4 BASIC TYPES OF TISSUES

Epithelial

Connective
characterized by the abundant ECM produced by its cells

Muscular
composed of elongated cells specialized for contraction and movement

Nervous
composed of cells with long, fi ne processes specialized to receive, generate, and transmit nerve impulses

Remember: These tissues, which all contain cells and molecules of the extracellular matrix (ECM), exist in association with one another and in variable proportions and morphologies, forming the different organs of the body.

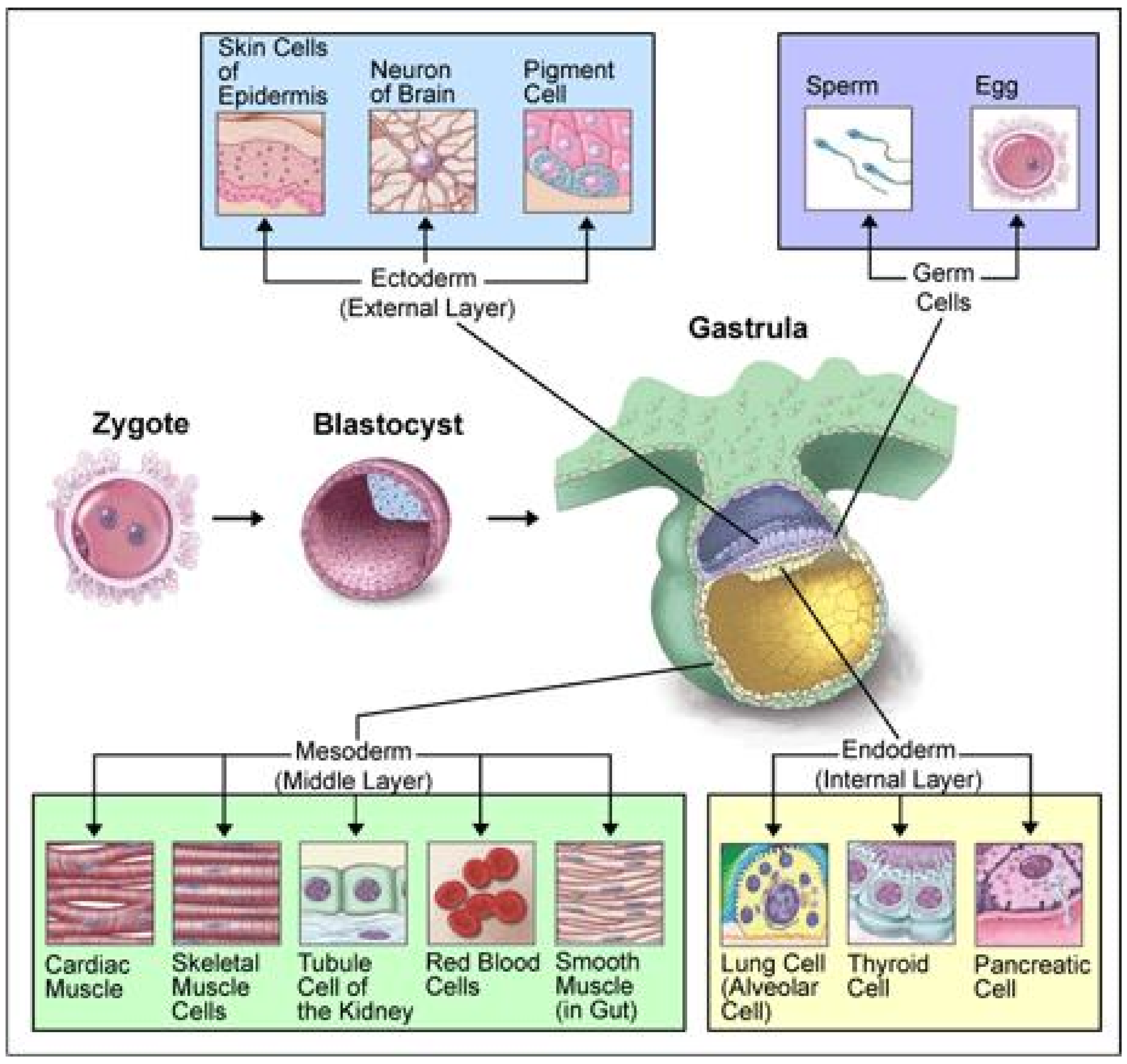
EPITHELIAL TISSUE

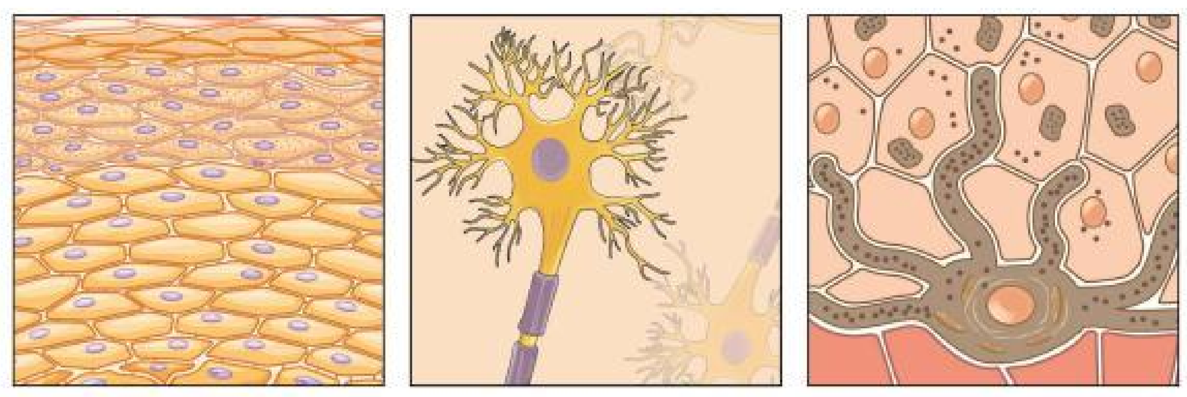
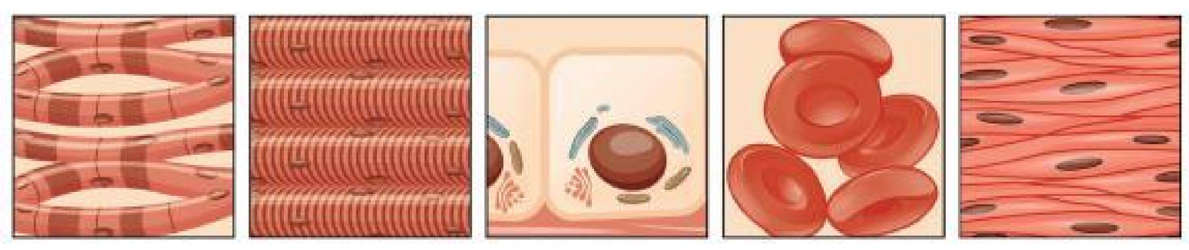
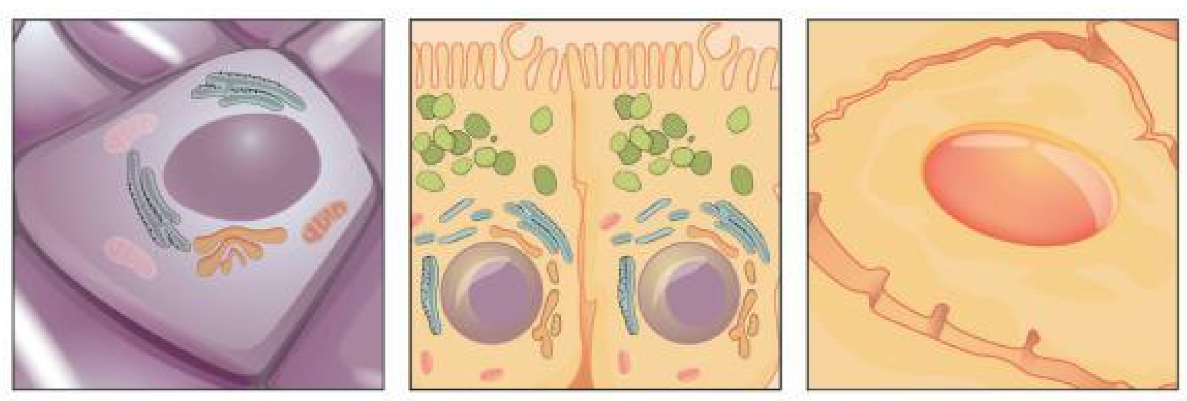
- Are cellular sheets that line the cavities of organs and cover the body surface
- The shapes and dimensions of epithelial cells are quite variable, ranging from tall columnar to cuboidal to low squamous cells.
- composed of closely aggregated polyhedral cells with strong adhesion to one another and attached to a thin layer of ECM

FUNCTIONS
✓ Covering, lining, and protecting surfaces (eg, epidermis)
✓ Absorption (eg, the intestinal lining)
✓ Secretion (eg, parenchymal cells of glands)

Specific cells of certain epithelia may be contractile (myoepithelial cells) or specialized sensory cells, such as those of taste buds or the olfactory epithelium.

Because epithelial cells line all external and internal surfaces of the body, all substances that enter or leave tissues and organs must cross an epithelium.



Germ Layer	Gives rise to:
Ectoderm	Epidermis, glands on skin, some cranial bones, pituitary and adrenal medulla, the nervous system, the mouth between cheek and gums, the anus  Skin cells, Neurons, Pigment cell
Mesoderm	Connective tissues proper, bone, cartilage, blood, endothelium of blood vessels, muscle, synovial membranes, serous membranes lining body cavities, kidneys, lining of gonads  Cardiac muscle, Skeletal muscle, Tubule cell of kidney, Red blood cells, Smooth muscle
Endoderm	Lining of airways and digestive system except the mouth and distal part of digestive system (rectum and anal canal); glands (digestive glands, endocrine glands, adrenal cortex)  Lung cell, Thyroid cell, Pancreatic cell

CHARACTERISTICS
They exhibit functional and morphological polarity, with organelles and membrane proteins distributed unevenly within the cell.
- Free surface or apical domain
- Lateral domain
- Basal domain

Basal pole
The region of the cell contacting the connective tissue

Apical pole.
opposite end, usually facing a space

Lateral surface
Regions of cuboidal or columnar cells that adjoin the neighboring cells; cell membranes here often have numerous in foldings to increase the area of that surface, increasing its functional capacity

Papillae
area of contact between the epithelium and connective tissue may be increased by irregularities at the interface in the form of small evaginations

All epithelial cells in contact with subjacent connective tissue have at their basal surfaces a specialized, felt like sheet of extracellular material referred to as the basement membrane

Basement Membrane
- A thin sheet of connective tissue that separates the epithelial tissue from the underlying tissue
- Provides structural support for the epithelium and also binds it to neighboring structures

Lamina propia
connective tissue that underlies the epithelia lining the organs of the digestive, respiratory, and urinary systems

Basal lamina
A thin meshwork of type IV collagen and laminin produced by the epithelial cells

Reticular lamina
Contains type III collagen and anchoring fibrils of VII collagen, all secreted by cells of the immediately adjacent connective tissue

Epithelial cells are closely apposed and adhere to one another by means of specific cell-to-cell adhesion molecules that form specialized cell junctions (possible because of the cell to cell adhesion molecules)

TABLE 4–1 Main characteristics of the four basic types of tissues.

Tissue	Cells	Extracellular Matrix	Main Functions
Nervous	Elongated cells with extremely fine processes	Very small amount	Transmission of nerve impulses
Epithelial	Aggregated polyhedral cells	Small amount	Lining of surface or body cavities; glandular secretion
Muscle	Elongated contractile cells	Moderate amount	Strong contraction; body movements
Connective	Several types of fixed and wandering cells	Abundant amount	Support and protection of tissues/ organs

Intercellular Adhesion & Other Junctions
Epithelial cells adhere strongly to neighboring cells and basal laminae, particularly in epithelia subject to friction or other mechanical forces.

Tight or occluding junctions *(zonulae occludens)*
- form a seal between adjacent cells
- Seal between the membranes is due to interactions between the transmembrane proteins claudin and occludin
- The term "zonula" indicates that the junction forms a band completely encircling each cell

Adherent or anchoring junctions *(zonula adherens)*
sites of string cell adhesion
Cell adhesion here is mediated by cadherins (transmembrane glycoproteins of each cell that interact in the presence of Ca^{2+})

Desmosomes (macula adherens)
- resembles a single "spot-weld" and does not form a belt around the cell
- discshaped structures at the surface of one cell that are matched with identical structures at an adjacent cell surface

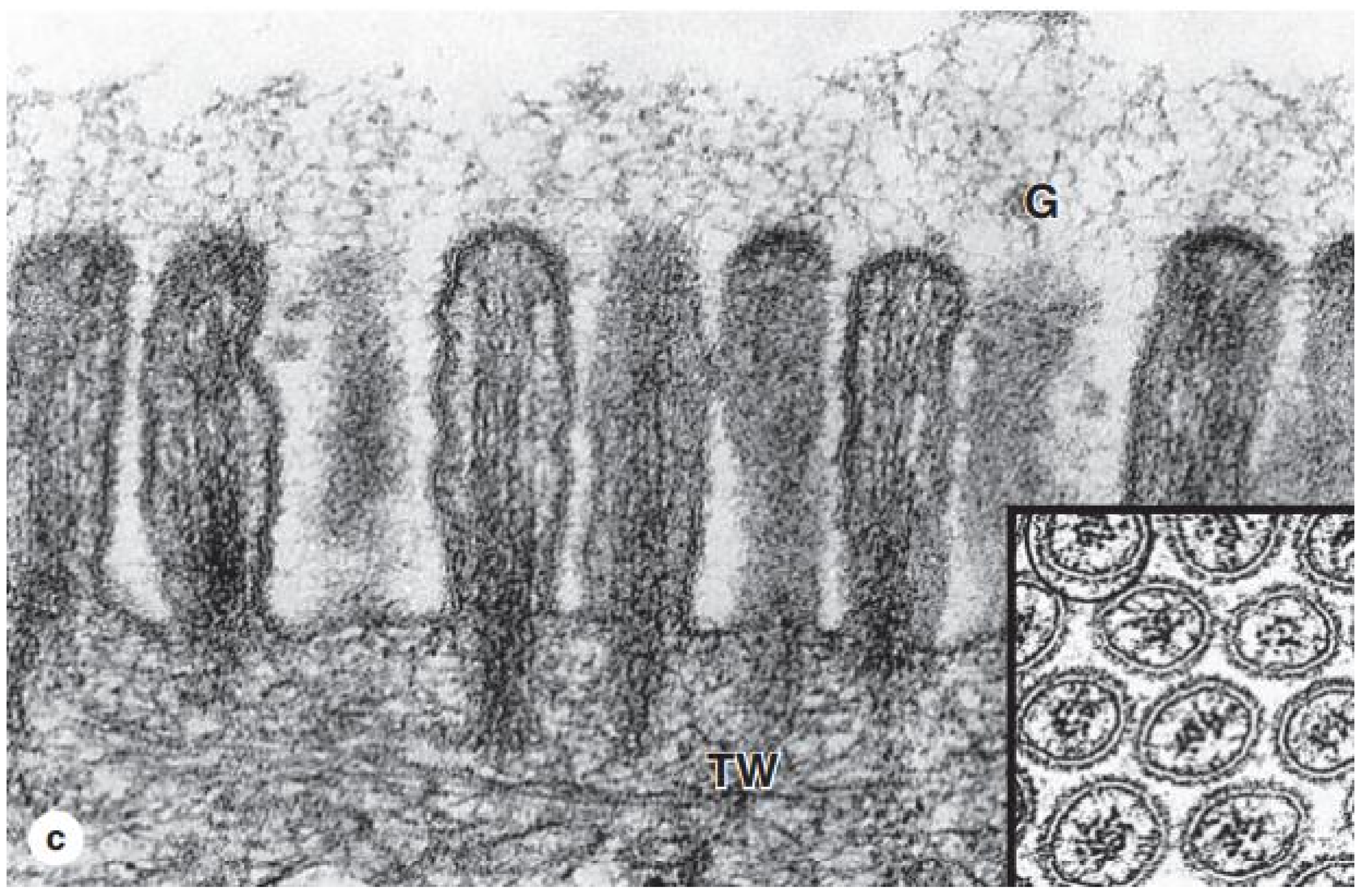
Gap Junctions
- mediate communication rather than adhesion or occlusion between cells
- The gap junction proteins, called connexins, form hexameric complexes called connexons

SPECIALIZATIONS OF APICAL CELL SURFACE

Microvilli
- Short or long fingerlike extensions or folds
- Increase the cell surface area *(for absorption)* or to move substances or particles bound to epithelium
- Commonly seen on:

Intestinal absorptive cells (striated border)
Kidney tubules cells (brush border)

The glycocalyx (G) extending from glycoproteins and glycolipids of the microvilli plasmalemma contains certain enzymes for late stages of macromolecule digestion



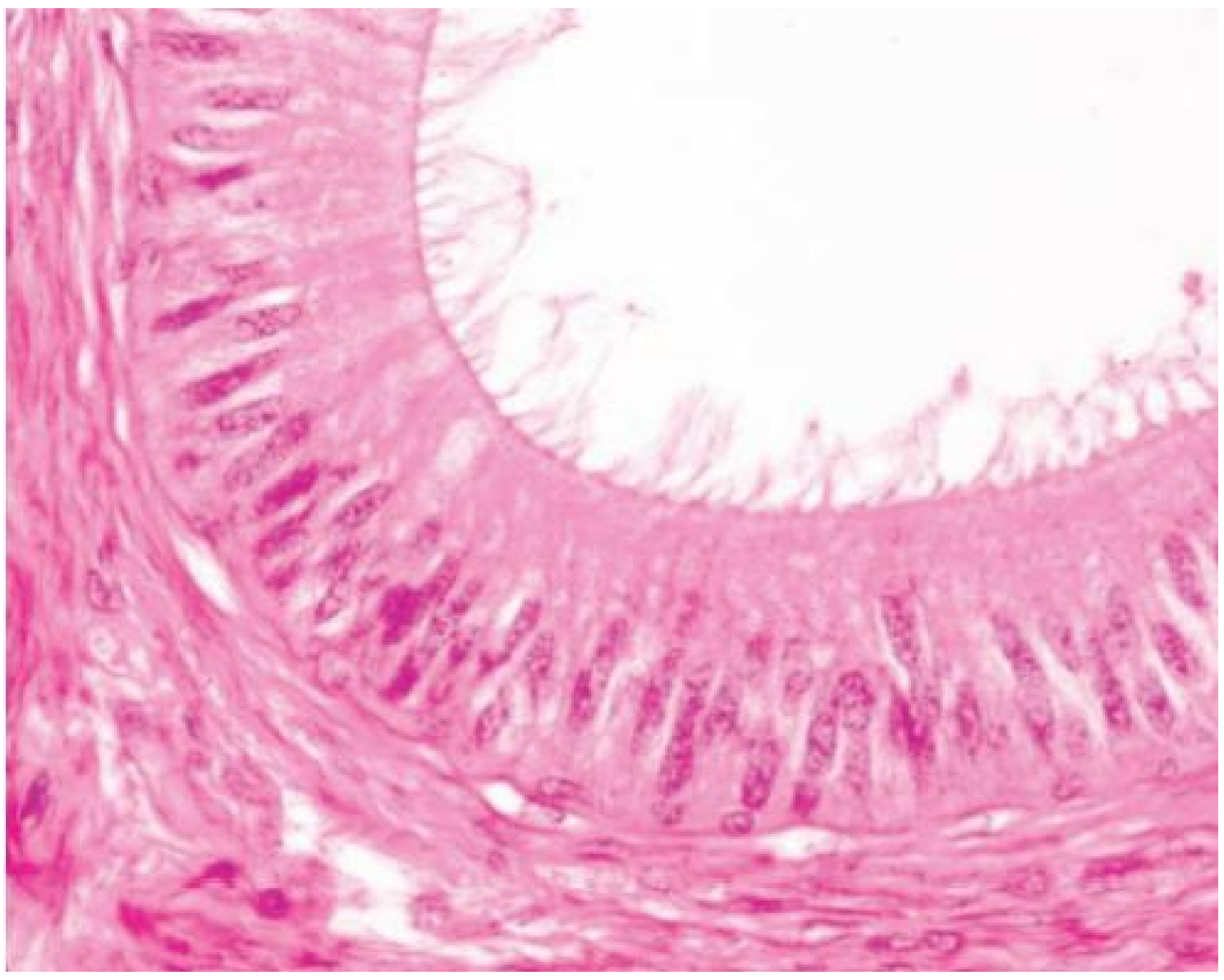
Stereocilia
- a much less common type of apical process, restricted to absorptive epithelial cells lining the epididymis and the proximal part of ductus deferens in the male reproductive system

- Increase the cell surface area
- Facilitating absorption

More specialized stereocilia with a motion-detecting function are important components of inner ear sensory cells

Stereocilia resemble microvilli in containing arrays of actin filaments and various actin-binding proteins, with similar diameters, and with similar connections to the cell's terminal web.

However, stereocilia are typically much longer and much less motile than microvilli, and may show distal branching along their length.



Cilia

- long projecting hairlike extensions structures of the apical plasma membrane , larger than microvilli, which contain internal arrays of microtubules (axenomes)
- exhibit rapid beating patterns of movement that propel a current of fluid and suspended matter in one direction over the epithelium (sweeping)

Motile Cilia

- are found only in epithelia
- abundant on the apical domains of many cuboidal or columnar cells
- Motile cilia with a 9+2 (axenomes) pattern display a precise and synchronous undulating movement

Metachronal rhythm

Responsible for moving mucus over epithelial surfaces or facilitating the flow of fluid and other surfaces through tubular organs and ducts

Primary Cilia

- Nonmotile and contain a 9+0 pattern of microtubules

Function as signal receptors sensing a flow of fluid in developing organs

- Found in almost all eukaryotic cells
- Found in cells that are important for normal tissue morphogenesis

Nodal Cilia

- Important in establishing the left right asymmetry of the internal organs
- Are found in the embryo on the bilaminar embryonic disc at the time of gastrulation
- Concentrated in the area that surrounds the primitive node
- Have similar axonemal internal architechture as primary cilia
- Has ability to perform rotational movement
- Play an important role in early embryonic development

Example of where we can locate Cilia

Motile Cilia	Oviduct, trachea, bronchial tree, brain ependyma, olfactory epithelium, sperm cells (flagella)
Primary cilia	Kidney ducts, bile duct epithelium, thyroid gland, thymus, Schwann cells, chondrocytes, fibroblasts, adrenal cortex, pituitary cells
Nodal cilia	embryo

CLASSIFICATION & NAMING OF EPITHELIA

First name of tissue indicates the number of layers

- Simple - one layer of cells
- Stratified - more than one layer of cells

Last name of tissue describes shape of cells

- Squamous - cells wider than tall (plate or "scale" like)
- Cuboidal - cells are as wide as tall, as in cubes
- Columnar - cells are taller that they are wide, like columns

TYPES OF EPITHELIA

- Epithelia can be divided into two main groups: covering (or lining) epithelia
- secretory (glandular) epithelia

This is an arbitrary division, for there are lining epithelia in which all the cells also secrete *(eg, the lining of the stomach)* or in which glandular cells are distributed among the lining cells *(eg, mucous cells in the small intestine or trachea)*

Lining Epithelia

- organized into one or more layers that cover the external surface or line the cavities of an organ
- classified according to the number of cell layers and the cell morphology in the surface layer

Simple Squamous Epithelium

Single layer of flat cells w/ disc-shaped nuclei

Special types

- Endothelium (inner covering)

Slick lining of hollow organs (lymph vessels, blood vessels)

- Mesothelium (middle covering)

Lines peritoneal, pleural, and pericardial cavities
Cover visceral organs of those cavities

Function

- Acts as boundary where simple passage of materials by passive diffusion and filtration happen
- Secretes lubricating substances in serosae

Location

- Renal corpuscles, alveoli of lungs, lining of heart, blood and lymphatic vessels, lining of ventral body cavity (serosae)

This is a single layer of thin cells, in which the cell nuclei (arrows) are the thickest and most visible structures. Simple epithelia are typically specialized as lining of vessels and cavities, where they regulate passage of substances into the underlying tissue. The thin cells often exhibit transcytosis.

