

# Pathology

*“Digressions, objections, delight in mockery, carefree mistrust are signs of health; everything unconditional belongs in pathology.”*

—Friedrich Nietzsche

*“You cannot separate passion from pathology any more than you can separate a person’s spirit from his body.”*

—Richard Selzer

*“My business is not prognosis, but diagnosis. I am not engaged in therapeutics, but in pathology.”*

—H.L. Mencken

The fundamental principles of pathology are key to understanding diseases in all organ systems. Major topics such as inflammation and neoplasia appear frequently in questions across different organ systems, and such topics are definitely high yield. For example, the concepts of cell injury and inflammation are key to understanding the inflammatory response that follows myocardial infarction, a very common subject of board questions. Similarly, a familiarity with the early cellular changes that culminate in the development of neoplasias—for example, esophageal or colon cancer—is critical. Make sure you recognize the major tumor-associated genes and are comfortable with key cancer concepts such as tumor staging and metastasis. Finally, take some time to learn about the major systemic changes that come with aging, and how these physiologic alterations differ from disease states.

► Cellular Injury 202

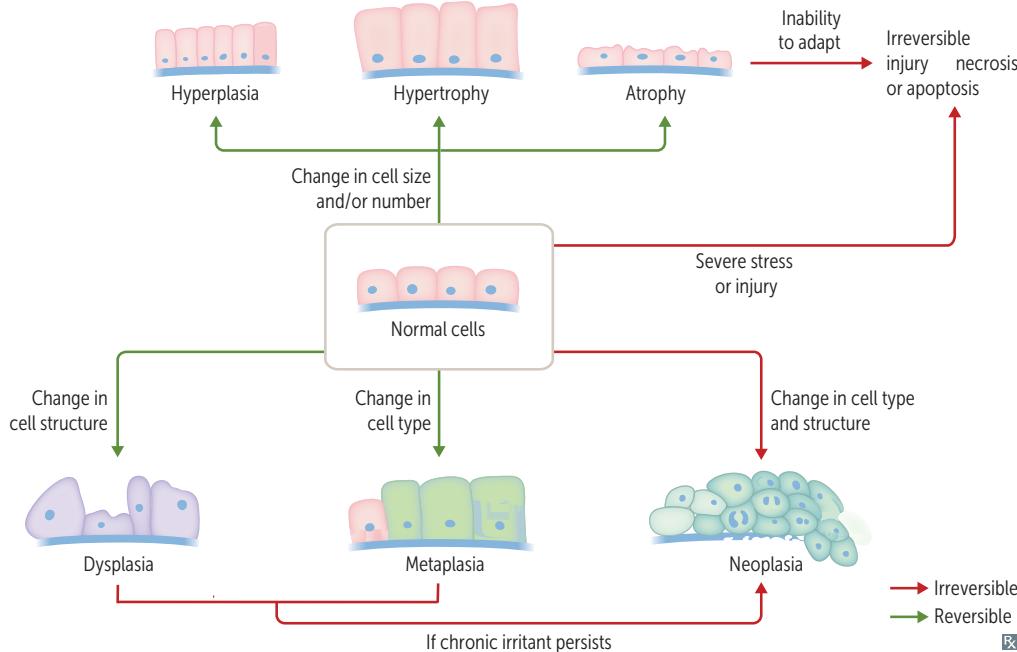
► Inflammation 209

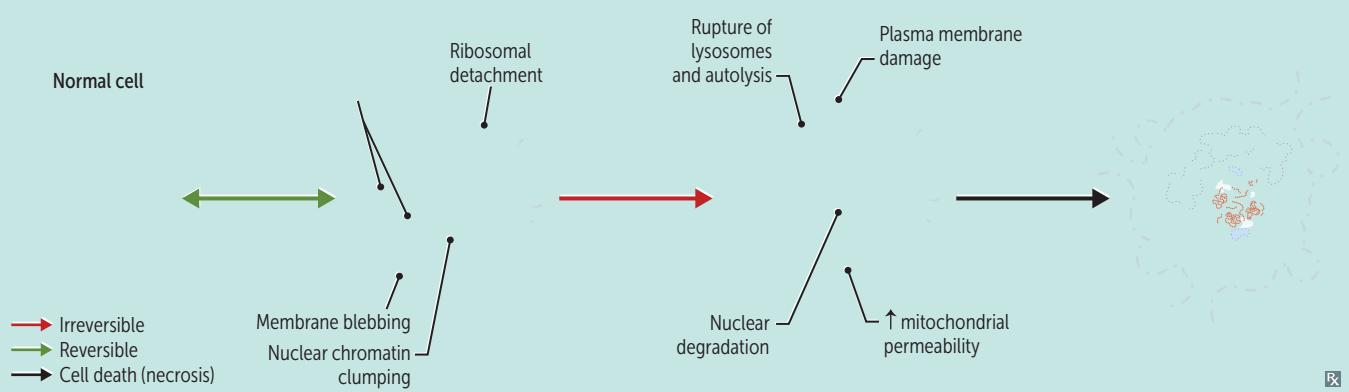
► Neoplasia 215

► Aging 225

## ► PATHOLOGY—CELLULAR INJURY

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





**Apoptosis**

ATP-dependent programmed cell death.

Intrinsic, extrinsic, and perforin/granzyme B pathways → activate caspases (cytosolic proteases)  
→ cellular breakdown including cell shrinkage, chromatin condensation, membrane blebbing, and formation of apoptotic bodies, which are then phagocytosed.

Characterized by deeply eosinophilic cytoplasm and basophilic nucleus, pyknosis, and karyorrhexis.  
Cell membrane typically remains intact without significant inflammation (unlike necrosis).  
DNA laddering (fragments in multiples of 180 bp) is a sensitive indicator of apoptosis.

**Intrinsic (mitochondrial) pathway**

Involved in tissue remodeling in embryogenesis. Occurs when a regulating factor is withdrawn from a proliferating cell population (eg, ↓ IL-2 after a completed immunologic reaction → apoptosis of proliferating effector cells). Also occurs after exposure to injurious stimuli (eg, radiation, toxins, hypoxia).

Regulated by Bcl-2 family of proteins. **BAX** and **BAK** are proapoptotic (**BAd** for survival), while **Bcl-2** and **Bcl-xL** are antiapoptotic (**Be clever, live**).

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

Bcl-2 keeps the mitochondrial membrane impermeable, thereby preventing cytochrome C release.  
Bcl-2 overexpression (eg, follicular lymphoma t[14;18]) → ↓ caspase activation → tumorigenesis.

