Mechanisms and Morphology of Cellular Injury, Adaptation, and Death-1

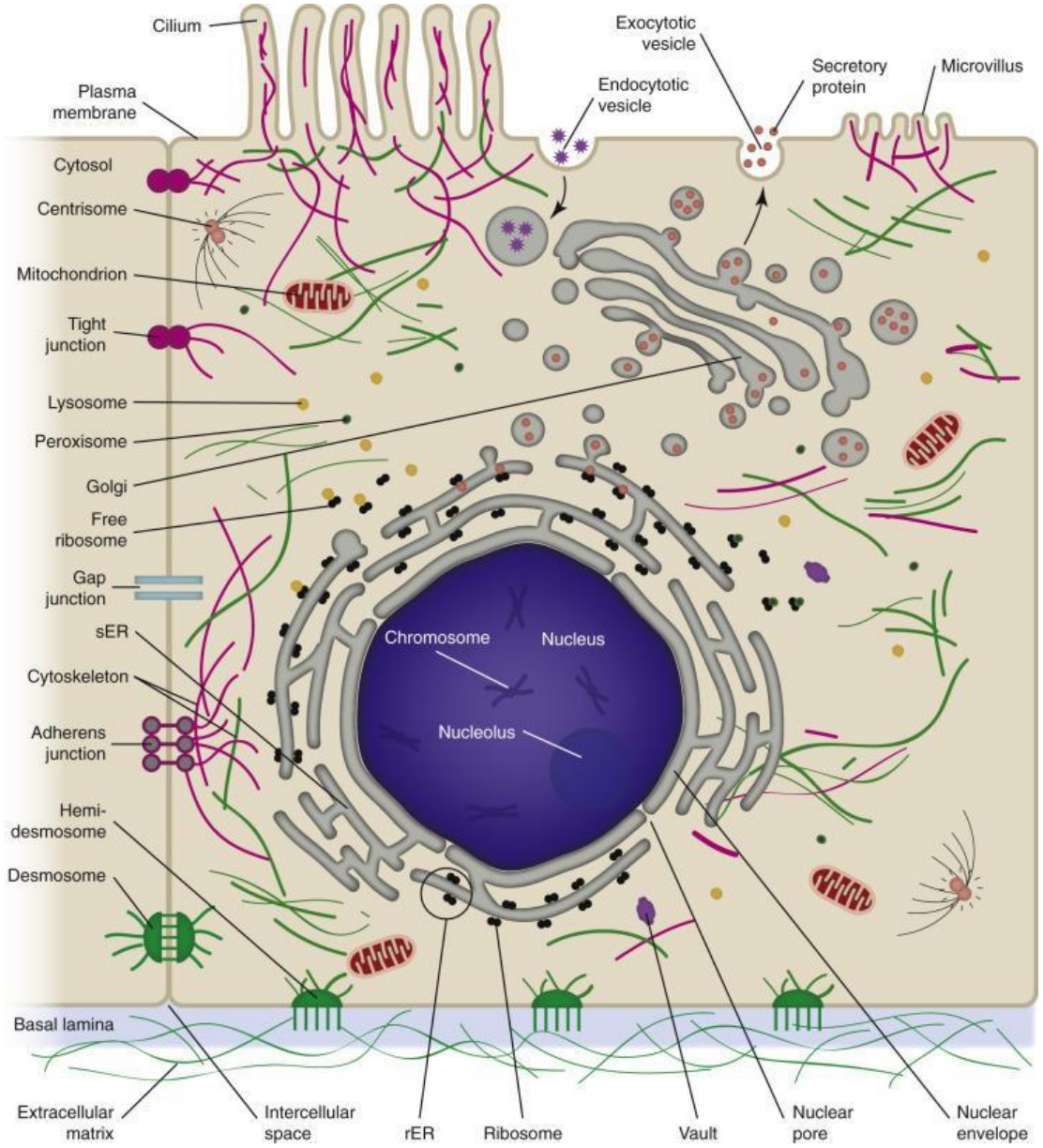
Su-Hyung Lee, DVM, PhD

The Normal Cell

The Normal Cells

Basic Features of the Normal Cell

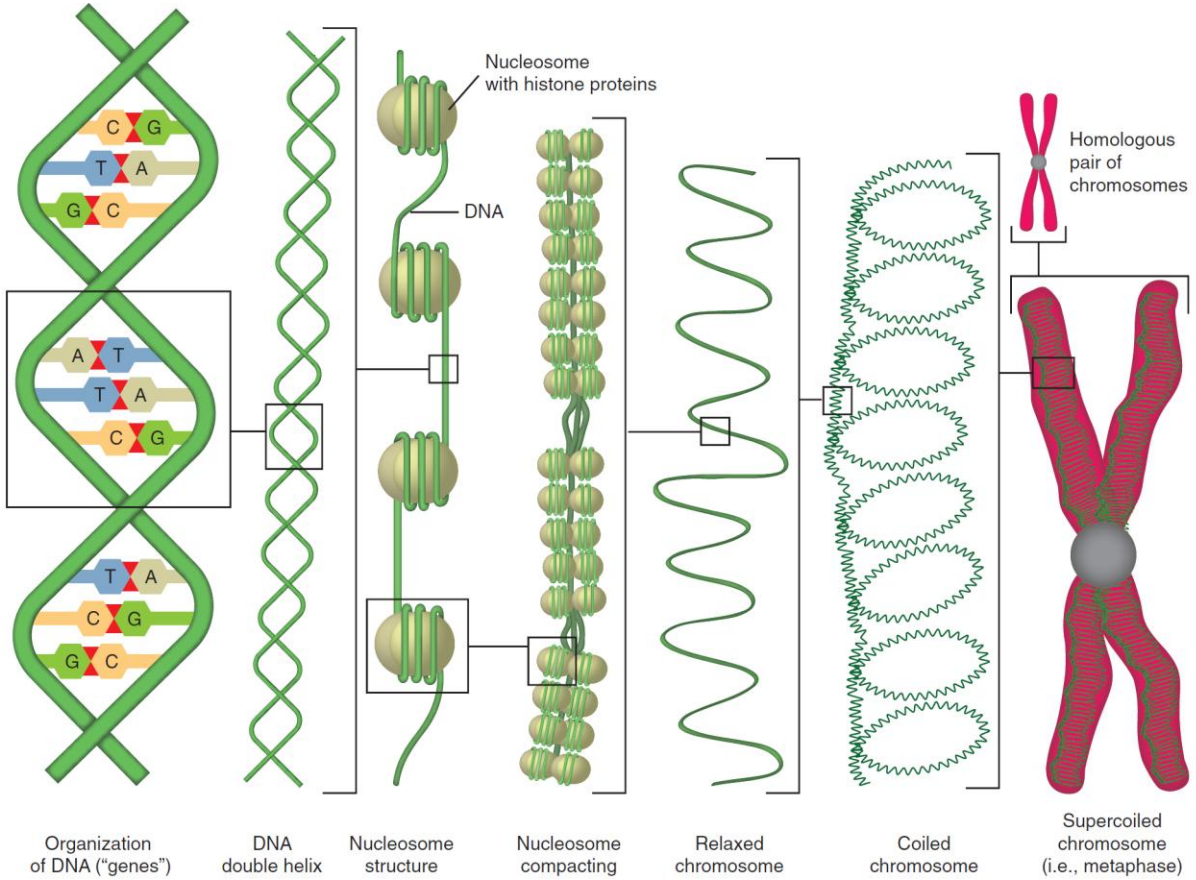
- The cell is the structural and functional unit of life.
- Homeostasis maintains a dynamic balance in response to stimuli.
- Key compartments: nucleus, cytoplasm, plasma membrane.
- Intracellular organelles support specialized functions.



The Normal Cells

Nucleus

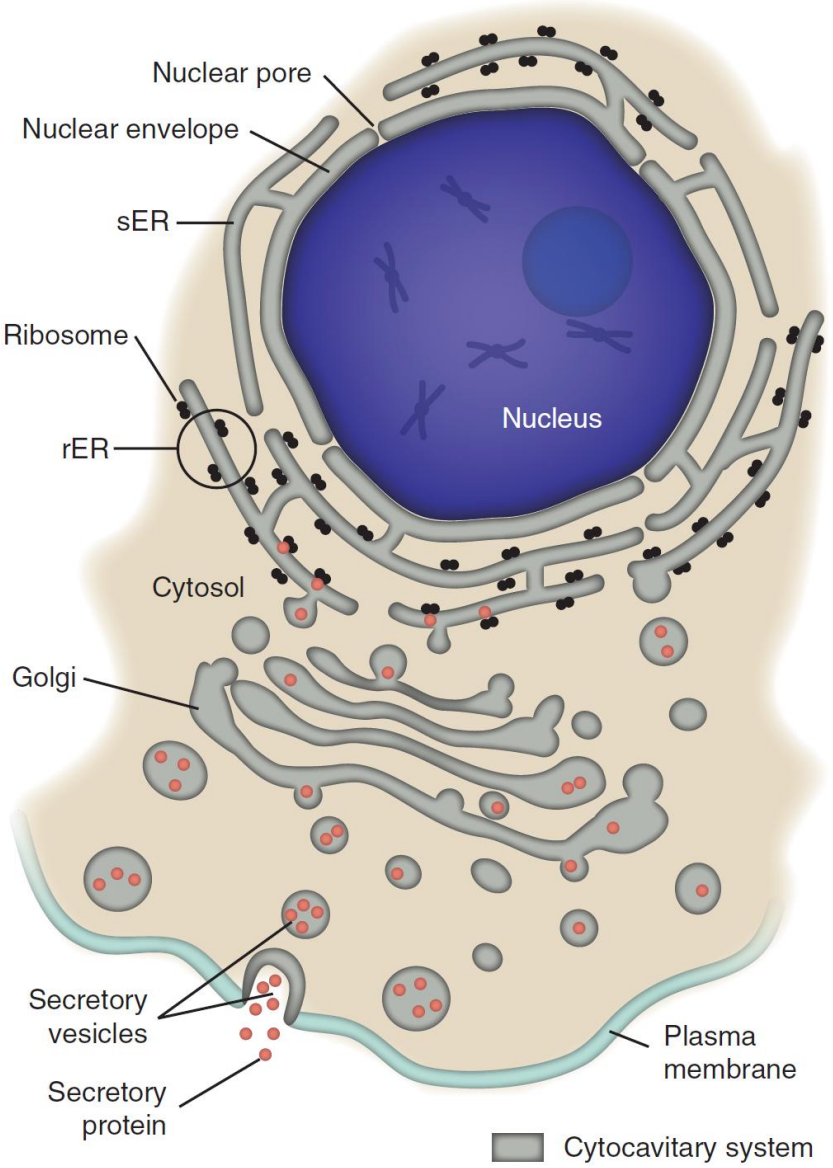
- ❖ Contains genetic material (DNA), packaged as chromatin, and a nucleolus for ribosome synthesis.
- ❖ Nuclear envelope (double membrane with pores) regulates exchange of RNA and proteins.
- ❖ Functions as the control center for transcription and cell-cycle regulation.
- ❖ Nuclear morphology provides clues about cell activity (e.g., euchromatin in active cells).
- ❖ Damage to nuclear components is a hallmark of irreversible cell injury.



The Normal Cells

Cytoplasm and Organelles

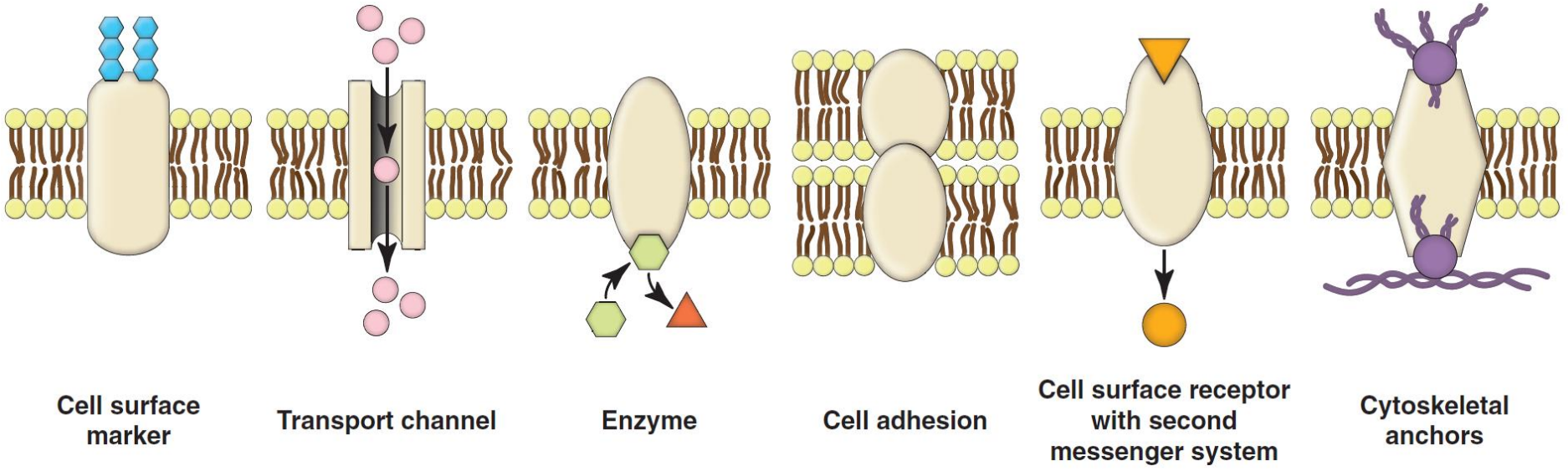
- Mitochondria: generate ATP through oxidative phosphorylation; also regulate apoptosis.
- Endoplasmic reticulum: rough ER synthesizes proteins, smooth ER handles lipids and detoxification.
- Golgi apparatus: modifies and packages proteins for secretion or membrane insertion.
- Lysosomes & peroxisomes: degrade cellular waste, foreign material, and neutralize toxins.
- Distribution and abundance of organelles reflect cell function (e.g., abundant RER in plasma cells).



The Normal Cells

Plasma Membrane

- ❖ A dynamic lipid bilayer embedded with proteins and glycoproteins.
- ❖ Maintains ionic gradients and regulates nutrient/waste transport.
- ❖ Contains receptors for hormones, cytokines, and growth factors → enables signaling.
- ❖ Membrane integrity is critical; disruption is often the point of no return in cell injury.
- ❖ Intercellular junctions (tight junctions, desmosomes) support adhesion and barrier function.



The Normal Cells

Cellular Homeostasis

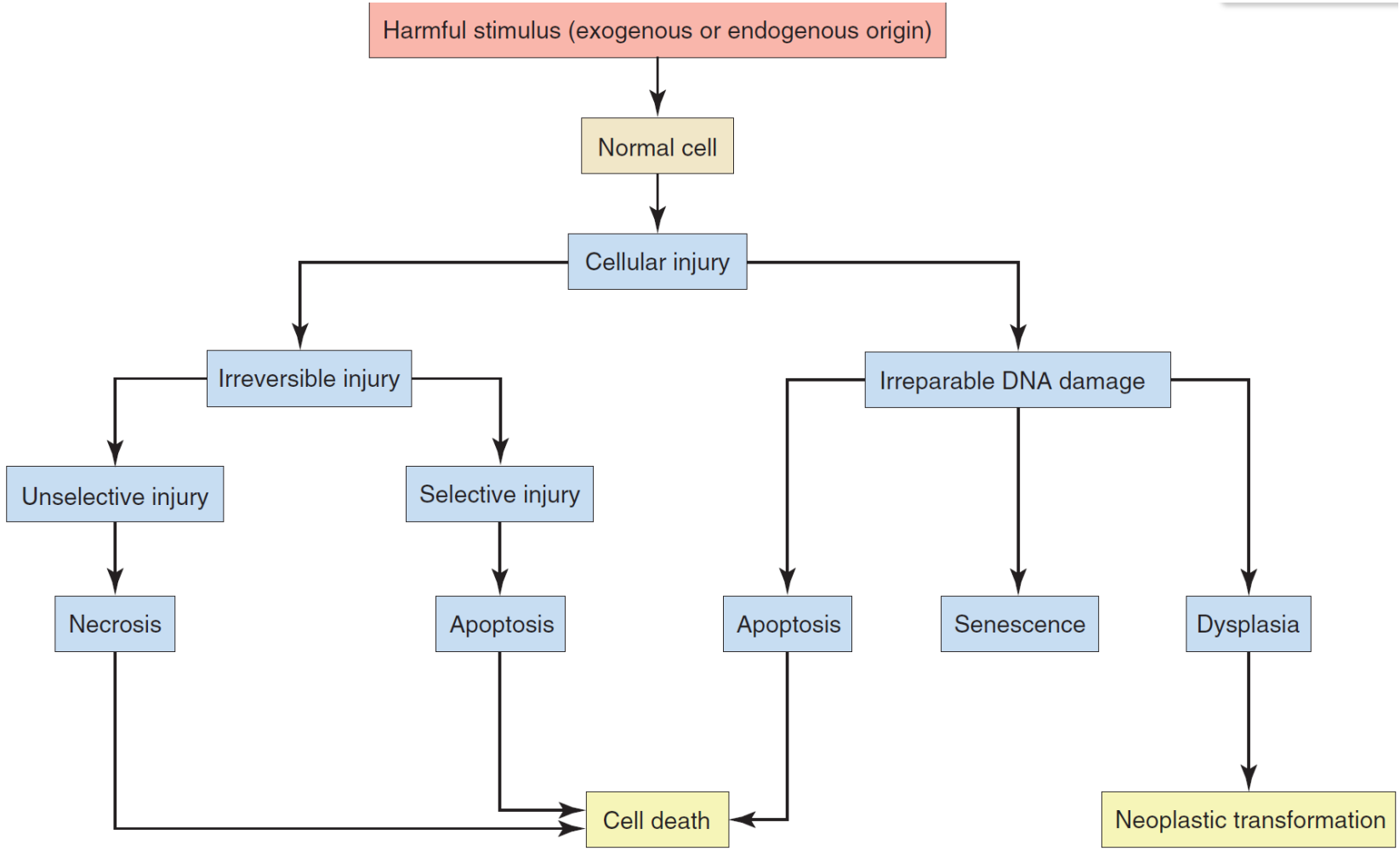
- ❖ Cells adapt through hypertrophy, hyperplasia, or metabolic shifts.
- ❖ Reversible adaptation allows survival under mild stress.
- ❖ Persistent stress overwhelms adaptation, leading to **injury**.
- ❖ Injury may be reversible or irreversible, depending on severity.
- ❖ Understanding normal balance is key to pathology.

Causes of Cell Injury

Causes of Cell Injury

Introduction to Cell Injury

- Injury arises when external or internal stress exceeds adaptive capacity.
- Determinants: type of injury, duration, intensity, and cell vulnerability.
- Outcomes: reversible injury, irreversible injury, or cell death.
- Mechanisms often converge on ATP depletion and membrane damage.



Causes of Cell Injury

Oxygen Deprivation

- Hypoxia: decreased oxygen availability (respiratory, anemia, CO toxicity).
- Ischemia: reduced blood supply, most common cause of hypoxia.
- Consequences: ATP depletion, ion pump failure, anaerobic glycolysis.
- Brain, heart, kidney are especially vulnerable.

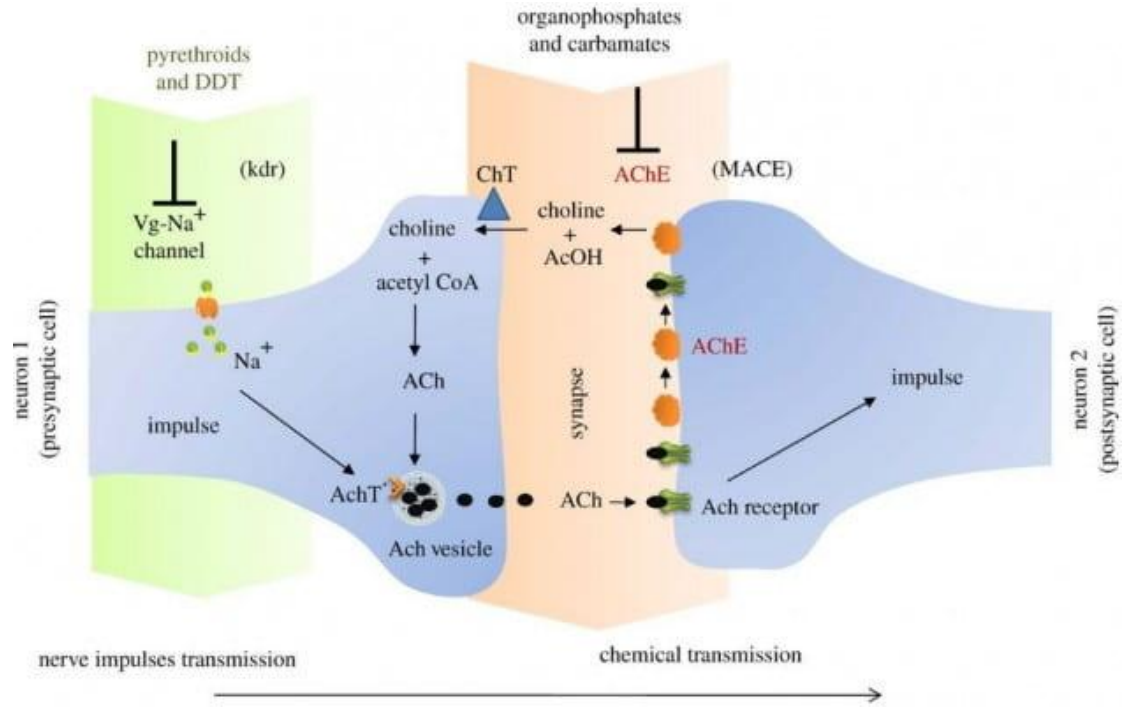
Infectious and Immune Causes

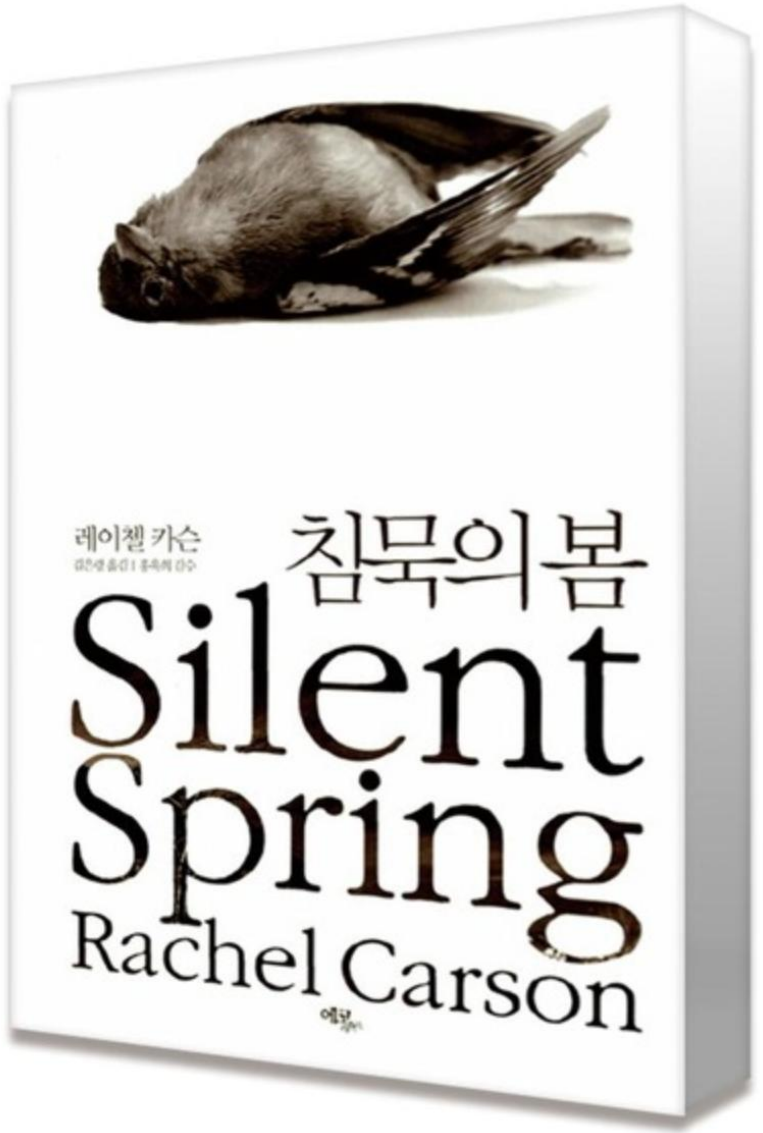
- Pathogens: viruses, bacteria, fungi, parasites.
- Injury may result from direct cytopathic effect or immune response.
- Immunologic injury: hypersensitivity, autoimmune diseases.
- Inflammation often amplifies tissue damage.

Causes of Cell Injury

Physical and Chemical Agents

- ❖ Trauma, temperature extremes, radiation, pressure.
- ❖ Toxins: heavy metals, drugs, pesticides, alcohol.
- ❖ Mechanisms: protein denaturation, membrane disruption, DNA damage.

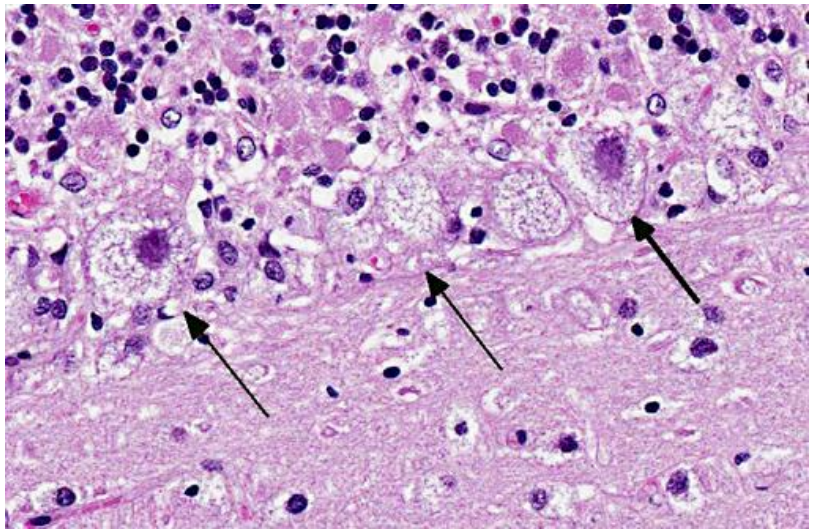




Causes of Cell Injury

Nutritional and Genetic Factors

- Malnutrition (protein, vitamin deficiencies) impairs cell metabolism.
- Overnutrition and obesity predispose to metabolic disease.
- Genetic defects alter enzymes, receptors, structural proteins.
- Example: lysosomal storage diseases, sickle cell anemia.



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Reversible Cell Injury

Reversible Cell Injury

General Concepts

- ❖ Early stage of injury; stress removal allows recovery.
- ❖ Cells maintain membrane integrity and nuclear viability.
- ❖ Energy metabolism is impaired but not destroyed.

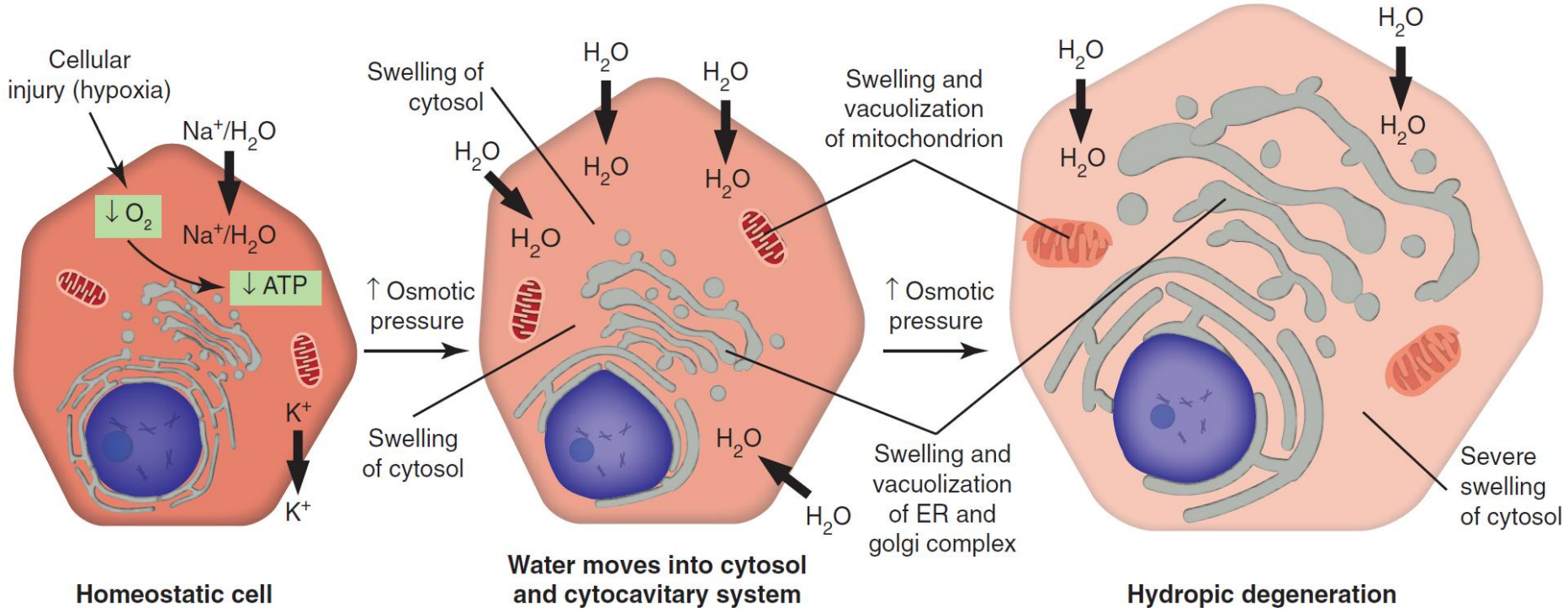
Morphologic Features

- ❖ Acute cell swelling (hydropic change) = hallmark.
- ❖ Plasma membrane blebs, loss of microvilli.
- ❖ Swollen mitochondria, dilated ER, ribosome detachment.
- ❖ Cytoplasmic vacuolization may be seen.

Reversible Cell Injury

Pathogenesis

- ATP depletion → Na^+/K^+ pump failure.
- Sodium and water influx → cytoplasmic and organelle swelling.
- Loss of ionic gradients drives further dysfunction.



Reversible Cell Injury

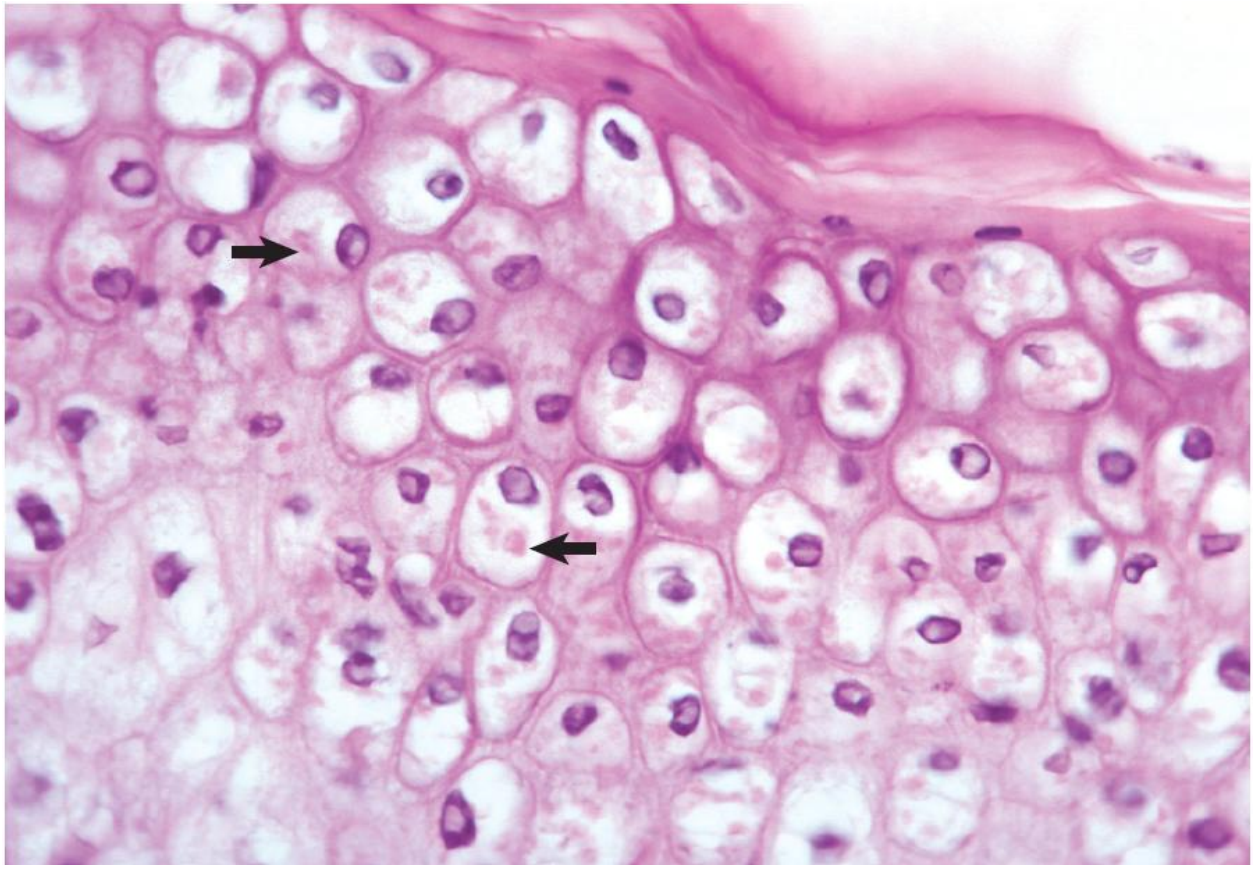
Biochemical Features

- ❖ Decreased oxidative phosphorylation and ATP.
- ❖ Reduced protein and enzyme synthesis.
- ❖ Switch to anaerobic glycolysis → lactic acidosis.
- ❖ Impaired ion homeostasis.

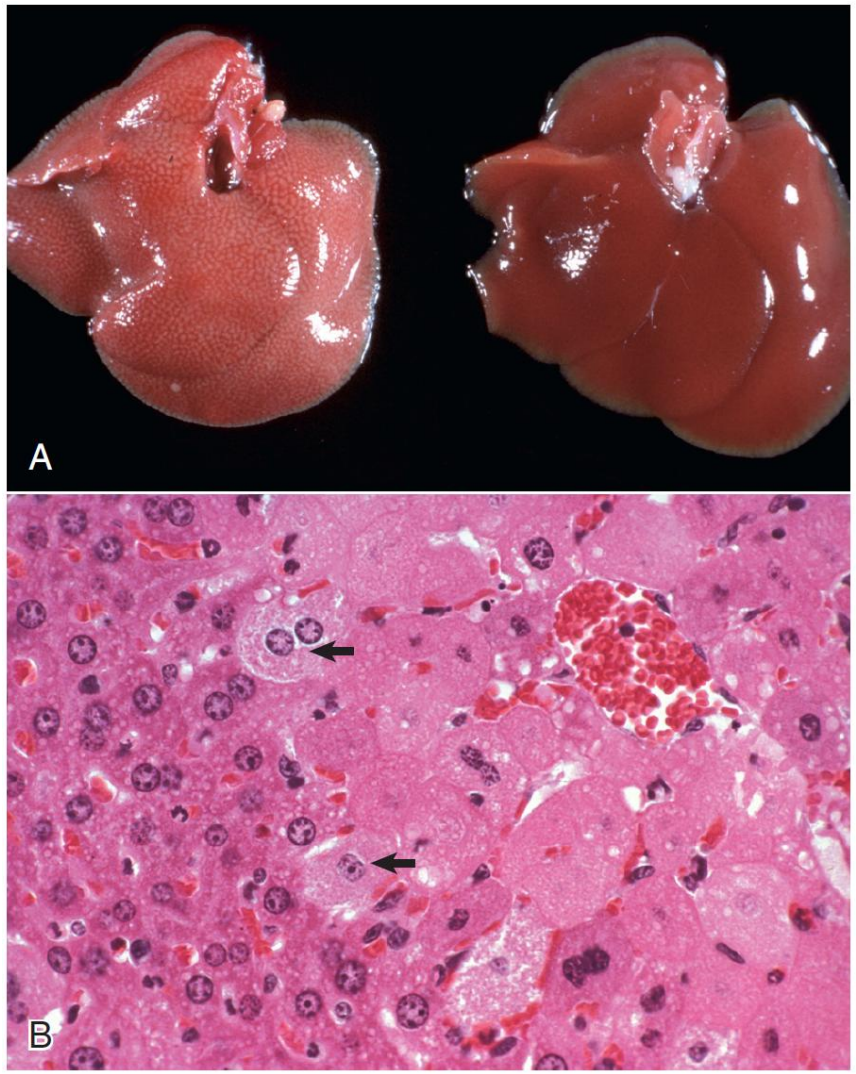
Functional Consequences

- ❖ Loss of ionic gradients → Na^{+}, Ca^{2+} influx, K^{+} efflux.
- ❖ Reduced contractility in muscle, impaired secretion in glands.
- ❖ Transient disturbances, not permanent.

Reversible Cell Injury



Ballooning degeneration in popular stomatitis,
Poxvirus infection

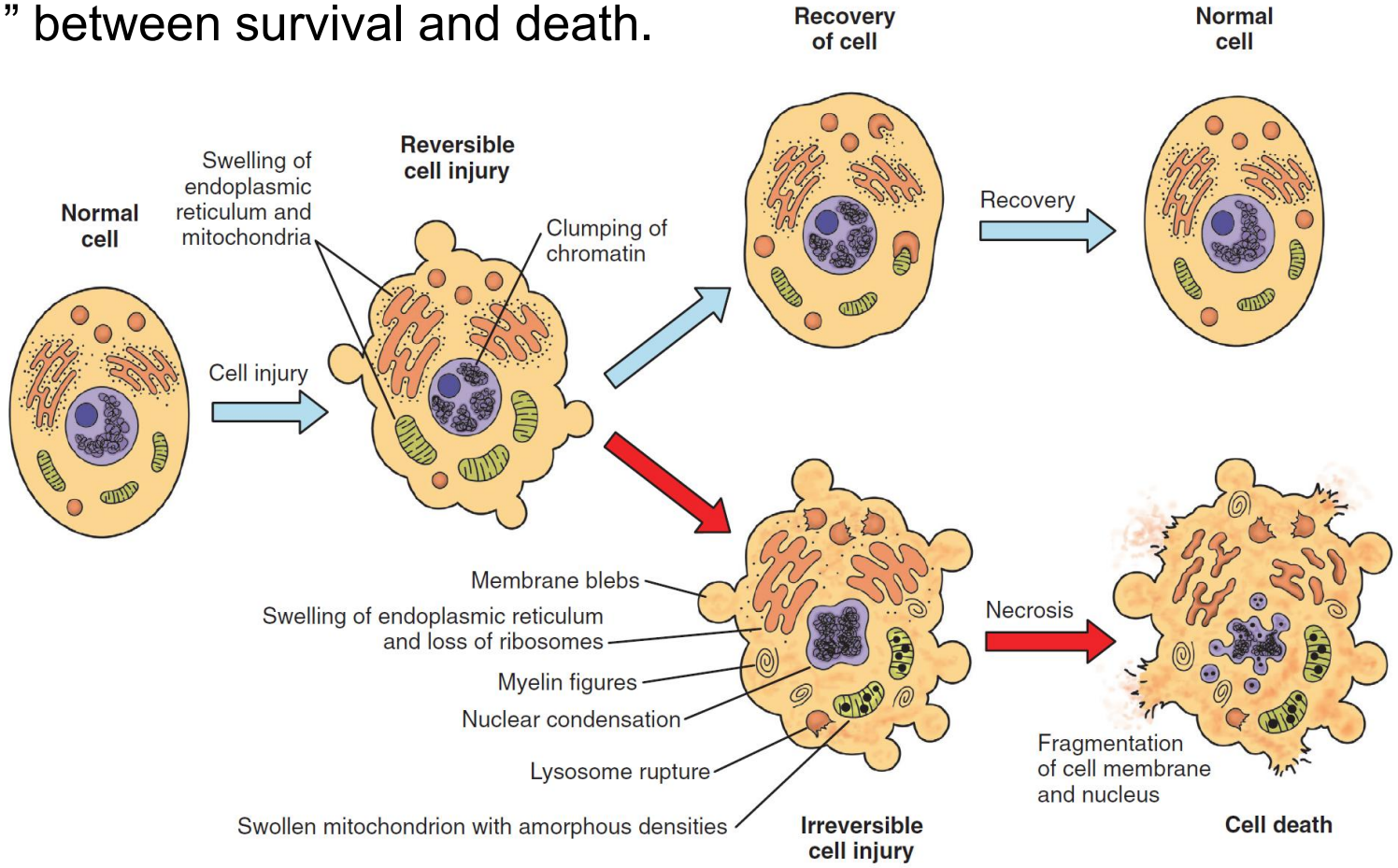


CCl4-treated mouse livers

Reversible Cell Injury

Recovery Potential

- ❖ Removal of stress → full structural and functional recovery.
- ❖ Prolonged injury → transition to irreversible damage.
- ❖ Represents “point of decision” between survival and death.



Cell Death by Oncosis

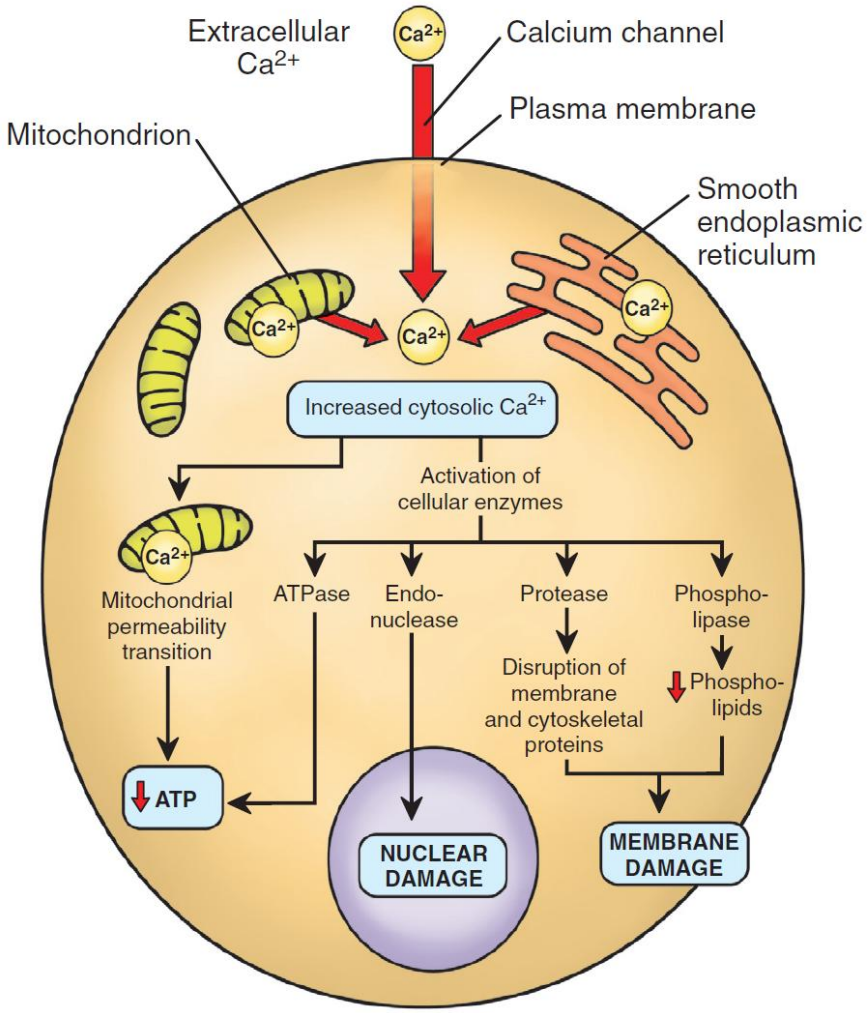
Cell Death by Oncosis (Oncotic Necrosis)

Definition and Contrast

- Oncosis = necrotic cell death with swelling ("onco" = swelling).
- Distinguished from apoptosis (programmed cell death).
- Typically results from ischemia, toxins, or severe infections.

Pathogenesis

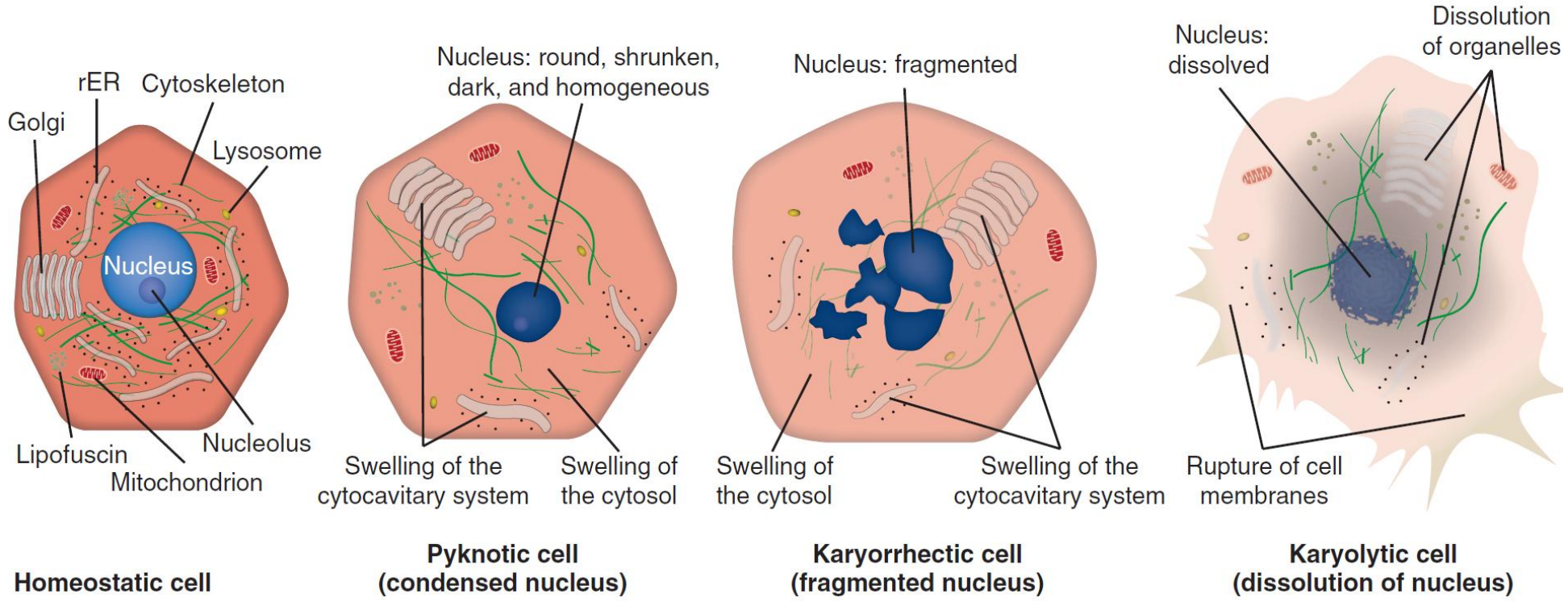
- Severe ATP depletion → irreversible pump failure.
- Na^+ and water influx → massive swelling, organelle rupture.
- Membrane integrity lost, cell contents leak.



Cell Death by Oncosis (Oncotic Necrosis)

Morphologic Features

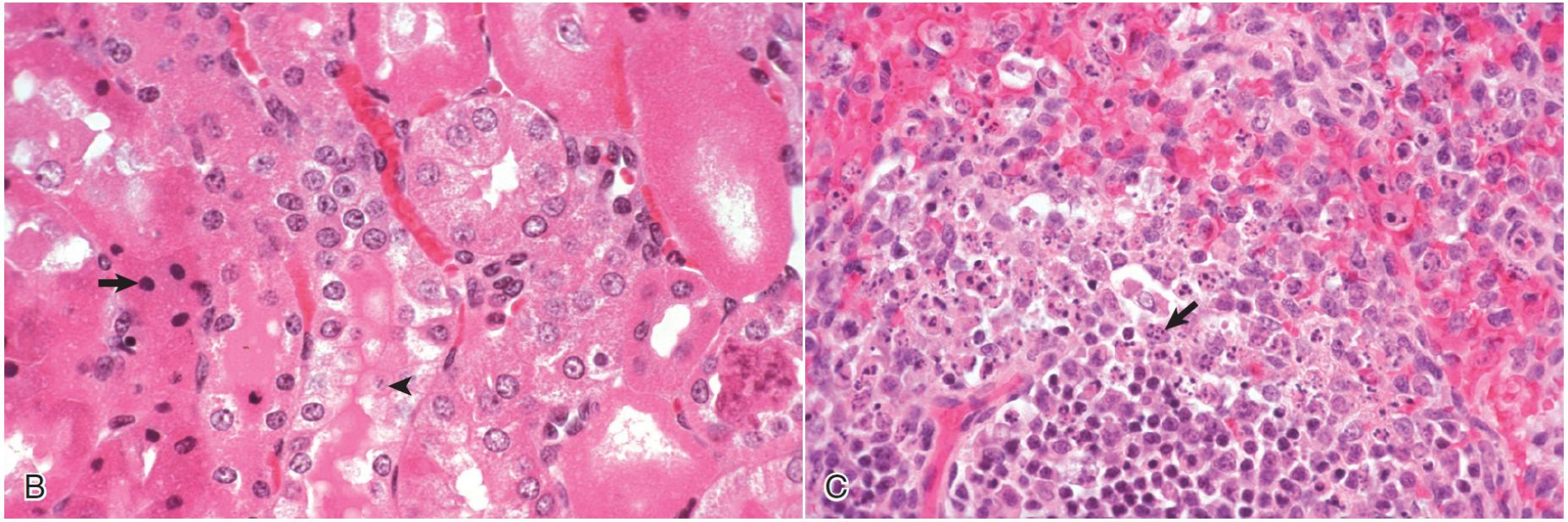
- Cytoplasmic: increased eosinophilia, loss of detail.
- Nuclear: pyknosis (shrinkage), karyorrhexis (fragmentation), karyolysis (fading).
- Cells appear ghost-like, eventually lysed.



Cell Death by Oncosis (Oncotic Necrosis)

Tissue-Level Changes

- ❖ Gross: pallor, friability, tissue softening.
- ❖ Histology: disrupted architecture, inflammatory cell infiltration.
- ❖ Often coexists with vascular congestion and edema.



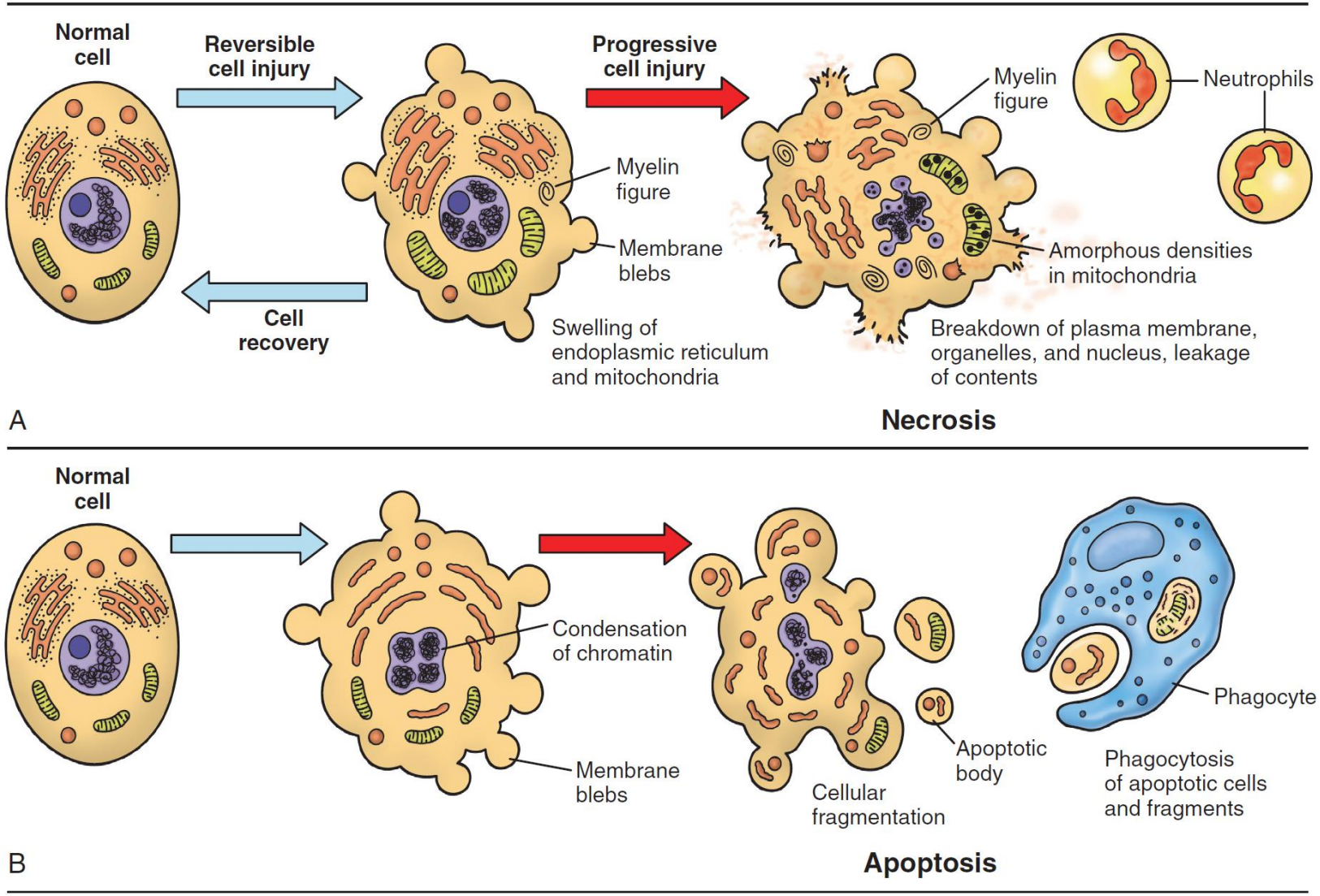
Kidney

Spleen

Cell Death by Oncosis (Oncotic Necrosis)

Biological Consequences

- Strongly pro-inflammatory due to release of DAMPs (damage signals).
- Always pathologic, unlike apoptosis which can be physiologic.
- Represents irreversible cell injury with functional tissue loss.

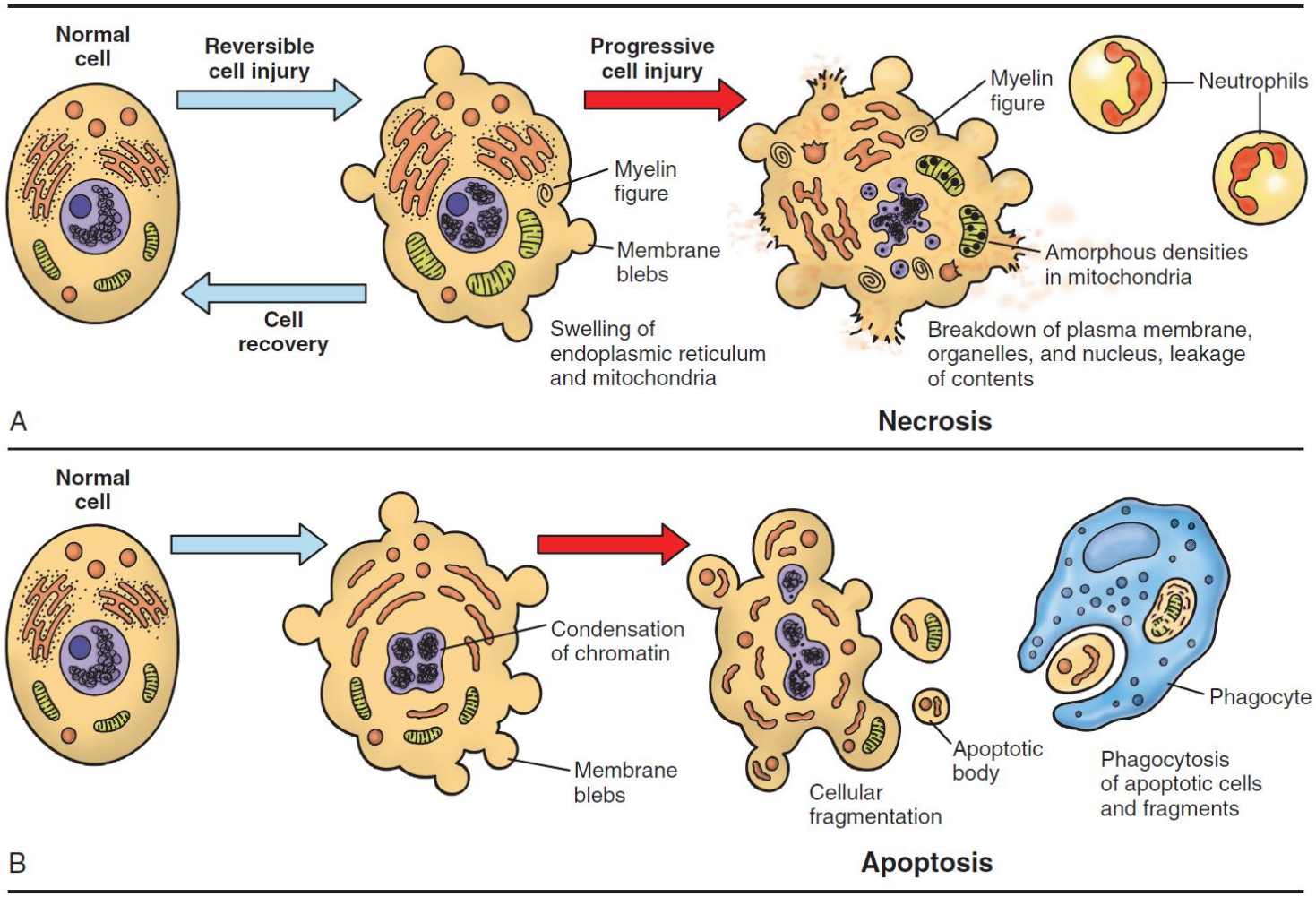


Apoptosis

Apoptosis (Programmed Cell Death)

Definition & Significance

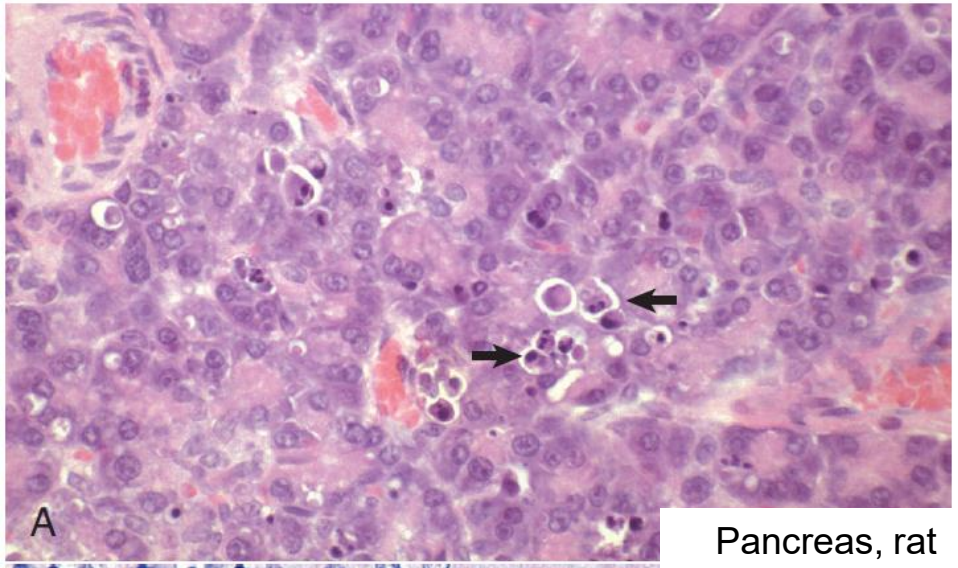
- ❖ Programmed cell death, genetically controlled and energy-dependent.
- ❖ Removes unwanted or damaged cells without inflammation.
- ❖ Essential in embryogenesis, immune regulation, and tissue homeostasis.
- ❖ Dysregulation → cancer, autoimmunity, or degenerative disease.



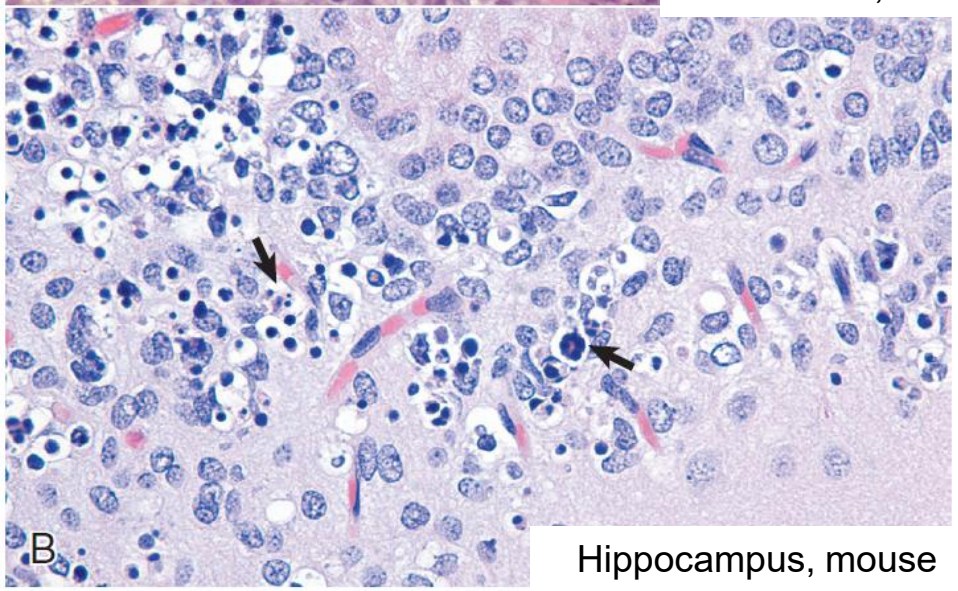
Apoptosis (Programmed Cell Death)

Morphologic Features

- Cell shrinkage and cytoplasmic eosinophilia.
- Chromatin condensation (pyknosis) and nuclear fragmentation (karyorrhexis).
- Membrane blebbing, formation of apoptotic bodies.
- Phagocytosis by macrophages or neighboring cells; no inflammatory response.



Pancreas, rat

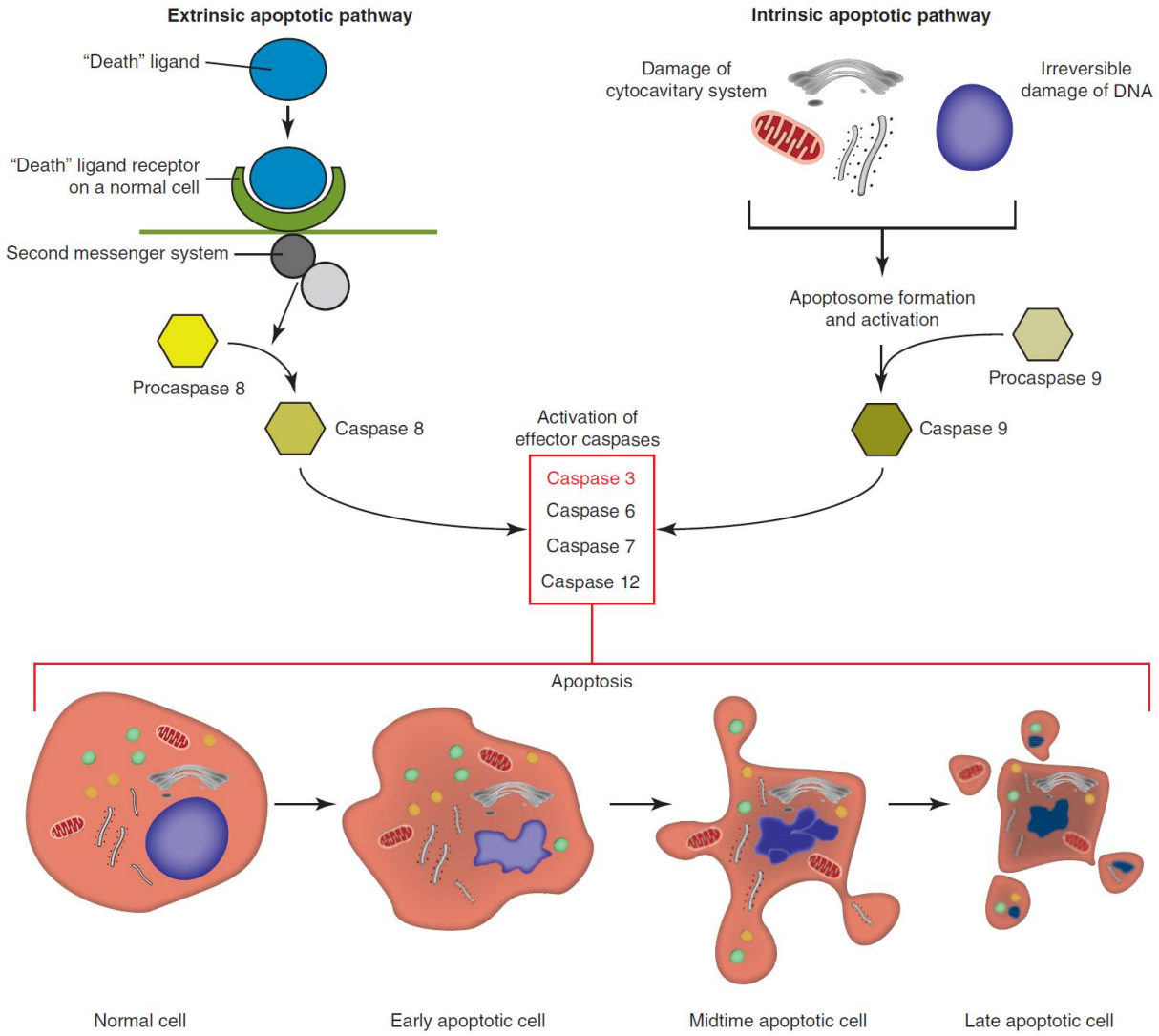


Hippocampus, mouse

Apoptosis (Programmed Cell Death)

Molecular Pathways

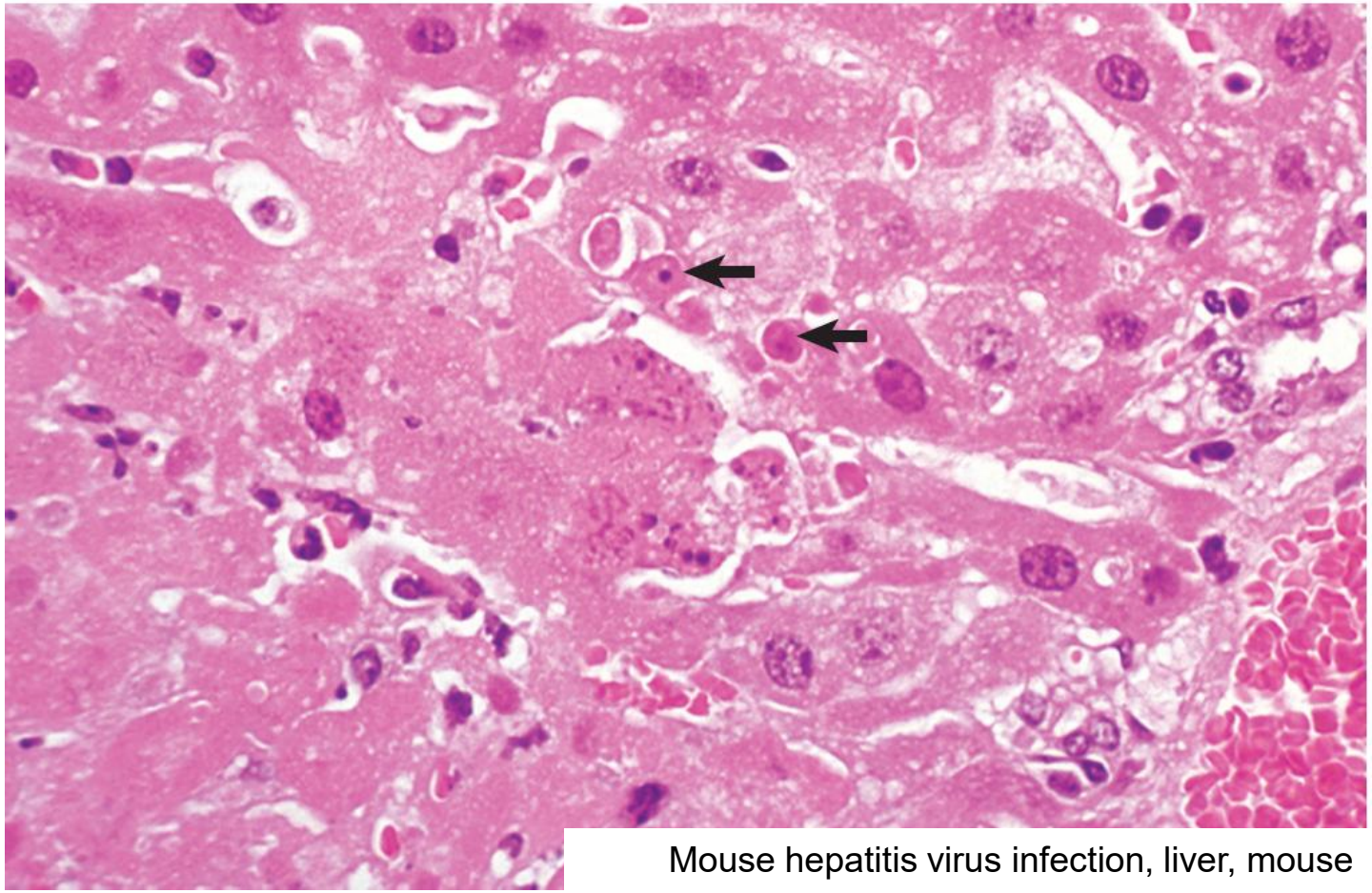
- Intrinsic (mitochondrial) pathway: Bcl-2 family, cytochrome c release.
- Extrinsic (death receptor) pathway: Fas/FasL, TNF receptor.
- Both converge on caspase activation (initiator → executioner caspases).
- Caspase-3 → DNA fragmentation, protein degradation, cytoskeletal breakdown.



Apoptosis (Programmed Cell Death)

Physiologic vs Pathologic Roles

- Physiologic: embryonic digit separation, thymic involution, endometrial shedding, immune cell deletion.
- Pathologic: DNA damage (radiation, hypoxia), viral infections, misfolded proteins.
- Acts as a defense mechanism against neoplasia and persistent infection.



Mouse hepatitis virus infection, liver, mouse

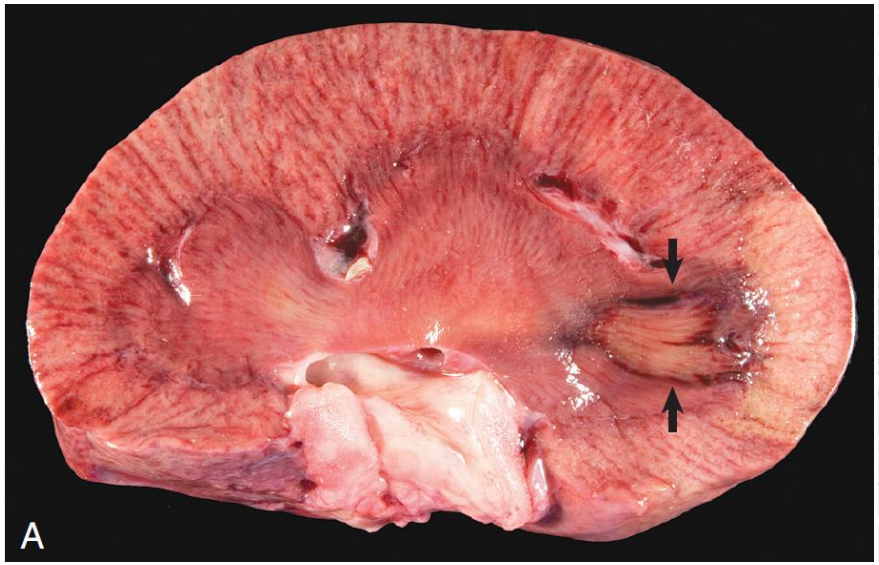
Patterns of Necrosis

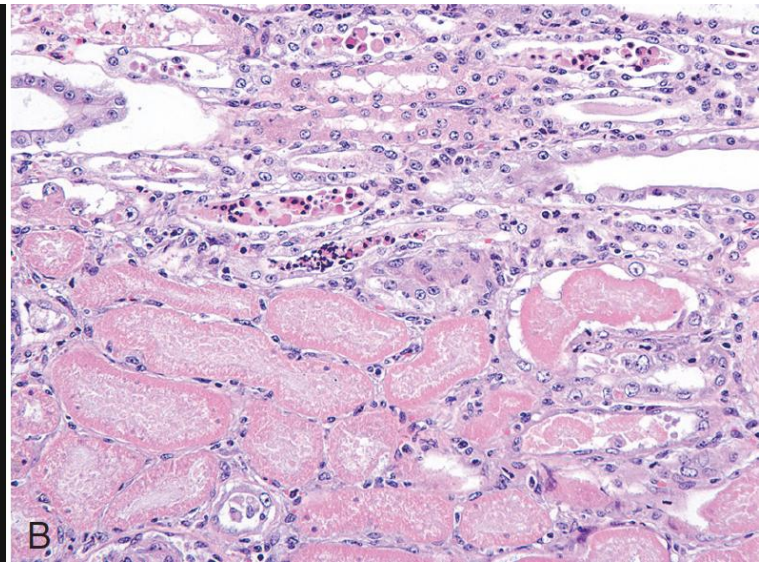
Patterns of Necrosis

Coagulative Necrosis

- ❖ Most common pattern of necrosis; usually due to ischemia/hypoxia.
- ❖ Protein denaturation > enzymatic digestion → cell outlines preserved.
- ❖ Gross: firm, pale, wedge-shaped infarcts in solid organs.
- ❖ Microscopy: eosinophilic “ghost cells” with nuclear pyknosis, karyorrhexis, karyolysis.
- ❖ Examples: infarcts in kidney, heart, spleen.