Examples shown here are those lining the thin renal loops of Henle
(a) covering the outer wall of the intestine
(b) and lining the inner surface of the cornea

Simple Cuboidal Epithelium

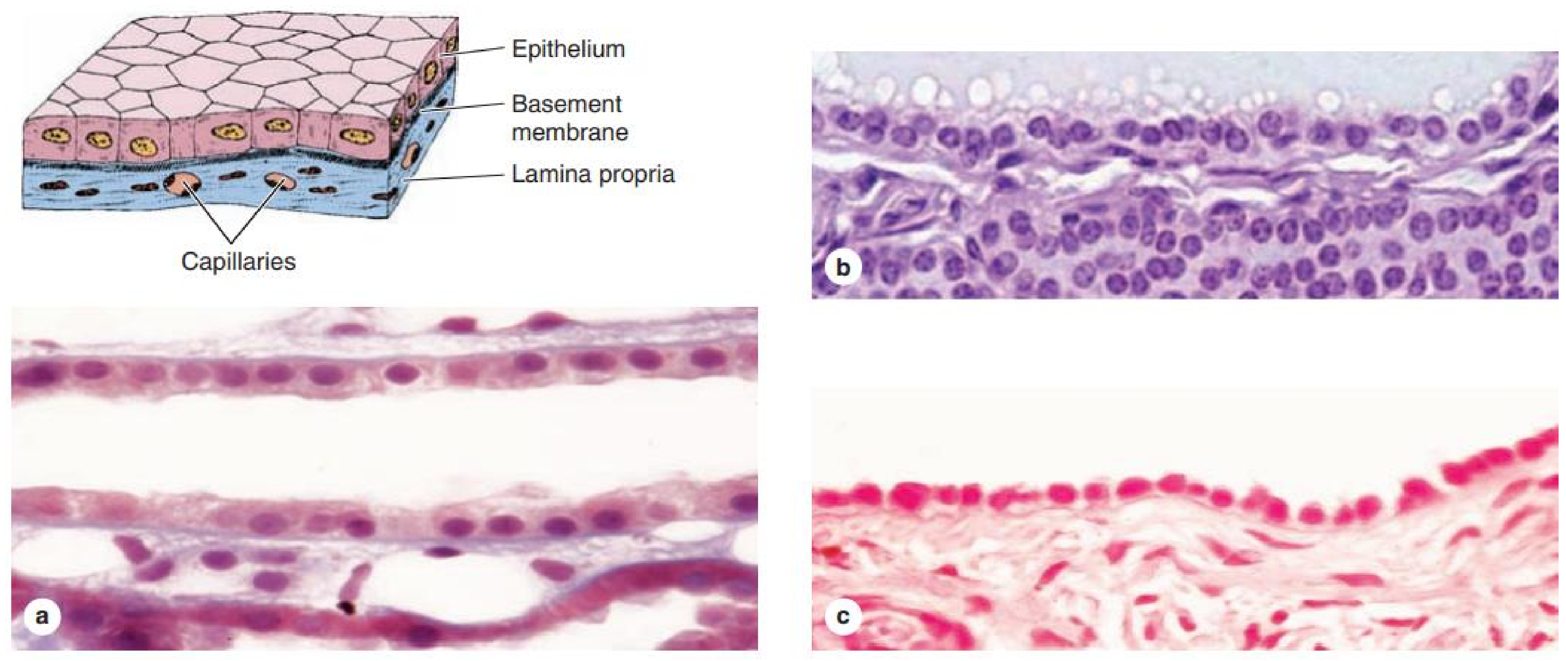
Single layer of cube-like cells w/ large, spherical central nuclei

Function

Secretion, absorption, barrier, conduit

Location

Small ducts of exocrine gland
Surface of ovary (germinal epithelium)
Kidney tubes
Thyroid follicles



Cells here are roughly as tall as they are wide. Their greater thickness allows cytoplasm to be rich in mitochondria and other organelles for a high level of active transport across the epithelium and other functions.

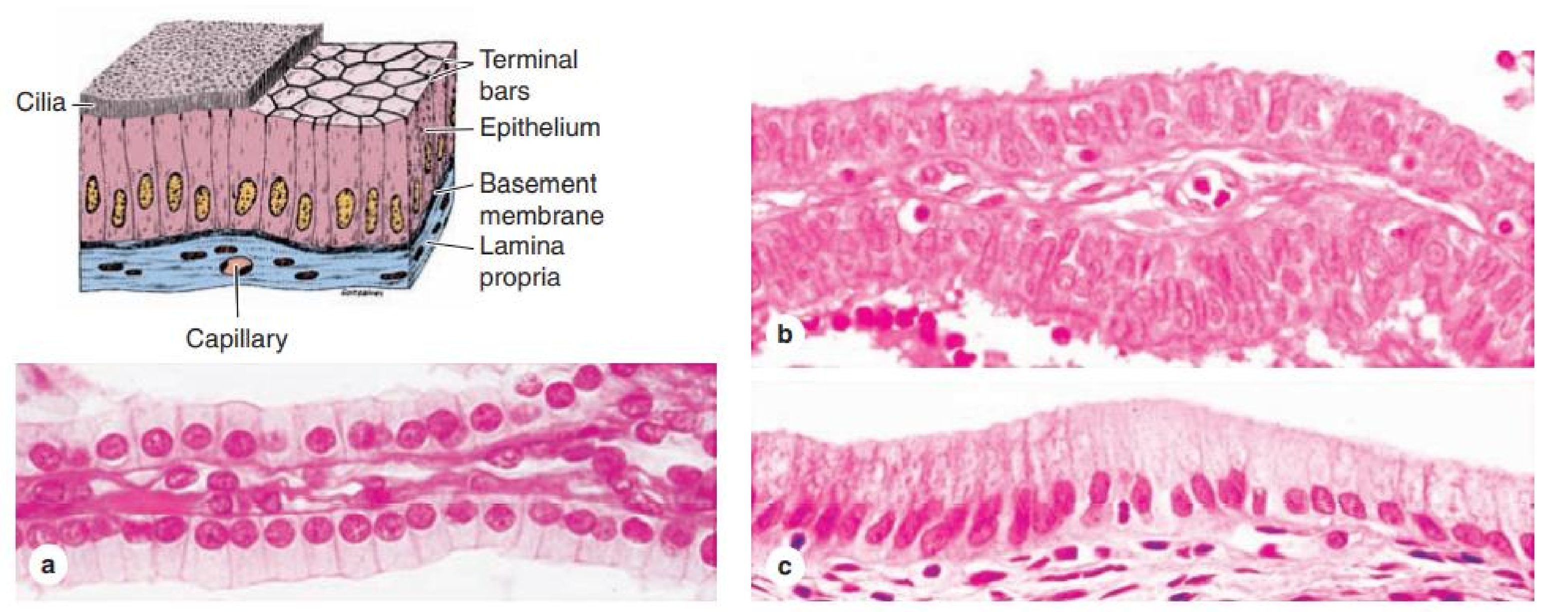
Examples shown here are from a renal collecting tubule
(a) , a large thyroid follicle
(b), and the thick mesothelium covering an ovary

Simple Columnar Epithelium

- Single layer of column-shaped (rectangular) cells w/ oval nuclei
- Some bear cilia at their apical surface
- Always have tight and adherent complexes at their apical ends

Function

- Absorption secretion of mucus, enzymes, and other substances
- Ciliated type propels mucus or reproductive cells by ciliary action



Cells here are always taller than they are wide, with apical cilia or microvilli, and are often specialized for absorption.

Complexes of tight and adherent junctions, sometimes called "terminal bars" in light microscopic images, are present at the apical ends of cells.

The examples shown here are from a renal collecting duct (a), the oviduct lining, with both secretory and ciliated cells (b), and the lining of the gall bladder

Location

Non-ciliated form
Lines digestive tract
Gallbladder
Gastric glands

Ciliated form
Lines small bronchi
Uterine tubes
Uterus

Stratified Epithelia

Classified according to the cell shape of the superficial layers : squamous, cuboidal, columnar, and translational

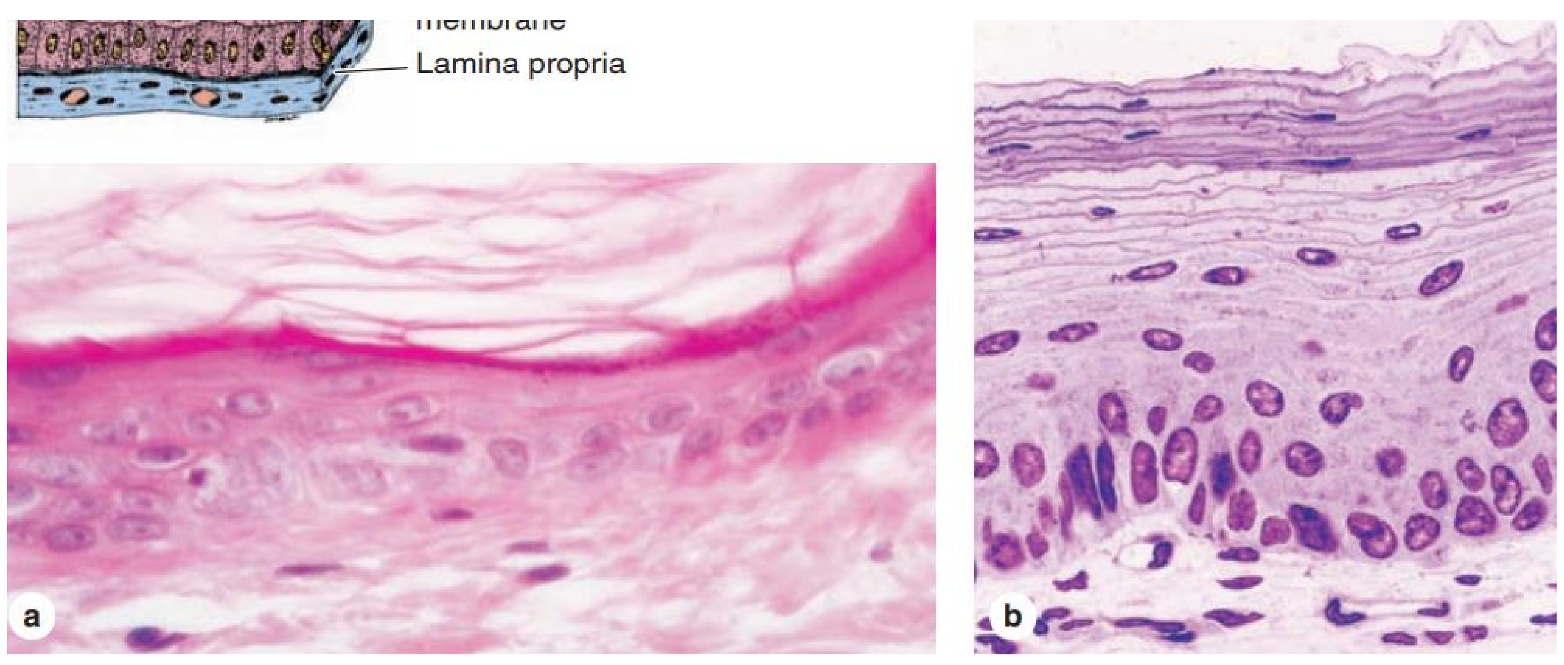
- Contain two or more layers of cells
- Regenerate from below
- Major role is protection
- Are named according to the shape of cells at apical layer

Stratified Squamous Epithelium

The cells closer to the underlying connective tissue are usually cuboidal or low columnar
Thickest epithelial tissue- adapted for protection

Specific types

- Keratinized- contain the protective protein keratin (Surface cells are dead and full of keratin)
- Non-keratinized - forms moist lining of body openings



These cells become more irregular in shape and flatten as they accumulate keratin in the process of keratinization and are moved progressively closer to the skin surface, where they become thin, metabolically inactive packets (squames) of keratin lacking nuclei

Function
Protection against easy invason of underlying tissue by microorganisms and protection against water loss

Location

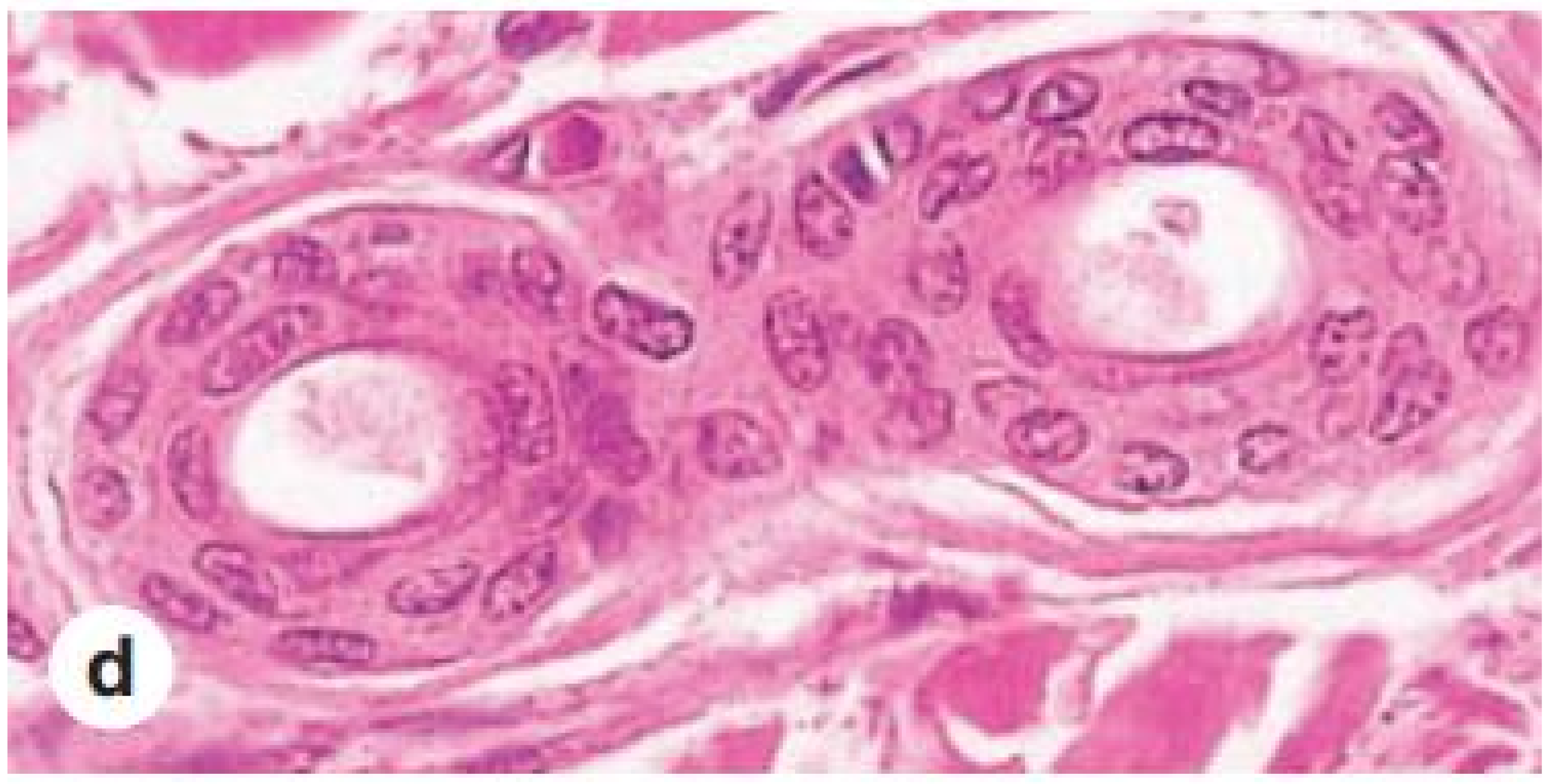
- Stratified squamous keratinized epithelium found mainly in the epidermis of skin, where it helps prevent dehydration from the tissue.

- Stratified squamous nonkeratinized epithelium lines wet cavities (eg, mouth, esophagus, and vagina, covering cornea) where water loss is not a problem. Here the flattened cells of the surface layer contain much less keratin, retaining their nuclei and metabolic function

Stratified Cuboidal Epithelium

Provides a lining more robust than that of a simple epithelium

Location
Excretory ducts of salivary
Sweat gland ducts
Large ducts of exocrine glands
Anorectal junction

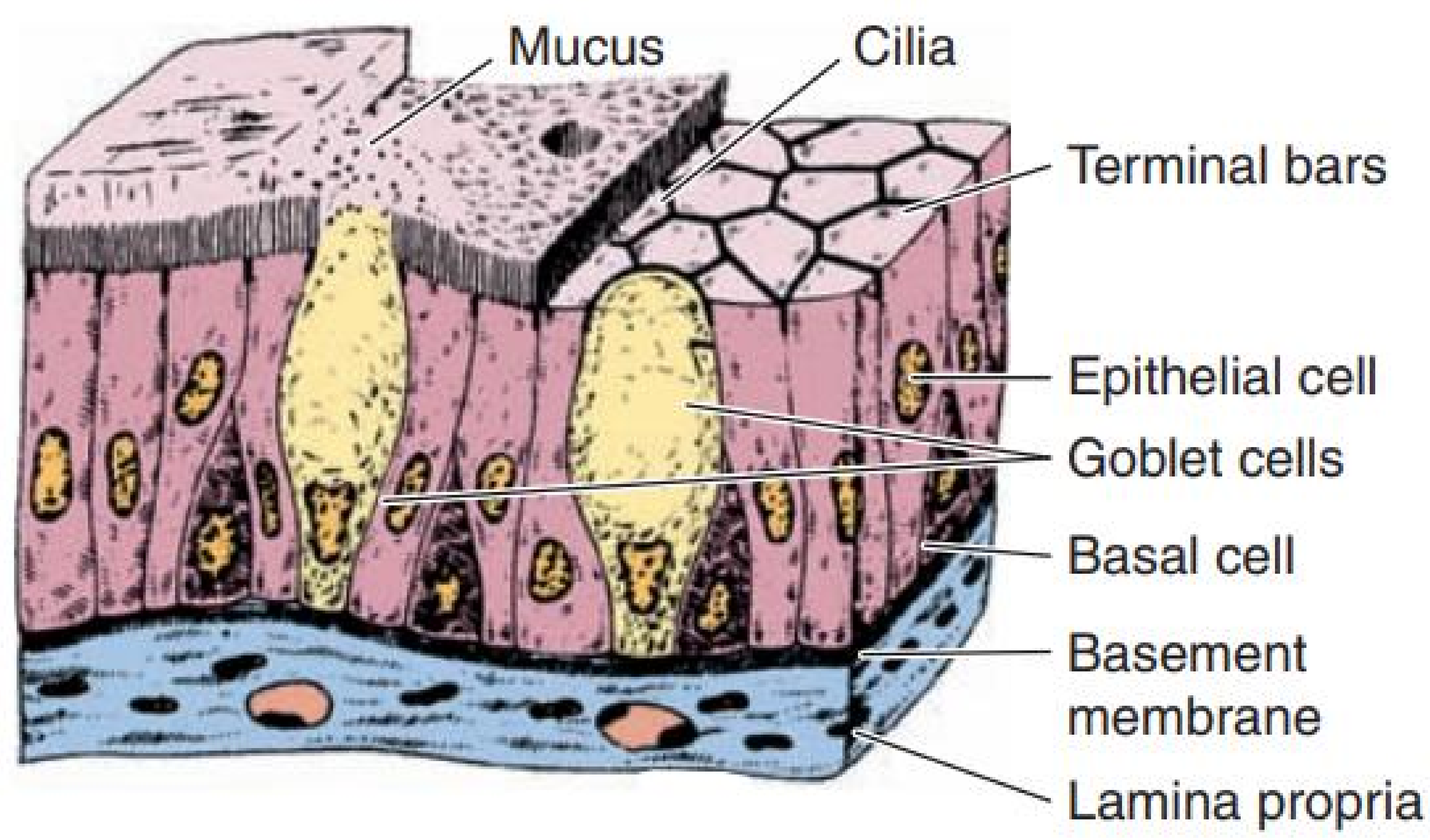


Stratified Columnar Epithelium

found in the conjunctiva lining the eyelids, where it is both protective and mucus secreting.

- Large ducts of exocrine glands
- Anorectal junction

Pseudostratified Epithelia



tall, irregular cells all are attached to the basement membrane but their nuclei are at different levels and not all cells extend to the free surface, giving a stratified appearance

Function
Secretion and propulsion of mucus by cilia

Location
■ Non-ciliated type
Ductus deferens
Efferent ductules of epididymis

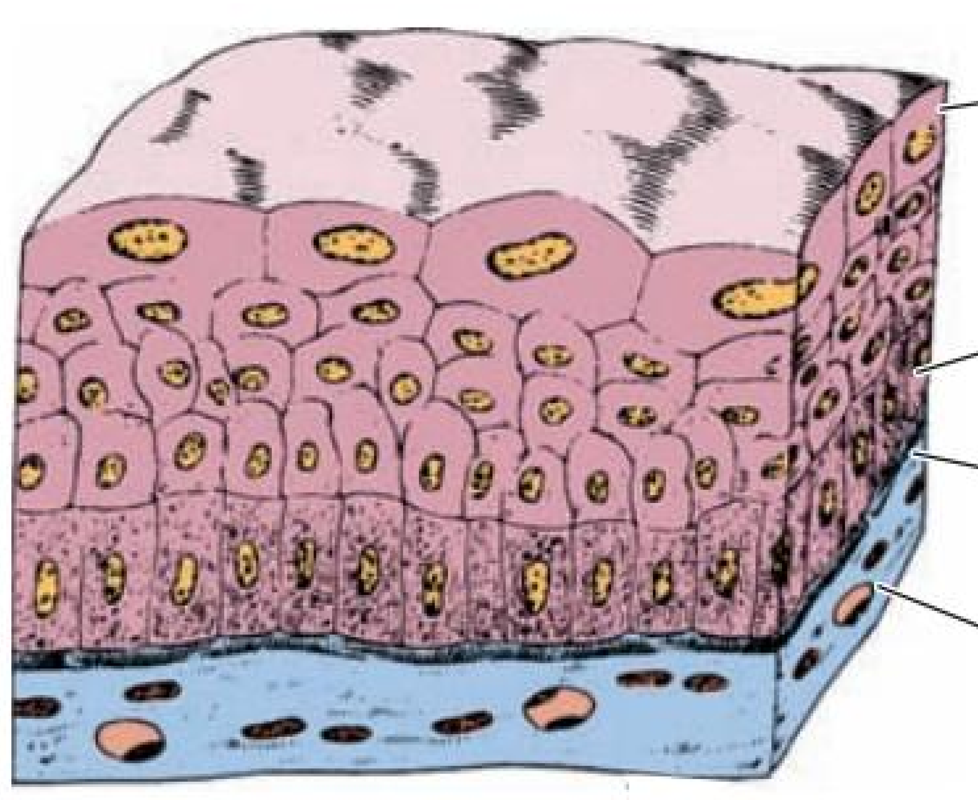
■ Ciliated variety
Trachea and bronchial tree

Transitional Epithelium
Urothelium
- lines much of the urinary tract, extending from the kidneys to the proximal part of the urethra
- characterized by a superficial layer of large, dome-like cells sometimes called umbrella cells

Urothelium is stratified and lines much of the urinary tract. The superficial cells are rounded or dome-shaped, and have specialized membrane features enabling them to withstand the hypertonic effects of urine and protect underlying cells from this toxic solution. Cells of this epithelium are also able to adjust their relationships with one another and undergo a transition in their appearance as the urinary bladder fills and the wall is distended.