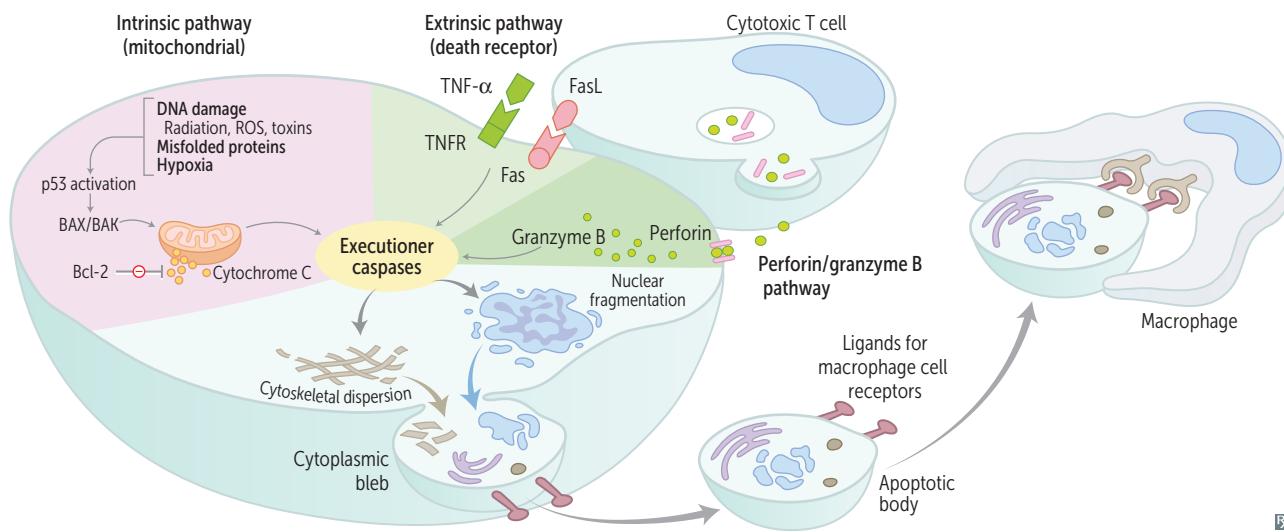
**Extrinsic (death receptor) pathway**

Ligand receptor interactions: FasL binding to Fas (CD95) or TNF- $\alpha$  binding to its receptor.  
Fas-FasL interaction is necessary in thymic medullary negative selection.

**Autoimmune lymphoproliferative syndrome**—caused by defective Fas-FasL interaction → failure of clonal deletion → ↑ numbers of self-reacting lymphocytes. Presents with lymphadenopathy, hepatosplenomegaly, autoimmune cytopenias.

**Perforin/granzyme B pathway**

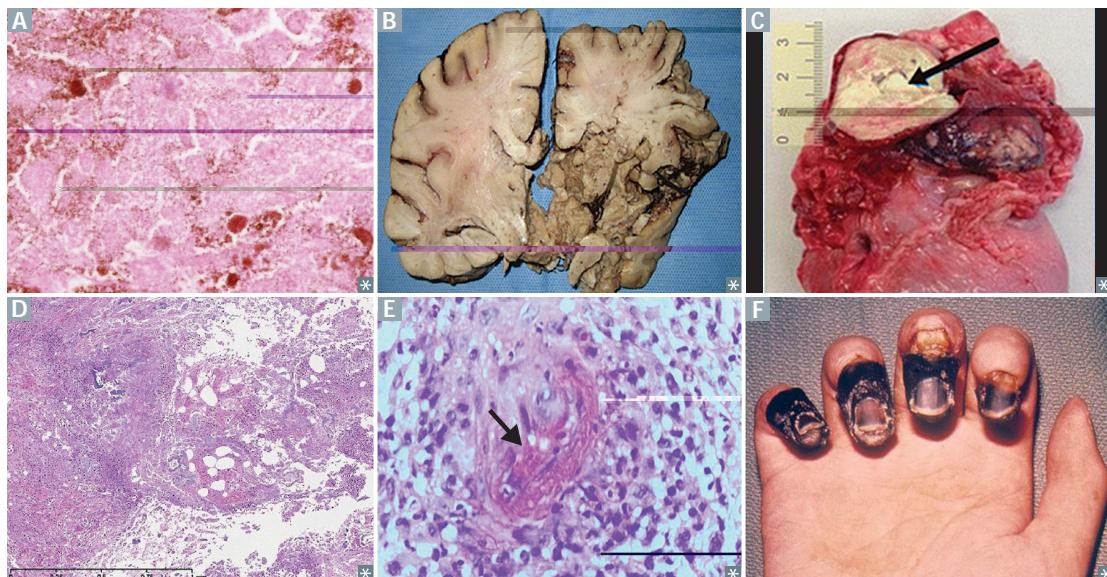
Release of granules containing perforin and granzyme B by immune cells (cytotoxic T-cell and natural killer cell) → perforin forms a pore for granzyme B to enter the target cell.

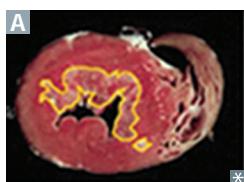


**Necrosis**

Exogenous injury → plasma membrane damage → cell undergoes enzymatic degradation and protein denaturation, intracellular components leak → local inflammatory reaction (unlike apoptosis).

TYPE	SEEN IN	DUE TO	HISTOLOGY
<b>Coagulative</b>	Ischemia/infarcts in most tissues (except brain)	Ischemia or infarction; injury denatures enzymes → proteolysis blocked	Preserved cellular architecture (cell outlines seen), but nuclei disappear; ↑ cytoplasmic binding of eosin stain (→ ↑ eosinophilia; red/pink color) <b>A</b>
<b>Liquefactive</b>	Bacterial abscesses, CNS infarcts	Neutrophils release lysosomal enzymes that digest the tissue	Early: cellular debris and macrophages Late: cystic spaces and cavitation (CNS) <b>B</b> Neutrophils and cell debris seen with bacterial infection
<b>Caseous</b>	TB, systemic fungi (eg, <i>Histoplasma capsulatum</i> ), <i>Nocardia</i>	Macrophages wall off the infecting microorganism → granular debris	Fragmented cells and debris surrounded by lymphocytes and macrophages (granuloma) Cheeselike gross appearance <b>C</b>
<b>Fat</b>	Enzymatic: acute pancreatitis (saponification of peripancreatic fat) Nonenzymatic: traumatic (eg, injury to breast tissue)	Damaged pancreatic cells release lipase, which breaks down triglycerides; liberated fatty acids bind calcium → saponification (chalky-white appearance)	Outlines of dead fat cells without peripheral nuclei; saponification of fat (combined with Ca <sup>2+</sup> ) appears dark blue on H&E stain <b>D</b>
<b>Fibrinoid</b>	Immune vascular reactions (eg, PAN) Nonimmune vascular reactions (eg, hypertensive emergency, preeclampsia)	Immune complex deposition (type III hypersensitivity reaction) and/or plasma protein (eg, fibrin) leakage from damaged vessel	Vessel walls contain eosinophilic layer of proteinaceous material <b>E</b>
<b>Gangrenous</b>	Distal extremity and GI tract, after chronic ischemia	Dry: ischemia <b>F</b> Wet: superinfection	Coagulative Liquefactive superimposed on coagulative