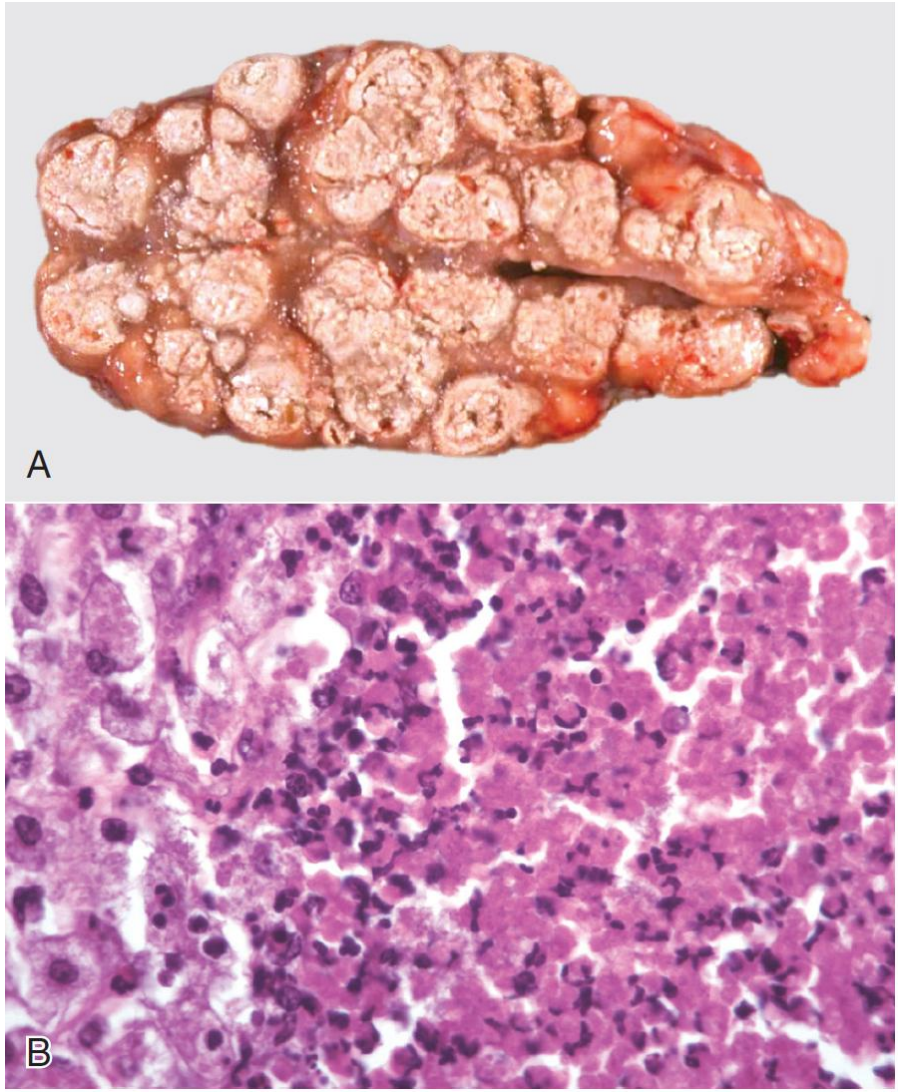




Patterns of Necrosis

Caseous Necrosis

- Often caused by granulomatous inflammation (e.g., Mycobacterium, some fungi).
- Gross: soft, friable, “cheese-like” necrotic material.
- Microscopy: amorphous, granular debris, loss of tissue architecture.
- Surrounded by macrophages, epithelioid cells, and giant cells (granuloma).
- Examples: tuberculous lymphadenitis, fungal infections.

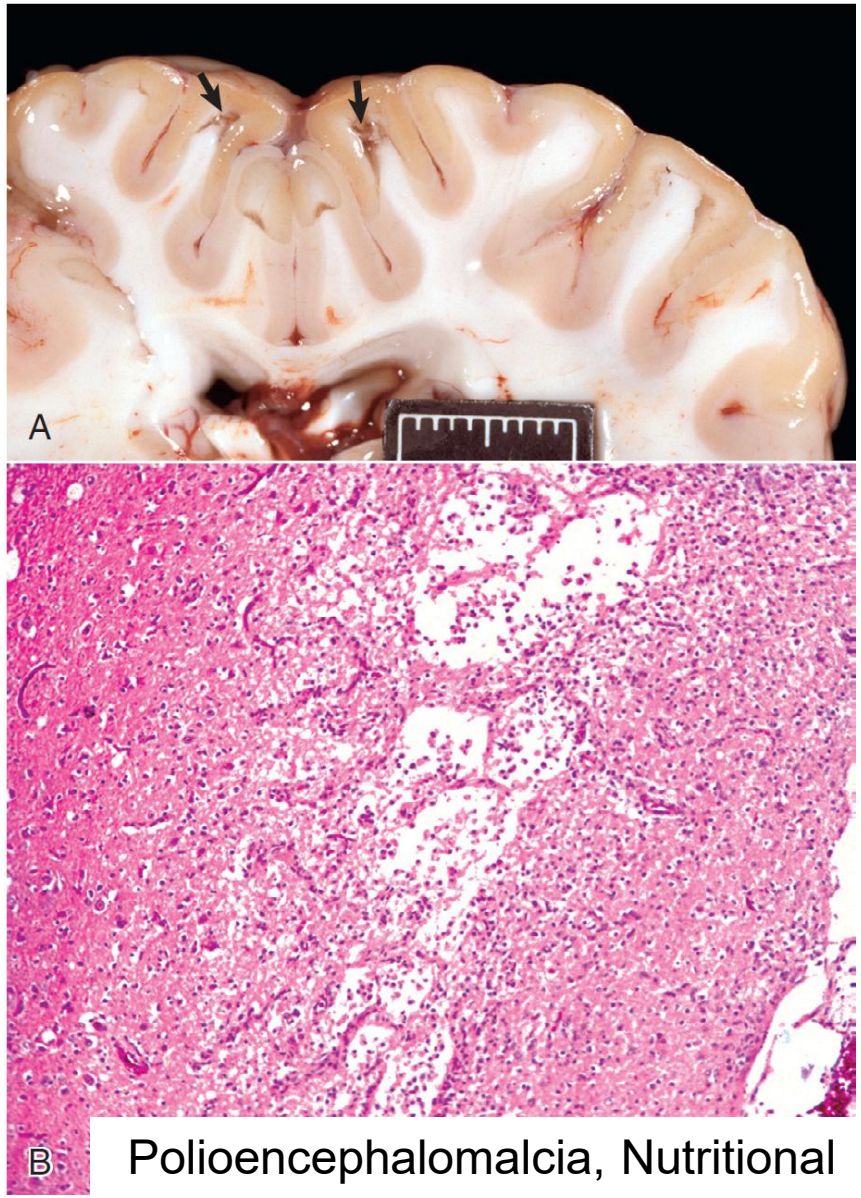


Tuberculosis, Lymph node

Patterns of Necrosis

Liquefactive Necrosis

- Enzymatic digestion predominates over protein denaturation.
- Tissue transformed into a soft, liquid, viscous mass.
- Typical in CNS infarction (due to high lipid content, little stroma).
- Seen in bacterial/fungal abscesses → pus formation.
- Microscopy: loss of architecture, numerous neutrophils and cell debris.

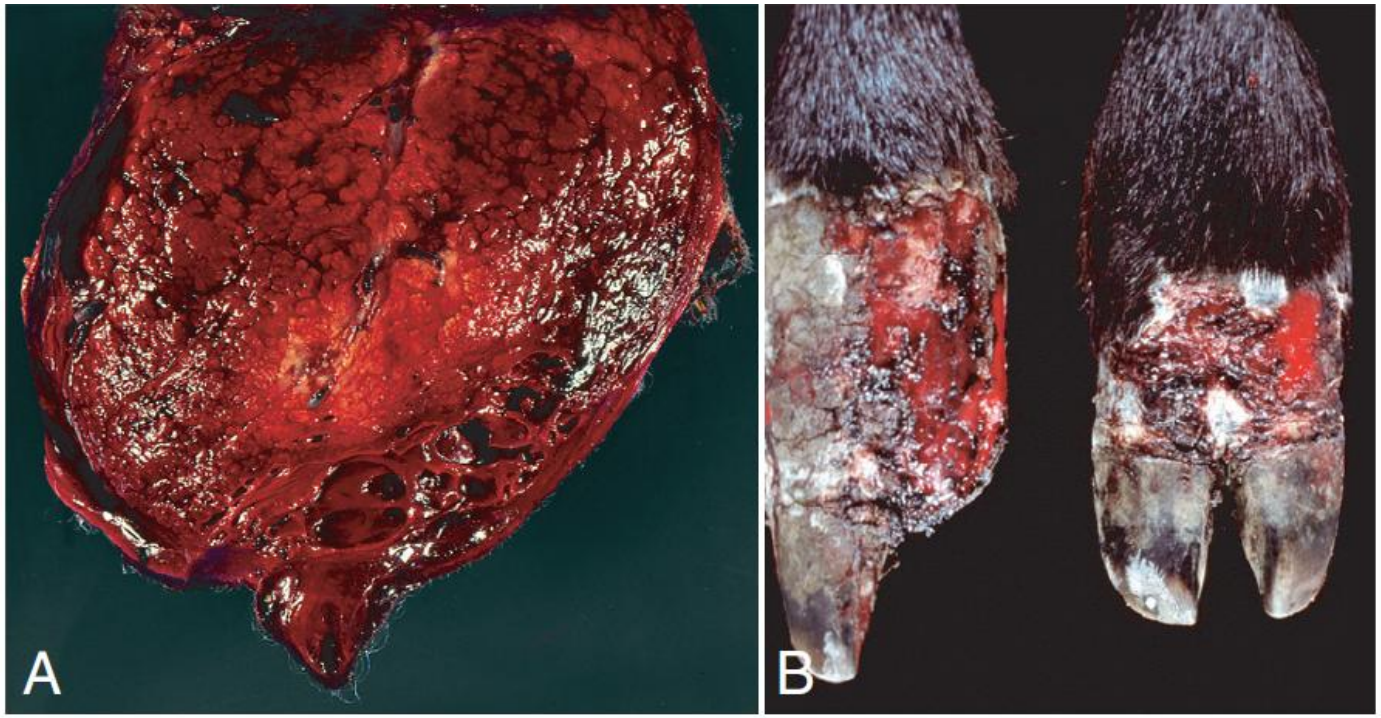


Polioencephalomalcia, Nutritional

Patterns of Necrosis

Gangrenous Necrosis

- ❖ A clinical term, not a distinct histologic pattern.
- ❖ Dry gangrene: ischemic coagulative necrosis of extremities (limbs, tails, ears).
- ❖ Wet gangrene: superimposed bacterial infection → liquefaction.
- ❖ Gross: black, shriveled (dry) vs swollen, foul-smelling (wet).
- ❖ Example: limb ischemia, frostbite, severe intestinal torsion.



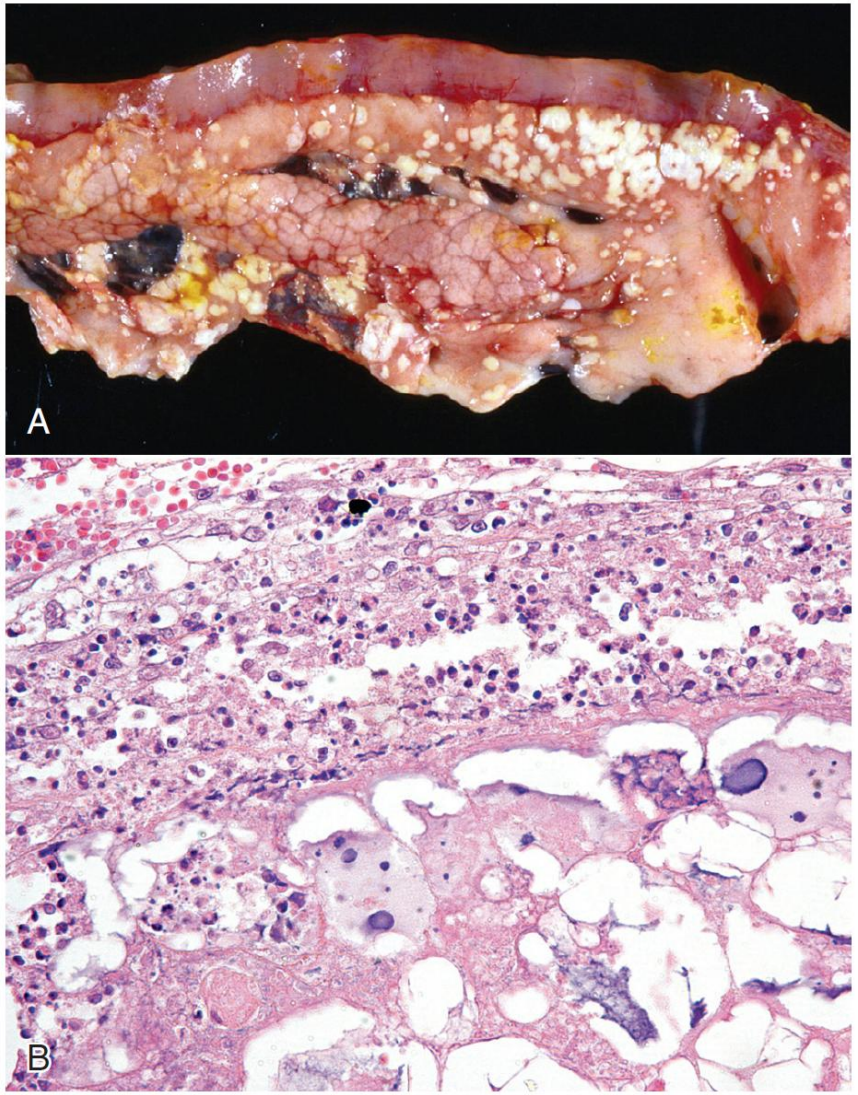
Mastitis, Wet form

Ergot alkaloids, Dry form

Patterns of Necrosis

Fat Necrosis

- Caused by lipase activity on triglycerides in adipose tissue.
- Free fatty acids + calcium → soap formation (saponification).
- Gross: chalky-white, firm deposits within fat.
- Common in acute pancreatitis or trauma to fat tissue.
- Microscopy: necrotic adipocytes with basophilic calcium deposits.

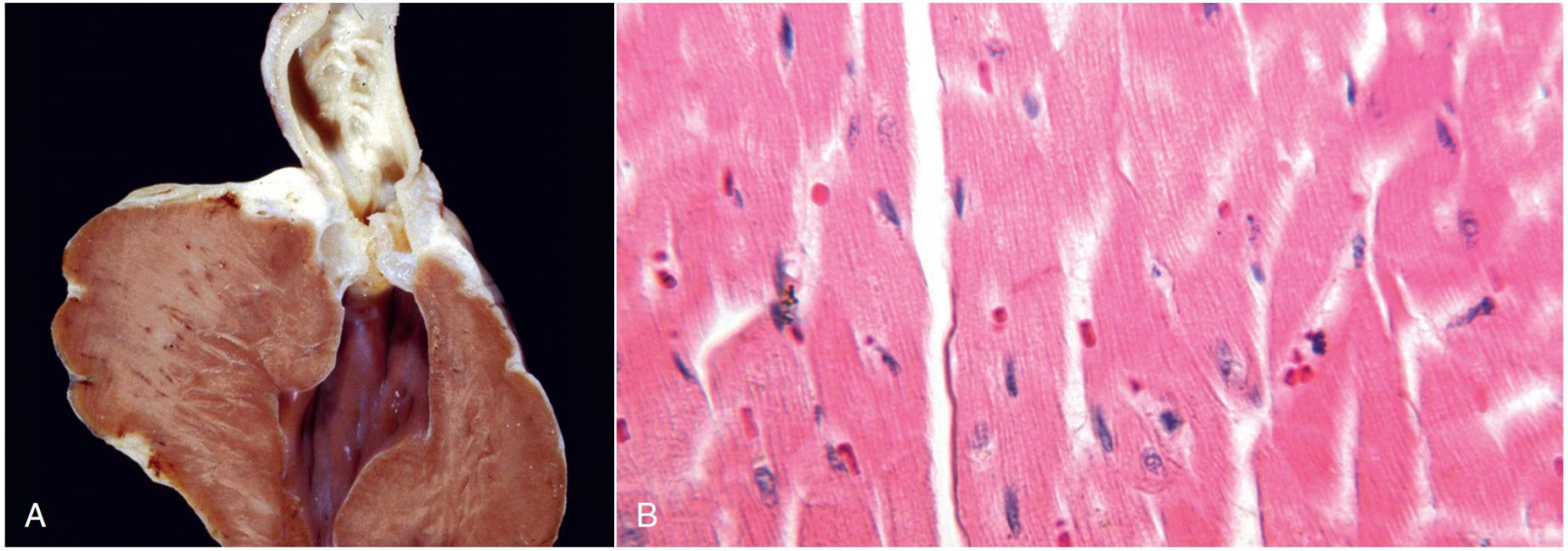


Cellular Adaptation to Stress

Cellular Adaptations to Stress

Hypertrophy

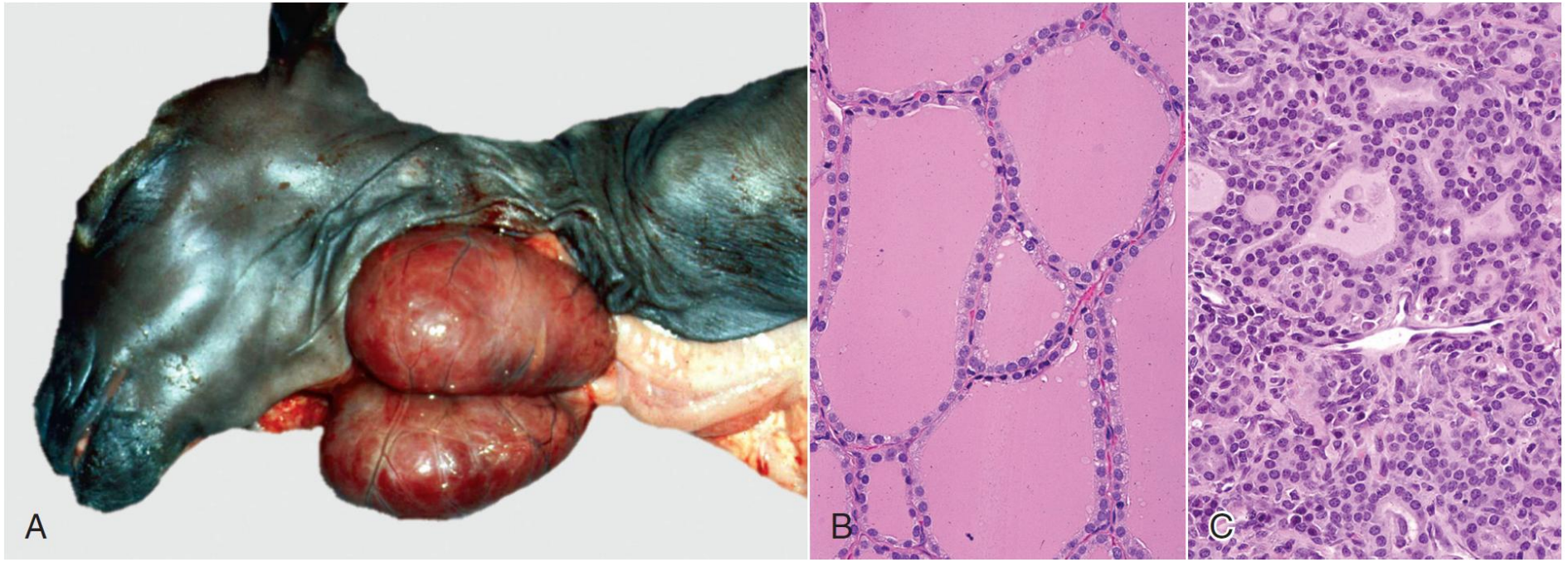
- ❖ Increase in cell size due to increased synthesis of proteins and organelles
- ❖ Occurs in non-dividing cells (e.g., skeletal muscle, cardiac muscle)
- ❖ Physiologic: exercise → skeletal muscle hypertrophy
- ❖ Pathologic: chronic hypertension → left ventricular hypertrophy
- ❖ Gross: enlarged organ;
  Microscopy: enlarged cells with increased cytoplasm.



Cellular Adaptations to Stress

Hyperplasia

- ❖ Increase in cell number due to mitotic activity.
- ❖ Occurs in cells capable of division (epithelial, glandular).
- ❖ Physiologic: hormonal (endometrium during estrus), compensatory (liver regeneration).
- ❖ Pathologic: excessive hormonal stimulation (prostate hyperplasia), viral infections (papilloma virus).
- ❖ May predispose to neoplasia if stimulus persists.

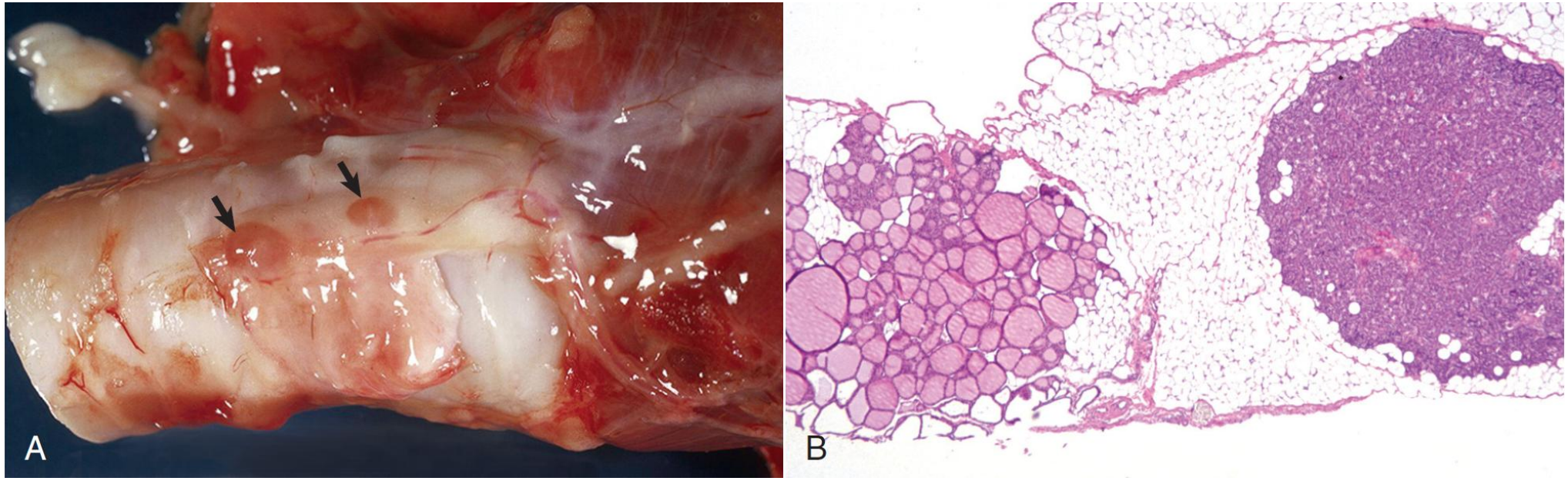


Thyroid gland

Cellular Adaptations to Stress

Atrophy

- ❖ Decrease in cell size and/or number → reduced organ/tissue mass.
- ❖ Causes: ↓ workload (disuse), ↓ innervation, ↓ blood supply, ↓ nutrition, aging.
- ❖ Morphology: smaller cells, loss of cytoplasmic substance, autophagic vacuoles.
- ❖ Physiologic: thymic involution with age.
- ❖ Pathologic: muscle atrophy after nerve injury, cachexia.

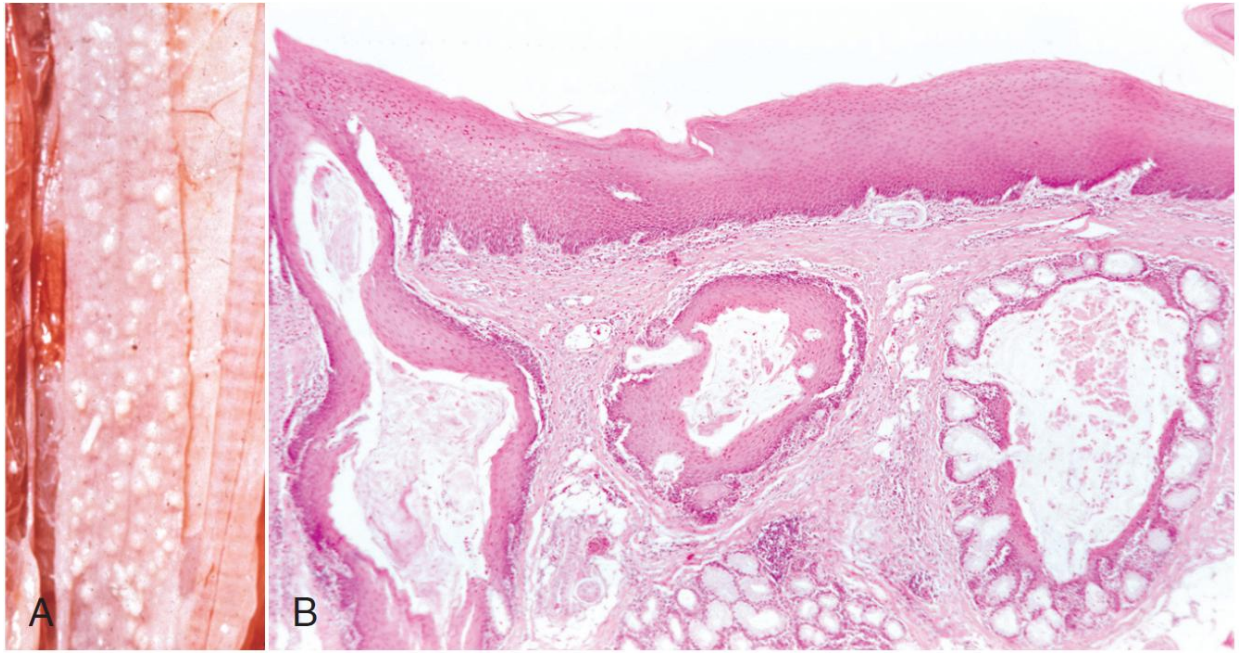


Thyroid gland

Cellular Adaptations to Stress

Metaplasia

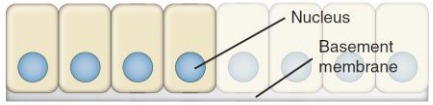
- ❖ Reversible change: one differentiated cell type replaced by another.
- ❖ Common in epithelia (e.g., squamous metaplasia of respiratory tract with chronic irritation).
- ❖ Protective substitution: less specialized but more resistant cell type.
- ❖ Pathologic: chronic smoking → columnar → squamous epithelium.
- ❖ Important precursor to malignancy (e.g., Barrett's esophagus → adenocarcinoma risk).

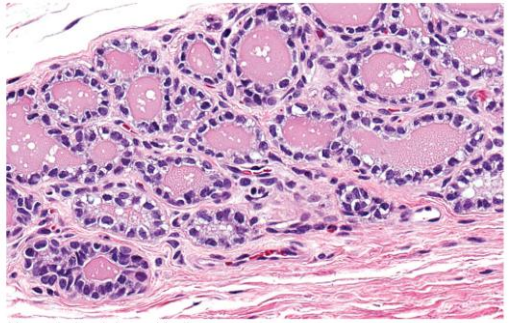


Esophagus, parrot

Cellular Adaptations to Stress

Normal epithelium (low columnar type - mammary gland)

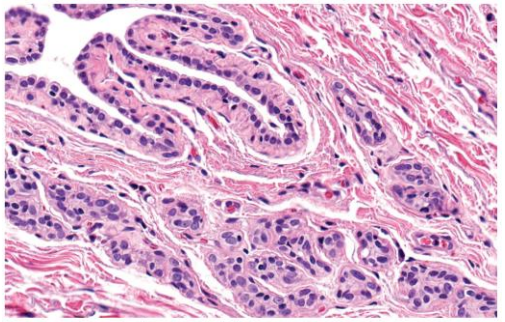




Normal glandular epithelium

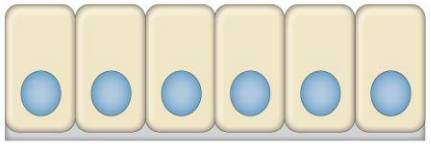
Atrophy (decreased size of cells)



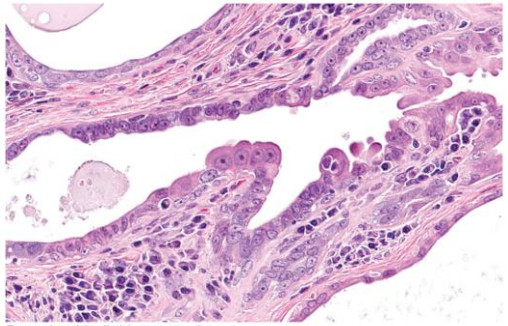


Mammary atrophy in a spayed dog

Hypertrophy (increased size of cells)



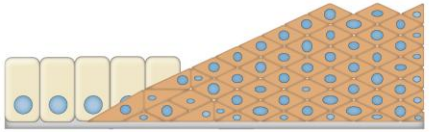
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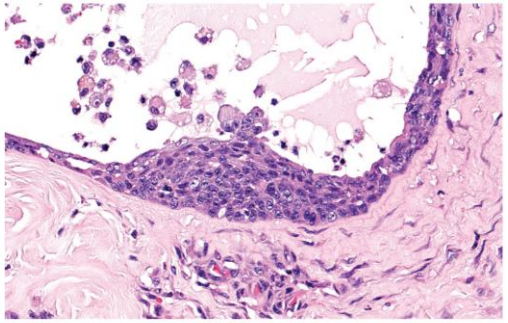


Ductal epithelial hypertrophy

Metaplasia (replacement of a cell type by another of the same germline)

Healing after mastitis
(low columnar → squamous)

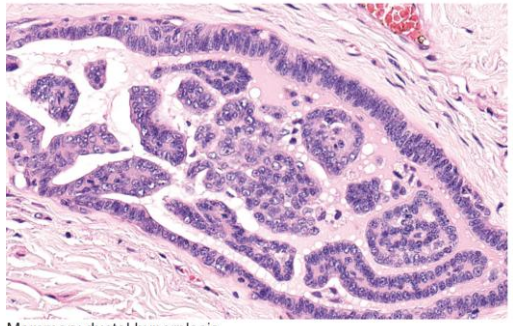




Squamous metaplasia in an ectatic mammary duct

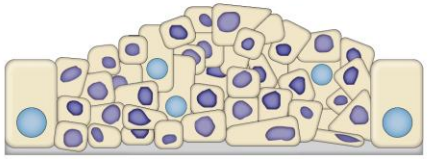
Hyperplasia (increased number of cells)



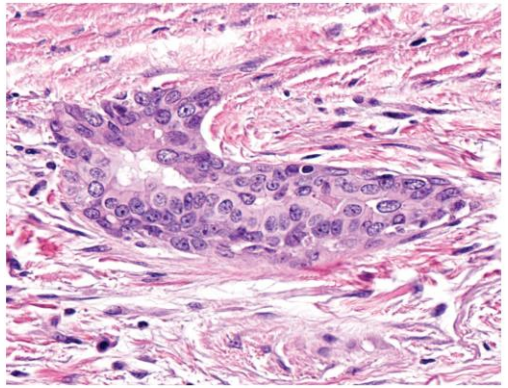


Mammary ductal hyperplasia

Dysplasia (abnormal pattern of tissue growth, disorderly arrangement of cells within epithelium)



B



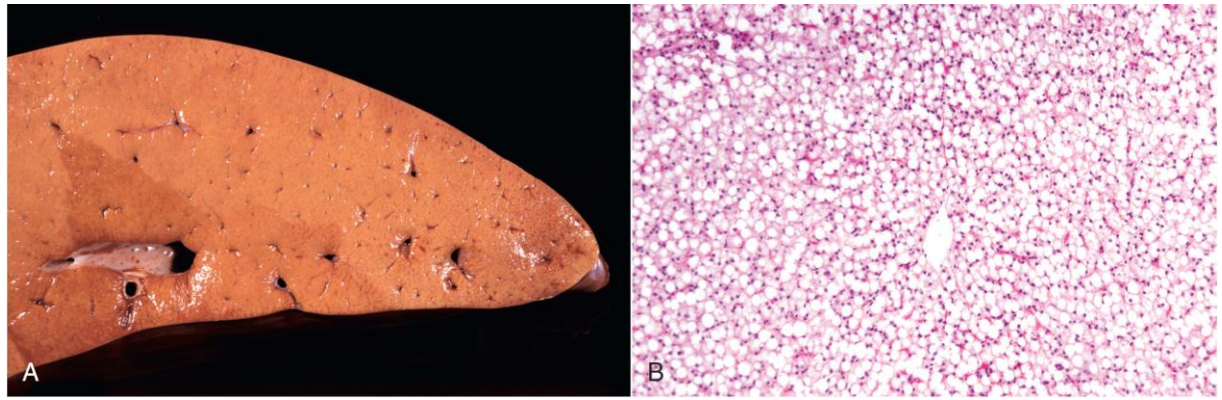
Dysplasia (atypical ductal hyperplasia)

Intracellular Accumulations

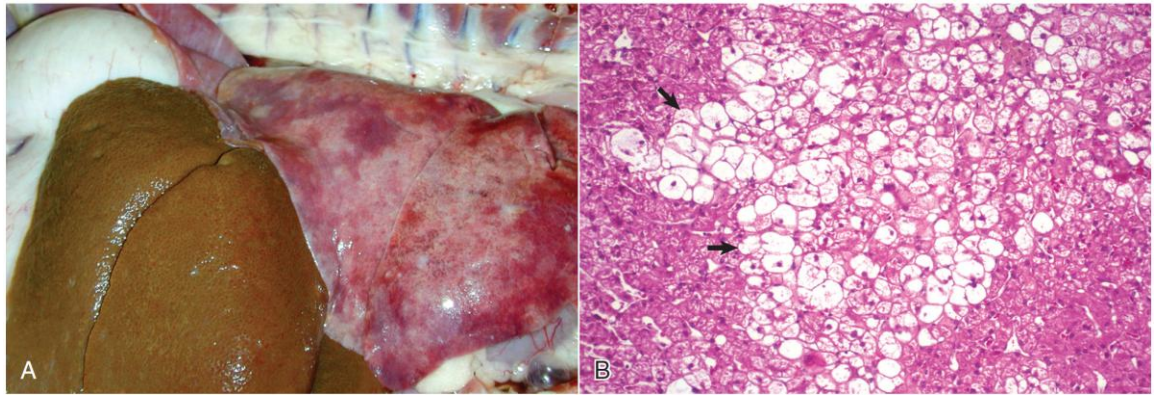
Intracellular Accumulations

Lipid Accumulation (Steatosis, Lipidosis)

- ❖ Abnormal accumulation of triglycerides or other lipids in parenchymal cells.
- ❖ Common in liver, also in heart, kidney, muscle.
- ❖ Causes: toxins (CCl_4), hypoxia, protein malnutrition, diabetes, obesity.
- ❖ Gross: enlarged, yellow, greasy organ.
- ❖ Microscopy: clear cytoplasmic vacuoles (fat droplets), can be macro- or microvesicular.



Liver, Steatosis

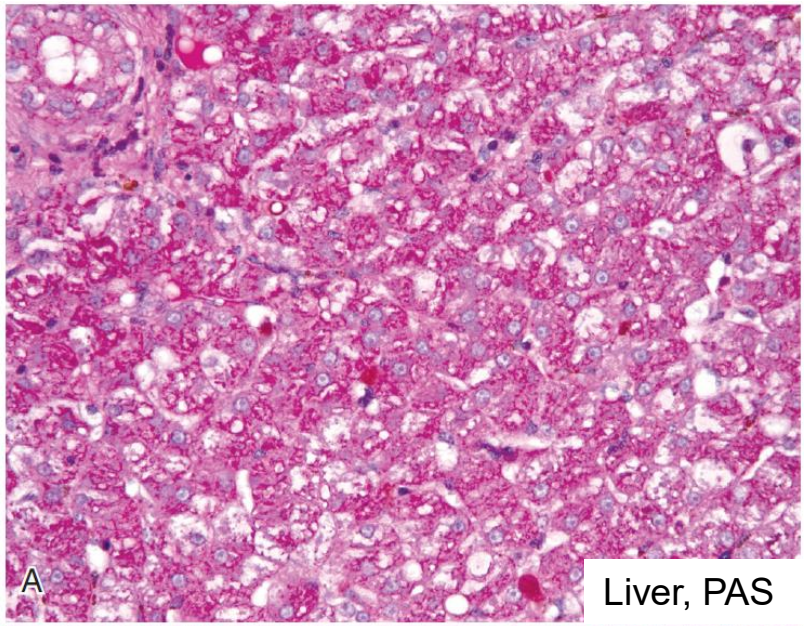


Liver, Glucocorticoid hepatopathy

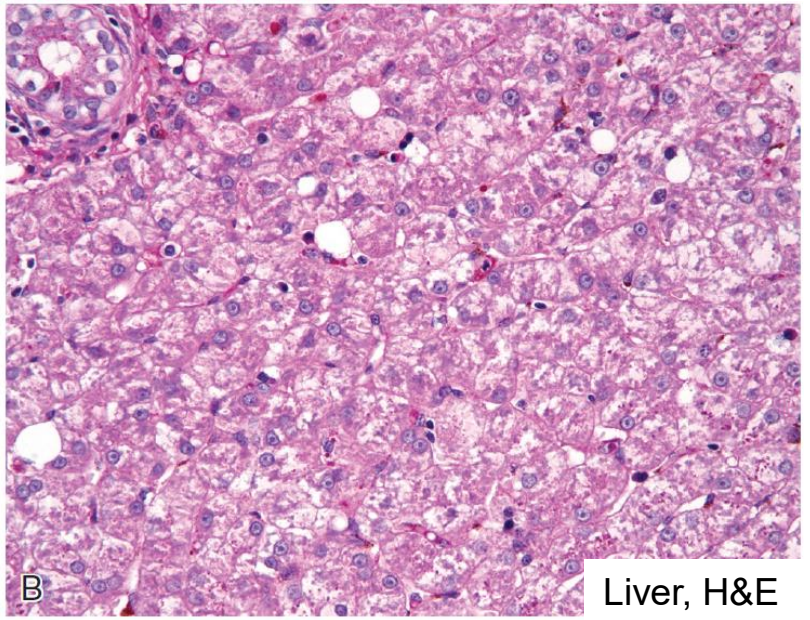
Intracellular Accumulations

Glycogen Accumulation

- Excess intracellular glycogen in hepatocytes, renal tubular cells, β-cells, cardiomyocytes.
- Causes: diabetes mellitus, steroid therapy, glycogen storage diseases.
- Microscopy: clear cytoplasm with PAS-positive material.
- May mimic lipid accumulation but differs with special stains.
- Gross changes usually minimal unless severe.



Liver, PAS

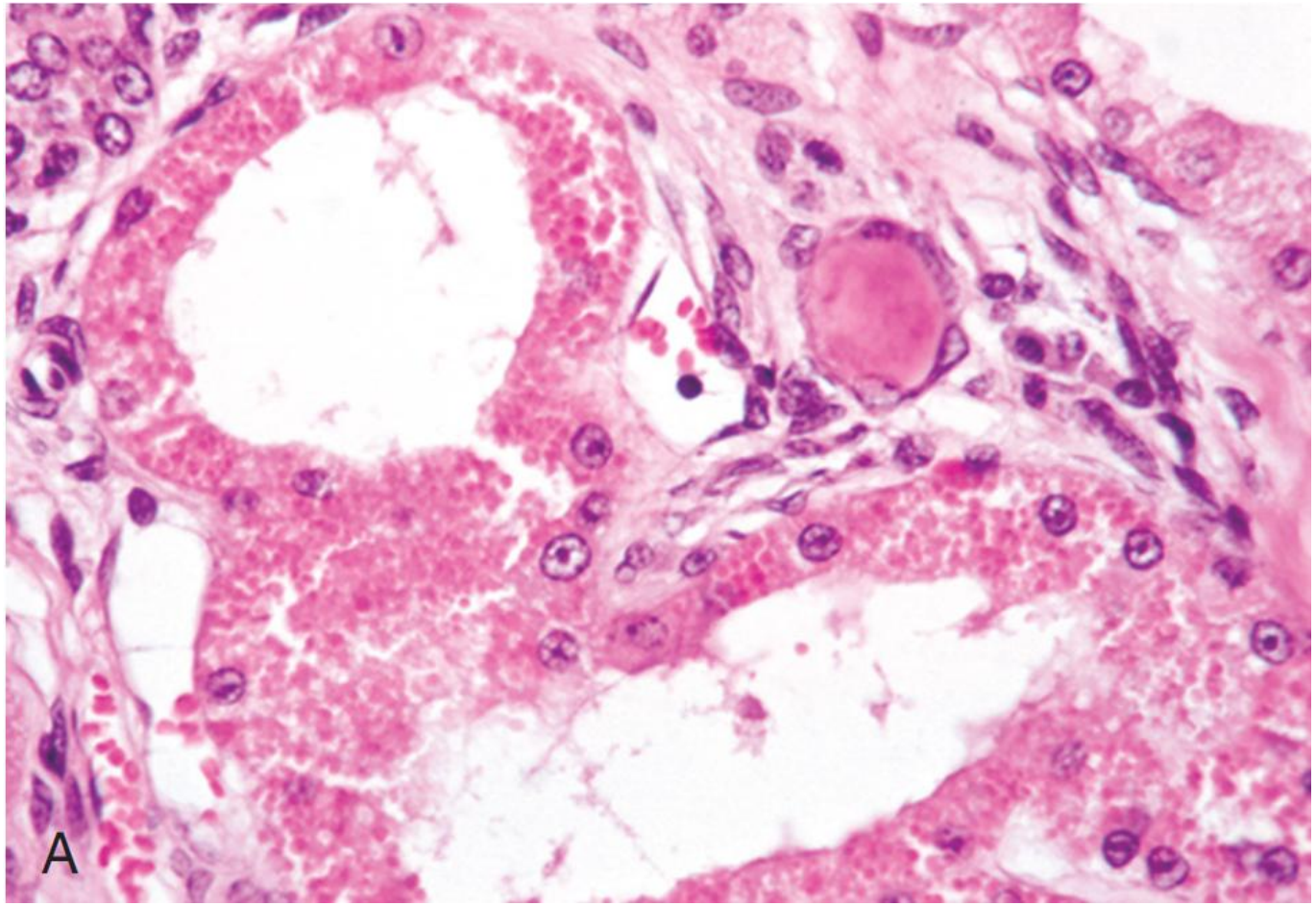


Liver, H&E

Intracellular Accumulations

Protein Accumulation

- Excessive presence of abnormal or misfolded proteins in cytoplasm.
- Causes: reabsorption droplets in renal tubular epithelium, defective protein folding (α1-antitrypsin deficiency).
- Also seen as Russell bodies in plasma cells (immunoglobulin).
- Microscopy: eosinophilic cytoplasmic inclusions.
- May trigger ER stress and apoptosis.

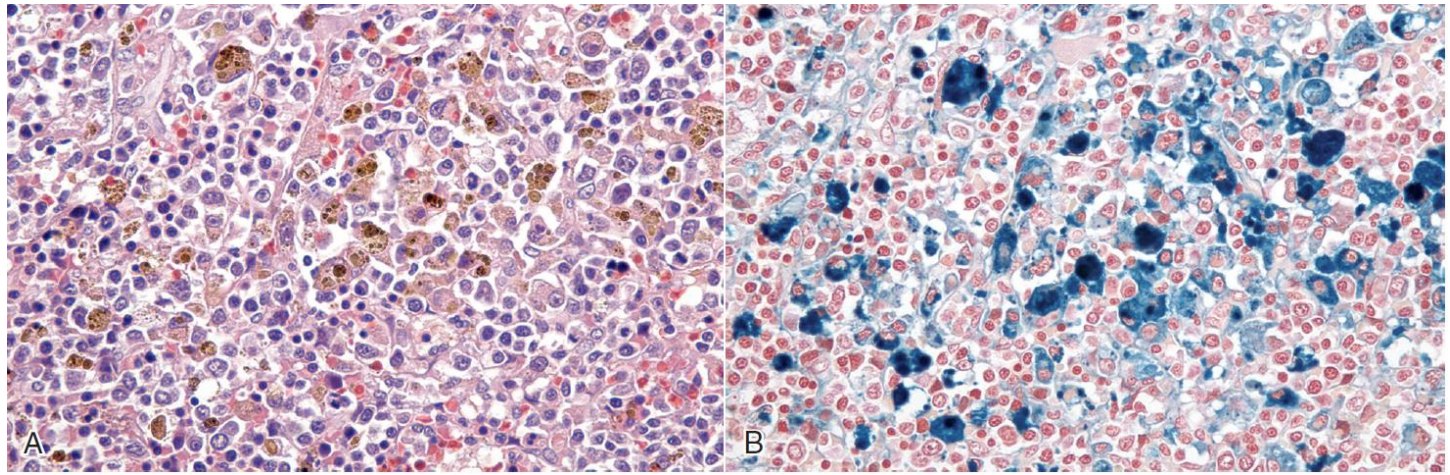


Kidney, protein resorption droplet

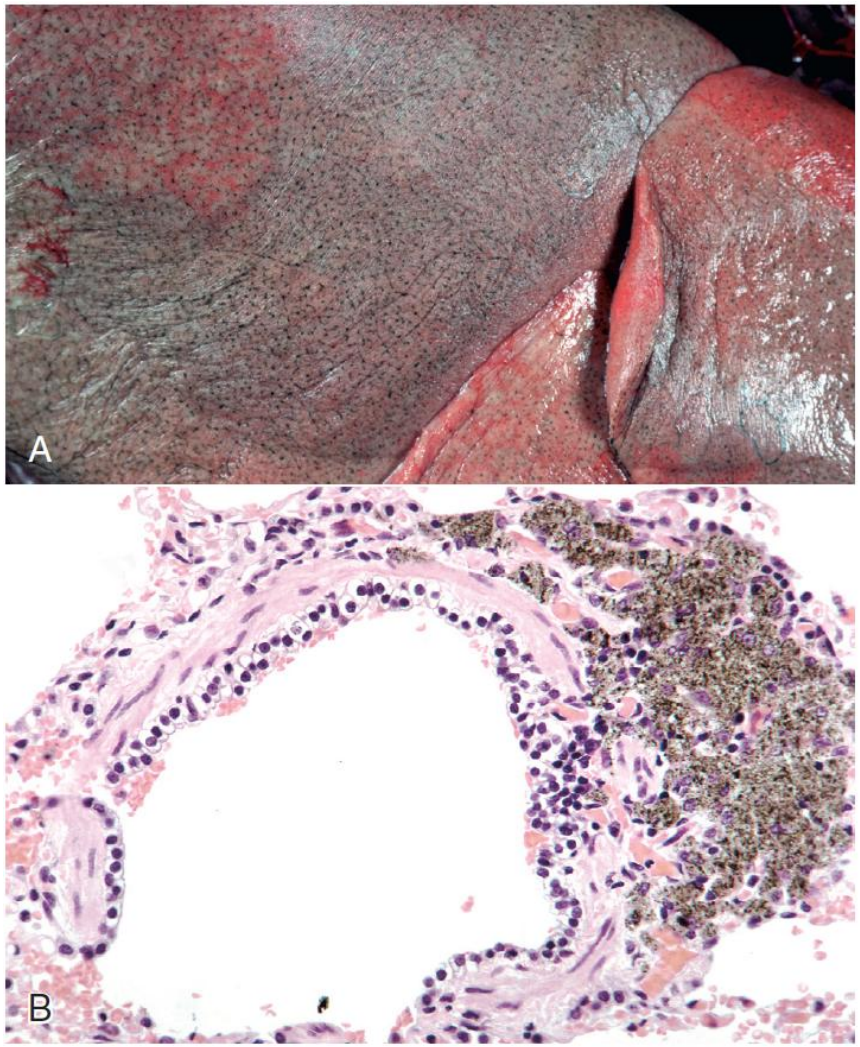
Pigment Accumulation

Pigment Accumulation

- ❖ Exogenous: carbon (anthracosis), tattoos.
- ❖ Endogenous: lipofuscin (“wear-and-tear” pigment), melanin, hemosiderin, bilirubin.
- ❖ Lipofuscin: aging, oxidative stress marker (brown-yellow granules).
- ❖ Hemosiderin: iron overload, hemorrhage.
- ❖ Bilirubin: jaundice, cholestasis.



hemosiderosis



anthracosis

Pathologic Calcification

Pathologic Calcification

Dystrophic Calcification

- Deposition of calcium salts in dead or degenerating tissues.
- Occurs with normal serum calcium.
- Gross: white, gritty, firm areas.
- Microscopy: basophilic, granular deposits in necrotic cells.
- Examples: calcified granulomas, necrotic fat.

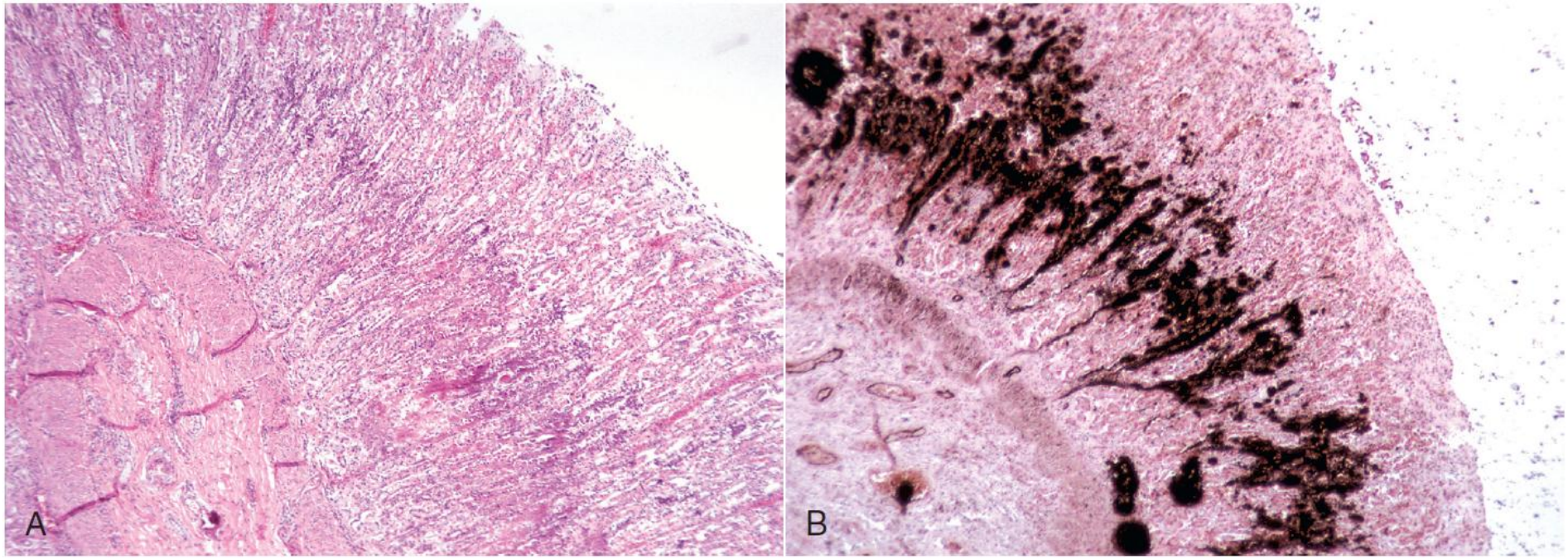


Calcification, VitE or Selenium deficiency, Heart, Lamb

Pathologic Calcification

Metastatic Calcification

- ❖ Deposition of calcium salts in normal tissues due to hypercalcemia.
- ❖ Causes: hyperparathyroidism, vitamin D toxicity, renal failure, bone destruction.
- ❖ Common sites: gastric mucosa, kidneys, lungs, systemic arteries.
- ❖ Microscopy: interstitial basophilic deposits.
- ❖ May impair organ function if extensive.

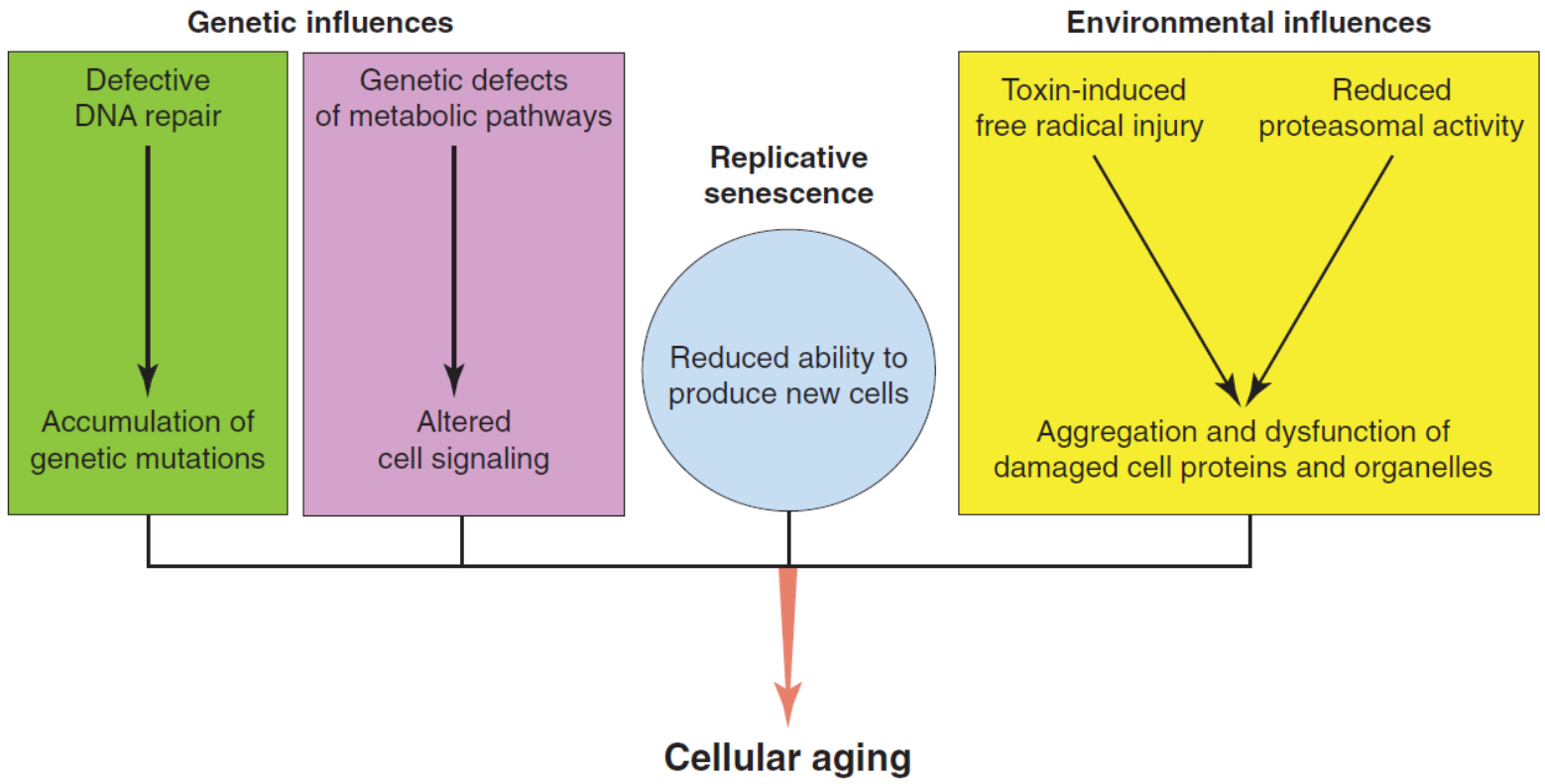


Uremic calcification, Stomach, Dog

Cellular Aging

Mechanisms of Cellular Aging

- ❖ Progressive decline in cell function and viability.
- ❖ Causes: cumulative DNA damage, telomere shortening, defective protein homeostasis.
- ❖ ROS (reactive oxygen species) contribute to cellular senescence.
- ❖ Reduced regenerative capacity in tissues with age.



Genetic Basis of Disease

Genetic Basis of Disease

General Concepts

- ❖ Many diseases result from inherited or acquired genetic alterations.
- ❖ Mutations may be in single genes, multiple genes, or entire chromosomes.
- ❖ Genetic defects can predispose cells to injury or dysfunction.
- ❖ Interact with environmental influences to shape disease expression.

Types of Genetic Mutations

- ❖ Point mutations: single nucleotide changes → missense, nonsense.
- ❖ Insertions/deletions: frameshifts altering reading frame.
- ❖ Trinucleotide repeat expansions: e.g., Huntington's, fragile X.
- ❖ Chromosomal abnormalities: deletions, duplications, translocations.
- ❖ Somatic vs germline mutations → different clinical impact.

Genetic Basis of Disease

Single-Gene Disorders

- ❖ Enzyme defects: lysosomal storage diseases (e.g., GM1 gangliosidosis, α-mannosidosis).
- ❖ Structural protein defects: collagen mutations → osteogenesis imperfecta.
- ❖ Receptor/channel defects: familial hypercholesterolemia, ion channelopathies.
- ❖ Often inherited in Mendelian patterns (dominant, recessive, X-linked).

Multifactorial Disorders

- ❖ Common diseases from gene + environment interactions.
- ❖ Examples: hip dysplasia in dogs, diabetes mellitus, cancer predisposition.
- ❖ Polygenic basis with additive effects of multiple alleles.
- ❖ Environmental modifiers: diet, toxins, lifestyle, infections.

Chromosomal & Mitochondrial Abnormalities

- ❖ Chromosomal: aneuploidy (trisomy, monosomy), structural rearrangements.
- ❖ Mitochondrial mutations: defects in oxidative phosphorylation.
- ❖ Inherited maternally → affect tissues with high energy demand.
- ❖ Examples: exercise intolerance, neurologic deficits.

Genetic Disorders by Species

Dog
- Amyloidosis (Shar-Pei, Beagle)
- Muscular dystrophy (Golden Retriever, Irish Terrier)
- Copper toxicosis (Bedlington Terrier, Labrador Retriever)
- Osteogenesis imperfecta (Beagle, Dachshund)

Cat
- Polycystic kidney disease (Persian, related breeds)
- Mucopolysaccharidosis VI (Siamese, Domestic Shorthair)
- GM1 gangliosidosis (Korats)
- Hypokalemic polymyopathy (Burmese)

Pig
- Porcine stress syndrome (malignant hyperthermia) (Landrace, Pietrain)
- Splay leg (various breeds)

Horse
- Hyperkalemic periodic paralysis (HYPP) (Quarter Horse)
- Glycogen branching enzyme deficiency (Quarter Horse, Paint Horse)
- Severe combined immunodeficiency (SCID) (Arabian)
- Overo lethal white foal syndrome (Paint Horse)

Cattle
- BLAD (Bovine leukocyte adhesion deficiency) (Holstein)
- Deficiency of uridine monophosphate synthase (DUMPS) (Holstein)
- Complex vertebral malformation (CVM) (Holstein)
- Bovine citrullinemia (Holstein)

Vascular Disorders and Thrombosis

Su-Hyung Lee, DVM, PhD

Circulatory System

Circulatory System

Introduction to Circulatory Pathology

- Purpose of Circulation
  - Require a circulatory system to deliver nutrients to cells and remove waste products.
  - Maintains homeostasis and integrates the functions of all tissues in complex organisms.
- Circulatory disturbances are fundamental to many systemic and organ-specific diseases.
- Failures in vascular integrity, blood flow, or fluid distribution → lead to edema, hemorrhage, thrombosis, infarction, or shock.
- Veterinary significance: major cause of morbidity and mortality in domestic animals.

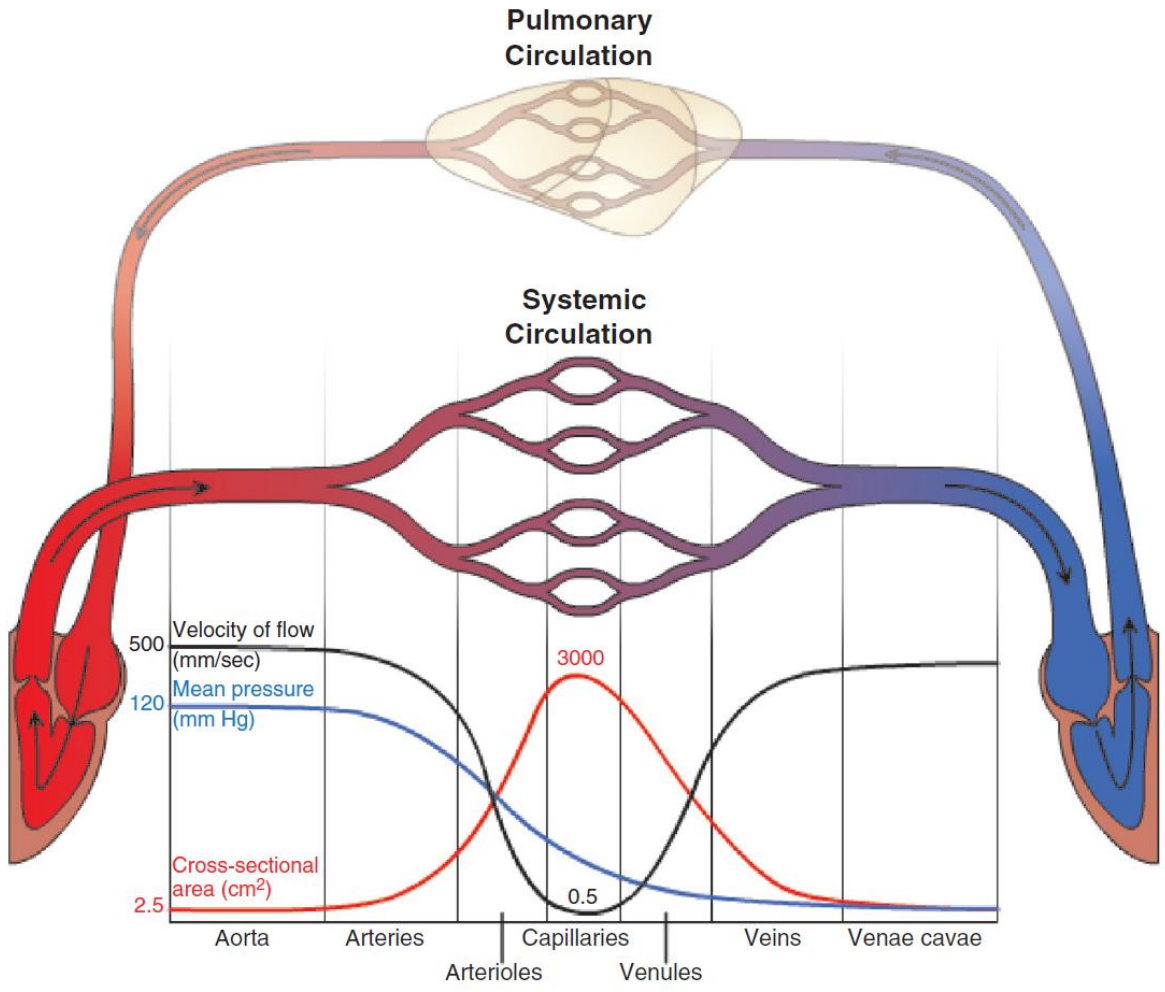
Functions of Circulatory System

- Delivery of O_2, nutrients, hormones.
- Removal of CO_2, waste products.
- Fluid balance between blood and interstitium.
- Immune surveillance and inflammatory cell trafficking.

Circulatory System

Introduction to Circulatory Pathology

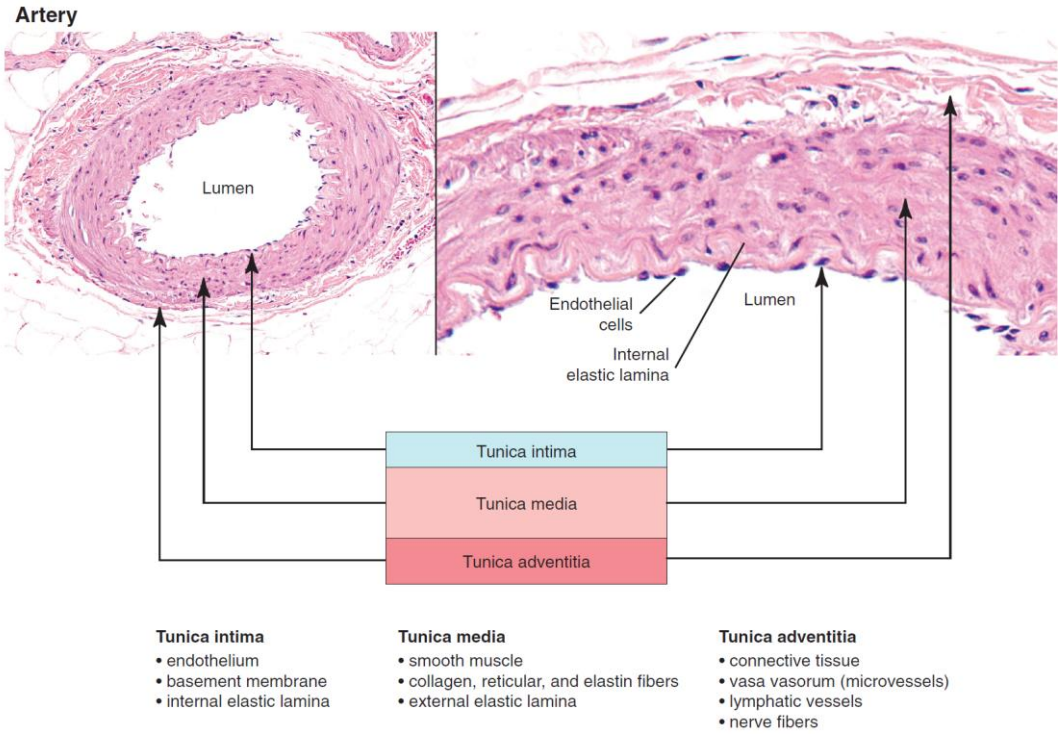
- **The Central Pump**
  - The heart provides the driving force for blood distribution.
- **Dual Circulation**
  - The right side of the heart distributes blood to the pulmonary circulation.
  - The left side of the heart distributes an equal volume of blood to the systemic circulation.
- **Cardiac Output**
  - Definition: The volume of blood pumped by each half of the heart per minute.
  - Formula: Cardiac Output = Heart Rate × Stroke Volume.
  - Efficiency: Each half of the heart typically pumps a volume equivalent to the animal's entire blood volume every minute.

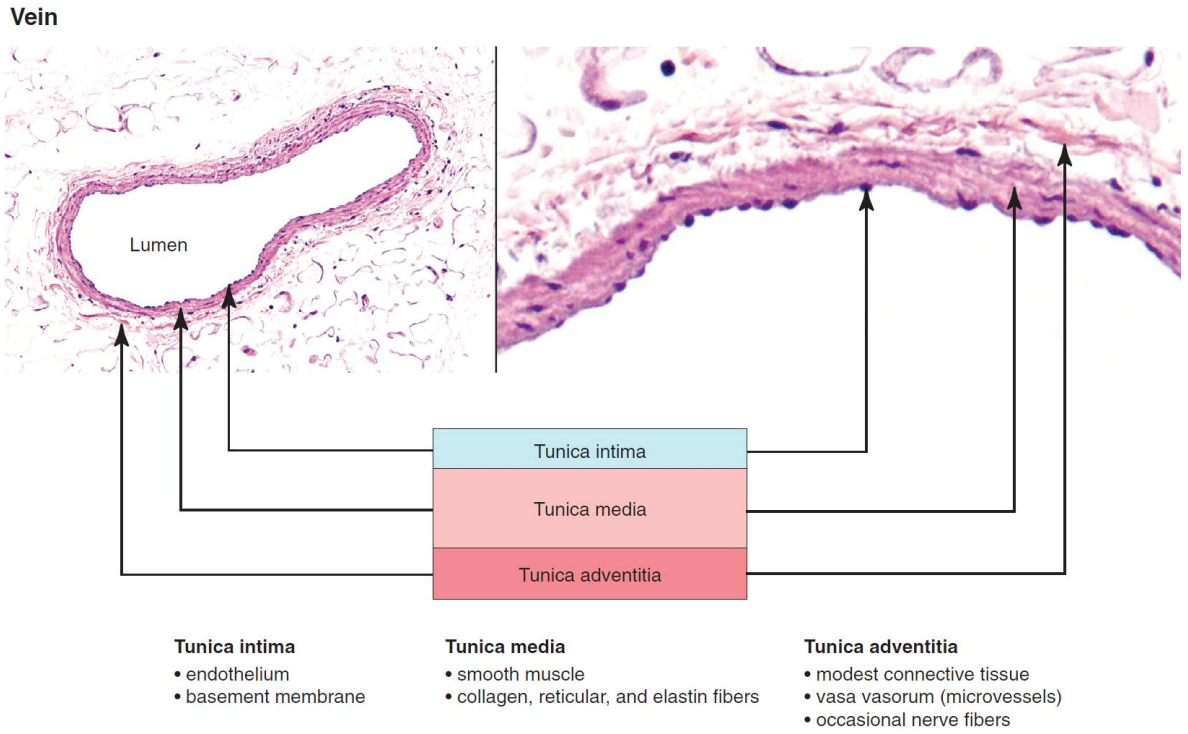


Circulatory System

Components of Circulatory System

- ❖ Macrocirculation: arteries, veins, lymphatic vessels.
- ❖ Microcirculation: arterioles, capillaries, venules.
- ❖ Regulatory role of endothelium: dynamic organ with anti- and pro-thrombotic functions.





Circulatory System

Arteries

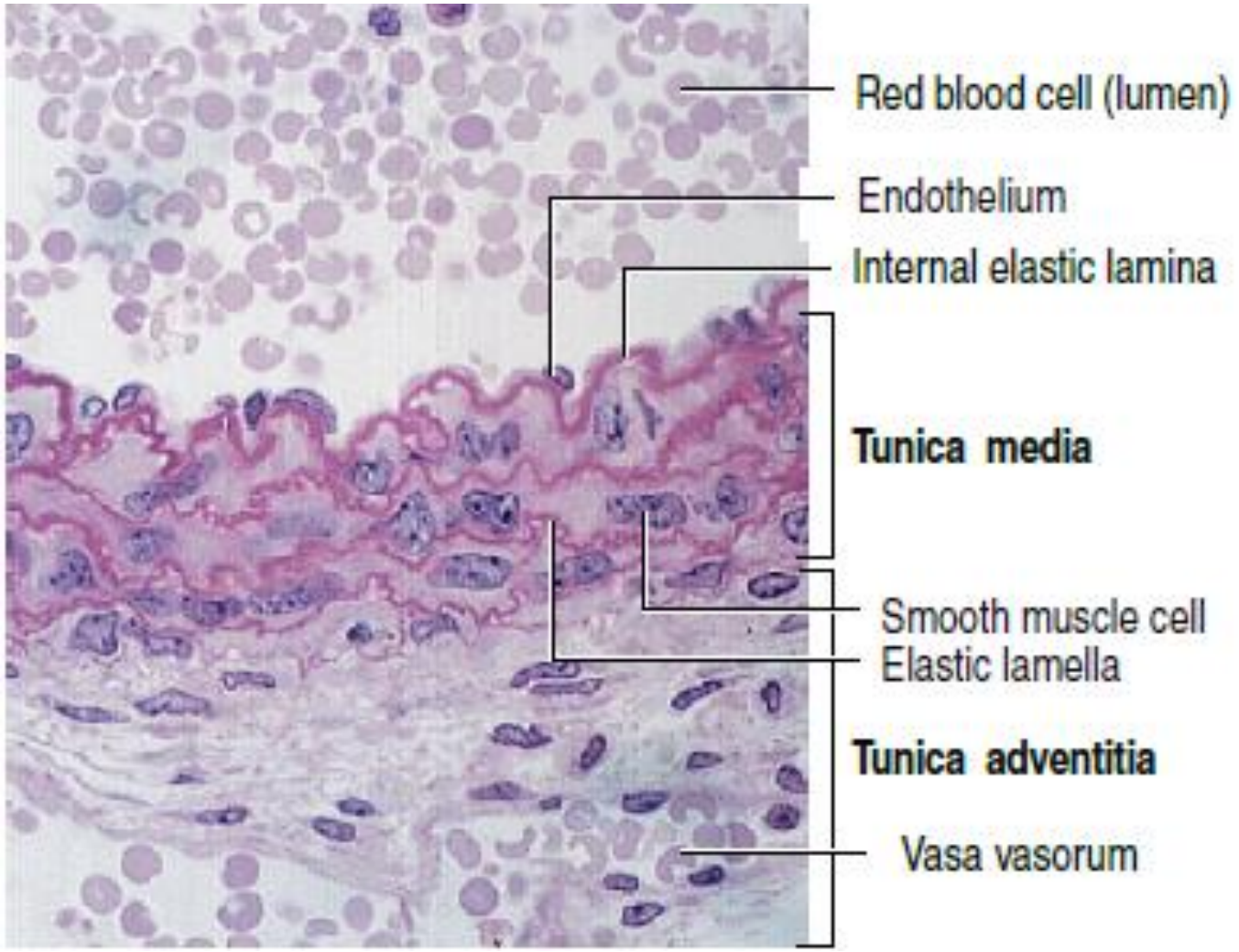
- Structure: They have large-diameter lumens for rapid blood flow with minimal resistance. Their walls are thick, with smooth muscle and elastic fibers.
- Function: Arteries act as pressure reservoirs. They expand to hold blood during heart contraction and then passively recoil to provide continuous flow.