Function
- Stretches and permits distension of urinary bladder
- specialized to protect underlying tissues from the hypertonic and potentially cytotoxic effects of urine
- unique morphological features of the cells allow distension of transitional epithelium as the urinary bladder fills

Location
Renal calyces
Ureters
Bladder
Proximal part of urethra



Grandular Epithelia
Glands
Epithelial cells that function mainly to produce and secrete various macromolecules

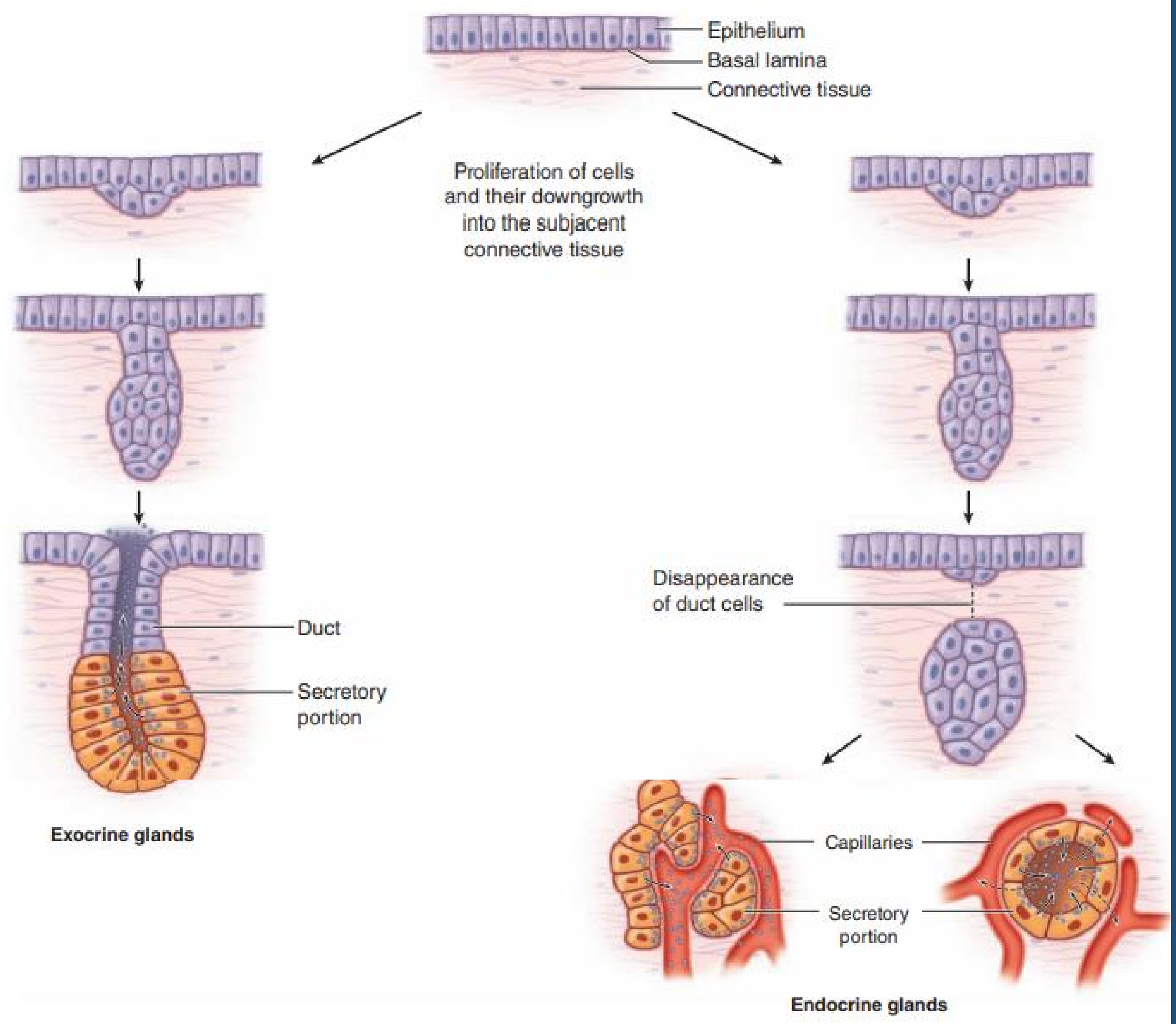
Products to be secreted are generally stored in the cells within small membrane-bound vesicles called secretory granules.

Secretory epithelial cells may synthesize, store, and release:
- proteins (eg, in the pancreas)
- lipids (eg, adrenal, sebaceous glands)
- complexes of carbohydrates
- proteins (eg, salivary glands)

The cells of some glands (eg, sweat glands) have little synthetic activity and secrete mostly water and electrolytes (ions) transferred from the blood.

Exocrine glands
- Secrete their products onto a surface directly or through epithelial ducts or tubes that are connected to a surface

Endocrine glands
- Lack a duct system
- Secrete their products into the connective tissue, from which they enter the bloodstream to reach their target cells
- Main secretion = hormones



During fetal development epithelial cells proliferate and penetrate the underlying connective tissue. These cells may—or may not—maintain a connection with the surface epithelium.

The connection is maintained to form a duct in exocrine glands; it is lost as endocrine glands develop.

Exocrine glands secrete substances to specific organs via duct systems. Endocrine glands *produce hormones and are always rich in capillaries. Hormones are released outside the cells and picked up by these blood vessels for distribution throughout the body, where specific target cells are identified by receptors for the hormones.*

Endocrine glands can have secretory cells arranged as irregular cords (left) or as rounded follicles (right) with lumens for temporary storage of the secretory product.

UNICELULLAR EXOCRINE GLANS

The Goblet Cell

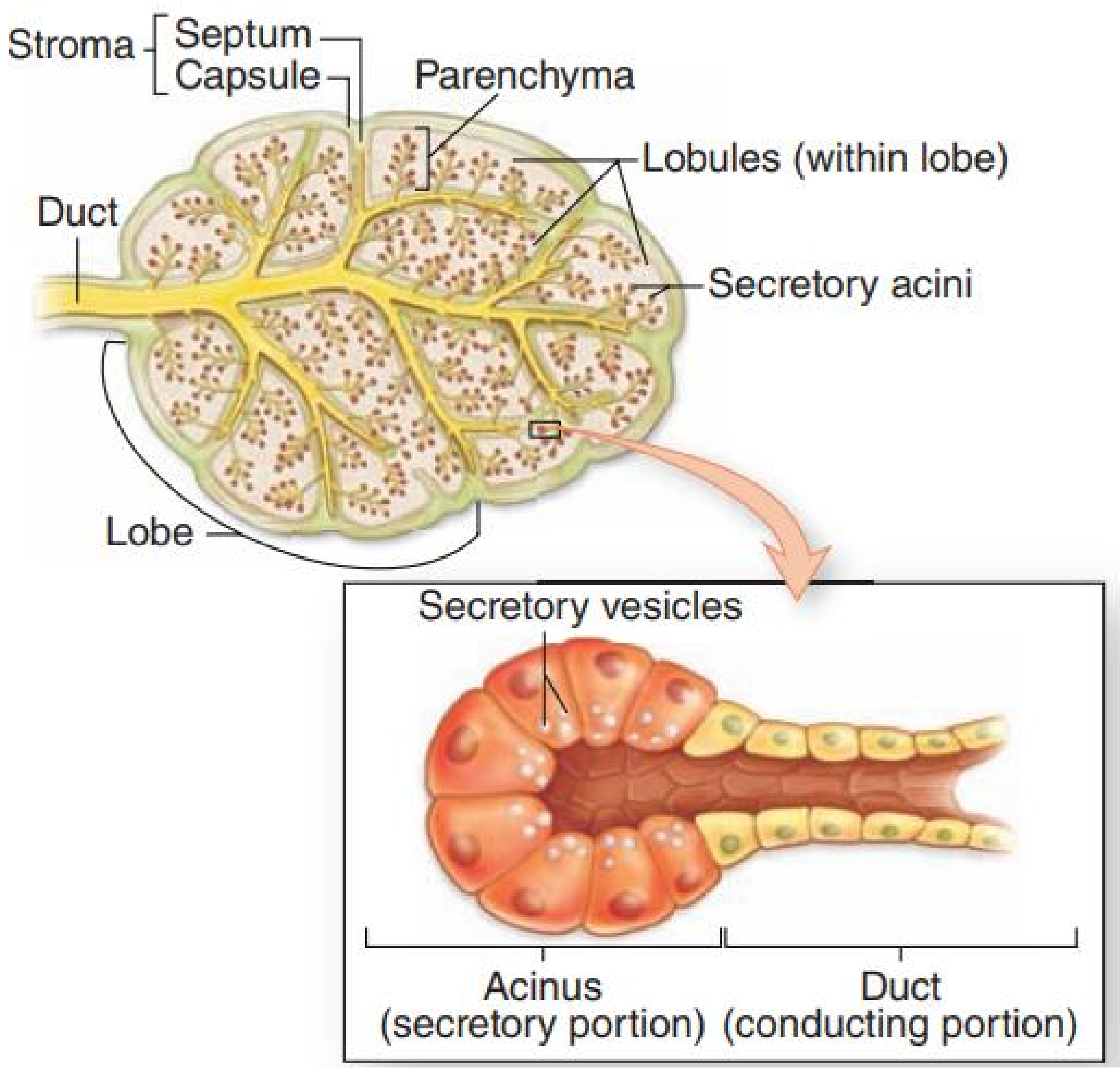
- Produce mucin (highly glycosylated protein)
- Mucin + water = mucus
- abundant in the lining of the small intestine and respiratory tract, which secretes lubricating mucus that aids the function of these organs
- Protects and lubricates many internal body surfaces

MULTICELLULAR EXOCRINE GLANS

Epithelia of exocrine glands are organized as a continuous system composed of many small secretory portions and ducts that transport the secretion out of the gland.

In both exocrine and endocrine glands the secretory units are supported by a stroma of connective tissue.

A layer of connective tissue also encloses the gland as its capsule, surrounds the larger ducts, and forms partitions or septa that separate the gland into lobules, each containing secretory units connected to a small part of the duct system.



- Septum and capsule forms the stroma (like a skeleton)
- Functional unit = parenchyma

Mode of Secretion

Merocrine secretion

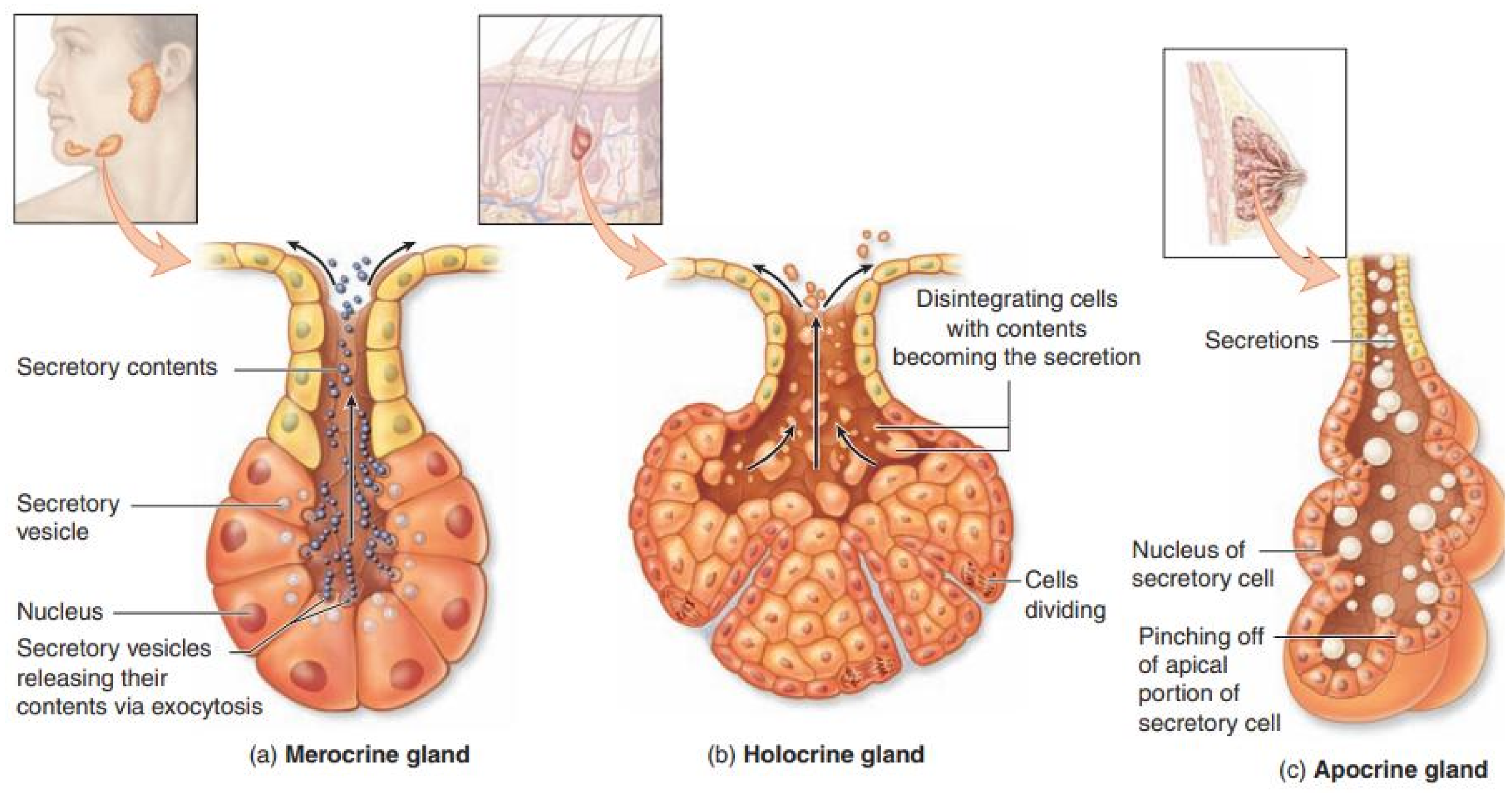
- This is the most common method of protein secretion
- involves typical exocytosis of proteins or glycoproteins from membrane-bound vesicles (salivary glands)

Holocrine secretion

- Involves disintegrating cells with contents becoming the secretion
- Entire cell is being destroyed during secretion (sebaceous glands)

Apocrine secretion

- Pinching off of apical portion of secretory cell
- Mammary glands



Three basic types of secretion are used by cells of exocrine glands, depending on what substance is being secreted.

(a) Merocrine secretion releases products, usually containing proteins, by means of exocytosis at the apical end of the secretory cells. Most exocrine glands are merocrine.

(b) Holocrine secretion is produced by the disintegration of the secretory cells themselves as they complete their terminal differentiation, which involves becoming filled with product. Sebaceous glands of hair follicles are the best examples of holocrine glands.

(c) Apocrine secretion involves loss of membrane-enclosed apical cytoplasm, usually containing one or more lipid droplets. Apocrine secretion, along with merocrine secretion, is seen in mammary glands.

Exocrine glands classified bybtypes of secretions from exocrine glands

Serous
Mostly watery but also contains some enzymes
Ex. Parotid glands, pancreas

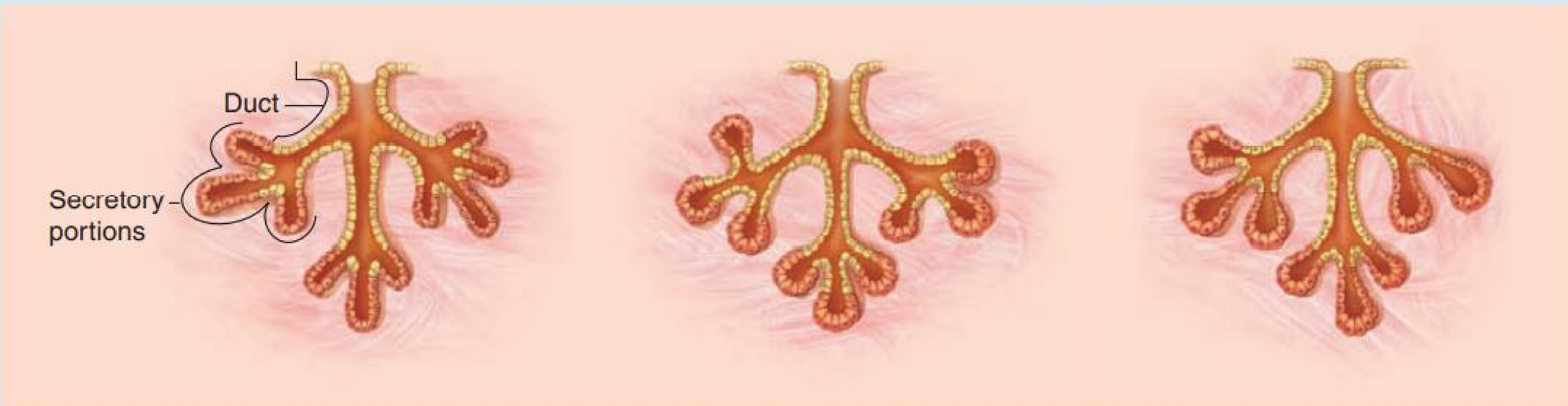
Mucus
Viscous and slimy
Ex. Sublingual glands, goblet cells

Mixes
Serous & mucus combined (submandibular gland)

SIMPLE Glands **(Ducts Do Not Branch)**

Class	Simple Tubular	Branched Tubular	Coiled Tubular	Acinar (or Alveolar)	Branched Acinar
Features	Elongated secretory portion; duct usually short or absent	Several long secretory parts joining to drain into 1 duct	Secretory portion is very long and coiled	Rounded, saclike secretory portion	Multiple saclike secretory parts entering the same duct
Examples	Mucous glands of colon; intestinal glands or crypts (of Lieberkühn)	Glands in the uterus and stomach	Sweat glands	Small mucous glands along the urethra	Sebaceous glands of the skin

COMPOUND Glands **(Ducts from Several Secretory Units Converge into Larger Ducts)**



Class	Tubular	Acinar (Alveolar)	Tubuloacinar
Features	Several *elongated*, coiled secretory units and their ducts converge to form larger ducts	Several *saclike* secretory units with small ducts converge at a larger duct	Ducts of both tubular and acinar secretory units converge at larger ducts
Examples	Submucosal mucous glands (of Brunner) in the duodenum	Exocrine pancreas	Salivary glands

Epithelial Tissue SUMMARY OF KEY POINTS

- An **epithelium** is a tissue in which cells are bound tightly together structurally and functionally to form a sheetlike or tubular structure with little extracellular material between the cells.
- Cells in epithelia each have an **apical side** facing the sheet's free surface and a **basal side** facing a basement membrane and underlying connective tissue.
- Epithelia are often specialized for absorption or **transcytosis**, pinocytosis of material at the apical side and exocytosis at the basolateral side (or vice versa).
- Cells of most epithelia exhibit **continuous renewal**, with the locations of stem cells and rates of cell turnover variable in various specialized epithelia.

Basement Membrane

- The **basement membrane** of all epithelia is a thin extracellular layer of specialized proteins, usually having two parts: a basal lamina and a more fibrous reticular lamina.
- The **basal lamina** is a thin meshwork of type IV collagen and laminin produced by the epithelial cells.
- The **reticular lamina** contains type III collagen and anchoring fibrils of VII collagen, all secreted by cells of the immediately adjacent connective tissue.
- Together, these components **attach** epithelia to connective tissue, regulate (**filter**) substances passing from connective tissue into epithelia, provide a guide or **scaffold** during tissue regeneration after injury, and **compartmentalize** epithelial cells from other tissues.

Intercellular Junctions

- Intercellular junctions are well developed in epithelia and consist of three major types, with different functions.
- **Tight or occluding junctions** are formed by interacting transmembrane proteins such as **claudin** and **occludin**; linear arrangements of these linked proteins surround the apical ends of the cells and **prevent paracellular passage** of substances (between the cells.)
- **Adherent or anchoring junctions**, formed by interacting proteins of the **cadherin** family, are points of strong **attachment** holding together cells of the epithelium.
- Adherent junctions may form **zonula adherens** that encircle epithelial cells just below their tight junctions or scattered, spot-like attachment sites called **desmosomes** or **maculae adherens**, both of which are attached to cytoplasmic **keratins**.
- **Hemidesmosomes** composed of transmembrane **integrins** attach cells to proteins of the basal lamina.
- **Gap or communicating junctions** are points of cell contact where both plasma membranes have numerous hexameric complexes of transmembrane **connexons**, each forming a channel allowing passage of small molecules from one cell to the other.

Apical Structures of Epithelial Cells

- **Microvilli** are small membrane projections with cores of **actin filaments** that generally function to increase epithelial cells' apical surface area for **absorption**.
- **Stereocilia** are long microvilli with specialized mechanosensory function in cells of the inner ear and for absorption in tissues of the male reproductive tract.
- **Cilia** are larger projecting structures with a well-organized core of **microtubules** (in a 9 + 2 arrangement called the **axoneme**) in which restricted, dynein-based sliding of microtubules causes ciliary movement that propel material along an epithelial surface.

Morphological Types of Epithelia

- An epithelium in which the basement membrane has one cell layer is **simple**; the cells of different simple epithelia range widely in height, from very thin or **squamous**, to roughly **cuboidal**, to very tall or **columnar**.
- Epithelia with two or more layers of cells are **stratified** and almost all such epithelia are stratified squamous, in which the outer cell layers are thin and flattened.
- Cells of stratified squamous epithelia move gradually from the basal to the surface layers, changing shape and becoming filled with **keratin** intermediate filaments.
- Stratified squamous epithelia such as the epidermis cover the body surface, **protecting** underlying tissues from excess water loss (dehydration) and microbial invasion.
- **Pseudostratified epithelia** are thick and appear to have several cell layers; all cells attach to the basal lamina but not all extend to the free epithelial surface.

- **Transitional epithelium or urothelium**, found only in the lining of the urinary system, is stratified, with large rounded surface cells protective against urine.

Epithelial Secretion/Glands

- The major function in many epithelial cells is synthesis and secretion of specialized products; organs composed primarily of such epithelia are called **glands**.
- **Exocrine glands** have epithelial ducts carrying secretions to specific sites; the ducts of **simple glands** are unbranched and those of **compound glands** are branched.
- The secretory portions of exocrine glands may form round, saclike **acini** (also called **alveoli**) or elongated **tubules**; both types of secretory units may themselves branch.
- **Endocrine glands** lack ducts; secreted substances are hormones carried throughout the body by the interstitial fluid and blood, with specificity produced by the hormone receptors of target cells.
- Glands have three basic secretory mechanisms: **merocrine**, which uses exocytosis; **holocrine**, in which terminally differentiated cells filled with lipid product are released; and **apocrine**, in which apical, product-filled areas of cells are extruded.
- Exocrine glands producing mucus, or similar individual cells called **goblet cells**, are called **mucous glands**; oligosaccharide components of mucus stain poorly with routine dyes but stain well with PAS stain.
- Exocrine glands producing largely enzymes (proteins) are called **serous glands** and stain darkly with H&E due to the cells' content of RER and secretory granules.

FUNCTION

- Acts as the binding tissue of the other 3 types
- of tissue
- maintain the form of organs throughout the body
- provide a matrix that supports and physically connects other tissues and cells together in organs
- interstitial fluid of connective tissue gives metabolic support to cells as the medium for diffusion of nutrients and waste products

Connective tissue place a more varied and wider range of functions as compared to your epithelial tissue.