**Ischemia**

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

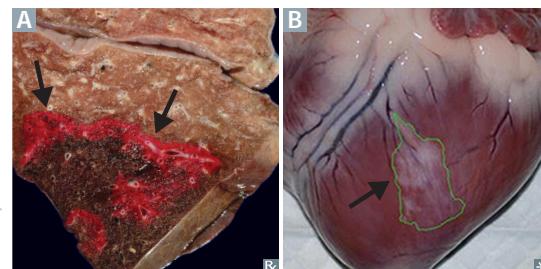
ORGAN	REGION
Brain	ACA/MCA/PCA boundary areas <sup>a,b</sup>
Heart	Subendocardium of LV (yellow lines in A outline a subendocardial infarction)
Kidney	Straight segment of proximal tubule (medulla) Thick ascending limb (medulla)
Liver	Area around central vein (zone III)
Colon	Splenic flexure (Griffith point), <sup>a</sup> rectosigmoid junction (Sudeck point) <sup>a</sup>

<sup>a</sup>Watershed areas (border zones) receive blood supply from most distal branches of 2 arteries with limited collateral vascularity. These areas are susceptible to ischemia from hypoperfusion.

<sup>b</sup>Neurons most vulnerable to hypoxic-ischemic insults include Purkinje cells of the cerebellum and pyramidal cells of the hippocampus and neocortex (layers 3, 5, 6).

**Types of infarcts****Red infarct**

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

**Pale infarct**

Occurs in solid organs with a single (end-arterial) blood supply (eg, heart B, kidney).

**Free radical injury**

Free radicals damage cells via membrane lipid peroxidation, protein modification, DNA breakage. Initiated via radiation exposure (eg, cancer therapy), metabolism of drugs (phase I), redox reactions, nitric oxide (eg, inflammation), transition metals (eg, iron, copper; form free radicals via Fenton reaction), WBC (eg, neutrophils, macrophages) oxidative burst.

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

Examples:

- Oxygen toxicity: retinopathy of prematurity (abnormal vascularization), bronchopulmonary dysplasia, reperfusion injury after thrombolytic therapy
- Drug/chemical toxicity: acetaminophen overdose (hepatotoxicity), carbon tetrachloride (converted by cytochrome P-450 into  $\text{CCl}_3$  free radical → fatty liver [cell injury → ↓ apolipoprotein synthesis → fatty change], centrilobular necrosis)
- Metal storage diseases: hemochromatosis (iron) and Wilson disease (copper)

### Ionizing radiation toxicity

Ionizing radiation causes DNA (eg, double strand breaks) and cellular damage both directly and indirectly through the production of free radicals. Complications usually arise when patient is exposed to significant doses (eg, radiotherapy, nuclear reactor accidents):

- Localized inflammation and fibrosis
- Neoplasia (eg, leukemia, thyroid cancer)

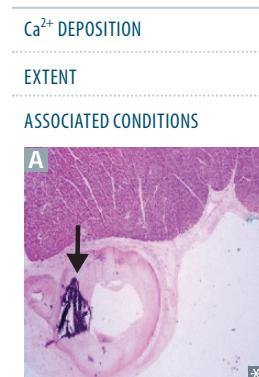
**Acute radiation syndrome**—develops after sudden whole-body exposure to high doses of ionizing radiation → nausea, vomiting, diarrhea, hair loss, erythema, cytopenias, headache, altered mental status.

Stem cells of rapidly regenerating tissues (eg, skin, bone marrow, GI tract, gonads) are the most susceptible to radiation injury. Radiotherapy damages cancer cells more than healthy cells because cancer cells have dysfunctional DNA repair mechanisms in addition to high replicative rates.

### Types of calcification

Calcium deposits appear deeply basophilic (arrow in A) on H&E stain.

#### Dystrophic calcification



In abnormal (diseased) tissues

#### EXTENT

Tends to be localized (eg, calcific aortic stenosis)

#### ASSOCIATED CONDITIONS

TB (lung and pericardium) and other granulomatous infections, liquefactive necrosis of chronic abscesses, fat necrosis, infarcts, thrombi, schistosomiasis, congenital CMV, toxoplasmosis, rubella, psammoma bodies, CREST syndrome, atherosclerotic plaques can become calcified

#### ETIOLOGY

2° to injury or necrosis

#### Metastatic calcification

In normal tissues

Widespread (ie, diffuse, metastatic)

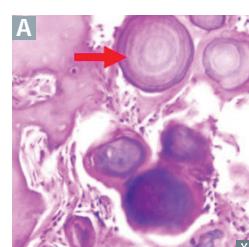
Predominantly in interstitial tissues of kidney, lung, and gastric mucosa (these tissues lose acid quickly; ↑ pH favors Ca<sup>2+</sup> deposition)

Nephrocalcinosis of collecting ducts may lead to nephrogenic diabetes insipidus and renal failure

2° to hyperphosphatemia (eg, chronic kidney disease) or hypercalcemia (eg, 1° hyperparathyroidism, sarcoidosis, hypervitaminosis D)

### Psammoma bodies

Concentrically laminated calcified spherules A.



Usually seen in certain types of tumors:

- Papillary thyroid carcinoma
- Meningioma
- Serous Ovarian carcinoma
- Mesothelioma
- Prolactinoma (Milk)

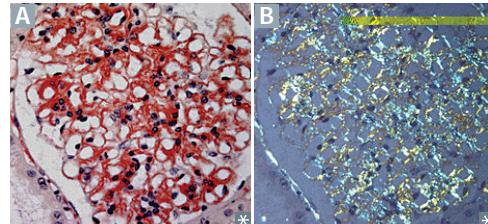
Please, **MOM**, don't forget the **Milk!**

**Amyloidosis**

Extracellular deposition of protein in abnormal fibrillar form ( $\beta$ -pleated sheet configuration) → cell injury and apoptosis. Manifestations vary depending on involved organ and include:

- Renal—nephrotic syndrome.
- Cardiac—restrictive cardiomyopathy.
- GI—hepatosplenomegaly.
- Neurologic—peripheral neuropathy.
- Musculoskeletal—muscle enlargement (eg, macroglossia), carpal tunnel syndrome.
- Skin—waxy thickening, easy bruising.

Amyloid deposits are visualized by Congo red stain (red/orange on nonpolarized light **A**, apple-green birefringence on polarized light **B**), and H&E stain (amorphous pink).