Arterioles

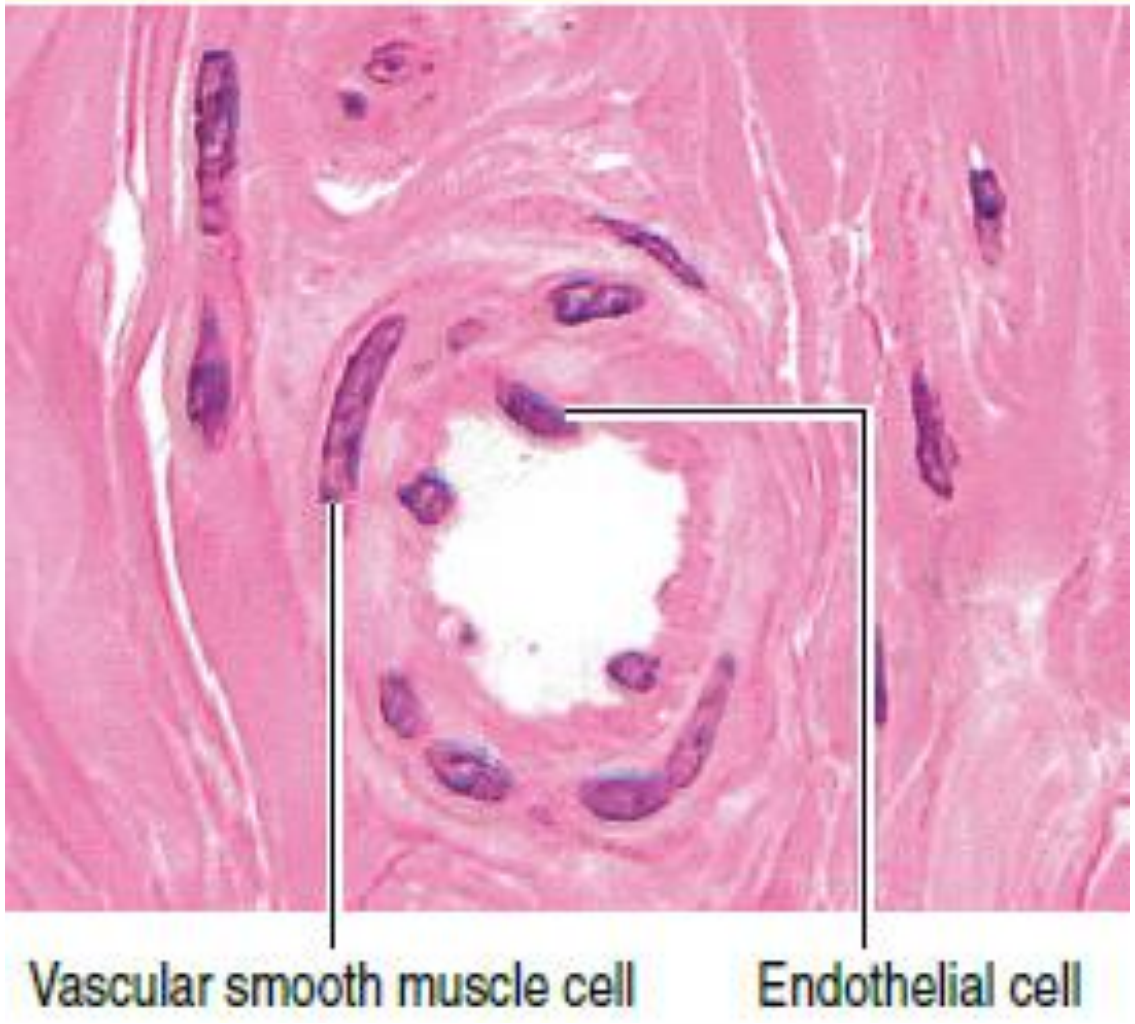
- Function: They are the major resistance vessels in the circulatory system. Blood pressure can fall by nearly half after passing through them.
- Regulation: Their narrow lumens are controlled by smooth muscle, allowing them to dilate or constrict to selectively distribute blood.

Circulatory System

Artery



Arterioles

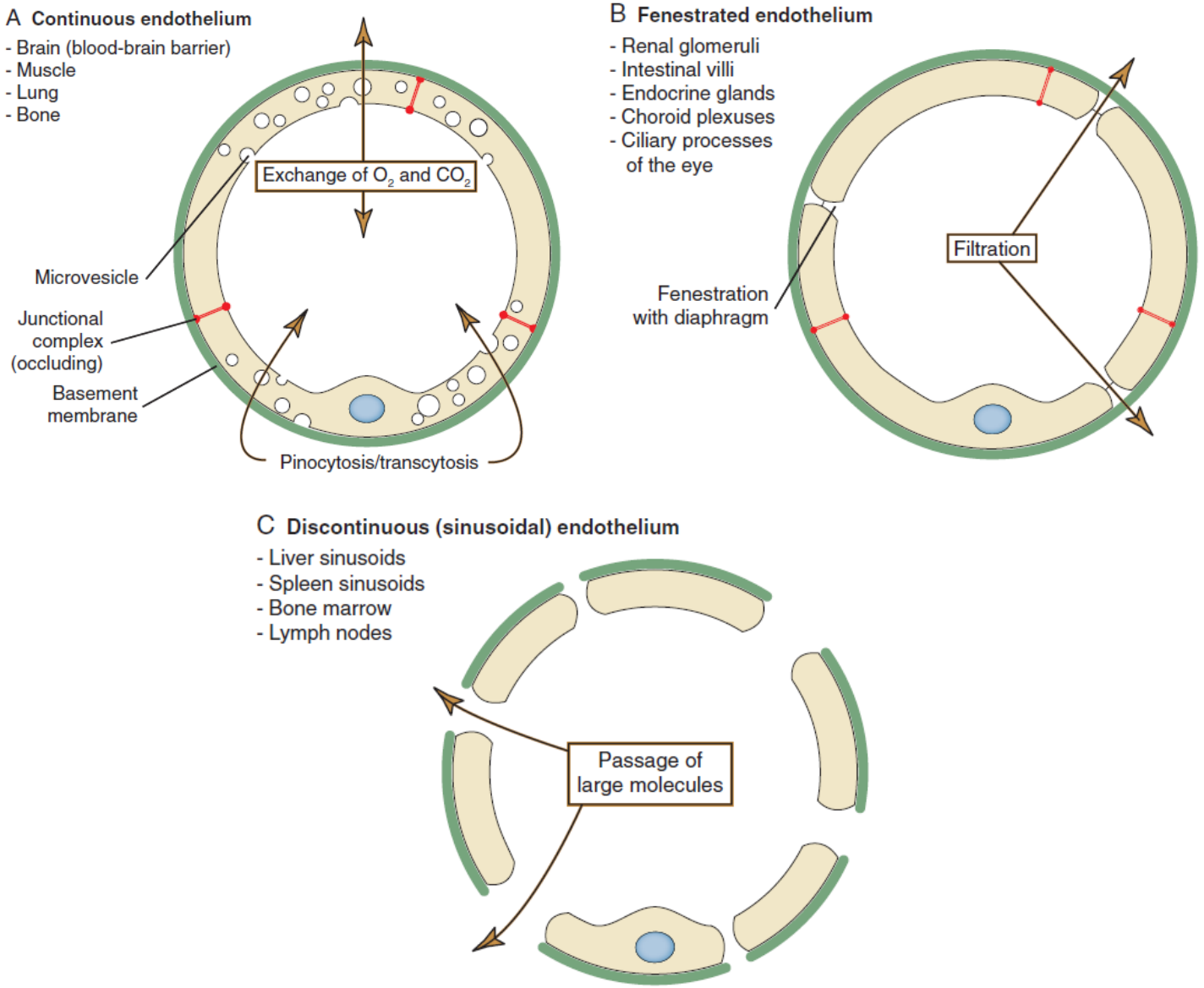


Circulatory System

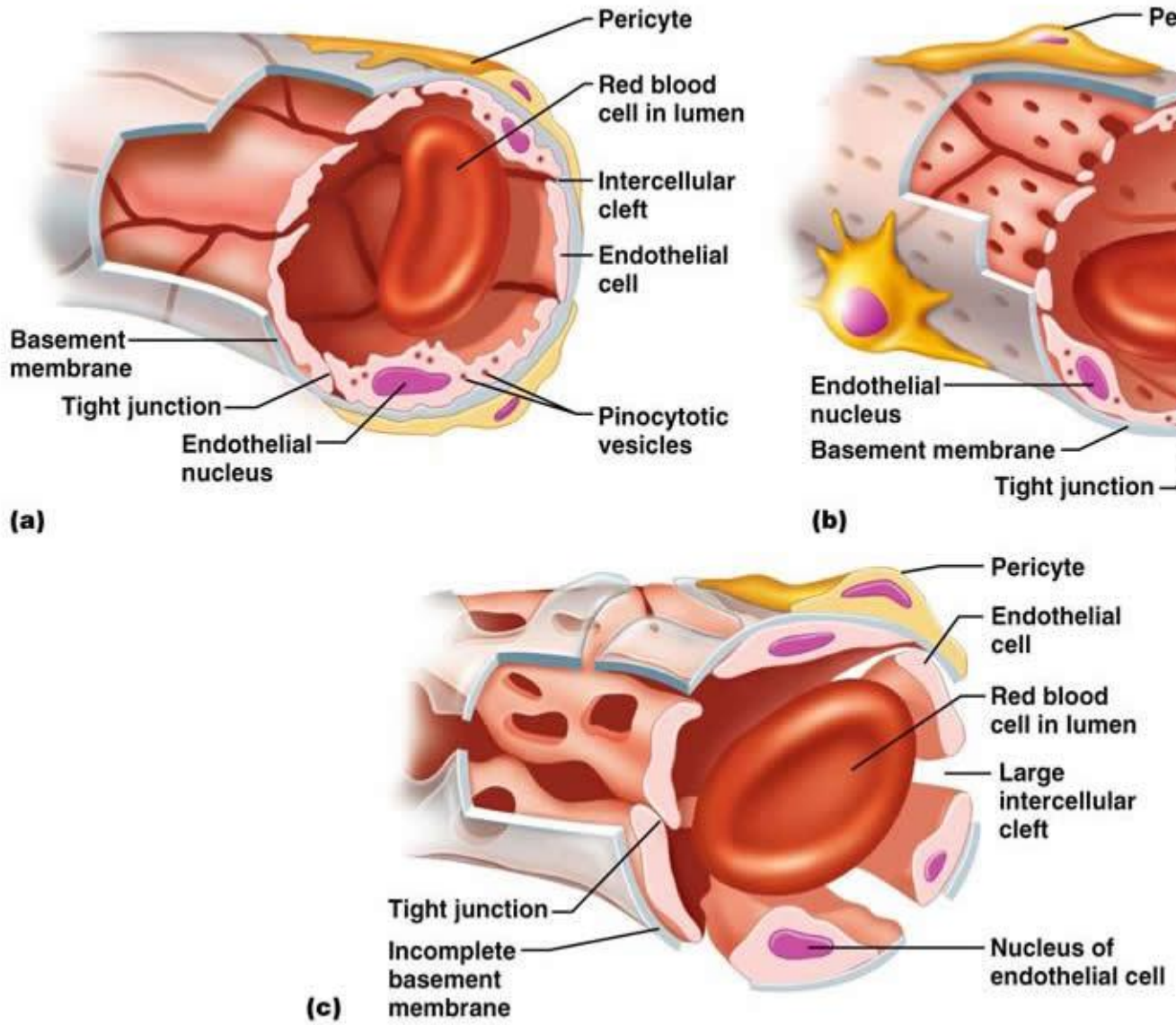
The Exchange Network: Capillaries

❖ Primary Role
- Capillaries are the site of nutrient and waste product exchange between the blood and tissue.

❖ Key Characteristics
- The most numerous vessel type in the body.
- Contain only about 5% of the total blood volume.
- Very slow, and red blood cells move in single file to facilitate diffusion.
- Wall: extremely thin (approximately 1 μm) and consist of a single layer of endothelial cells.
- Interendothelial pores make them semipermeable.



Circulatory System



a. Continuous C

b. Fenestrated C

c. Sinusoidal C

Circulatory System

The Collection Network: Veins & Lymphatics

❖ Venules and Veins

- **Function**: Provide a low-resistance pathway for returning blood to the heart.
- **Blood Reservoir**: Due to their high distensibility, veins can store large amounts of blood; nearly 65% of total blood volume is normally within systemic veins.
- **Assisted Flow**: Since pressure and velocity are low, flow is aided by factors like venous valves, skeletal muscle contraction, and pressure changes from breathing (respiratory variation of venous return).

❖ The Lymphatic System

- This network of vessels runs parallel to the veins.
- Its function is to drain fluid from extravascular spaces back into the blood vascular system.

Circulatory System

Homeostatic Regulation

- Tight balance among vascular tone, blood pressure, plasma protein concentration, and lymphatic drainage.
- Disturbances → pathologic manifestations: congestion, ischemia, edema, thrombosis.

Clinical Relevance

- Shock and DIC are final common pathways in critical illness.
- Circulatory pathology links metabolic, cardiovascular, respiratory, and inflammatory diseases.
- Essential for necropsy interpretation in veterinary practice.

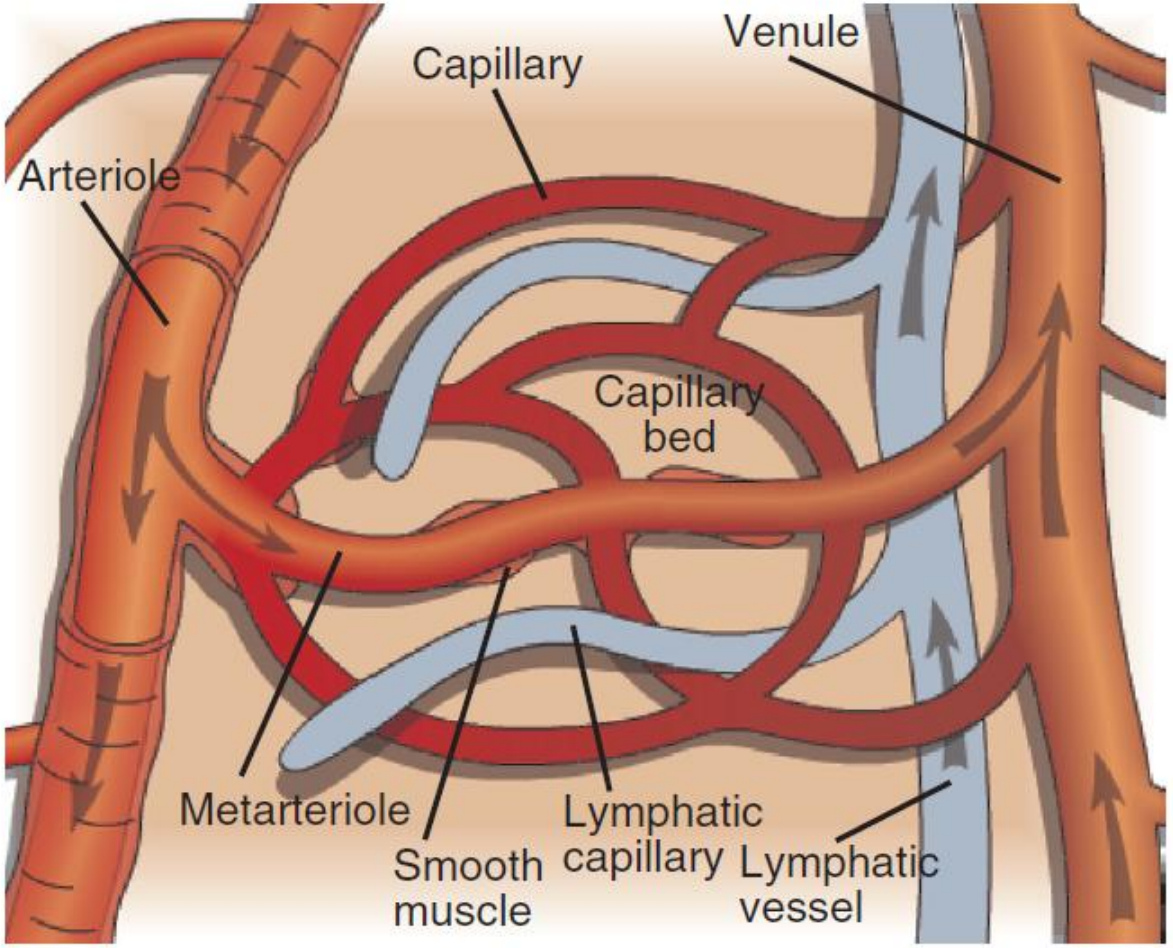
Microcirculation, Interstitium, and Cells

Microcirculation, Interstitium, and Cells

Microcirculation Overview

- Consists of arterioles, capillaries, and venules.
- Site of exchange of gases, fluids, nutrients, and waste.

  : a dramatic drop in pressure and flow rate from the arterial to the venous side of the microcirculation.
- Vulnerable to injury due to thin-walled structure.



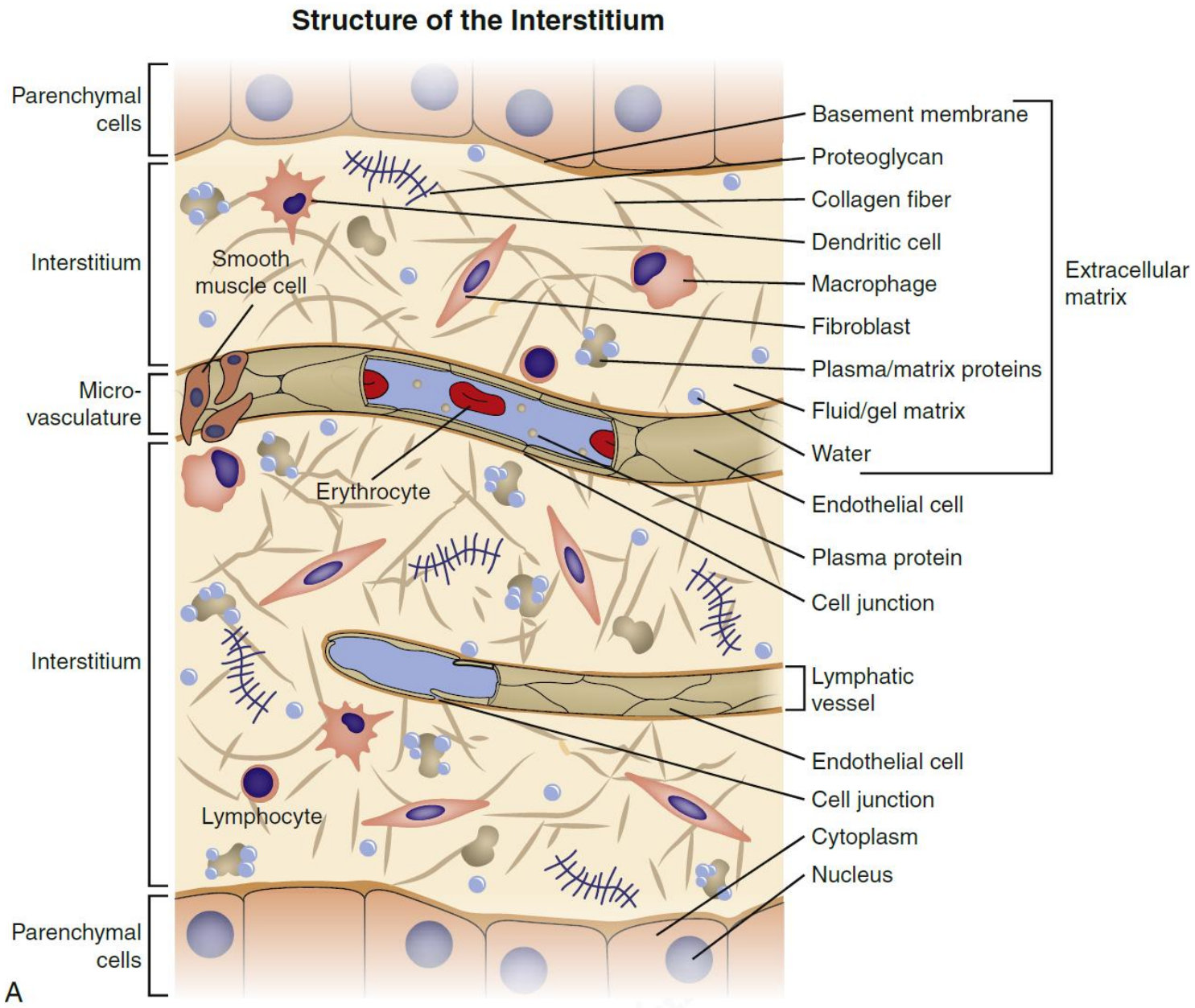
Microcirculation, Interstitium, and Cells

Interstitium and Cellular Components

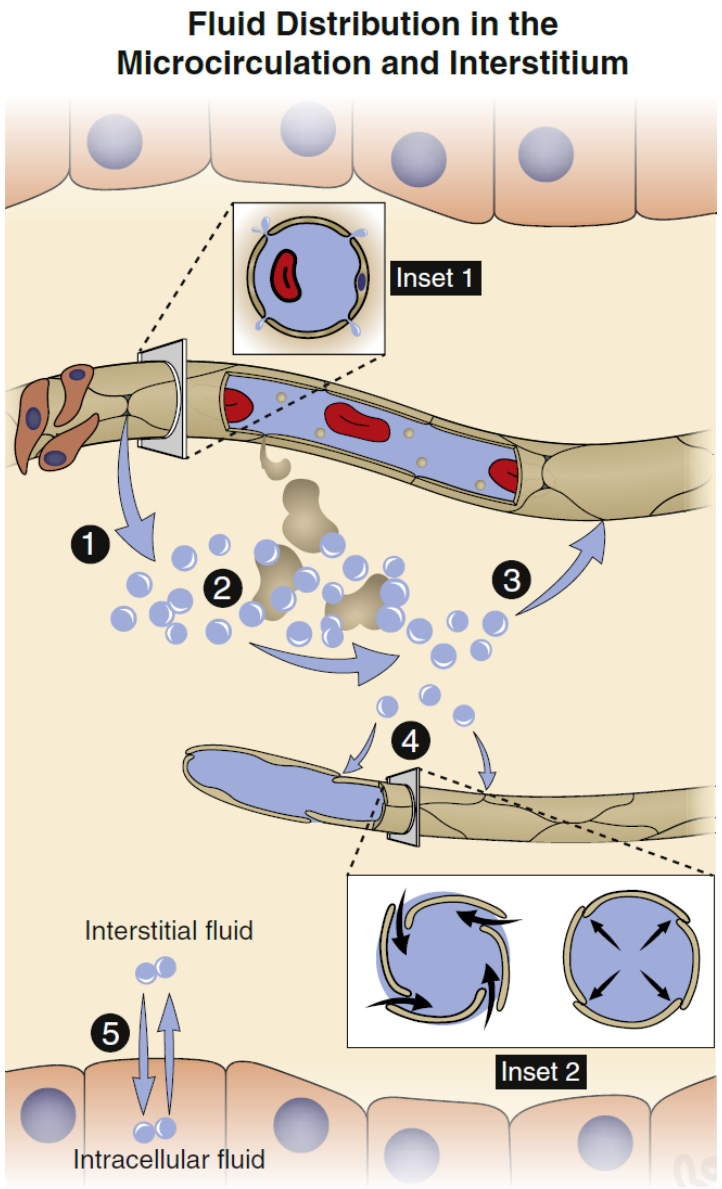
- Extracellular matrix (collagen, elastin, proteoglycans) maintains tissue structure.
- Fibroblasts regulate ECM production.
- Pericytes stabilize capillaries.
- Mast cells release vasoactive mediators (histamine).

- Structural Components
  Type I collagen is the major structural component, forming the framework in which cells reside.
- Adhesive Components
  Adhesive glycoproteins provide attachment sites for structural components and serve as receptors for cells moving through the interstitium.
- Absorptive Components
  Glycosaminoglycans and proteoglycans are hydrophilic complexes that can bind large amounts of water and other soluble molecules.

Microcirculation, Interstitium, and Cells



Microcirculation, Interstitium, and Cells



1: High arteriolar hydrostatic pressure forces fluid into the interstitium

2: Plasma proteins (e.g., albumin) and molecules within the extracellular matrix exert an osmotic effect to attract and retain water

3: Interstitial hydrostatic pressure forces interstitial fluid into lower-pressure venules

4: The slight excess of interstitial fluid not returned to the venules enters the lymphatic vessels to be drained from the area

5: Exchange of intracellular and interstitial fluid is balanced by osmotic forces and concentration gradients of electrolytes and other molecules across the cell plasma membrane

Microcirculation, Interstitium, and Cells

The Endothelium: A Dynamic Interface

❖ Ubiquitous Lining

- A single layer of endothelium lines all components of the circulatory system.

❖ Critical Participant

- Forms a dynamic interface between blood and tissue.
- A critical participant in:

- Fluid distribution
- Inflammation & Immunity
- Angiogenesis (new vessel formation)
- Hemostasis (blood clotting)

Microcirculation, Interstitium, and Cells

Endothelial Function

❖ Normal Endothelium
- Antithrombotic (prevents clots) and Profibrinolytic (helps dissolve clots).
- These properties help maintain blood in a fluid state.

❖ Injured or Activated Endothelium
- When injured, the endothelium becomes prothrombotic (promotes clots) and antifibrinolytic (prevents clot dissolution).

Triggers for Activation

❖ Endothelial activation can be caused by a variety of events:
- Oxidative stress
- Hypoxia (low oxygen)
- Inflammation
- Infectious agents
- Tissue injury.

❖ Response to Activation
- Production and release of numerous substances with wide-ranging roles.
- Typically a localized response, designed to restrict the host response to a specific area without affecting normal blood flow elsewhere.

Microcirculation, Interstitium, and Cells

Box 2-1 Endothelial Cell Functions and Responses in Homeostasis and Disease

FLUID DISTRIBUTION AND BLOOD FLOW

Semipermeable membrane for fluid distribution
- Interendothelial junctions

Vasodilation
- Nitric oxide
- Prostacyclin (PGI_2)
- Endothelial-derived hyperpolarizing factor
- C-type natriuretic peptide

Vasoconstriction
- Endothelin
- Reactive oxygen species
- Angiotensin II
- Products of prostaglandin H_2 (e.g., thromboxane A_2)

HEMOSTASIS

Antihemostatic substances
- PGI_2
- Endothelial cell protein C receptor
- Tissue factor pathway inhibitor (TFPI)
- Tissue plasminogen activator (tPA)
- Heparan sulfate
- Adenosine diphosphatase (ADPase) and adenosine triphosphatase (ATPase)
- Protein S
- Thrombomodulin

Prohemostatic substances
- von Willebrand factor
- Tissue factor (TF) (factor III)
- Plasminogen activator inhibitor-1 (PAI-1)
- Protease-activated receptors (PARs)

INFLAMMATION

Cytokines
- Interleukin (IL) -1, IL-6, IL-8

Acute Phase Proteins
- C-reactive protein

Enhanced expression of TF

Expression of leukocyte adhesion molecules:
- Cell adhesion molecule family
  - Mucosal addressin cell adhesion molecule 1 (MAdCAM-1)
  - Intercellular adhesion molecule 1 (ICAM-1)
  - Vascular cell adhesion molecule 1 (VCAM-1)
  - Platelet endothelial cell adhesion molecule 1 (PECAM-1)
- Selectin family
  - P-selectin
  - E-selectin

GROWTH FACTORS

Platelet-derived growth factor (PDGF)
Colony-stimulating factor (CSF)
Fibroblast growth factor (FGF)
Transforming growth factor-β (TGF-β)
Heparin

FIBRINOLYSIS

Synthesis and secretion of fibrinolytic components under certain circumstances
Regulation of formation of plasmin
tPA
Urokinase plasminogen activator receptor
PAI-1
Annexin II

Fluid Distribution and Homeostasis

Fluid Distribution and Homeostasis

Body Fluid Compartments

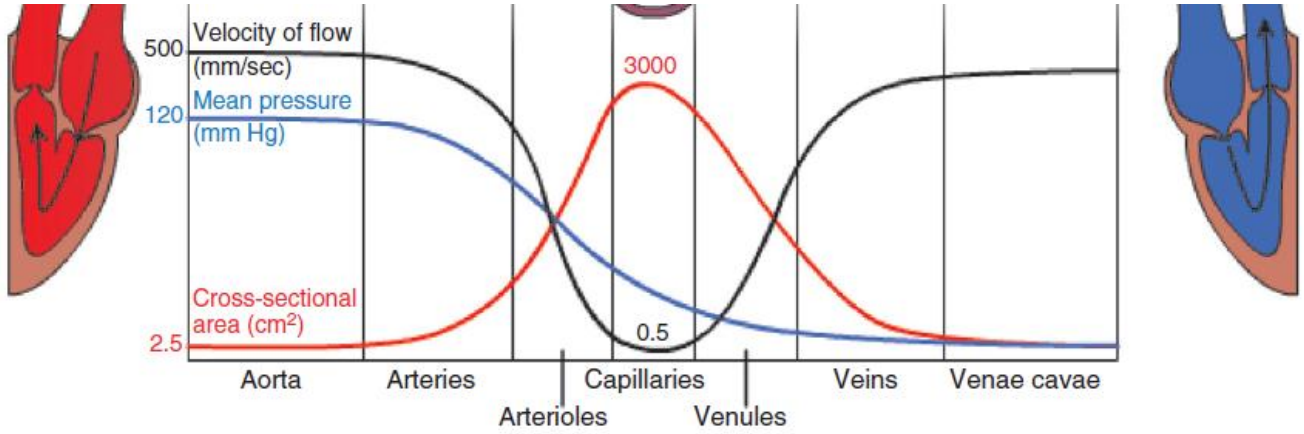
- Total body water = ~60% body weight.
- **Distribution**
  - Approximately two-thirds of body water is intracellular (inside cells).
  - Approximately one-third is extracellular.
    - 80% of extracellular fluid is in the interstitium.
    - 20% of extracellular fluid is in the plasma.
- **Regulation**

  Controlled by physical barriers, as well as pressure and concentration gradients between compartments.

Fluid Distribution and Homeostasis

Normal Homeostasis

- Hydrostatic pressure: pushes water out.
- Oncotic pressure (albumin): pulls water in.
- Lymphatics: prevent accumulation of interstitial fluid.



Dynamics of Microcirculation Exchange

- **Arteriolar End**
  High hydrostatic pressures within the arteriolar end of the capillary bed result in a net filtration of fluid into the interstitium.
- **Venular End**
  Lower hydrostatic pressures in the venular end of the capillary bed result in a net absorption pressure and reentry of fluid into the microvasculature.
- **Role of Lymphatics**
  The slight excess of fluid that is retained in the interstitium, along with any plasma proteins that have escaped, enters lymphatic capillaries to be drained from the area.

Fluid Distribution and Homeostasis

Interstitial Fluid as a Buffer

- ❖ Maintaining Plasma Volume
  Provides a fluid buffer to either increase or decrease the plasma volume, ensuring effective circulatory function.
- ❖ Response to Excess Fluid
  Excessive fluid intake expands plasma volume and increases hydrostatic pressure, resulting in greater filtration into the interstitium to maintain a relatively constant plasma volume.
- ❖ Response to Reduced Fluid
  Reduced fluid intake decreases plasma volume, shifting the movement of water from the interstitium into the plasma to increase circulating fluid volume.

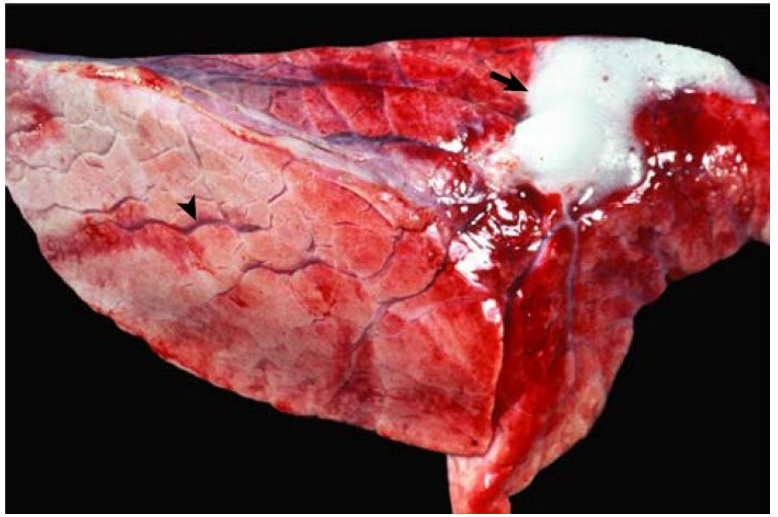
Key Regulatory Mechanisms

- ❖ Sodium and water balance (renal function, RAAS system).
- ❖ Albumin synthesis (liver function).
- ❖ Vascular integrity (endothelial health).

Fluid Distribution and Homeostasis

Failure of Homeostasis

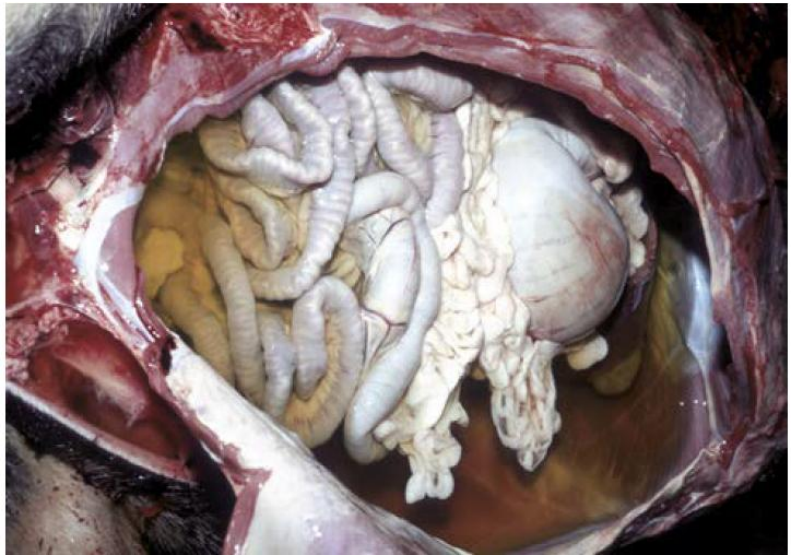
- Hypoproteinemia → ↓ oncotic pressure → generalized edema.
- Cardiac failure → ↑ venous hydrostatic pressure → pulmonary or dependent edema.
- Lymphatic obstruction → localized lymphedema.



Pulmonary edema, Lung, pig

Veterinary Examples

- Right-sided heart failure in dogs → ascites.
- Hypoproteinemia in horses with protein-losing enteropathy → ventral edema.
- Ruminants with Johne's disease → severe intermandibular edema ("bottle jaw").



Ascites (hydroperitoneum), Dog.

Abnormal Fluid Distribution (Edema)

Abnormal Fluid Distribution (Edema)

❖**What is Edema?**

Edema is the accumulation of excess interstitial fluid.

❖**Four Major Mechanisms** of Edema

- Increased microvascular permeability
- Increased intravascular hydrostatic pressure
- Decreased intravascular osmotic pressure
- Decreased lymphatic drainage

Abnormal Fluid Distribution (Edema)

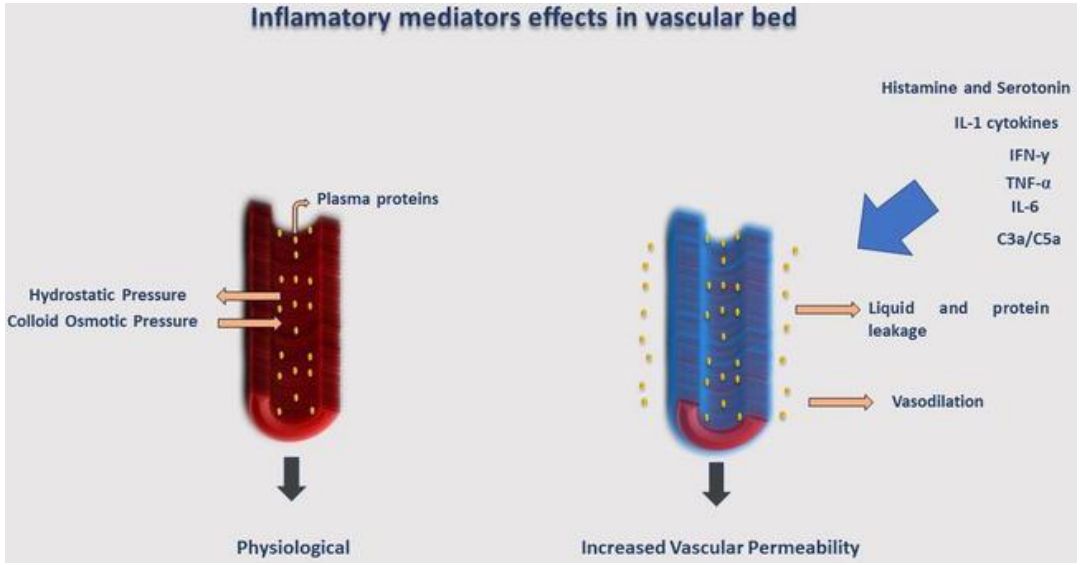
Edema Mechanism 1: Increased Permeability

❖ Primary Cause

Most commonly associated with the initial microvascular reaction to inflammatory or immunologic stimuli.

❖ Process

- Mediators like histamine, bradykinin, and leukotrienes cause endothelial cell contraction and widening of interendothelial gaps
  → immediate increases in permeability.
- Later, cytokines like IL-1 and TNF induce endothelial cell retraction
  → more persistent widening of the gaps.
- This allows intravascular fluid and proteins to move into the interstitium
  → localized edema.



https://www.intechopen.com/chapters/78035

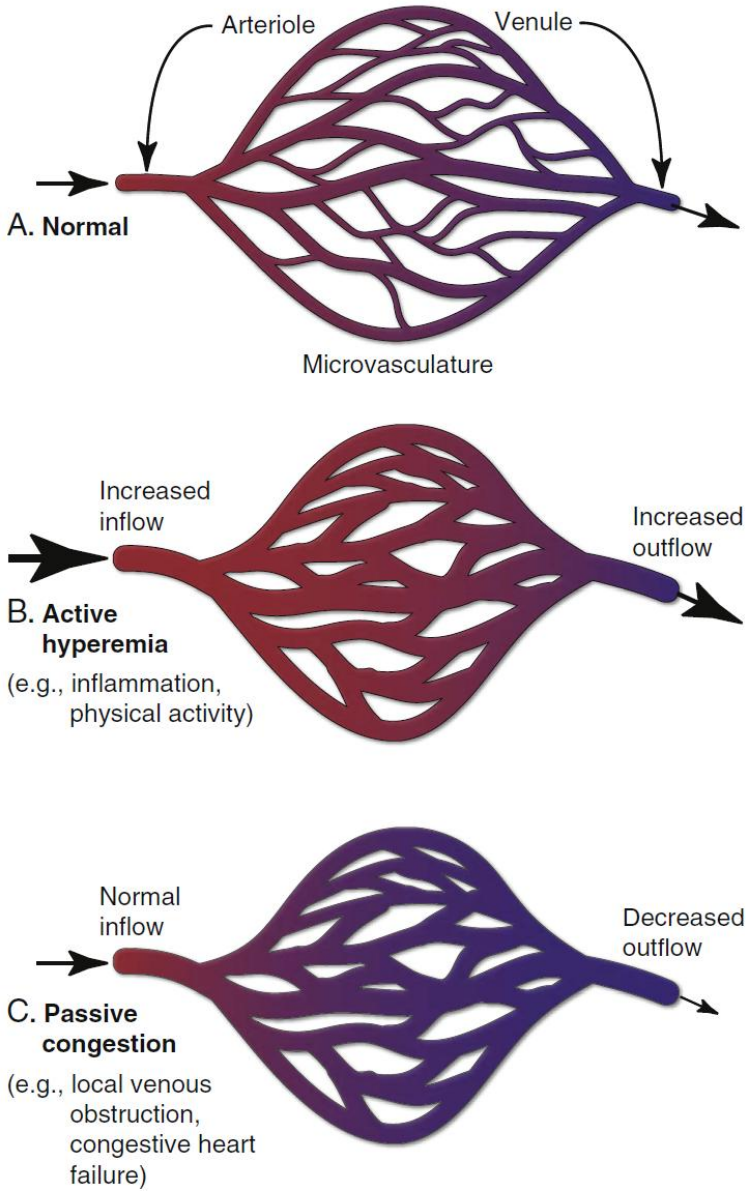
Abnormal Fluid Distribution (Edema)

Edema Mechanism 2: Increased Hydrostatic Pressure

- Primary Cause
  Most often due to increased blood volume in the microvasculature.

- Two Forms
  - Hyperemia: An active increased flow of blood into the microvasculature.
  - Congestion: A passive accumulation of blood, often caused by heart failure or localized venous compression or obstruction.

- Effect
  Increased microvascular pressure causes increased filtration of fluid out of the vessel and reduced absorption of fluid back into it.



Abnormal Fluid Distribution (Edema)

Edema Mechanism 3 & 4

❖ Decreased Intravascular Osmotic Pressure

- Cause: Most commonly results from decreased concentrations of plasma proteins, particularly albumin (hypoalbuminemia).
- Reasons for Hypoalbuminemia
  - Decreased production of albumin by **the liver** (e.g., due to malnutrition or severe liver disease).
  - Excessive loss of albumin from the plasma (e.g., through the **gastrointestinal tract** or **kidneys**).

❖ Decreased Lymphatic Drainage

- Cause: This occurs because of lymph vessel compression, constriction, or internal blockage.
- Effect: Reduces the ability of the lymphatic system to remove the slight excess of fluid that normally accumulates in the interstitium.

Abnormal Fluid Distribution (Edema)

Morphology and Significance of Edema

❖ Gross Appearance
- Characterized by clear to slightly yellow watery fluid that thickens and expands the affected interstitium.
- When it occurs in body cavities, it is named accordingly
  - Hydrothorax (thoracic cavity)
  - Hydropericardium (pericardial sac)
  - Ascites or Hydroperitoneum (abdominal cavity)

❖ Clinical Significance
- Depends mainly on its location.
- Subcutaneous edema or ascites may have minimal clinical impact.
- Edema in a confined space, like the brain or pericardial sac, can be life-threatening by causing pressure that impairs organ function.



Subcutaneous edema, Congenital Lymphedema, Skin, Dog.

Vascular Disorders and Thrombosis-2

Su-Hyung Lee, DVM, PhD

Alterations in Blood Flow and Perfusion

Alterations in Blood Flow and Perfusion

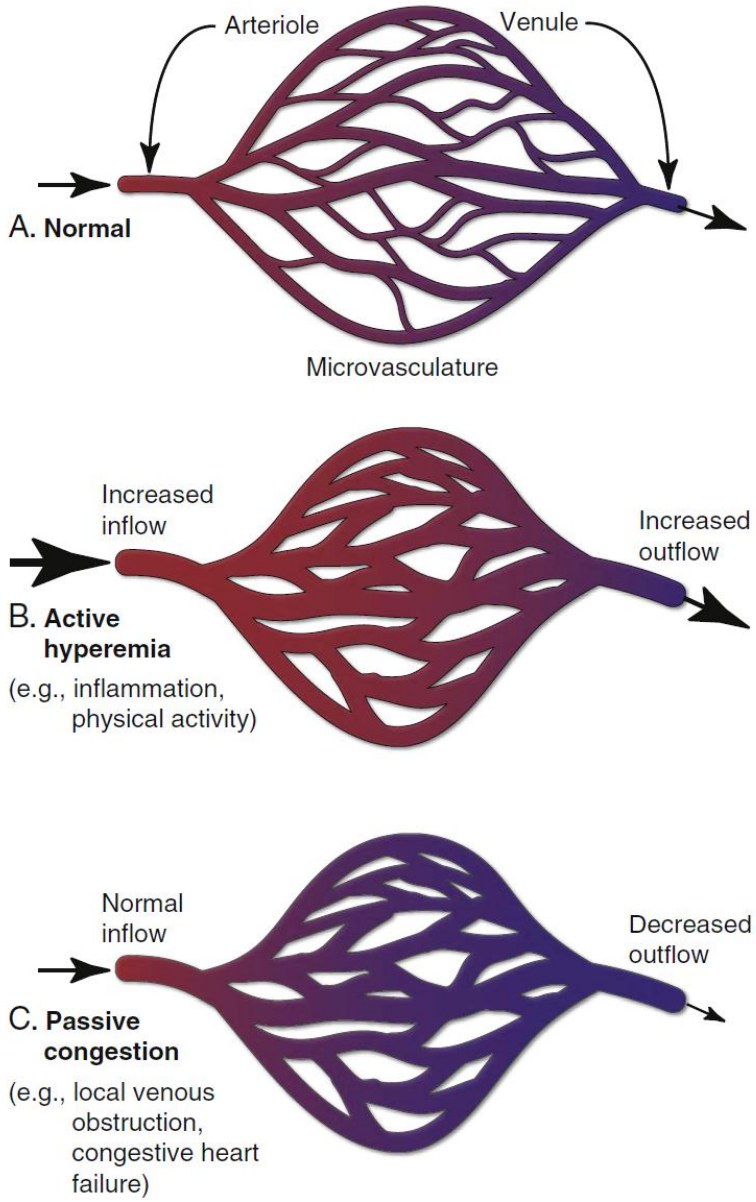
Hyperemia vs. Congestion

❖ **Hyperemia**

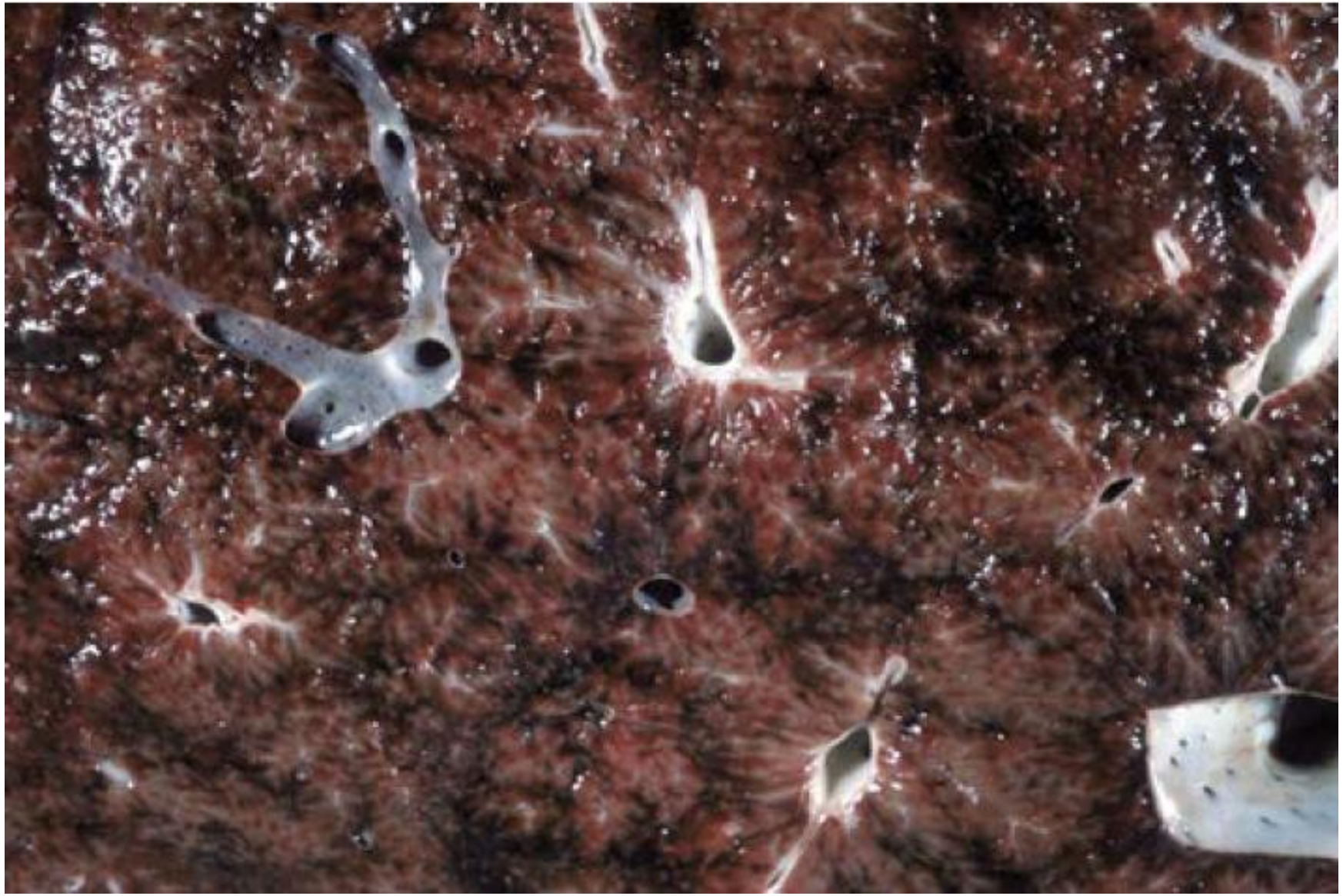
- Definition: An active engorgement of vascular beds due to arteriolar dilation and increased inflow.
- Causes: Can be physiologic (e.g., dissipating heat, digestion) or pathologic (e.g., the first stage of inflammation).
- Appearance: Tissues are bright red and warm.

❖ **Congestion**

- Definition: The passive engorgement of a vascular bed generally caused by a decreased outflow of blood.
- Causes: Can be local (e.g., venous obstruction) or generalized (e.g., heart failure).
- Appearance: Tissues are dark red, swollen (due to edema), and cooler than normal.



Alterations in Blood Flow and Perfusion

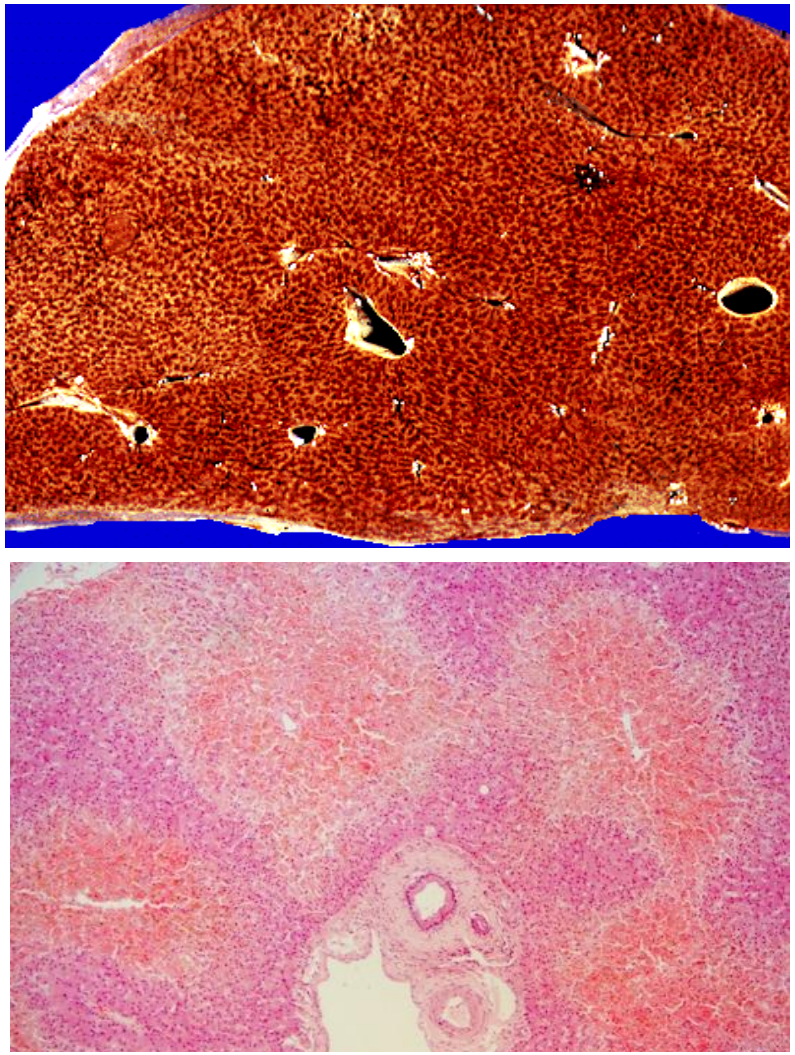


Chronic passive congestion (Nutmeg liver), Cow

Right-sided Heart failure

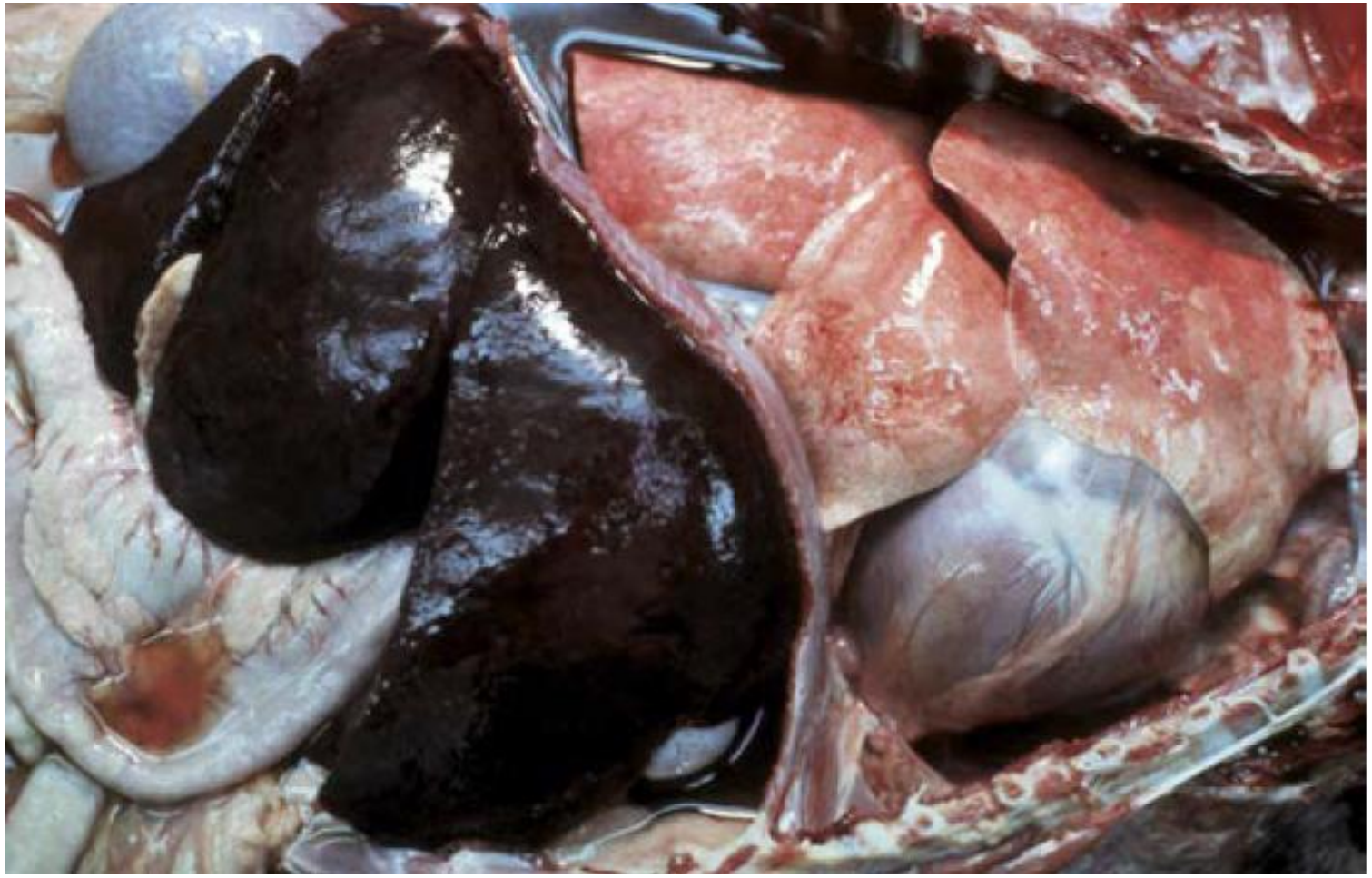
Consequences

- Progressive dilatation of right ventricle & atrium
- Right ventricular & atrial hypertrophy
- Generalized venous congestion
- Centrilobular (periacinar) congestion (nutmeg liver), degeneration, necrosis, and fibrosis of the liver
- Congestion of splenic red pulp
- Congestion of gastrointestinal tract → functional impairment → diarrhea
- Nasal hemorrhages; particularly common in horses
- Cyanosis may occur
- Generalized edema; varies by species: subcutaneous edema (horse, cow), ascites (dog), hydrothorax (cat)
- Left-sided heart failure; may occur if the animal survives for an extended period

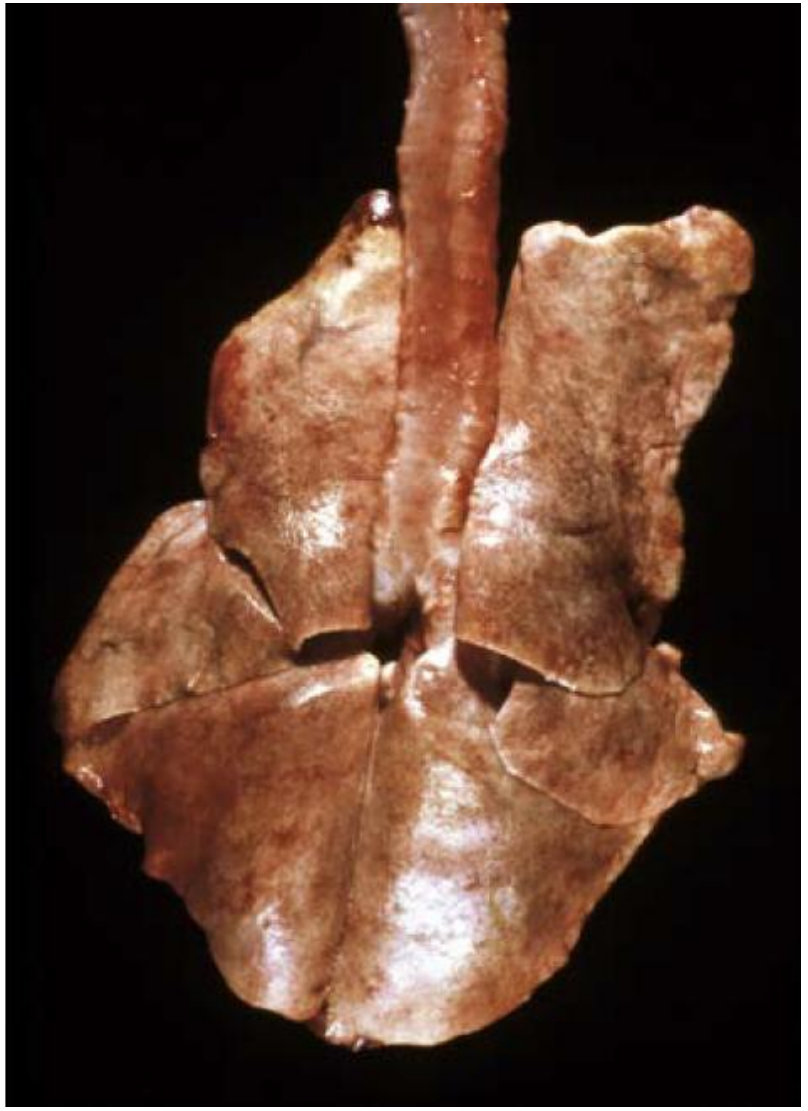


Nutmeg liver: chronic passive congestion
(Central necrosis + adjacent fatty change)

Alterations in Blood Flow and Perfusion



Acute passive congestion, Liver, Dog



Chronic passive congestion, lung, Dog

Alterations in Blood Flow and Perfusion

Ischemia

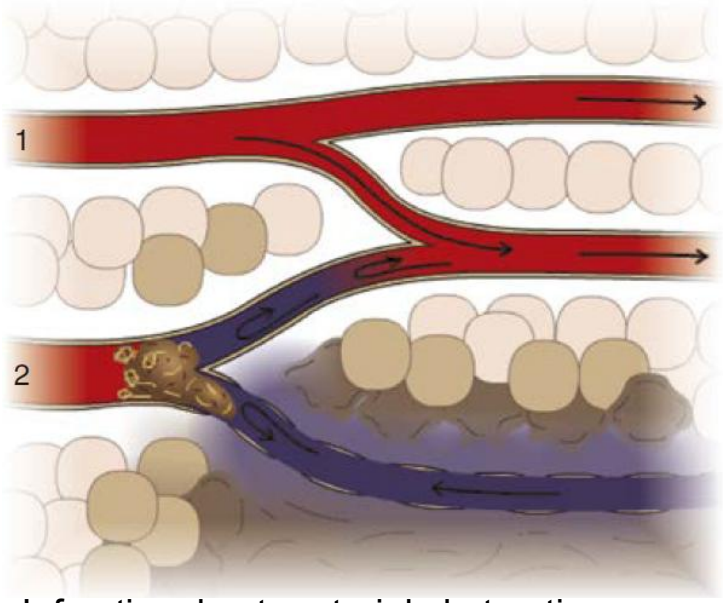
❖ Definition

- Ischemia occurs when the perfusion of a tissue becomes inadequate to meet its metabolic needs.

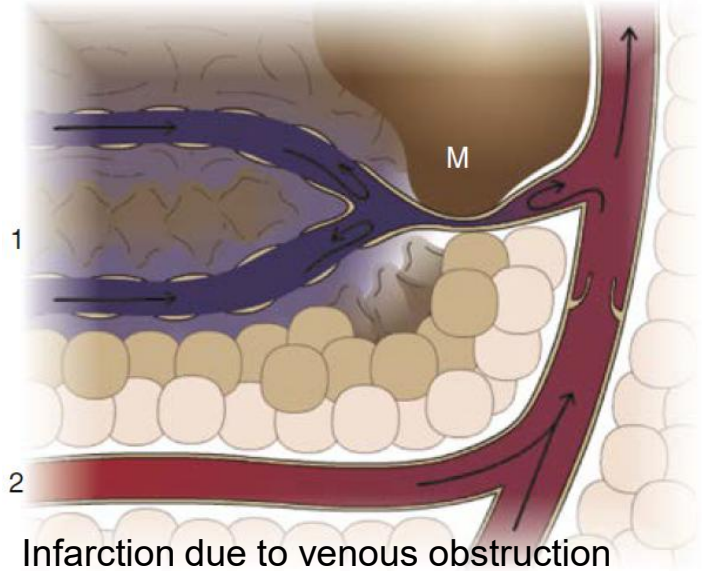
❖ Causes

- Arterial Causes: Most commonly the result of incomplete luminal blockage by a thrombus or embolus, or from prolonged arteriolar vasoconstriction. This leads to decreased inflow of oxygenated blood.
- Venous Causes: Can be caused by an intraluminal thrombus or, more commonly, by external pressure that occludes a vein (e.g., from a tumor or displaced organ). This leads to congestion, edema, and stagnation of blood.

Alterations in Blood Flow and Perfusion



Infarction due to arterial obstruction



Infarction due to venous obstruction

Infarction

❖ **Definition**

- An infarct is a local area of peracute ischemia that undergoes coagulative necrosis (tissue death).

❖ **Causes**

- Caused by the same events that result in ischemia, most commonly secondary to thrombosis or thromboembolism.

❖ **Susceptibility**

- Tissues with a single blood supply and minimal collateral circulation (e.g., brain, heart, kidney) are highly susceptible to infarction.
- Tissues with dual blood supplies (e.g., liver, lung) are not commonly susceptible unless there is a concurrent underlying disease.

Alterations in Blood Flow and Perfusion

Characteristics of an Infarct

❖ **Appearance**

- Initially dark red due to hemorrhage from damaged vessels. Over time (1 to 5 days), as cells undergo necrosis and swell, blood can be forced out of the region, giving it a progressively paler appearance.

❖ **Tissue-Specific Differences**

- In loose, spongy tissues like the lungs, infarcts usually remain red because pressure does not build up to force blood out.
- In solid parenchymal tissues like the kidney, they generally become pale over time.

❖ **Healing**

- The necrotic debris is cleared by leukocytes and macrophages, and the region is eventually replaced with fibrous tissue (a scar).



Acute hemorrhagic infarct, Kidney, Dog

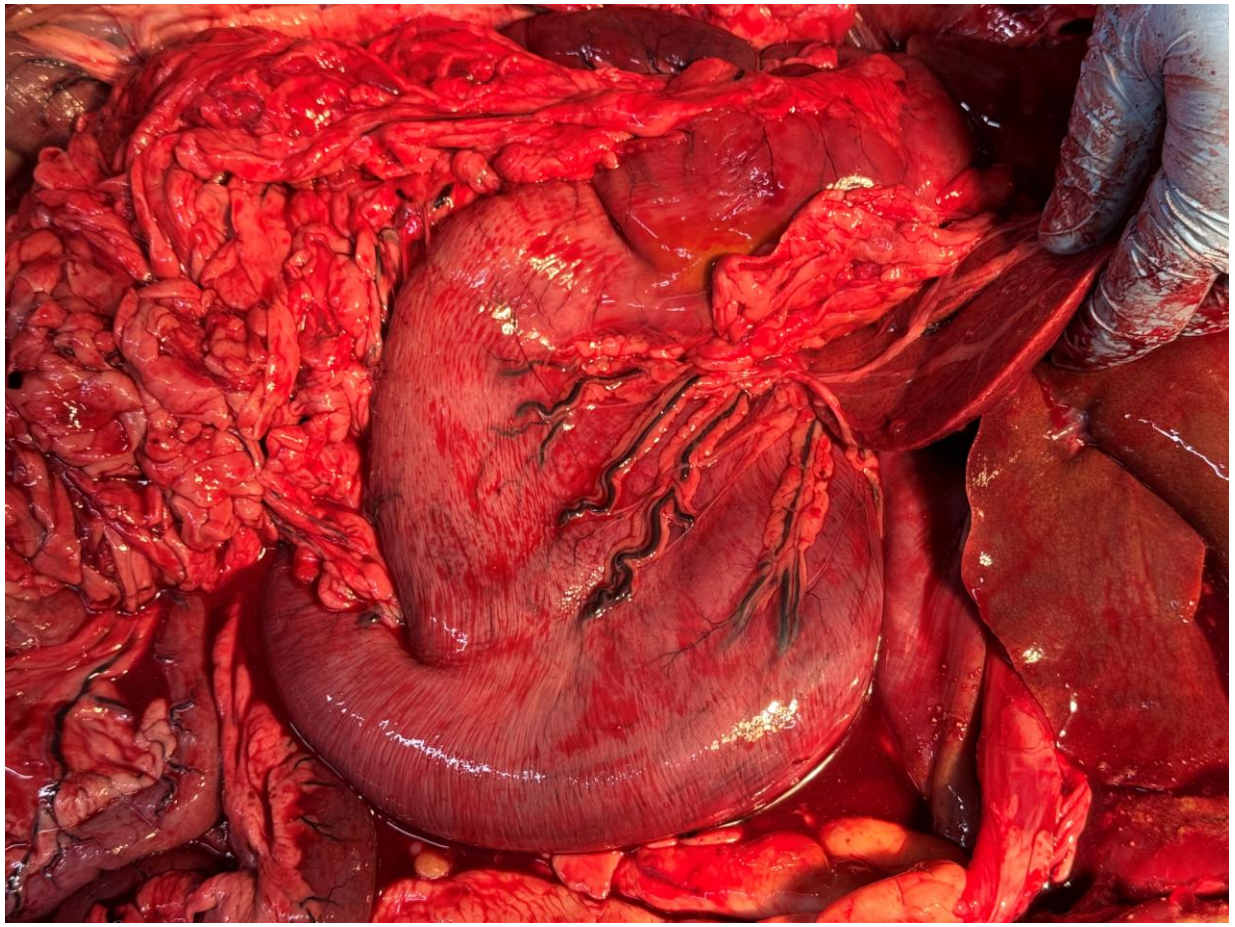


Acute pale infarct, Kidney, Rabbit

Alterations in Blood Flow and Perfusion



Venous infarction, small intestinal volvulus, Pig



Venous infarction, Gastric dilation and volvulus, Dog, SNU case 2024

Abnormal Fluid Distribution (Shock)

Abnormal Fluid Distribution (Shock)

Definition and Progression

❖ Definition

- Shock (cardiovascular collapse) is a circulatory dyshomeostasis associated with loss of circulating blood volume, reduced cardiac output, and/or inappropriate peripheral vascular resistance.

❖ Underlying Events

- The primary problem is hypotension, which results in impaired tissue perfusion and cellular hypoxia.

❖ Progression

- While the cellular effects are initially reversible, persistence of shock results in irreversible cell and tissue injury.
- Shock is rapidly progressive and life-threatening when compensatory responses are inadequate.

Abnormal Fluid Distribution (Shock)

Types of Shock: Cardiogenic & Hypovolemic

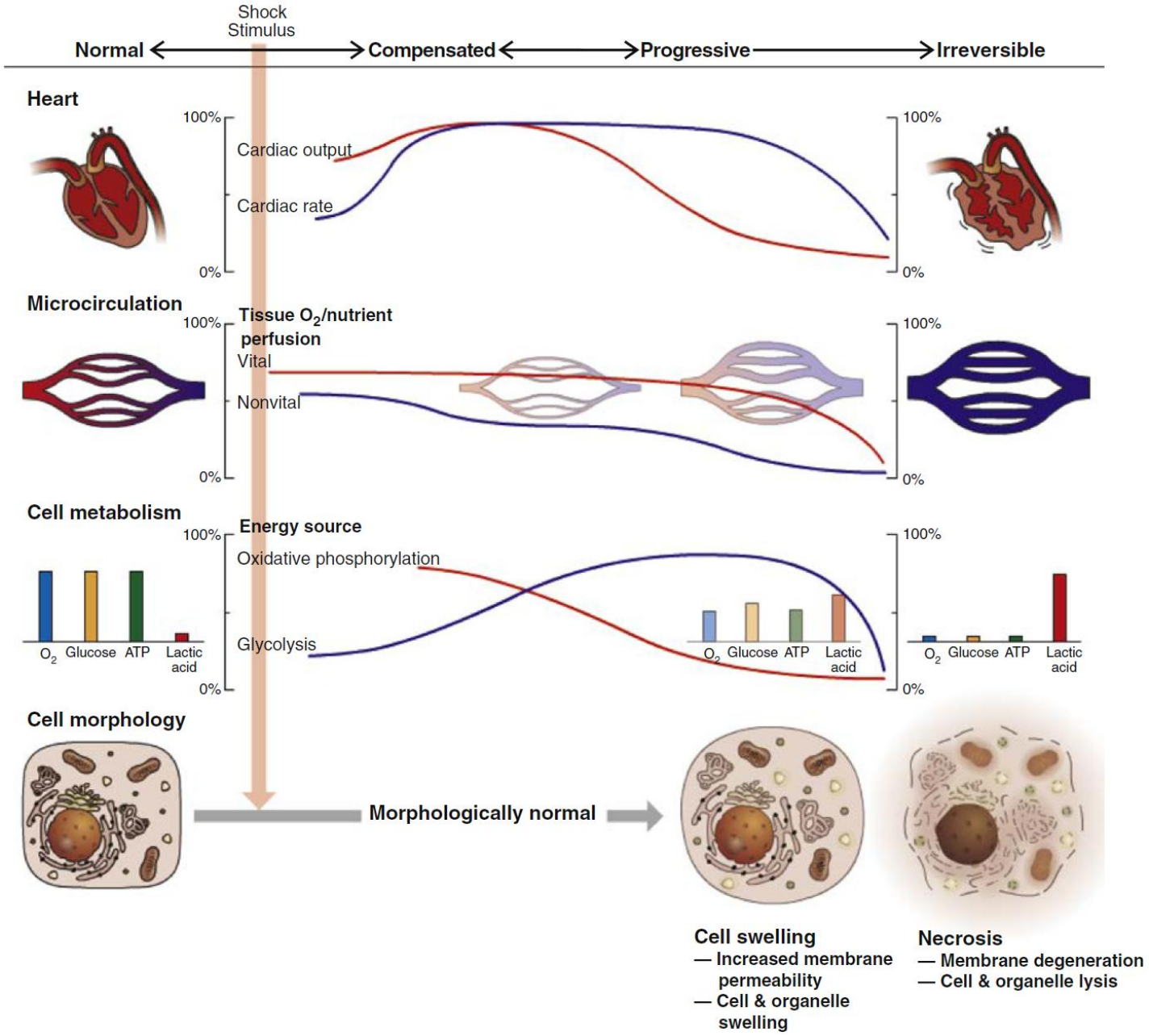
❖ Cardiogenic Shock

- Cause: Results from the failure of the heart to adequately pump blood.
- Examples: Can be caused by myocardial infarction, severe arrhythmias, cardiomyopathy, or obstruction of blood flow from the heart (e.g., pulmonary embolism).

❖ Hypovolemic Shock

- Cause: Arises from reduced circulating blood volume.
- Examples: Can be the result of blood loss from hemorrhage or fluid loss secondary to severe vomiting, diarrhea, or burns.
- Loss of approximately 10% of blood volume can be compensated for, but losses approaching 35-45% can cause blood pressure and cardiac output to fall dramatically.

Abnormal Fluid Distribution (Shock)



- In hypovolemic shock, there is initially compensation characterized by increased cardiac rate and output, vasoconstriction of nonessential vascular beds, and predominantly oxidative metabolism by morphologically normal cells.
- With progression, cardiac output falls as peripheral vasodilation occurs
- Then, cell metabolism shifts to glycolysis with progressive morphologic deterioration of cells.

Abnormal Fluid Distribution (Shock)

Types of Shock: Blood Maldistribution

❖ General Mechanism

- Characterized by decreased peripheral vascular resistance and pooling of blood in peripheral tissues, caused by neural or cytokine-induced vasodilation.
- Although blood volume is normal, the effective circulating blood volume is decreased.

❖ Subtypes

- Anaphylactic Shock: A generalized type I hypersensitivity reaction where widespread mast cell degranulation releases histamine, causing systemic vasodilation.
- Neurogenic Shock: Induced by trauma (especially to the nervous system), electrocution, or severe emotional stress, leading to autonomic discharges that cause peripheral vasodilation.
- Septic Shock: The most common type of shock associated with blood maldistribution.

Abnormal Fluid Distribution (Shock)

Stages of Shock

- ❖ Nonprogressive Stage
  - Characterized by compensatory mechanisms that counteract the initial insult. These include increased heart rate, peripheral vasoconstriction, and activation of hormonal systems (renin-angiotensin, ADH) to maintain blood pressure and perfusion to vital organs like the heart and brain.
- ❖ Progressive Stage
  - Occurs when compensatory mechanisms are inadequate. This stage is characterized by widespread tissue hypoperfusion and a shift from aerobic to anaerobic metabolism, leading to lactic acidosis. This acidosis causes arteriolar dilation, leading to blood pooling and a further drop in cardiac output.
- ❖ Irreversible Stage
  - Occurs when widespread cell and tissue injury becomes so severe that recovery is not possible. This stage is often associated with the syndrome of multiple organ dysfunction, where the failure of one organ contributes to the failure of another.