Unlike the other tissue types (epithelium, muscle, and nerve), which consist mainly of cells, the major constituent of connective tissue is the extracellular matrix (ECM) .

Extracellular matrix

- Major constituent of cells
- consist of different combinations of protein fibers (such as collagens and elastic fibers) and ground substance

Ground substance

a complex of anionic, hydrophilic proteoglycans, glycosaminoglycans (GAGs), and multiadhesive glycoproteins (laminin, fibronectin, and others)

Connective tissues originate from embryonic mesenchyme

Mesenchyme

a tissue developing mainly from the middle layer of the embryo, the mesoderm
consists largely of viscous ground substance with few collagen fibers

Mesenchymal Cells

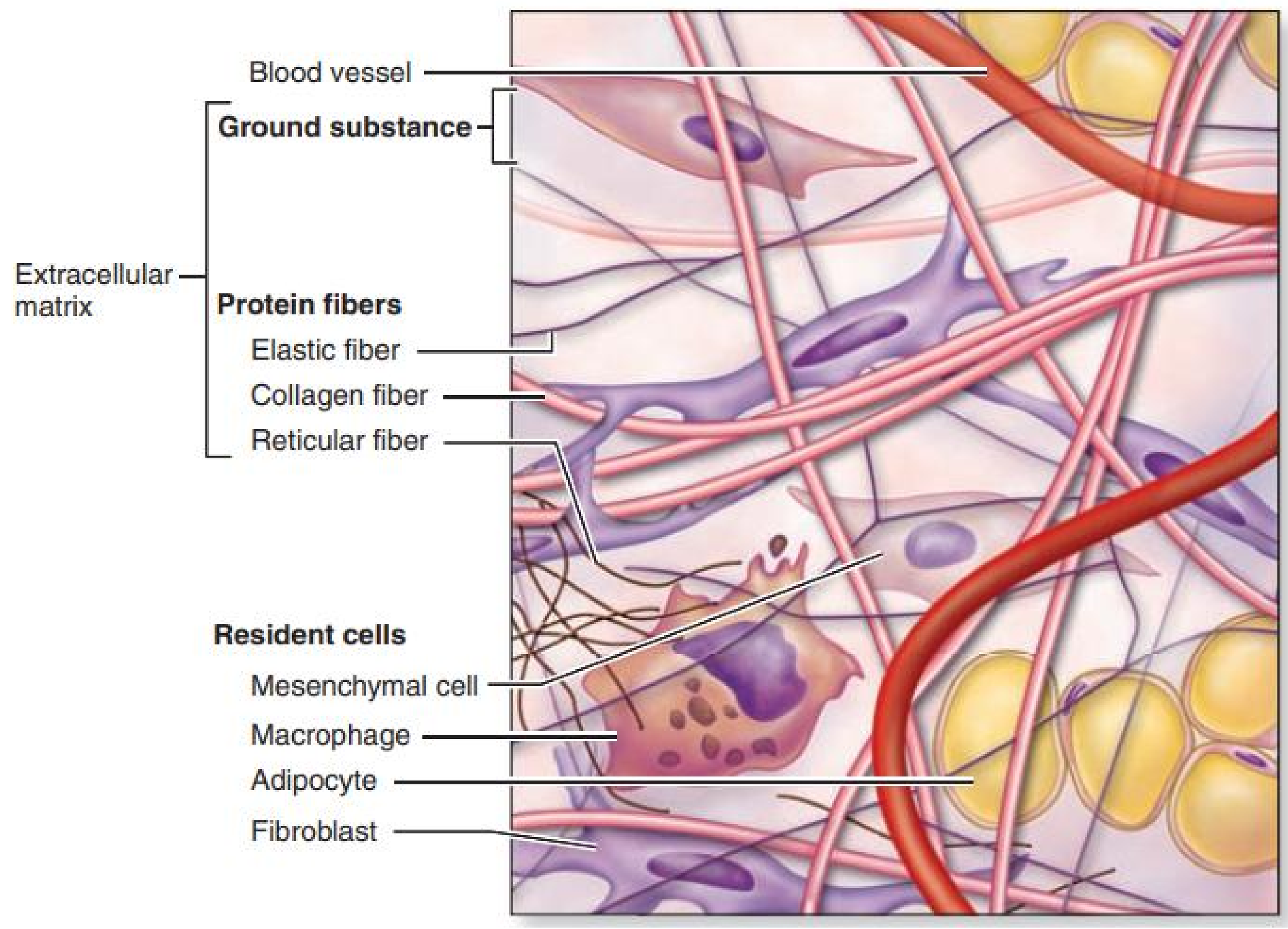
- undifferentiated and have large nuclei, with prominent nucleoli and fi ne chromatin
- "spindle-shaped," with their scant cytoplasm extended as two or more thin cytoplasmic processes

Mesodermal cells migrate from their site of origin in the embryo, surrounding and penetrating developing organs. In addition to producing all types of connective tissue proper and the specialized connective tissues bone and cartilage,the embryonic mesenchyme includes stem cells for other tissues such as blood, the vascular endothelium, and muscle.

CELLS OF CONNECTIVE TISSUE

Fibroblasts and certain other cells are typically present in connective tissue proper

Fibroblasts originate locally from mesenchymal cells and are permanent residents of connective tissue; other cells found here, such as macrophages , plasma cells , and mast cells , originate from hematopoietic stem cells in bone marrow, circulate in the blood, and then move into connective tissue where they function.



Connective tissue is composed of fibroblasts and other cells and an extracellular matrix (ECM) of various protein fibers, all of which are surrounded by watery ground substance. In all types of connective tissue the extracellular volume exceeds that of the cells.

Resident Cell Population

Relatively stable; they typically exhibit little movement and can be regarded as permanent residents of the tissue

Wandering Cell Population (transient cell population)

Consists primarily of cells that have migrated into the tissue from the blood in responses to specific stimuli

Example: macrophages; white blood cell

White blood cells (leukocytes) are transient cells of most connective tissues; they also originate in the bone marrow and move to the connective tissue where they function for a few days, then die by apoptosis.

FIBROBLAST

- Most common cells in connective tissue
- produce and maintain most of the tissue's extracellular components

- synthesize and secrete collagen (the most abundant protein of the body) and elastin, which form large fibers, as well as the GAGs, proteoglycans, & multiadhesive glycoproteins that **comprise the ground substance**

Two Classifications of Fibroblast

Active Fibroblast

- " fibroblast "
- more abundant and irregularly branched cytoplasm
- nucleus is large, ovoid, euchromatic, and has a prominent nucleolus
- cytoplasm has much rough endoplasmic reticulum (RER) and a well-developed Golgi apparatus

Quiescent Fibroblast

- "fibrocyte"
- smaller than the active fibroblast
- usually spindle-shaped with fewer processes and much less RER, and contains a darker, more heterochromatic nucleus

Myoblast

- Fibroblast involved in wound healing
- An elongated, spindly connective tissue cell not readily identifiable in routine H&E preparations
- have a well-developed contractile function and are enriched with a form of actin also found in smooth muscle cells

ADIPOCYTES

- Commonly known as the "fat cell"
- specialized for cytoplasmic storage of lipid as neutral fats
- production of heat
- serve to cushion and insulate the skin and other organs
- When they accumulate in large numbers, they are called **adipose tissue**

MACROPHAGES & THE MONONUCLEAR PHAGOCYTE SYSTEM

- characterized by their well-developed phagocytic ability and specialize in turnover of protein fibers and removal of dead cells, tissue debris, or other particulate material
- measures between 10 and 30 µm in diameter and has an eccentrically located, oval or kidney-shaped nucleus

Histiocytes

Macrophages found in connective tissues

Kupffer cells

Macrophages in the liver

Microglia

Macrophages in the nervous tissue

- When macrophages are stimulated (by injection of foreign substances or by infection), they change their morphologic characteristics and properties, becoming **activated macrophages**
- also secretory cells producing an array of substances, including various enzymes for ECM breakdown and various growth factors or cytokines that help regulate immune cells and reparative functions
- When adequately stimulated, macrophages may increase in size and fuse to form **multinuclear giant cells**, usually found only pathologic conditions (denotes chronic condition)
- generally have a well-developed Golgi apparatus and many lysosomes
- Can be distinguished by the presence of an indented or kidney-shaped nucleus.

Cells of Mononuclear Phagocytic System	
Name of cell	Location
Macrophages (histiocyte)	Connective tissue
Perisinusoidal (Kupffer cells)	Liver
Alveolar macrophage	Lungs
Fetal placenta antigen-presenting cell (Hofbauer cell)	Placenta
Macrophages	Spleen, lymph nodes. Bone marrow, and thymus
Pleural and peritoneal macrophage	Serous cavities
Osteoclast	Bone
Microglia	Central nervous system
Langerhan's cell	Epidermis
Fibroblast-derived macrophage	Lamina propria of intestine, endometrium of uterus
Dendritic cell	Lymph nodes, spleen

TABLE 5–2	Distribution and main functions of the cells of the mononuclear phagocyte system.	
Cell Type	**Major Locations**	**Main Function**
Monocyte	Blood	Precursor of macrophages
Macrophage	Connective tissue, lymphoid organs, lungs, bone marrow, pleural and peritoneal cavities	Production of cytokines, chemotactic factors, and several other molecules that participate in inflammation (defense), antigen processing, and presentation
Kupffer cell	Liver (perisinusoidal)	Same as macrophages
Microglial cell	Central nervous system	Same as macrophages
Langerhans cell	Epidermis of skin	Antigen processing and presentation
Dendritic cell	Lymph nodes, spleen	Antigen processing and presentation
Osteoclast (from fusion of several macrophages)	Bone	Localized digestion of bone matrix
Multinuclear giant cell (several fused macrophages)	In connective tissue under various pathological conditions	Segregation and digestion of foreign bodies

MAST CELLS

- oval or irregularly shaped connective tissue cells, between 7 and 20 µm in diameter, whose cytoplasm is filled with basophilic secretory granules
- Because of their high content of acidic radicals in their sulfated GAGs, mast cell granules display metachromasia, which means that they can change the color of some basic dyes (eg, toluidine blue) from blue to purple or red
- roles in the local inflammatory response, innate immunity, and tissue repair

Important molecules released from these cells' secretory granules includes the following:

✧ Heparin
a sulfated GAG that acts locally as an anticoagulant

✧ Histamine
promotes increased vascular permeability and smooth muscle contraction (broncho-constrictor)

✧ Serine proteases
activate various mediators of inflammation

✧ Eosinophil and neutrophil chemotactic factors
attract those leukocytes; signal other white blood cells

✧ Cytokines
polypeptides directing activities of leukocytes and other cells of the immune system

✧ Phospholipid
precursors for conversion to prostaglandins, leukotrienes, and other important lipid mediators of the inflammatory response

Perivascular mast cells
numerous near small blood vessels in skin and mesenteries

Mucosal mast cells
lines digestive and respiratory tracts

These major locations suggest that mast cells place themselves strategically to function as sentinels detecting invasion by microorganisms.

Mast cells originate from progenitor cells in the bone marrow. The progenitor cells circulate in the blood, cross the wall of venules and capillaries, and penetrate connective tissues, where they differentiate.

Release of certain chemical mediators stored in mast cells also promotes the allergic reactions, also known as immediate hypersensitivity reactions because they occur within a few minutes after the appearance of an antigen in an individual previously sensitized to the same or a very similar antigen.

Mast cell secretion is triggered by reexposure to certain antigens and allergens. Molecules of IgE antibody produced in an initial response to an allergen such as pollen or bee venom are bound to surface receptors for IgE (**1**), of which 300,000 are present per mast cell.

When a second exposure to the allergen occurs, IgE molecules bind this antigen and a few IgE receptors very rapidly become cross-linked (**2**). This activates adenylate cyclase, leading to phosphorylation of specific proteins (**3**), entry of Ca^{2+} and rapid exocytosis of some granules (**4**). In addition, phospholipases act on specific membrane phospholipids, leading to production and release of leukotrienes (**5**).

The components released from granules, as well as the leukotrienes, are immediately active in the local microenvironment and promote a variety of controlled local reactions that together normally comprise part of the inflammatory process called the **immediate hypersensitivity reaction**. "ECF-A" is the eosinophil chemotactic factor of anaphylaxis.

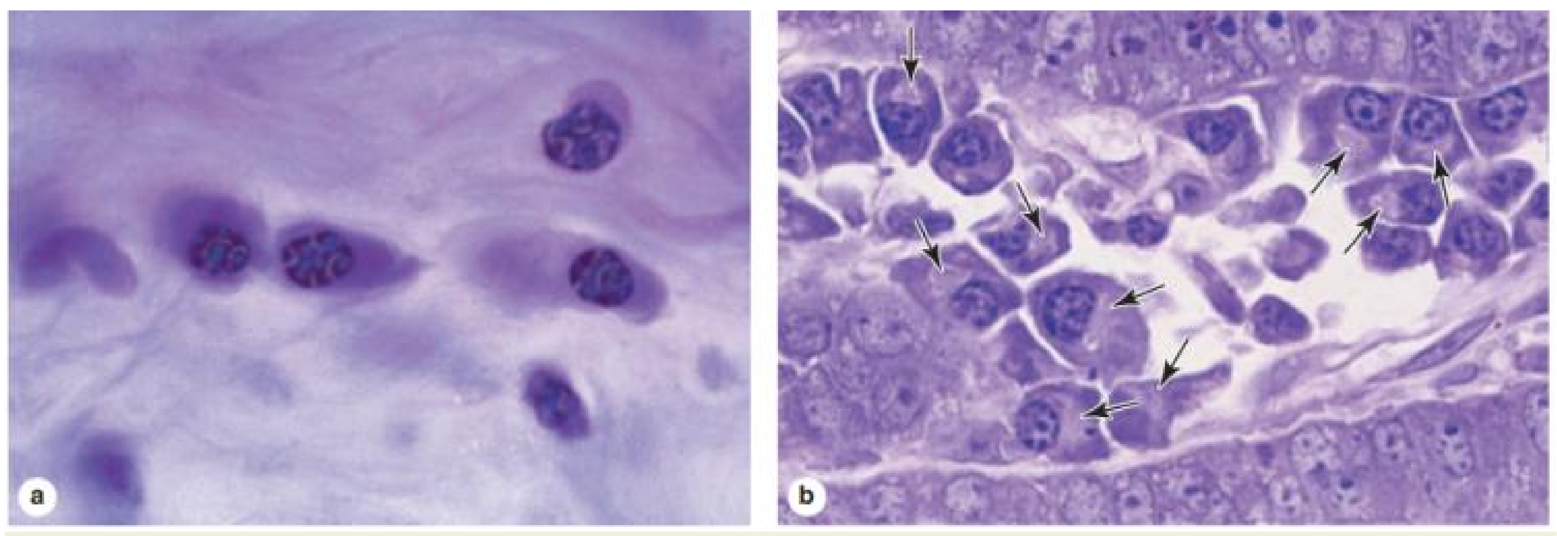
PLASMA CELLS

- lymphocyte–derived, antibody-producing cells
- large, ovoid cells have basophilic cytoplasm due to their richness in RER
- contain compact, peripheral regions of heterochromatin alternating with lighter areas of euchromatin, a configuration that can give the nucleus of a plasma cell the appearance of a clock face

There are at least a few plasma cells in most connective tissues. Their average lifespan is only 10-20 days.

>> MEDICAL APPLICATION

Plasma cells are derived from B lymphocytes and are responsible for the synthesis of immunoglobulin antibodies. Each antibody is specific for the one antigen that stimulated the clone of B cells and reacts only with that antigen or molecules resembling it (see Chapter 14). The results of the antibody-antigen reaction are variable, but they usually neutralize harmful effects caused by antigens. An antigen that is a toxin (eg, tetanus, diphtheria) may lose its capacity to do harm when it binds to its specific antibody. Bound antigen-antibody complexes are quickly removed from tissues by phagocytosis.



Antibody-secreting plasma cells are present in variable numbers in the connective tissue of many organs.

(a) Plasma cells are large, ovoid cells, with basophilic cytoplasm. The round nuclei frequently show peripheral clumps of heterochromatin, giving the structure a "clock-face" appearance. X640. H&E.

(b) Plasma are often more abundant in infected tissues, as in the inflamed lamina propria shown here. A large pale Golgi apparatus (arrows) at a juxtanuclear site in each cell is actively involved in the terminal glycosylation of the antibodies (glycoproteins). Plasma cells leave their sites of origin in lymphoid tissues, move to connective tissue, and produce antibodies that mediate immunity. X400 PT.

LEUKOCYTES

- make up a population of wandering cells in connective tissue
- leave blood by migrating between the endothelial cells lining venules to enter connective tissue by a process called diapedesis

This process increases greatly during inflammation, which is a vascular and cellular defensive response to injury or foreign substances, including pathogenic bacteria or irritating chemical substances.

Most leukocytes function for a few hours or days in connective tissue and then die.

>> MEDICAL APPLICATION

Increased vascular permeability is caused by the action of vasoactive substances such as histamine released from mast cells during **inflammation**. Increased blood flow and vascular permeability produce local swelling (edema), redness, and heat. **Pain** is due mainly to the action of the chemical mediators on nerve endings. All these activities help protect and repair the inflamed tissue. **Chemotaxis** (Gr. *chemeia*, alchemy + *taxis*, orderly arrangement), the phenomenon by which specific cell types are attracted by specific molecules, draws much larger numbers of leukocytes into inflamed tissues.

FIBERS

- elongated structures formed from proteins that polymerize after secretion from fibroblasts
- three main types of fibers include collagen, reticular, and elastic fibers

Collagen and reticular fibers are both formed by proteins of the collagen family, and elastic fibers are composed mainly of the protein ***elastin****.*

These fibers are distributed unequally among the different types of connective tissue, with the predominant fiber type usually responsible for conferring specific tissue properties

COLLAGEN

- Most abundant protein in the human body, representing 30% of its dry weight
- a key element of all connective tissues, as well as epithelial basement membranes and the external laminae of muscle and nerve cells
- extremely strong and resistant to normal shearing and tearing forces

>> MEDICAL APPLICATION

A **keloid** is a local swelling caused by abnormally large amounts of collagen that form in scars of the skin. Keloids occur most often in individuals of African descent and can be a troublesome clinical problem to manage. Not only can they be disfiguring, but excision is almost always followed by recurrence.

Important types	Location
I	Connective tissue of skin, bone, tendon, ligaments, dentin, sclera, fascia, and tension, and stretch organ capsules
II	Cartilage (hyaline and elastic), notochord, and intervertebral disk
III	Loose connective tissue and organs (uterus, liver, spleen, kidney, lung, etc.); smooth mucle; fibers, endoneurium; blood vessels & fetal skin
IV	Basal laminae of epithelia, kidney glomeruli, and lens capsule
V	Distributed uniformly throughout connective tissue stroma, may be related to reticular network
XI	Cartilage

Collagen	Types	Function/ Location
Fibrillar collagen	I, II, III, V, and XI	Forming structures such as tendons, organ capsules, and dermis
Fibril- associated collagens w/ interrupted triple helixes (FACITs)		
Hexagonal network-forming collagen	VIII and X	
Transmembrane collagen	XIII	Found in the focal adhesions
	XVII	Found w/in the hemidesmosomes
	XXIII	Found in metastatic cells
	XXV	A brain-specific collagen
Multiplexins	XV and XVIII	Reside in the basement membrane zones Collagen w/ multiple triple-helix domains an interruptions
Basement membrane forming collagen	IV	Responsible for the collagen suprastructure in the basement membrane of epithelial cells
	VI	Collagen forms beaded filaments
	VII	Forms anchoring fibrils that attach the basement membrane to the ECM

Collagen type I, the most abundant and widely distributed collagen, forms large, eosinophilic bundles usually called collagen fibers.

COLLAGEN

- Bundles of collagen appear white
- Birefringent under the polarizing microscope
- To be renewed, the collagen must first be degraded.

Degradation is initiated by specific enzymes called collagenases, which are members of an enzyme class called matrix metalloproteinases (MMPs)

Collagen turnover and renewal in normal connective tissue is generally a very slow but ongoing process. In some organs, such as tendons and ligaments, the collagen is very stable, whereas in others, as in the periodontal ligament surrounding teeth, the collagen turnover rate is high.

Collagenases clip collagen fibrils or sheets in such a way that they are then susceptible to further degradation by nonspecific proteases.

Various MMPs are secreted by macrophages and play an important role in remodeling the ECM during tissue repair.

RETICULAR FIBERS

- Provide a supporting franework for the celullar constituents of various tissues and organs
- consist mainly of collagen type III
- Found in delicate connective tissue of many organs
- characteristically stained black by impregnation with silver salts and are termed argyrophilic

This collagen forms an extensive network (reticulum) of extremely thin (diameter 0.5-2 μm), heavily glycosylated fibers

Reticular fibers are seldom visible in hematoxylin and eosin (H&E) preparations but are characteristically stained black by impregnation with silver salts and are termed argyrophilic

- occur in the reticular lamina of basement membranes and typically also surround adipocytes, smooth muscle and nerve fibers, and small blood vessels
- serve as the supportive stroma for the parenchymal secretory cells and rich microvasculature of the liver and endocrine glands
- also characterize the stroma of hemopoietic tissue (bone marrow) and some lymphoid organs (eg, spleen and lymph nodes) where they support rapidly changing populations of proliferating cells and phagocytic cells

ELASTIC FIBERS

- Allow tissues to respond to stretch and distension
- thinner than the type I collagen fibers and form sparse networks interspersed with collagen bundles in many organs, particularly those subject to much bending or stretching
- have physical properties similar to those of rubber, allowing tissues to be stretched or distended and return to their original shape

Elastic lamellae

Fenestrated sheets found in the wall of large blood vessels, especially arteries

- not strongly acidophilic and stain poorly with H&E; they are stained more darkly than collagen in other stains such as orcein and aldehyde fuchsin

- Composed of two structural components :

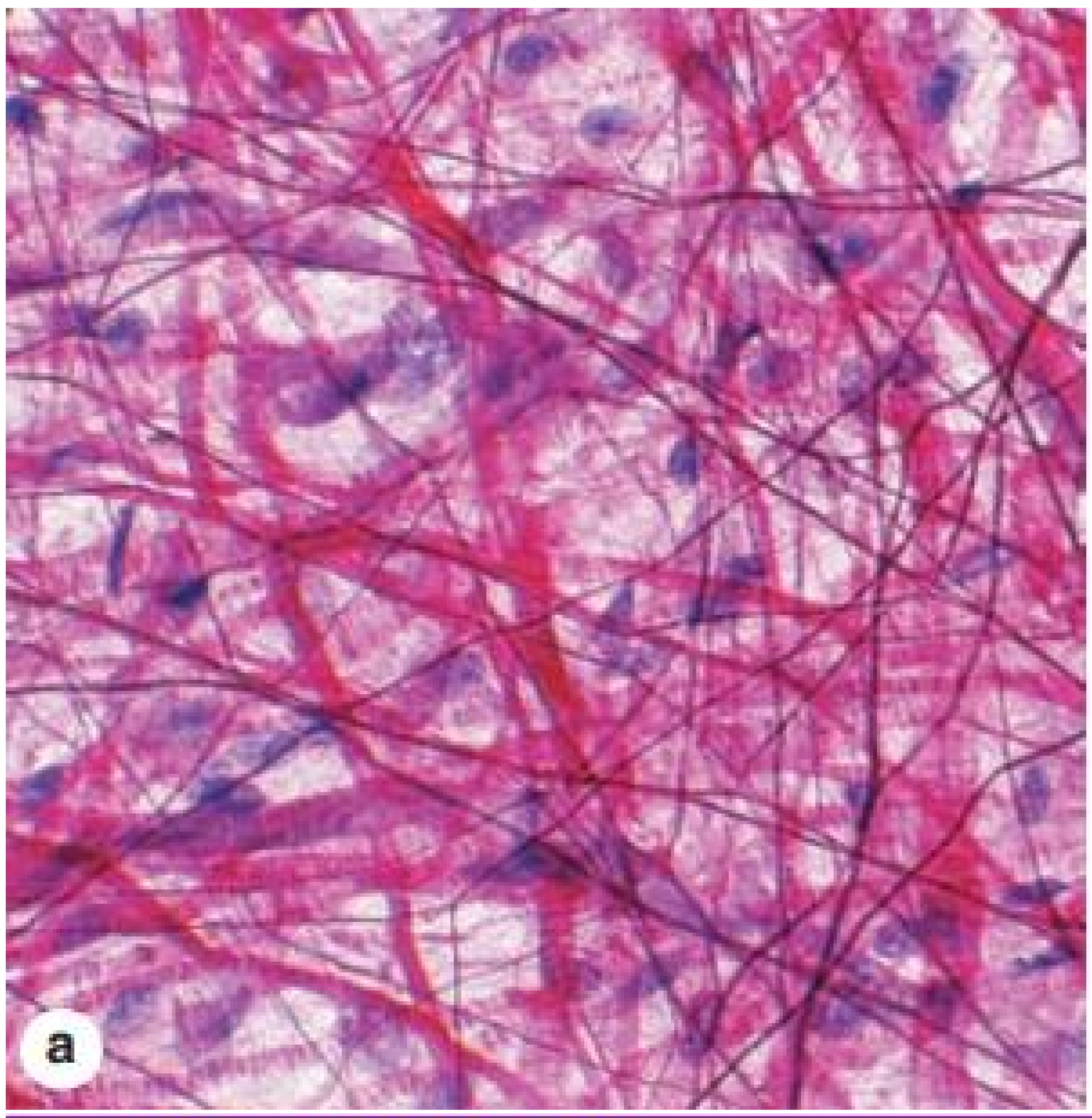
- central core of elastin
- surrounding network of fibrillin microfibrils

- Elastin is synthesized by fibroblasts and vascular smooth muscle cells in vascular walls
- Elastic material is a major extracellular substance in vertebral ligaments, larynx, and elastic arteries.

