}I) uptake	8%-30% of administered dose/24 h
Thyroxine (T_4), serum	5-12 µg/dL
Triglycerides, serum	35-160 mg/dL
Triiodothyronine (T_3), serum (RIA)	115-190 ng/dL
Triiodothyronine (T_3) resin uptake	25%-35%
Urea nitrogen, serum (BUN)	7-18 mg/dL
Uric acid, serum	3.0-8.2 mg/dL

Blood | Hematologic | Cerebrospinal | Sweat, Urine, BMI

Hematologic	Reference Range
Bleeding time (template)	2-7 minutes
CD4+ T-lymphocyte count	>500 mm^3
Erythrocyte count	
Male	4.3-5.9 million/mm^3
Female	3.5-5.5 million/mm^3
Erythrocyte sedimentation rate (Westergren)	
Male	0-15 mm/h
Female	0-20 mm/h
Hematocrit	
Male	41%-53%
Female	36%-46%
Hemoglobin A_{1c}	≤6%
Hemoglobin, blood	
Male	13.5-17.5 g/dL
Female	12.0-16.0 g/dL
Leukocyte count and differential	
Leukocyte count	4,500-11,000/mm^3
Neutrophils, segmented	54%-62%
Neutrophils, banded	3%-5%
Eosinophils	1%-3%
Basophils	0%-0.75%
Lymphocytes	25%-33%
Monocytes	3%-7%

Blood | Hematologic | Cerebrospinal | Sweat, Urine, BMI

Eosinophils	1%-3%
Basophils	0%-0.75%
Lymphocytes	25%-33%
Monocytes	3%-7%
Mean corpuscular hemoglobin (MCH)	25.4-34.6 pg/cell
Mean corpuscular hemoglobin concentration (MCHC)	31%-36% Hb/cell
Mean corpuscular volume (MCV)	80-100 μm^3
Partial thromboplastin time (activated)	25-40 seconds
Platelet count	150,000-400,000/mm^3
Prothrombin time	11-15 seconds
Reticulocyte count	0.5%-1.5% of red cells
Thrombin time	<2 seconds deviation from control
Volume	
Plasma	
Male	25-43 mL/kg
Female	28-45 mL/kg
Red cell	
Male	20-36 mL/kg
Female	19-31 mL/kg

Blood | Hematologic | Cerebrospinal | Sweat, Urine, BMI

Cerebrospinal Fluid	Reference Range
Cell count	0-5/mm^3
Chloride	118-132 mEq/L
Gamma globulin	3%-12% of total proteins
Glucose	40-70 mg/dL
Pressure	70-180 mm H_2O
Proteins, total	<40 mg/dL

Blood | Hematologic | Cerebrospinal | Sweat, Urine, BMI

Sweat	**Reference Range**
Chloride	0-35 mmol/L
Urine	**Reference Range**
Calcium	100-300 mg/24 h
Chloride	Varies with intake
Creatine clearance Male Female	 97-137 mL/min 88-128 mL/min
Estriol, total (in pregnancy) 30 wks 35 wks 40 wks	 6-18 mg/24 h 9-28 mg/24 h 13-42 mg/24 h
17-hydroxycorticosteroids Male Female	 3.0-10.0 mg/24 h 2.0-8.0 mg/24 h
17-ketosteroids, total Male Female	 8-20 mg/24 h 6-15 mg/24 h
Osmolality	50-1,400 mOsmol/kg H_2O
Oxalate	8-40 µg/mL
Proteins, total	<150 mg/24 h
Sodium, total	varies with diet

Blood | Hematologic | Cerebrospinal | Sweat, Urine, BMI

Urine	Reference Range
Calcium	100-300 mg/24 h
Chloride	Varies with intake
Creatine clearance Male Female	 97-137 mL/min 88-128 mL/min
Estriol, total (in pregnancy) 30 wks 35 wks 40 wks	 6-18 mg/24 h 9-28 mg/24 h 13-42 mg/24 h
17-hydroxycorticosteroids Male Female	 3.0-10.0 mg/24 h 2.0-8.0 mg/24 h
17-ketosteroids, total Male Female	 8-20 mg/24 h 6-15 mg/24 h
Osmolality	50-1,400 mOsmol/kg H_2O
Oxalate	8-40 µg/mL
Proteins, total	<150 mg/24 h
Sodium, total	varies with diet
Uric acid	varies with diet
Body Mass Index (Adult)	19-25 kg/m^2