Abnormal Fluid Distribution (Shock)

Morphologic Features of Shock

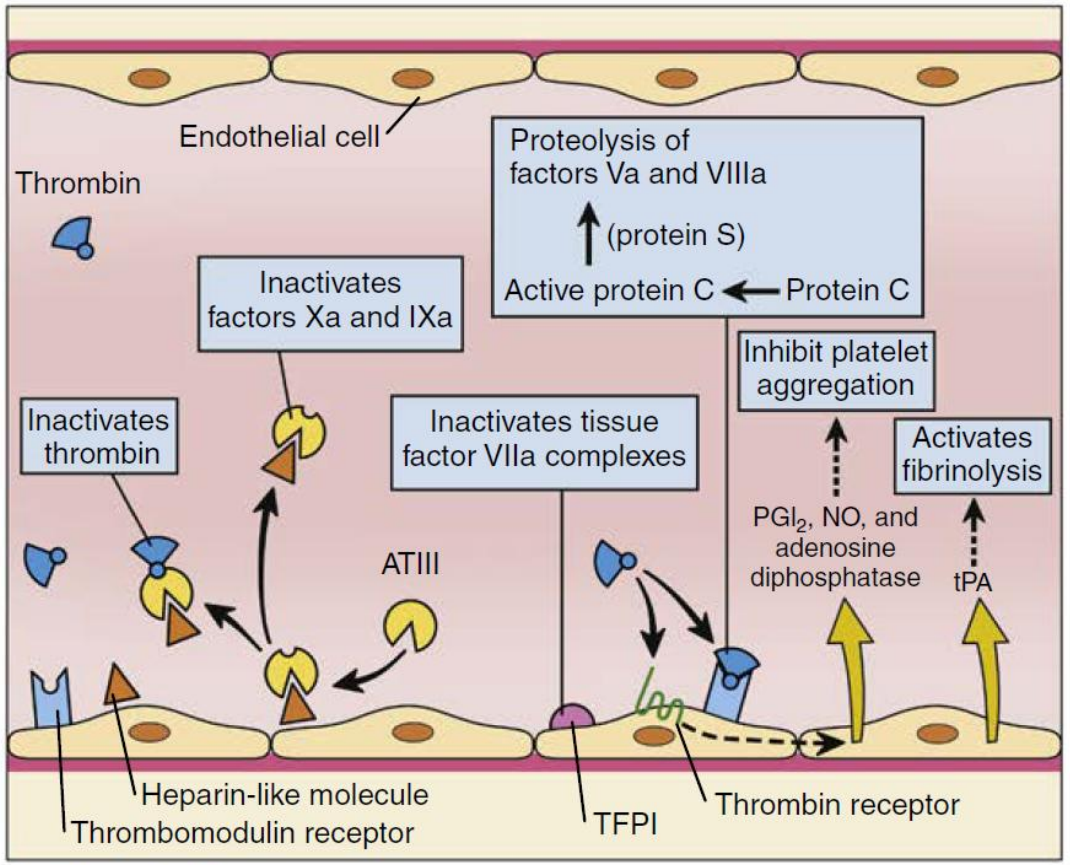
❖ General Findings
- Lesions are variable and depend on the cause and severity.
- Characteristically, there are vascular changes accompanied by cell degeneration and necrosis.

❖ Common Lesions
- Generalized congestion and pooling of blood.
- Edema, hemorrhage (petechial and ecchymotic), and microthrombosis.

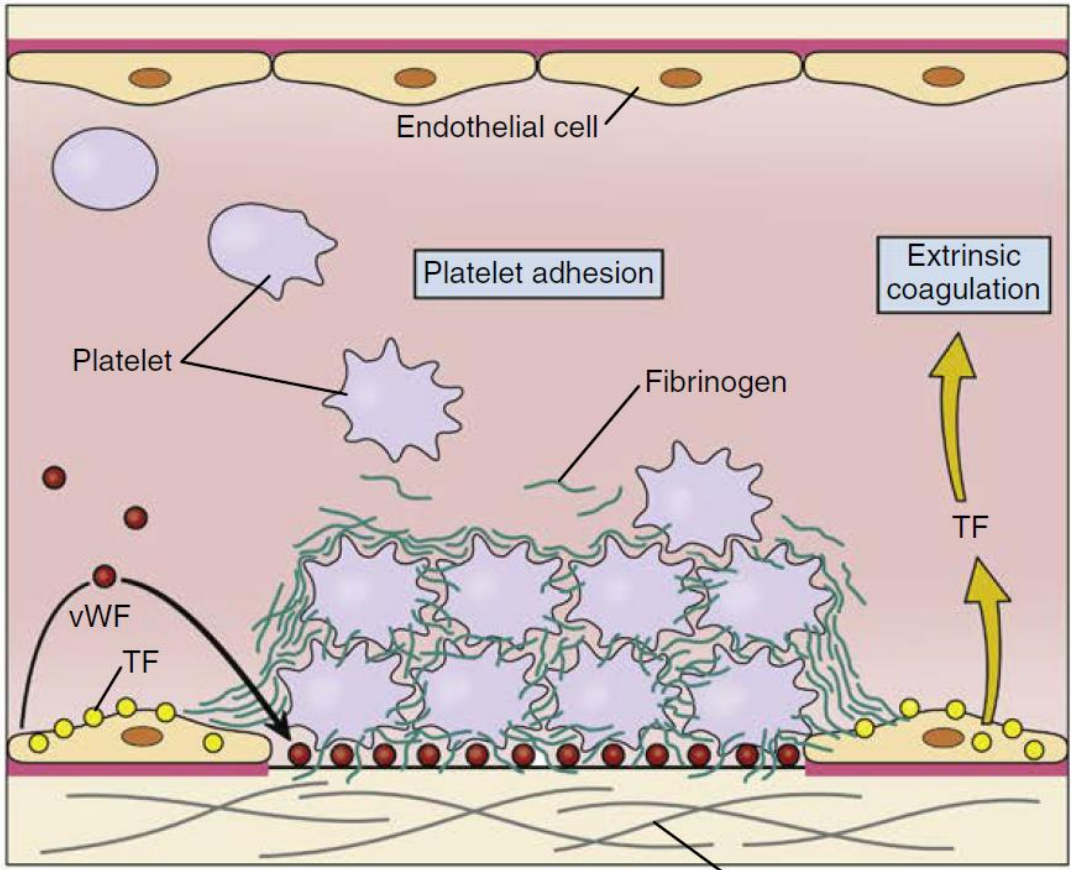
❖ Organ-Specific Changes
- Lungs: Severe congestion, edema, and hemorrhage.
- Liver: Centrilobular hepatic necrosis.
- Kidneys: Renal tubular necrosis.
- Gastrointestinal Tract: Mucosal necrosis.
- Heart: Myofibril coagulation necrosis.
- Brain: Cerebral edema and sometimes cerebrocortical laminar necrosis.

Hemostasis

Hemostasis

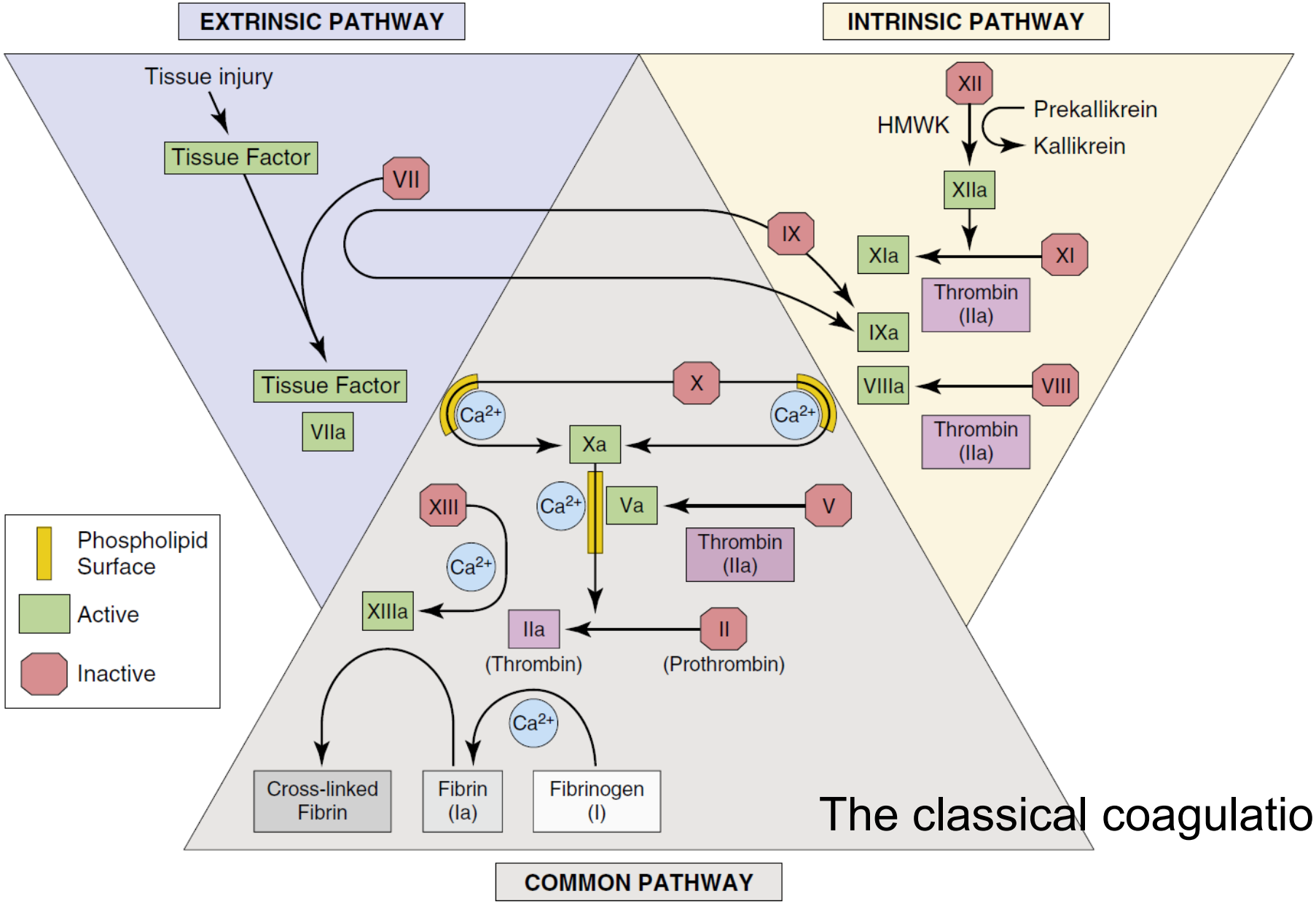


A **Antithrombotic events**



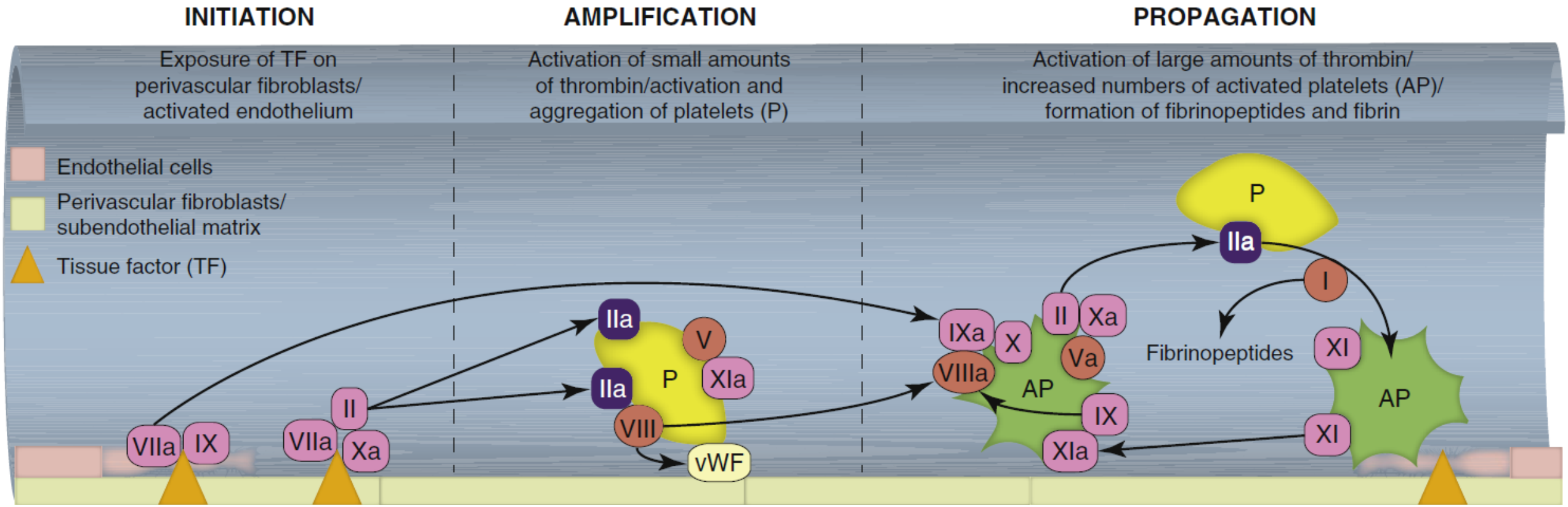
B **Prothrombotic events**

Hemostasis



The classical coagulation cascades

Hemostasis



Cell-based model of coagulation

Hemostasis

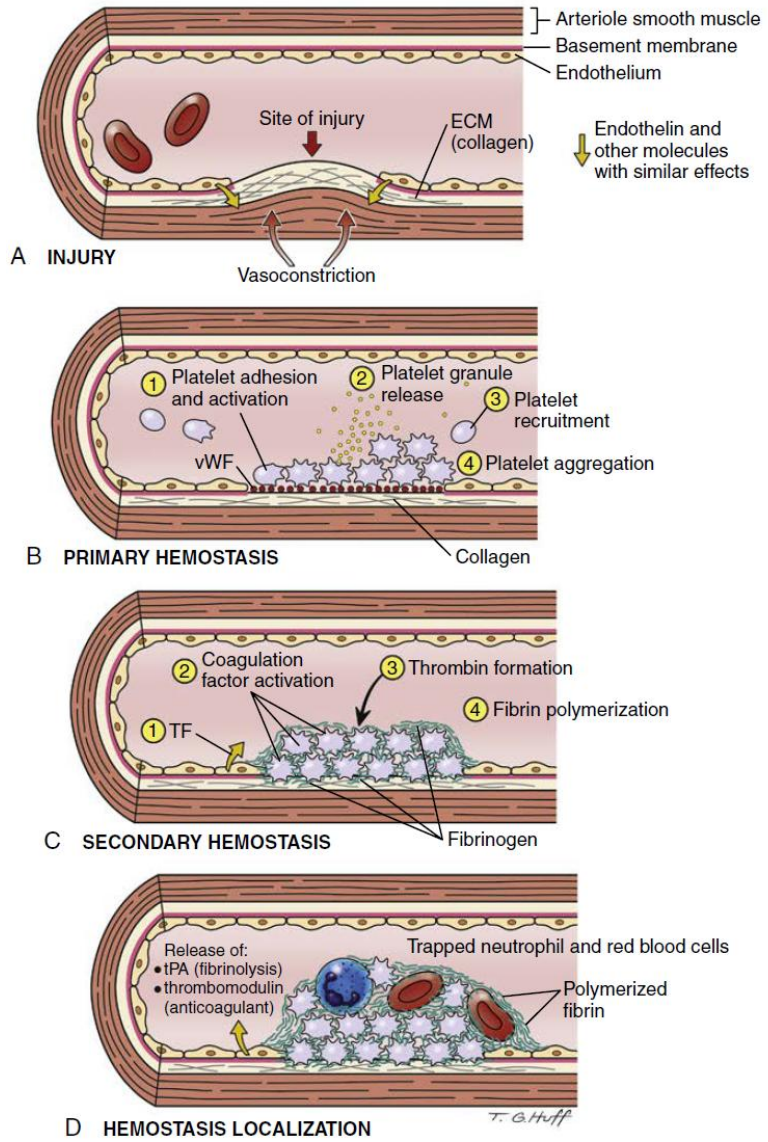
Hemostasis - An Overview

❖ Definition
- Hemostasis is the arrest of bleeding.
- A physiologic response to vascular damage to seal an injured vessel.

❖ Key Players
- It is a finely regulated process involving interactions between:
  - Endothelium
  - Platelets
  - Coagulation factors

❖ Balance

Disruption of the delicate balance of hemostasis can result in hemorrhage (blood loss) or thrombosis (inappropriate clotting).



Hemostasis

Primary Hemostasis

❖ Definition

Includes the initial vascular and platelet response to injury.

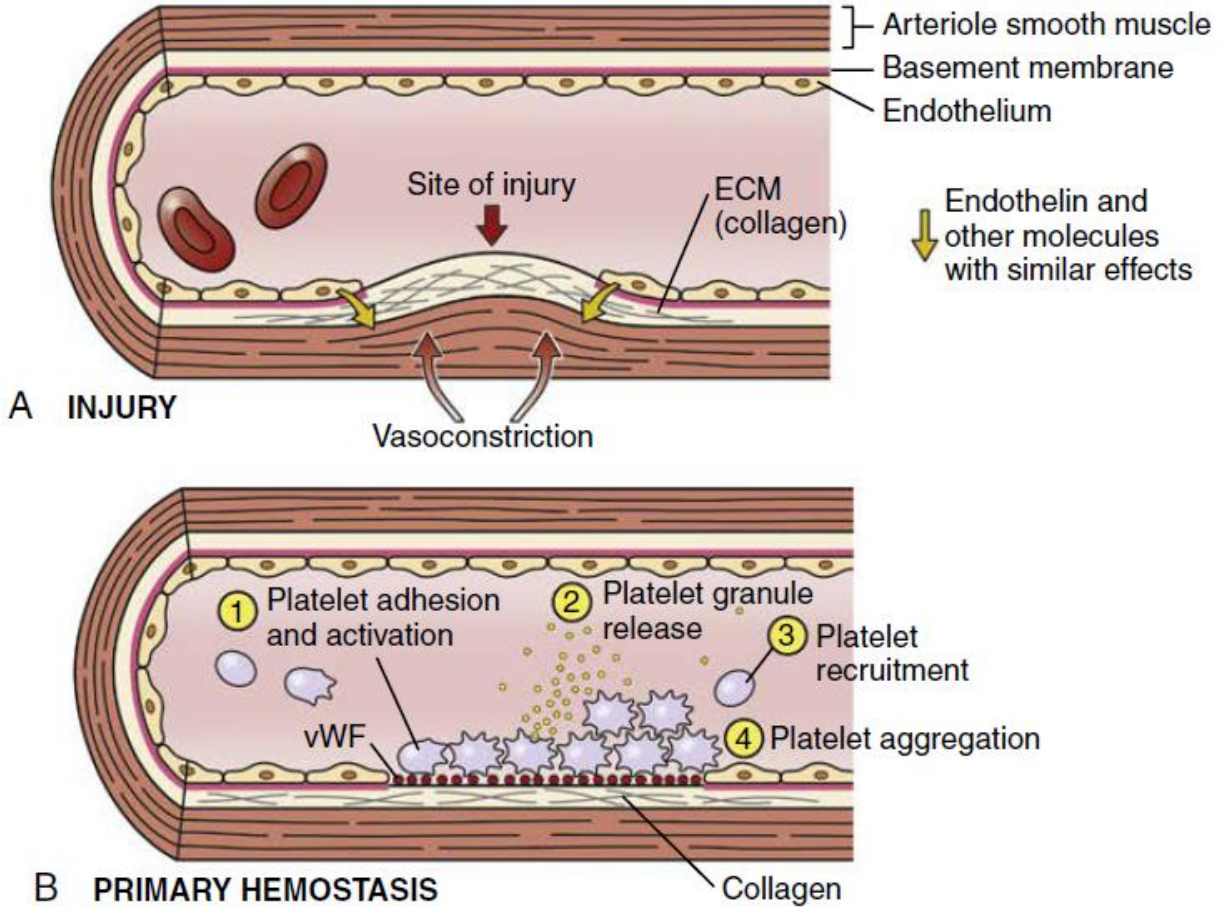
❖ Steps

✓ Vasoconstriction: Neurogenic stimuli and local mediators cause immediate vasoconstriction after damage.

✓ Platelet Adhesion: Platelets adhere to the exposed subendothelial matrix.
This adhesion is made more efficient by von Willebrand factor (vWF).

✓ Platelet Aggregation: ADP released from platelets triggers the binding of fibrinogen to platelet receptors, linking platelets into a loose aggregate.

✓ Platelet Plug Formation: Platelet contraction consolidates this loose aggregate into a dense plug, which can be sufficient to stop bleeding if the injury is minimal.



Hemostasis

Secondary Hemostasis

❖ Definition

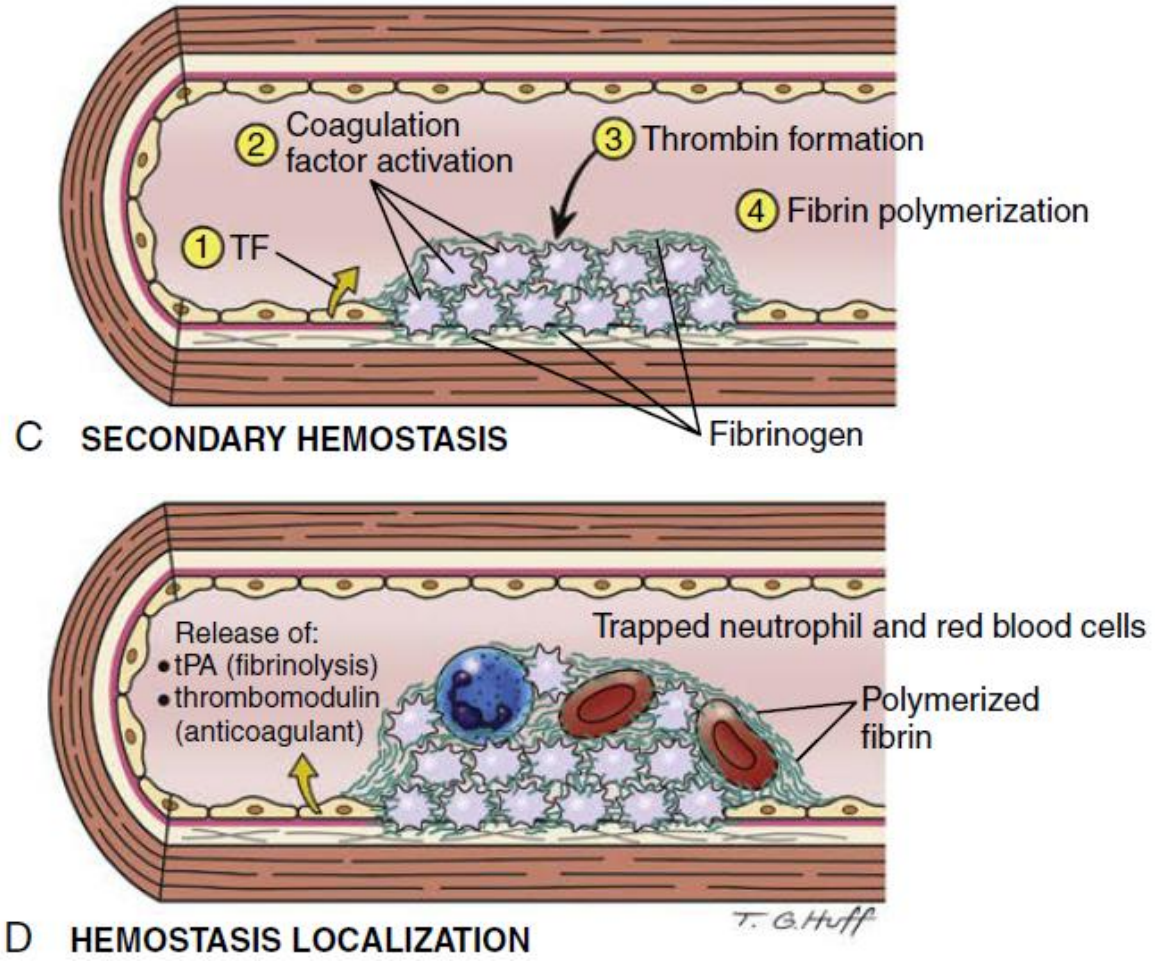
The formation of a fibrin meshwork to stabilize the initial platelet plug.

❖ The Coagulation Cascade

- A series of enzymatic reactions involving coagulation factors.
- Initiated by the exposure of blood to Tissue Factor (TF).
- Forms a complex with factor VIIa, activating factors X and IX.
- Small amounts of thrombin generated during initiation activate more platelets and factors (V, VIII, XI).
- This leads to a burst of thrombin generation.

❖ Fibrin Formation

- High concentrations of thrombin cleave fibrinogen into fibrin monomers.
- Fibrin monomers spontaneously self-polymerize, and are then cross-linked by factor XIIIa to form an insoluble fibrin polymer.



Hemostasis

Thrombolysis and Fibrinolysis

❖ **Purpose**

The fibrin-platelet aggregate is a temporary patch that is dissolved (thrombolysis) after the vessel heals.

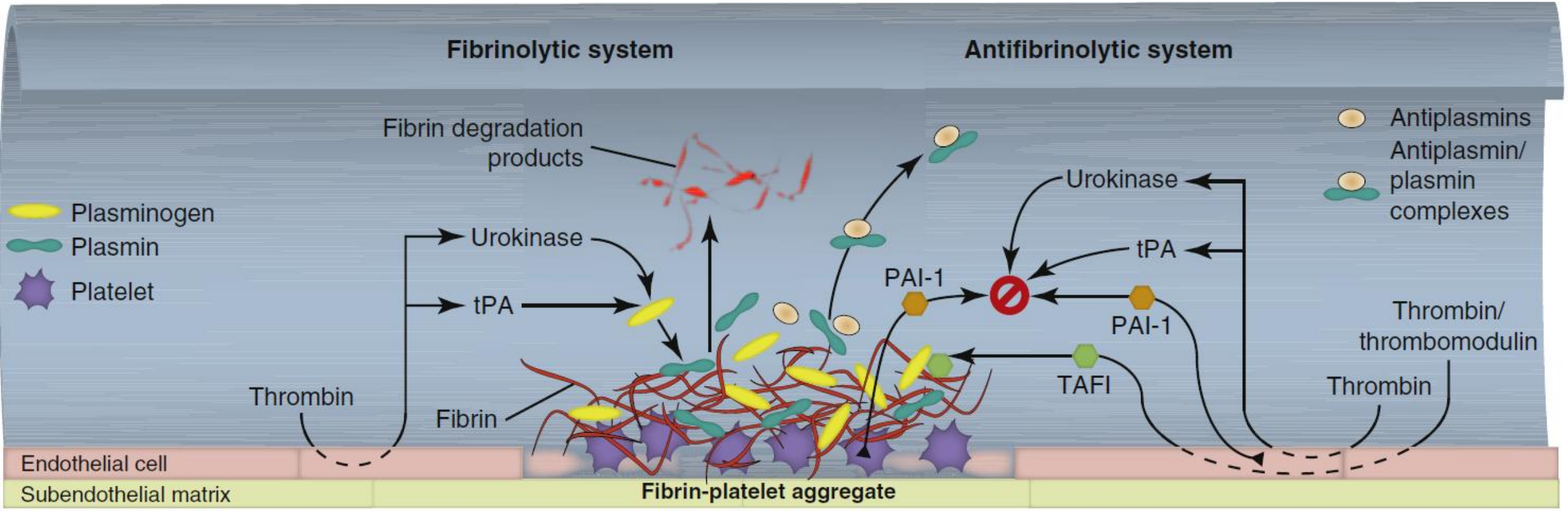
❖ **Fibrinolysis: The Key Process**

- The most important aspect of thrombolysis is fibrin dissolution (fibrinolysis).
- Initiated by the cleavage of the plasma protein **plasminogen into plasmin**, a potent **fibrinolytic agent**.
- Plasminogen activators, such as tissue plasminogen activator (tPA) released from endothelium, drive this conversion.

❖ **Action of Plasmin**

Plasmin degrades both cross-linked fibrin and fibrinogen, restricting the size of the aggregate and breaking it down.

Hemostasis



Fibrinolysis

Regulation of Hemostasis

❖ The Need for Control

- The potent biologic effects of hemostasis must be finely regulated to prevent detrimental effects from too little or too much activity.

❖ Major Anticoagulant Mechanisms

- **Antithrombin (AT)**: A circulating protease that degrades most activated coagulation factors, most importantly thrombin and factor Xa. Its activity is vastly accelerated by heparin-like molecules.

- **The Protein C Pathway**: Thrombin binds to the endothelial receptor thrombomodulin, which activates Protein C. Activated protein C, along with its cofactor Protein S, potently inhibits coagulation by destroying factors Va and VIIIa.

- **Tissue Factor Pathway Inhibitor (TFPI)**: Inhibits the TF:VIIa complex, providing negative feedback to the extrinsic pathway.

Disorders of Hemostasis

Disorders of Hemostasis

Hemorrhage - Causes

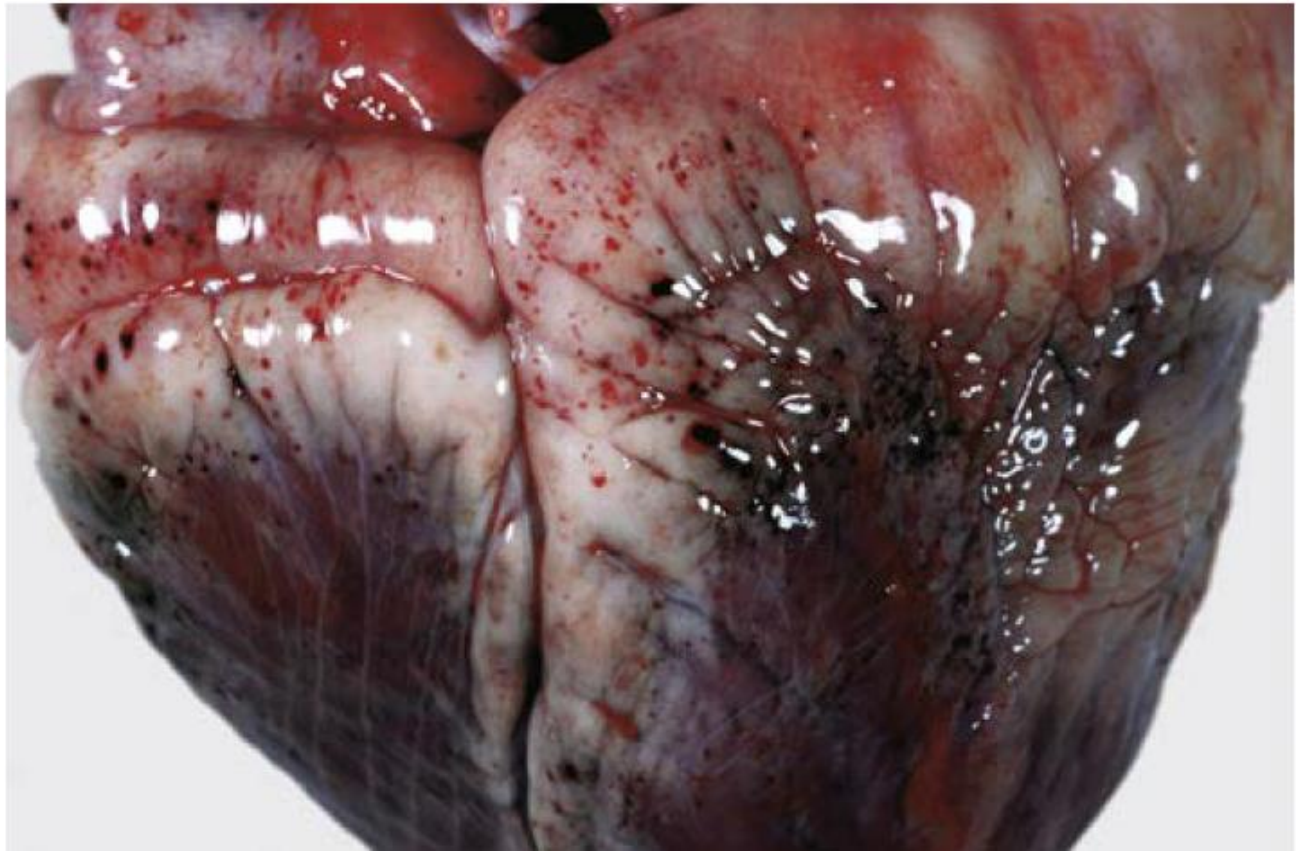
❖ Definition

- Hemorrhage occurs because of abnormal function or integrity of one or more major hemostatic factors: endothelium/blood vessels, platelets, or coagulation factors.

❖ Causes

- **Vascular Abnormalities**: Trauma can physically disrupt a vessel (rhexis). Endothelial injury from toxins (e.g., endotoxemia) or infections can also cause hemorrhage.
- **Platelet Disorders**:
  - Thrombocytopenia (decreased platelet numbers): Can result from decreased production, increased destruction, or increased use of platelets (e.g., **Immune-mediated thrombocytopenia (IMT)**).
  - Thrombocytopathy (abnormal platelet function): Can be inherited (e.g., Glanzmann's thrombasthenia) or acquired (e.g., from aspirin).
- **Coagulation Factor Deficiencies**:
  - Can be inherited (e.g., hemophilias A and B).
  - Can be acquired due to decreased production (severe liver disease) or factors that interfere with function (e.g., vitamin K deficiency from rodenticide toxicity).

Disorders of Hemostasis



Hemorrhage, endotoxemia, Heart, Cow

Escherichia coli (colibacillosis, septicemia)
Salmonella spp. (enteritis → septicemia)
Pasteurella multocida (septicemia)
Actinobacillus spp. (A. suis in pigs, A. equuli in foals)
Klebsiella spp.
Pseudomonas aeruginosa



Hemorrhage, Anticoagulant rodenticide toxicosis, skin and subcutis, Dog.

Disorders of Hemostasis

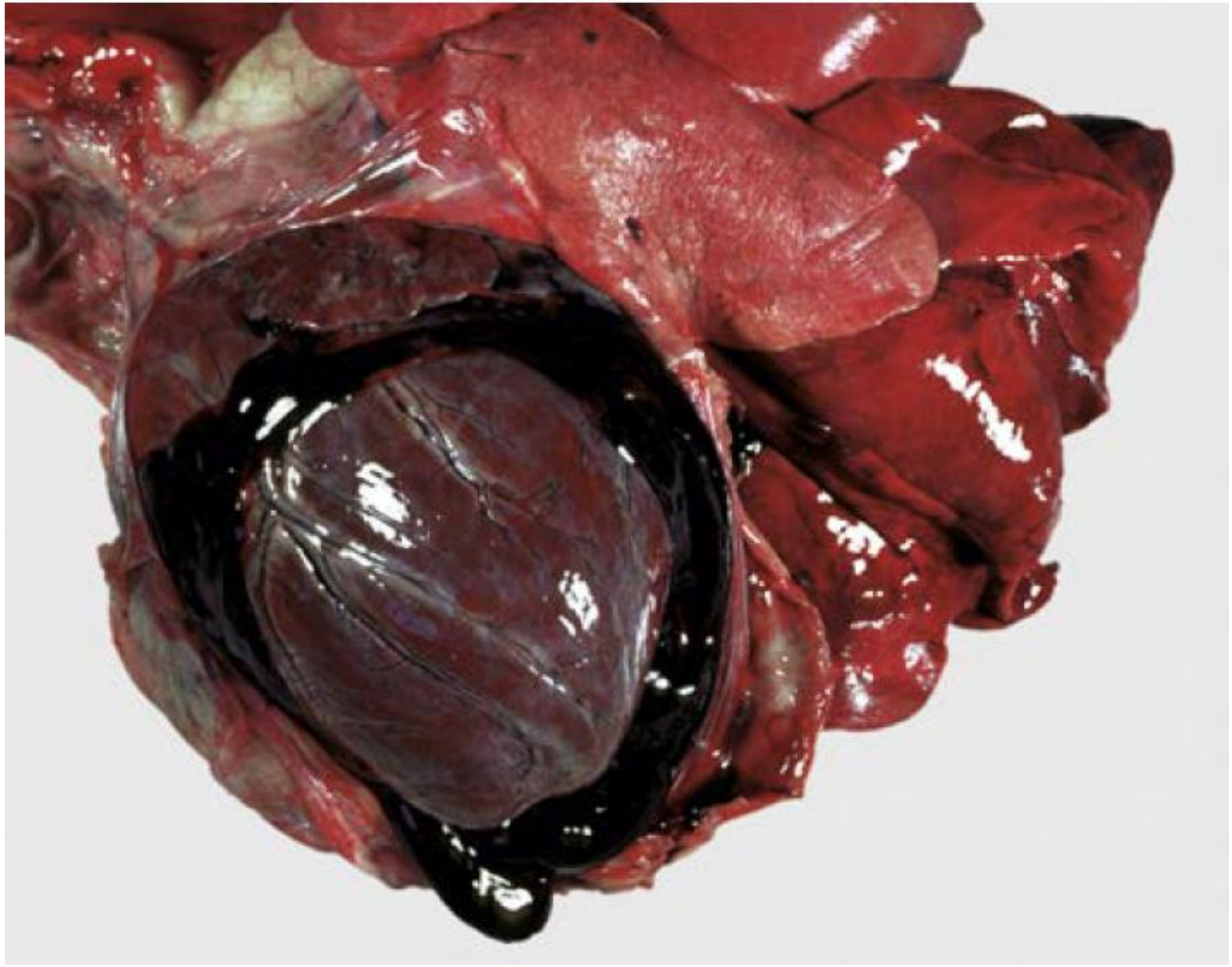


Ecchymotic hemorrhage, subcutis, Rabbit



Suffusive hemorrhage, serosa, stomach, Dog

Disorders of Hemostasis



Hemopericardium, Pericardial sac, Dog

Trauma
Rupture (e.g., hypertension -> aortic rupture)

Hemagiosarcoma
Chemodectoma

Rodenticide (e.g., warfarin)
DIC
Thrombocytopenia

Septicemia

Disorders of Hemostasis (Hemopericardium)

Species	Common Causes	Examples
Dog	**Neoplastic (most common)**	- **Right atrial hemangiosarcoma** (classic cause) - Chemodectoma (aortic body tumor) - Rare: lymphoma, mesothelioma
	Coagulopathy	- Anticoagulant rodenticide poisoning (warfarin, brodifacoum) - Disseminated intravascular coagulation (DIC) - Immune-mediated thrombocytopenia (IMT)
	Trauma	- Blunt trauma, traffic accident - Iatrogenic (during pericardiocentesis or cardiac puncture)
Horse	**Aortic rupture** (especially in stallions)	- Breeding stallions: spontaneous rupture of the ascending aorta leading to acute hemopericardium
	Trauma	- Severe thoracic trauma
Cat	**Cardiac/atrial rupture**	- Hypertrophic cardiomyopathy (HCM) → left atrial rupture
	Coagulopathy	- Anticoagulant rodenticide poisoning- Severe thrombocytopenia
Cattle / Ruminants	**Traumatic pericarditis** → vascular rupture	- Hardware disease (traumatic reticulopericarditis)
	Septicemia-associated vascular damage	- Bacterial endocarditis or septicemia causing vessel rupture
All species	**Toxic/hematologic disorders**	- Anticoagulant rodenticide toxicity- DIC
	Iatrogenic	- Complication of pericardiocentesis- Surgical vascular injury

Disorders of Hemostasis

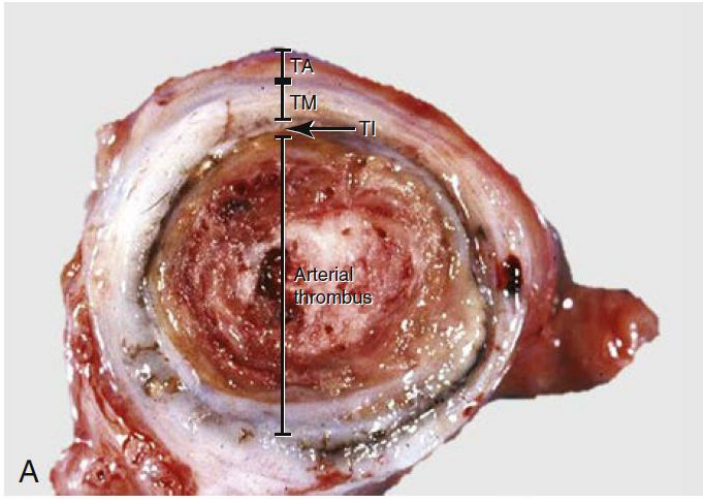
Thrombosis - Virchow's Triad

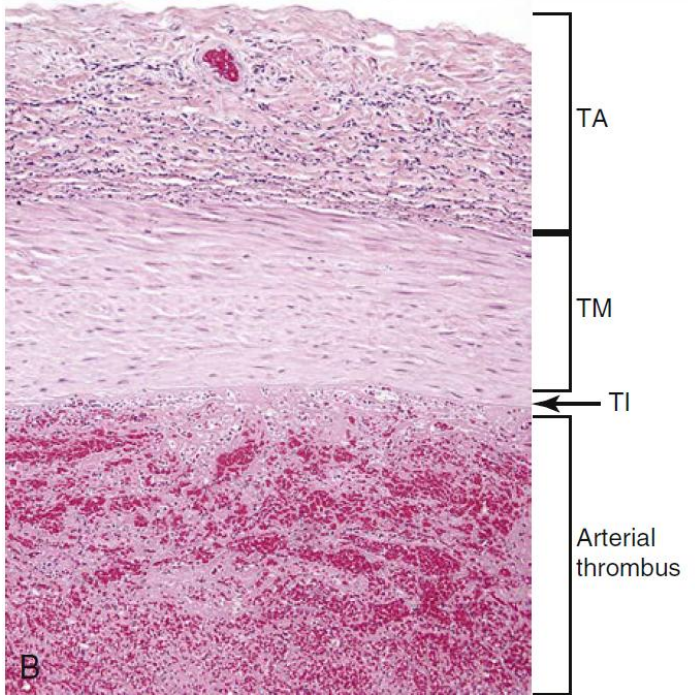
❖ **Definition**

- Thrombosis is the formation of a thrombus (an aggregate of platelets, fibrin, and other blood elements) on a vascular wall.

❖ Virchow's Triad

- The three major determinants of thrombosis are:
  - **Endothelial Injury**: The single most important factor. It exposes prothrombotic subendothelial components and causes endothelium to lose its anticoagulant properties.
  - **Abnormal Blood Flow** (Stasis or Turbulence): Disrupts laminar flow, allowing greater interaction between platelets and the endothelium. It also prevents the dilution and clearance of activated clotting factors.
  - **Hypercoagulability**: An increased coagulability of blood, which can be caused by inflammation, stress, neoplasia, or renal disease.





Disorders of Hemostasis

Fates of a Thrombus

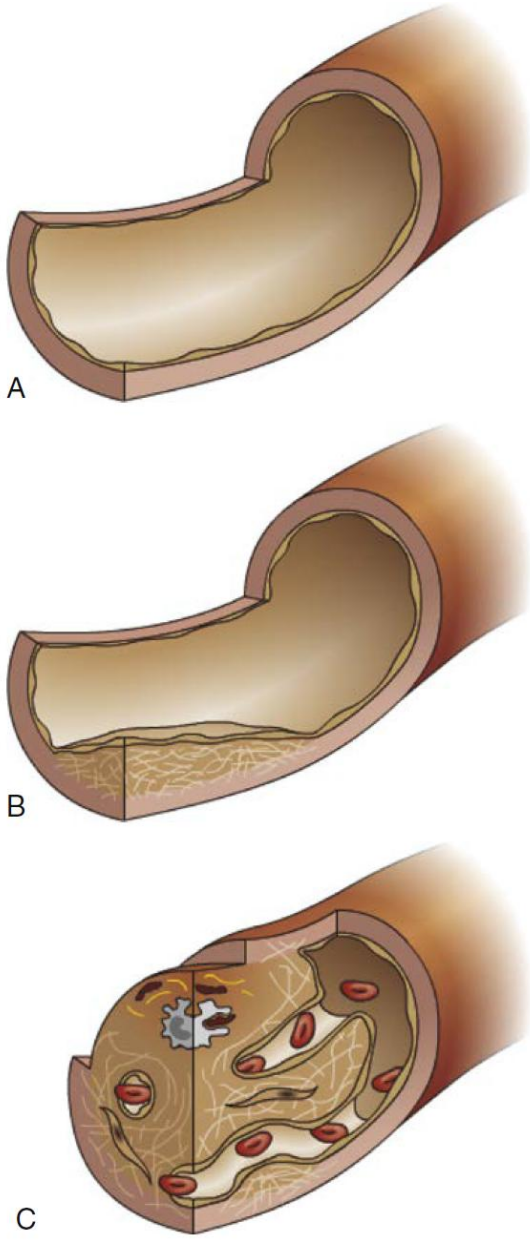
❖ A thrombus can have several outcomes:

- **Resolution**: Small thrombi can be completely removed by fibrinolysis, with a return to normal vessel structure.

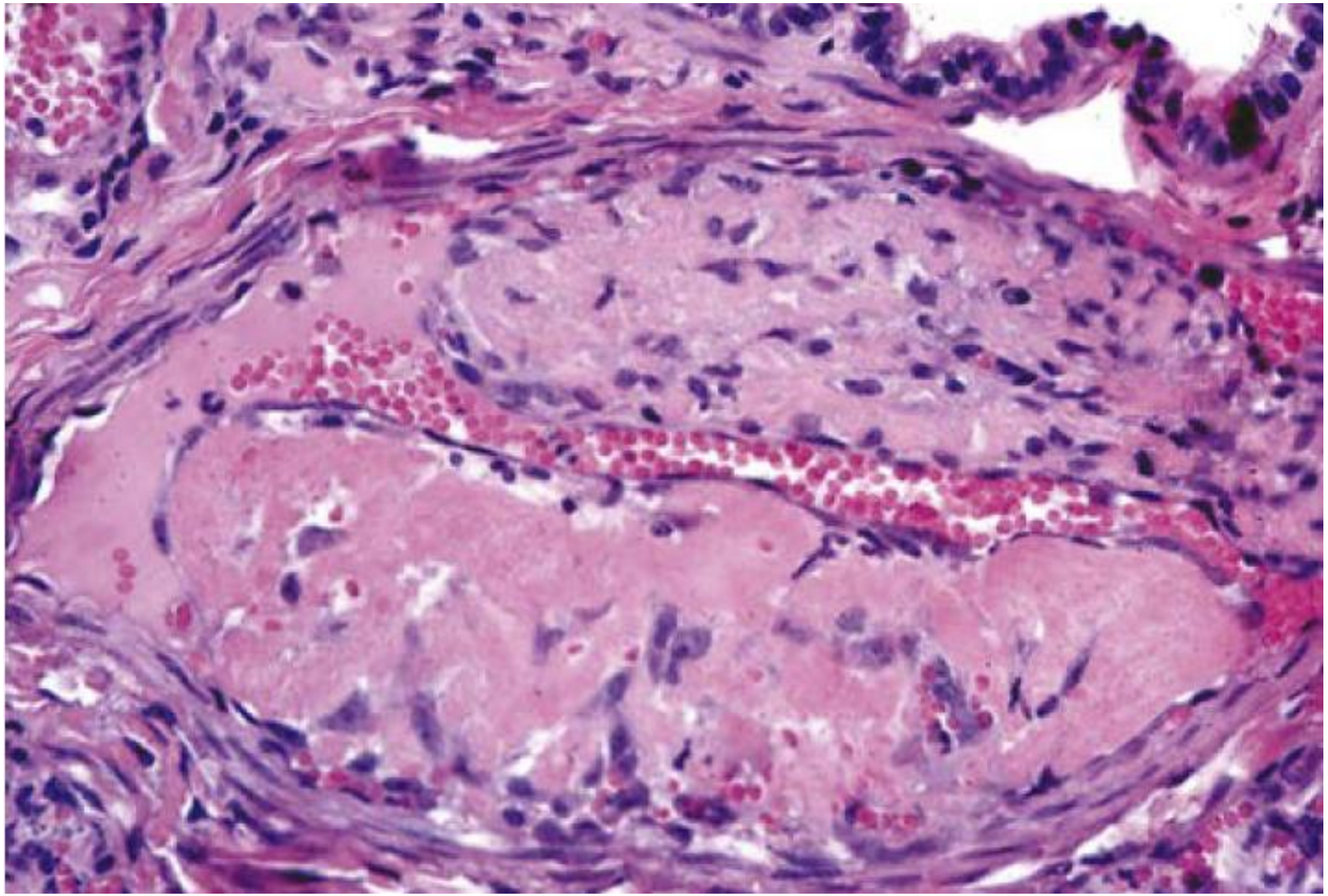
- **Organization and Incorporation**: The thrombus is replaced by granulation tissue and fibrosis, eventually becoming incorporated into the vessel wall.

- **Recanalization**: In large occlusive thrombi, new endothelial-lined channels may form through the organized thrombus, partially re-establishing blood flow.

- **Embolization**: A thrombus or a fragment of it can break loose, becoming a free-floating embolus that travels downstream and lodges in a smaller vessel.



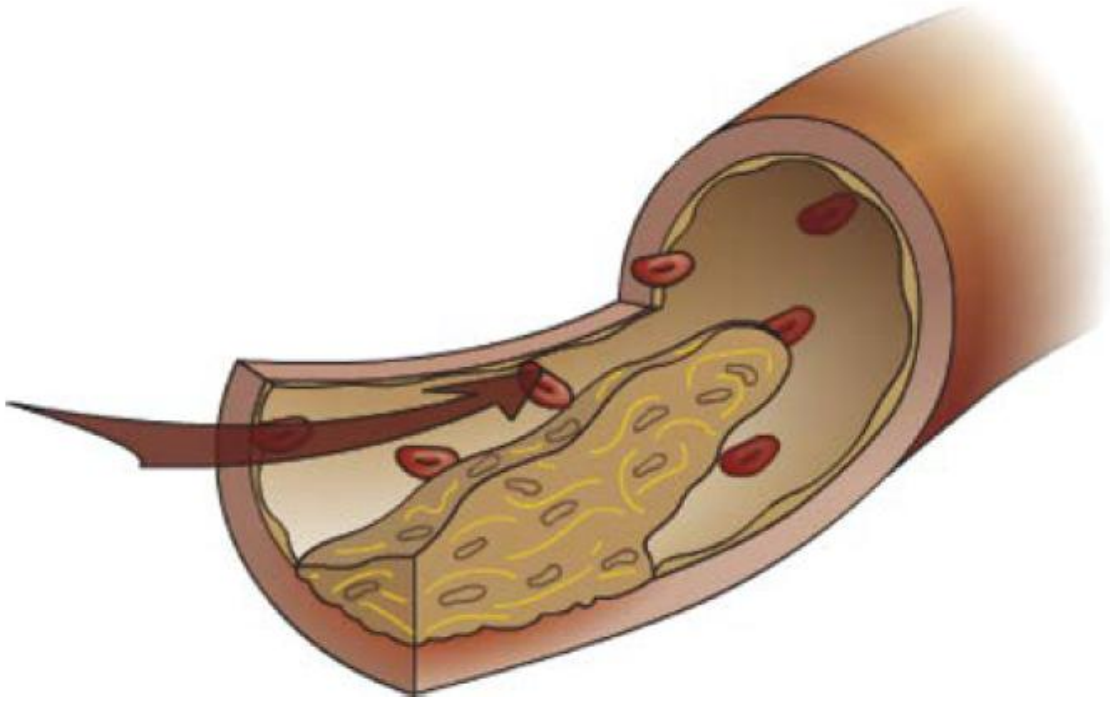
Disorders of Hemostasis



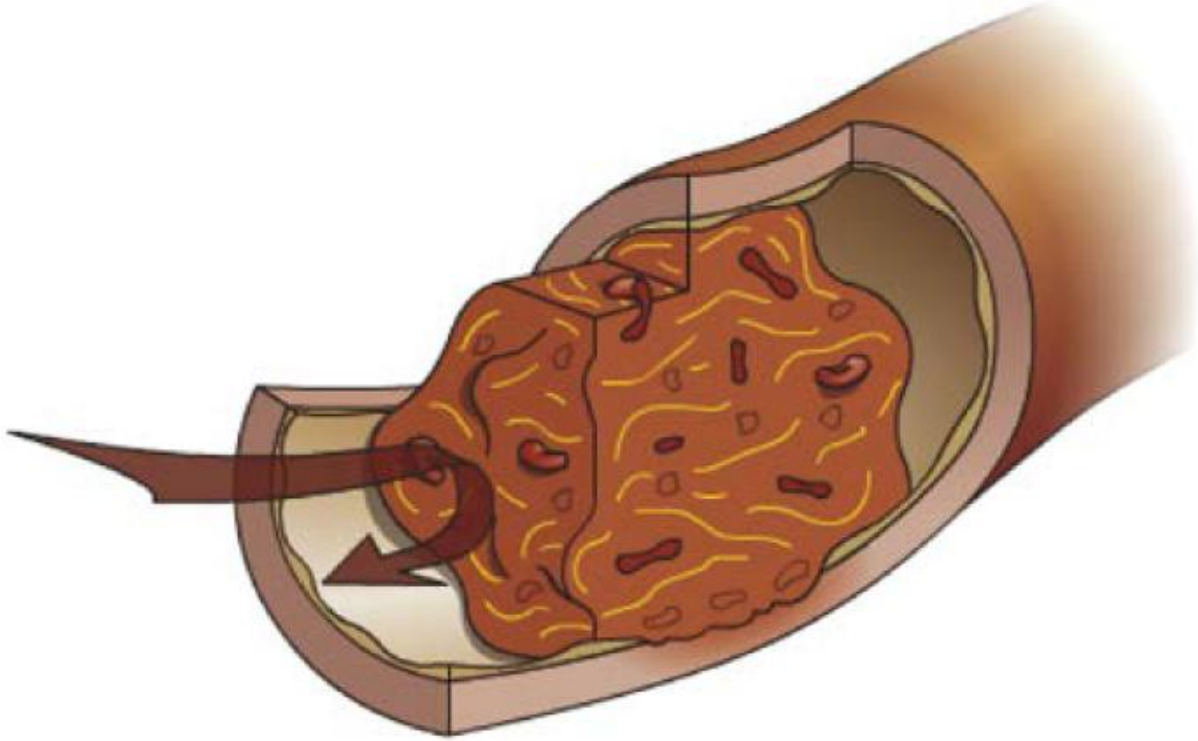
Occlusive mural thrombus, Recanalization, Cat

Disorders of Hemostasis

Arterial Thrombus



Venous Thrombus

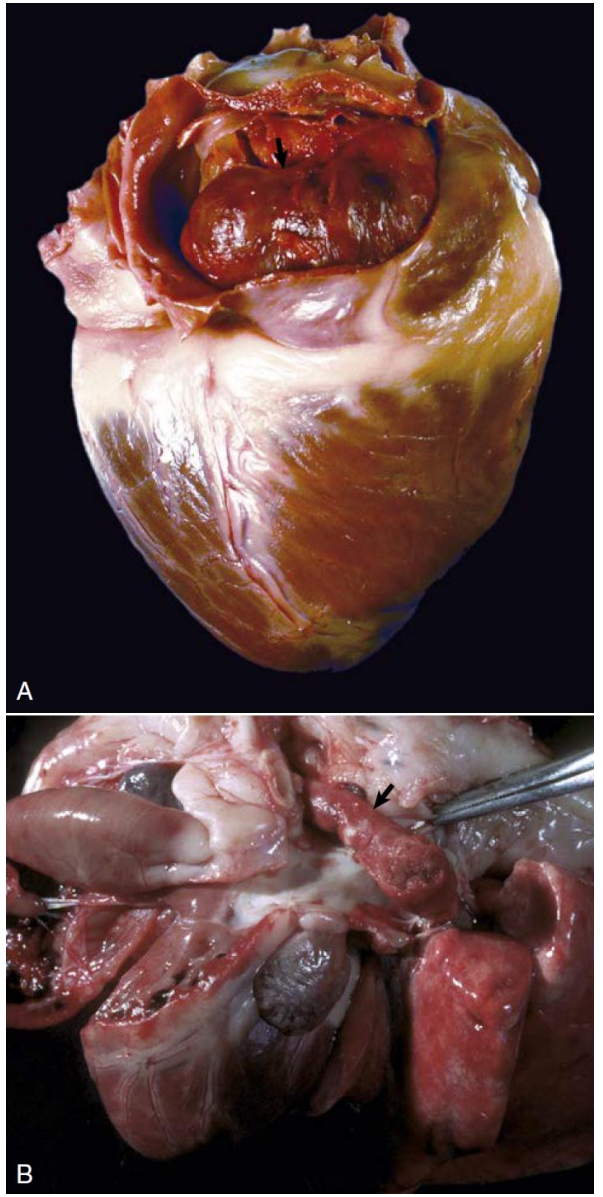


Disorders of Hemostasis

Embolism

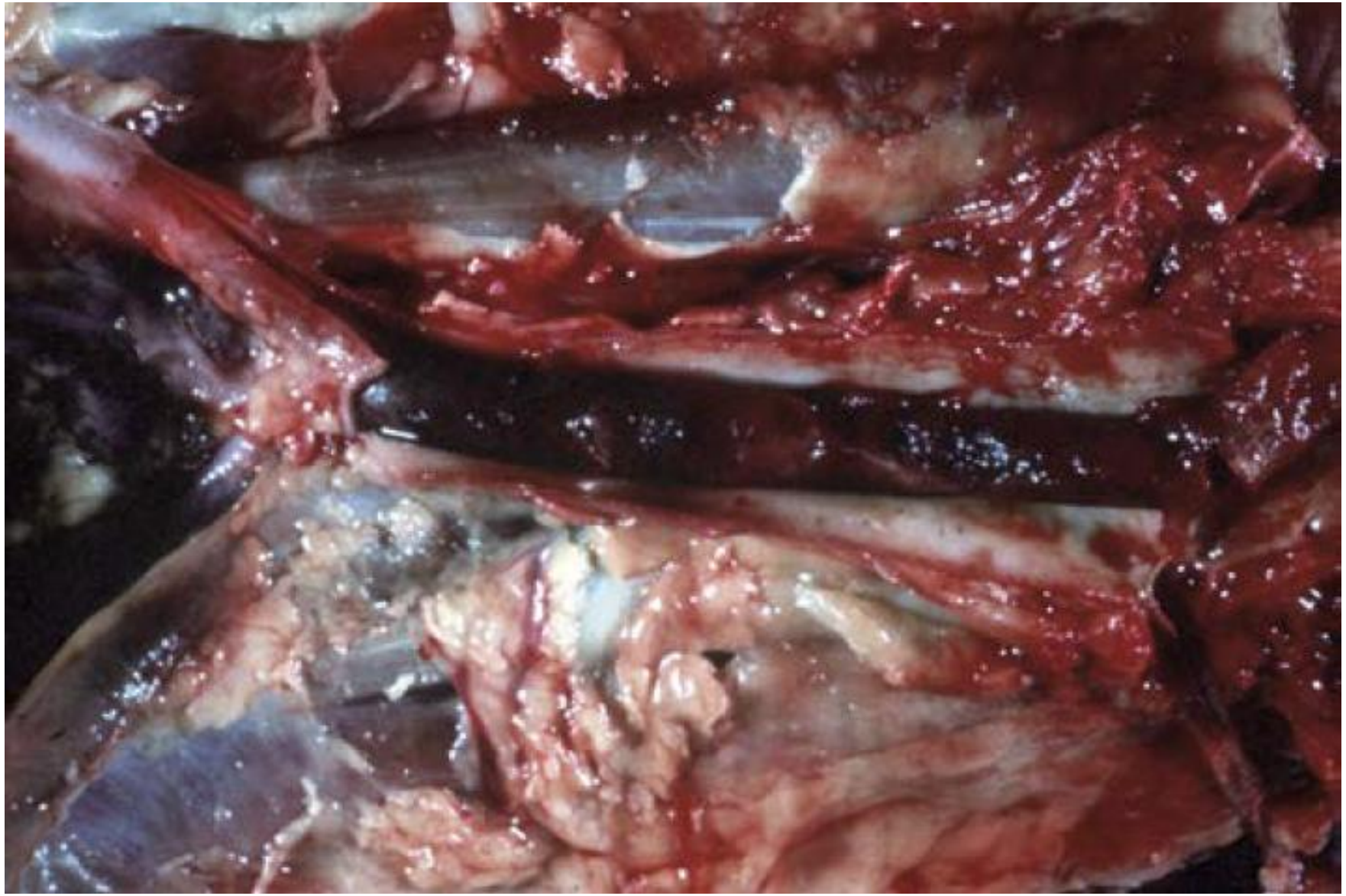
❖ Definition
- An embolus is a piece of free-floating foreign material within the blood.
- Embolization is the process of it becoming lodged in a smaller vessel.

❖ Types of Emboli
- **Thromboemboli**: Emboli derived from fragments of a thrombus (the most common type).
- Fat emboli: Can be released after the fracture of a long bone.
- Fibrocartilaginous emboli: Portions of an intervertebral disk.
- Bacterial emboli: Clumps of bacteria, often from lesions like vegetative endocarditis.
- Neoplastic emboli: Clumps of malignant tumor cells that have invaded a vessel.
- Other: Air bubbles (gas embolism), parasites, or clumps of other cells.



Thrombi, Cardiac and Arterial, Dogs

Disorders of Hemostasis



Saddle Thrombus, Iliac-Aortic bifurcation, Cat

Disorders of Hemostasis

Disseminated Intravascular Coagulation (DIC)

❖ Definition
- The loss of localization of the coagulation process and the generation of excess thrombin throughout the circulation.

❖ Causes
- Results from **widespread endothelial activation or injury**, such as extensive trauma, shock, systemic inflammation, sepsis, burns, or neoplasia.

❖ Pathogenesis
- Excess thrombin causes widespread microvascular thrombi, which consumes platelets and coagulation factors.
- Simultaneously, the high concentration of thrombin stimulates fibrinolytic pathways.

❖ Outcome
- This leads to a paradoxical state of **widespread microthrombosis** (causing ischemia and organ failure) and **widespread hemorrhages** (due to consumption of clotting components).

Inflammation and Healing-1

Veterinary Pathology-1

Su-Hyung Lee, DVM, PhD

Fundamental Concepts of Inflammation

Fundamental Concepts of Inflammation

What is Inflammation?

❖ Definition: A well-organized cascade of fluidic and cellular changes that occurs **within living, vascularized tissue in response to injury**.

❖ Purpose: It is a protective mechanism whose biological purpose is to dilute, isolate, and eliminate the cause of the injury and to repair the resulting tissue damage.

❖ The Five Cardinal Signs: Clinically recognized by five classic signs:

- **Redness (Rubor)**
- **Swelling (Tumor)**
- **Heat (Calor)**
- **Pain (Dolor)**
- **Loss of function (Functio Laesa)**

Fundamental Concepts of Inflammation

Acute vs. Chronic Inflammation

❖ Acute Inflammation
- Duration: Short, lasting from a few hours to a few days.
- Hallmarks: Characterized by the exudation of fluid and plasma proteins, and the emigration of leukocytes, principally **neutrophils**.
- Outcome: Typically leads to rapid repair and healing.

❖ Chronic Inflammation
- Duration: Prolonged, lasting from weeks to months, or even years.
- Hallmarks: Characterized by the presence of lymphocytes and macrophages, tissue destruction, and attempts at repair (like **fibrosis**) occurring simultaneously.
- Origin: Can be a sequela to acute inflammation or can be invoked directly by certain persistent agents.

Fundamental Concepts of Inflammation

Overview of the Acute Inflammatory Response

❖ Acute inflammation is a sequential process divided into three main phases:

- **Fluidic (Exudative)** Phase: The initial vascular response. Its goal is to dilute and contain the stimulus through the leakage of fluid and plasma proteins (like fibrinogen).

- **Cellular** Phase: Focused on eliminating the stimulus. This phase is defined by the delivery of leukocytes (primarily neutrophils) from the blood into the tissue.

- **Reparative** Phase: Begins early and is completed after the injurious agent is removed. Macrophages clean up debris, releasing molecules that initiate tissue repair and regeneration.

Fundamental Concepts of Inflammation

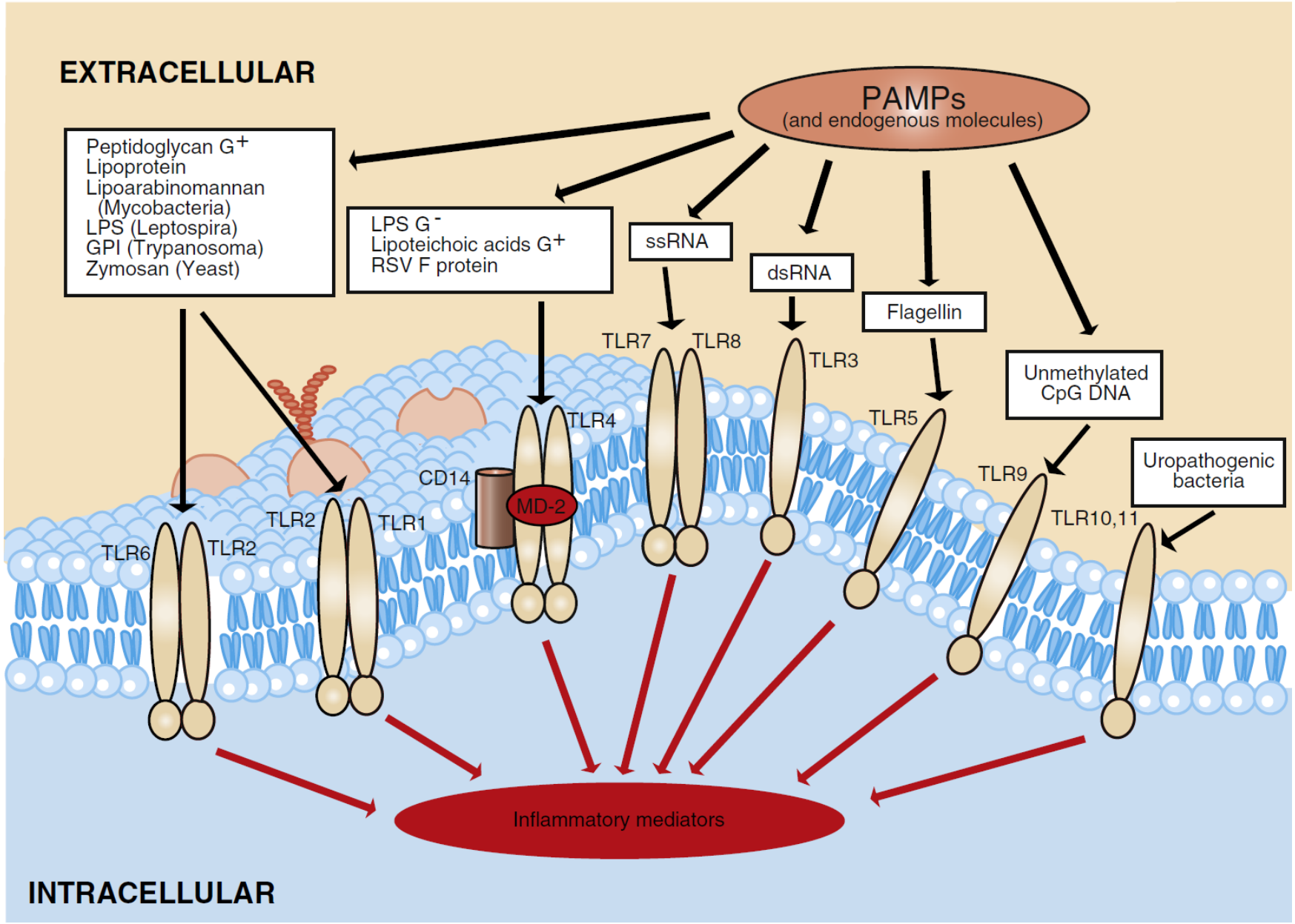
Triggers of Inflammation

❖ Exogenous Substances (from outside the body):
- **Microbes**: Viruses, bacteria, protozoa, and parasites.
- **Foreign Bodies**: Plant fibers, suture material.
- **Physical/Mechanical** Actions: Trauma, thermal injury (burns/cold), radiation.
- **Chemicals**: Caustic agents, poisons, venoms.

❖ Endogenous Substances (from inside the body):
- Molecules released from degenerate, dysplastic, or neoplastic cells.
- Triggers for autoreactive or hypersensitivity reactions.

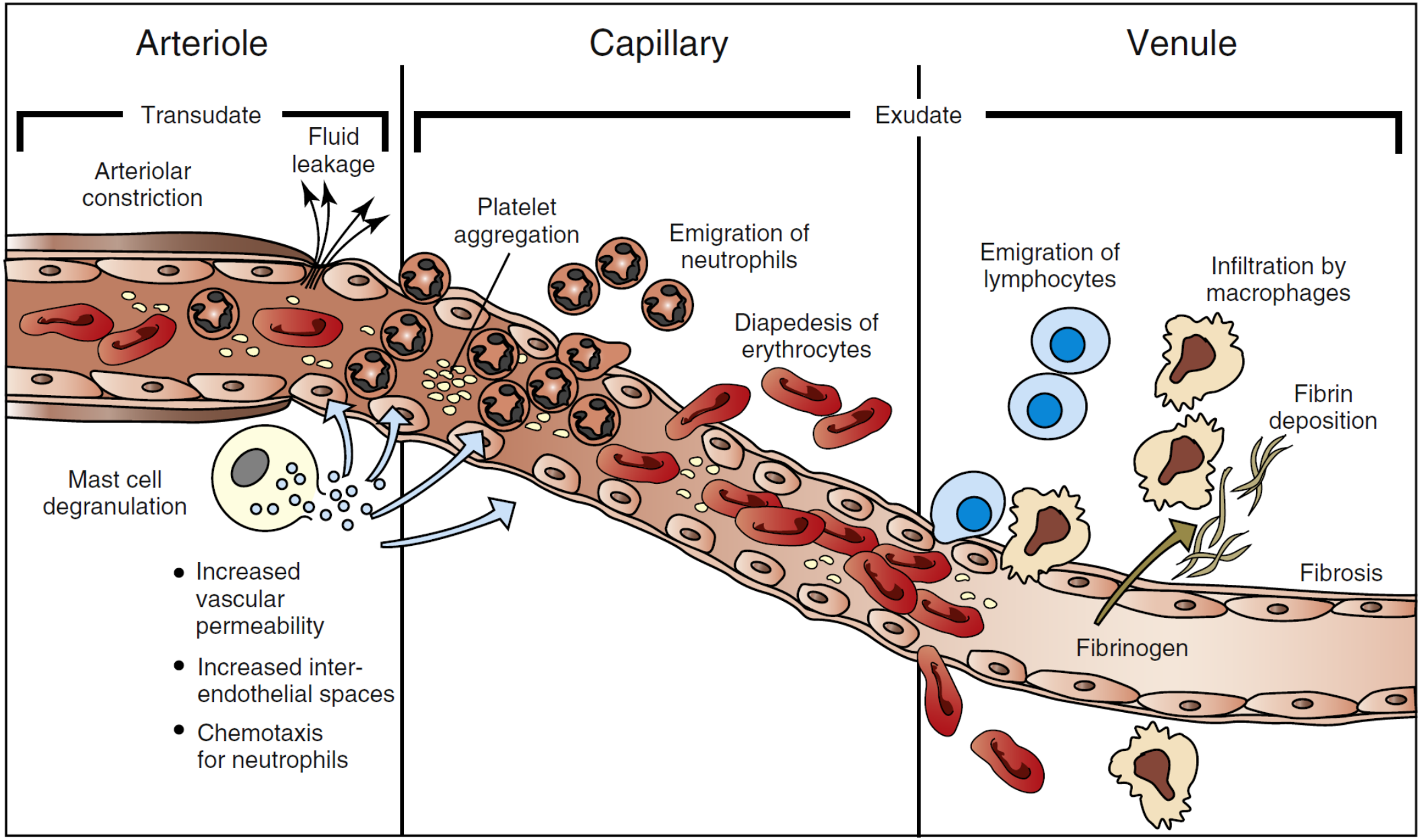
❖ PAMPs and DAMPs:
- **Microbes** have Pathogen-Associated Molecular Patterns (PAMPs) (e.g., LPS, peptidoglycan) that are recognized by cellular Pattern Recognition Receptors (PRRs).
- **Injured host cells** release Danger-Associated Molecular Patterns (DAMPs) (e.g., HMGB1, uric acid), which also trigger inflammation.

Fundamental Concepts of Inflammation



Acute Inflammation - Vascular & Fluidic Events

Acute Inflammation - Vascular & Fluidic Events



Acute Inflammation - Vascular & Fluidic Events

The Immediate Vascular Response

- **Active Hyperemia**: The response begins with an increased flow of blood to the injured tissue, secondary to the dilatation of arterioles and capillaries (vasodilation).
- **Clinical Signs**: This initial response is what causes the redness (rubor) and heat (calor) observed in injured tissues like the skin.
- **Slowing of Flow (Stasis)**: As fluid leaks from the vessels, the remaining blood becomes more viscous and flow slows down. This vascular congestion allows time for leukocytes to interact with the endothelium.

Acute Inflammation - Vascular & Fluidic Events

Increased Vascular Permeability - Mechanisms

❖ The leakage of fluid from the vasculature can occur through several mechanisms:

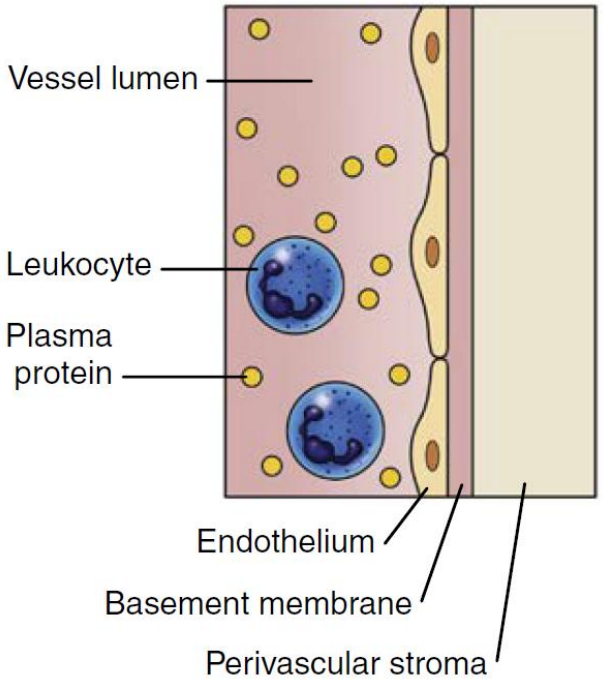
- Formation of **Endothelial Gaps**: The most common mechanism. Inflammatory mediators (like histamine and bradykinin) cause endothelial cells to contract, opening junctional complexes. This is rapid and short-lived.