Elastin molecules are rich in glycine, proline, and lysine, giving much of the protein a random-coil conformation (like that of natural rubber)

Oxidized lysines on two different elastin molecules then condense as a desmosine ring that acts as a covalent cross-link between the polypeptides, which maintain their rubberlike properties

Elastin resists digestion by most proteases, but it is hydrolyzed by pancreatic elastase.



MEDICAL APPLICATION

Fibrillins comprise a family of proteins involved in making the scaffolding necessary for the deposition of elastin. Mutations in the fibrillin genes result in **Marfan syndrome**, a disease characterized by a lack of resistance in tissues rich in elastic fibers. Because the walls of large arteries are rich in elastic components and because the blood pressure is high in the aorta, patients with this disease often experience aortic swellings called **aneurysms**, which are life-threatening conditions.

EXTRACELLULAR MATRIX (ECM)

- Is a complex and intricate structural network that surrounds and supports cells within the connective tissue

-provide mechanical and structural support for tissue
- influence extracellular communication

- Composed of:

- Fibers and ground substance

GROUND SUBSTANCE

Murag sabaw kay very dominant ang water molecule

- a highly hydrated (with much bound water), transparent, complex mixture of macromolecules
- principally of three classes:
  - ✓ glycosaminoglycans (GAGs)
  - ✓ Proteoglycans
  - ✓ multiadhesive glycoproteins

- fills the space between cells and fibers in connective tissue and, because it is viscous, acts as both a lubricant and a barrier to the penetration of invaders

When adequately fixed for histologic analysis, its components aggregate and precipitate in the tissues as granular material that is observed in TEM preparations as electron-dense filaments or granules

GAGs

- also called mucopolysaccharides
- Most abundant heteropolysaccharide components of ground substance
- long polysaccharides consisting of repeating disaccharide units, usually a uronic acid and a hexosamine
- GAGs (except hyaluronan) are synthesized by connective tissue cells as a covalent, posttranslational modification of proteins called proteoglycans

The hexosamine can be glucosamine or galactosamine, and the uronic acid can be glucuronic or iduronic acid

Types of GAGs

Hyaluronic acid

- largest, almost unique, and most ubiquitous GAG
- long polymer of the disaccharide glucosamine-glucuronate
- s synthesized directly into the ECM by an enzyme complex, hyaluronate synthase
- forms a dense, viscous network of polymers, which binds a considerable amount of water, giving it an important role in allowing diffusion of molecules in connective tissue and in lubricating various organs and joints

All other GAGs are much smaller (10-40 kDa), sulfated, covalently attached to proteins (as parts of proteoglycans), and are synthesized in Golgi complexes.

The four major GAGs found in proteoglycans are dermatan sulfate, chondroitin sulfates, keratan sulfate, and heparan sulfate

Proteoglycans

- composed of a core protein to which are covalently attached various numbers and combinations of the sulfated GAGs
- synthesized on RER, mature in the Golgi, where the GAG side chains are added, and secreted from cells by exocytosis

Decorin

- Small proteoglycan
- has few GAG side chains and binds fibrils of type I collagen

Syndecan

- Cell surface proteoglycans su
- have transmembrane core proteins and serve as additional attachments of the cell to the ECM

Aggrecan

- One of the best known proteoglycans
- very large (250 kDa), with a core protein bearing many chondroitin sulfate and keratan sulfate chains
- bound via a link protein to polymer of hyaluronic acid
- Important in the formation of cartilages

Multiadhesive glycoproteins

- Play an important role in stabilizing the ECM and linking it to the cell surface
- Possess binding sites for a variety of ECM proteins such as collagens, proteoglycans, and GAGs
- They also interact w/ cell surface receptors such as integrins and laminin
- Regulate and modulate functions of the ECM related to cell movement and cell migration
- Stimulate cell proliferation and differentiation

Fibronectin

- Most abundant glycoprotein in connective tissue
- provides specific binding sites for integrins
- important both for cell adhesion and cellular migration through the ECM

Laminin

- Present in basal and external laminae
- Possesses binding sites for collagen type IV molecules, heparan sulfate, heparin, entactin,

TABLE 5–5 **Composition and distribution of glycosaminoglycans in connective tissue and their interactions with collagen fibers.**

Glycosaminoglycan	Repeating Disaccharides: Hexuronic Acid	Repeating Disaccharides: Hexosamine	Distribution	Electrostatic Interaction with Collagen
Hyaluronic acid	D-glucuronic acid	D-glucosamine	Umbilical cord, synovial fluid, vitreous humor, cartilage	
Chondroitin 4-sulfate	D-glucuronic acid	D-galactosamine	Cartilage, bone, cornea, skin, notochord, aorta	High levels of interaction, mainly with collagen type II
Chondroitin 6-sulfate	D-glucuronic acid	D-galactosamine	Cartilage, umbilical cord, skin, aorta (media)	High levels of interaction, mainly with collagen type II
Dermatan sulfate	L-iduronic acid or D-glucuronic acid	D-galactosamine	Skin, tendon, aorta (adventitia)	Low levels of interaction, mainly with collagen type I
Heparan sulfate	D-glucuronic acid or L-iduronic acid	D-galactosamine	Aorta, lung, liver, basal laminae	Intermediate levels of interaction, mainly with collagen types III and IV
Keratan sulfate	D-galactose	D-glucosamine	Cartilage, nucleus pulposus, annulus fibrosus	None

laminin, and the laminin receptor on the cell surface

Tenascin

- Appears during embryogenesis, but its synthesis is switched off in mature tissues
- Reappears during wound healing and is also found within musculotendinous junctions and malignant tumors
- Has binding sites for fibrogen, heparin, and EGF-like growth factord; thus, it participates in cell attachment to the ECM

Osteopontin

- Present in the ECM of bone
- Binds osteoclasts and attaches them to the underlying bone surface
- Important role in sequestering calcium and promoting calcification of the ECM

Laminin and fibronectin are multiadhesive, with binding sites for ECM components and for integrins at cell surfaces, and have important roles in cell migration and maintaining tissue structure.

Instertitial fluid

- with ion composition similar to that of blood plasma
- contains plasma proteins of low molecular weight that pass through the thin walls of capillaries, the smallest blood vessels

it is estimated that as much as one-third of the body's plasma proteins are stored in the matrix of connective tissue because of its volume and wide distribution

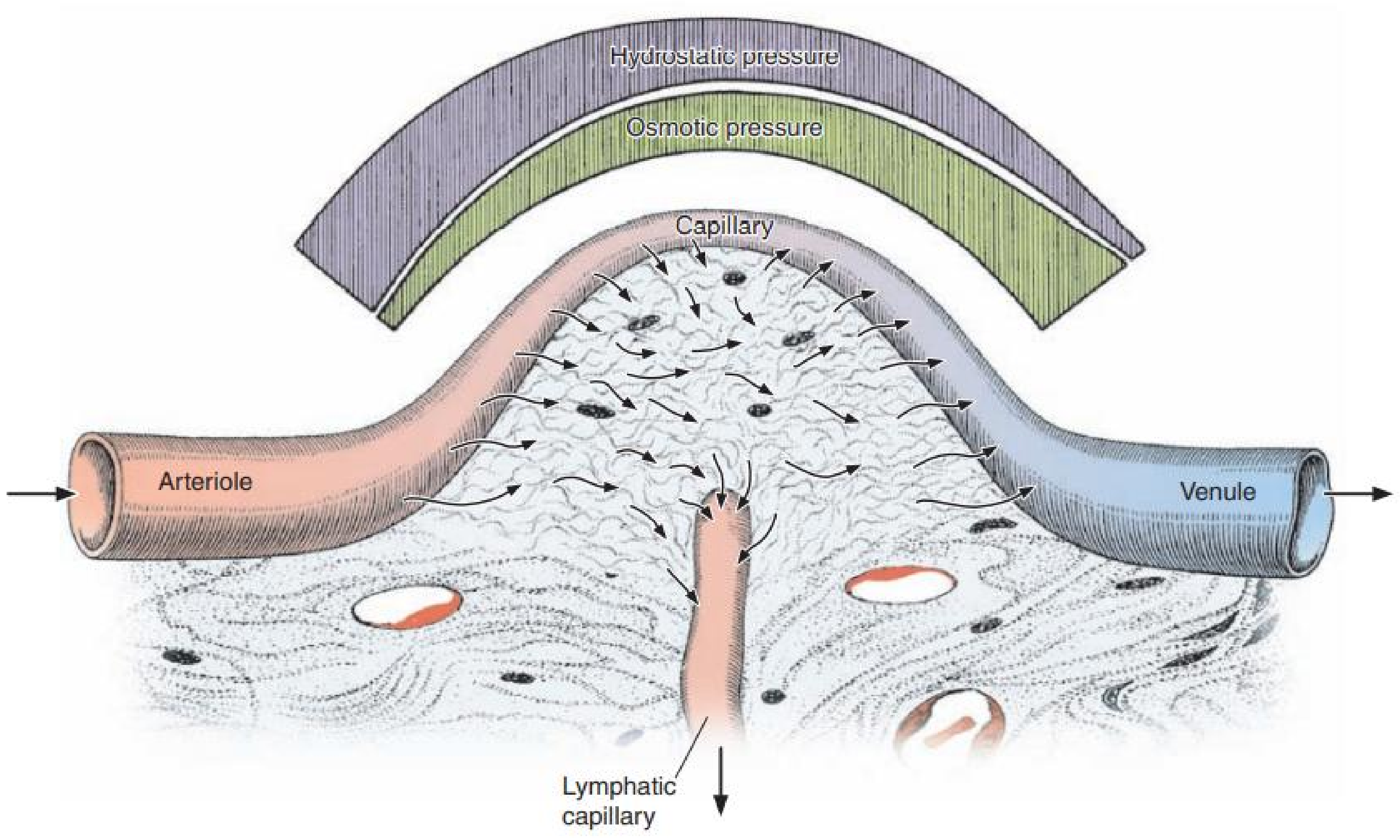
Two forces that maintain the interstitial fluid

Hydrostatic pressure

- caused by the pumping action of the heart, which forces water out across the capillary wall

Colloid osmotic pressure

- produced by plasma proteins such as albumin, which draws water back into the capillaries



Water normally passes through capillary walls into the ECM of surrounding connective tissues primarily at the arterial end of a capillary, because the **hydrostatic pressure** is greater than the colloid **osmotic pressure**. However, hydrostatic pressure decreases toward the venous end of the capillary, as indicated at the top of the figure. The fall in hydrostatic pressure parallels a rise in osmotic pressure of the capillary blood because the plasma protein concentration increases as water is pushed out across the capillary wall.

As a result of the increased protein concentration and decreased hydrostatic pressure, osmotic pressure at the venous end is greater than hydrostatic pressure and water is drawn back into the capillary. In this way plasma and interstitial fluid constantly mix, nutrients in blood circulate to cells in connective tissue, and cellular wastes are removed.

Not all water that leaves capillaries by hydrostatic pressure is drawn back in by osmotic pressure. This excess tissue fluid is normally drained by the lymphatic capillaries, open-ended vessels that arise in connective tissue and enter the one-way lymphatic system that eventually delivers the fluid (now called **lymph**) back to veins.

>> MEDICAL APPLICATION

Edema is the excessive accumulation of water in the extracellular spaces of connective tissue. This water comes from the blood, passing through the capillary walls that become more permeable during inflammation and normally producing slight swelling.

The quantity of water drawn back into capillaries is often less than that which was forced out. Normally this excess fluid does not accumulate in connective tissue but drains continuously into lymphatic capillaries that eventually return it to the blood.

TYPES OF CONNECTIVE TISSUE

Loose Connective Tissue (Areolar Tissue)

Dense Connective Tissue

- ✧ Dense irregular connective tissue
- ✧ Dense regular connective tissue
- ➢ terms that refer to amounts of collagen present

Loose Connective Tissue (Areolar Tissue)

- ➢ Thin and relatively sparse collagen fibers
- ➢ Fewer collagen fibers (more cells)
- ➢ very common and generally supports epithelial tissue
- ➢ Most numerous cells are fibroblasts
- ➢ Comprises a thick layer (the lamina propria) beneath the epithelial lining of the digestive system and fills the spaces between muscle and nerve fibers
- ➢ Well-vascularized *(whatever their location, thin layers of loose connective tissue surround most small blood vessels of the body)*
- ➢ typically contains cells, fibers, and ground substance in roughly equal parts
- ➢ has a delicate consistency; it is flexible and not very resistant to stress

Dense Connective Tissue (Areolar Tissue)

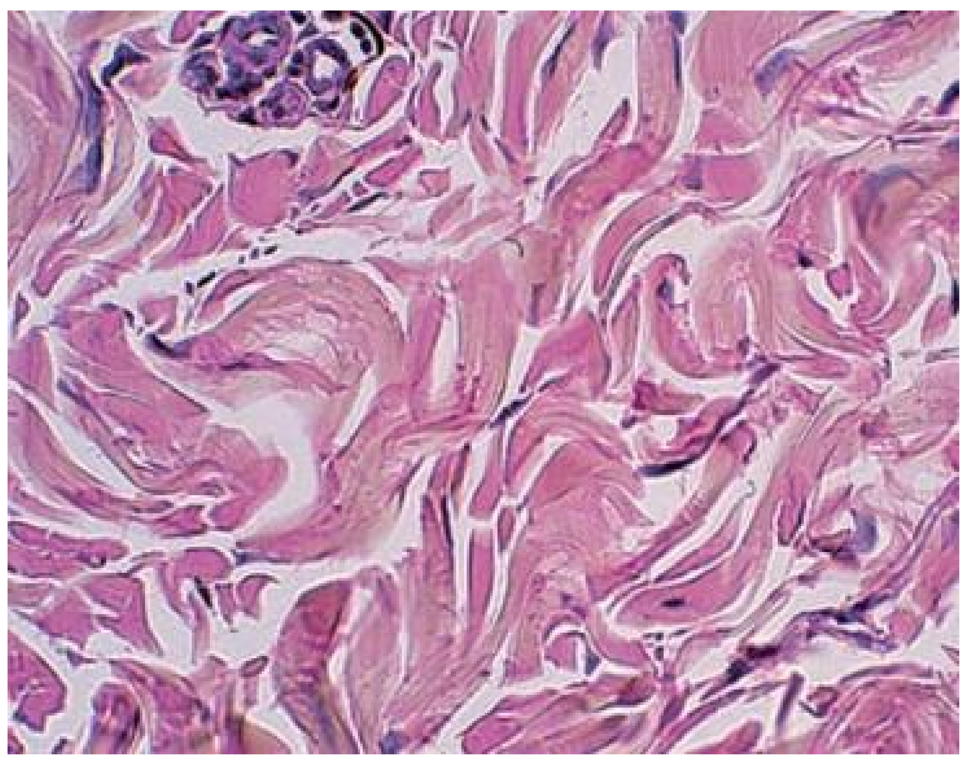
- ➢ adapted to offer stress resis tance and protection
- ➢ same components found in loose connective tissue, but with fewer cells and a clear predominance of collagen fibers over ground substance
- ➢ less flexible and far more resistant to stress than loose connective tissue

Dense Irregular Connective Tissue

- ➢ bundles of collagen fibers appear randomly interwoven, with no definite orientation; providing resistance to stress from all directions
- ➢ Contains mostly collagen fibers
- ➢ Cells are sparse and are typically of a single type, the fibroblast
- ➢ Fibers are arranged in bundles oriented in various directions
- ➢ Withstand stresses on organs or structures

Location:

- ✧ Submucosa *(hollow organs =intestinal tract)*
- ✧ Reticular layer of the dermis *(provides a resistance to tearing as a consequence of stretching forces from different directions)*
- ✧ Organ capsules



Dense Regular Connective Tissue

- ➢ Characterized by ordered and densely packed arrays of fibers and cells
- ➢ They are white in the fresh state and almost inextensible
- ➢ Separated by very little ground substance
- ➢ Strong, flexible straps or cords that hold together components of the musculoskeletal system

Location:

- ✧ Tendons
- ✧ Ligaments
- ✧ Aponeuroses

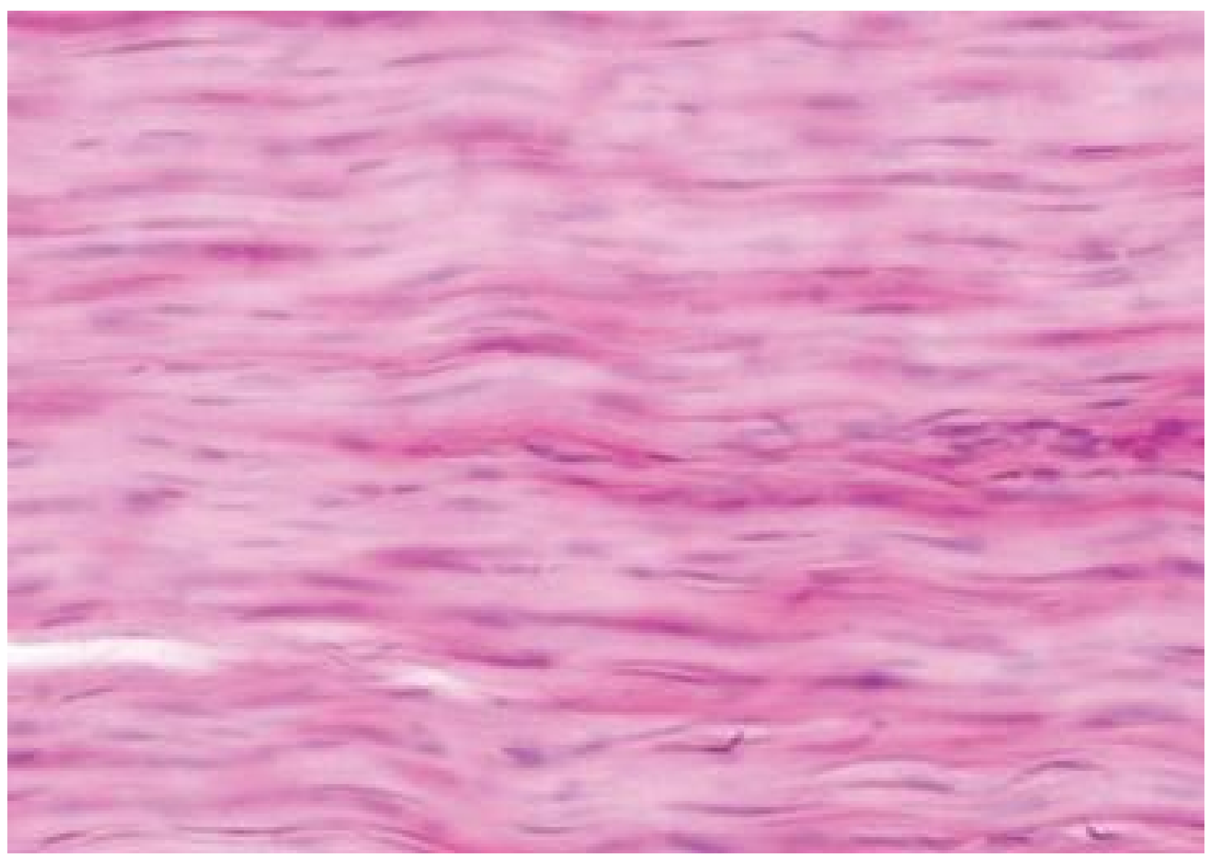


Table 5-6. Types of connective tissue.

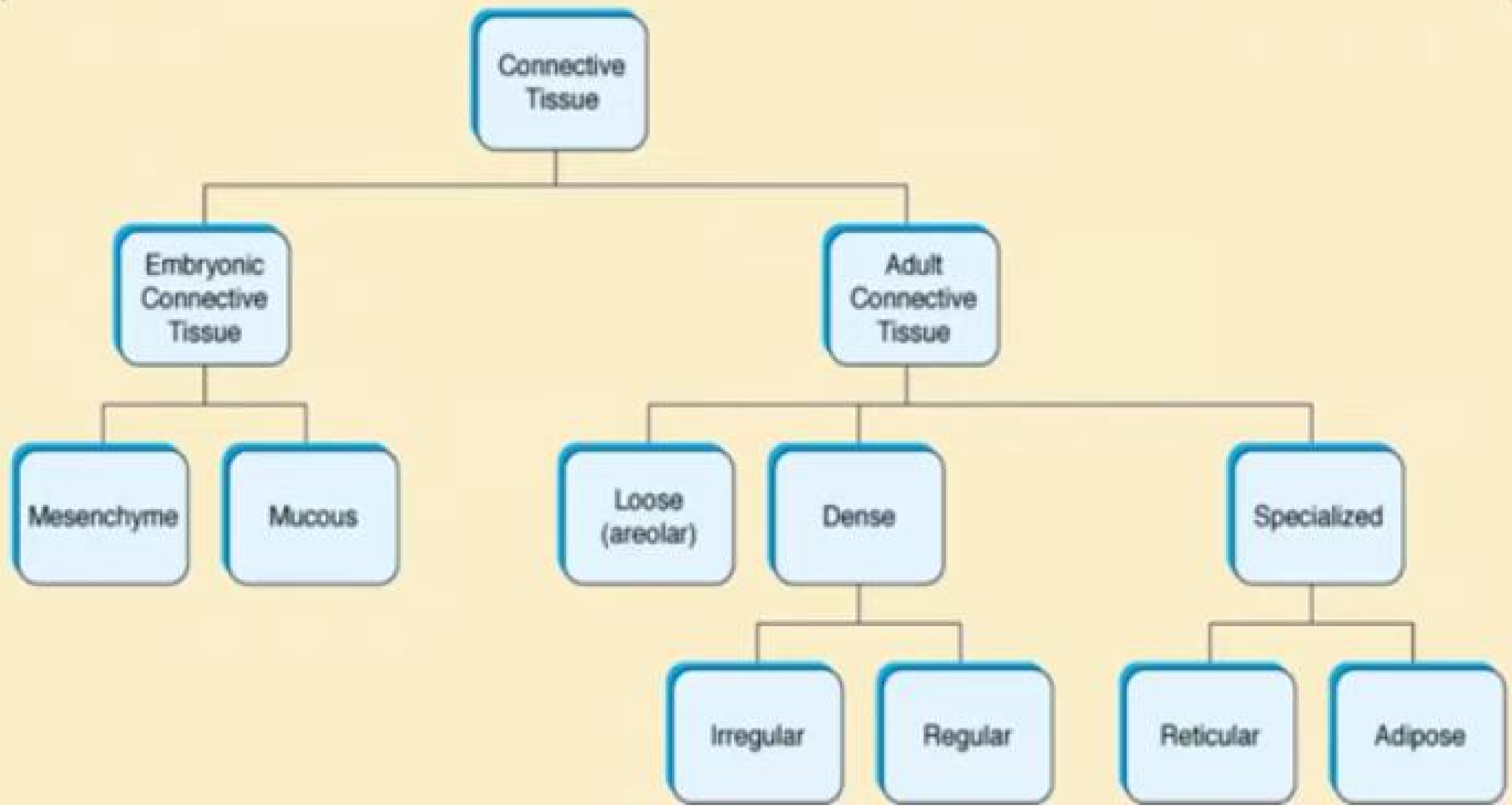


TABLE 5–6 Classification of connective or supporting tissues.