COMMON TYPES	FIBRIL PROTEIN	NOTES
<b>Systemic</b>		
<b>Primary amyloidosis</b>	AL (from Ig Light chains)	Seen in plasma cell dyscrasias (eg, multiple myeloma)
<b>Secondary amyloidosis</b>	AA (serum Amyloid A)	Seen in chronic inflammatory conditions, (eg, rheumatoid arthritis, IBD, familial Mediterranean fever, protracted infection)
<b>Transthyretin amyloidosis</b>	Transthyretin	Sporadic (wild-type TTR)—slowly progressive, associated with aging; mainly affects the heart Hereditary (mutated TTR)—familial amyloid polyneuropathy and/or cardiomyopathy
<b>Dialysis-related amyloidosis</b>	$\beta_2$ -microglobulin	Seen in patients with ESRD on long-term dialysis
<b>Localized</b>		
<b>Alzheimer disease</b>	$\beta$ -amyloid protein	Cleaved from amyloid precursor protein
<b>Isolated atrial amyloidosis</b>	ANP	Common, associated with aging; ↑ risk for atrial fibrillation
<b>Type 2 diabetes mellitus</b>	Islet amyloid polypeptide	Caused by deposition of amylin in pancreatic islets
<b>Medullary thyroid cancer</b>	Calcitonin	Secreted from tumor cells

## ► PATHOLOGY—INFLAMMATION

**Inflammation**

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

SIGN	MECHANISM
<b>Cardinal signs</b>	
<b>Rubor and calor</b>	Redness and warmth. Vasodilation (relaxation of arteriolar smooth muscle) → ↑ blood flow. Mediated by histamine, prostaglandins, bradykinin, NO.
<b>Tumor</b>	Swelling. Endothelial contraction/disruption (eg, from tissue damage) → ↑ vascular permeability → leakage of protein-rich fluid from postcapillary venules into interstitial space (exudate) → ↑ interstitial oncotic pressure. Endothelial contraction is mediated by leukotrienes (C <sub>4</sub> , D <sub>4</sub> , E <sub>4</sub> ), histamine, serotonin.
<b>Dolor</b>	Pain. Sensitization of sensory nerve endings. Mediated by bradykinin, PGE <sub>2</sub> , histamine.
<b>Functio laesa</b>	Loss of function. Inflammation impairs function (eg, inability to make fist due to hand cellulitis).
<b>Systemic manifestations (acute-phase reaction)</b>	
<b>Fever</b>	Pyrogens (eg, LPS) induce macrophages to release IL-1 and TNF → ↑ COX activity in perivascular cells of anterior hypothalamus → ↑ PGE <sub>2</sub> → ↑ temperature set point.
<b>Leukocytosis</b>	↑ WBC count; type of predominant cell depends on inciting agent or injury (eg, bacteria → ↑ neutrophils).
<b>↑ plasma acute-phase reactants</b>	Serum concentrations significantly change in response to acute and chronic inflammation. Produced by liver. Notably induced by IL-6.

**Acute phase reactants**

## POSITIVE (UPREGULATED)

<b>C-reactive protein</b>	Opsonin; fixes complement and facilitates phagocytosis. Measured clinically as a nonspecific sign of ongoing inflammation.
<b>Ferritin</b>	Binds and sequesters iron to inhibit microbial iron scavenging.
<b>Fibrinogen</b>	Coagulation factor; promotes endothelial repair; correlates with ESR.
<b>Haptoglobin</b>	Binds extracellular hemoglobin, protects against oxidative stress.
<b>Hepcidin</b>	↓ iron absorption (by degrading ferroportin) and ↓ iron release (from macrophages) → anemia of chronic disease.
<b>Procalcitonin</b>	Increases in bacterial infections; normal in viral infections.
<b>Serum amyloid A</b>	Prolonged elevation can lead to secondary amyloidosis.

## NEGATIVE (DOWNREGULATED)

<b>Albumin</b>	Reduction conserves amino acids for positive reactants.
<b>Transferrin</b>	Internalized by macrophages to sequester iron.
<b>Transthyretin</b>	Also called prealbumin. Reduction conserves amino acids for positive reactants.

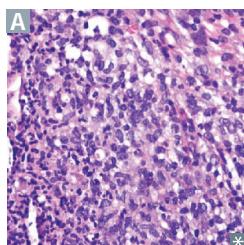
### Erythrocyte sedimentation rate

RBCs normally remain separated via  $\ominus$  charges. Products of inflammation (eg, fibrinogen) coat RBCs  $\rightarrow$   $\downarrow \ominus$  charge  $\rightarrow$   $\uparrow$  RBC aggregation. Denser RBC aggregates fall at a faster rate within a pipette tube  $\rightarrow$   $\uparrow$  ESR. Often co-tested with CRP (more specific marker of inflammation).

$\uparrow$ ESR	$\downarrow$ ESR <sup>a</sup>
Most anemias	Sickle cell anemia (altered shape)
Infections	Polycythemia ( $\uparrow$ RBCs “dilute” aggregation factors)
Inflammation (eg, giant cell [temporal] arteritis, polymyalgia rheumatica)	HF
Cancer (eg, metastases, multiple myeloma)	Microcytosis
Renal disease (end-stage or nephrotic syndrome)	Hypofibrinogenemia
Pregnancy	

<sup>a</sup>Lower than expected.

### Acute inflammation



Transient and early response to injury or infection. Characterized by neutrophils in tissue **A**, often with associated edema. Rapid onset (seconds to minutes) and short duration (minutes to days). Represents a reaction of the innate immune system (ie, less specific response than chronic inflammation).

#### STIMULI

Infections, trauma, necrosis, foreign bodies.

#### MEDIATORS

Toll-like receptors, arachidonic acid metabolites, neutrophils, eosinophils, antibodies (pre-existing), mast cells, basophils, complement, Hageman factor (factor XII).

**Inflammasome**—Cytoplasmic protein complex that recognizes products of dead cells, microbial products, and crystals (eg, uric acid crystals)  $\rightarrow$  activation of IL-1 and inflammatory response.

#### COMPONENTS

- Vascular: vasodilation ( $\rightarrow$   $\uparrow$  blood flow and stasis) and  $\uparrow$  endothelial permeability (contraction of endothelial cells opens interendothelial junctions)
- Cellular: extravasation of leukocytes (mainly neutrophils) from postcapillary venules  $\rightarrow$  accumulation of leukocytes in focus of injury  $\rightarrow$  leukocyte activation

To bring cells and proteins to site of injury or infection.

Leukocyte extravasation has 4 steps: margination and rolling, adhesion, transmigration, and migration (chemoattraction).