- **Direct Endothelial Injury**: Necrosis and detachment of endothelial cells, as occurs with severe burns, certain toxins, and some infections. This affects all vessel types and can be long-lived.

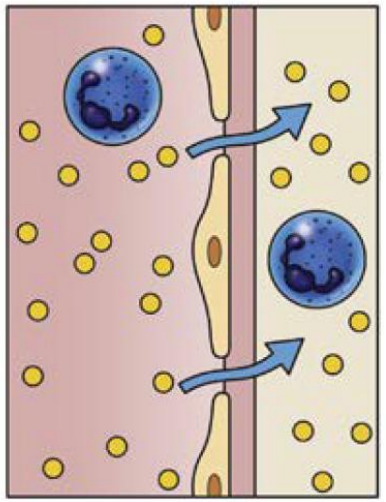
- **Leukocyte-Dependent Injury**: Activated leukocytes release reactive oxygen species and proteolytic enzymes during transmigration, which can damage and detach endothelial cells.

- Increased Transcytosis: Transport of fluids and proteins across the endothelial cell itself, mediated by factors like VEGF.

Acute Inflammation - Vascular & Fluidic Events

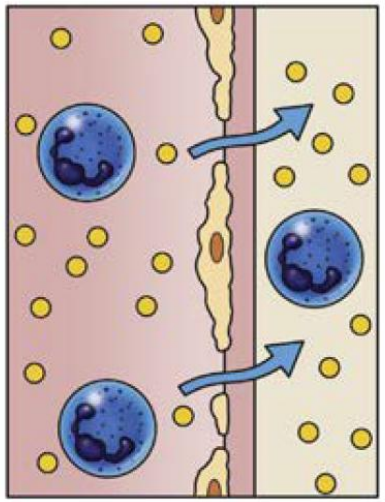


RETRACTION OF ENDOTHELIAL CELLS



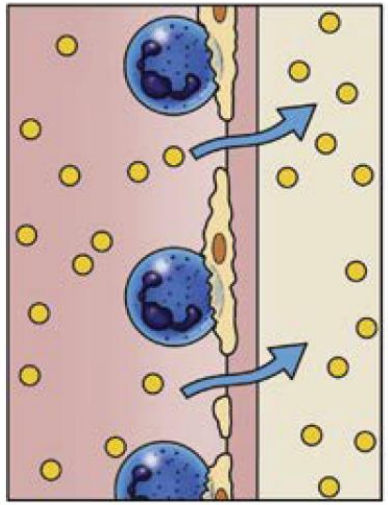
- Occurs mainly in venules
- Induced by histamine, NO, other mediators
- Rapid and short-lived (minutes)

ENDOTHELIAL INJURY



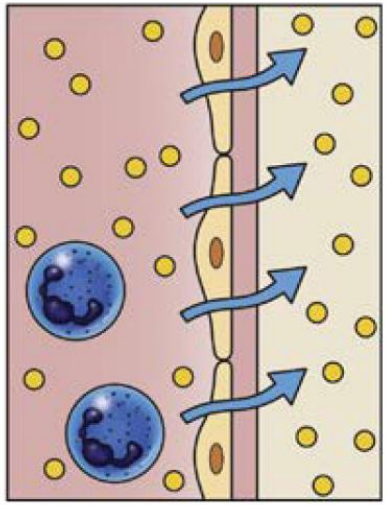
- Occurs in arterioles capillaries, venules
- Caused by burns, some microbial toxins
- Rapid; may be long-lived (hours to days)

LEUKOCYTE-MEDIATED VASCULAR INJURY



- Occurs in venules, pulmonary capillaries
- Associated with late stages of inflammation
- Long-lived (hours)

INCREASED TRANSCYTOSIS



- Occurs in venules
- Induced by VEGF

Acute Inflammation - Vascular & Fluidic Events

Transudate vs. Exudate

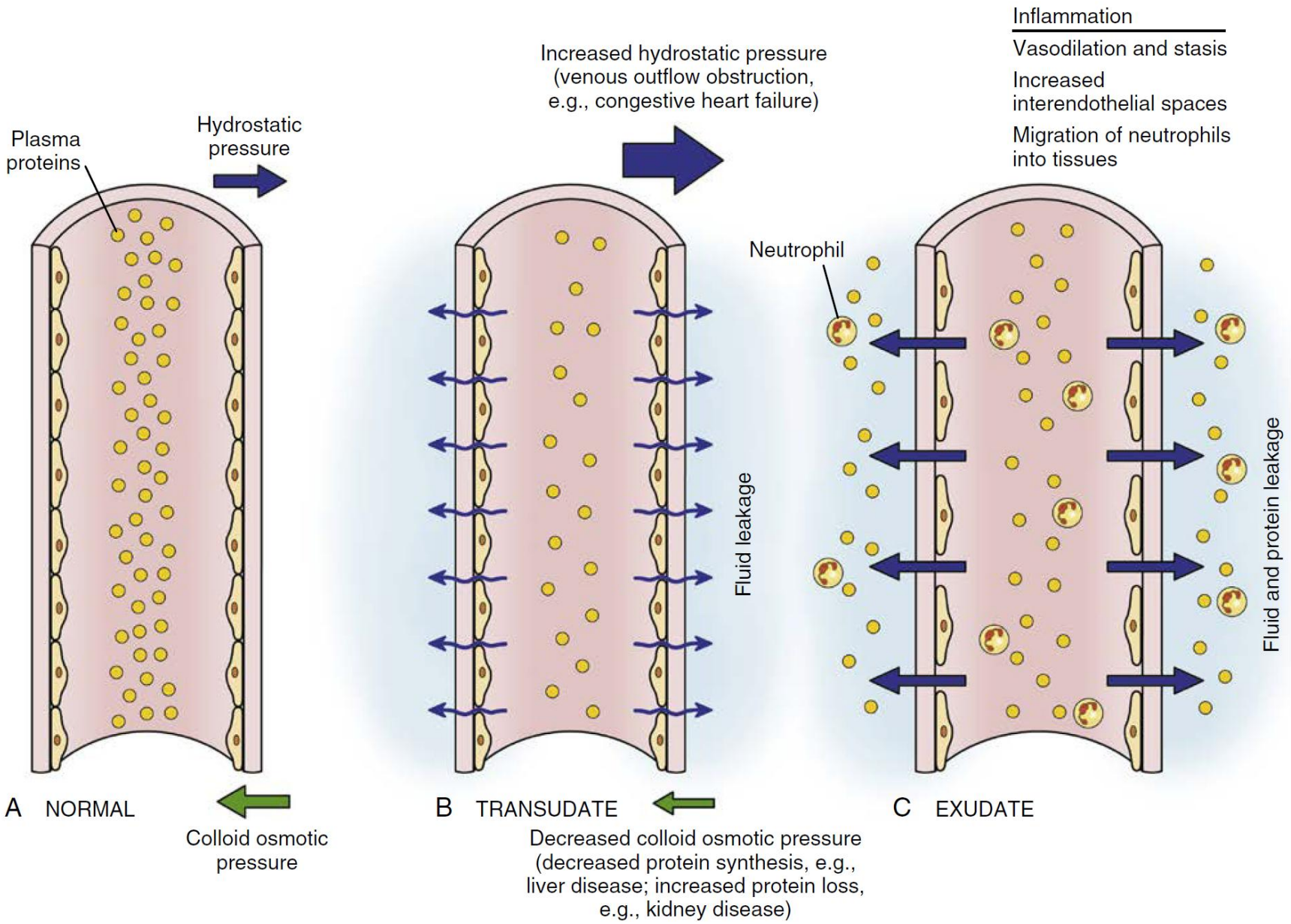
❖ **Transudate**

- Definition: A fluid with minimal protein (specific gravity < 1.012) and low numbers of cells.
- Formation: Occurs early in inflammation when endothelial gaps are small, or in non-inflammatory states with increased hydrostatic pressure (e.g., heart failure) or decreased osmotic pressure (e.g., liver disease).

❖ **Exudate**

- Definition: An opaque, viscous fluid with high protein content (specific gravity > 1.020) and numerous leukocytes.
- Formation: Forms during inflammation because vascular permeability increases enough to allow large molecules and cells to pass through endothelial gaps.
- Significance: The type of exudate (e.g., serous, fibrinous, suppurative) is used to classify the inflammatory lesion morphologically.

Acute Inflammation - Vascular & Fluidic Events



Acute Inflammation - Vascular & Fluidic Events

The Role of Fibrin

- From Fibrinogen to Fibrin: Fibrinogen is a large plasma protein that leaks from vessels into the tissue during the formation of an exudate.
- Polymerization: In the extravascular tissue, fibrinogen polymerizes to form fibrin.
- Key Functions of Fibrin:
  - Containment: Fibrin forms a meshwork that confines the inciting stimulus to an isolated area, preventing its spread.
  - Leukocyte Target: This confinement provides leukocytes with a well-defined target for migration during the cellular phase.
  - Scaffold for Healing: Fibrin forms a framework for fibroblast and endothelial cell migration during the initial stages of wound healing.



Pleural surface of the lung from an ox with **acute pleuritis** from fibrinous pneumonia



Acute fibrinonecrotic mastitis, mammary gland, frontal/dorsal plane, horizontal section, cow

Acute Inflammation - Cellular Events

Acute Inflammation - Cellular Events

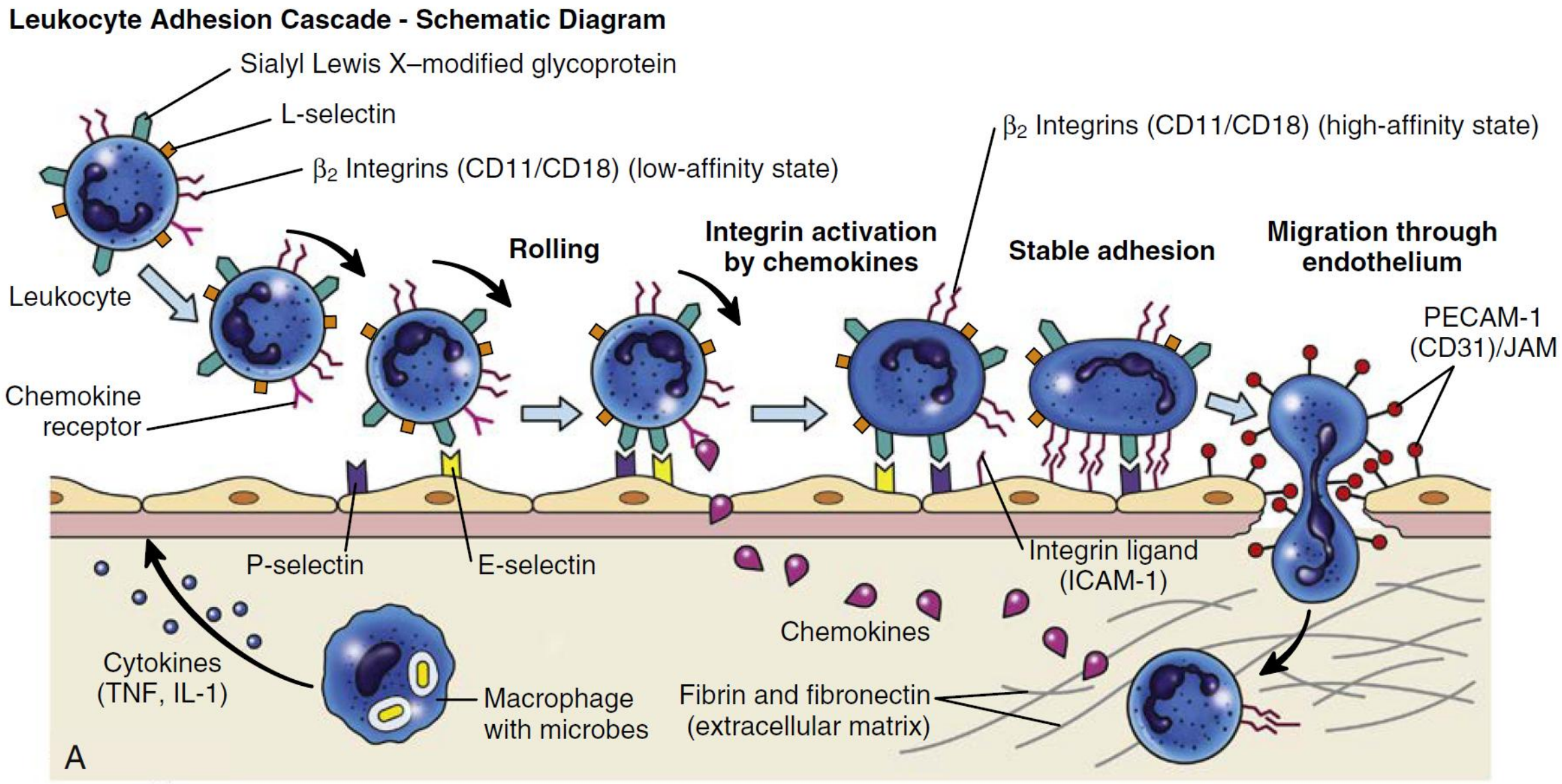
The Leukocyte Adhesion Cascade - Overview

❖ Purpose: The multi-step process that delivers leukocytes from the vessel lumen to the site of injury in the tissue.

❖ The Four Steps:

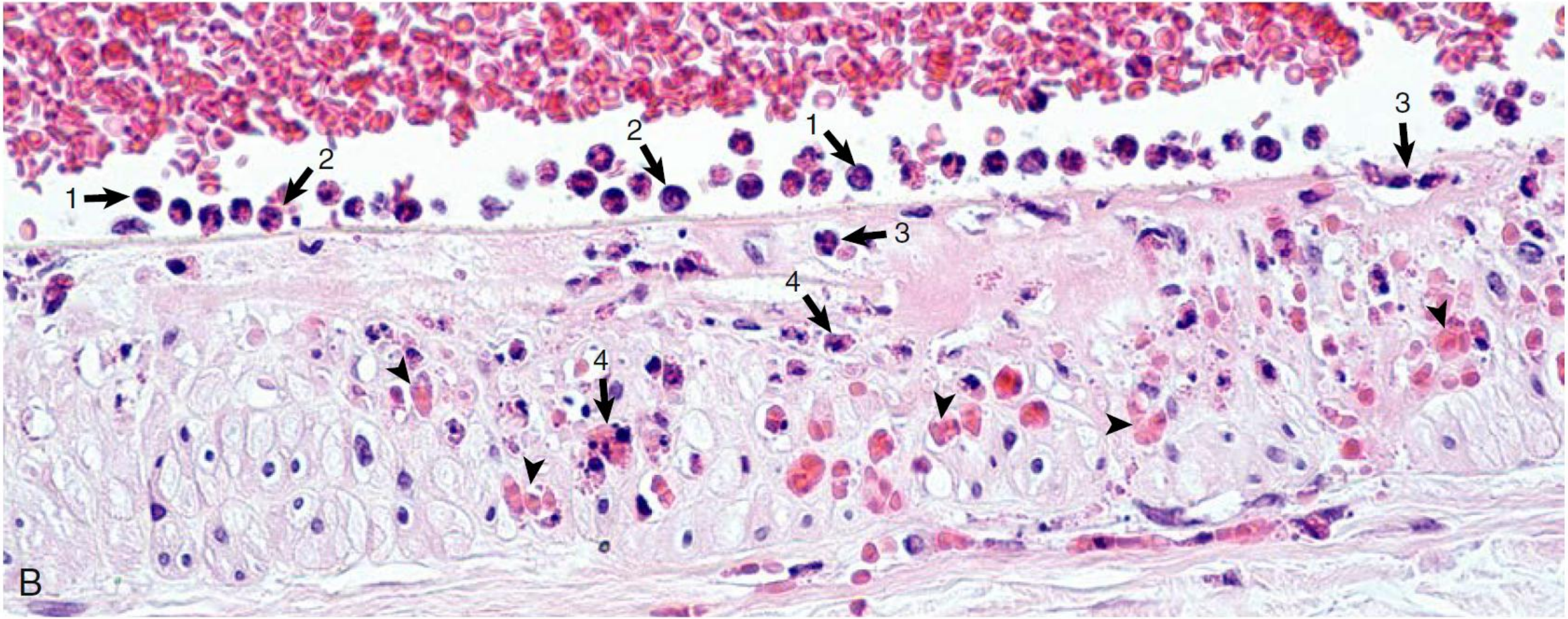
- **Margination**: As blood flow slows, leukocytes move from the central column of flow to the periphery, near the endothelial surface.
- **Rolling**: Leukocytes form transient, weak bonds with the endothelium and "roll" along the surface, significantly reducing their velocity.
- **Stable Adhesion**: Leukocytes become activated by chemokines and firmly adhere to the endothelium.
- **Transmigration** (Diapedesis): Leukocytes squeeze through the inter-endothelial junctions and cross the basement membrane to enter the extravascular tissue.

Acute Inflammation - Cellular Events



Acute Inflammation - Cellular Events

Leukocyte Adhesion Cascade - Histomorphology



Neutrophils encounter (1), interact with (2), migrate through (3), and degranulate within (4) the lamina propria intensifying the acute inflammation and injury (arrowheads)

Acute Inflammation - Cellular Events

Molecular Players in the Cascade: Selectins

❖ Role: Mediate the initial, weak binding interactions responsible for rolling.

❖ The Selectin Family:

- **L-selectin**: Expressed on **leukocytes**.
- **E-selectin**: Expressed on activated **endothelial cells**.
- **P-selectin**: Stored in **endothelial cells** (in Weibel-Palade bodies) and **platelets**; rapidly moved to the surface upon activation.

❖ Mechanism: Selectins bind to specific carbohydrate ligands (like sialyl Lewis X) on the opposing cell surface, creating temporary attachments that are formed at the leading edge and broken at the trailing edge of the rolling leukocyte.

Acute Inflammation - Cellular Events

Molecular Players in the Cascade: Integrins

❖ Role: Mediate the firm adhesion of leukocytes to the endothelium.

❖ The Integrin Family:
- Integrins are heterodimeric proteins expressed on the leukocyte surface.
- **Normally, they are in a low-affinity state**.

❖ Activation: Chemokines and other mediators released at the site of inflammation bind to receptors on the rolling leukocyte, triggering a conformational change in the integrins to a high-affinity state.

❖ Binding: These high-affinity integrins (e.g., LFA-1, Mac-1) on the leukocyte bind firmly to their ligands on the endothelial cell surface, primarily Intercellular Adhesion Molecule-1 (ICAM-1).

Acute Inflammation - Cellular Events

The Cellular Phase: Transmigration

- Movement Between Cells: Firmly adhered leukocytes migrate to the intercellular junctions between endothelial cells.

- Key Molecules: This process is mediated by several adhesion molecules present at the junctions, most notably PECAM-1 (CD31) and Junctional Adhesion Molecules (JAMs).

- Crossing the Basement Membrane: After passing through the endothelial layer, leukocytes secrete collagenases and other enzymes to digest a path through the underlying basement membrane.

- Chemotaxis: Once in the extravascular tissue, leukocytes migrate toward the site of injury by following a chemical gradient of chemoattractants (e.g., C5a, LTB_4, chemokines).

Acute Inflammation - Cellular Events

Effector Cells: Neutrophils

- **The First Responders**: Neutrophils are often the first type of leukocyte recruited into an inflammatory exudate, dominating the response in the first 6 to 24 hours.
- Primary Functions:
  - **Phagocytosis**: To engulf and internalize microbes or foreign material.
  - **Killing and Degradation**: To destroy pathogens through the release of antimicrobial peptides and enzymes from their cytoplasmic granules.
  - **NET Formation**: They can undergo a unique form of cell death where they release a meshwork of their own DNA embedded with antimicrobial proteins, called Neutrophil Extracellular Traps (NETs), which entrap and kill bacteria.
- **Pus Formation**: The accumulation of neutrophils, liquefied debris, and edema fluid is termed pus.

Acute Inflammation - Cellular Events

Effector Cells: Macrophages

❖ Arrival: Macrophages, derived from blood monocytes, enter inflammatory lesions roughly 12 to 48 hours after initiation, becoming the predominant cell type after 24-48 hours.

❖ Key Functions:

- **Phagocytosis (Clean-up)**: They are highly phagocytic and are responsible for cleaning up the lesion by removing apoptotic neutrophils, necrotic tissue debris, and fibrin.
- **Initiation of Repair**: They secrete a variety of growth factors (e.g., PDGF, TGF-β) that are essential for initiating the reparative phase, including fibroblast proliferation and angiogenesis.
- **Antigen Presentation**: They process and present antigens to T lymphocytes, serving as a critical link between the innate and adaptive immune responses.
- Central Role in **Chronic Inflammation**: If the injurious agent persists, macrophages orchestrate the chronic inflammatory response.

Acute Inflammation - Cellular Events

Effector Cells: Mast Cells & Eosinophils

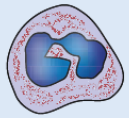
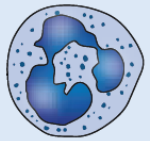
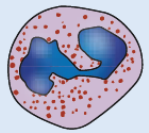
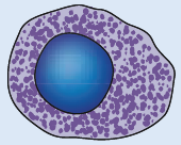
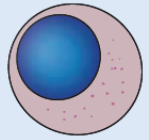
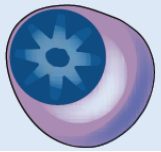
❖ Mast Cells

- Location: Reside in connective tissue, strategically located next to small blood vessels.
- Role: Act as "**sentinels**" that initiate the acute inflammatory response. Upon activation (e.g., by allergens binding to IgE), they rapidly release preformed granules containing **histamine** and other mediators.

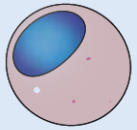
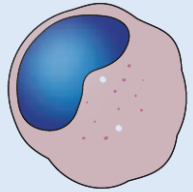
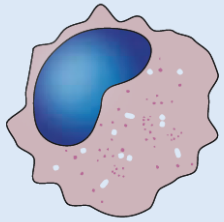
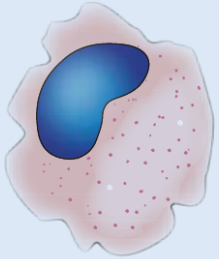
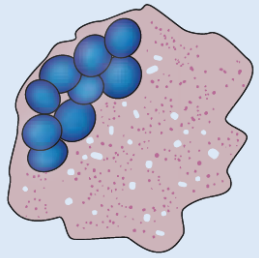
❖ Eosinophils

- Recruitment: Recruited into tissues in response to allergic reactions and parasitic (especially helminthic) infections.
- Function: Their granules contain proteins, like Major Basic Protein (MBP), that are toxic to parasites. They can also contribute to tissue damage in allergic diseases like asthma.

Acute Inflammation - Cellular Events

Cell Type	Schematic Examples*	Cell Diameter	Nucleus	Cytoplasm
Erythrocyte		4-7 μm	no nucleus	round to oval shape; central concavity of cell (biconcave disk)
Neutrophil		12-15 μm	segmented nucleus	oval to round shape with undulating surface; medium volume of cytoplasm; small neutral to faint eosinophilic staining granules
Basophil		12-18 μm	segmented nucleus	oval to round shape with undulating surface; medium volume cytoplasm with medium-sized purple granules
Eosinophil		12-18 μm	segmented nucleus	oval to round shape with undulating surface; medium volume of cytoplasm with medium-sized eosinophilic (reddish)/orange granules
Mast Cell		15-25 μm	round to oval central to eccentric nucleus	oval to round shape with undulating surface; medium volume of cytoplasm; numerous medium-sized purple granules
Small Lymphocyte		9-12 μm	round to oval eccentric nucleus	round shape; small volume of cytoplasm
Larger (Reactive) Lymphocyte		12-20 μm	round to oval often eccentric nucleus	round shape; larger volume of cytoplasm; can have medium-sized azurophilic granules
Plasma Cell		12-20 μm	round to oval eccentric “cartwheel-shaped” nucleus	oval to elongate shape; large volume of cytoplasm; prominent perinuclear “clear (negative Golgi)” region

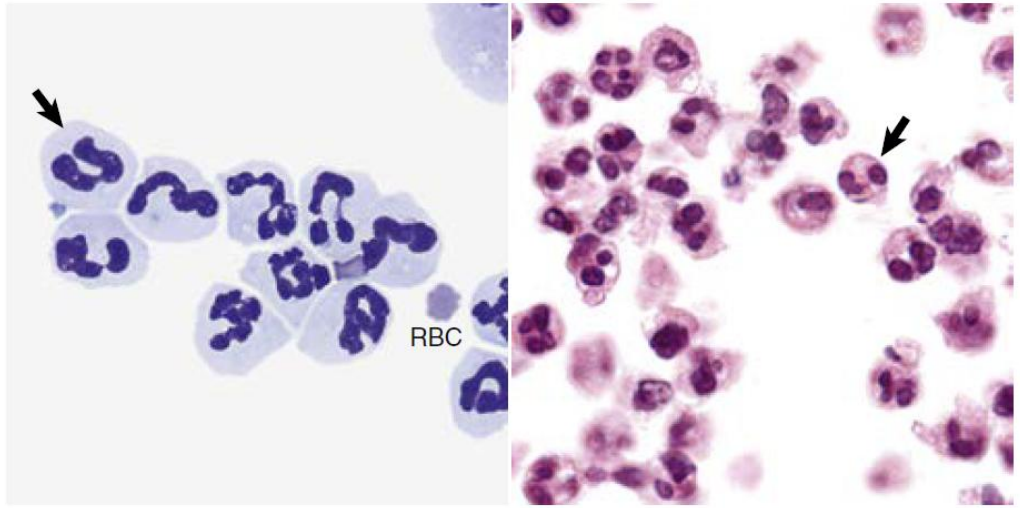
Acute Inflammation - Cellular Events

Cell Type	Schematic Examples*	Cell Diameter	Nucleus	Cytoplasm
Monocyte		12-20 μm	oval to bean shaped (ellipsoid/reniform) eccentric nucleus	oval to polygonal shape; large volume of cytoplasm
Resting Macrophage		15-30 μm	oval to bean shaped (ellipsoid/reniform) eccentric nucleus	polygonal shape; very large volume of cytoplasm; small granules and occasional vacuoles and membrane surface projections
Activated Macrophage		17-30 μm or larger	oval to bean shaped (ellipsoid/reniform) eccentric nucleus	as above; in addition, activated macrophages can be up to twice as large as resting macrophages and have more vacuoles. This increase in size is caused by the synthesis of cytoplasmic lysosomal enzymes in response to microbes and foreign bodies.
Epithelioid Macrophage		20-30 μm or larger	oval to bean shaped (ellipsoid/reniform) eccentric nucleus	as above; resemble epithelial cells. They are larger than activated macrophages and have ovoid to elongate nuclei and finely granular, pale cytoplasm that generally lacks vacuoles. Cell membranes are often indistinct.
Multinucleated Giant Cell (MGC)		20-40 μm or larger	multiple nuclei of varied sizes, shapes, and patterns of distribution	polygonal shape; very large volume of cytoplasm; small granules and occasional vacuoles and membrane surface projections

Acute Inflammation - Cellular Events

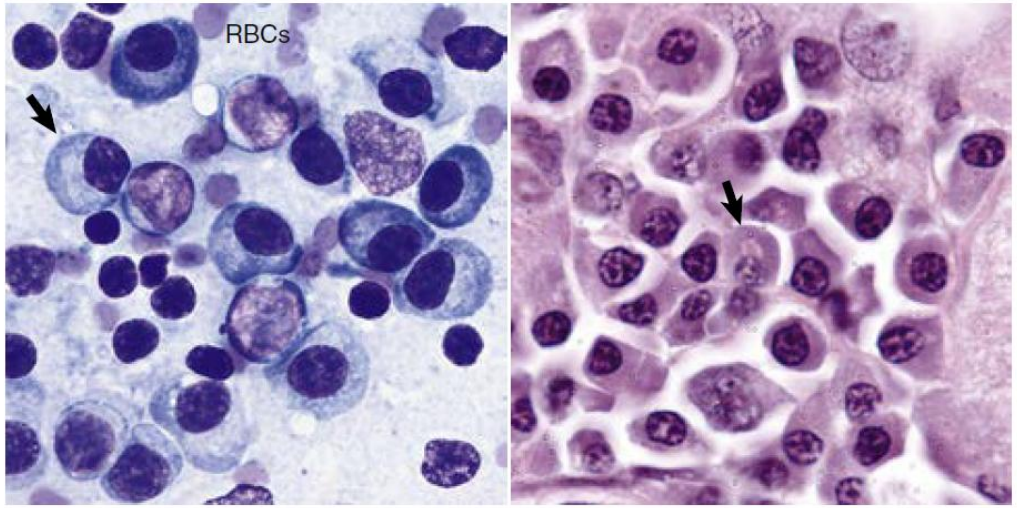
Cytomorphology **Histomorphology**

Neutrophils

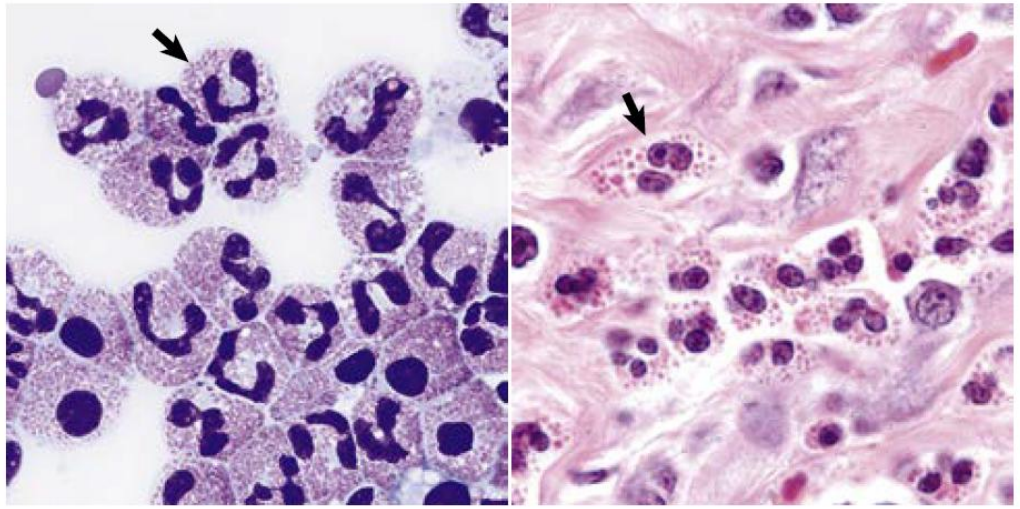


Cytomorphology **Histomorphology**

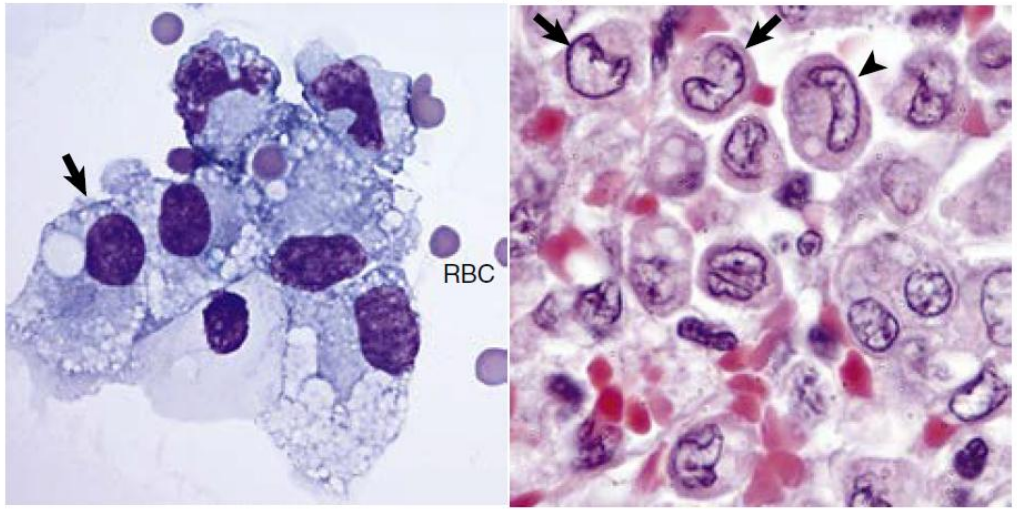
Plasma Cells



Eosinophils



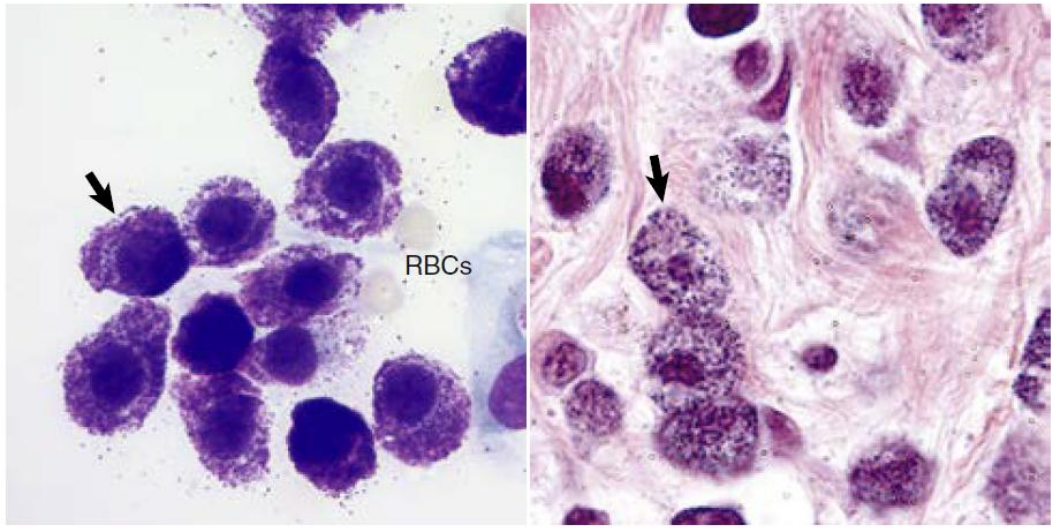
Macrophages



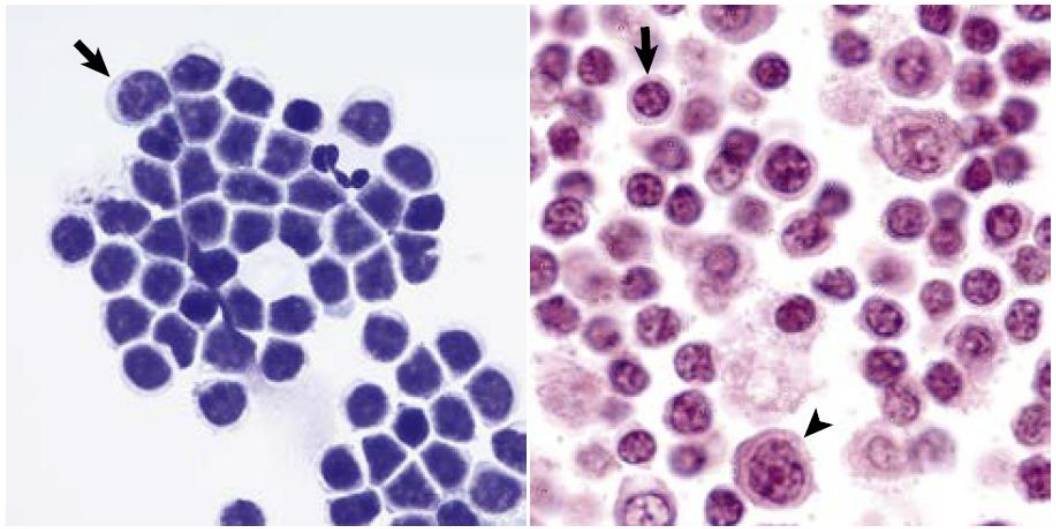
Acute Inflammation - Cellular Events

Cytomorphology **Histomorphology**

Mast Cells

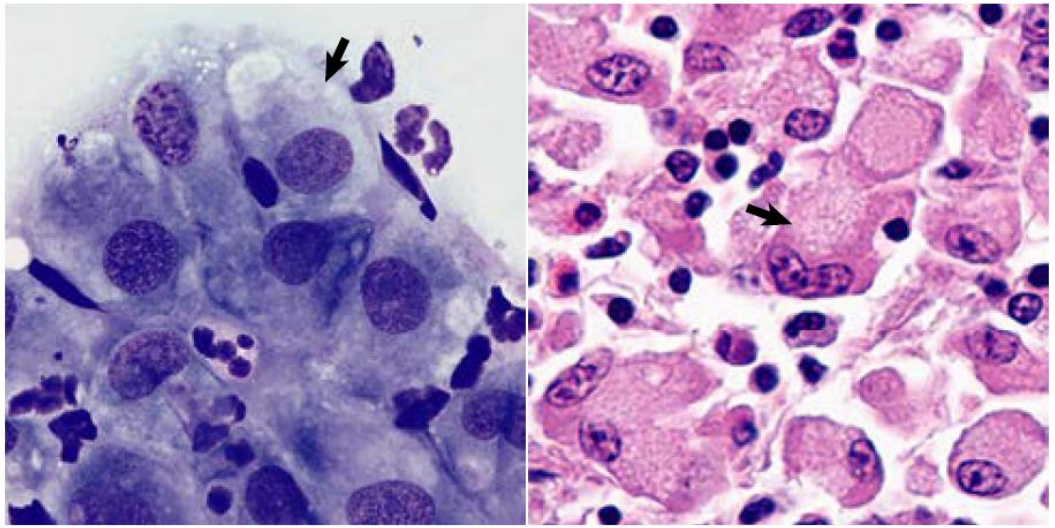


Lymphocytes

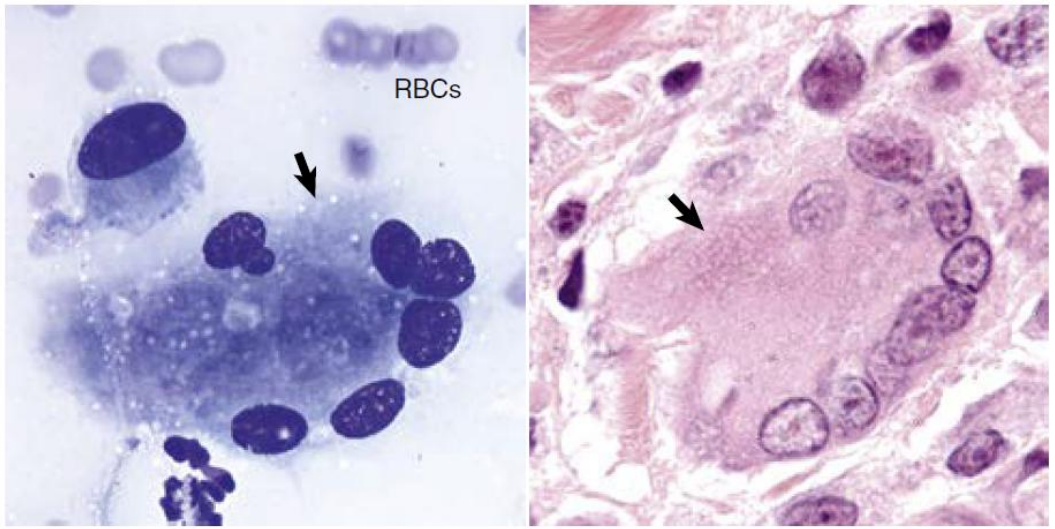


Cytomorphology **Histomorphology**

Epithelioid Macrophages



Multinucleated Giant Macrophages



Acute Inflammation - Cellular Events

Other Key Cells

- Lymphocytes: Essential for the adaptive immune response. They enter inflammatory sites after 24-48 hours and become central players if the inflammation becomes chronic.

- Basophils: Circulate in the blood and share some features with mast cells, including having IgE receptors. They release mediators like histamine and cytokines (IL-4, IL-13) that contribute to allergic (Th2-type) responses.

- Endothelial Cells: Not just a passive barrier. They are active participants that regulate vascular tone, express adhesion molecules for leukocytes, and produce inflammatory mediators.

Chemical Mediators of Inflammation

Chemical Mediators of Inflammation

Overview of Chemical Mediators

❖ Origin: Mediators can be derived from either plasma proteins or from cells.

❖ Plasma-Derived Mediators:
- Synthesized mainly by the liver and circulate as inactive precursors that must be activated (usually by proteolytic cleavage).
- Examples: Complement proteins, kinins.

❖ Cell-Derived Mediators:
- Can be preformed and stored in granules for rapid release (e.g., histamine in mast cells).
- Can be synthesized de novo in response to a stimulus (e.g., prostaglandins, cytokines).

❖ General Properties: Most mediators are short-lived, decay rapidly, are inactivated by enzymes, or are otherwise scavenged or inhibited to provide a system of checks and balances.

Chemical Mediators of Inflammation

Vasoactive Amines & The Kinin System

❖ Histamine
- Source: Preformed in granules of mast cells, basophils, and platelets.
- Action: A principal mediator of the immediate transient phase of increased vascular permeability. It also causes arteriolar dilation.

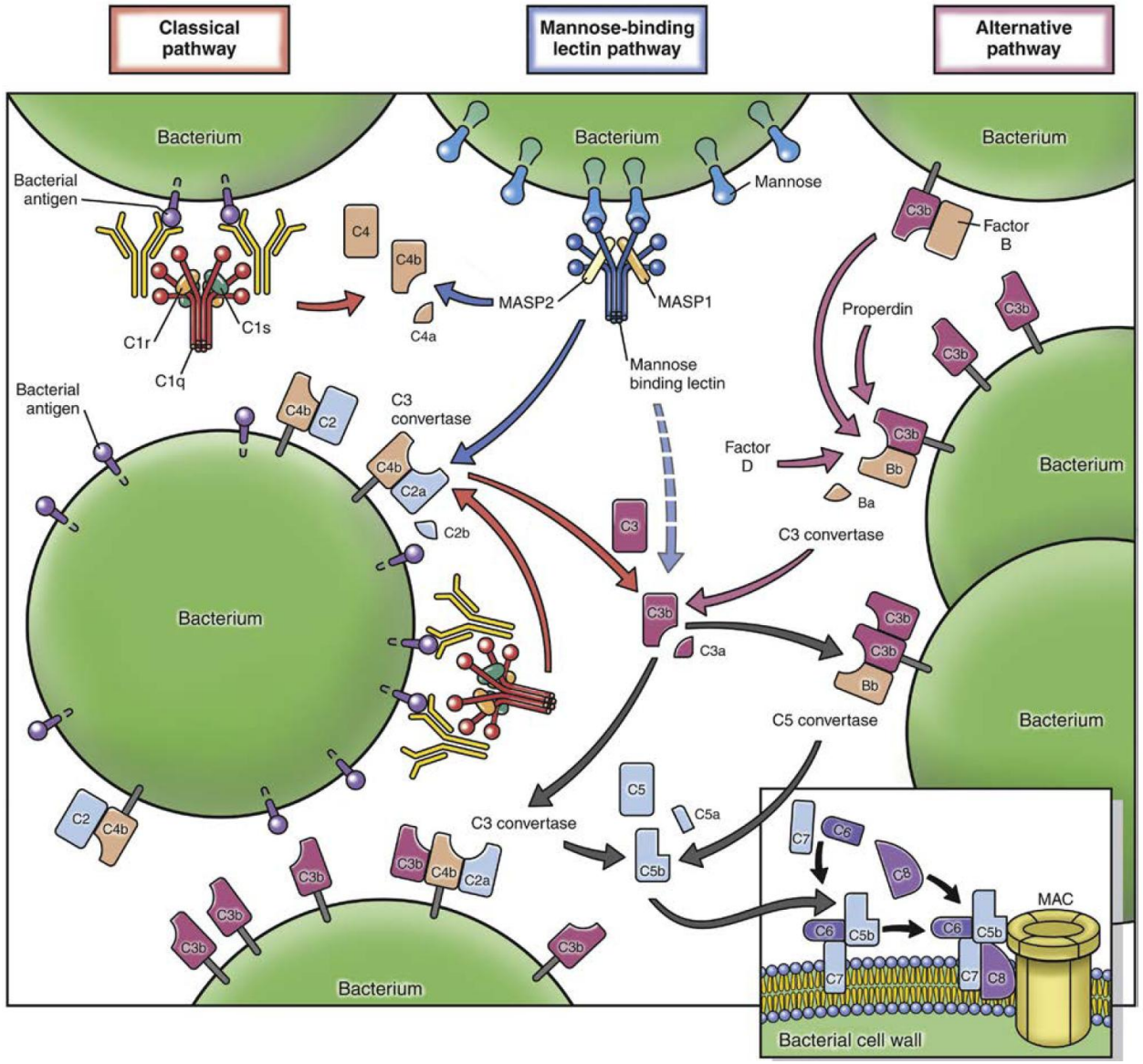
❖ Serotonin (5-hydroxytryptamine)
- Source: Found in platelets of mammals and mast cells of rodents.
- Action: Similar actions to histamine.

❖ The Kinin System
- Activation: An enzymatic cascade triggered by activation of Hageman factor (factor XII).
- Product: Leads to the formation of bradykinin.
- Action: Bradykinin increases vascular permeability, causes arteriolar dilation, smooth muscle contraction, and is a major mediator of pain.

Chemical Mediators of Inflammation

The Complement Cascade

- Overview: A system of over 20 plasma proteins that, upon activation, generate biologically active molecules with roles in host defense and inflammation.
- Activation Pathways:
  - Classical Pathway: Triggered by antibodies (IgM or IgG) that have bound to antigen.
  - Alternative Pathway: Triggered by microbial surface molecules (e.g., endotoxin), in the absence of antibody.
  - Lectin Pathway: Triggered when mannose-binding lectin binds to mannose residues on microbes.
- Central Event: All three pathways converge on the activation of the C3 component.



Chemical Mediators of Inflammation

Key Functions of Complement

- Inflammation (C3a and C5a): These fragments are called anaphylatoxins. They stimulate histamine release from mast cells and act as powerful chemoattractants for leukocytes (especially C5a).

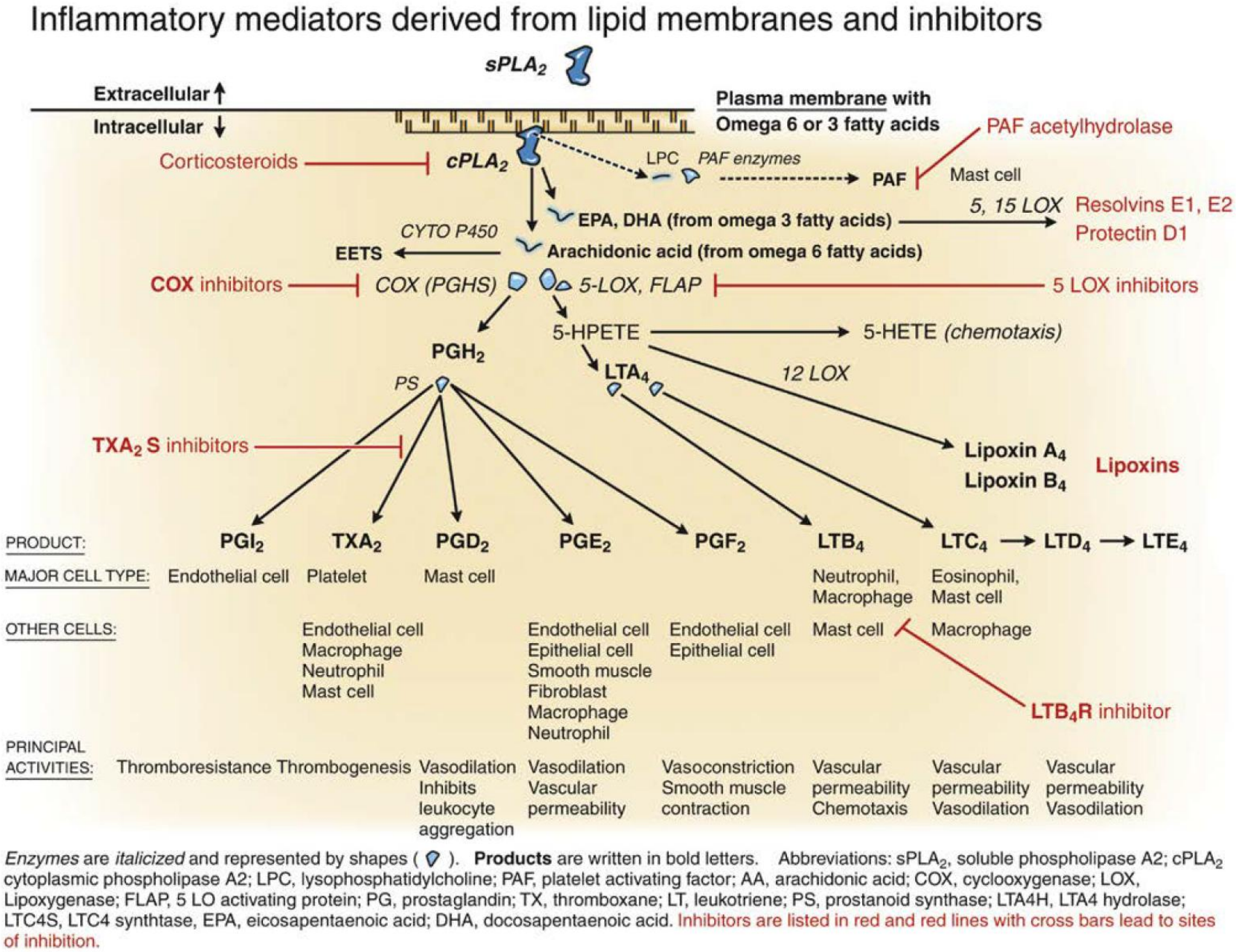
- Opsonization and Phagocytosis (C3b): C3b is a major opsonin. It coats microbes and targets them for phagocytosis by neutrophils and macrophages, which have receptors for C3b.

- Cell Lysis (Membrane Attack Complex - MAC): The terminal components (C5b-C9) assemble to form the MAC, which creates a pore in the microbial membrane, leading to lysis and death of the pathogen.

Chemical Mediators of Inflammation

Mechanism of Action: Broad Blockade of Inflammatory Mediators

- The anti-inflammatory effect of corticosteroids stems from their ability to inhibit
- Phospholipase A_2 (PLA_2), the enzyme that releases arachidonic acid from cell membrane phospholipids.
- Arachidonic acid is the essential precursor for two major classes of inflammatory mediators:
  - Prostaglandins, which are involved in pain, fever, and vasodilation.
  - Leukotrienes, which are potent chemoattractants for leukocytes.
- By blocking the very first step in the production of these lipids, steroids shut down both pathways, resulting in a powerful and broad anti-inflammatory effect.



Enzymes are *italicized* and represented by shapes ( ). **Products** are written in bold letters. Abbreviations: $sPLA_2$, soluble phospholipase A2; $cPLA_2$ cytoplasmic phospholipase A2; LPC, lysophosphatidylcholine; PAF, platelet activating factor; AA, arachidonic acid; COX, cyclooxygenase; LOX, Lipoxygenase; FLAP, 5 LO activating protein; PG, prostaglandin; TX, thromboxane; LT, leukotriene; PS, prostanoid synthase; LTA4H, LTA4 hydrolase; LTC4S, LTC4 synthtase, EPA, eicosapentaenoic acid; DHA, docosapentaenoic acid. Inhibitors are listed in red and red lines with cross bars lead to sites of inhibition.

Chemical Mediators of Inflammation

Arachidonic Acid Metabolites

- Origin: Arachidonic Acid (AA) is a fatty acid released from cell membrane phospholipids by the action of phospholipases.

- Two Major Pathways: Once released, AA is metabolized by two main enzymatic pathways:
  - Cyclooxygenase (COX) Pathway: Produces prostaglandins and thromboxanes.
  - Lipoxygenase (LOX) Pathway: Produces leukotrienes and lipoxins.

- Therapeutic Relevance: The synthesis of these mediators is the target of many anti-inflammatory drugs. For example, corticosteroids inhibit phospholipases, while NSAIDs (like aspirin) inhibit the COX enzymes.

Chemical Mediators of Inflammation

Prostaglandins and Leukotrienes

❖ Prostaglandins (PGs)
- Function: Involved in nearly every step of inflammation. They are major mediators of vasodilation, pain, and fever.
- Example: PGE_2 is particularly important in fever and pain.

❖ Thromboxanes
- Function: A major product of platelets, thromboxane A_2 promotes platelet aggregation and vasoconstriction.

❖ Leukotrienes (LTs)
- Function: LTB_4 is a potent chemoattractant for neutrophils. Other leukotrienes (LTC_4, LTD_4, LTE_4) cause intense vasoconstriction and increased vascular permeability.

Chemical Mediators of Inflammation

Major Resulting Diseases and Their Causes

❖ The problem arises because some of these lipid mediators are also vital for normal physiological "housekeeping" functions.

❖ **Gastric Ulcers and Gastrointestinal Damage**

- By blocking the production of the protective prostaglandins, corticosteroids leave the stomach lining vulnerable to its own acid, which can lead to ulcers.

❖ **Impaired Wound Healing**

- The initial acute inflammatory response is an essential first step for proper healing; it clears debris and sets the stage for repair. The potent suppression of this phase by steroids can disrupt the entire repair process, delaying collagen synthesis and new blood vessel formation.

❖ **Increased Susceptibility to Infection**

- By suppressing the migration and activation of leukocytes, steroids weaken the defense, leaving the body vulnerable to infections.

❖ **Iatrogenic Cushing's Syndrome**

- This is the most well-known side effect of long-term use and is related to the drug's hormonal effects. It disrupts the body's metabolic balance, leading to symptoms like muscle weakness, skin thinning, and fat redistribution.

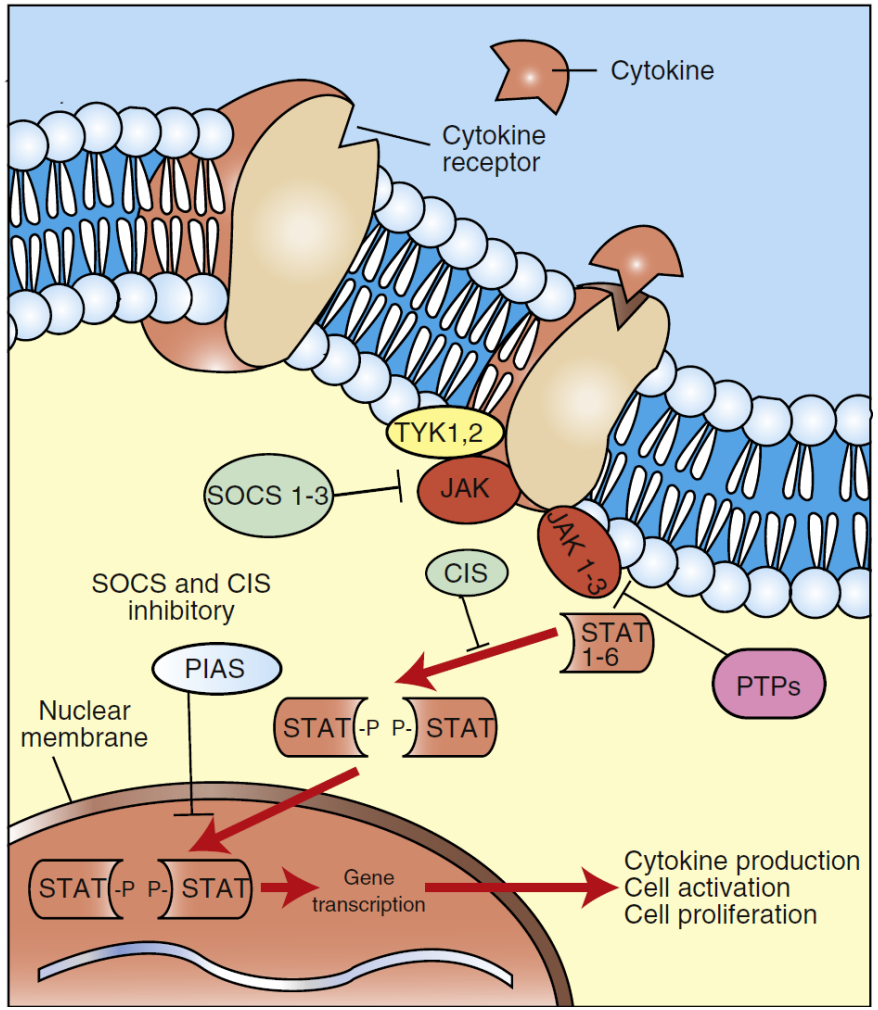
Chemical Mediators of Inflammation

Cytokines - The Master Regulators

- Definition: A large group of proteins produced by many cell types (especially activated lymphocytes and macrophages) that modulate the function of other cells.

- Key Inflammatory Cytokines:
  - Tumor Necrosis Factor (TNF) and Interleukin-1 (IL-1) are two of the most important.
  - Source: Produced mainly by activated macrophages.

- Principal Roles in Inflammation:
  - Endothelial Activation: Stimulate endothelial cells to express adhesion molecules (selectins and ICAM-1).
  - Systemic Effects: Responsible for the systemic acute-phase response, including fever, lethargy, and production of acute-phase proteins by the liver.
  - Fibroblast Activation: Stimulate fibroblast proliferation and collagen synthesis.



Chemical Mediators of Inflammation

Chemokines

- Definition: A family of small cytokines whose primary function is to act as chemoattractants for specific types of leukocytes.

- Function:
  - They are responsible for recruiting leukocytes to the site of inflammation.
  - They are also involved in the normal migration of cells through tissues (e.g., homing of lymphocytes to lymph nodes).

- Mechanism: They establish a chemical gradient that migrating cells can follow.

- Classification: They are classified into families (e.g., CC, CXC) based on the arrangement of conserved cysteine residues. Different families and specific chemokines attract different cell types (e.g., IL-8/CXCL8 is a potent chemoattractant for neutrophils).

E-Table 3.7 Chemokine Ligands of the CC and CXC Families and Their Receptors

Family	Ligand	Receptor
CC	CCL3, 7, 9, 15, 16, 23	CCR1
	CCL2, 7, 8, 12, 13	CCR2
	CCL5, 7, 8, 11, 13, 24, 26	CCR3
	CCL17, 22	CCR4
	CCL3, 4, 5	CCR5
	CCL20	CCR6
	CCL19, 21	CCR7
	CCL1, 16, 17	CCR8
	CCL25	CCR9
	CCL27, 28	CCR10
	CCL2, 7, 8, 11, 12, 13	CCR11
CXC	CXCL1, 6, 7, 8	CXCR1
	CXCL1, 2, 3, 5, 6, 7, 8	CXCR2
	CXCL9, 10, 11	CXCR3
	CXCL12	CXCR4
	CXCL13	CXCR5
	CXCL14	Unknown
	CXCL16	CXCR6

Chronic Inflammation

Chronic Inflammation

Transition to Chronic Inflammation

❖ Chronic inflammation arises when the acute inflammatory response fails to eliminate the inciting stimulus. This can be due to:

- Persistence of the inciting stimulus for weeks to months.
- Extensive tissue injury and necrosis.
- A shift of the cellular infiltrate from neutrophils to mononuclear cells (lymphocytes, macrophages, plasma cells).
- Extensive connective tissue reorganization and **fibrosis**.

Chronic Inflammation

Causes and Mechanisms

- Persistence/Resistance: Caused by microorganisms that are difficult to eradicate, such as Mycobacterium spp., certain fungi, and parasites. These agents **resist phagocytosis or killing by leukocytes**.
- Isolation: Some bacteria (e.g., Staphylococcus spp.) can isolate themselves from immune responses and antimicrobial drugs by "hiding" within the center of an abscess.
- Unresponsiveness: Occurs in response to certain foreign materials that are virtually indestructible and cannot be broken down by enzymes (e.g., plant material, asbestos fibers, silica).
- Autoimmunity: Results from immune responses directed against an individual's own tissues.
- Leukocyte Defects: Genetic defects in leukocyte function (e.g., chronic granulomatous disease) can impair killing of microbes, leading to persistent inflammation.

Chronic Inflammation

Key Cellular Players in Chronic Inflammation

- Macrophages: The signature cell of chronic inflammation. They are activated by microbial products or by cytokines (especially IFN-γ) from T lymphocytes.
- Lymphocytes: T and B lymphocytes are mobilized by persistent antigens. They interact with macrophages in a bidirectional way: macrophages present antigen to T cells, and activated T cells produce cytokines that activate macrophages.
- Plasma Cells: Differentiated B lymphocytes that produce antibodies directed against the persistent antigen.
- Eosinophils: A feature of some forms of chronic inflammation, especially those driven by parasitic infections or allergic responses.
- **Fibroblasts**: Proliferate and deposit collagen in response to growth factors and cytokines, leading to fibrosis.

Chronic Inflammation

Macrophage Activation

❖ Macrophages can be activated into functionally distinct populations:

❖ **Classically Activated Macrophages (M1)**

- Induced by: Microbial products (e.g., LPS) and Th1-derived cytokines (e.g., IFN-γ).
- Function: Potent microbicidal activity. They produce reactive oxygen species (ROS) and nitric oxide (NO) to kill phagocytosed organisms and secrete **proinflammatory** cytokines (IL-1, IL-12).

❖ **Alternatively Activated Macrophages (M2)**

- Induced by: Th2-derived cytokines (e.g., IL-4, IL-13).
- Function: Primarily involved in tissue repair. They secrete growth factors (like TGF-β) that promote angiogenesis, activate fibroblasts, and stimulate collagen synthesis. They have **anti-inflammatory** effects.

Chronic Inflammation

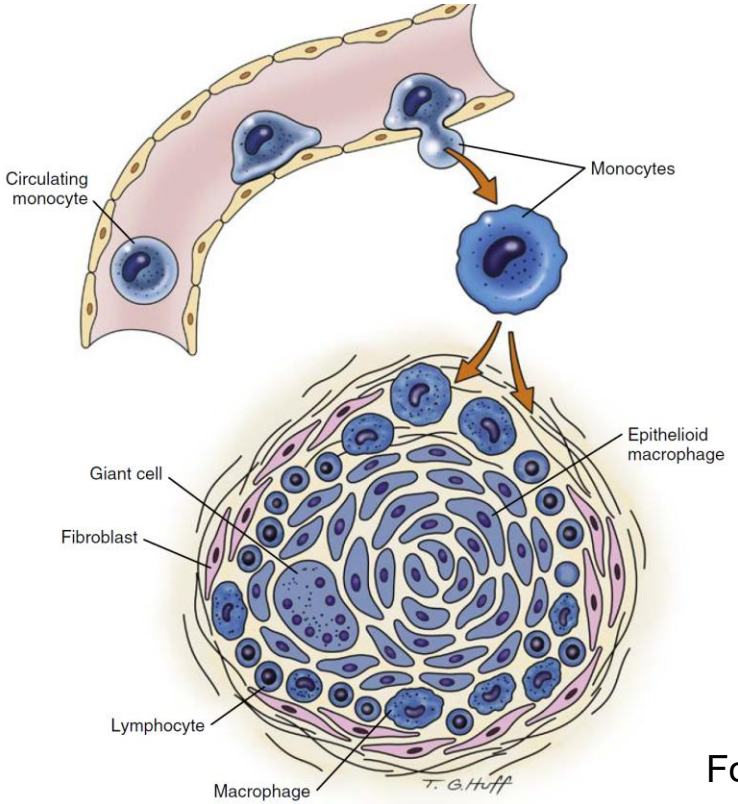
Granulomatous Inflammation

- Definition: A distinctive pattern of chronic inflammation characterized by a predominance of activated macrophages, which are often transformed into epithelioid macrophages.

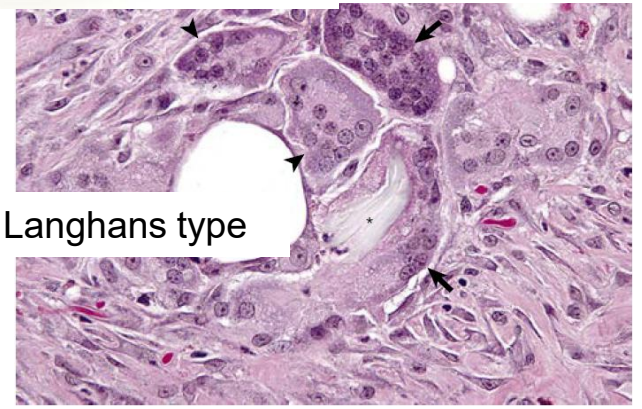
- **Epithelioid Macrophages**: Resemble epithelial cells; they have abundant pink cytoplasm and are organized in aggregates. They have reduced phagocytic capacity but are adapted for extracellular secretion.

- **Multinucleated Giant Cells**: Formed by the fusion of two or more activated macrophages.
  - Langhans-type: Nuclei are arranged in a horseshoe pattern at the periphery.
  - Foreign Body-type: Nuclei are arranged haphazardly in the center.

- Purpose: A mechanism to contain or "wall off" an inciting agent that is difficult to eradicate.



Foreign body type



Langhans type

Chronic Inflammation

Types of Granulomas

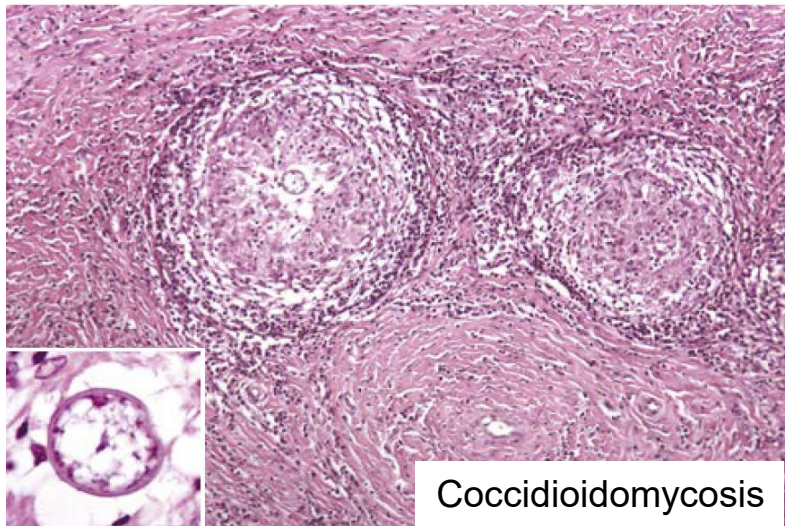
❖ Nodular (Tuberculoid) Granulomas

- Cause: Typically form in response to agents that elicit a strong Th1-mediated immune response (e.g., Mycobacterium bovis, certain fungi).
- Structure: Organized, discrete masses or nodules of macrophages, often surrounded by a collar of lymphocytes and a fibrous capsule.
- Caseation: The center of the granuloma may have a core of caseous (cheesy) necrotic debris.

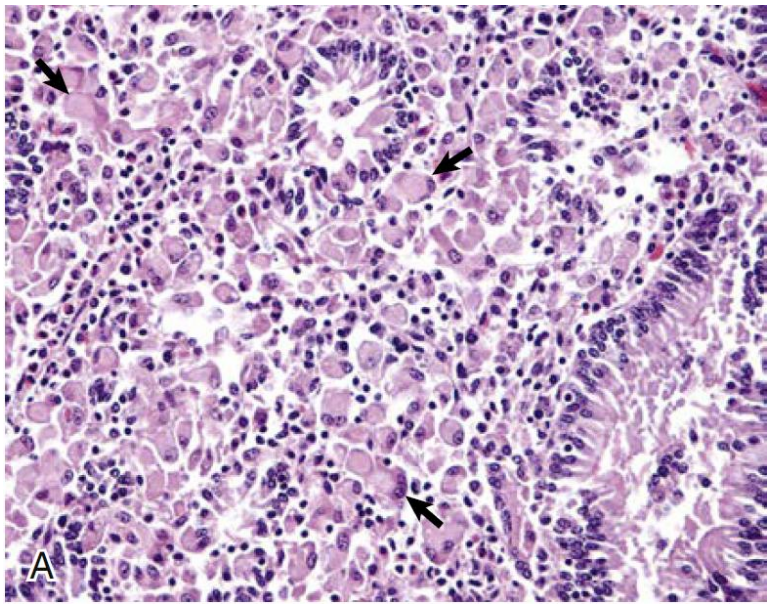
❖ Diffuse (Lepromatous) Granulomas

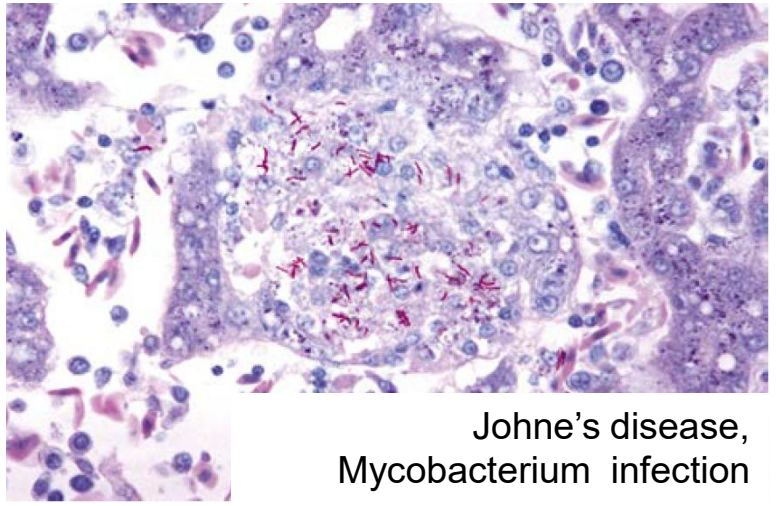
- Cause: Form in response to agents that elicit a weak cell-mediated immunity or a Th2-biased response (e.g., **Johne's disease**).
- Structure: Poorly delineated, diffuse sheets of macrophages that spread throughout the tissue, with few lymphocytes and no capsule. They often contain a heavy burden of organisms.

Chronic Inflammation

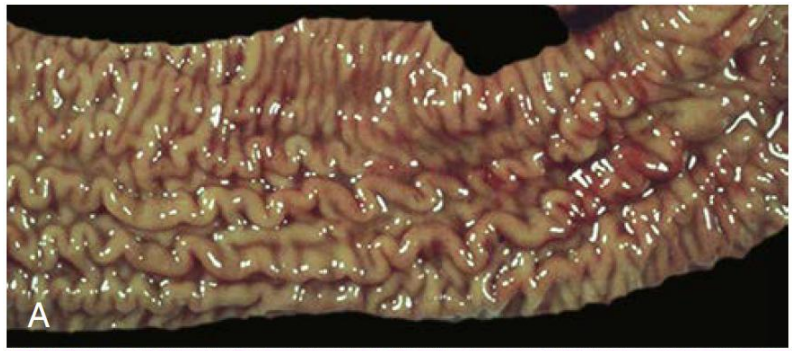


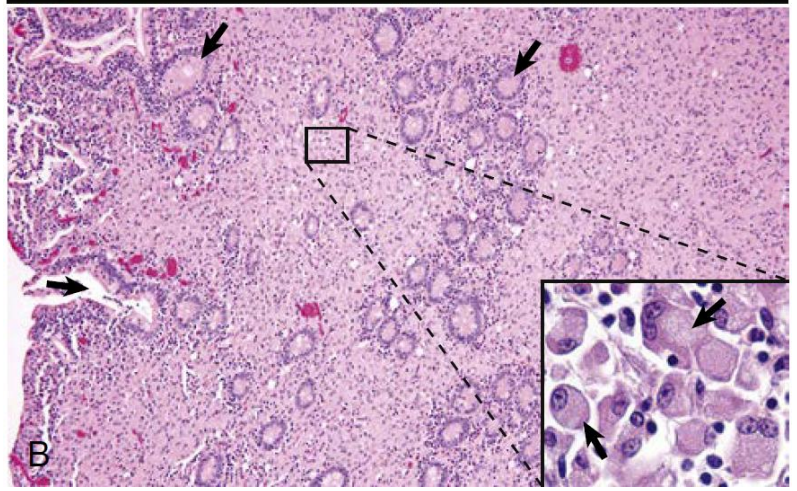
Coccidioidomycosis





Johne's disease,
Mycobacterium infection





Johne's disease,
Mycobacterium infection

Chronic Inflammation

Eosinophilic Granulomas

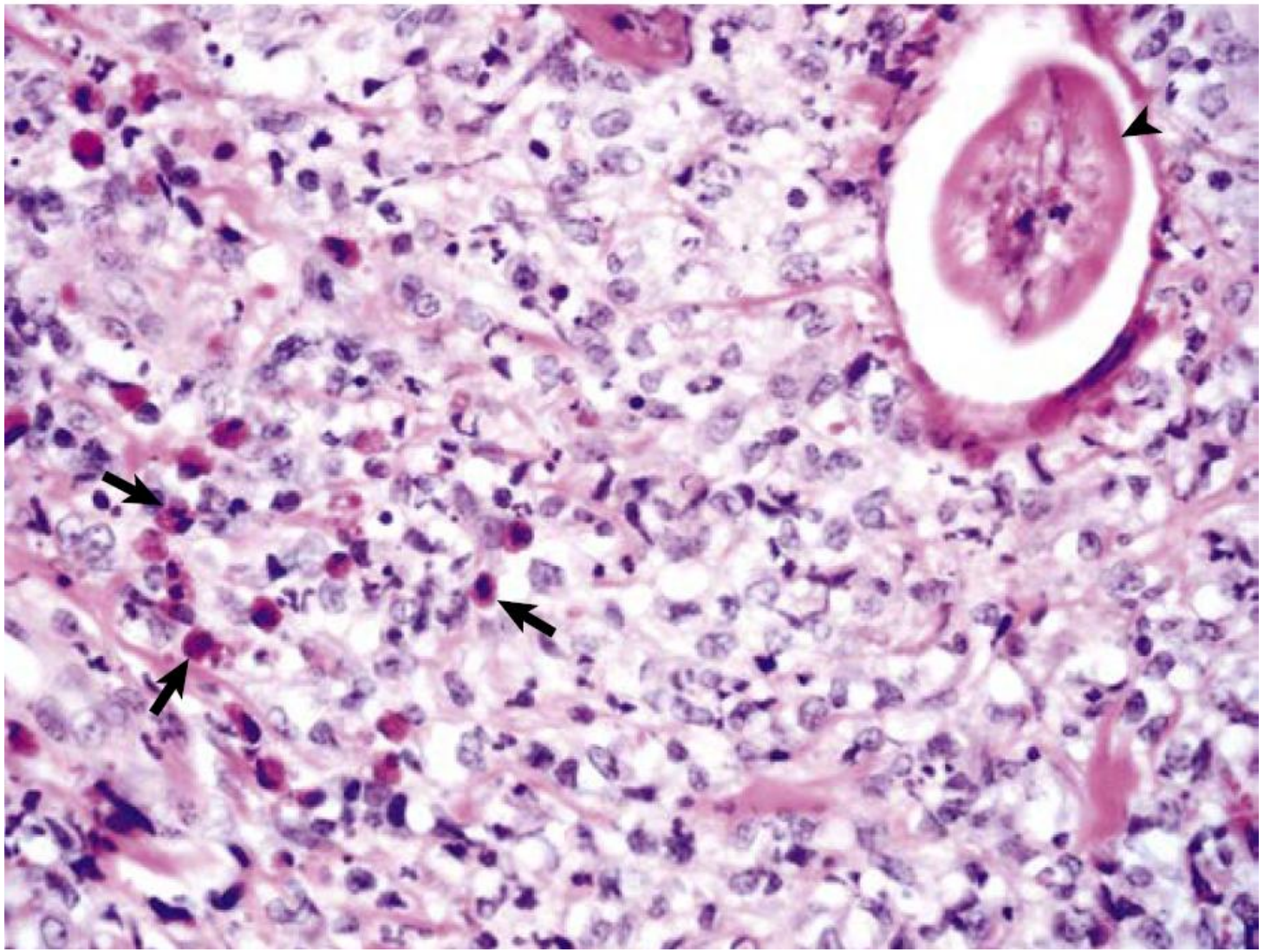
- Definition: A type of chronic inflammation characterized by dense infiltrates of eosinophils mixed with macrophages, and varying numbers of lymphocytes and plasma cells.