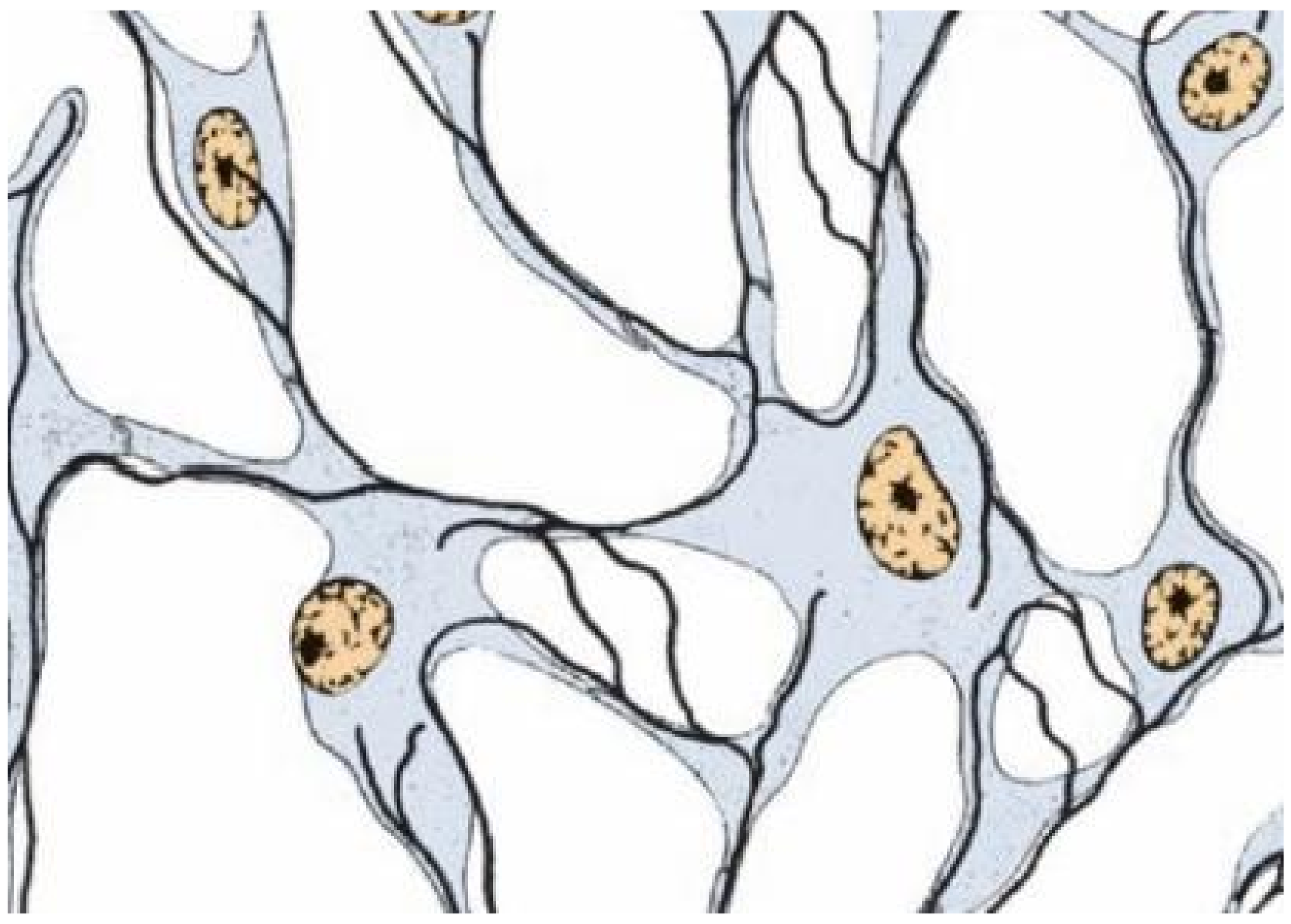
	General Organization	Major Functions	Examples
Connective Tissue Proper			
Loose (areolar) connective tissue	Much ground substance; many cells and little collagen, randomly distributed	Supports microvasculature, nerves, and immune defense cells	Lamina propria beneath epithelial lining of digestive tract
Dense irregular connective tissue	Little ground substance; few cells (mostly fibroblasts); much collagen in randomly arranged fibers	Protects and supports organs; resists tearing	Dermis of skin, organ capsules, submucosa layer of digestive tract
Dense regular connective tissue	Almost completely filled with parallel bundles of collagen; few fibroblasts, aligned with collagen	Provide strong connections within musculoskeletal system; strong resistance to force	Ligaments, tendons, aponeuroses, corneal stroma
Embryonic Connective Tissues			
Mesenchyme	Sparse, undifferentiated cells, uniformly distributed in matrix with sparse collagen fibers	Contains stem/progenitor cells for all adult connective tissue cells	Mesodermal layer of early embryo
Mucoid (mucous) connective tissue	Random fibroblasts and collagen fibers in viscous matrix	Supports and cushions large blood vessels	Matrix of the fetal umbilical cord
Specialized Connective Tissues			
Reticular connective tissue (see Chapter 14)	Delicate network of reticulin/collagen III with attached fibroblasts (reticular cells)	Supports blood-forming cells, many secretory cells, and lymphocytes in most lymphoid organs	Bone marrow, liver, pancreas, adrenal glands, all lymphoid organs except the thymus

RETICULAR TISSUE

- fibers of type III collagen form a delicate 3D network that supports various types of cells
- produced by modified fibroblasts called reticular cells that remain associated with and partially covering the fibers
- provides a framework with specialized microenvironments for cells in hemopoietic tissue and some lymphoid organs
- Forms a soft internal skeleton (stroma) that supports other cell types including white blood cells, mast cells, and macrophages

Reticular fibers of type III collagen are produced and enveloped by the reticular cells, forming an elaborate network through which interstitial fluid or lymph and wandering cells from blood pass continuously

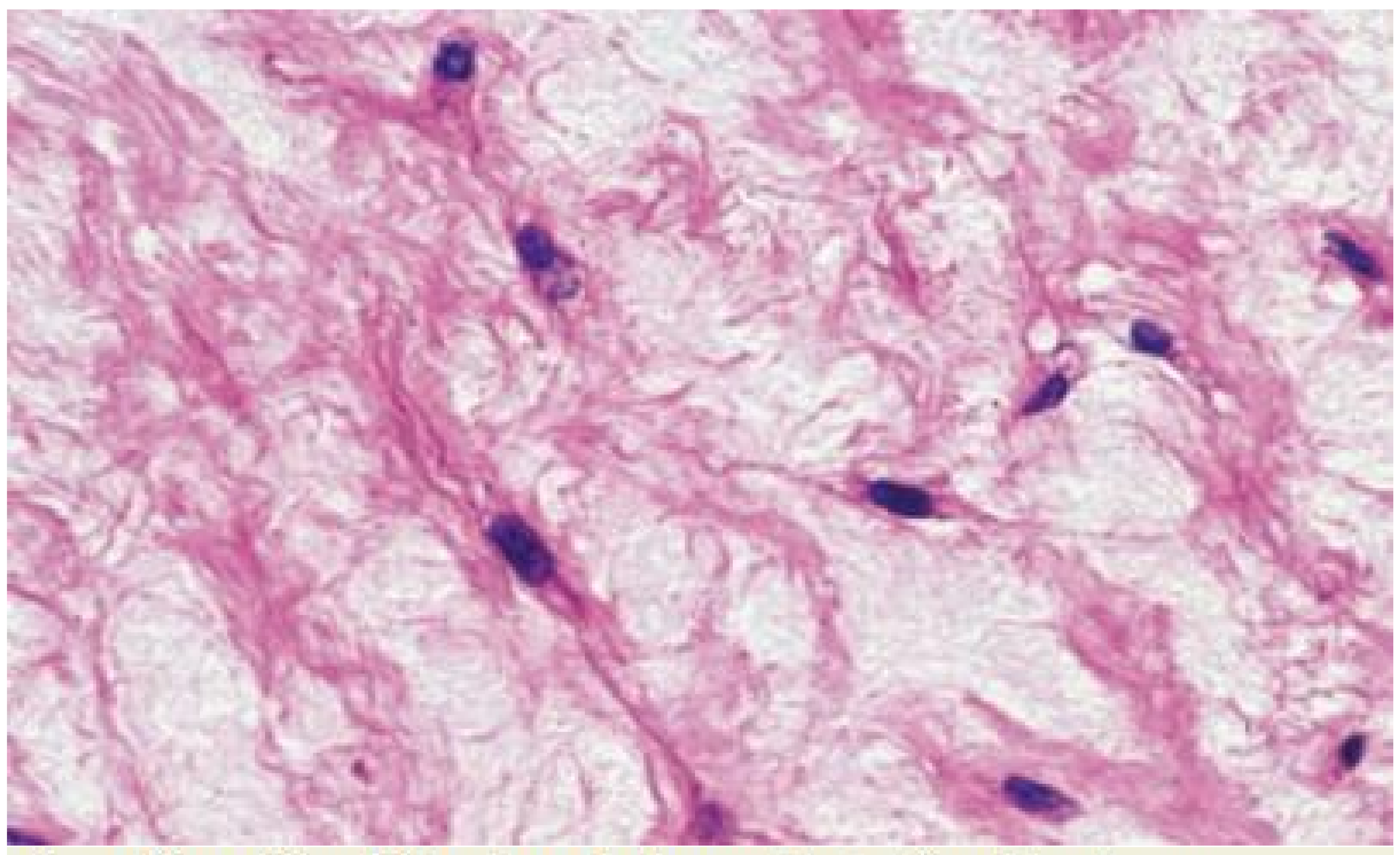
Location:
- ✧ Bone marrow
- ✧ Spleen
- ✧ Lymph nodes



MUCOID TISSUE

- embryonic type of connective tissue, found mainly in the umbilical cord and fetal organs
- abundant ground substance composed chiefly of hyaluronic acid, mucoid tissue is jellylike with sparse collagen fibers and scattered fibroblasts
- principal component of the umbilical cord, where it is referred to as Wharton's jelly

found in the pulp cavities of young teeth, which remain as a postnatal source of mesenchymal stem cells



A section of umbilical cord shows large fibroblasts surrounded by a large amount of very loose ECM containing mainly ground substances very rich in hyaluronan, with wisps of collagen. Histologically mucoid (or mucous) connective tissue resembles embryonic mesenchyme in many respects and is rarely found in adult organs. X200. H&E

Location:
- ✧ Umbilical cord
- ✧ Fetal organs

ADIPOSE TISSUE

- connective tissue in which adipocytes or fat cells predominate
- found isolated or in small groups within loose or dense irregular connective tissue but occur in large aggregates as adipose tissue or "fat" in many body regions and organs
- serving as storage depots for neutral fats (triglyceride)
- key regulators of the body's over all energy metabolism
- Endocrine tissue *(release hormones and various other important substances)*
- conducts heat poorly and helps thermally insulate the body
- fills up spaces between other tissues and helps cushion and keep some organs in place
- help shape the body surface, where pad-like deposits act as shock absorbers, chiefly in the soles and palms

2 TYPES OF ADIPOSE TISSUE

There are two types of adipose tissue with different locations: structures, colors, and pathologic characteristics.

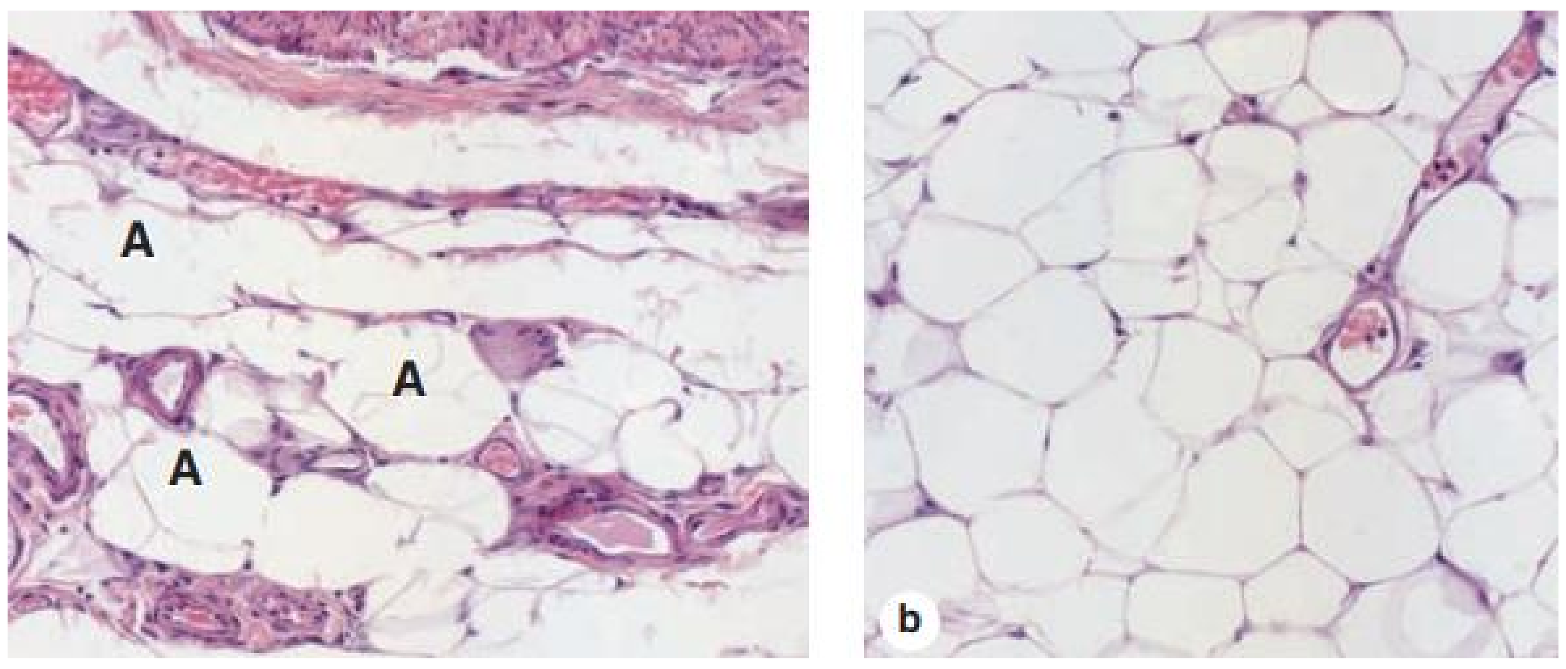
White Adipose Tissue

- Specialized for relatively long-term energy storage
- Unilocular (triglycerides are stored in this single large droplet; often empty in standard light microscope preparations)
- have a signet-ring appearance,with the lipid droplet displacing and flattening the nucleus against the cell membrane
- surrounded by a thin external lamina containing type IV collagen
- Enerygy storage, insulation, cushioning of vital organs, & secretion of hormones

Location:
- Subcutaneous layer of connective tissue
- Mammary fat pad
- Around the kidneys
- Bone marrow & between other tissues, where it fills in spaces
- Palms of the hands and the soles of the feet
- Beneath the visceral pericardium
- Orbits around the eyeballs

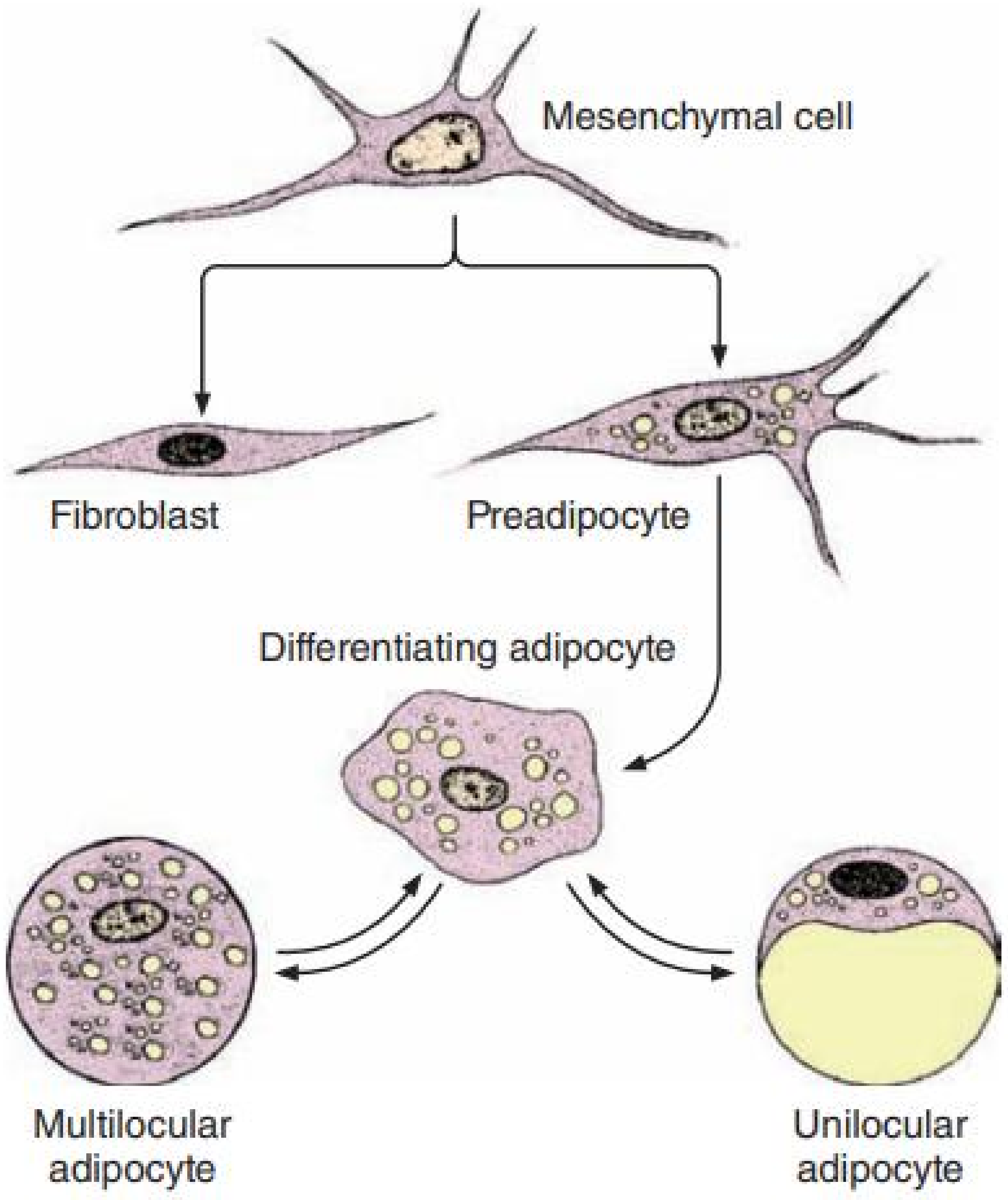
Distribution of this tissue changes significantly through childhood and adult life and is partly regulated by sex hormones, which control adipose deposition in the breasts and thighs.

The color of freshly dissected white adipose tissue depends on the diet, varying from white to yellow with the amount of carotenoids dissolved in the lipid



The fat cells are empty because lipid was dissolved away in slide preparation. Nuclei at the cell membranes are visible in some of the fat cells

FIGURE 6–3 Development of white and brown fat cells.



Like the fiber-producing cells of connective tissue, adipocytes differentiate from embryonic mesenchymal cells. Such differentiation is first seen with the appearance of preadipocytes (Figure 6–3). These cells have the appearance of fibroblasts but accumulate lipid droplets in their cytoplasm. Lipid accumulations are isolated from one another at first but soon fuse to form the single large droplet characteristic of cells in unilocular adipose tissue.

>> MEDICAL APPLICATION

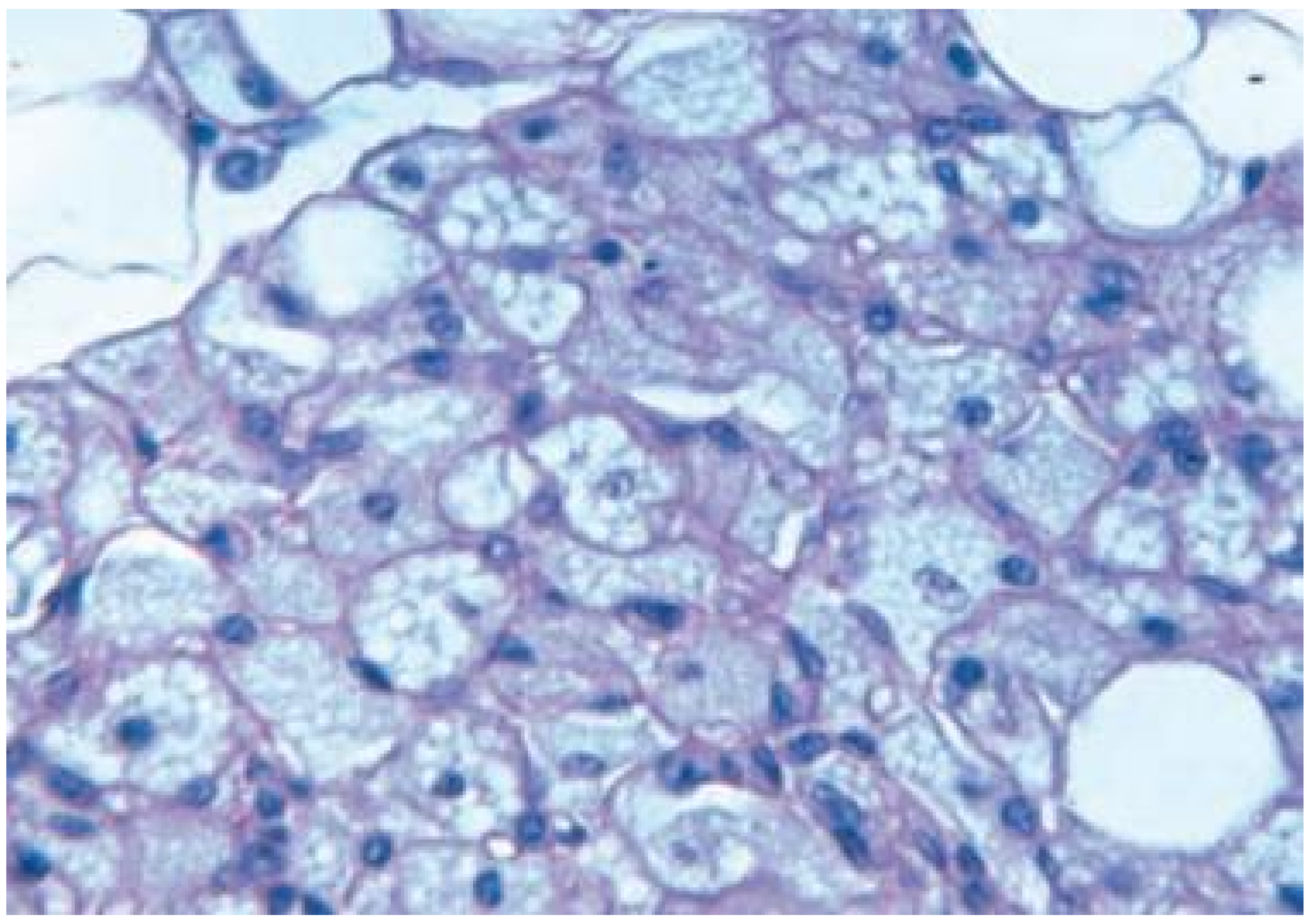
Unilocular adipocytes can generate benign tumors called **lipomas** that are relatively common, although malignant adipose tumors (**liposarcomas**) occur infrequently. Fetal lipomas of brown fat are sometimes called **hibernomas**.