#### OUTCOMES

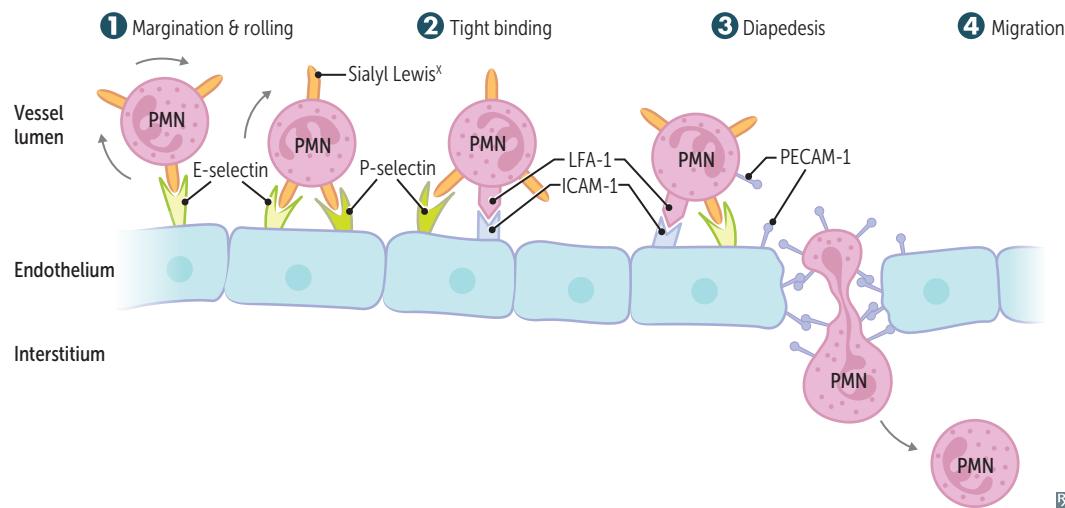
- Resolution and healing (IL-10, TGF- $\beta$ )
- Persistent acute inflammation (IL-8)
- Abscess (acute inflammation walled off by fibrosis)
- Chronic inflammation (antigen presentation by macrophages and other APCs  $\rightarrow$  activation of CD4+ Th cells)
- Scarring

Macrophages predominate in the late stages of acute inflammation (peak 2–3 days after onset) and influence outcome by secreting cytokines.

## Leukocyte extravasation

Extravasation predominantly occurs at postcapillary venules.

STEP	VASCULATURE/STROMA	LEUKOCYTE
❶ Margination and rolling—defective in leukocyte adhesion deficiency type 2 ( $\downarrow$ Sialyl Lewis <sup>X</sup> )	E-selectin (upregulated by TNF and IL-1) P-selectin (released from Weibel-Palade bodies) GlyCAM-1, CD34	Sialyl Lewis <sup>X</sup> Sialyl Lewis <sup>X</sup>
❷ Tight binding (adhesion)—defective in leukocyte adhesion deficiency type 1 ( $\downarrow$ CD18 integrin subunit)	ICAM-1 (CD54) VCAM-1 (CD106)	L-selectin CD11/18 integrins (LFA-1, Mac-1) VLA-4 integrin
❸ Diapedesis (transmigration)—WBC travels between endothelial cells and exits blood vessel	PECAM-1 (CD31)	PECAM-1 (CD31)
❹ Migration—WBC travels through interstitium to site of injury or infection guided by chemotactic signals	Chemotactic factors: C5a, IL-8, LTB <sub>4</sub> , 5-HETE, kallikrein, platelet-activating factor, N-formylmethionyl peptides	Various



<b>Chronic inflammation</b>	Prolonged inflammation characterized by mononuclear infiltration (macrophages, lymphocytes, plasma cells), which leads to simultaneous tissue destruction and repair (including angiogenesis and fibrosis). May be preceded by acute inflammation.
<b>STIMULI</b>	Persistent infections (eg, TB, <i>T. pallidum</i> , certain fungi and viruses) → type IV hypersensitivity, autoimmune diseases, prolonged exposure to toxic agents (eg, silica) and foreign material.
<b>MEDIATORS</b>	Macrophages are the dominant cells. Interaction of macrophages and T cells → chronic inflammation. <ul style="list-style-type: none"> <li>▪ Th1 cells secrete IFN-<math>\gamma</math> → macrophage classical activation (proinflammatory)</li> <li>▪ Th2 cells secrete IL-4 and IL-13 → macrophage alternative activation (repair and anti-inflammatory)</li> </ul>
<b>OUTCOMES</b>	Scarring, amyloidosis, and neoplastic transformation (eg, chronic HCV infection → chronic inflammation → hepatocellular carcinoma; <i>Helicobacter pylori</i> infection → chronic gastritis → gastric adenocarcinoma).

**Wound healing**

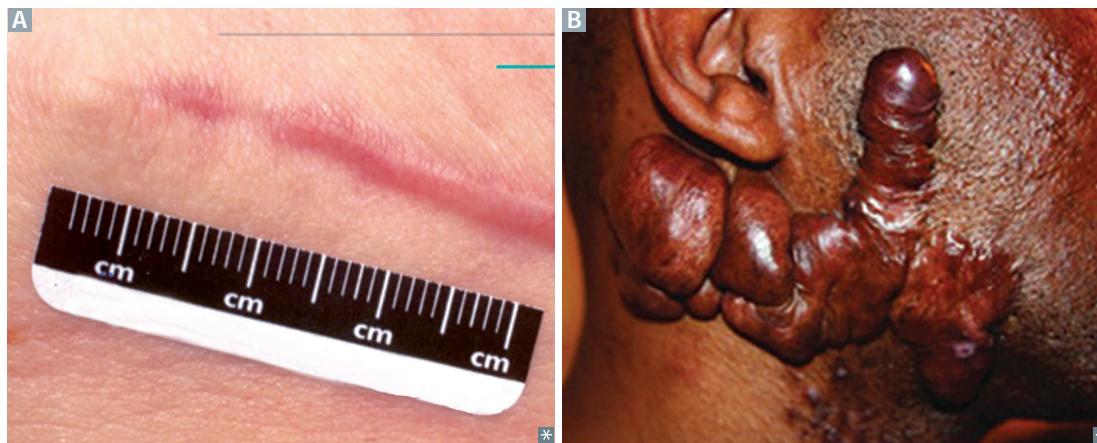
<b>Tissue mediators</b>		<b>MEDIATOR</b>	<b>ROLE</b>
		FGF	Stimulates angiogenesis
		TGF- $\beta$	Angiogenesis, fibrosis
		VEGF	Stimulates angiogenesis
		PDGF	Secreted by activated platelets and macrophages Induces vascular remodeling and smooth muscle cell migration Stimulates fibroblast growth for collagen synthesis
		Metalloproteinases	Tissue remodeling
		EGF	Stimulates cell growth via tyrosine kinases (eg, EGFR/ErbB1)
<b>PHASE OF WOUND HEALING</b>	<b>EFFECTOR CELLS</b>		<b>CHARACTERISTICS</b>
<b>Inflammatory (up to 3 days after wound)</b>	Platelets, neutrophils, macrophages		Clot formation, ↑ vessel permeability and neutrophil migration into tissue; macrophages clear debris 2 days later
<b>Proliferative (day 3–weeks after wound)</b>	Fibroblasts, myofibroblasts, endothelial cells, keratinocytes, macrophages		Deposition of granulation tissue and type III collagen, angiogenesis, epithelial cell proliferation, dissolution of clot, and wound contraction (mediated by myofibroblasts) Delayed second phase of wound healing in vitamin C and copper deficiency
<b>Remodeling (1 week–6+ months after wound)</b>	Fibroblasts		Type III collagen replaced by type I collagen, ↑ tensile strength of tissue Collagenases (require zinc to function) break down type III collagen Zinc deficiency → delayed wound healing



**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. Excess TGF- $\beta$  is associated with aberrant scarring, such as hypertrophic and keloid scars.