- Causes: Often develop in response to migrating parasites (e.g., larva migrans) or in suspected allergic/hypersensitivity conditions in species like cats, dogs, and horses (e.g., **feline eosinophilic granuloma complex**).

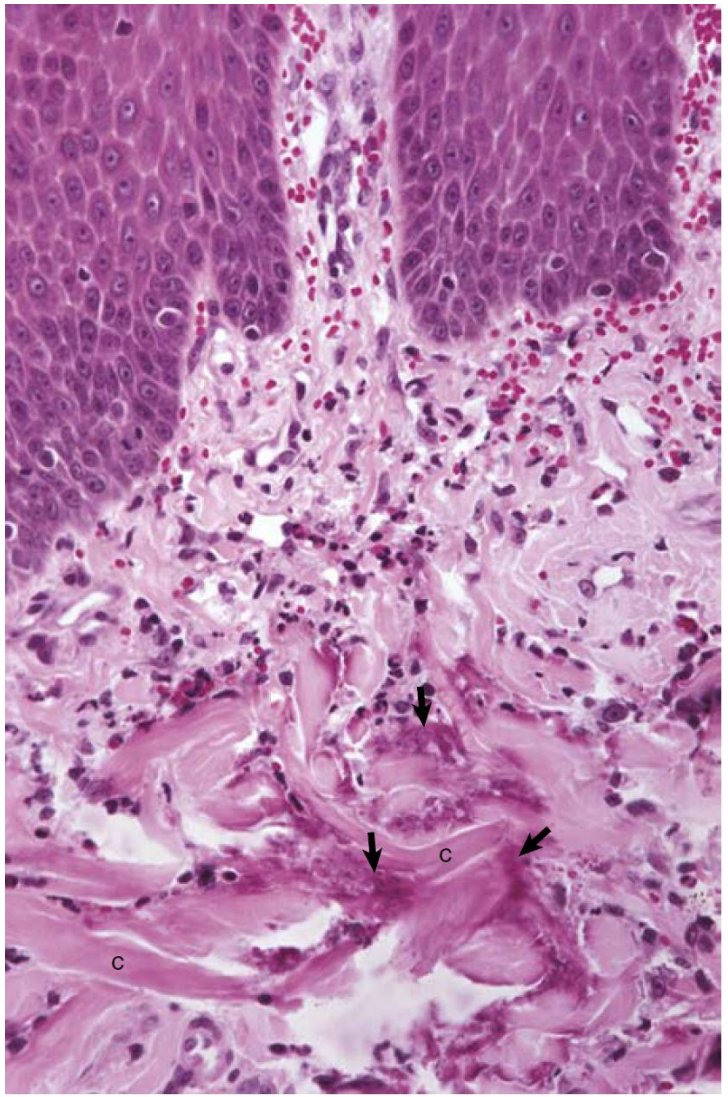
- Mechanism: Thought to be a Th2-directed immune response.

- Histology: Characterized by eosinophils, macrophages, and areas of dense eosinophilic material around collagen, which is composed largely of degranulated eosinophil proteins like Major Basic Protein (MBP).

Chronic Inflammation



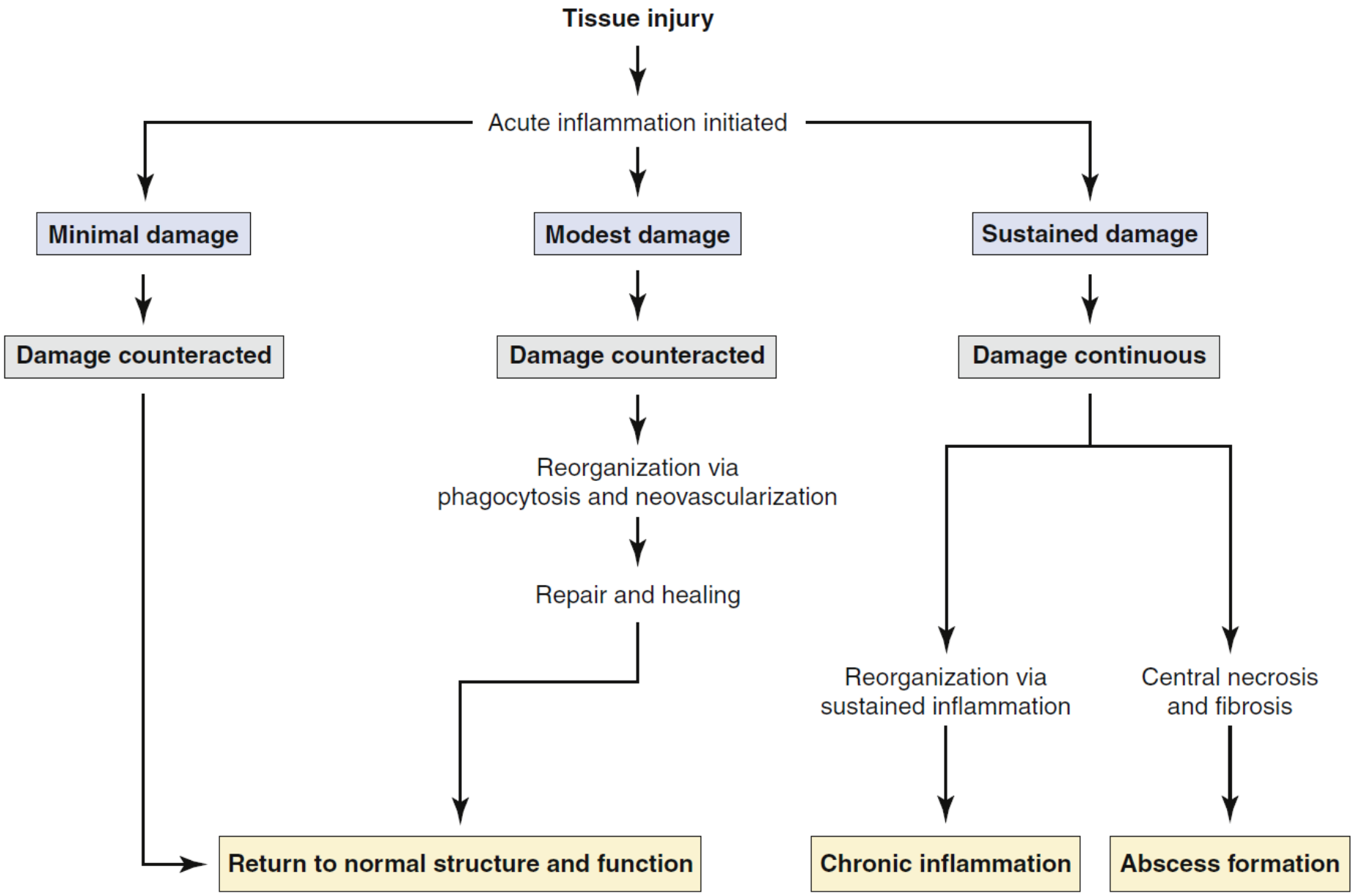
Granuloma with eosinophils, Parasitic infection



Eosinophilic granuloma, oral mucosa, cat

Outcomes & Healing

Outcomes & Healing



Outcomes & Healing

The Four Outcomes of Acute Inflammation

- Resolution: The ideal outcome. The inciting agent is removed, the exudate is cleared by macrophages and lymphatics, and the tissue returns to its normal structure and function. This requires an intact stromal framework.

- Healing by Fibrosis (Scarring): Occurs after substantial tissue destruction where the underlying framework is also destroyed. The area of defect is filled by connective tissue, which restores structural integrity but not the original, specialized function of the tissue.

- Abscess Formation: Occurs typically with pyogenic (pus-forming) bacterial infections. It is a localized collection of pus (neutrophils and liquefied debris) that becomes walled off by a fibrous capsule.

- **Progression to Chronic Inflammation**: Occurs if the injurious agent cannot be eliminated by the acute response.

Outcomes & Healing

Wound Healing - An Overview

❖ The process of healing begins almost immediately after a wound develops.

❖ Four Temporal Phases: Wounds classically heal through four overlapping phases:

- **Hemostasis**: Immediate vasoconstriction and formation of a platelet plug and fibrin clot to stop bleeding.
- **Inflammation**: Neutrophils and then macrophages enter the wound to remove debris and bacteria.
- **Proliferation**: Lasts up to 3-4 weeks. Characterized by the formation of granulation tissue, angiogenesis, and re-epithelialization.
- **Remodeling**: Begins after 3-4 weeks and can last for years. The newly formed connective tissue is reorganized, and collagen is remodeled to increase the tensile strength of the wound.

Outcomes & Healing

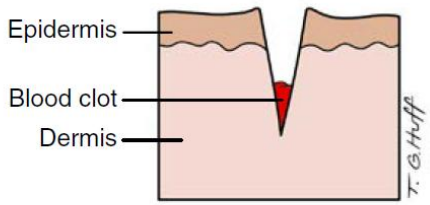
Healing by First vs. Second Intention

- First Intention Healing (primary intention)
  - Applies to: Clean, uninfected wounds where the edges are brought into direct apposition (e.g., a sutured surgical incision).
  - Process: Healing is rapid, with minimal inflammation, minimal granulation tissue, and results in a small, linear scar with good tensile strength.

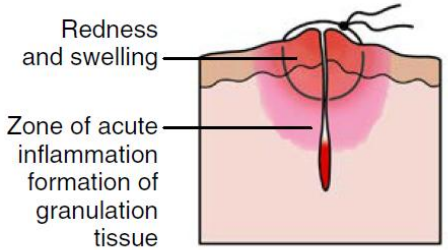
- Second Intention Healing (secondary intention)
  - Applies to: Larger wounds with significant tissue loss, infection, or unapposed edges.
  - Process: Involves a more intense inflammatory response, the formation of abundant granulation tissue to fill the defect, and significant wound contraction mediated by myofibroblasts.
  - Result: Healing is slower and results in a larger, often irregular scar with reduced tensile strength.

Outcomes & Healing

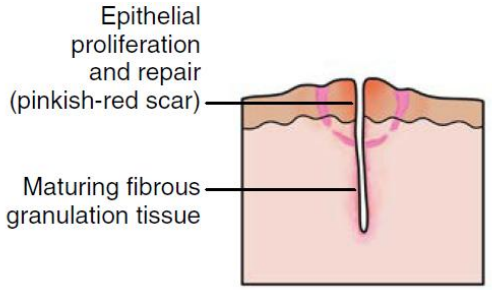
Primary intention



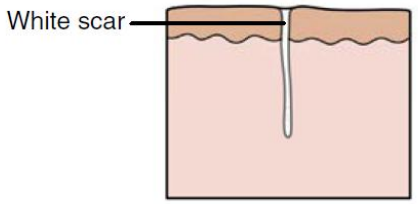
Simple incision



Sutured incision
acute inflammatory
response (2-7 days)

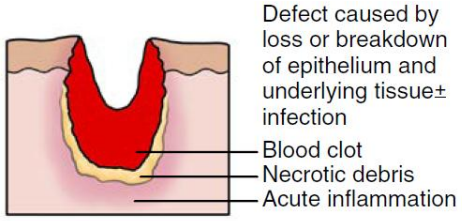


Healing incision
(early weeks)

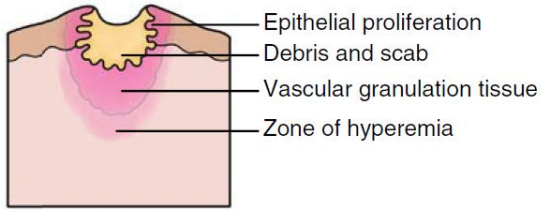


Linear fibrous scar
(6-12 months)

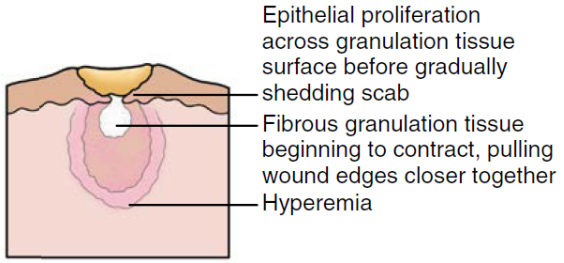
Secondary intention



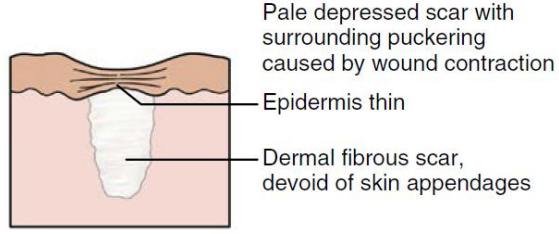
Ragged infected wound
(at 2-3 days)



Phase of rapid proliferation
of vascular granulation tissue
(about 1-2 weeks)



Phase of granulation tissue
maturation and wound
contraction (about 3-6 weeks)

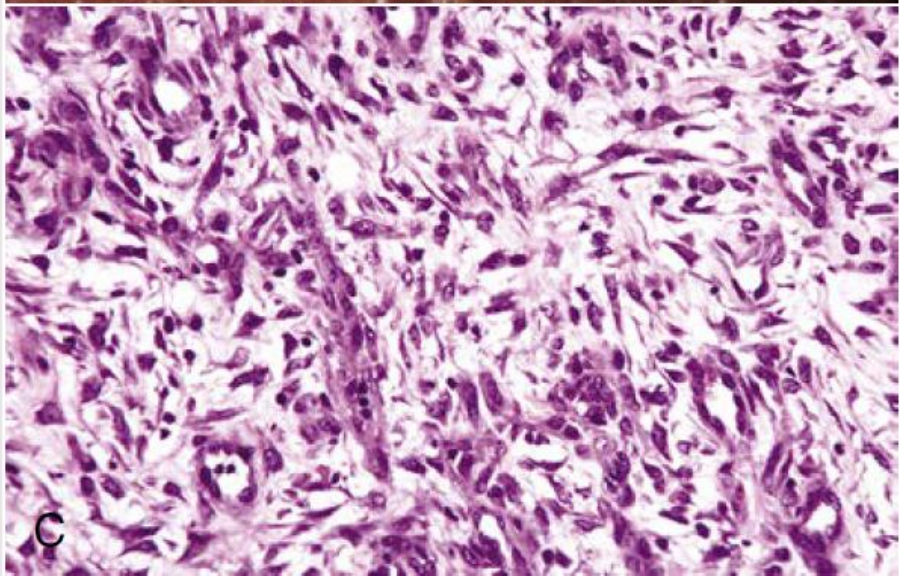


Healed wound

Outcomes & Healing







Granulation Tissue, Nonhealing Ulcer, Distal limb, horse

A mixture of newly formed blood vessels, extracellular matrix (ECM), and fibroblasts, with minimal or no collagen deposition. It provides the support for wound repair and remodeling via fibroplasia and reepithelialization.

Outcomes & Healing

The Proliferation Phase: Granulation Tissue

- Definition: The exposed connective tissue that forms within a healing wound, particularly in second intention healing.

- Gross Appearance: Appears red and has a finely granular surface (the "granulations" are new capillary loops). It bleeds easily due to the fragility of the new vessels.

- Microscopic Appearance: **A hallmark of healing**, it consists of:
  - Proliferating fibroblasts.
  - Newly formed, thin-walled capillaries (angiogenesis).
  - A loose extracellular matrix.

- Function: Fills the wound defect and provides **support for re-epithelialization** and subsequent fibrosis.

Outcomes & Healing

The Proliferation Phase: Angiogenesis

❖ Definition: The formation of new blood vessels from pre-existing vessels.

❖ Purpose: Essential for healing, as new vessels supply oxygen and nutrients, remove waste, and provide a pathway for inflammatory and stem cells.

❖ Process:
- Proteolysis of the basement membrane of a parent vessel.
- Migration and proliferation of endothelial cells to form a solid "sprout" or "bud.“
- Maturation of the sprout into a new capillary with a lumen.
- Recruitment of pericytes and smooth muscle cells to support the new vessel.

❖ Key Mediators: Driven by growth factors, most importantly Vascular Endothelial Growth Factor (VEGF), and regulated by hypoxia via Hypoxia-Inducible Factor (HIF-1α).

Outcomes & Healing

The Proliferation Phase: Re-epithelialization

- Definition: The process by which the skin and mucous membranes replace superficial epithelial cells lost in a wound.

- Mechanism: Epithelial cells at the edge of the wound proliferate and migrate over the surface of the granulation tissue until they contact one another, covering the defect.

- Importance of Basement Membrane: The presence of an intact basement membrane greatly facilitates this process by providing a scaffold for epithelial cells to migrate along. If the basement membrane is destroyed, healing is impaired.

- Role of Stem Cells: Epithelial stem cells, often located in the basal layer or in skin appendages like hair follicles, are responsible for **generating the new cells**.

Outcomes & Healing

The Remodeling Phase

❖ Timing: Begins approximately 3-4 weeks after injury and can continue for 2 or more years.

❖ Key Events:

- The granulation tissue matures into a scar.
- The initially deposited Type III collagen is replaced by the much stronger Type I collagen.
- The collagen fibers become more organized and cross-linked, increasing the tensile strength of the wound.
- Wound Contraction: The size of the scar is reduced, a process mediated by myofibroblasts, which are specialized fibroblasts with contractile ability.
- The scar eventually becomes largely acellular and avascular.

Outcomes & Healing

Factors that Impair Wound Healing

❖ Local Factors:

- Infection: The single most important cause of delayed healing.
- Poor Vascular Supply/Oxygenation: Ischemia impairs the healing process.
- Foreign Bodies: Provide a nidus for infection and persistent inflammation.
- Mechanical Stress: Motion can disrupt the healing wound.

❖ Systemic Factors:

- Nutrition: Deficiencies, especially in protein and vitamin C (required for collagen synthesis), can impair healing.
- Metabolic Status: Diseases like diabetes mellitus are associated with poor wound healing.
- **Glucocorticoids (Steroids)**: Have a well-documented anti-inflammatory effect that can inhibit fibrosis and delay healing.

Outcomes & Healing

Abscess Formation

- Mechanism: Occurs when the acute inflammatory response fails to rapidly eliminate the stimulus. Enzymes from the large number of neutrophils in the exudate **liquefy** the affected tissue and the neutrophils themselves, forming **pus**.

- Structure: A collection of pus that becomes circumscribed by a fibrous capsule over time in an attempt to "wall off" the infection.

- Types:
  - Septic Abscesses: Most common, caused by bacterial infection (e.g., Staphylococcus spp.).
  - Sterile Abscesses: Can arise from incompletely degraded foreign bodies or injected medications.

- **Clinical Relevance**: The fibrous capsule can prevent antibiotics from effectively reaching the bacteria inside, which is why larger abscesses are often surgically drained.

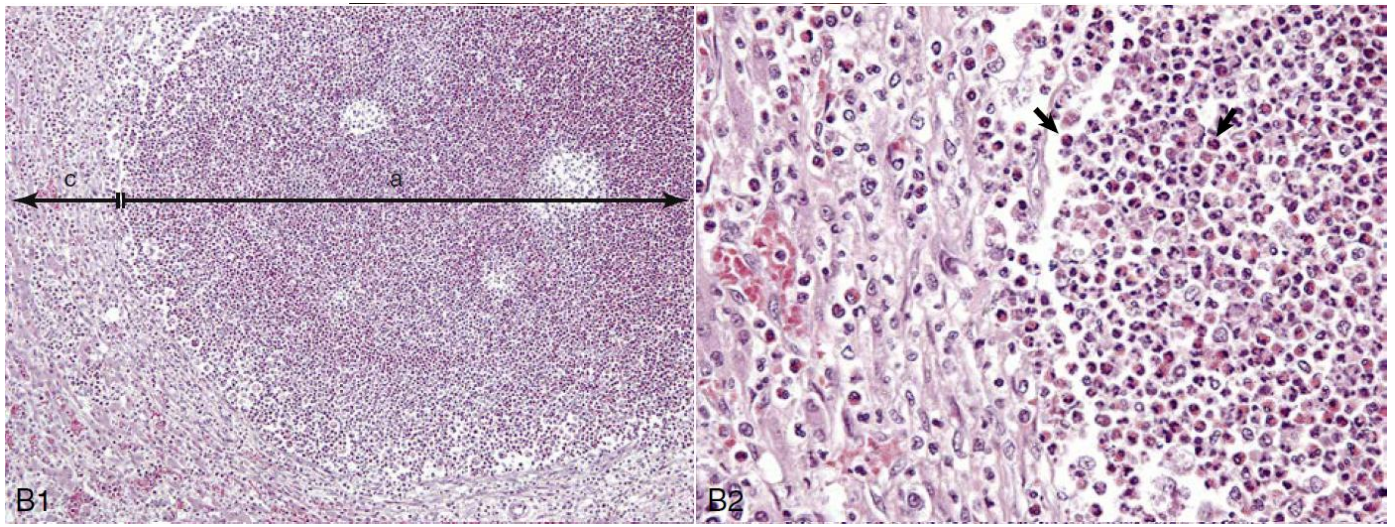
Outcomes & Healing

Abscess Formation

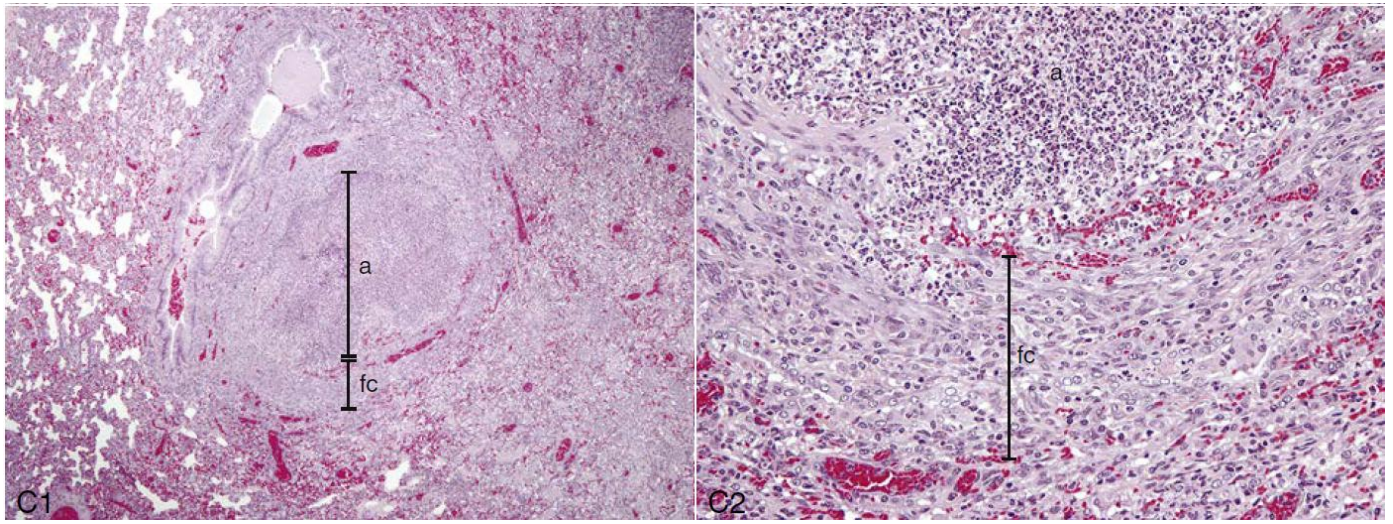
Lung, cow



Acute to subacute



Chronic



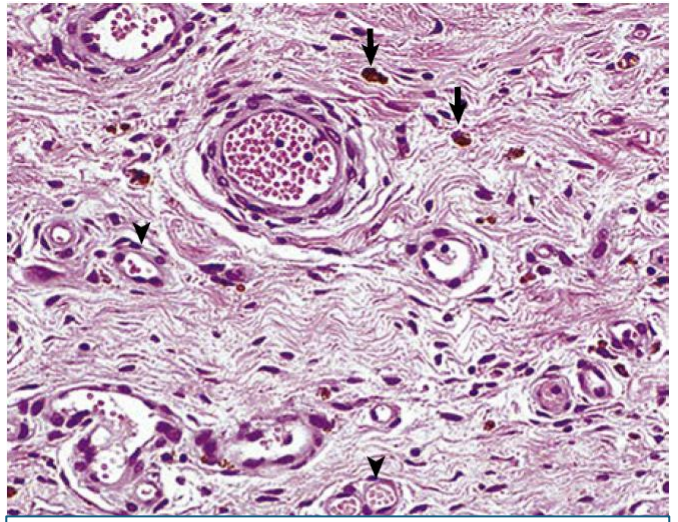
Outcomes & Healing

Healing by Fibrosis (Scarring)

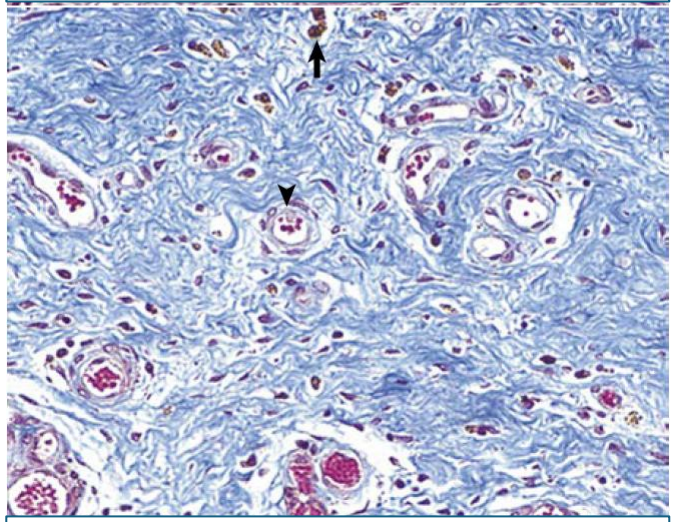
- When it Occurs: This is the outcome when tissue injury is severe, resulting in necrosis of both the parenchymal cells and the underlying stromal framework (connective tissue and basement membranes).

- The Process:
  - The dead tissue and inflammatory exudate are removed by macrophages.
  - The space is filled with granulation tissue.
  - The granulation tissue is eventually replaced by mature fibrous connective tissue, forming a scar (cicatrix).

- Result: Structural integrity may be reestablished, but **functional integrity is often lost or diminished** due to the replacement of specialized parenchyma with non-functional connective tissue.



H&E



Masson's trichrome staining

Systemic Effects & Nomenclature

Systemic Effects & Nomenclature

Systemic Effects of Inflammation

- While inflammation is a local response, it can induce systemic reactions known as the acute-phase response.

- Fever: A hallmark of the systemic response. It is produced in response to pyrogens, which stimulate the production of prostaglandins (PGE_2) in the hypothalamus.

- Acute-Phase Proteins: Plasma proteins, mostly synthesized by the liver, whose concentrations increase dramatically during inflammation. Examples include C-reactive protein (CRP) and fibrinogen. Their synthesis is stimulated by cytokines, especially IL-1 and TNF.

- Leukocytosis: An increase in the number of circulating leukocytes, particularly neutrophils, due to accelerated release from the bone marrow.

Systemic Effects & Nomenclature

Septicemia and Septic Shock

- **Septicemia**: A clinically significant form of bacteremia (bacteria in the blood) where microorganisms are actively multiplying. It is complicated by toxemia, fever, malaise, and often leads to shock.

- Septic Shock: A life-threatening syndrome that is **a common sequela of septicemia**.

- Pathogenesis: Caused by the systemic effects of microbial products (especially endotoxin/LPS from Gram-negative bacteria) and the host's massive inflammatory response.

- Key Elements: The syndrome involves hemodynamic derangements (hypotension), disseminated intravascular coagulation (DIC), progressive hypoperfusion, hypoxic injury to cells, and ultimately, multiple organ failure (MOF).

Systemic Effects & Nomenclature

Morphologic Diagnosis of Inflammation

- Veterinary pathologists use a standardized system of names to provide a concise, descriptive diagnosis of a lesion.

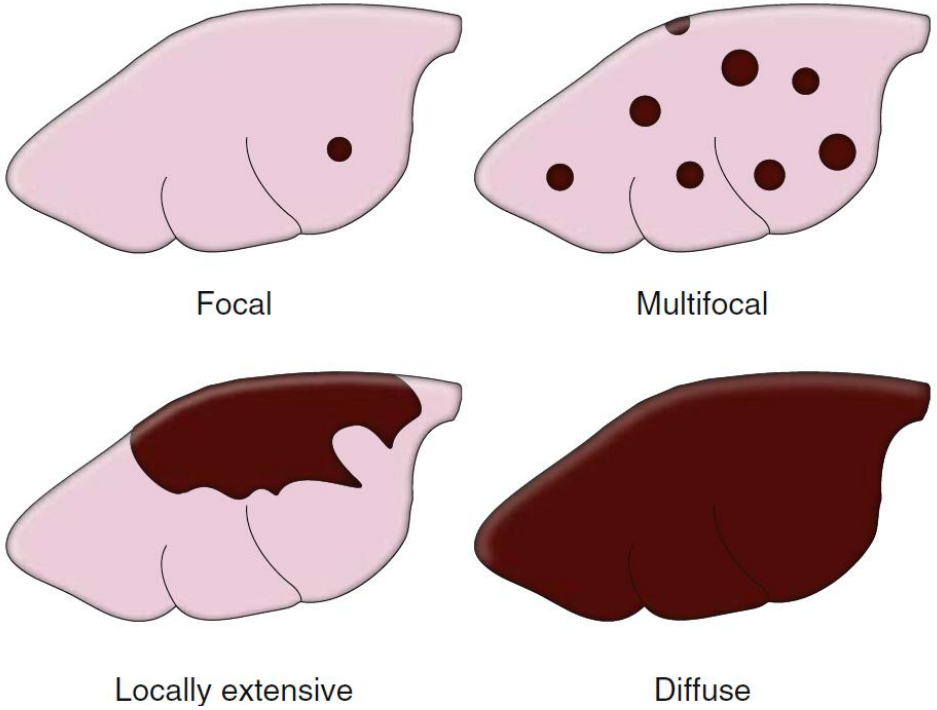
- The Six Components (DDDEMT): A morphologic diagnosis typically includes:
  - Degree: Minimal, Mild, Moderate, Marked/Severe.
  - Duration: Acute, Subacute, Chronic.
  - Distribution: Focal, Multifocal, Locally Extensive, Diffuse.
  - Exudate: The type of inflammation (e.g., Suppurative, Fibrinous, Granulomatous).
  - Modifier: An additional descriptor (e.g., Necrotizing, Hemorrhagic).
  - Tissue: The name of the organ, usually ending in "-itis" (e.g., Hepatitis, Nephritis, Encephalitis).

Systemic Effects & Nomenclature

Table 3.7 DDDEMT: Examples of the Nomenclature Used to Construct a Morphologic Diagnosis*

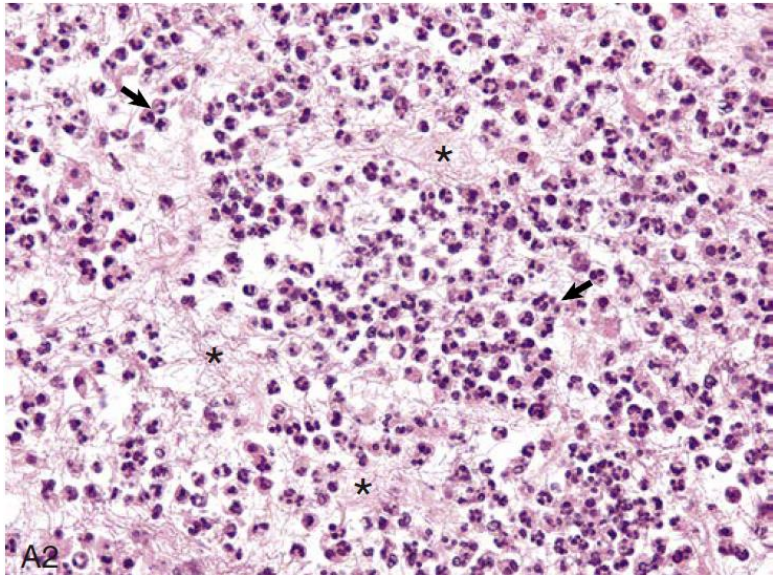
Degree	Minimal • Mild • Moderate • Marked (severe)
Duration	Acute • Subacute • Chronic
Distribution	Focal • Multifocal • Locally extensive • Diffuse (interstitial) • Cranioventral†
Exudate‡	Serous • Catarrhal • Fibrinous • Suppurative • Granulomatous • Pyogranulomatous
Modifier‡	Necrotizing • Bronchointerstitial • Hemorrhagic • Embolic
Tissue‡	Nephritis • Cystitis • Enteritis • Pneumonia§ • Hepatitis • Encephalitis

Patterns of Lesion Distribution, as an example, in the Lung



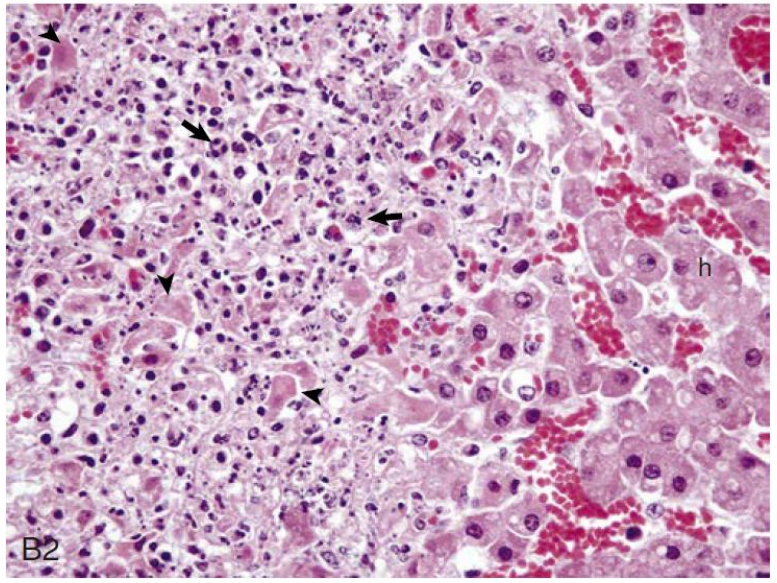
Systemic Effects & Nomenclature

Acute (Suppurative/Purulent) Inflammation



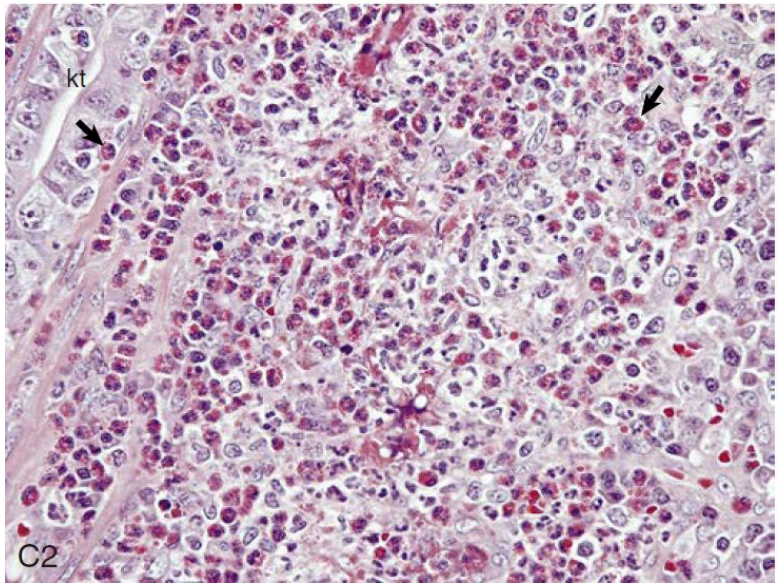
Neutrophils, fibrin, edema

Necrosuppurative (Lytic) Inflammation



Neutrophils,
necrotic neutrophils and parenchyma

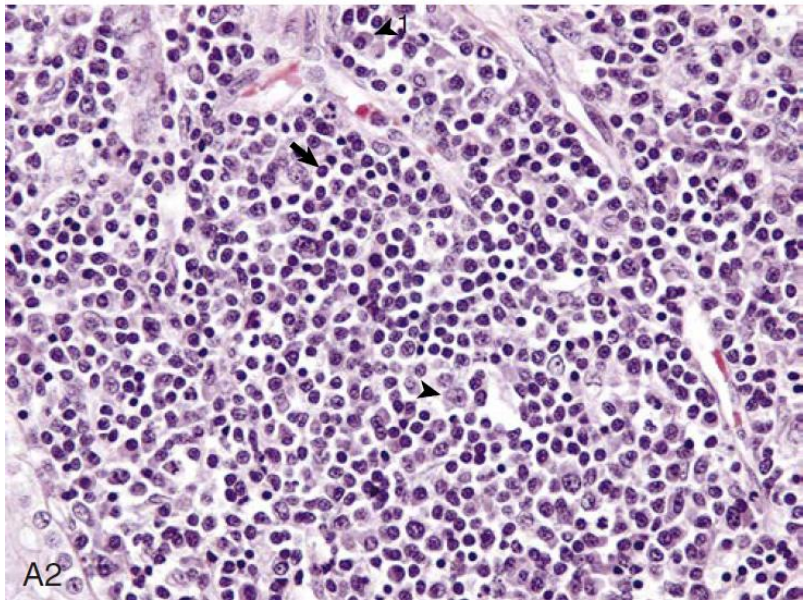
Eosinophilic Inflammation



Eosinophils, lesser numbers of neutrophils, lymphocytes, and macrophages

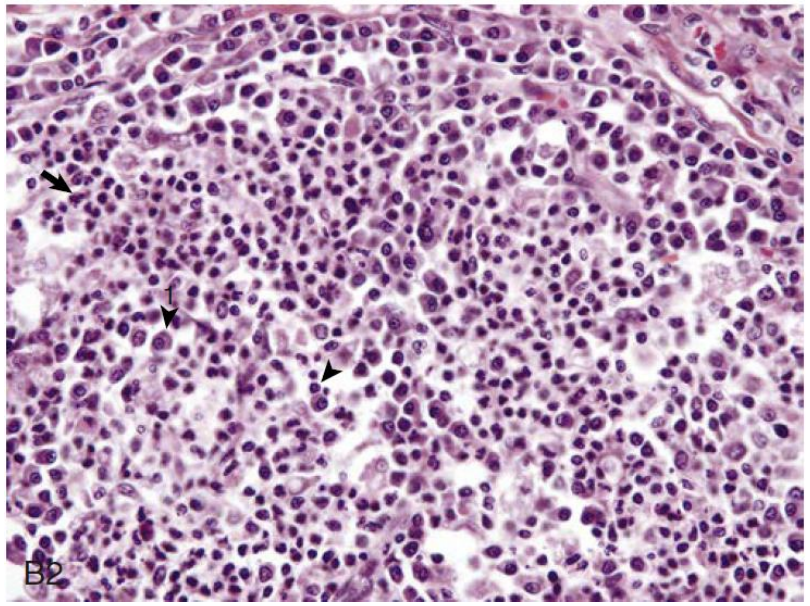
Systemic Effects & Nomenclature

Chronic Inflammation



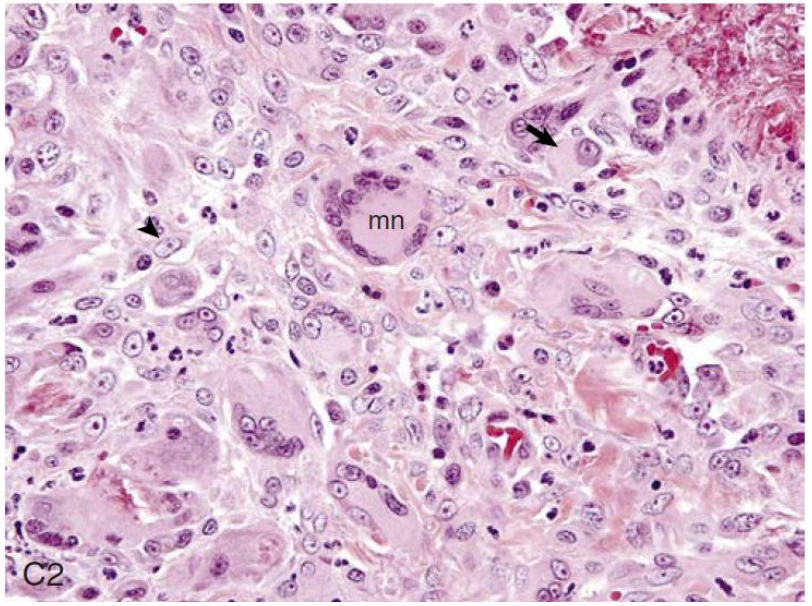
Lymphocytes, macrophages, and plasma cells

Chronic-Active Inflammation



Chronic + neutrophils

Granulomatous Inflammation



Reactive, epithelioid, and multinucleated macrophages

Systemic Effects & Nomenclature

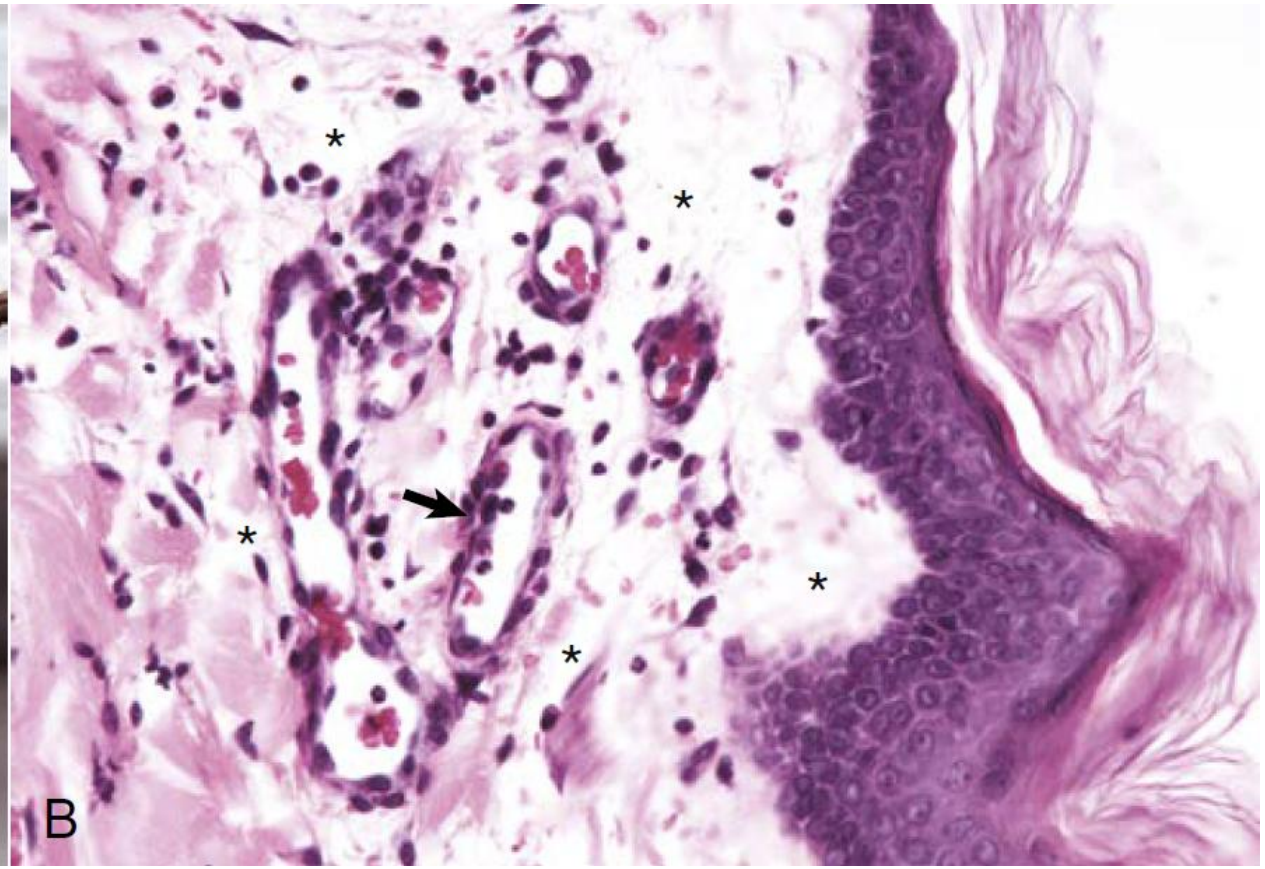
Morphologic Classification of Exudates

- The type of exudate reflects the nature and severity of the inflammatory response.
- Serous Inflammation: Leakage of fluid with low protein and few cells (a transudate). Seen in mild injury like a blister from a burn.
- Fibrinous Inflammation: An exudate with a high concentration of plasma proteins, leading to the deposition of fibrin. Common on serous membranes (pleura, peritoneum).
- Catarrhal (Mucoid) Inflammation: Secretion of thick, gelatinous fluid containing mucus. Occurs on mucous membranes (e.g., respiratory or intestinal tracts).
- Suppurative (Purulent) Inflammation: An exudate consisting predominantly of neutrophils, forming pus. The hallmark of bacterial infections.
- Combinations: Lesions often have combined features, e.g., Fibrinosuppurative or Pyogranulomatous.

Systemic Effects & Nomenclature

Serous Exudate/Subcutaneous Edema, Photosensitization

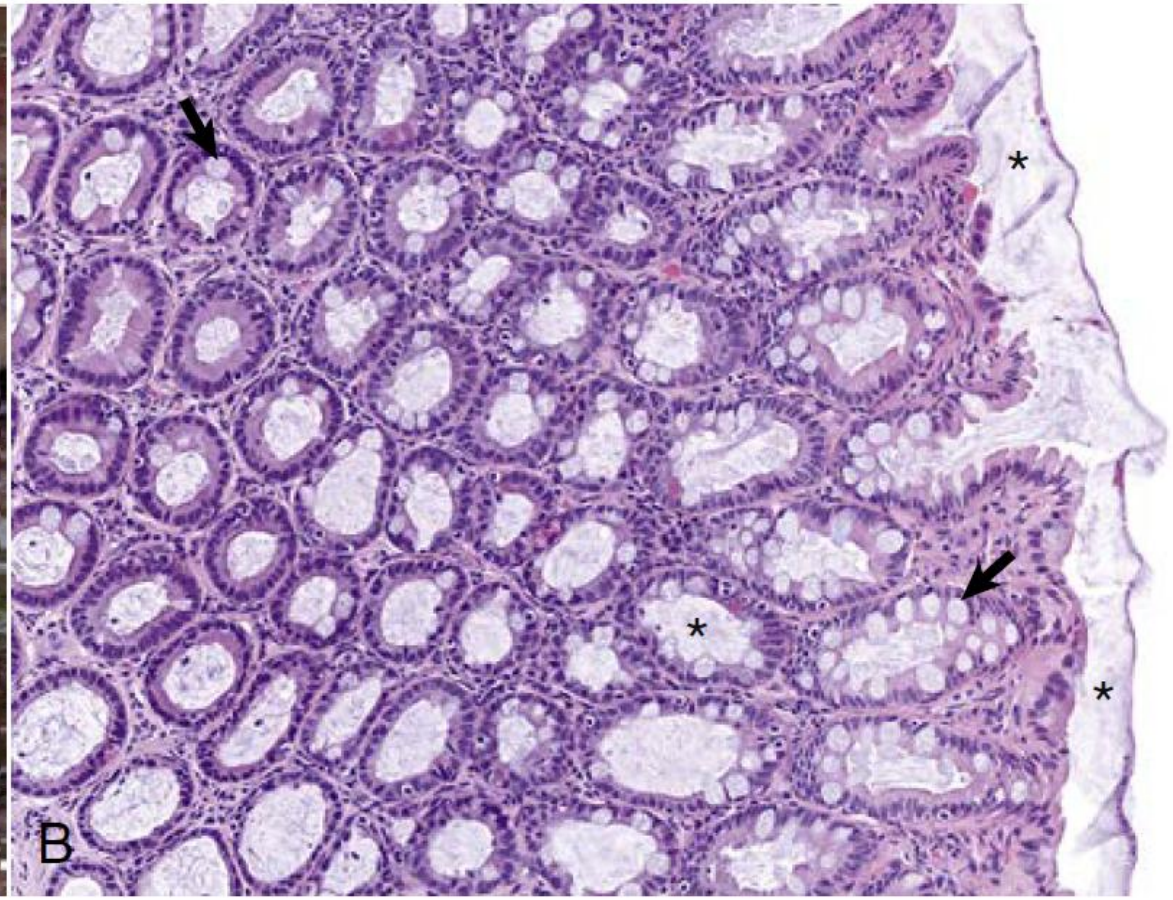




Systemic Effects & Nomenclature

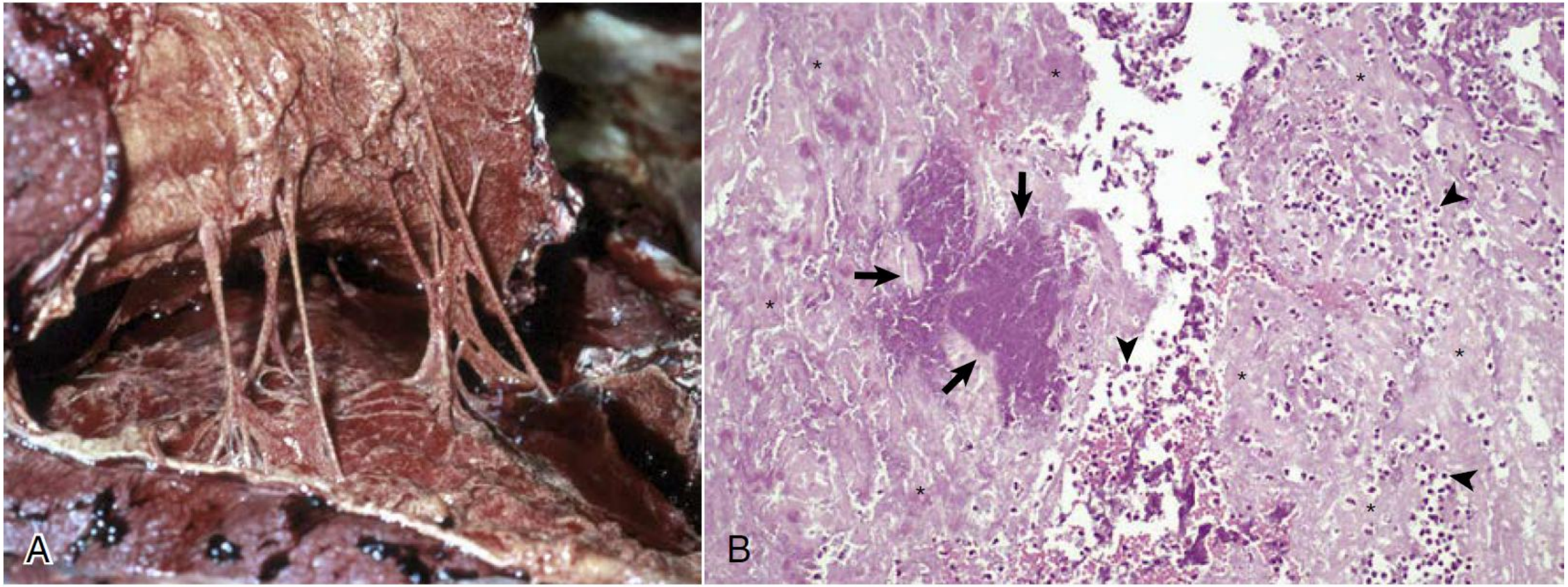
Catarrhal inflammation





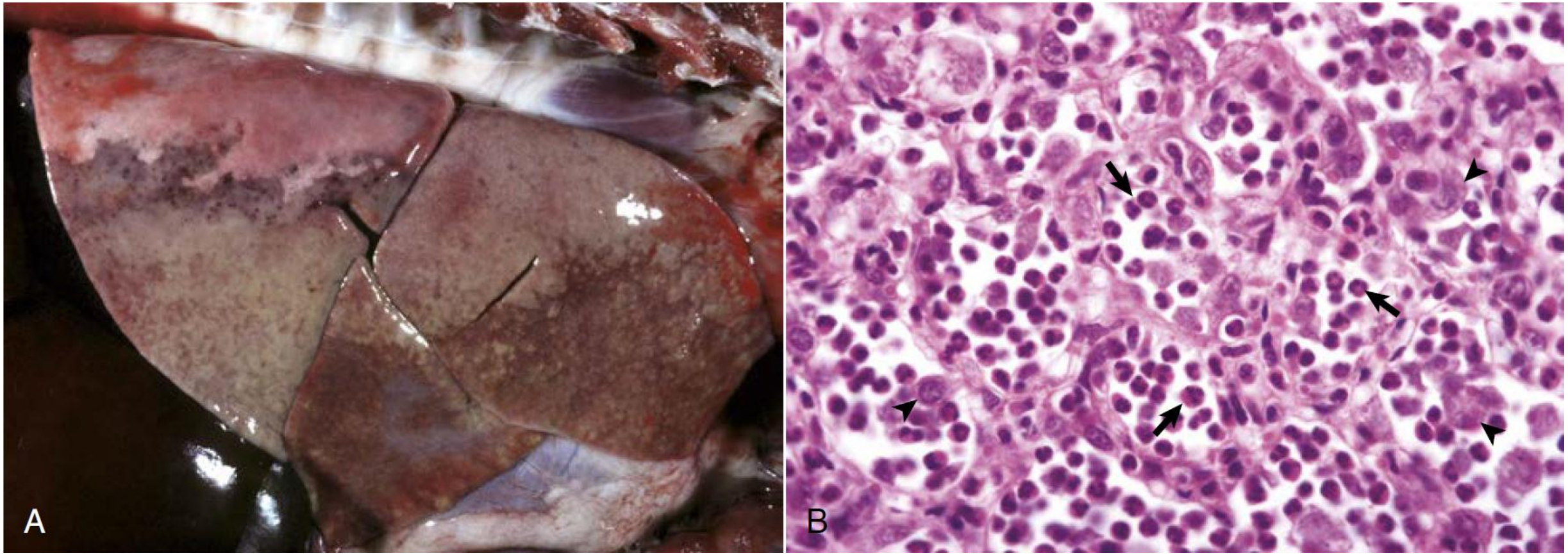
Systemic Effects & Nomenclature

Fibrinous inflammation, Pleural cavity



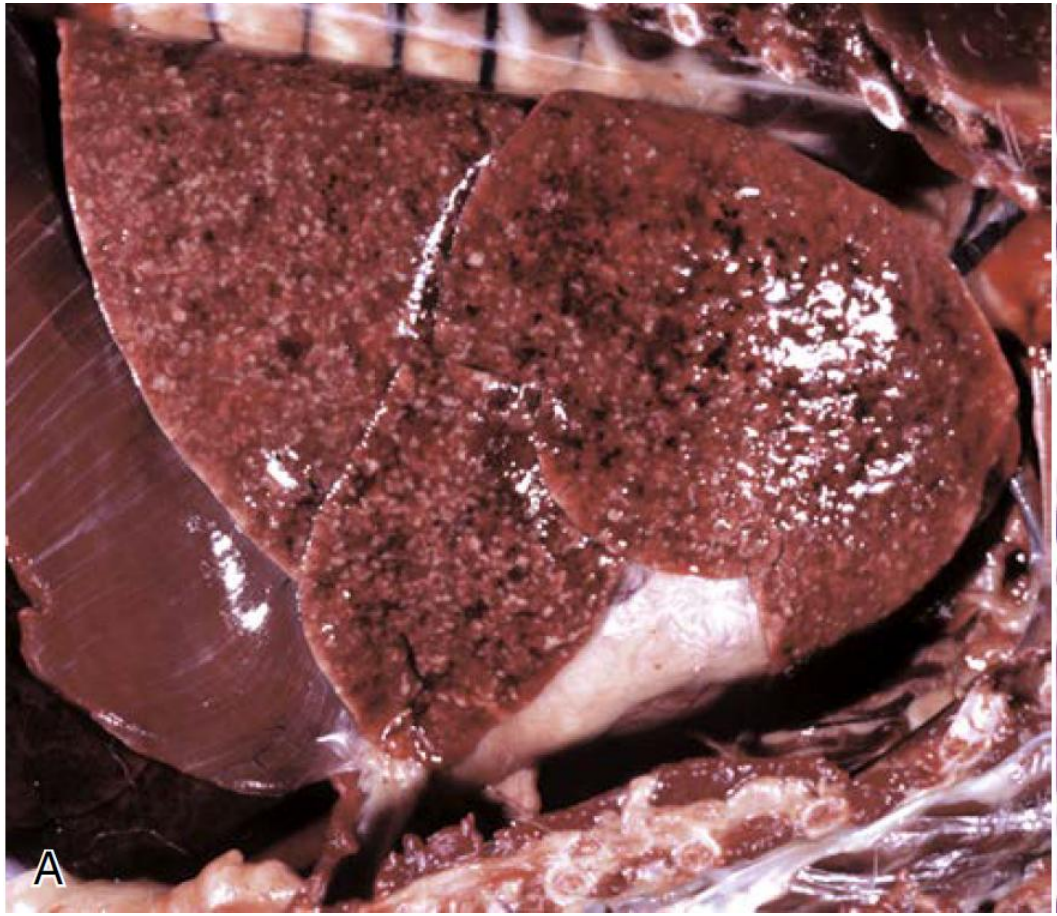
Systemic Effects & Nomenclature

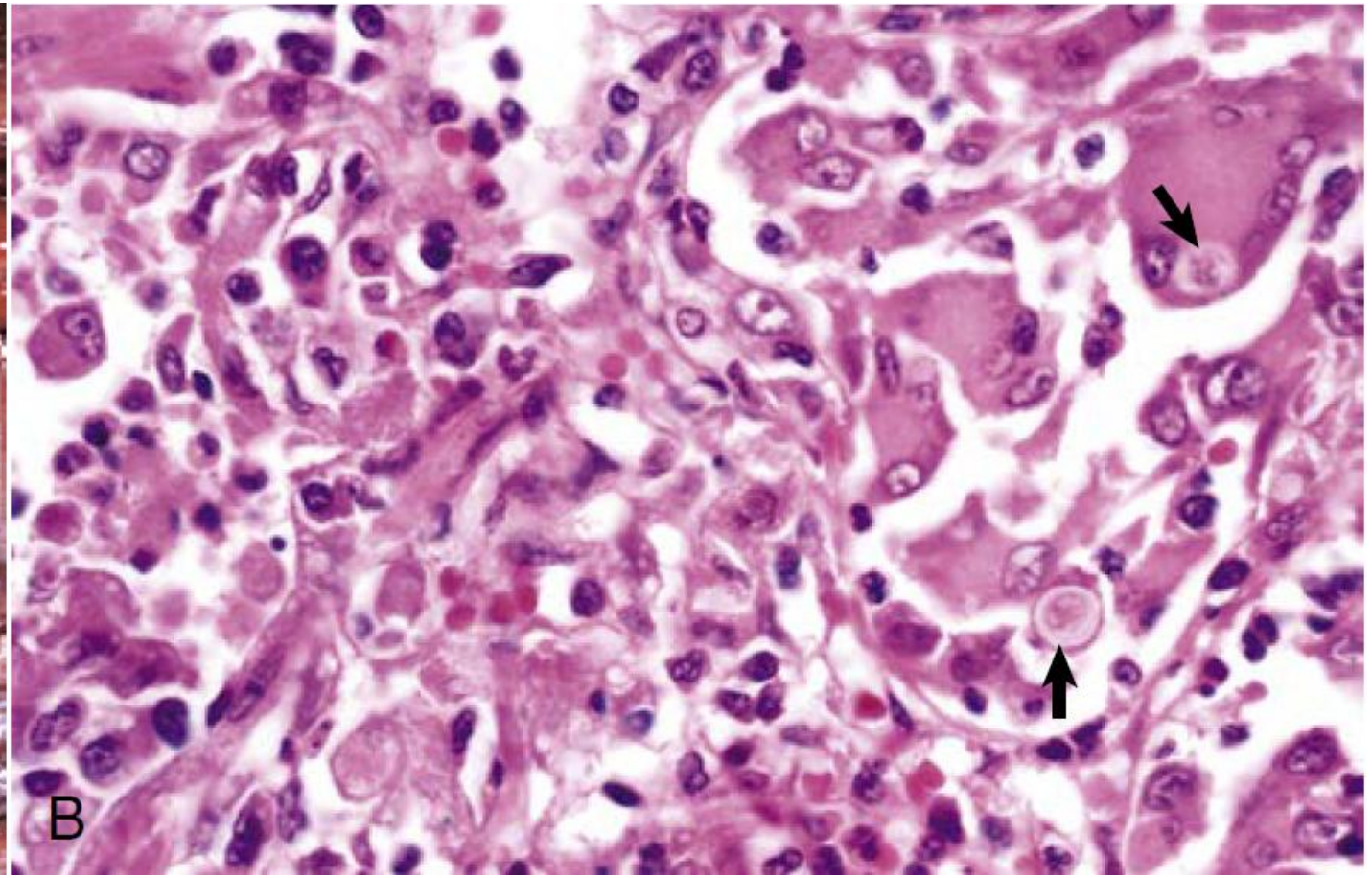
Suppurative (purulent) inflammation



Systemic Effects & Nomenclature

Granulomas and pyogranulomas, Blastomycosis





Systemic Effects & Nomenclature

Disease Dx:

Dermatophytic pseudomycetoma

Morphologic Dx:

Severe multifocal to coalescing pyogranulomatous dermatitis and panniculitis with intralesional fungal hyphae

Comments:

의뢰하신 좌측 전지 피부 조직에 대한 병리조직학적 검사 결과, 진피, 피하지방층에서는 광범위한 양상의 염증성 결절이 다발성으로 관찰되었으며 그 중심부에서는 특징적인 형태를 띠는 다수의 hyphae 가 관찰되었습니다. 원인체의 형태 및 병변의 특징적인 양상을 고려하였을 때, dermatophytic pseudomycetoma 로 사료됩니다.

Microscopic findings:

의뢰하신 피부조직에 대한 병리조직학적 검사 결과, 진피, 피하에서는 다소성으로 다수의 염증성 결절이 관찰되었고, 간혹 이러한 결절들은 서로 융합하여 더 큰 결절을 하며 정상 진피, 피하조직의 구조를 완전히 대체하고 있었습니다. 결절의 중심부에는 대체로 둥글거나, 타원형으로 다형태성을 보이는 다수의 hyphae 가 다발성으로 응집되어 있었으며, 그 주변을 소수에서 중정도의 호중구가 둘러싸고 있었고 가장 바깥쪽으로는 풍부한 호산성 세포질을 갖는 다수의 epithelioid macrophage 가 solid 한 양상으로 침윤해 있었습니다. 일부 소수의 macrophage 세포질 내에서는 위와 같은 hyphae 가 관찰되었습니다. 그 외 다르 특이적인 소견은 관찰되지 않았습니다.

Summary

- Inflammation is a fundamental, complex, and vital protective response to injury.
- The process involves a highly coordinated series of vascular changes, cellular migrations, and chemical signaling.
- While essential for survival, if inflammation is uncontrolled or persistent, it can become a major cause of tissue damage and disease.
- The ultimate goal of the inflammatory process is the removal of the injurious agent, followed by healing and repair, which can range from perfect resolution to permanent scarring.

Neoplasia and Tumor Biology-1

Veterinary Pathology-1
Su-Hyung Lee, DVM, PhD

Introduction and Nomenclature

Introduction and Nomenclature

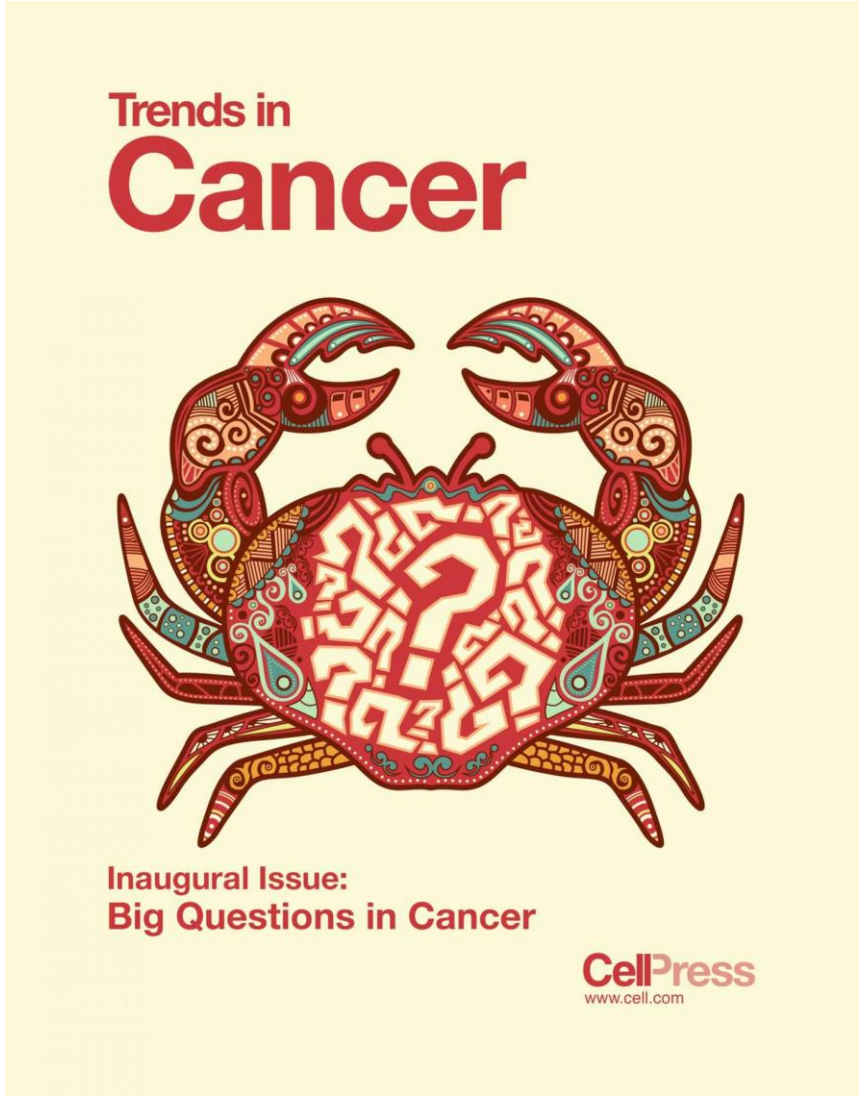
Basic Definitions

- **Neoplasia**: A process of "new growth" where normal cells undergo irreversible genetic changes, making them unresponsive to normal growth controls. The resulting mass is called a neoplasm.

- **Tumor**: A common term for a neoplasm, derived from the word for "swelling". It can refer to both benign and malignant growths.

- **Cancer**: This term is always used to denote a malignant growth.

- **Oncology**: The study of neoplasia, from the Greek word oncos ("tumor").



Introduction and Nomenclature

Benign vs. Malignant Tumors

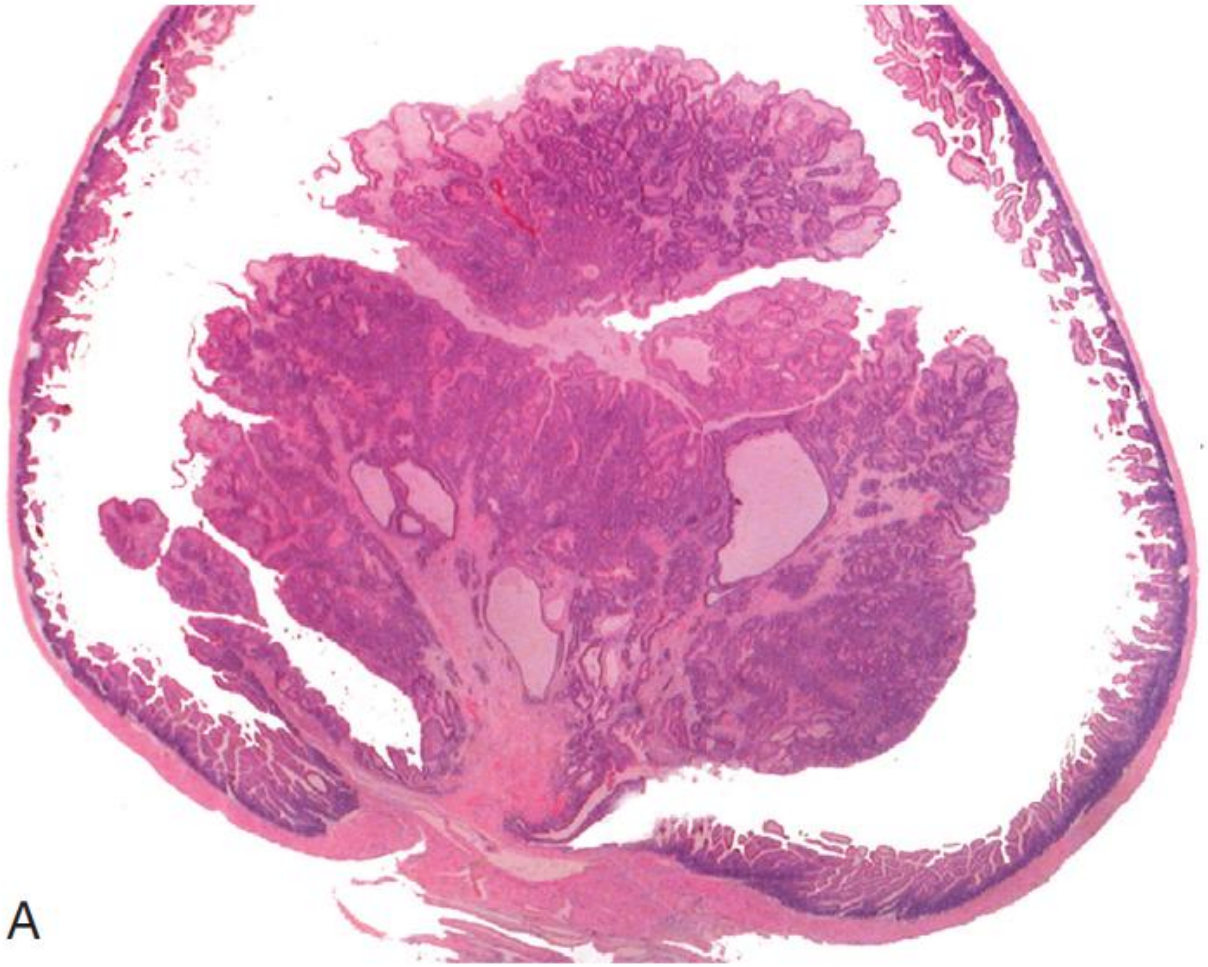
❖ Benign ("Harmless") Tumors:
- Do not invade surrounding tissue.
- Do not spread to new locations (metastasize).
- They are usually curable and rarely cause death.
- Often grow in an expansile way, compressing adjacent tissue, and are frequently encapsulated.

❖ Malignant ("Harmful") Tumors:
- Invade local tissues.
- Can spread to distant sites via metastasis.
- Can ultimately kill the animal by interfering with critical body functions.
- Often unencapsulated and grow by infiltrating surrounding tissues.