Brown Adipose Tissue

Brown adipose tissue constitutes 2% to 5% of the newborn body weight, located mainly in the back, neck, and shoulders, but it is greatly reduced during childhood and adolescence

color of brown adipose tissue or brown fat is due to both the very abundant mitochondria (containing cytochrome pigment) scattered among the lipid droplets of the fat cells and the large number of blood capillaries in this tissue

- Multilocular (contain many small lipid inclusions)
- The many small lipid droplets, abundant mitochondria, and rich vasculature all help mediate this tissue's principal function of heat production
- Very abundant mitochondria
- Large number of blood capillaries in the tissue
- Cytoplasm contains a great number of lipid droplets of various sizes and nuclei are often centrally located



*The main function of the multilocular adipose cells is to produce heat by nonshivering **thermogenesis**.*

In animals ending their hibernation period, or in newborn humans exposed to an environment colder than the uterus, nerve impulses liber ate norepinephrine into brown adipose tissue.

As in white fat, this neurotransmitter activates the hormone-sensitive lipase of adipocytes, promoting hydrolysis of triglycerides to fatty acids and glycerol.

However, unlike the process in white fat, liberated fatty acids of multilocular adipocytes are not released but are quickly metabolized, with a consequent increase in oxygen consumption and heat production.

This then raises the temperature within the tissue and warms the locally circulating blood, which then distributes the heat throughout the body

*Heat production is increased in these cells because the mitochondria have in their inner membrane much greater levels of a transmembrane protein called **thermogenin or uncoupling protein (UCP-1) .***

Brown adipose tissue also develops from embryonic mesenchyme, with cells developing as growing preadipocytes, and emerges earlier than white fat during fetal development.

In humans the amount of brown fat is maximal relative to body weight at birth, when thermogenesis is most needed and partially disappears by apoptosis and involution during childhood.

In adults the amount and activity of brown fat are higher in lean individuals.

The number of brown adipocytes increases during cold adaptation in adults, usually appearing as clusters of multilocular cells in white adipose tissue.

This may represent proliferation and differentiation of new adipocytes from preexisting progenitor cells or a change in the diff erentiated state of the white adipocytes.

Besides stimulating thermogenic activity, autonomic nerves also promote brown adipocyte differentiation and prevent apoptosis in mature brown fat cells.

CARTILAGE

- An **avascular** (does not received any blood supply) tissue that consists of chondrocytes and an extensive ECM
- tough, flexible form of connective tissue, characterized by an extracellular matrix (ECM) with high concentrations of GAGs and proteoglycans, which interact with collagen and elastic fibers
- allows the tissue to bear mechanical stresses without permanent distortion
- provides shock absorbing and sliding regions within joints and facilitates bone movements
- guides development and growth of long bones, both before and after birth

It receives nutrients by diffusion from capillaries of its adjacent tissues.

Perichondrium
- sheath of dense con nective tissue that surrounds cartilage in most places, forming an interface between the cartilage and the tissues supported by the cartilage

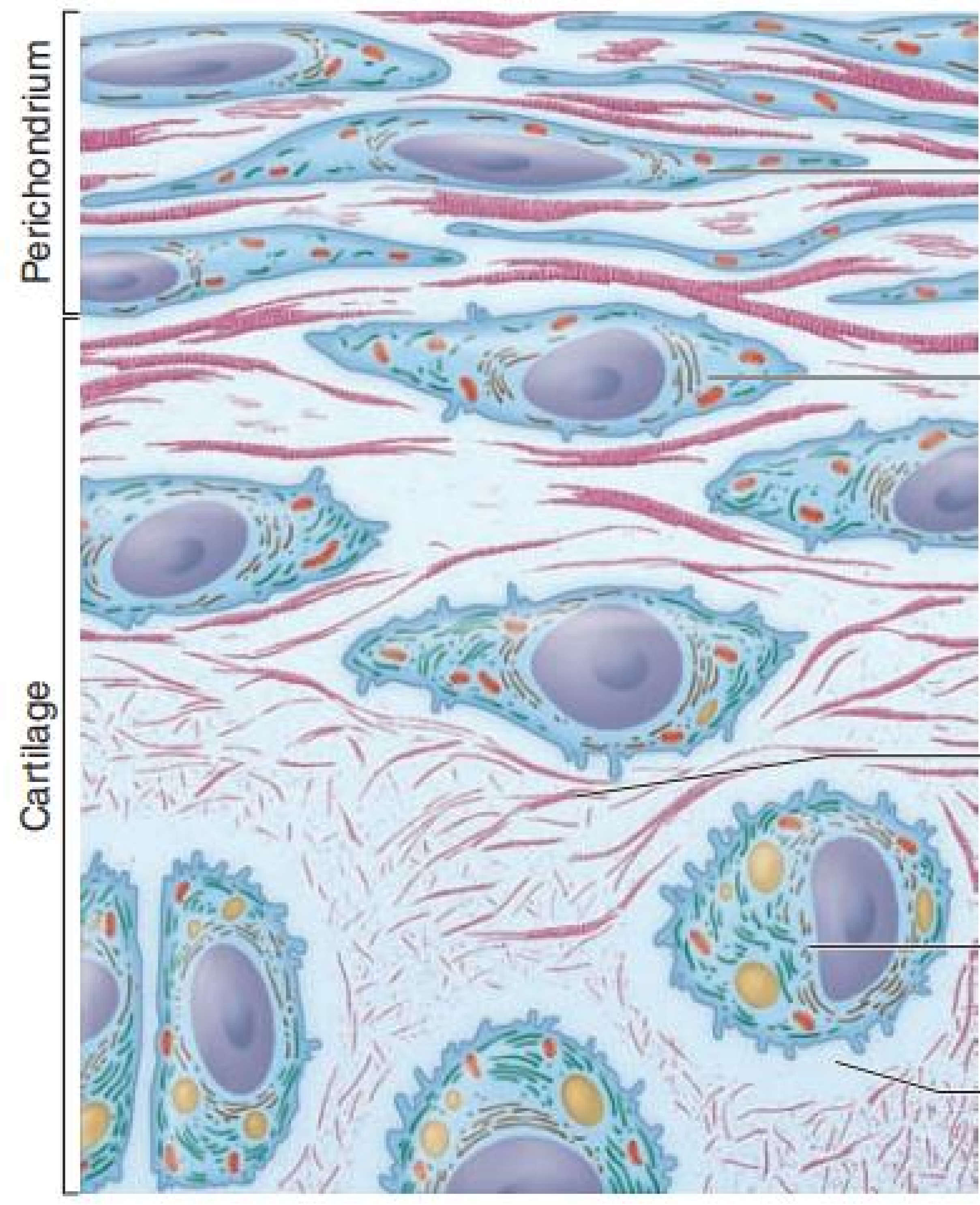
Articular cartilage, which covers the surfaces of bones in movable joints, lacks perichondrium and is sustained by the diffusion of oxygen and nutrients from the synovial fluid.

Chondrocytes
- synthesize and maintain ECM components
- located in matrix cavities called **lacunae**

>> MEDICAL APPLICATION

Many genetic conditions in humans or mice that cause defective cartilage, joint deformities, or short limbs are due to recessive mutations in genes for collagen type II, the aggrecan core protein, the sulfate transporter, and other proteins required for normal chondrocyte function.

3 Major Forms of cartilage
Hyaline Cartilage
Elastic Cartilage
Fibrocartilage



Fibroblast-like progenitor cells in the perichondrium give rise to larger chondroblasts, which divide and differentiate as chondrocytes. These functional cells produce matrix components and exist in lacunae embedded in the matrix.

Territorial matrix
- matrix immediately around each lacuna

Interterritorial matrix
- Region that surrounds the territorial matrix & occupies the space between groups of chondrocytes
- more distant from lacunae

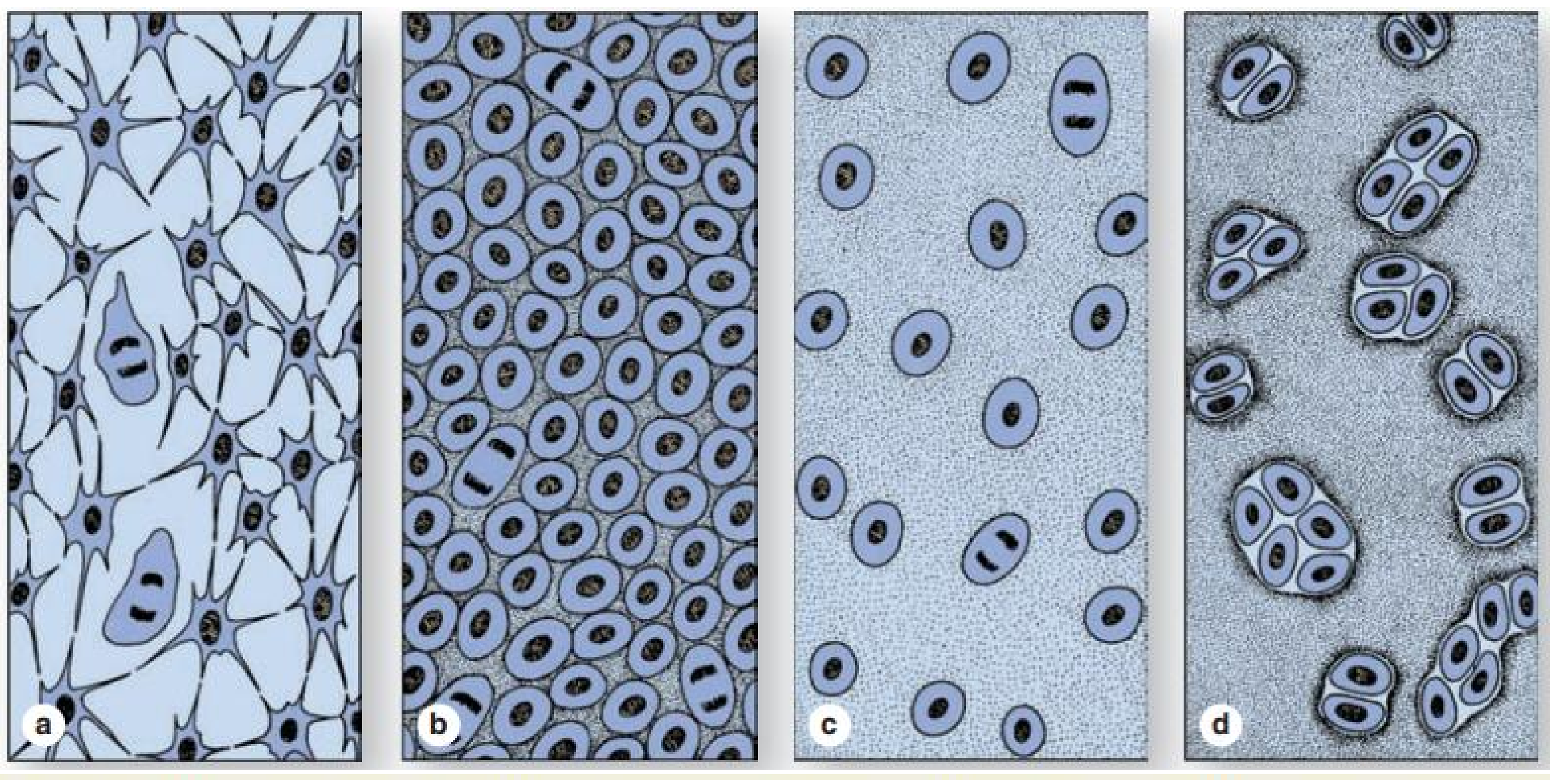
Collagen is more abundant in the interterritorial parts of the matrix.

Isogenous aggregates
- Cluster of chondrocytes
- appear in groups of up to eight cells that originate from mitotic divisions of a single chondrocyte

Chondrogenesis
- Pricess of cartilage development, begins w/ the aggregation of chondroprogenitor

mesenchymal cells to form a mass of rounded, closely apposed cells

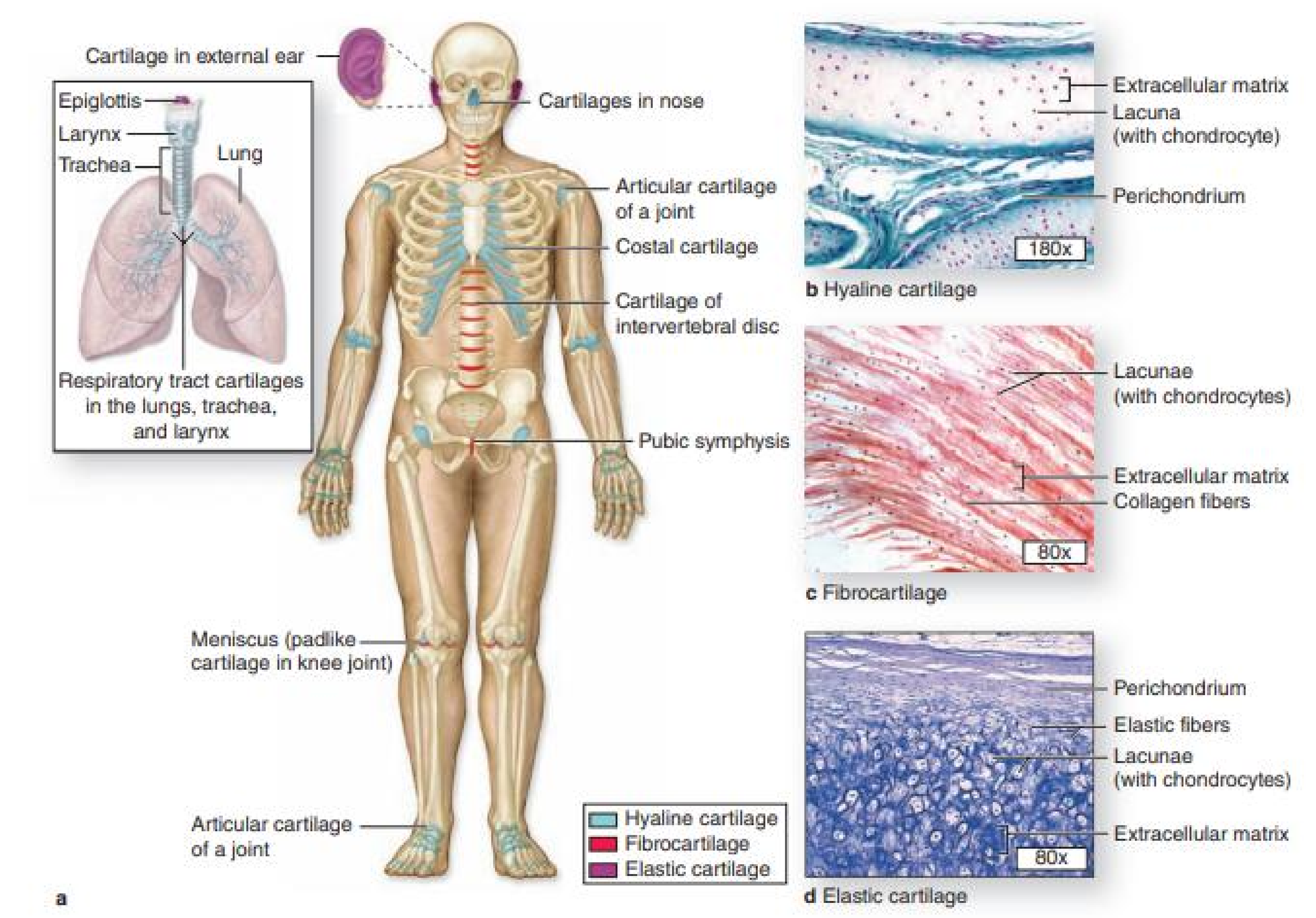
- The dividing cells are typically called **chondroblasts** and **chondrocytes** when proliferation has ceased.



The diagrams show the major stages by which embryonic cartilage is formed. **(a)** Mesenchyme is the precursor for all types of cartilage. **(b)** Mitosis and early differentiation produces a tissue with condensations of rounded cells called **chondroblasts**. **(c)** Chondroblasts are then separated from one another again by their production of various matrix components, which collectively swell with water and form the very extensive ECM.

(d) Multiplication of chondroblasts within the matrix gives rise to **isogenous cell aggregates** surrounded by a condensation of territorial matrix. In mature cartilage, this interstitial mitotic activity ceases and all chondrocytes typically become more widely separated by their production of matrix.

FIGURE **7–1** **Distribution of cartilage in adults.**



(a) There are three types of adult cartilage distributed in many areas of the skeleton, particularly in joints and where pliable support is useful, as in the ribs, ears, and nose. Cartilage support of other tissues throughout the respiratory tract is also prominent. The photomicrographs show the main features of **(b)** hyaline cartilage, **(c)** fibrocartilage, and **(d)** elastic cartilage. Dense connective tissue of perichondrium is shown here with hyaline and elastic cartilage.

HYALINE CARTILAGE

- Most common form of cartilage
- homogeneous and semitransparent in the fresh state

Location (Adults)

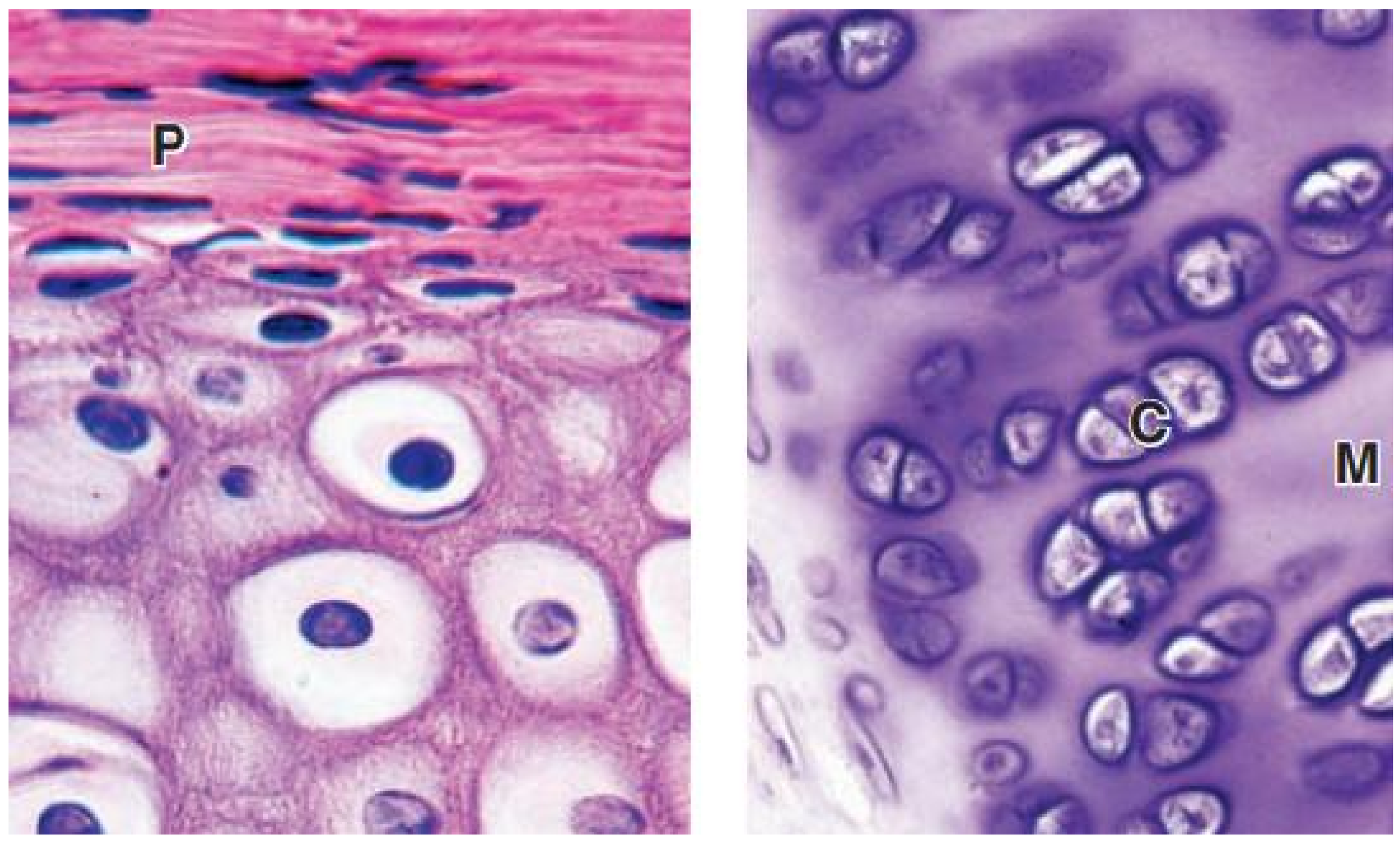
- articular surfaces of movable joints
- walls of larger respiratory passages (nose, larynx, trachea, bronchi)
- ventral ends of ribs *(where they articulate with the sternum)*
- epiphyseal plates of long bones (makes possible longitudinal bone growth)

Embryo

- hyaline cartilage forms the temporary skeleton that is gradually replaced by bone

- type II collagen
- most abundant proteoglycan of hyaline cartilage = **aggrecan**

Another important component of cartilage matrix is the structural multiadhesive glycoprotein ***chondronectin***