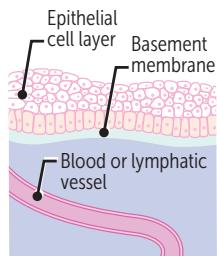
	<b>Hypertrophic scar [A]</b>	<b>Keloid scar [B]</b>
<b>COLLAGEN SYNTHESIS</b>	↑ (type III collagen)	↑↑↑ (types I and III collagen)
<b>COLLAGEN ORGANIZATION</b>	Parallel	Disorganized
<b>EXTENT OF SCAR</b>	Confined to borders of original wound	Extends beyond borders of original wound with “clawlike” projections typically on earlobes, face, upper extremities
<b>RECURRENCE</b>	Infrequent	Frequent
<b>PREDISPOSITION</b>	None	↑ incidence in people with darker skin



## ► PATHOLOGY—NEOPLASIA

**Neoplasia and neoplastic progression**

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



**Tumor nomenclature**

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

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

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

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

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

**Tumor grade vs stage****Grade**

Degree of cell differentiation (tissue of origin resemblance) and mitotic activity on histology.

Ranges from low-grade (well differentiated) to high-grade (poorly differentiated or undifferentiated [anaplastic]).

Higher grade often correlates with higher aggressiveness.



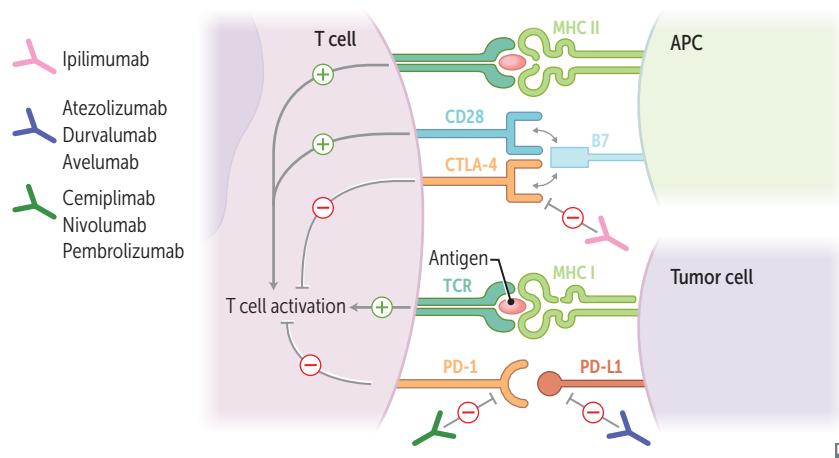
**Hallmarks of cancer** Cancer is caused by (mostly acquired) DNA mutations that affect fundamental cellular processes (eg, growth, DNA repair, survival).

HALLMARK	MECHANISM
<b>Growth signal self-sufficiency</b>	Mutations in genes encoding: <ul style="list-style-type: none"><li>▪ Proto-oncogenes → ↑ growth factors → autocrine loop (eg, ↑ PDGF in brain tumors)</li><li>▪ Growth factor receptors → constitutive signaling (eg, HER2 in breast cancer)</li><li>▪ Signaling molecules (eg, RAS)</li><li>▪ Transcription factors (eg, MYC)</li><li>▪ Cell cycle regulators (eg, cyclins, CDKs)</li></ul>
<b>Anti-growth signal insensitivity</b>	<ul style="list-style-type: none"><li>▪ Mutations in tumor suppressor genes (eg, Rb)</li><li>▪ Loss of E-cadherin function → loss of contact 0.6 1 xG05 Td [b (y)11 (t)428 (a)10.1 (t)-21.7 (i)11.2(e)-9.6 (s (</li></ul>

### Immune checkpoint interactions

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

- Interaction between PD-1 (on T cells) and PD-L1/2 (on tumor cells or immune cells in tumor microenvironment) → T-cell dysfunction (exhaustion). Inhibited by antibodies against PD-1 (eg, ipilimumab, nivolumab, pembrolizumab) 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 antibodies against CTLA-4 (eg, ipilimumab).



### Cancer epidemiology

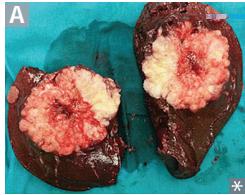
Skin cancer (basal > squamous >> melanoma) is the most common cancer (not included below).

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

**Common metastases**

Most **Carcinomas** spread via **Lymphatics**; most **Sarcomas** spread **Hematogenously (CLaSH)**. However, four **carcinomas route hematogenously**: **follicular thyroid carcinoma, choriocarcinoma, renal cell carcinoma, and hepatocellular carcinoma**. Metastasis to bone, liver, lung, and brain is more common than  $1^{\circ}$  malignancy in these organs. Metastases often appear as multiple lesions (vs  $1^{\circ}$  tumors which generally appear as solitary lesions).

SITE OF METASTASIS	$1^{\circ}$ TUMOR	NOTES
<b>Bone</b>	Prostate, breast >> lung > kidney, colon	Predilection for axial skeleton Bone metastasis can be: <ul style="list-style-type: none"> <li>▪ Blastic (eg, prostate, small cell lung cancer)</li> <li>▪ Mixed (eg, breast)</li> <li>▪ Lytic (eg, kidney, colon, non-small cell lung cancer)</li> </ul>
<b>Liver</b>	Colon > breast >> pancreas, lung, prostate	Scattered throughout liver parenchyma <b>A</b>
<b>Lung</b>	Colon, breast >> kidney, prostate	Typically involve both lungs
<b>Brain</b>	Lung > breast >> melanoma > colon, prostate	Usually seen at gray/white matter junction