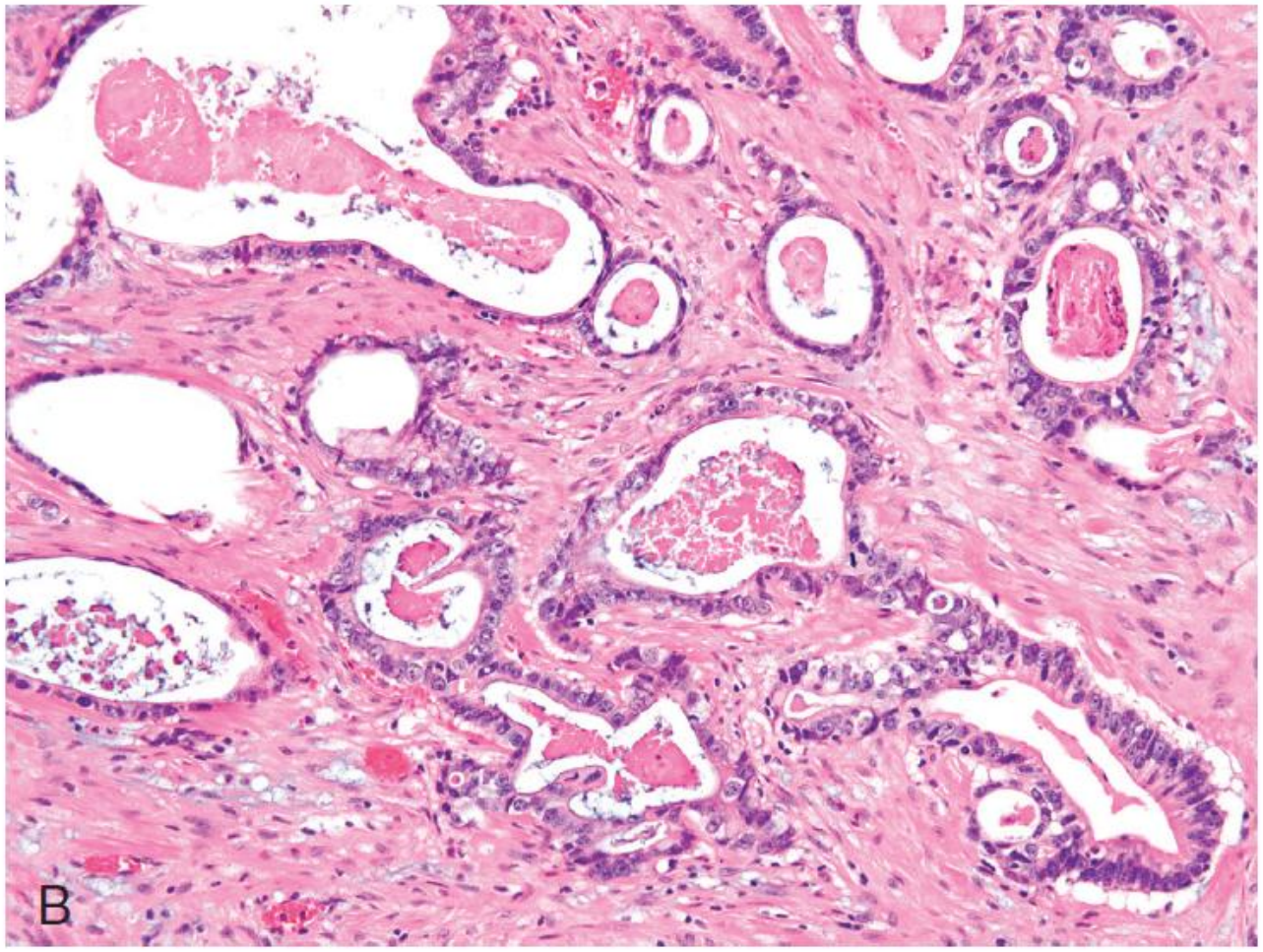
Introduction and Nomenclature

Characteristic	Benign	Malignant
Differentiation	Well-differentiated morphologic features and function	Poorly differentiated morphologic features and function
	Structure similar to tissue of origin	Tissue of origin sometimes unclear
	Little or no anaplasia	Variable degrees of anaplasia
Growth rate	Slow, progressive expansion	Rapid growth
	Rare mitotic figures	Frequent mitotic figures
	Normal mitotic figures	Abnormal mitotic figures
	Little necrosis	Necrosis if poor blood supply
Local invasion	No invasion	Local invasion
	Cohesive and expansile growth	Infiltrative growth
	Capsule often present	Capsule often absent or incomplete
Metastasis	No metastasis	Metastasis sometimes present

Introduction and Nomenclature

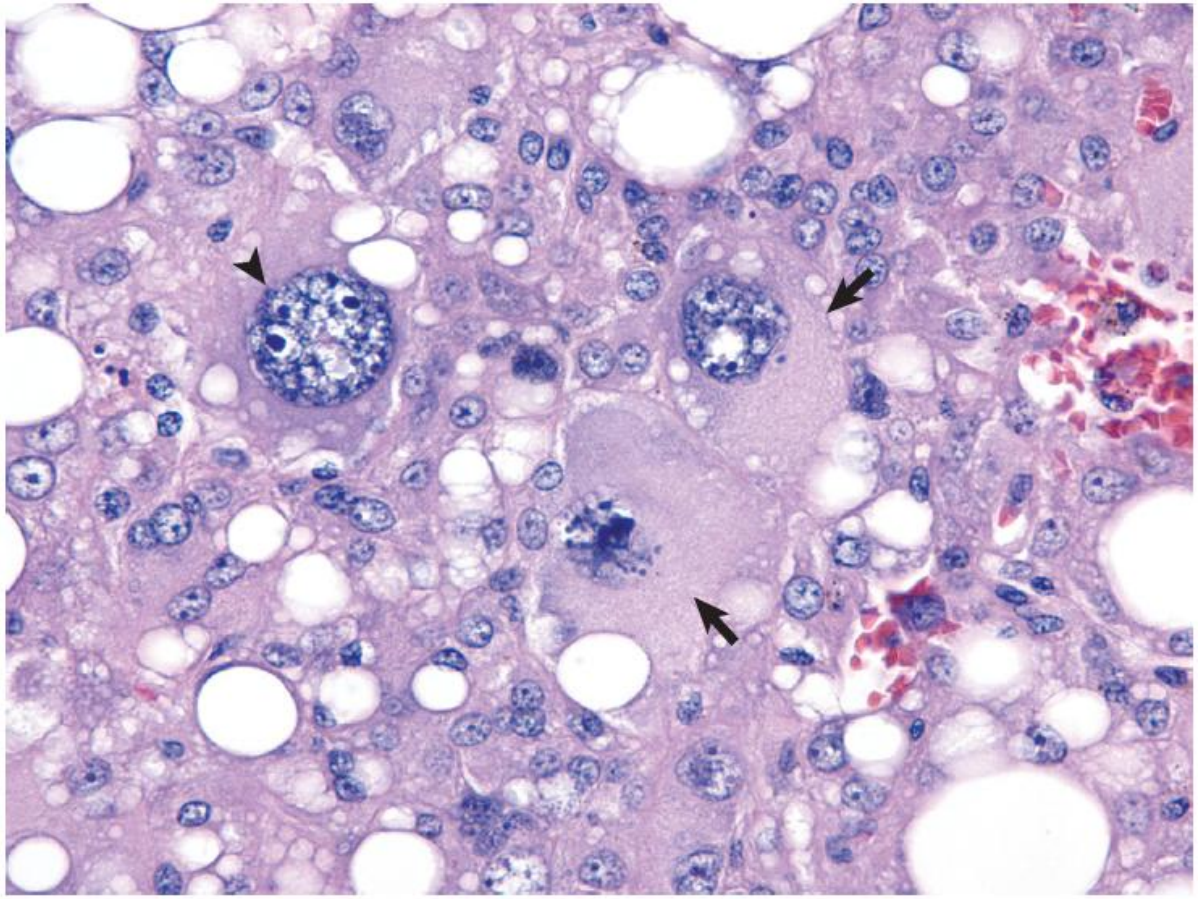


Intestinal polyp (adenoma)

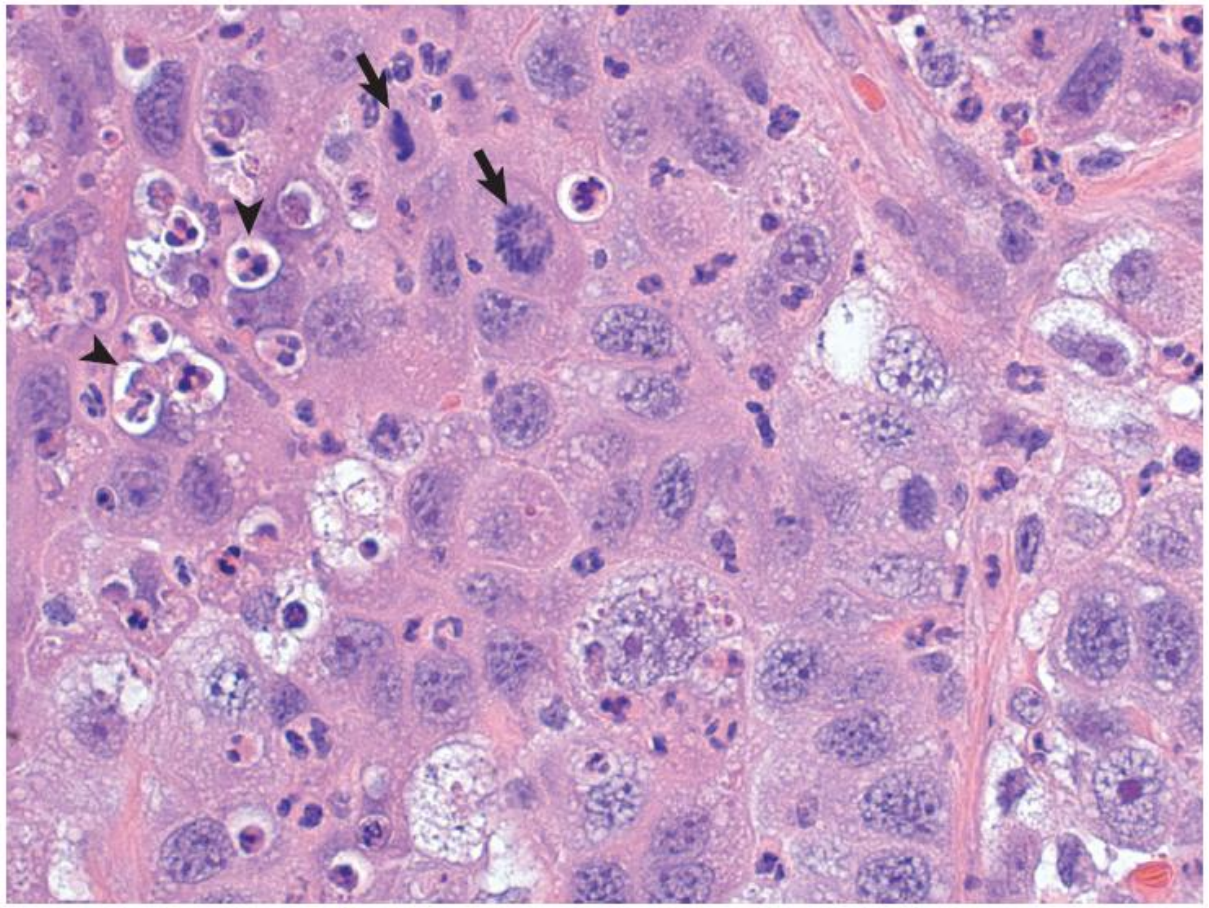


Intestinal adenocarcinoma

Introduction and Nomenclature

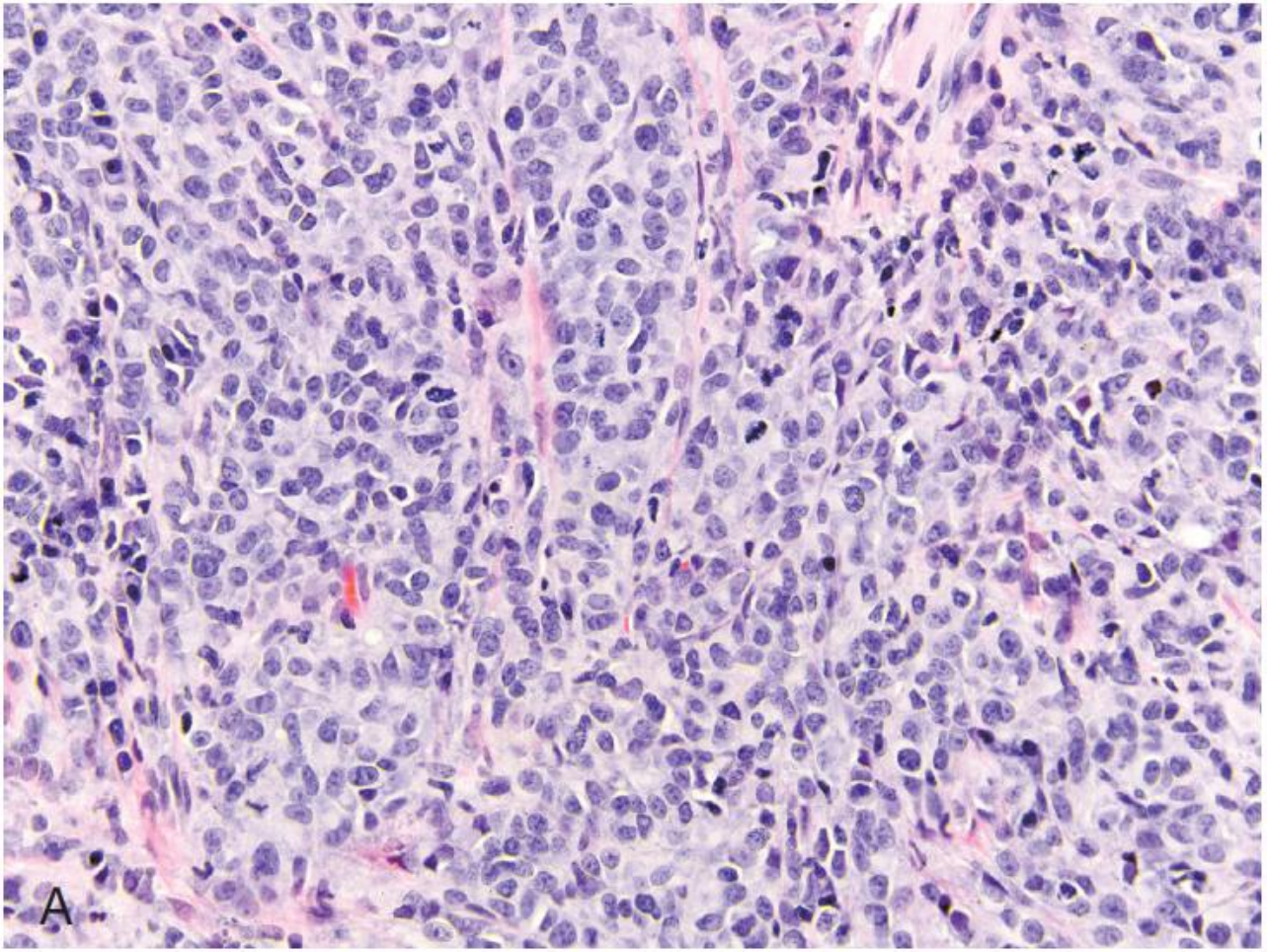


Anaplastic liposarcoma

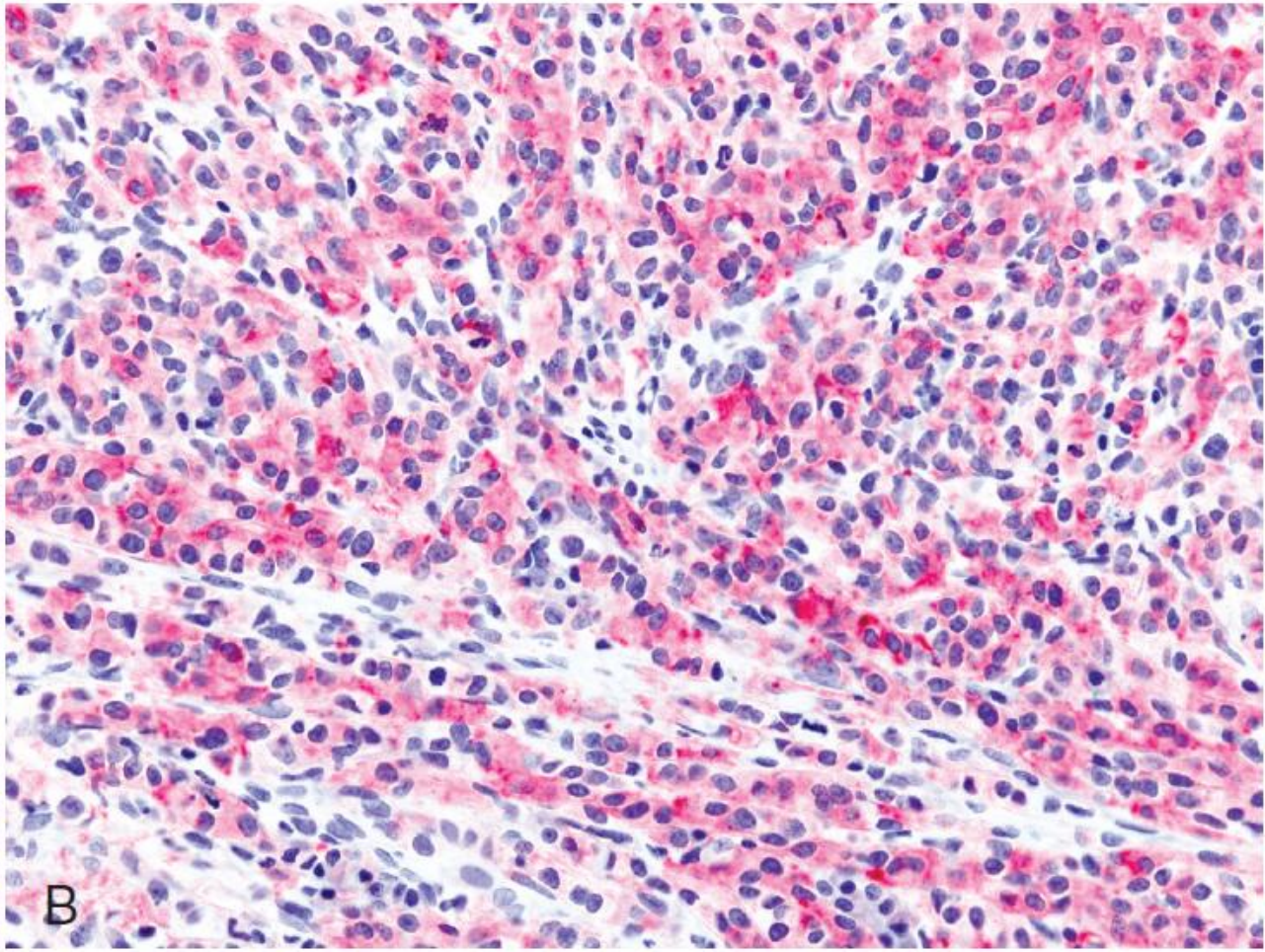


Anaplastic bronchoalveolar carcinoma

Introduction and Nomenclature



H&E

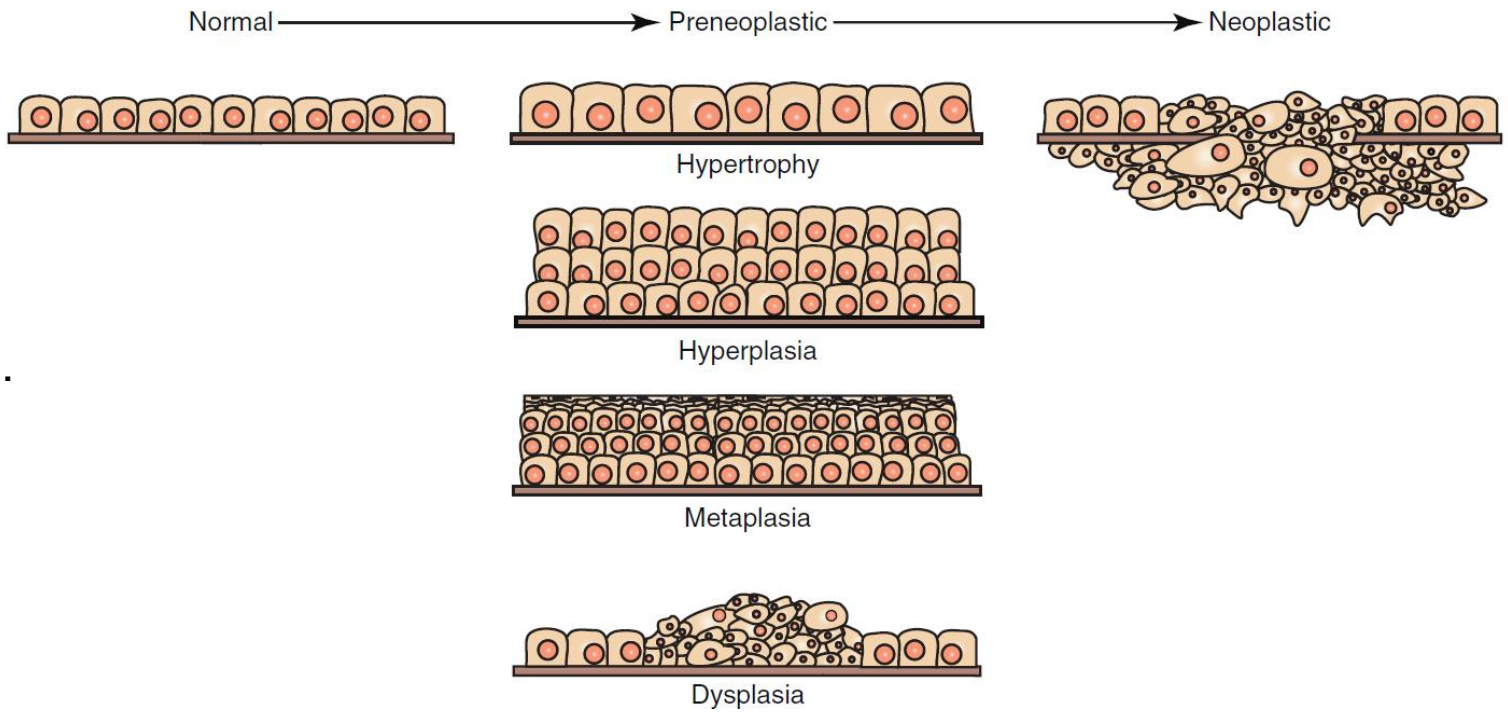


Melan A

Introduction and Nomenclature

Preneoplastic Changes

- Tumor development is a stepwise process, often preceded by reversible, non-neoplastic changes. These signal an increased risk for progression to neoplasia.
- **Hypertrophy**: An increase in the size of individual cells.
- **Hyperplasia**: An increase in the number of cells in a tissue through mitotic division.
- **Metaplasia**: The transformation of one differentiated cell type into another (e.g., columnar epithelium changing to squamous epithelium).
- **Dysplasia**: An abnormal pattern of tissue growth with a disorderly arrangement of cells.
- **Anaplasia**: The loss of cellular differentiation; this often indicates an irreversible progression to neoplasia.



Introduction and Nomenclature

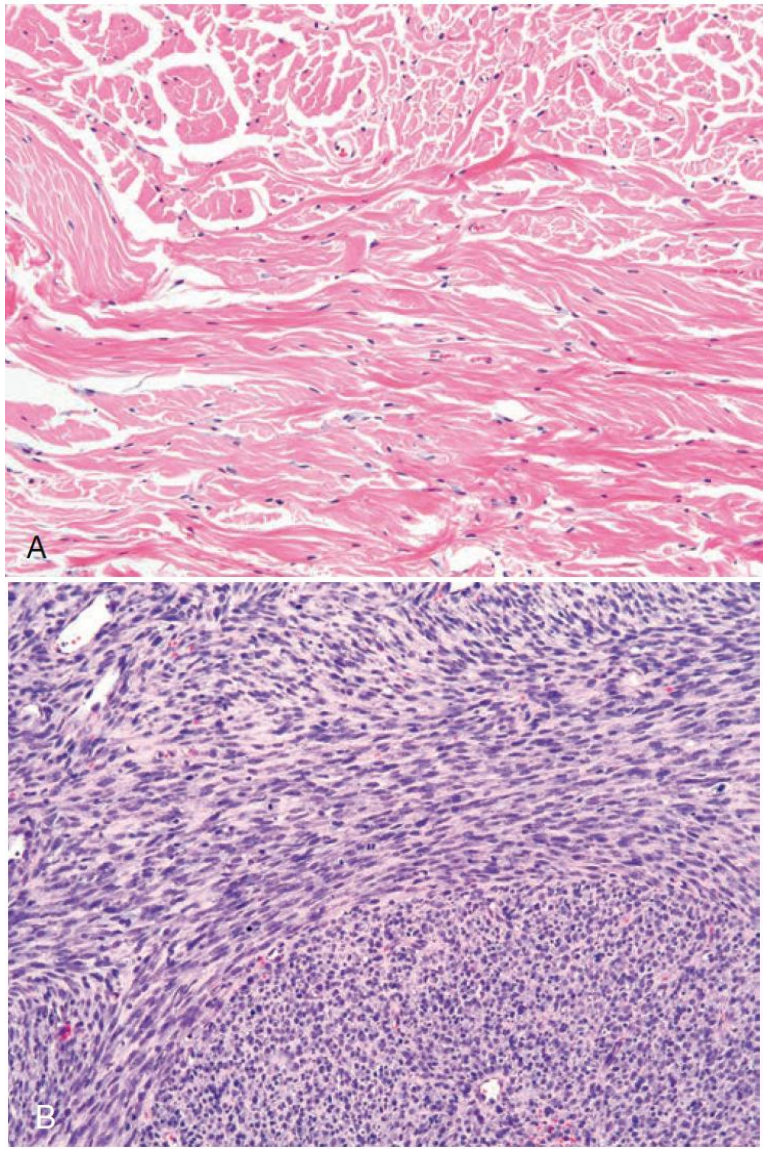
Naming Tumors: Mesenchymal Origin

- Mesenchymal tumors arise from cells of embryonic mesodermal origin, such as fibroblasts, bone, and cartilage. They are generally composed of spindle cells in bundles or round cells in sheets.

- Benign Mesenchymal Tumors: Named by adding the suffix -oma to the cell of origin.
  - Example: Fibroma = a benign tumor of fibroblasts.

- Malignant Mesenchymal Tumors: Called a sarcoma. A prefix indicates the tissue of origin.
  - Example: Fibrosarcoma = a malignant tumor of fibroblasts.

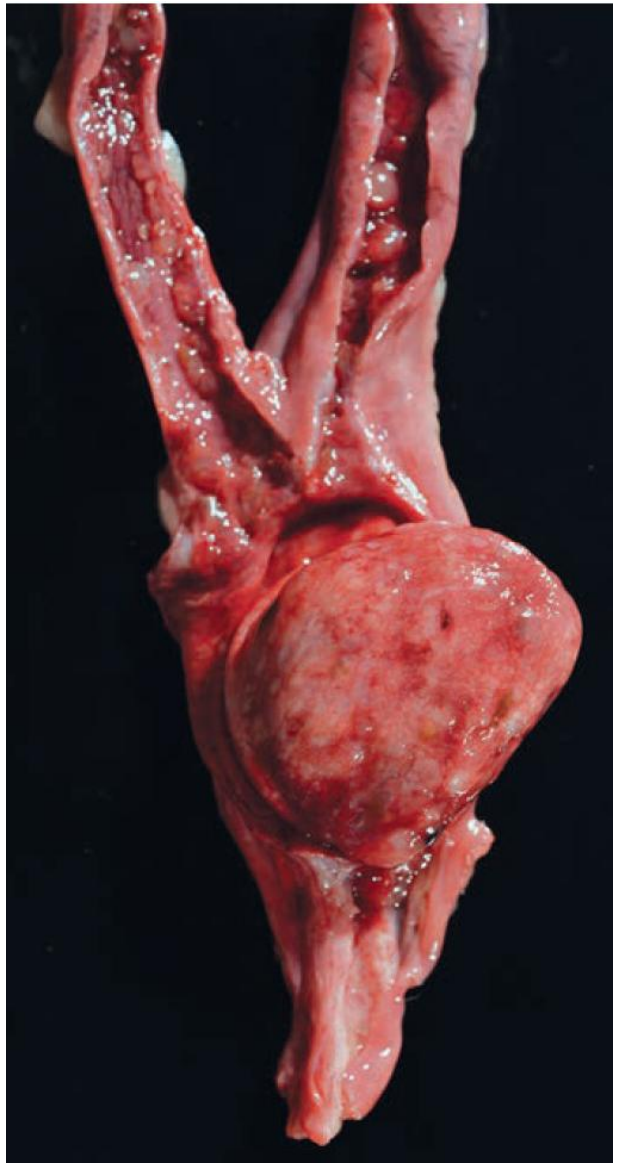
- Hematopoietic Tumors: Tumors of hematopoietic cells (e.g., lymphocytes) are also mesenchymal and thus are sarcomas.
  - **Lymphoma** (also called lymphosarcoma) is a malignant tumor of lymphocytes.
  - **Leukemia** refers to malignancies of circulating blood cells or their precursors in the bone marrow.

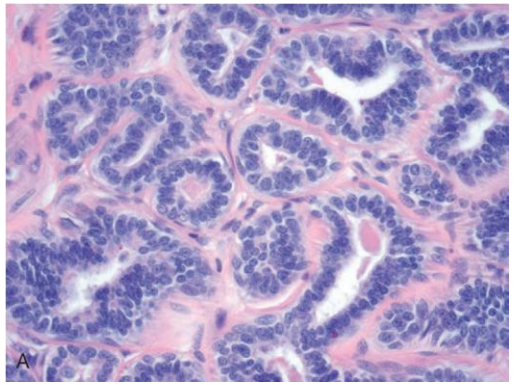


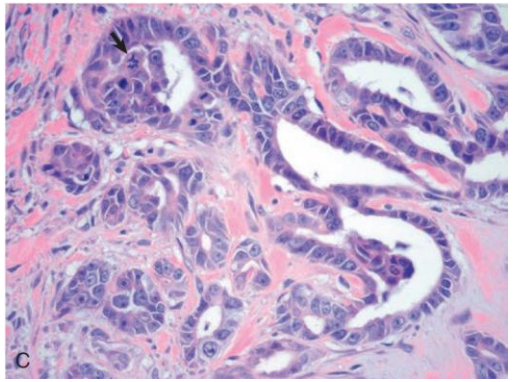
Introduction and Nomenclature

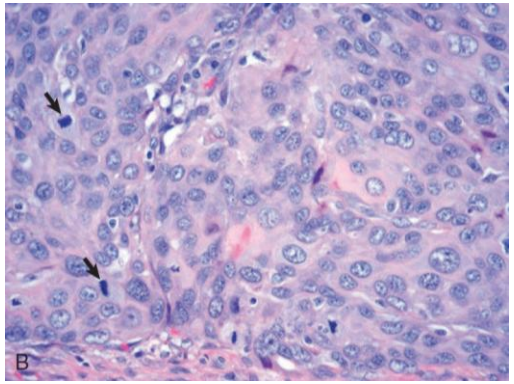
Naming Tumors: Epithelial Origin

- Epithelial tumors can arise from all three embryonic cell layers (ectoderm, mesoderm, endoderm).
- Benign Epithelial Tumors:
  - **Adenoma**: A benign tumor arising from glandular epithelium or one that forms a tubular pattern.
  - **Papilloma**: A benign, exophytic growth from a cutaneous or mucocutaneous surface.
  - **Polyp**: A benign epithelial tumor projecting from a mucosal surface.
- Malignant Epithelial Tumors: Called a carcinoma.
  - **Adenocarcinoma**: A carcinoma with a distinct glandular or acinar growth pattern.
  - **Carcinoma in situ**: A pre-invasive carcinoma that has not penetrated the basement membrane.









Introduction and Nomenclature

Naming Other Tumors

- ❖ Mixed Tumors: Contain multiple cell types, believed to arise from a single pluripotent stem cell.
  - • Example: Benign mixed mammary tumor in dogs can contain epithelial, fibrous, cartilage, and bone elements.
- ❖ Teratomas / Teratocarcinomas: Arise from totipotential germ cells and can contain tissues from all three embryonic layers.
- ❖ Tumors of Uncertain Origin: Highly malignant tumors that have lost all features of differentiation are termed undifferentiated or anaplastic neoplasms.
- ❖ Tumor-Like Lesions: Non-neoplastic growths that can mimic tumors.
  - • Hamartoma: A disorganized but mature tissue found in its normal location.
  - • Choristoma: Normal, mature tissue located at an ectopic (abnormal) site (e.g., a dermoid on the cornea).

Introduction and Nomenclature

Origin	Tissue of Origin	Cell of Origin	Benign	Malignant
MESENCHYMAL				
Connective tissue and related tissue	Fibrous connective tissue	Fibroblast	Fibroma	Fibrosarcoma
	Fat	Adipocyte	Lipoma	Liposarcoma
	Cartilage	Chondrocyte	Chondroma	Chondrosarcoma
	Bone	Osteoblast	Osteoma	Osteosarcoma
Endothelium and related tissue	Blood vessel	Vascular endothelium	Hemangioma	Hemangiosarcoma
	Lymphatic vessel	Lymphatic endothelium	Lymphangioma	Lymphangiosarcoma
	Synovium	Synovial lining cell	Synovioma	Synovial sarcoma
	Mesothelium	Mesothelial cell	*	Mesothelioma
	Meninges	Meningeal connective tissue cell	Meningioma	Malignant meningioma
	Ovary	Modified mesothelium†	Adenoma	Adenocarcinoma
Hematopoietic and lymphoid tissue	Lymphoid tissue	Lymphocytes	*	Lymphoma
	Bone marrow	Leukocytes and erythrocytes	*	Leukemia
	Connective tissue	Mast cell	Mast cell tumor	Mast cell tumor
		Histiocytes	Histiocytoma	Histiocytic sarcoma (malignant histiocytosis)
Muscle	Smooth muscle	Smooth muscle cell	Leiomyoma	Leiomyosarcoma
	Skeletal muscle	Skeletal muscle cell	Rhabdomyoma	Rhabdomyosarcoma

Introduction and Nomenclature

Origin	Tissue of Origin	Cell of Origin	Benign	Malignant
EPITHELIAL				
Lining or covering epithelia	Skin	Squamous epithelial cell	Papilloma	Squamous cell carcinoma
		Adnexal cells	Adenoma	Adenocarcinoma Carcinoma
		Melanocyte	Benign melanoma (melanocytoma)	Malignant melanoma
	Upper alimentary tract (oral cavity, esophagus)	Squamous epithelial cell	Papilloma	Carcinoma
	Lower alimentary tract (intestine)	Columnar epithelium	Adenoma	Adenocarcinoma Carcinoma
	Upper respiratory tract (nasal cavity, trachea)	Columnar respiratory epithelium	Adenoma	Adenocarcinoma Carcinoma
	Lower respiratory tract (lung)	Columnar epithelium of bronchi and bronchioles Alveolar lining epithelium	Adenoma	Adenocarcinoma Carcinoma
	Urinary tract	Transitional epithelium	Papilloma	Transitional cell carcinoma
	Uterus	Columnar epithelium	Uterine polyp	Endometrial carcinoma Endometrial adenocarcinoma
	Lining of glands or ducts	E.g., prostate, thyroid, bile ducts of liver	Adenoma	Adenocarcinoma Carcinoma

Introduction and Nomenclature

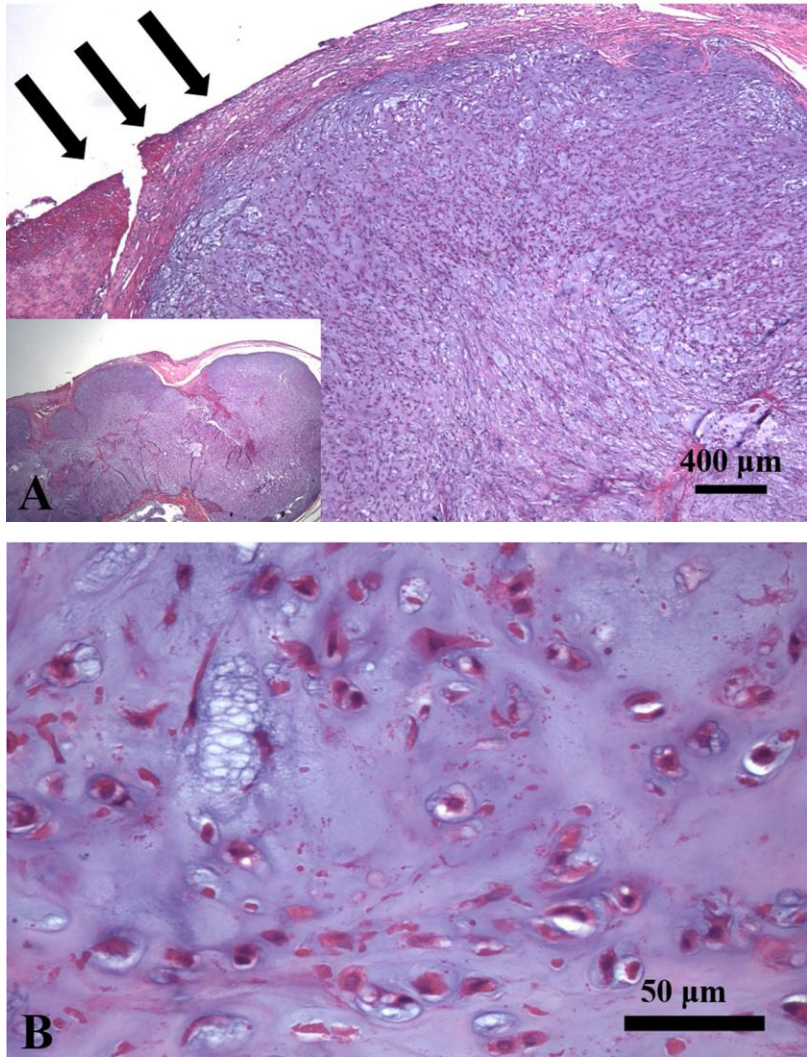
Origin	Tissue of Origin	Cell of Origin	Benign	Malignant
Solid epithelial organs	Glands	Pancreas, salivary gland, and others	Adenoma	Adenocarcinoma
	Liver	Hepatocyte	Hepatoma	Hepatocellular carcinoma
	Kidney	Renal tubular cell	Renal tubular adenoma	Renal cell carcinoma
	Testicle	Sertoli cell	Sertoli cell tumor	Malignant Sertoli cell tumor
		Interstitial cell	Interstitial/Leydig cell tumor	*
		Germ cell	Seminoma	Malignant Seminoma
			Teratoma	Teratocarcinoma
	Ovary	Stromal cell	Granulosa cell tumor	*
			Luteoma	*
			Thecoma	*
		Germ cell	Dysgerminoma	Dysgerminoma
			Teratoma	Teratocarcinoma

Introduction and Nomenclature

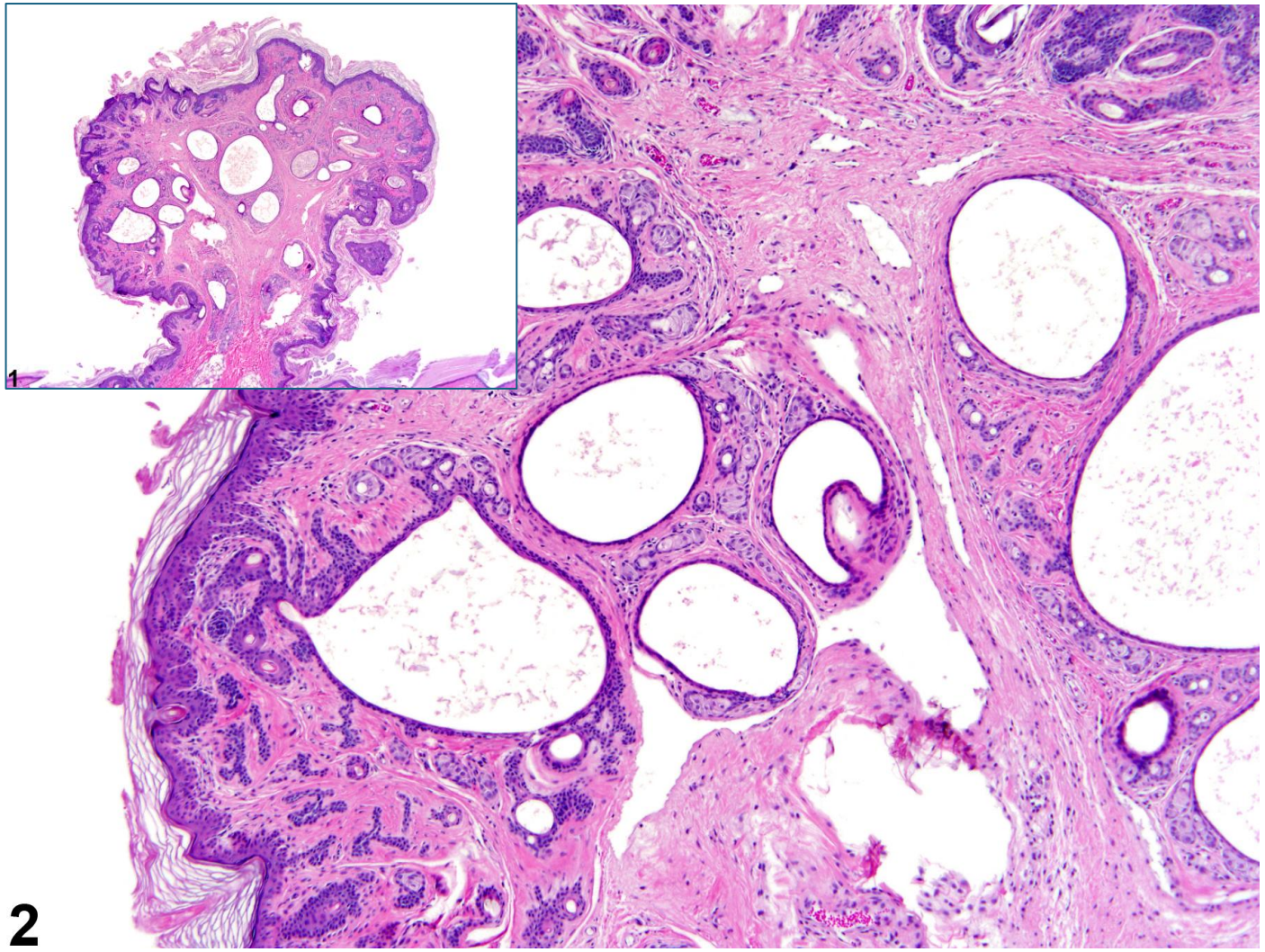
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			Teratoma	Teratocarcinoma
	Ovary	Stromal cell	Granulosa cell tumor	*
			Luteoma	*
			Thecoma	*
		Germ cell	Dysgerminoma	Dysgerminoma
			Teratoma	Teratocarcinoma
NERVOUS TISSUE				
Glial cells	Central nervous system	Astrocyte	*	Astrocytoma
				Glioblastoma
		Oligodendrocyte	*	Oligodendroglioma
		Microglial cell	*	Microgliomatosis
	Peripheral nervous system	Schwann cell	Benign peripheral nerve sheath tumor (schwannoma)	Malignant peripheral nerve sheath tumor (malignant schwannoma)

Introduction and Nomenclature

Cartilaginous choristoma on the lip of a dog



Fibroadnexal hamartoma



The Hallmarks of Neoplasia

The Hallmarks of Neoplasia

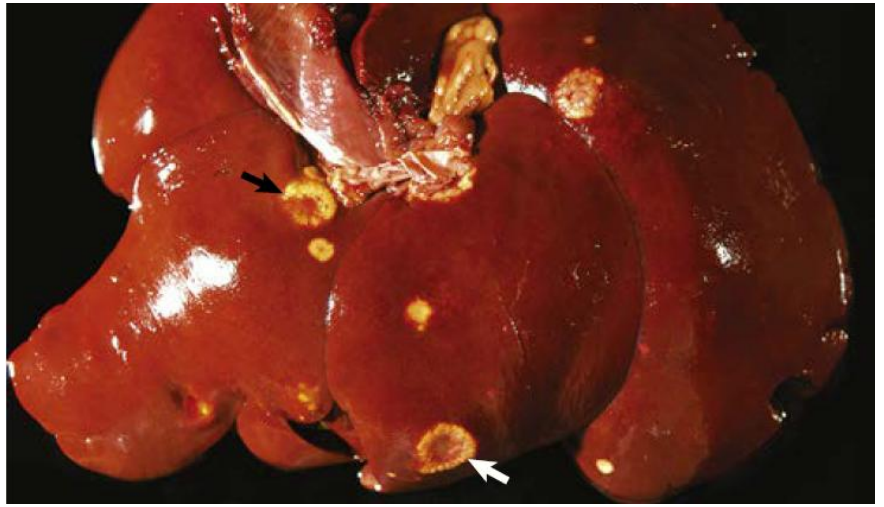
Tumor Characteristics: An Overview

- ❖ Malignant tumors are distinguished from benign tumors by a collection of morphologic and behavioral features.
- ❖ Key Characteristics of Malignant Tumors:
  - Loss of differentiation (anaplasia) and architectural organization.
  - Unlimited proliferative potential, resulting from continuous cell division and resistance to cell death.
  - Local invasion of surrounding tissues.
  - The potential to metastasize (spread) to distant sites.



Metastatic hemangiosarcoma

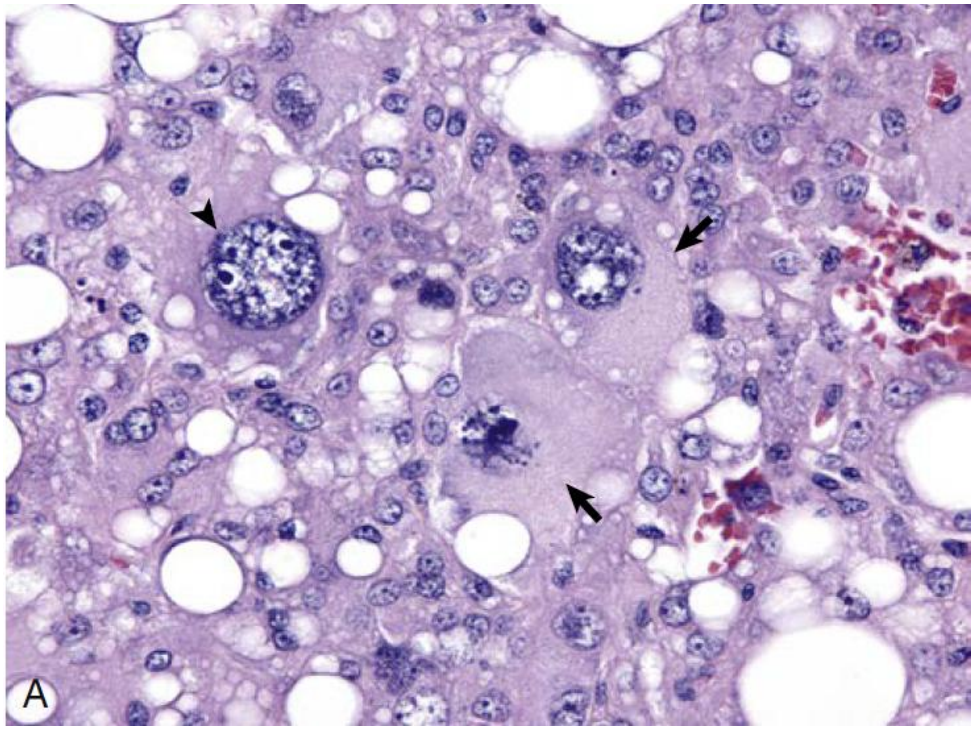
Metastatic carcinoma

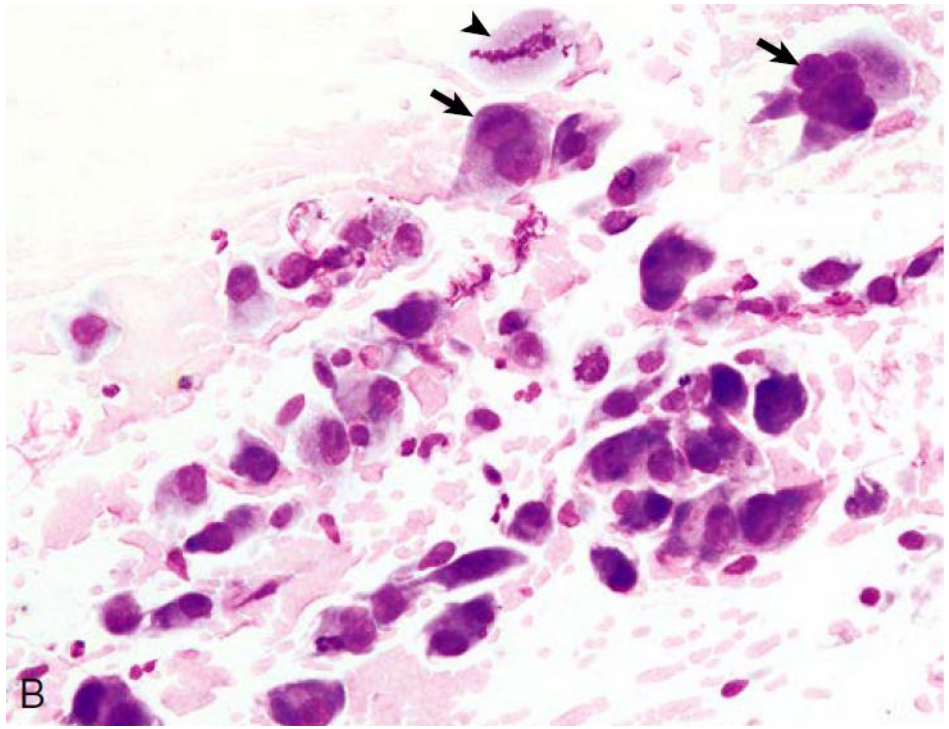


The Hallmarks of Neoplasia

Differentiation and Anaplasia

- Differentiation refers to the extent to which neoplastic cells resemble their normal, mature counterparts, both morphologically and functionally.
- Benign tumors are typically well-differentiated, with a structure similar to the tissue of origin.
- Malignant tumors range from well-differentiated to poorly differentiated.
- Anaplasia is the term for a lack of differentiation and is a hallmark of malignancy. Anaplastic cells show marked variation in cell size and shape (pleomorphism) and nuclear features.

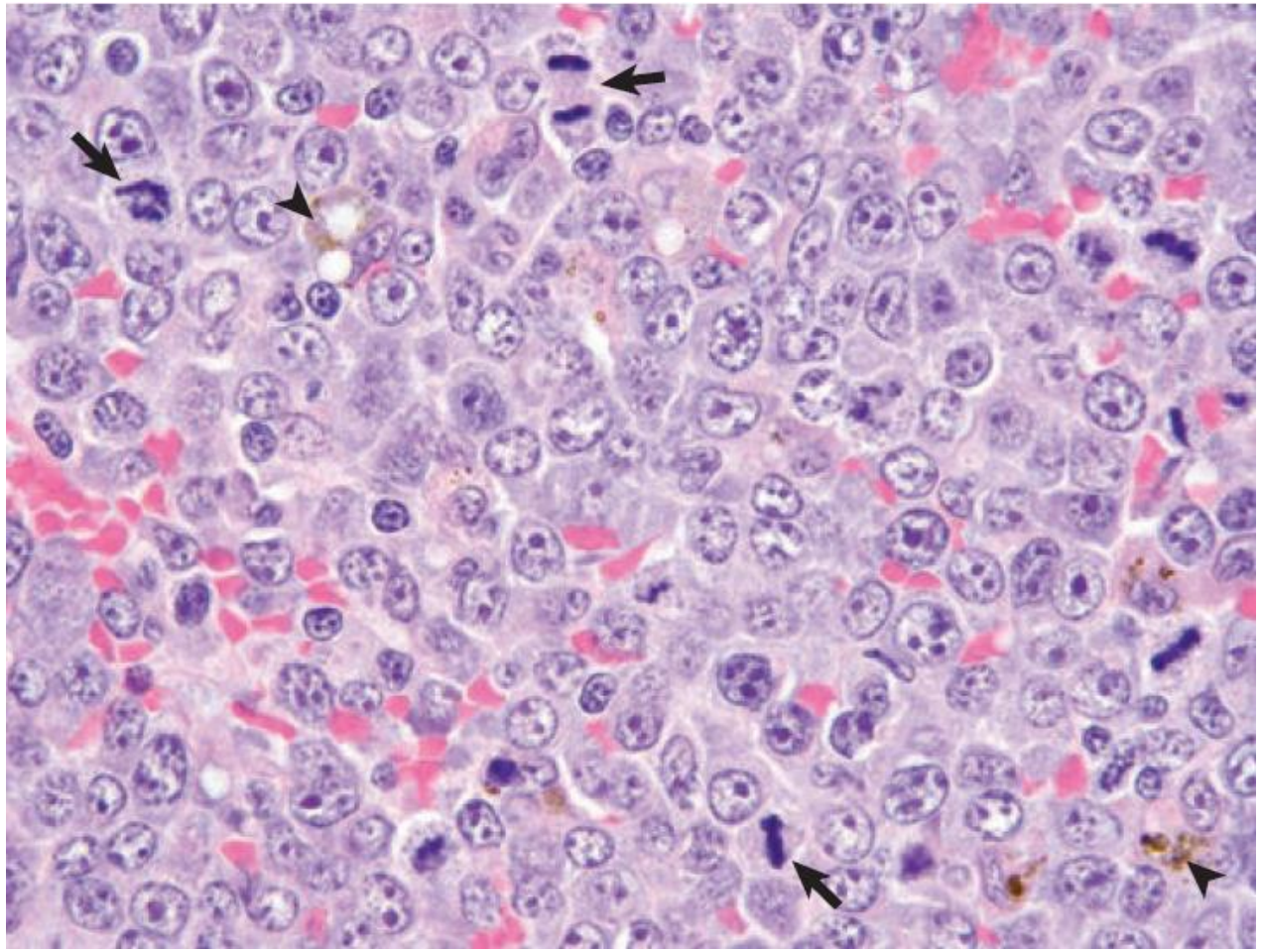




The Hallmarks of Neoplasia

Rate of Growth & Mitotic Activity

- Growth Rate: Benign tumors generally grow slowly, while malignant tumors tend to grow rapidly. Rapid growth in malignant tumors can outstrip the blood supply, leading to areas of necrosis.
- Mitotic Figures: These are visible signs of cell division (condensed chromosomes) seen microscopically.
  - Benign tumors have rare mitotic figures, and they appear normal.
  - Malignant tumors often have numerous mitotic figures, and they may be abnormal or bizarre in shape.
- Mitotic Count: The number of mitotic figures per ten 400x microscopic fields is a key criterion used in tumor grading to predict malignant potential.



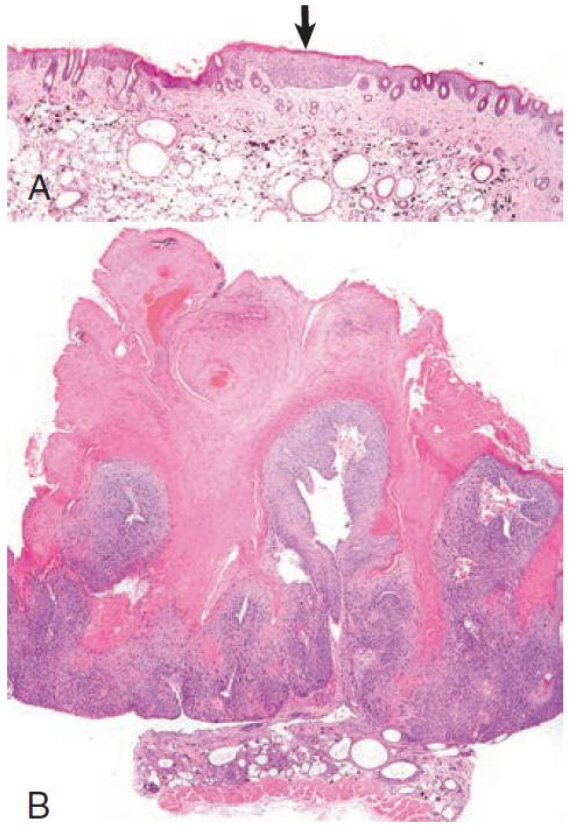
Lymphoma

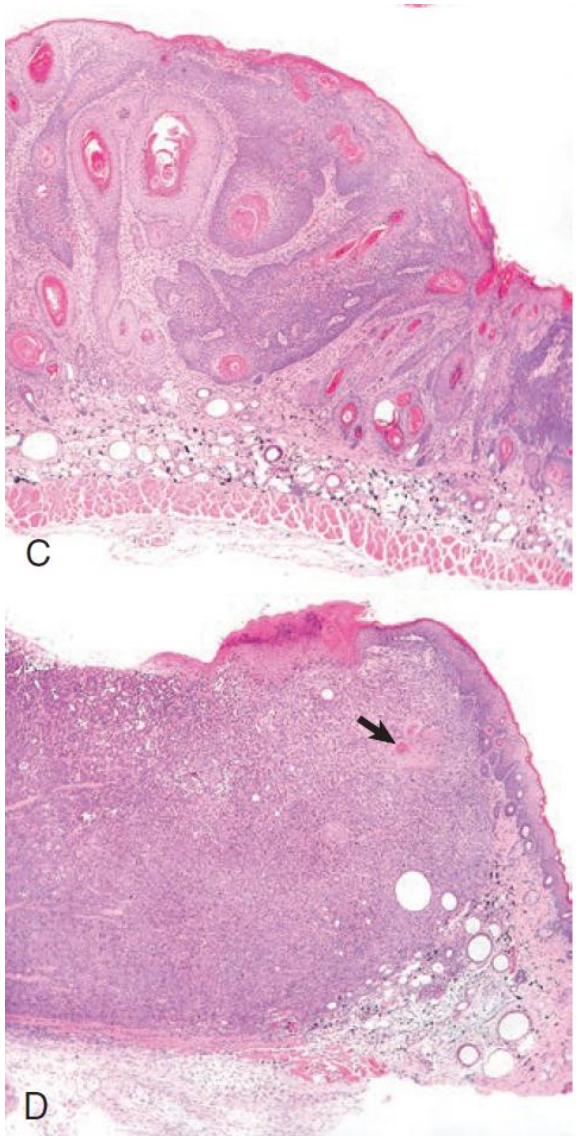
The Hallmarks of Neoplasia

Local Invasion and Encapsulation

❖ Benign Tumors:
- Grow as cohesive, expansile masses that compress surrounding tissue.
- They do not invade.
- They are often surrounded by a fibrous capsule.

❖ Malignant Tumors:
- Grow by infiltration and invasion of surrounding tissues.
- They are often unencapsulated or grow through their capsule.
- Invasion is enabled by alterations in cell adhesion, motility, and the production of proteases that degrade surrounding tissue.





The Hallmarks of Neoplasia

Tumor Cell Proliferation & The Cell Cycle

- Unlimited proliferative potential is a hallmark of neoplasia.
- Normal cells are controlled by signals that stimulate or inhibit division, and many reside in a quiescent G_0 state.
- In response to DNA damage, normal cells undergo cell cycle arrest at checkpoints, a process initiated by the tumor suppressor p53.
- Many neoplastic cells no longer respond to signals to enter G_0 and lack functional p53.
- Because they do not arrest to repair DNA damage, tumor cells progressively accumulate potentially mutagenic DNA damage as they move continuously through the cell cycle.

The Hallmarks of Neoplasia

Evasion of Cell Death

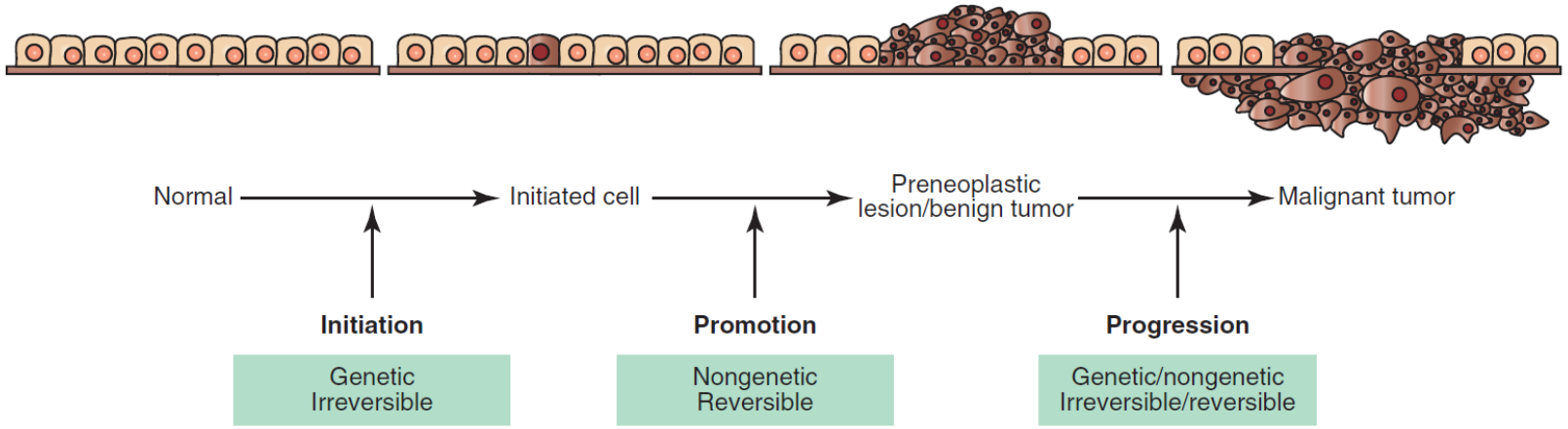
- ❖ Tumor growth results from an imbalance between cell production and cell loss. Malignant cells are adept at avoiding cell death.
- ❖ Evading Senescence:
  - • Normal somatic cells can only divide a limited number of times before they enter replicative senescence (permanent cell-cycle arrest), a process linked to the shortening of chromosomal ends called telomeres.
  - • Many neoplastic cells evade this by reactivating the enzyme telomerase, which maintains telomere length, allowing them to escape senescence and achieve "immortality".
- ❖ Evading Apoptosis:
  - • Apoptosis (programmed cell death) is a crucial mechanism for eliminating damaged or unwanted cells.
  - • Cancer cells become resistant to apoptotic triggers by inactivating key pro-apoptotic molecules (like p53) or activating survival signaling pathways.

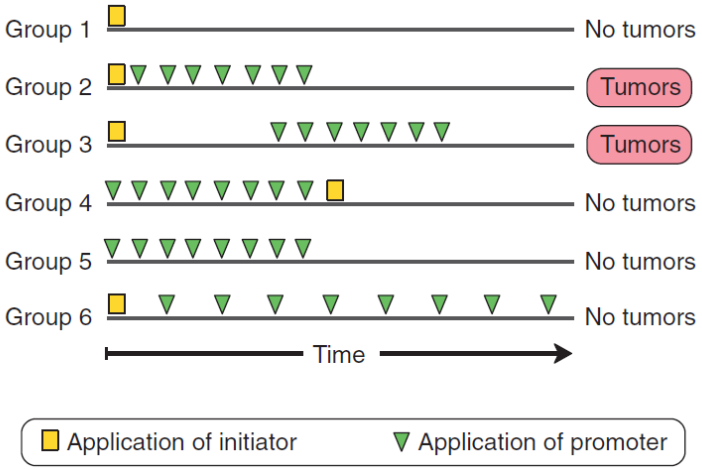
Carcinogenesis - The Stepwise Development of Cancer

Carcinogenesis - The Stepwise Development of Cancer

Neoplastic Transformation: An Overview

- Neoplasms develop through a gradual, multi-step process involving the accumulation of multiple genetic and epigenetic changes over a long period. This is called stepwise tumor development or multistage carcinogenesis.
- The three classic stages of this process are **Initiation**, **Promotion**, and **Progression**.





Carcinogenesis - The Stepwise Development of Cancer

The Latent Period

- The latent period is the time before a tumor becomes clinically detectable.
- The smallest clinically detectable mass is about 1 cm in diameter, containing roughly 1 billion (10^9) cells.
- To reach this size from a single transformed cell requires approximately 30 rounds of cell division.
- This means that by the time most tumors are discovered, they may have been developing in the host for many years.

Carcinogenesis - The Stepwise Development of Cancer

Stage 1: Initiation

- Definition: The introduction of an irreversible genetic change (a mutation) into a normal cell.
- Cause: Caused by the action of a mutagenic initiating agent or initiator (e.g., a chemical or physical carcinogen) that damages DNA.
- Mechanism: The genetic change becomes permanent ("fixed") only after at least one round of DNA replication occurs on the damaged template.
- Result: Initiated cells may appear morphologically normal and remain dormant for years, but they harbor a mutation that gives them a potential growth advantage.

Carcinogenesis - The Stepwise Development of Cancer

Stage 2: Promotion

- Definition: The outgrowth of initiated cells in response to selective stimuli.
- Cause: Driven by promoting agents or promoters, which are typically non-mutagenic but create a proliferative environment where initiated cells have a growth advantage.
- Mechanism: The effects of promoters are usually reversible. They drive cell division, creating a large population of initiated cells that are at risk for acquiring additional mutations.
- Result: The process of promotion leads to the formation of a benign tumor.

Carcinogenesis - The Stepwise Development of Cancer

Stage 3: Progression

- Definition: The final stage, where a benign tumor evolves into an increasingly malignant tumor, a process termed malignant transformation.
- Mechanism: Progression is a complex process involving the accumulation of additional genetic and epigenetic changes in the tumor cells.
- Hallmarks: Genetic instability and increasing tumor cell heterogeneity are hallmarks of progression.
- Result: The tumor becomes more aggressive, invasive, and ultimately acquires the ability to metastasize.

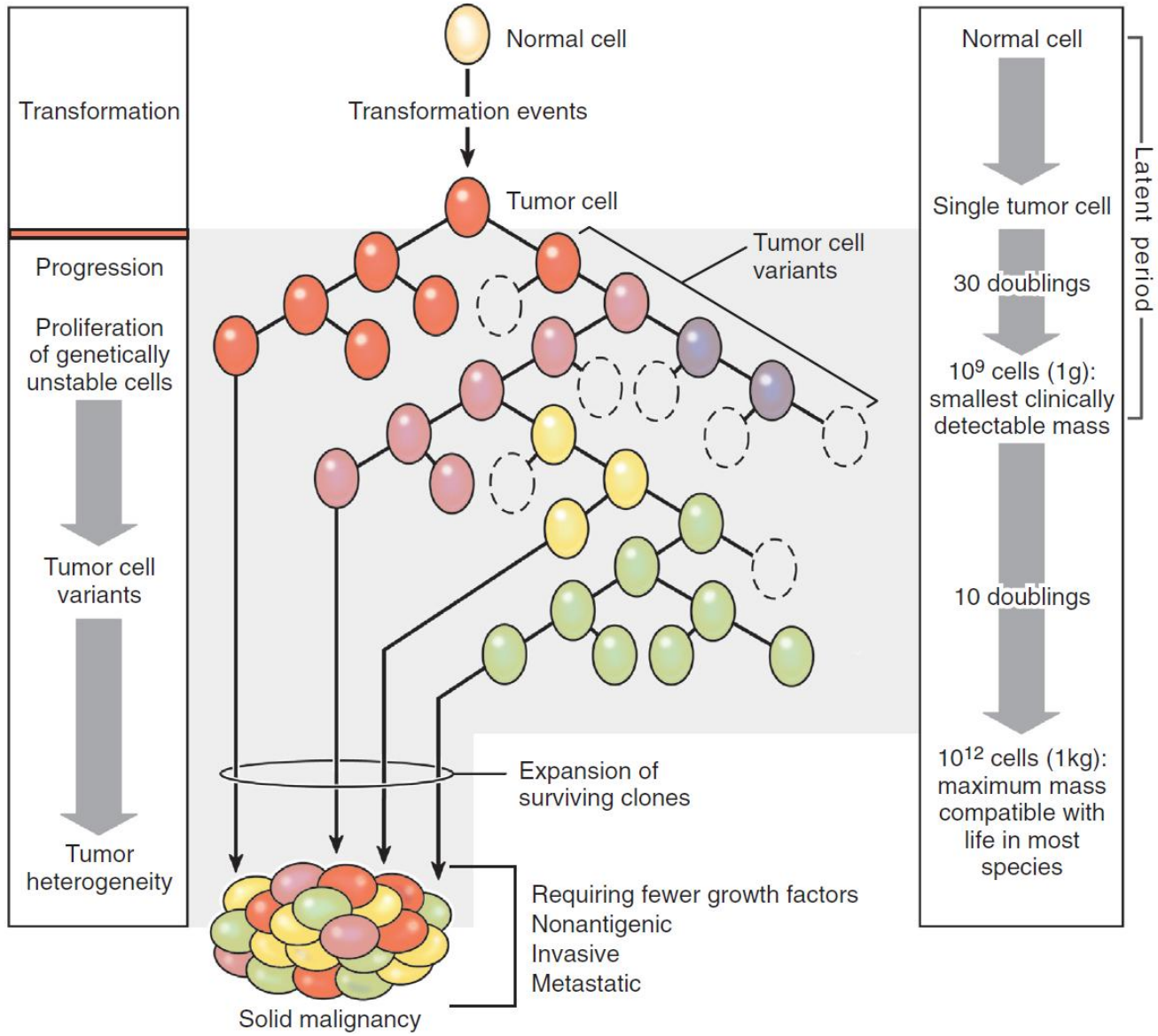
Carcinogenesis - The Stepwise Development of Cancer

Stage	Key Features	Molecular/Cellular Events	Reversibility
Initiation	First, irreversible step in carcinogenesis	- DNA damage (mutations, deletions, insertions) - Caused by carcinogens (chemical, physical, viral) - Mutations often affect oncogenes, tumor suppressor genes, or DNA repair genes	**Irreversible** (once mutation is fixed in DNA)
Promotion	Clonal expansion of initiated cells	- Non-mutagenic agents stimulate proliferation (e.g., hormones, growth factors, chronic inflammation) - Epigenetic changes (altered gene expression, not DNA sequence) - Multiple rounds of cell division increase risk of additional mutations	**Reversible** (depends on removal of promoting stimulus)
Progression	Final step: development of malignant phenotype	- Accumulation of further genetic and epigenetic alterations - Increased genetic instability - Acquisition of hallmarks of cancer (angiogenesis, invasion, metastasis, resistance to apoptosis)	**Irreversible** (malignant transformation established)

Carcinogenesis - The Stepwise Development of Cancer

Tumor Heterogeneity and Clonal Selection

- Most tumors are clonal, meaning they originate from a single transformed cell.
- However, as the tumor grows, its cells become genetically unstable and accumulate more mutations, leading to the formation of multiple subclones. This results in tumor cell heterogeneity.
- Subclones that have a selective advantage (e.g., faster growth, evasion of immunity, ability to metastasize) will eventually outcompete other cells and predominate in the tumor.
- This process is referred to as clonal selection or tumor evolution.



Carcinogenesis - The Stepwise Development of Cancer

The Role of Cancer Stem Cells

- The cancer stem cell hypothesis suggests that tumors may arise directly from the small population of stem cells found in all adult tissues.
- These stem cells are required for normal tissue renewal and often have unlimited replicative potential.
- A tumor arising from a stem cell may exhibit maturation arrest, where the neoplastic cells are "stuck" at a particular stage of differentiation.
- This model helps explain the embryonic characteristics of many tumors and the diversity of cell types seen in some neoplasms (e.g., mixed tumors).

Neoplasia and Tumor Biology-2

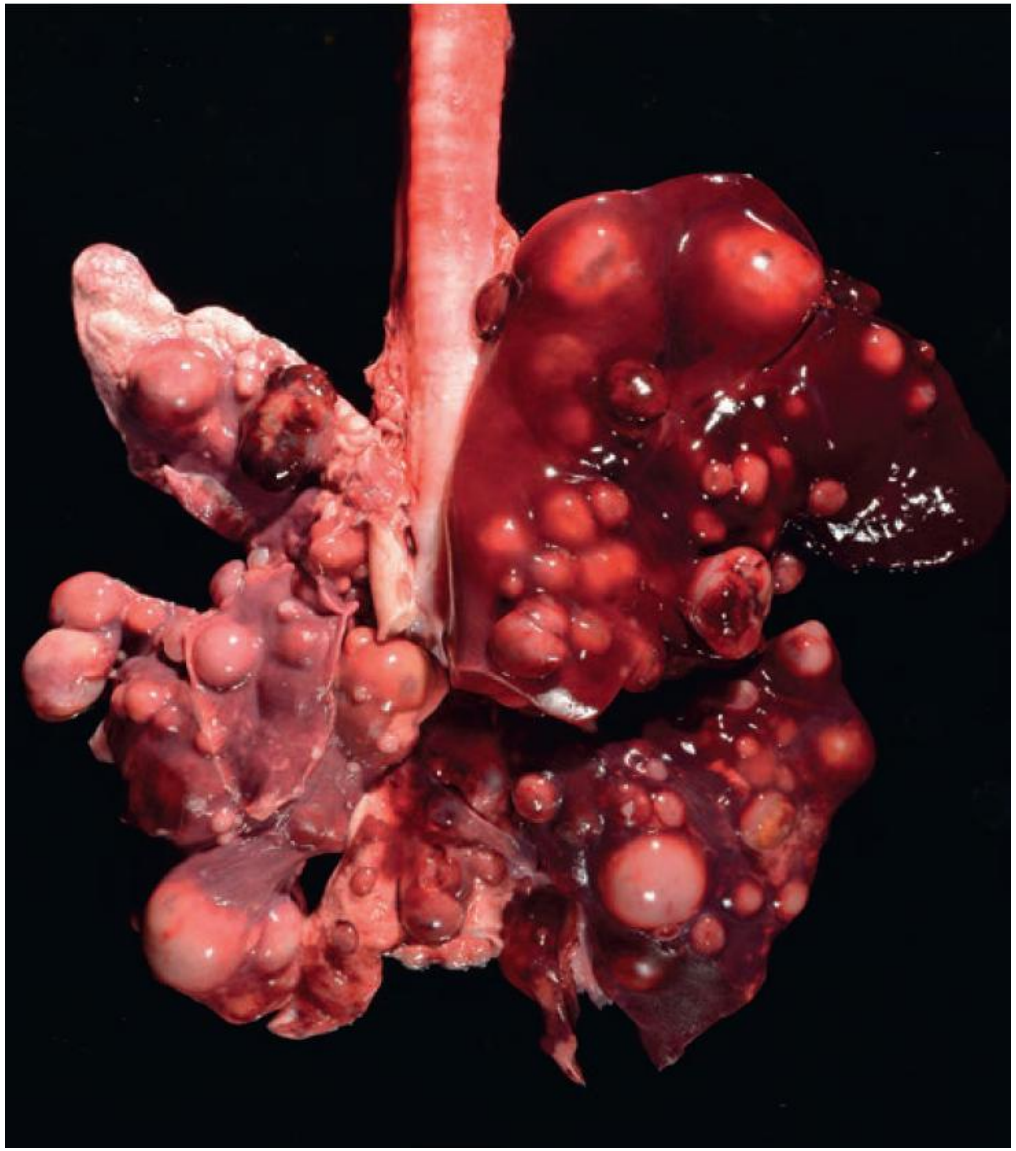
Veterinary Pathology-1
Su-Hyung Lee, DVM, PhD

Metastasis - The Spread of Cancer

Metastasis - The Spread of Cancer

The Significance of Metastasis

- Metastasis is the spread of a tumor to sites distant from the original tumor location.
- The primary tumor is not usually the cause of death for cancer patients.
- Death is usually due to metastases that interfere with critical bodily functions.
- In humans, tumor metastasis is responsible for approximately 90% of cancer mortality from solid tumors.
- Metastasis is a highly inefficient process; very few cells that leave the primary tumor successfully establish a metastatic colony.