**Oncogenes**

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

GENE	GENE PRODUCT	ASSOCIATED NEOPLASM
<b>ALK</b>	Receptor tyrosine kinase	Lung adenocarcinoma
<b>EGFR (ERBB1)</b>	Receptor tyrosine kinase	Lung adenocarcinoma
<b>HER2 (ERBB2)</b>	Receptor tyrosine kinase	Breast and gastric carcinomas
<b>RET</b>	REceptor Tyrosine kinase	MEN2A and 2B, medullary and papillary thyroid carcinoma, pheochromocytoma
<b>BCR-ABL</b>	Non-receptor tyrosine kinase	CML, ALL
<b>JAK2</b>	Non-receptor tyrosine kinase	Myeloproliferative neoplasms
<b>BRAF</b>	Serine/threonine kinase	Melanoma, non-Hodgkin lymphoma, colorectal carcinoma, papillary thyroid carcinoma, hairy cell leukemia
<b>c-KIT</b>	CytoKine receptor (CD117)	Gastrointestinal stromal tumor (GIST), mastocytosis
<b>MYCC (c-myc)</b>	Transcription factor	Burkitt lymphoma
<b>MYCN (N-myc)</b>	Transcription factor	Neuroblastoma
<b>KRAS</b>	RAS GTPase	Colorectal, lung, pancreatic cancers
<b>BCL-2</b>	Antiapoptotic molecule (inhibits apoptosis)	Follicular and diffuse large <b>B-Cell Lymphomas</b>

**Tumor suppressor genes**

Loss of function → ↑ cancer risk; both (**two**) alleles of a tumor suppressor gene must be lost for expression of disease (the Knudson 2-hit hypothesis).

GENE	GENE PRODUCT	ASSOCIATED CONDITION
<b>APC</b>	Negative regulator of β-catenin/WNT pathway	Colorectal cancer (associated with FAP)
<b>BRCA1/BRCA2</b>	BRCA1/BRCA2 proteins	BReast, ovarian, prostate, pancreatic CAncers
<b>CDKN2A</b>	p16, blocks G <sub>1</sub> → S phase	Many cancers (eg, melanoma, lung, pancreatic)
<b>DCC</b>	<b>DCC</b> —Deleted in Colorectal Cancer	Colorectal cancer
<b>SMAD4 (DPC4)</b>	<b>DPC</b> —Deleted in Pancreatic Cancer	Pancreatic cancer, colorectal cancer
<b>MEN1</b>	<b>MEN</b> in	Multiple Endocrine Neoplasia type 1
<b>NF1</b>	Neurofibromin (Ras GTPase activating protein)	NeuroFibromatosis type 1
<b>NF2</b>	Merlin (schwannomin) protein	NeuroFibromatosis type 2
<b>PTEN</b>	Negative regulator of PI3k/AKT pathway	Prostate, breast, and ENdometrial cancers
<b>RB1</b>	Inhibits E2F, blocks G <sub>1</sub> → S phase	Retinoblastoma, osteosarcoma (Bone cancer)
<b>TP53</b>	p53, activates p21, blocks G <sub>1</sub> → S phase	Most cancers, Li-Fraumeni ( <b>SBLA</b> ) syndrome (multiple malignancies at early age; Sarcoma, Breast/Brain, Lung/Leukemia, Adrenal gland)
<b>TSC1</b>	Hamartin protein	Tuberous sclerosis
<b>TSC2</b>	Tuberin (“2berin”)	Tuberous sclerosis
<b>VHL</b>	Inhibits hypoxia-inducible factor 1α	von Hippel-Lindau disease
<b>WT1</b>	Urogenital development transcription factor	Wilms Tumor (nephroblastoma)

**Carcinogens**

TOXIN	EXPOSURE	ORGAN	IMPACT
Aflatoxins ( <i>Aspergillus</i> )	Stored grains and nuts	Liver	Hepatocellular carcinoma
Alkylating agents	Oncologic chemotherapy	Blood	Leukemia/lymphoma
Aromatic amines (eg, benzidine, 2-naphthylamine)	Textile industry (dyes), tobacco smoke (2-naphthylamine)	Bladder	Transitional cell carcinoma
Arsenic	Herbicides (vineyard workers), metal smelting, wood preservation	Liver Lung Skin	Hepatic angiosarcoma Lung cancer Squamous cell carcinoma
Asbestos	Old roofing material, shipyard workers	Lung	Bronchogenic carcinoma > mesothelioma
Tobacco smoke		Bladder Cervix Esophagus  Kidney Larynx Lung  Oropharynx Pancreas	Transitional cell carcinoma Squamous cell carcinoma Squamous cell carcinoma/ adenocarcinoma  Renal cell carcinoma Squamous cell carcinoma Squamous cell and small cell carcinoma  Squamous cell carcinoma Pancreatic adenocarcinoma
Ethanol		Esophagus Liver Breast	Squamous cell carcinoma Hepatocellular carcinoma Breast cancer
Ionizing radiation		Blood Thyroid	Leukemia Papillary thyroid carcinoma
Nickel, chromium, beryllium, silica	Occupational exposure	Lung	Lung cancer
Nitrosamines	Smoked foods	Stomach	Gastric cancer (intestinal type)
Radon	Byproduct of uranium decay, accumulates in basements	Lung	Lung cancer (2nd leading cause after tobacco smoke)
Vinyl chloride	Used to make PVC pipes	Liver	Hepatic angiosarcoma

**Field cancerization**

Replacement of a large area of normal cells by premalignant cells due to widespread carcinogen exposure. Affected area is at ↑ risk of developing multiple independent 1° malignancies. Involved in head and neck cancer (mucosal exposure to tobacco smoke), skin cancer (skin exposure to UV light), bladder cancer (urothelial exposure to urinary carcinogens).

**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 ("Kaposi's") sarcoma
HPV (usually types 16, 18)	Cervical and penile/anal carcinoma, head and neck cancer
<i>H pylori</i>	Gastric adenocarcinoma and MALT lymphoma
HTLV-1	Adult T-cell Leukemia/Lymphoma
Liver fluke ( <i>Clonorchis sinensis</i> )	Cholangiocarcinoma
<i>Schistosoma haematobium</i>	Squamous cell bladder cancer

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

MARKER	IMPORTANT ASSOCIATIONS	NOTES
Alkaline phosphatase	Metastases to bone or liver, Paget disease of bone, seminoma (PLAP).	Exclude hepatic origin by checking LFTs and GGT levels.
$\alpha$ -fetoprotein	Hepatocellular carcinoma, endodermal sinus (yolk sac) tumor, mixed germ cell tumor, ataxia-telangiectasia, neural tube defects.	Normally made by fetus. Transiently elevated in pregnancy. High levels associated with neural tube and abdominal wall defects, low levels associated with Down syndrome.
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	Epithelial ovarian cancer.	
Calcitonin	Medullary thyroid carcinoma (alone and in MEN2A, MEN2B).	Calci <sup>2</sup> nin.
CEA	Colorectal and pancreatic cancers. Minor associations: gastric, breast, and medullary thyroid carcinomas.	Carcino <sup>E</sup> mbyronic 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. Also elevated in BPH and prostatitis. Questionable risk/benefit for screening. Marker for recurrence after treatment.