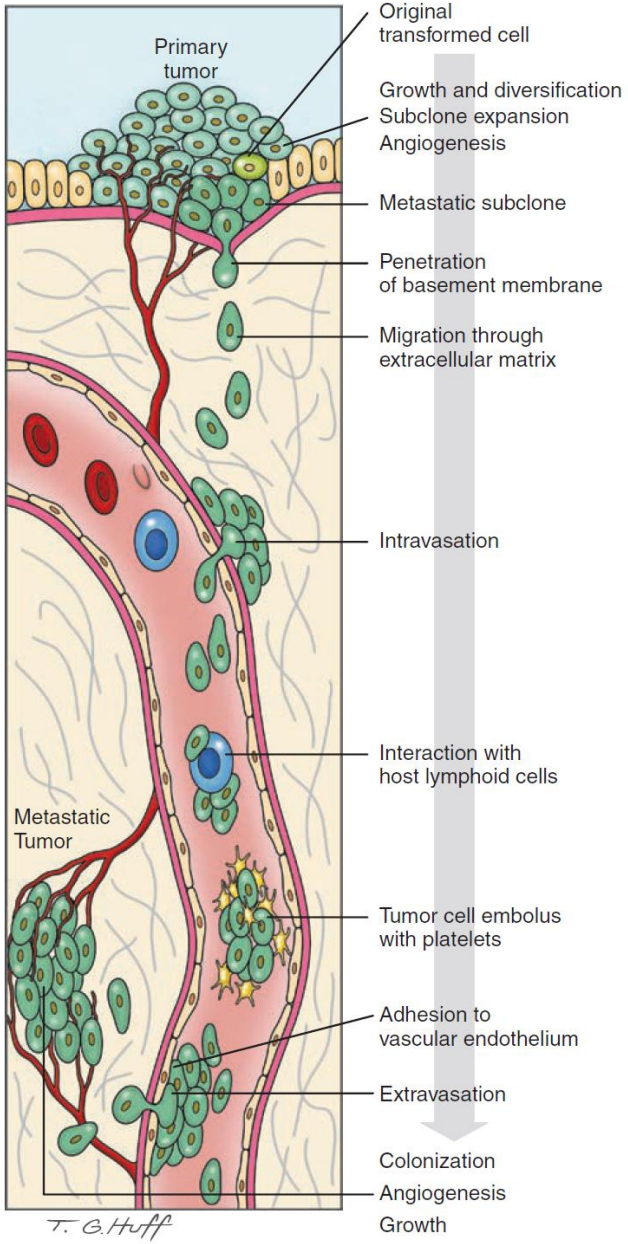
Metastatic Sarcoma, Lung, Dog.

Metastasis - The Spread of Cancer

The Metastatic Cascade: An Overview

❖ For a tumor cell to metastasize, it must complete a sequence of steps:

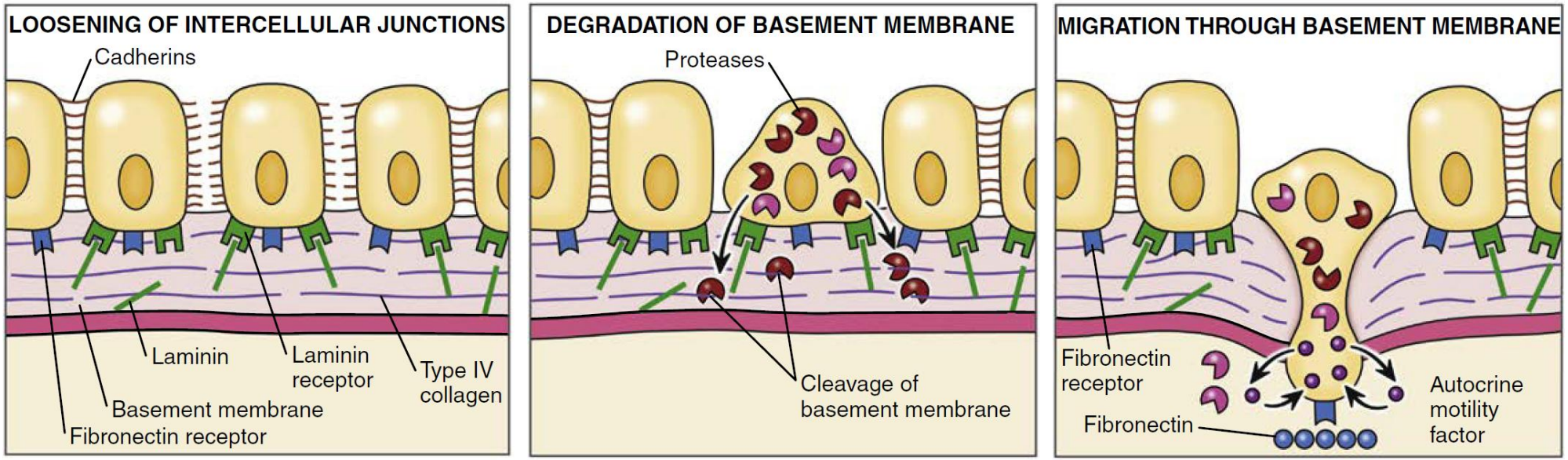
1. Local Invasion: Detach from the primary tumor and invade the surrounding stroma.
2. Intravasation: Enter a blood or lymphatic vessel.
3. Survival in Circulation: Evade host immune cells while traveling as a tumor embolus.
4. Arrest and Extravasation: Adhere to the endothelium at a distant site and exit the vessel.
5. Colonization: Survive and proliferate in the new microenvironment, forming a micrometastasis.
6. Angiogenesis: Induce new blood vessel formation to grow into a macroscopic tumor.



Metastasis - The Spread of Cancer

Local Invasion

- Loosening of Intercellular Junctions: Tumor cells must first detach from the main tumor mass. This often involves the downregulation of cell-to-cell adhesion molecules like E-cadherin.
- Degradation of Basement Membrane and ECM: To invade surrounding tissue, malignant epithelial cells actively degrade the basement membrane and ECM components.
- Protease Production: This degradation is accomplished by increasing net protease activity. Key enzymes include matrix metalloproteinases (MMPs), such as type IV collagenase, and urokinase.



Metastasis - The Spread of Cancer

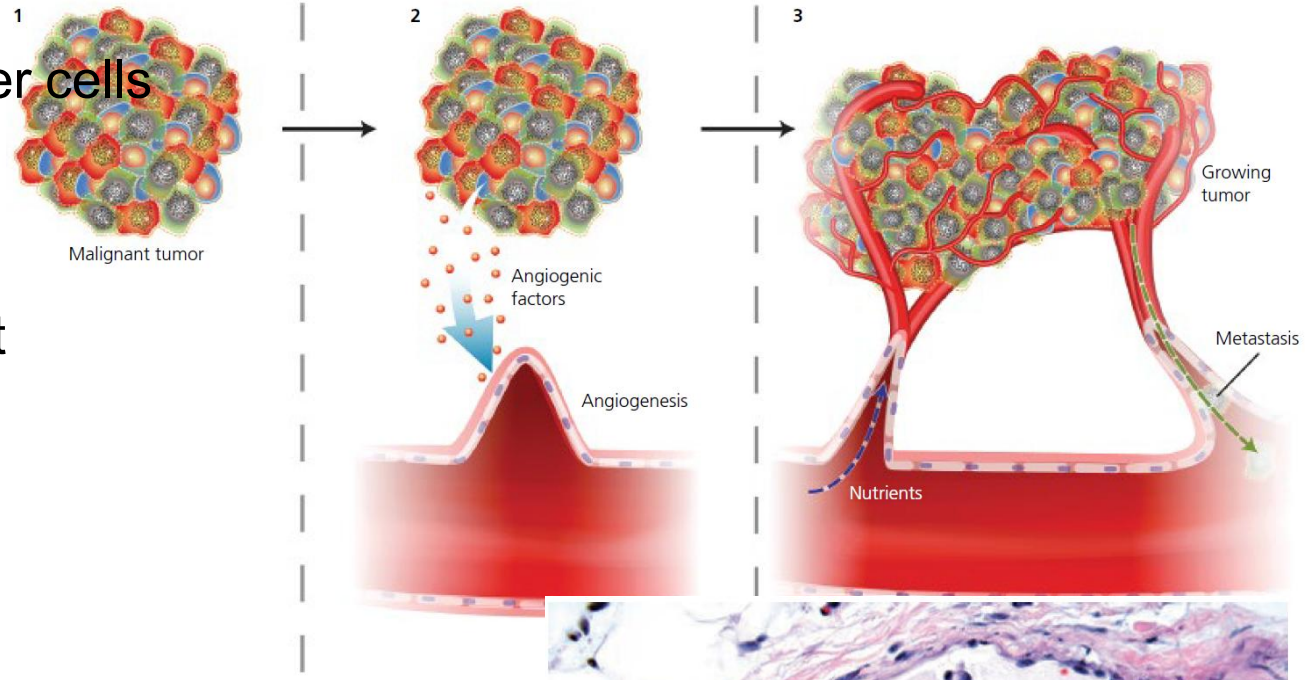
Epithelial-Mesenchymal Transition (EMT)

- Definition: A process where sessile, polarized epithelial cells are transformed into motile, fibroblast-like mesenchymal cells.
- Characteristics:
  - Loss of intercellular adhesion (e.g., decreased E-cadherin).
  - Enhanced expression of proteases.
  - Acquisition of migratory capabilities.
  - Change in shape from polygonal to spindle-shaped.
- Role in Cancer: EMT allows neoplastic epithelial cells to dissociate and migrate, thus fostering local invasion and distant metastasis.

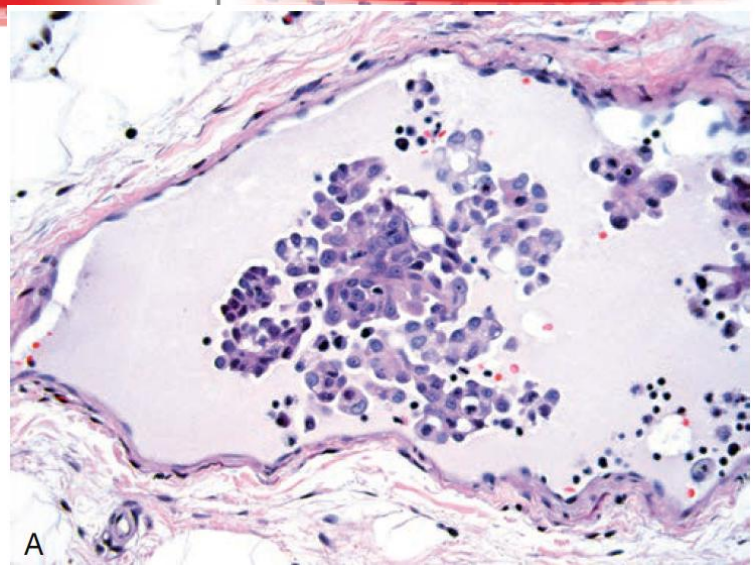
Metastasis - The Spread of Cancer

Intravasation and Transport

❖ Intravasation: The process by which cancer cells invade blood or lymphatic vessels.
- Tumor cells are attracted to vessels by chemotactic factors.
- They penetrate the endothelial basement membrane and pass between or through endothelial cells into the lumen.
- The process is facilitated by the inherent leakiness of tumor-associated vessels.



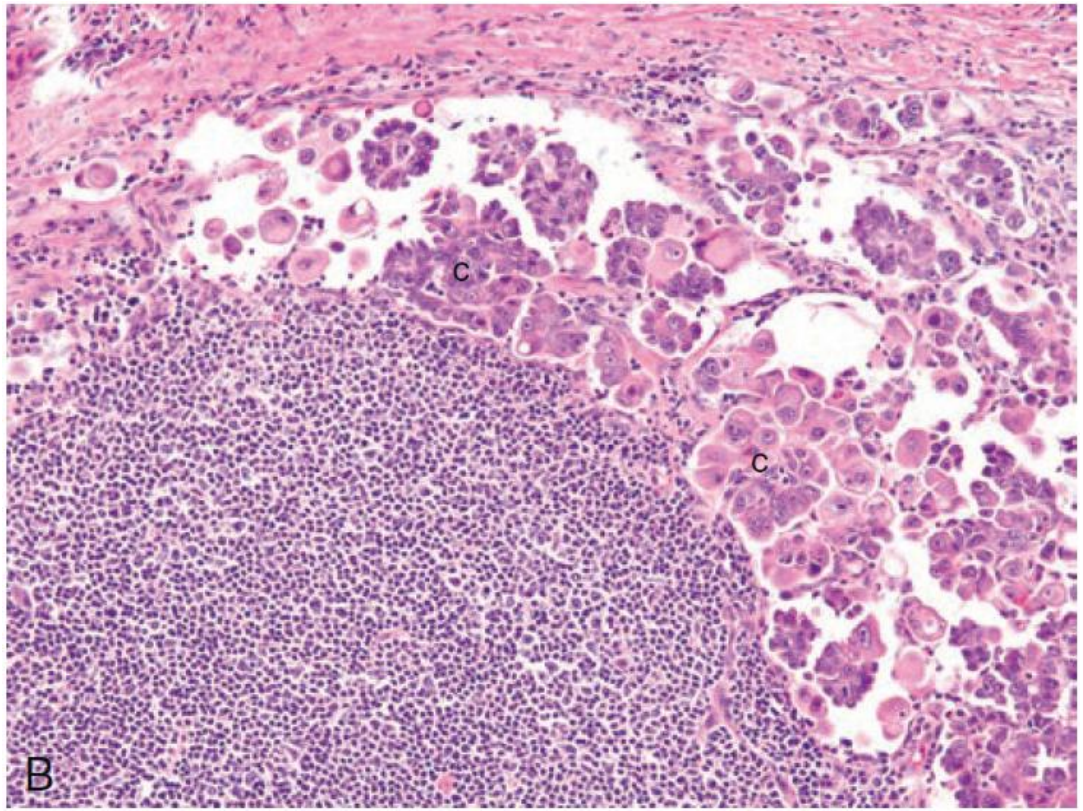
❖ Survival in Circulation:
- Once in a vessel, tumor cells tend to form small emboli.
- They may be attacked by host lymphocytes.
- They often become coated with platelets, which may actually protect the tumor embolus from immune-mediated destruction.



Metastasis - The Spread of Cancer

Extravasation and Colonization

- Extravasation: The process by which intravascular tumor cells leave the vessels at a distant site.
  - The site of extravasation is largely determined by the ability of tumor cells to interact with specific adhesion molecules on the endothelium of the target organ.
  - Once attached, they penetrate the vessel wall to enter the new tissue.
- Colonization:
  - The metastatic site must provide a suitable microenvironment ("soil") for the tumor cell ("seed") to grow.
  - Many metastatic cells may fail to grow or may enter a state of dormancy, where they survive for long periods without proliferating.



Metastasis - The Spread of Cancer

Pathways of Tumor Spread

❖ Lymphatic Spread:
- The most common pathway for initial dissemination of carcinomas.
- Tumor cells travel to regional lymph nodes following the normal routes of lymphatic drainage. The subcapsular sinus is often the first site of involvement.

❖ Hematogenous Spread:
- Typical for sarcomas, but also used by carcinomas.
- Tumors generally invade veins rather than arteries due to their thinner walls.
- The most frequent sites of hematogenous metastasis are the lungs and the liver, as they receive venous drainage from most of the body.

❖ Transcoelomic Spread (Seeding):
- Occurs when neoplasms invade a natural body cavity (e.g., peritoneal, pleural).
- Examples include ovarian carcinomas and mesotheliomas, which can spread widely on the surfaces of abdominal or thoracic organs, a condition termed **carcinomatosis**.

Systemic Effects of Cancer on the Host

Systemic Effects of Cancer on the Host

Direct Effects of Tumors

❖ Tumors directly compromise organ function by:

- Replacing (effacing) normal tissue.
- Compressing surrounding normal tissue or blood vessels, resulting in pressure atrophy or necrosis. This is particularly critical in confined spaces like the cranium.
- Causing obstruction or rupture of hollow organs.
- Eroding into blood vessel walls, causing acute hemorrhage.

Systemic Effects of Cancer on the Host

Paraneoplastic Syndromes: An Overview

- Definition: Systemic clinical signs that are indirect and remote effects of a tumor, caused by tumor cell products rather than the physical mass of the primary tumor or its metastases.
- Incidence: Occur in approximately 75% of human cancer patients; incidence in veterinary patients is unknown but they are well-described.
- Significance:
  - May facilitate early tumor diagnosis.
  - Metabolic abnormalities may require treatment for effective cancer management.
  - The severity of the syndrome may reflect the tumor burden and can be used to monitor response to therapy.

System	Syndrome	Associated neoplasms
Endocrine	Hypercalcemia of malignancy	Lymphoma Apocrine gland carcinoma of anal sac Mammary carcinoma Thymoma Others
	Hypoglycemia	Hepatocellular carcinoma Salivary gland carcinoma Leiomyoma/leiomyosarcoma Plasma cell tumor Lymphoma Others
	Ectopic ACTH	Pulmonary carcinoma
Cutaneous	Paraneoplastic pemphigus	Lymphoma
	Alopecia	Pancreatic carcinoma (cat) Others
	Necrolytic migratory erythema	Glucagonoma
Hematologic	Hypergammaglobulinemia	Multiple myeloma Lymphoma
	Anemia	Many neoplasms
	Erythrocytosis	Renal carcinoma
Neurologic	Myasthenia gravis	Thymoma Others
	Peripheral neuropathy	Insulinoma Others
Renal	Glomerulonephritis	Multiple myeloma Polycythemia vera Others
Gastrointestinal	Gastroduodenal ulceration	Mast cell tumors Gastrinoma
Miscellaneous	Hypertrophic osteopathy	Pulmonary carcinoma Other thoracic masses Urinary bladder rhabdomyosarcoma

Tumors in Domestic Animals (2016)

Systemic Effects of Cancer on the Host

Paraneoplastic Syndromes: Cachexia

- ❖ Definition: Significant weight loss and debility seen in many cancer patients.
- ❖ Characteristics:
  - Both muscle and fat are lost, in contrast to simple starvation where fat is lost preferentially.
  - The basal metabolic rate does not decrease as it does in starvation.
  - The condition cannot be reversed by simply increasing caloric intake.
- ❖ Etiology: Complex, but due in part to cytokines and hormones released by the tumor or host, particularly TNF-α (also known as cachectin), IL-1, and IL-6, which cause anorexia and debilitation.



https://onlinelibrary.wiley.com/doi/10.1111/jvim.16915

Systemic Effects of Cancer on the Host

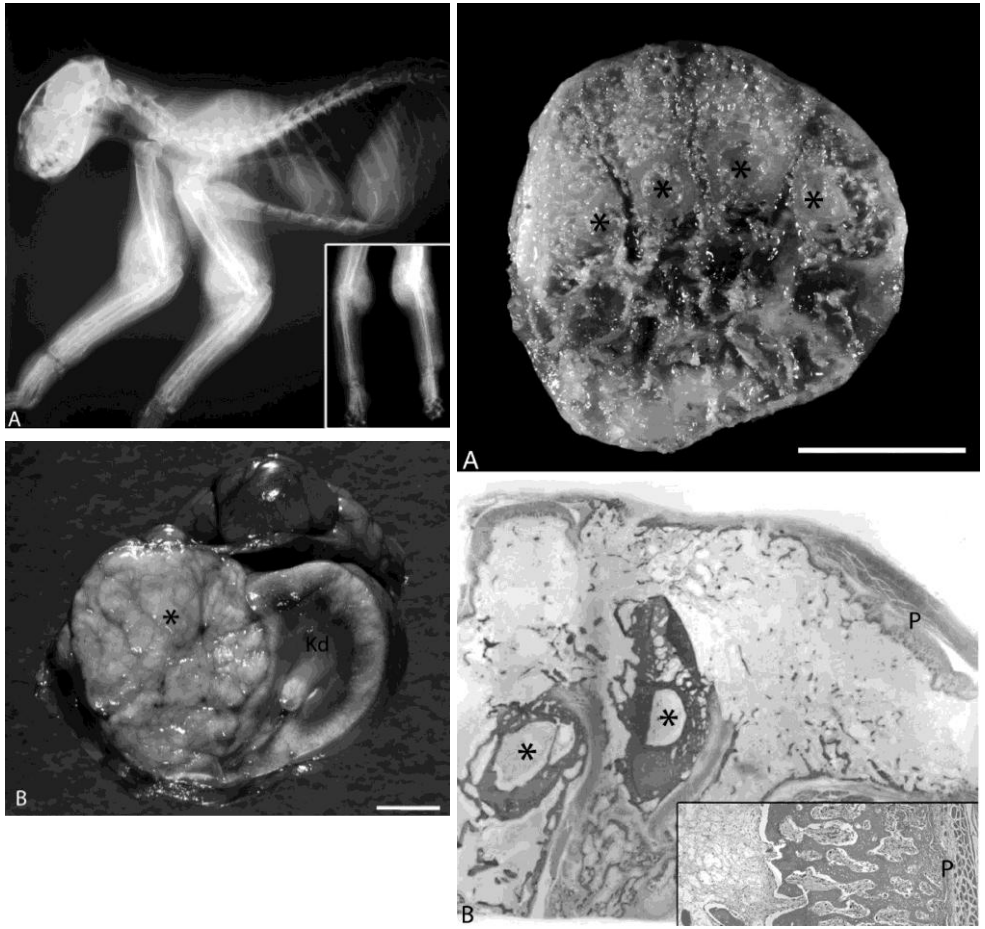
Paraneoplastic Syndromes: Endocrinopathies

- Functioning Endocrine Tumors: Tumors of endocrine glands may overproduce their normal hormonal products (e.g., thyroid adenomas causing hyperthyroidism).
- Ectopic Hormone Production: Non-endocrine tumors may produce hormonally active substances not normally found in their tissue of origin.
- **Humoral Hypercalcemia of Malignancy (HHM)**:
  - The most common example in veterinary medicine.
  - Caused by tumor secretion of parathyroid hormone-related peptide (PTHrP).
  - In dogs, it is most frequently seen with adenocarcinoma of the anal sac, lymphoma, and multiple myeloma.
  - PTHrP acts like parathyroid hormone, increasing serum calcium by releasing it from bones and enhancing its reabsorption in the kidneys.

Systemic Effects of Cancer on the Host

Paraneoplastic Syndromes: Skeletal & Hematologic

- ❖ Hypertrophic Osteopathy:
  - A condition characterized by extensive periosteal new bone growth, particularly on the extremities.
  - It is strongly associated with space-occupying lesions in the thoracic cavity.
- ❖ Myelofibrosis:
  - Overgrowth of non-neoplastic fibroblasts in the bone marrow, which impairs normal hematopoiesis and can result in cytopenias.
- ❖ Anemia:
  - Commonly seen in cancer patients.
  - Causes are numerous, including anemia of inflammation, bone marrow effacement, blood loss, and hemolysis.
- ❖ Coagulopathies:
  - Disseminated intravascular coagulation (DIC) is frequently seen in dogs with hemangiosarcoma.



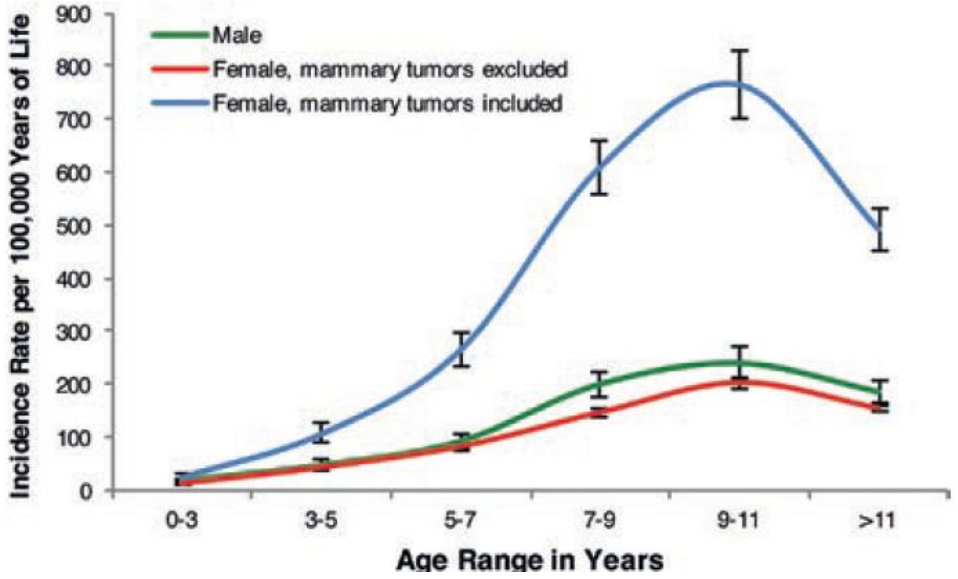
Hypertrophic Osteopathy Associated with a Renal Adenoma in a Cat, ***JVDI*** (2011)

The Molecular Basis of Cancer

The Molecular Basis of Cancer

Heritable Alterations in Cancer

- Cancer occurs as the result of the progressive accumulation of heritable genetic and epigenetic abnormalities in cells.
- Genetic Changes: Alterations in the DNA sequence itself, known as mutations. These are passed to all progeny of the cancer cell.
- Epigenetic Changes: Heritable changes in gene expression that are not due to a change in the DNA sequence. Examples include DNA methylation and histone modification.
- Driver Mutations: While tumor cells may have many mutations, only a few, termed driver mutations, are predominantly responsible for tumor development.



The Molecular Basis of Cancer

Types of Genetic Changes

- **Point Mutations**: Alteration of a single base in the DNA sequence.
- **Insertions** and **Deletions**: Addition or loss of DNA base pairs, ranging from a single base to an entire chromosome arm. Small insertions/deletions can cause a frameshift mutation.
- **Gene Amplification**: Results in the presence of multiple extra copies of a DNA sequence, often leading to overexpression of the encoded gene.
- **Aneuploidy**: An abnormal number of chromosomes in a cell, resulting from mistakes in chromosome segregation during mitosis.
- **Translocations**: Occur when pieces of two separate chromosomes break off and reattach inappropriately.

The Molecular Basis of Cancer

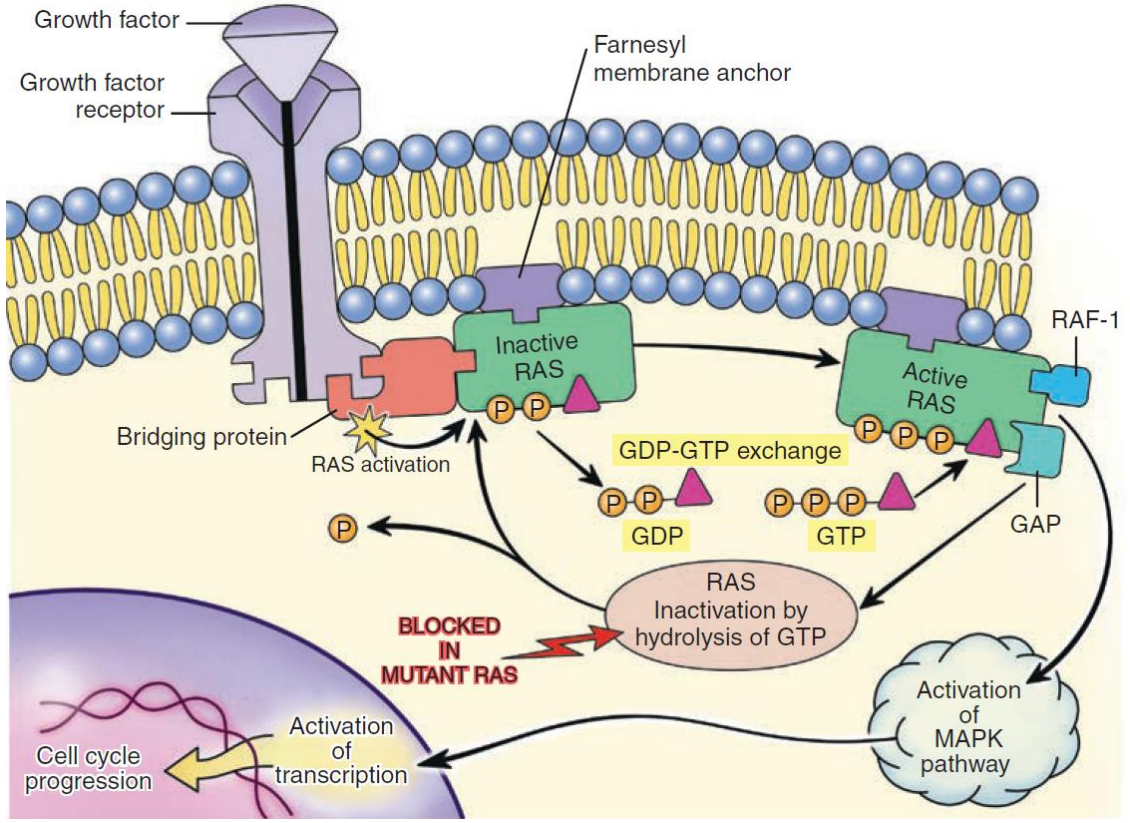
Epigenetic Changes

- **DNA Methylation**:
  - The addition of a methyl group to cytosine bases in DNA.
  - Hypermethylation of a gene's promoter region generally leads to gene silencing.
  - Cancer cells often exhibit global hypomethylation with paradoxical, gene-specific hypermethylation of tumor suppressor genes.
- **Histone Modification**:
  - Post-translational modifications of histone proteins (e.g., acetylation, methylation) alter the structure of chromatin.
  - Histone acetylation, for example, results in a more relaxed chromatin configuration (euchromatin), making DNA more accessible for transcription.
- **Non-coding RNAs** (e.g., microRNAs):
  - Small RNA molecules that do not encode proteins but regulate the expression of other genes, usually by blocking their translation.
  - Dysregulated miRNA expression contributes significantly to cancer development.

The Molecular Basis of Cancer

Oncogenes: The "Accelerators"

- Proto-oncogenes: Normal cellular genes that regulate cell growth and differentiation. They often encode products like growth factors, receptors, and signal transduction proteins.
- Oncogenes: When "activated" by overexpression or mutation, proto-oncogenes become oncogenes.
- Function: Oncogenes drive uncontrolled cell proliferation and render the cell unresponsive to normal growth inhibitory signals.
- Example: *RAS*
  - The *ras* genes encode proteins that transmit growth-stimulatory signals from receptors to the nucleus.
  - In many cancers, a mutation in a *RAS* gene leads to a constitutively active protein, resulting in continued signaling for proliferation even in the absence of growth factors.

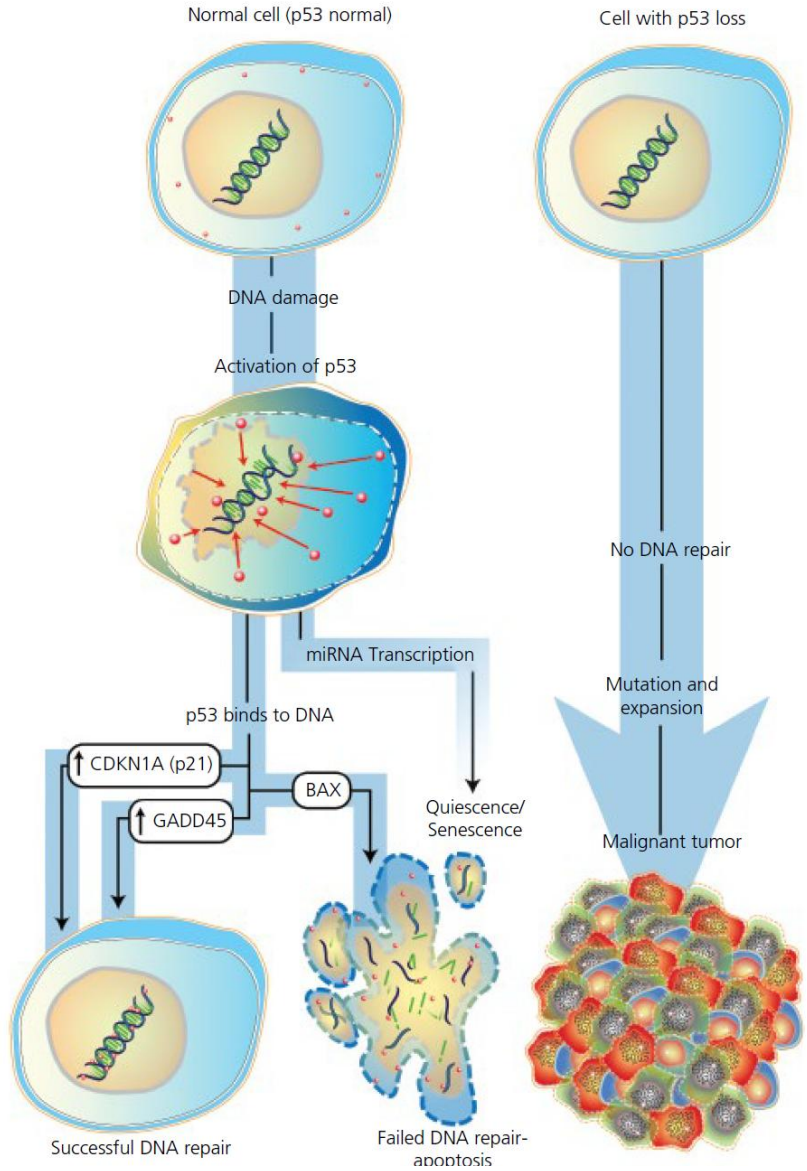


Tumors in Domestic Animals (2016)

The Molecular Basis of Cancer

Tumor Suppressor Genes: The "Brakes"

- ❖ Definition: Genes that normally inhibit cell proliferation and tumor growth. They include genes that control the cell cycle, apoptosis, and DNA repair.
- ❖ Inactivation: Unlike oncogenes which require activation, tumor suppressor genes contribute to cancer when they are inactivated.
- ❖ Example: TP53
  - The p53 protein is called the "guardian of the genome".
  - In response to DNA damage, p53 levels rise and it can either:
    - Stop the cell cycle to allow time for DNA repair.
    - Induce apoptosis if the damage is irreparable.
  - Loss of functional p53 is one of the most common events in human cancers, allowing genetically damaged cells to proliferate.

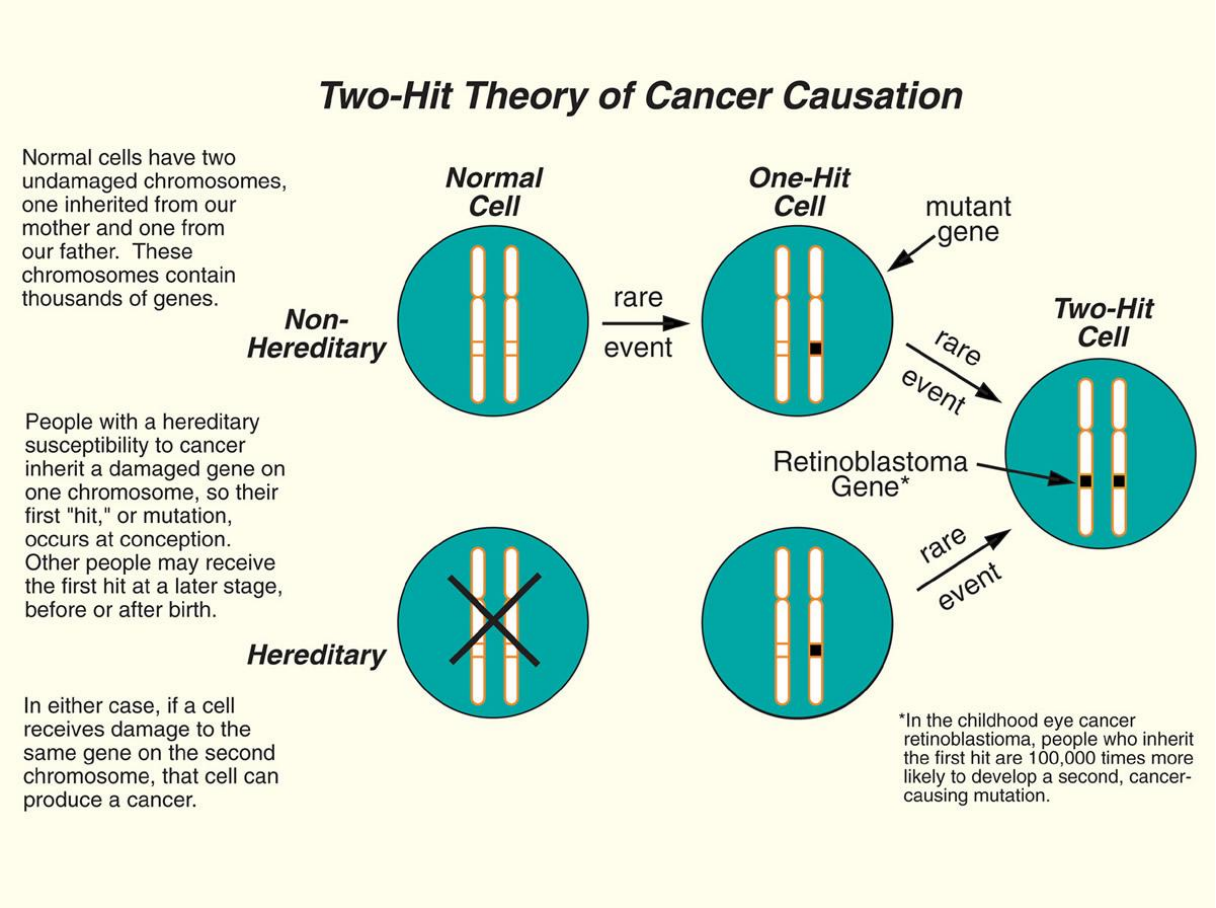


Tumors in Domestic Animals (2016)

The Molecular Basis of Cancer

Knudson's "Two-Hit" Hypothesis

- This hypothesis explains the mechanism of inactivation for many tumor suppressor genes.
- It states that both alleles of a tumor suppressor gene must be inactivated (suffer a "hit") for cancer to develop. Inactivation of only one allele is not sufficient, as the remaining normal allele can still produce a functional protein.
- **Sporadic Cancers**: An individual starts with two normal alleles. A single cell must undergo two independent, rare somatic mutations to inactivate both alleles, which is a much less likely event.
- **Familial Cancers**: Individuals inherit one mutated allele (the first hit) in every cell of their body. They then only need a single somatic mutation in the second allele (the second hit) in a given cell to initiate a tumor. This explains why these cancers appear at an earlier age and are often multifocal.



https://www.foxchase.org/about-us/history/discoveries-fox-chase-research/knudsons-two-hit-theory-cancer-causation

The Molecular Basis of Cancer

Defects in DNA Repair Genes

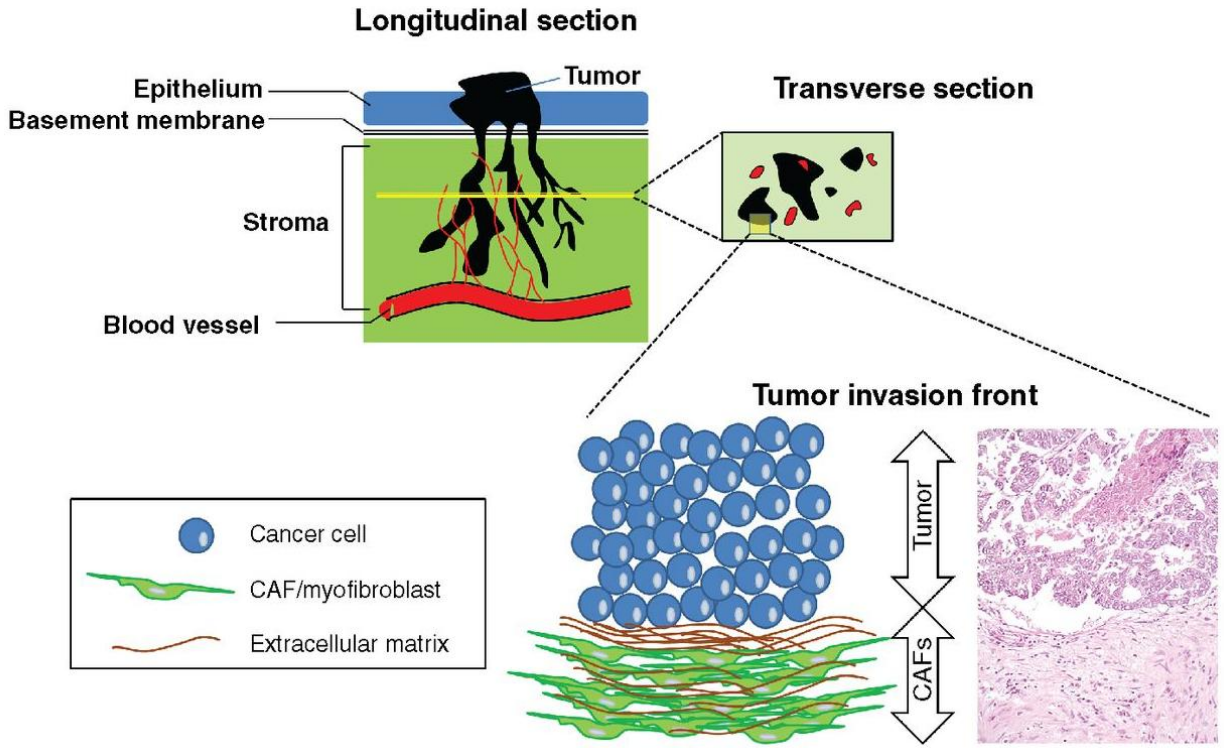
- The integrity of the genome is maintained by several DNA repair systems.
- Mismatch Repair: Enzymes like MLH1 and MSH2 "proofread" DNA to fix single nucleotide mismatches that occur during replication.
- Nucleotide Excision Repair: Repairs bulky DNA lesions, such as the pyrimidine dimers caused by UV radiation.
- Consequence of Defects: When a DNA repair gene itself is inactivated (e.g., through mutation), the cell can no longer fix DNA damage effectively. This leads to a dramatic increase in the rate of mutations throughout the genome (genomic instability), which exponentially increases cancer susceptibility.

The Tumor Microenvironment & Immunity

The Tumor Microenvironment & Immunity

Tumor Microenvironment: Parenchyma & Stroma

- ❖ A tumor consists of two main components:
  - Parenchyma: The neoplastic cells themselves.
  - Stroma: The non-neoplastic supporting structure.
- ❖ The stroma is composed of:
  - Extracellular Matrix (ECM): Collagen, glycoproteins, proteoglycans.
  - Blood vessels that supply nutrients.
  - Fibroblasts that synthesize the ECM.
  - A variety of inflammatory and immune cells.
- ❖ The amount of stroma varies considerably among tumors.

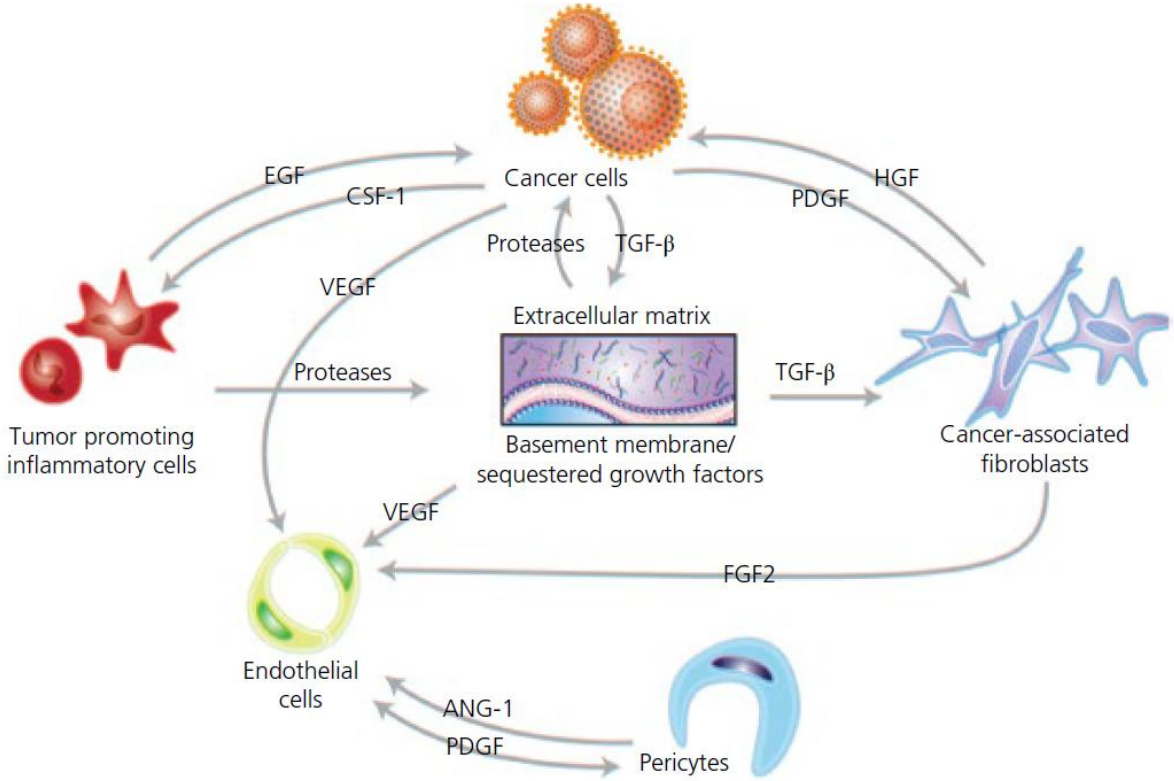


Mol Cancer Res. 2012;10(11):1403-1418

The Tumor Microenvironment & Immunity

Tumor-Stroma Interactions

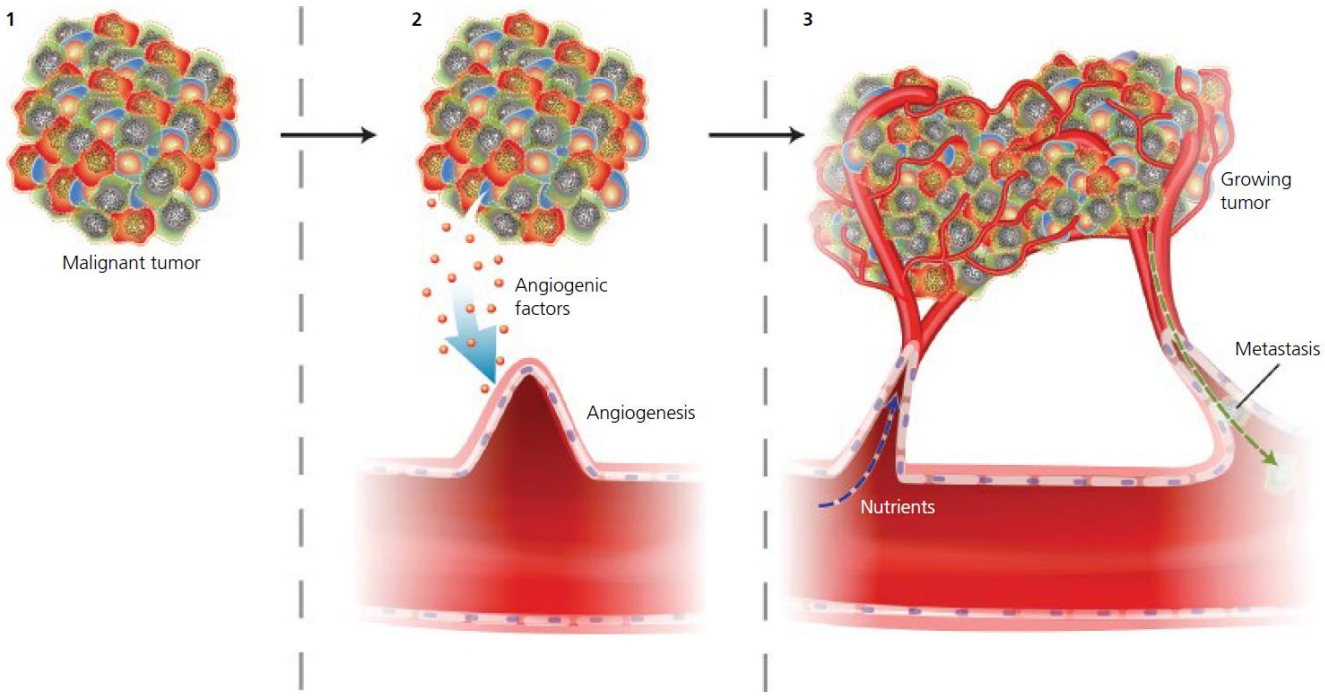
- ❖ Tumor cells and their stroma engage in complex, bidirectional signaling.
- ❖ Tumor cells influence the stroma:
  - They can stimulate the formation of new blood vessels (angiogenesis).
  - They can cause an extensive fibroblastic response with collagen deposition, termed a desmoplastic or scirrhous response.
- ❖ The stroma influences the tumor:
  - Proteases from stromal cells can release growth factors that are sequestered in the ECM, fostering tumor proliferation.
  - Inflammatory cells in the stroma can release mediators that may promote tumor growth



The Tumor Microenvironment & Immunity

Angiogenesis - The Tumor's Blood Supply

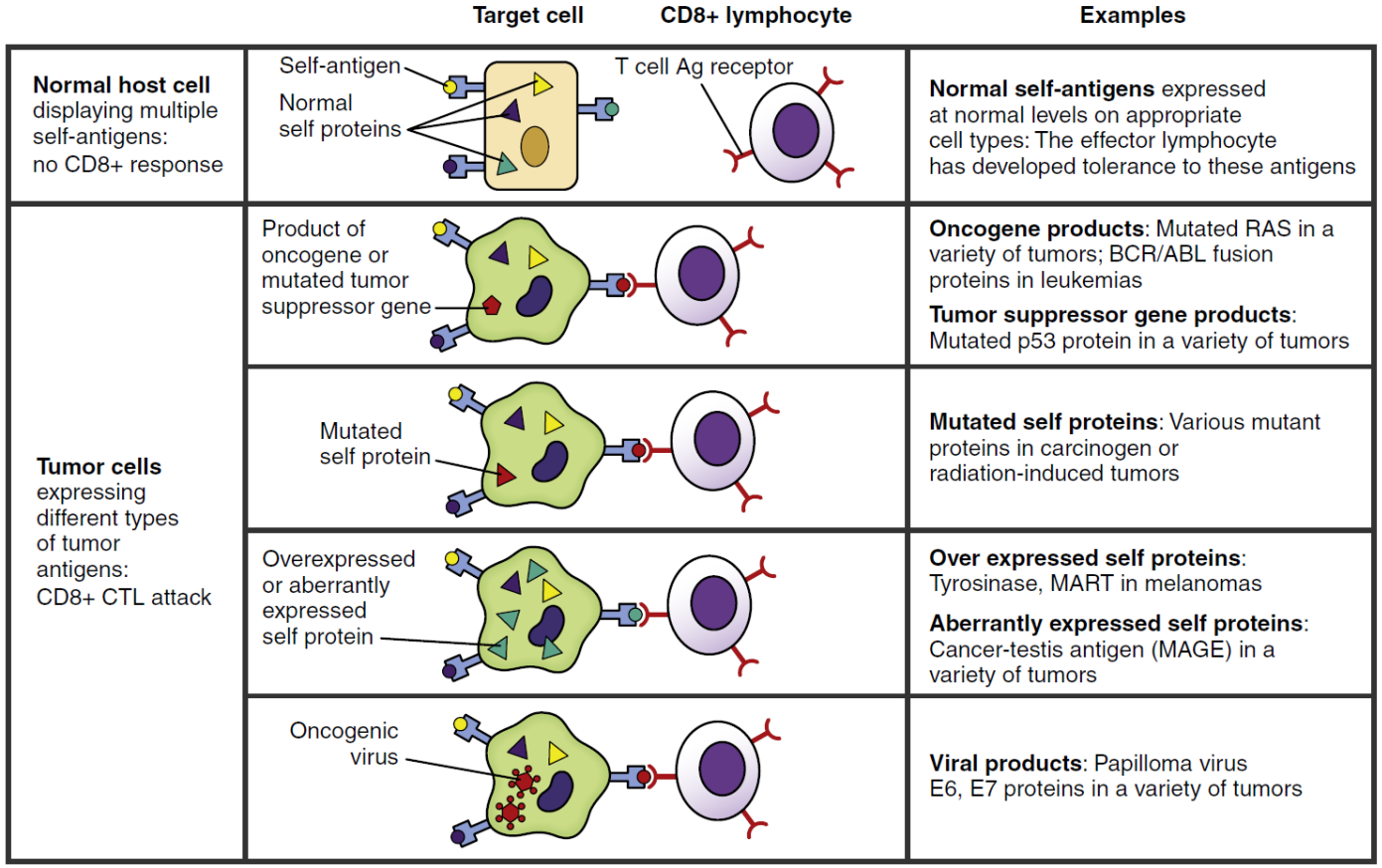
- Continued growth of solid tumors beyond 1-2 mm in diameter is dependent on an adequate blood supply.
- At some point, tumors undergo an angiogenic switch, allowing them to induce and sustain the formation of new blood vessels.
- Mechanism: Tumors initiate angiogenesis by producing angiogenic factors, most importantly Vascular Endothelial Growth Factor (VEGF), or by downregulating antiangiogenic factors.
- Tumor Vasculature: The resulting blood vessels are typically more dilated, tortuous, disorganized, and leaky than normal vessels, which can facilitate metastasis.



The Tumor Microenvironment & Immunity

Tumor Immunity and Immunosurveillance

- The immune system can recognize and destroy tumor cells, a process termed immunosurveillance.
- The hypothesis is that effective immunosurveillance suppresses tumor development, and a failure of this process allows tumors to emerge.
- Evidence for Immunosurveillance:
  - Immunosuppressed human transplant recipients have a dramatically increased susceptibility to tumors.
  - Many tumors are infiltrated by lymphocytes and macrophages, suggesting an ongoing immune response.



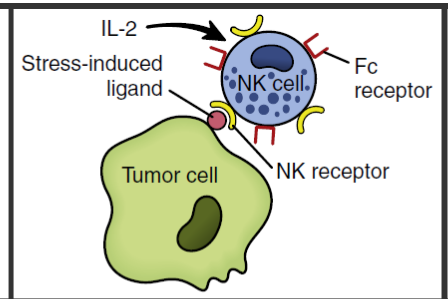
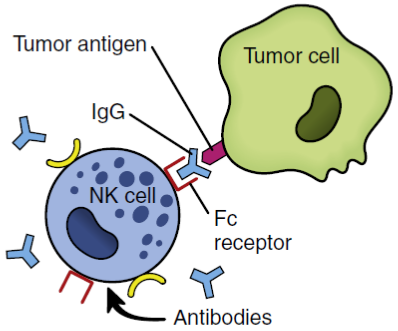
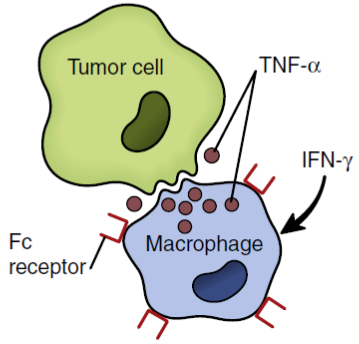
The Tumor Microenvironment & Immunity

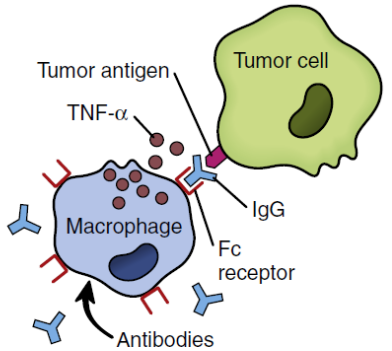
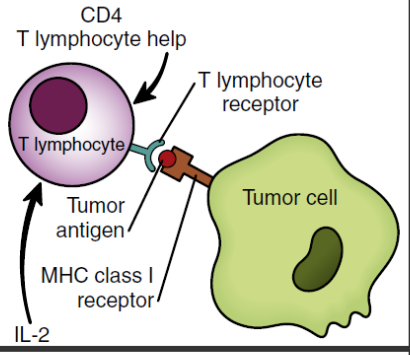
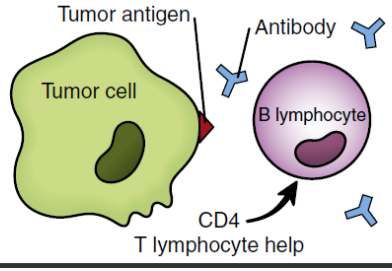
Tumor Antigens

- ❖ Tumor antigens are molecules expressed on the surface of tumor cells that can be recognized by the immune system.
- ❖ Tumor-Specific Antigens:
  - • Restricted to tumor cells.
  - • Examples
    - - Products of mutated oncogenes (e.g., mutated RAS)
    - - Mutated tumor suppressor genes (e.g., mutated p53)
    - - Proteins from oncogenic viruses (e.g., papillomavirus E6/E7 proteins).
- ❖ Tumor-Associated Antigens:
  - • Present on both tumor cells and some normal cells.
  - • Examples
    - - Oncofetal antigens (like CEA) that are expressed during embryonic development but re-expressed by tumors
    - - Differentiation antigens that are overexpressed on tumor cells compared to their normal counterparts.

The Tumor Microenvironment & Immunity

Cells Involved in Immunosurveillance against Tumors

Effector Cell		Activation/ Assistance	Target	Mode of Attack
NK cell		IL-2	Stress-induced ligand	Immunologic synapse (perforin/granzymes)
NK cell (ADCC)		Antibodies produced by B lymphocytes	Tumor antigen	Immunologic synapse (perforin/granzymes)
Macrophage		IFN-γ activation	Tumor cell membrane	TNF-α, reactive oxygen species, nitric oxide, lysosomal enzymes

Effector Cell		Activation/ Assistance	Target	Mode of Attack
Macrophage (ADCC)		Antibodies produced by B lymphocytes	Tumor antigen	TNF-α, reactive oxygen species, nitric oxide, lysosomal enzymes
T lymphocyte (CTL)		Help by CD4 T lymphocyte, IL-2 activation	Tumor antigen presented in MHC class I context	Immunologic synapse (perforin/granzymes)
B lymphocyte		Help by CD4 T lymphocyte	Tumor antigen	Membrane-attack complex (activated complement)

The Tumor Microenvironment & Immunity

Antitumor Mechanisms: Innate Immunity

- The innate immune system is the first line of defense and does not require prior sensitization.
- Natural Killer (NK) Cells:
  - A subset of lymphocytes that can kill tumor cells without previous encounter.
  - Preferentially target and kill cells that have lost or downregulated the expression of MHC class I molecules.
  - Killing is mediated by the release of perforin and granzymes, which induce apoptosis in the target cell.
- Macrophages:
  - Can kill tumor cells by releasing reactive oxygen species, lysosomal enzymes, nitric oxide, and TNF.
  - Their role is complex, as some tumor-associated macrophages can actually promote tumorigenesis by enhancing angiogenesis and suppressing other immune cells.

The Tumor Microenvironment & Immunity

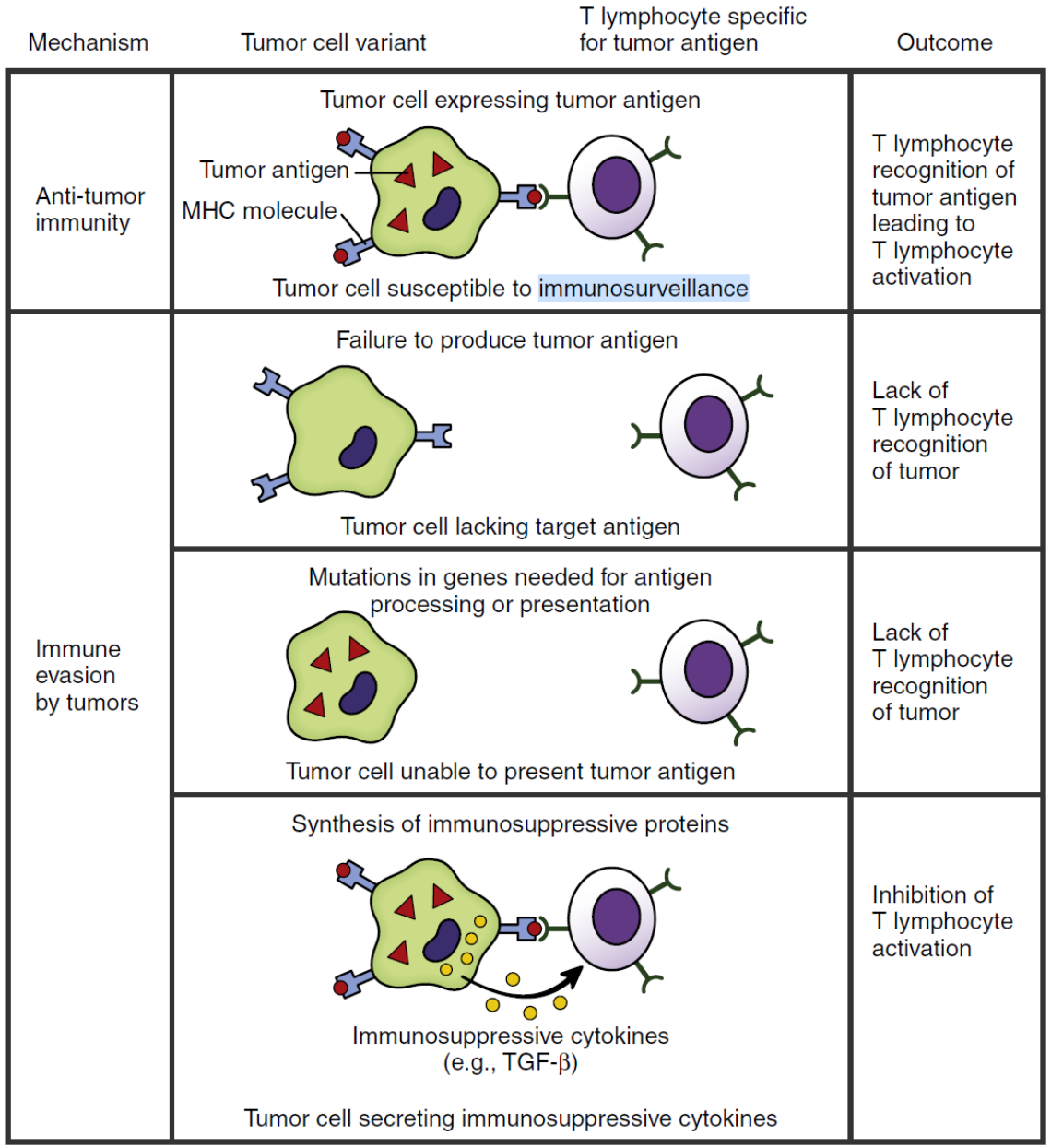
Antitumor Mechanisms: Adaptive Immunity

- The cell-mediated arm of the adaptive immune system is believed to mount the most effective antitumor defenses.
- Cytotoxic T Lymphocytes (CTLs):
  - The primary effector cells of the adaptive antitumor response.
  - They are typically CD8+ T cells that have been primed by dendritic cells to recognize a specific tumor antigen presented on MHC class I molecules.
  - They kill target tumor cells by the same perforin/granzyme mechanism as NK cells.
- B Lymphocytes (Humoral Immunity):
  - Differentiate into plasma cells that produce antibodies against tumor antigens.
  - Antibodies can kill tumor cells by activating the complement cascade or by arming NK cells and macrophages for antibody-dependent cell-mediated cytotoxicity (ADCC).

The Tumor Microenvironment & Immunity

How Tumors Evade the Immune Response

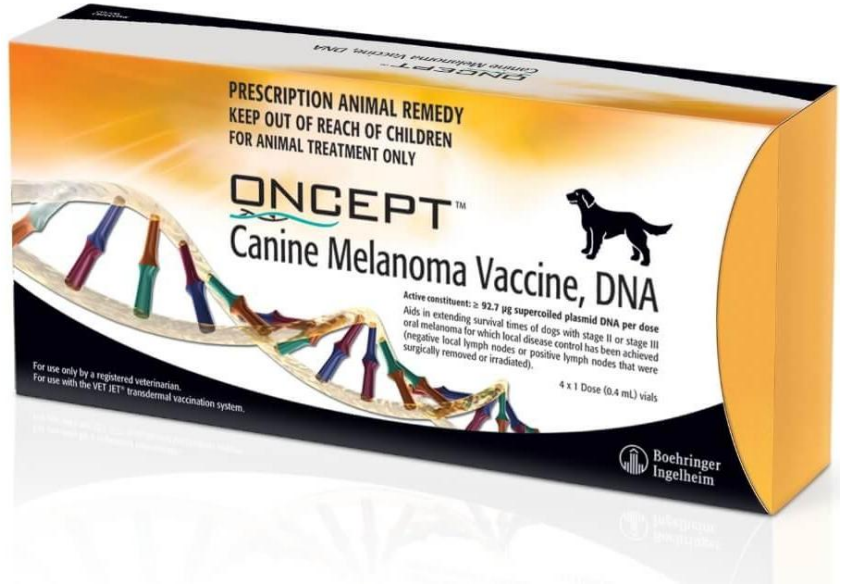
- Many tumors develop strategies to evade immunosurveillance:
  - **Altered MHC Expression**: They can lose or downregulate MHC class I expression to hide from CTLs.
  - **Antigen Masking**: They can stop expressing tumor antigens or hide them with a thick glycocalyx coat.
  - **Inducing Tolerance**: They can be perceived as "self" if antigens are presented without proper costimulatory signals, or through the action of regulatory T cells (Tregs), which actively suppress immune responses.
  - **Immunosuppression**: Tumors can produce immunosuppressive factors, like TGF-β, or express molecules (like Fas ligand) that trigger apoptosis in attacking T lymphocytes.



The Tumor Microenvironment & Immunity

Tumor Immunotherapy

- ❖ Immunotherapeutic strategies aim to boost the host's immune response against the tumor.
- ❖ Passive Immunotherapy: Provides the patient with mature effector cells or antibodies.
  - • Example: Administration of monoclonal antibodies that are specific for a tumor antigen.
- ❖ Active Immunotherapy: Stimulates the patient's own immune system to attack the tumor.
  - • Example: Vaccination with tumor antigens to generate antitumor CTLs.
  - • A melanoma vaccine for dogs stimulates an immune response against tyrosinase.
- ❖ New Approaches: Blocking the activity of immunosuppressive cells like Tregs or tumor-associated macrophages is a promising new strategy.



Causes of Cancer & Animal Models

Causes of Cancer & Animal Models

Mechanisms of Carcinogenesis

- ❖ Carcinogens are agents that cause cancer.
- ❖ Chemical Carcinogens:
  - Direct-acting: Effective in the form they enter the body.
  - Indirect-acting (Procarcinogens): Require metabolic activation (often by cytochrome P450 enzymes in the liver) to become carcinogenic.
  - Most chemical carcinogens are mutagens that bind covalently to DNA to form DNA adducts.
- ❖ Radiation Carcinogenesis:
  - UV radiation (from sunlight) causes the formation of pyrimidine dimers, and is a major cause of skin cancer in sparsely haired areas.
  - Ionizing radiation causes chromosome breakage, translocations, and point mutations.
  - All forms of radiation are complete carcinogens, meaning they can both initiate and promote tumorigenesis.

Causes of Cancer & Animal Models

Oncogenic Viruses

❖ Viruses that cause cancer employ a variety of mechanisms:

- Dominant Oncogene Mechanism: Some retroviruses carry a viral oncogene (often a captured and mutated host proto-oncogene) in their genome. Uncontrolled expression of this oncoprotein drives cell proliferation.
- Insertional Mutagenesis: Viruses without their own oncogene can insert their DNA into the host genome in a way that activates a nearby cellular proto-oncogene, leading to its unregulated expression.
- Inhibition of Tumor Suppressors: Some viruses (e.g., papillomaviruses) produce proteins (like E6 and E7) that bind to and inactivate host tumor suppressor proteins like p53 and pRb.
- Indirect Mechanisms: Some viruses cause cancer by stimulating chronic inflammation or by suppressing the immune system, reducing immunosurveillance.

Causes of Cancer & Animal Models

Oncogenic Viruses

E-Table 6.2 Oncogenic Viruses of Animals

Classification	Virus	Species Affected	Associated Tumors
Retrovirus	Mouse mammary tumor virus	Mouse	Mammary adenocarcinomas
	Avian sarcoma-leukosis virus complex	Fowl	Various sarcomas, carcinomas, lymphomas, leukemias
	Avian reticuloendotheliosis virus complex	Fowl	Lymphomas, leukemias
	Mouse leukemia and sarcoma viruses	Mouse	Various sarcomas, carcinomas, lymphomas, leukemias
	Feline leukemia virus	Cat	Leukemias, lymphomas
	Bovine leukosis virus	Cattle	Leukemias, lymphomas
	Primate leukemia and sarcoma viruses	Primate	Fibrosarcomas, leukemias
	Mason-Pfizer monkey virus	Primate	Fibrosarcomas
	Feline immunodeficiency viruses	Cat	Lymphomas
	Maedi-visna virus	Sheep	Pulmonary carcinomas
Hepadnavirus	Hepatitis B group	Primate, rodent, duck	Hepatocellular carcinomas
Papovavirus	Polyoma	Mouse, raccoon	Various carcinomas, sarcomas
	Simian virus 40 (SV40)	Primate	Sarcomas (in rodents)
	Papilloma	Many species	Papillomas, carcinomas
Adenovirus	Types 2, 5, 12	Human	Sarcomas (in hamsters)
Herpesvirus	Frog herpesvirus	Frog	Adenocarcinomas
	Marek's disease	Fowl	Lymphoproliferative disease/ lymphomas
	Herpesvirus ateles and saimiri	Primate	Lymphomas, leukemias
Poxvirus	Various	Various	Fibromas, papillomas

Modified from Wyke J: Viruses and cancer. In Franks LM, Reich NM, editors: *Cellular and molecular biology of cancer*, New York, 2003, Oxford University Press.

Causes of Cancer & Animal Models

Naturally Occurring Tumors in Animals

- Many naturally occurring cancers in animals serve as important models for human cancer.
- The Dog as a Cancer Model:
  - Dogs have a comparable cancer incidence rate to humans.
  - They are outbred and share a common environment with humans, including exposure to carcinogens.
  - Many canine tumors, such as osteosarcoma and lymphoma, are biologically very similar to their human counterparts.
  - The more rapid progression of tumors in dogs allows clinical trials to be completed in a reasonable timeframe.
- Biobanking: The collection and storage of animal tumor tissues and related clinical information is becoming increasingly important for cancer research.

Diagnosis and Prognosis

Diagnosis and Prognosis

Cytologic Diagnosis

- Purpose: A useful and quick screening test for assessing masses. Can sometimes provide a definitive diagnosis.
- Techniques:
  - Fine-Needle Aspirate/Non-aspirate: A needle is used to collect cells from a mass, which are then expelled onto a slide.
  - Impression Smear: The freshly cut surface of an excised mass is blotted and then gently pressed onto a slide.
- Advantages: Quick, easy, minimally invasive, and allows for excellent evaluation of fine cellular detail.
- Limitations: Does not allow for evaluation of tissue architecture, making it difficult to assess for invasion or distinguish hyperplasia from benign neoplasia. The sample may not be representative of the entire lesion.

Diagnosis and Prognosis

Cytologic Criteria of Malignancy

❖ These are features of cellular atypia that suggest a potential for malignant behavior:

- Anisocytosis: Variation in cell size.
- Anisokaryosis: Variation in nuclear size.
- Macrocytosis / Macrokaryosis: Abnormally large cells or nuclei.
- High Nuclear-to-Cytoplasmic Ratio: Nuclei are disproportionately large relative to the cell size.
- Multiple/Prominent Nucleoli: Suggests high metabolic and synthetic activity.
- Coarse or "Stippled" Chromatin: Instead of smooth, evenly dispersed chromatin.
- Multinucleation or Bizarre Mitotic Figures.

❖ Caution: These criteria are only suggestive. Some reactive non-neoplastic cells can show atypia, and some malignant tumors (e.g., neuroendocrine) show very little atypia.

Diagnosis and Prognosis

Histopathologic Diagnosis

- The Golden Standard: A definitive diagnosis is frequently obtained by histologic evaluation of a biopsy specimen.
- Biopsy Types:
  - Incisional Biopsy: A portion of the lesion is removed to establish a diagnosis.
  - Excisional Biopsy: The entire mass is removed with the intent of both diagnosis and cure.
- Surgical Margin Evaluation: The margins of an excisional biopsy are evaluated to determine if the tumor has been completely removed. "Clean" margins are free of tumor cells, while "dirty" margins indicate incomplete excision and a risk of local recurrence.

Diagnosis and Prognosis

Tumor Grading

- Definition: A process performed by a pathologist to provide an indication of a tumor's biologic behavior and potential for malignancy.
- Basis: All grading schemes evaluate the degree of differentiation of the tumor cells (e.g., well-differentiated, moderately differentiated, poorly differentiated).
- Other Criteria: Schemes may also incorporate other histologic features:
  - Mitotic count (number of dividing cells).
  - The extent of tumor necrosis.
  - Evidence of invasiveness.
- Prognosis: The grade (e.g., Grade I, II, or III) is used to help predict the clinical outcome.

Diagnosis and Prognosis

Tumor Staging

- Definition: A process, generally performed by the clinician, to determine the extent of tumor growth and spread in the animal.
- Purpose: Staging guides the therapeutic plan and provides crucial prognostic information.
- The TNM System: A widely used staging scheme based on:
  - T: The size of the primary tumor (T0 to T4).
  - N: The degree of regional lymph node involvement (N0 to N3).
  - M: The extent of distant metastasis (M0 to M2).

Conclusion

- Neoplasia is a complex, multistep process driven by the accumulation of genetic and epigenetic alterations.
- These alterations allow tumor cells to bypass normal controls on growth, evade cell death, and acquire malignant characteristics like invasion and metastasis.
- Understanding the fundamental biology of tumors—from their nomenclature and classification to their interactions with the host and their molecular drivers—is essential for accurate diagnosis, prognosis, and the development of effective therapies.