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

STAIN	TARGET	TUMORS IDENTIFIED
<b>Chromogranin and synaptophysin</b>	Neuroendocrine cells	Small cell carcinoma of the lung, carcinoid tumor, neuroblastoma
<b>Cytokeratin</b>	Epithelial cells	Epithelial tumors (eg, squamous cell carcinoma)
<b>Desmin</b>	Muscle	Muscle tumors (eg, rhabdomyosarcoma)
<b>GFAP</b>	NeuroGlia (eg, astrocytes, Schwann cells, oligodendrocytes)	Astrocytoma, Glioblastoma
<b>Neuro filament</b>	Neurons	Neuronal tumors (eg, neuroblastoma)
<b>PSA</b>	Prostatic epithelium	Prostate cancer
<b>PECAM-1/CD-31</b>	Endothelial cells	Vascular tumors (eg, angiosarcoma)
<b>S-100</b>	Neural crest cells	Melanoma, schwannoma, Langerhans cell histiocytosis
<b>TRAP</b>	Tartrate-resistant acid phosphatase	Hairy cell leukemia
<b>Vimentin</b>	Mesenchymal tissue (eg, fibroblasts, endothelial cells, macrophages)	Mesenchymal tumors (eg, sarcoma), but also many other tumors (eg, endometrial carcinoma, renal cell carcinoma, meningioma)

**P-glycoprotein** ATP-dependent efflux pump also called multidrug resistance protein 1 (MDR1). Expressed in some cancer cells to pump out toxins, including chemotherapeutic agents (one mechanism of ↓ responsiveness or resistance to chemotherapy over time).

**Cachexia** Weight loss, muscle atrophy, and fatigue that occur in chronic disease (eg, cancer, AIDS, heart failure, COPD). Mediated by TNF- $\alpha$ , IFN- $\gamma$ , IL-1, and IL-6.

**Paraneoplastic syndromes**

MANIFESTATION	DESCRIPTION/MECHANISM	MOST COMMONLY ASSOCIATED TUMOR(S)
<b>Musculoskeletal and cutaneous</b>		
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
<b>Endocrine</b>		
Hypercalcemia	PTHrP ↑ 1,25-(OH) <sub>2</sub> vitamin D <sub>3</sub> (calcitriol)	SCa <sup>2+</sup> mous cell carcinomas of lung, head, and neck; renal, bladder, breast, and ovarian carcinomas Lymphoma
Cushing syndrome	↑ ACTH	Small cell lung cancer
Hyponatremia (SIADH)	↑ ADH	
<b>Hematologic</b>		
Polycythemia	↑ Erythropoietin Paraneoplastic rise to High hematocrit levels	Pheochromocytoma, renal cell carcinoma, HCC, hemangioblastoma, leiomyoma
Pure red cell aplasia	Anemia with low reticulocytes	
Good syndrome	Hypogammaglobulinemia	Thymoma
Trousseau syndrome	Migratory superficial thrombophlebitis	
Nonbacterial thrombotic endocarditis	Deposition of sterile platelet thrombi on heart valves	Adenocarcinomas, especially pancreatic
<b>Neuromuscular</b>		
Anti-NMDA receptor encephalitis	Psychiatric disturbance, memory deficits, seizures, dyskineticias, 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	
Lambert-Eaton myasthenic syndrome	Antibodies against presynaptic (P/Q-type) Ca <sup>2+</sup> channels at NMJ	Small cell lung cancer
Myasthenia gravis	Antibodies against postsynaptic ACh receptors at NMJ	Thymoma

## ► PATHOLOGY—AGING

<b>Normal aging</b>	Time-dependent progressive decline in organ function resulting in ↑ susceptibility to disease. Associated with genetic (eg, telomere shortening), epigenetic (eg, DNA methylation), and metabolic (eg, mitochondrial dysfunction) alterations.
<b>Cardiovascular</b>	↓ arterial compliance (↑ stiffness), ↑ aortic diameter, ↓ left ventricular cavity size and sigmoid-shaped interventricular septum (due to myocardial hypertrophy), ↑ left atrial cavity size, aortic and mitral valve calcification, ↓ maximum heart rate.
<b>Gastrointestinal</b>	↓ LES tone, ↓ gastric mucosal protection, ↓ colonic motility.
<b>Hematopoietic</b>	↓ bone marrow mass, ↑ bone marrow fat; less vigorous response to stressors (eg, blood loss).
<b>Immune</b>	Predominant effect on adaptive immunity: ↓ naïve B cells and T cells, preserved memory B cells and T cells. Immunosenescence impairs response to new antigens (eg, pathogens, vaccines).
<b>Musculoskeletal</b>	↓ skeletal muscle mass (sarcopenia), ↓ bone mass (osteopenia), joint cartilage thinning.
<b>Nervous</b>	↓ brain volume (neuronal loss), ↓ cerebral blood flow; function is preserved despite mild cognitive decline.
<b>Special senses</b>	Impaired accommodation (presbyopia), ↓ hearing (presbycusis), ↓ smell and taste.
<b>Skin</b>	Atrophy with flattening of dermal-epidermal junction; ↓ dermal collagen and ↓ elastin (wrinkles, senile purpura), ↓ sweat glands (heat stroke), ↓ sebaceous glands (xerosis cutis). <ul style="list-style-type: none"> <li>■ Intrinsic aging (chronological aging)—↓ biosynthetic capacity of dermal fibroblasts.</li> <li>■ Extrinsic aging (photoaging)—degradation of dermal collagen and elastin from sun exposure (UVA); degradation products accumulate in dermis (solar elastosis).</li> </ul>
<b>Renal</b>	↓ GFR (↓ nephrons), ↓ RBF, ↓ hormonal function. Voiding dysfunction (eg, urinary incontinence).
<b>Reproductive</b>	Males—testicular atrophy (↓ spermatogenesis), prostate enlargement, slower erection/ejaculation, longer refractory period. Less pronounced ↓ in libido as compared to females. Females—vulvovaginal atrophy; vaginal shortening, thinning, dryness, ↑ pH.
<b>Respiratory</b>	↑ lung compliance (↓ elastic recoil), ↓ chest wall compliance (↑ stiffness), ↓ respiratory muscle strength; ↓ FEV <sub>1</sub> , ↓ FVC, ↑ RV (TLC is unchanged); ↑ A-a gradient, ↑ $\dot{V}/\dot{Q}$ mismatch. Ventilatory response to hypoxia/hypercapnia is blunted. Less vigorous cough, slower mucociliary clearance.

**Lipofuscin**

A yellow-brown, autofluorescent, “wear and tear” pigment **A** associated with normal aging. Composed of polymers of lipids and phospholipids complexed with protein. May be derived through lipid peroxidation of polyunsaturated lipids of subcellular membranes. Autopsy of older adult will reveal deposits in heart, colon, liver, kidney, eye, and other organs.