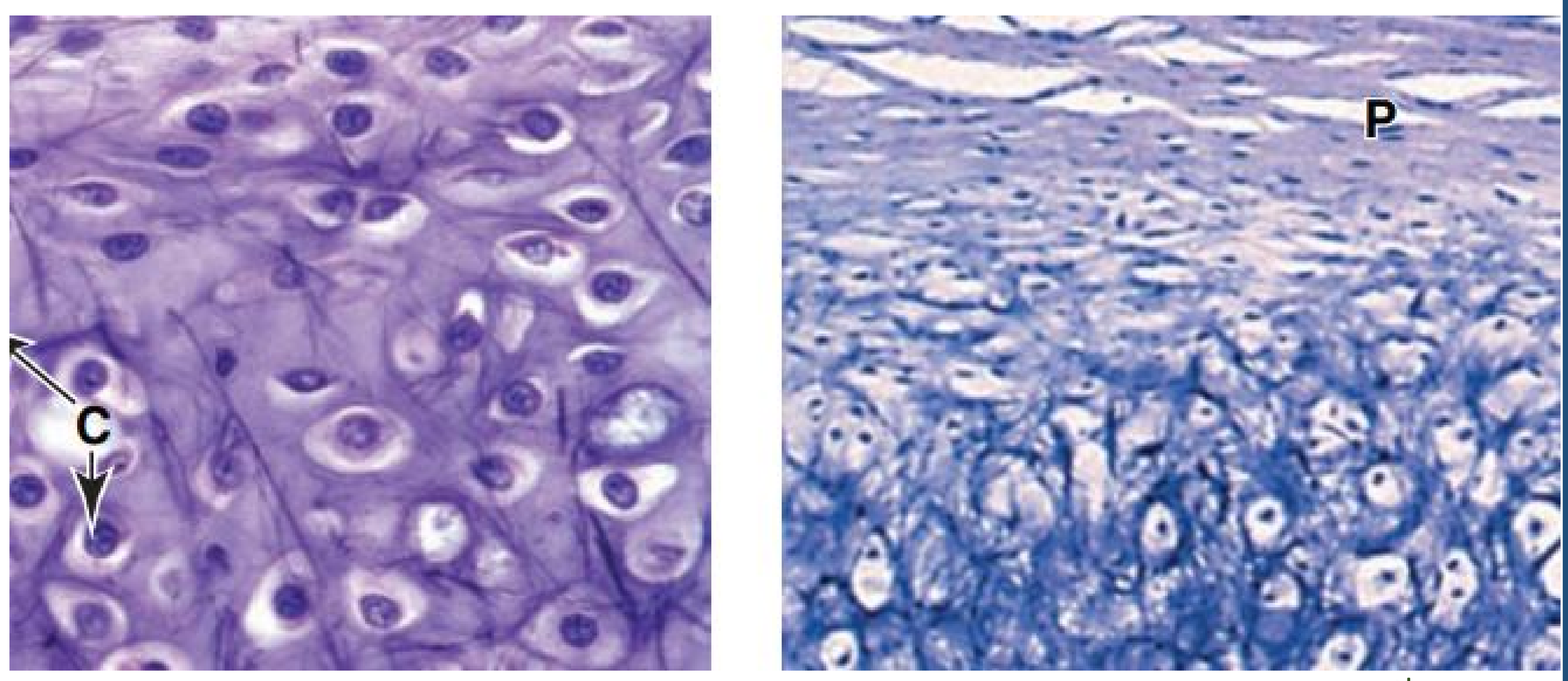
ELASTIC CARTILAGE

- contains an abundant network of elastic fibers
- collagen type II *(give fresh elastic cartilage a yellowish color)*
- Elastic material gives the cartilage elastic properties in addition to resilience and pliability
- Dark bundles distributed unevenly through the matrix

Demonstration of the elastic fibers usually requires stains such as orcein or resorcin fuchsin

Location

- Ear
- Epiglottis
- Cuneiform cartilage in the larynx
- auricle of the ear
- walls of the external auditory canals, the auditory (eustachian)



Lesser isogenous groups compared to other cartilages

FIBROCARTILAGE

- combination of hyaline cartilage and dense connective tissue with gradual transitions between these tissues
- Chondrocytes of fibrocartilage occur singly and in aligned isogenous aggregates
- produce matrix containing type II collagen
- Regions with chondrocytes and hyaline matrix are separated by other regions contain ing bundles of type I collagen and scattered fibroblasts
- more acidophilic than that of hyaline or elastic cartilage (relative scarcity of proteoglycans)
- no distinct surrounding perichondrium

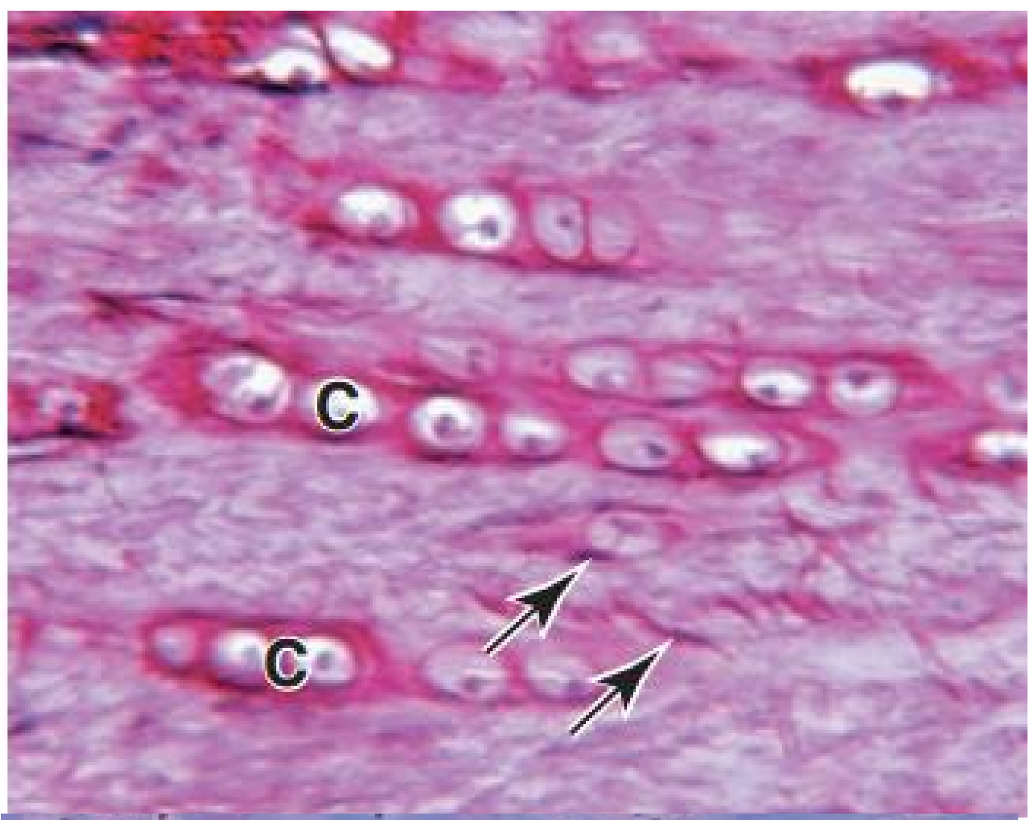
Location (Adults)

- Intervetebral discs
- Attachments of certain ligaments
- Pubic symphysis

Intervertebral discs of the spinal column are composed primarily of fibrocartilage and act as lubricated cushions and shock absorbers preventing adjacent vertebrae from being damaged by abrasive forces or impacts

FUNCTIONS OF ALL 3 TYPES OF CARTILAGES

HYALINE	ELASTIC	FIBROCARTILAGE
• Resists compression • Provides cushioning, smooth, and low-friction surface for joints • Provides structural support in respiratory system (*larynx, trachea, and bronchi*) • Forms foundation for development of fetal skeleton • endochondral bone formation and bone growth	Provides flexible support	Resists deformation under stress



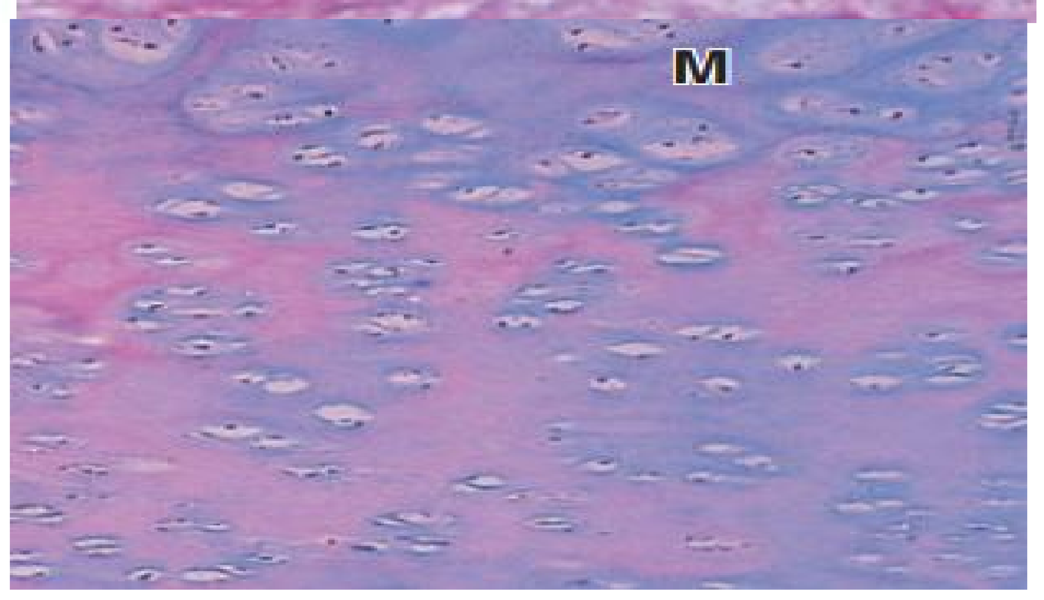


TABLE 7–1 Important features of the major cartilage types.

	Hyaline Cartilage	Elastic Cartilage
Main features of the extracellular matrix	Homogeneous, with type II collagen and aggrecan	Type II collagen, aggrecan, and darker elastic fibers
Major cells	Chondrocytes, chondroblasts	Chondrocytes, chondroblasts
Typical arrangement of chondrocytes	Isolated or in small isogenous groups	Usually in small isogenous groups
Presence of perichondrium	Yes (except at epiphyses and articular cartilage)	Yes
Main locations or examples	Many components of upper respiratory tract; articular ends and epiphyseal plates of long bones; fetal skeleton	External ear, external acoustic meatus, auditory tube; epiglott and certain other laryngeal cartilages
Main functions	Provides smooth, low-friction surfaces in joints; structural support for respiratory tract	Provides flexible shape and support of soft tissues

BONE

- specialized connective tissue composed of **calcified extracellular material**, the **bone matrix** , and three major cell types
- provides solid support for the body
- protects vital organs such as those in the cranial and thoracic cavities
- harbors cavities containing bone marrow where blood cells are formed
- serves as a reservoir of calcium, phosphate, and other ions that can be released or stored in a controlled fashion to maintain constant concentrations in body fluids
- Bodily movement

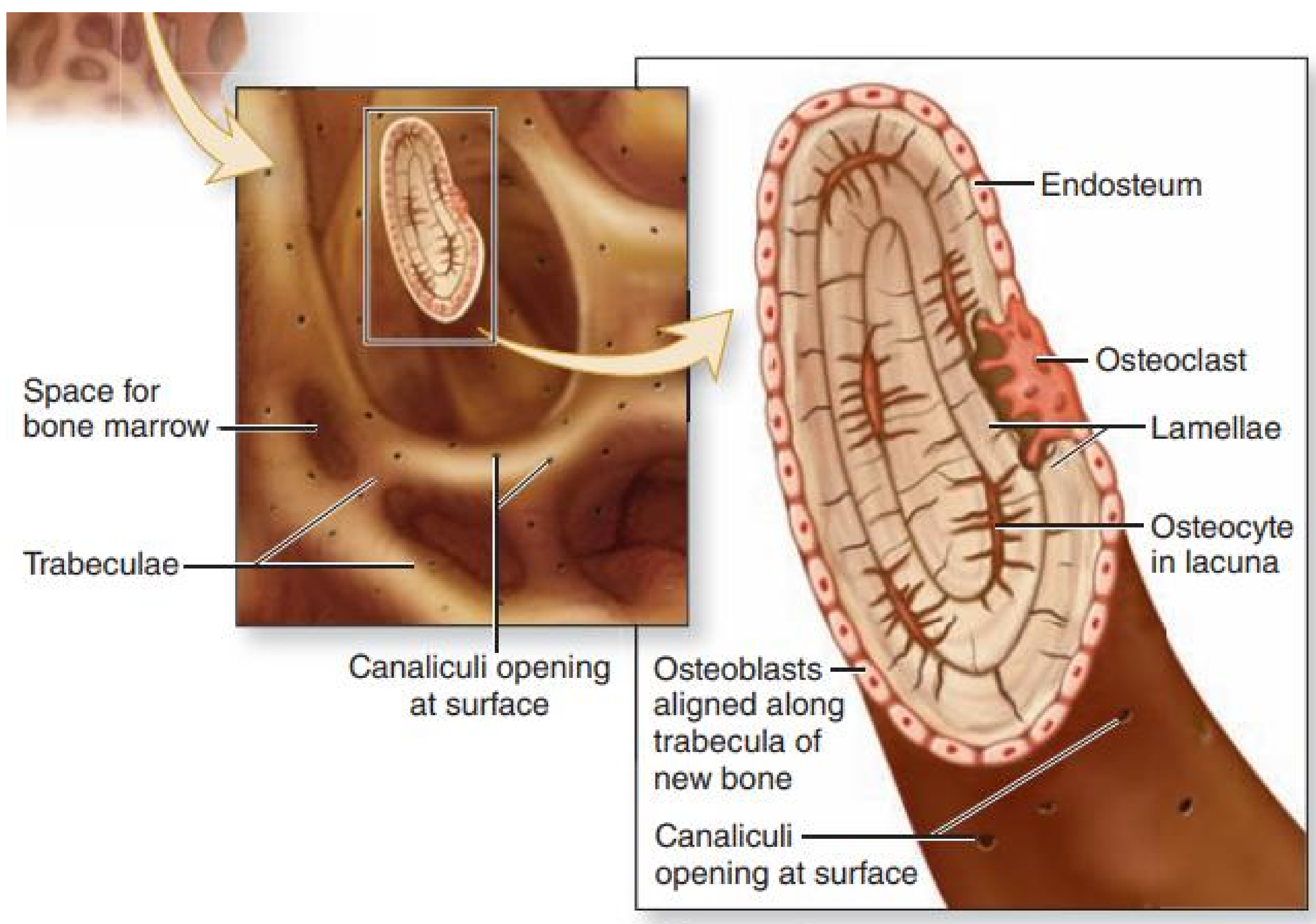
The feature that distinguishes bone from other connective tissue is the mineralization of its matrix which provides an extremely hard tissue capable of providing support and protection.

*The mineral is **calcium phosphate** in the form of **hydroxyapatite crystals***

- Bone tissue is classified as either compact (dense) or spongy (cancellous)

Compact Bone
A compact, dense layer forming the outside of the bone

Spongy Bone
- spongelike meshwork consisting of trabeculae (thin, anastomosing spicules of bone tissue) forming the interior of the bone



(c) Spongy bone

Osteocytes
maintain the calcified matrix and receive nutrients from microvasculature in the central canals of the osteons via very small channels called **canaliculi** that interconnect the lacunae

Periosteum
- A fibrous connective tissue capsule that covers the outer surface of the bone

Endosteum
- a layer of connective tissue containing osteogenic cells that lines bone cavities
- covers all trabeculae around the marrow cavities

Perforating (or Sharpey) fibers
- Bundles of periosteal collagen fibers that penetrate the bone matrix
- Binds the periosteum to bone

Lacunae
Spaces within the bone matrix, each of which contains a bone cell

Canaliculi
- Small channels that interconnects the lacunae
- Small tunnels into which the osteocyte extends numerous processes

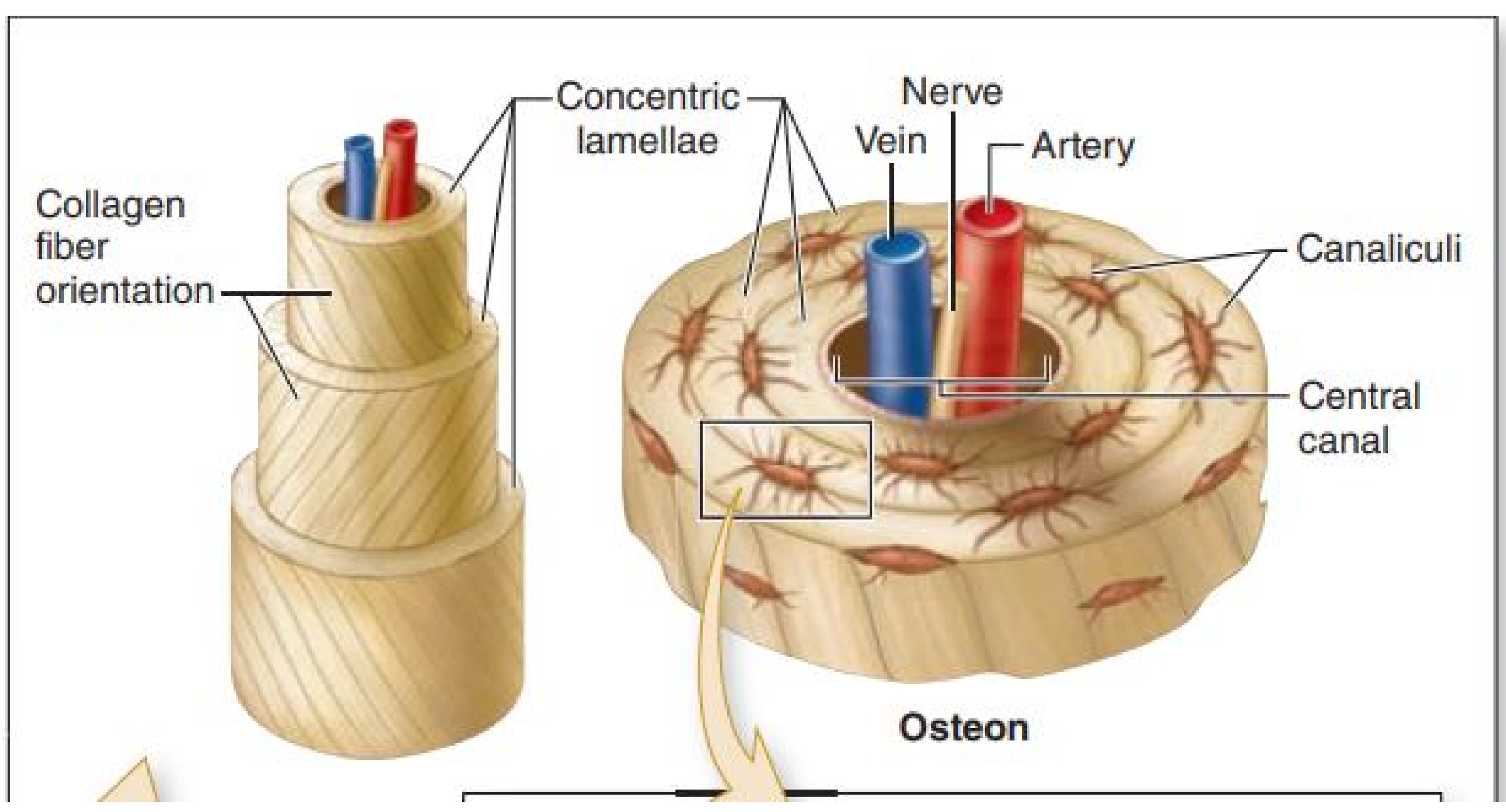
3 Major Cell types

Osteocytes
- Osteon (bone) + kytos (cell)
- are found in cavities (lacunae) between bone matrix layers (lamellae), with cytoplasmic processes extending into small canaliculi between lamellae

Osteoblasts
- Osteon + blastos (germ)
- synthesize the organic components of the matrix

Osteoclasts
- Osteon + klastos (broken)
- are multinucleated, giant cells involved in the resorption and remodeling of bone tissue

OSTEON



- Bundles covered by your endosteum
- Forms born as an organ
- Supply the blood vessels from the periosteum
- Known as Haversian system

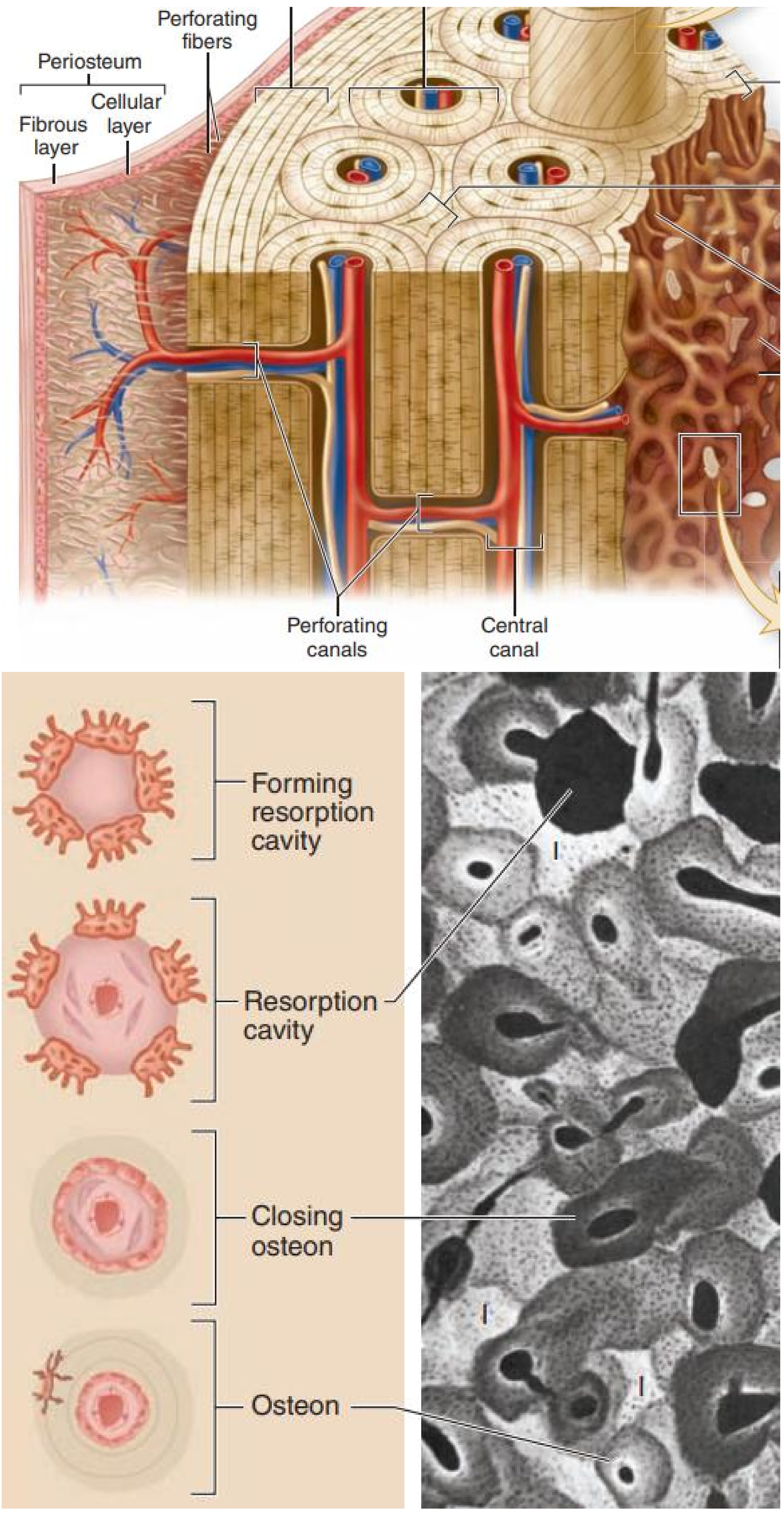
- Refers to the complex of concentric lamellae surrounding a small central canal that contains blood vessels, nerves, loose connective tissue, and endosteum

Cement Line

- outer boundary of each osteon is a more collagen-rich layer

Perforating Canals (Volkman's canals)

- Channels in lamellar bone through which blood vessels and nerves travel from the periosteal and endosteal surfaces to reach the osteonal canal
- They also connect osteonal canals to one another



During remodeling of compact bone, osteoclasts act as a cutting cone tunneling into existing bone matrix. Behind the osteoclasts, a population of osteoblasts enters the newly formed tunnel and lines its walls. The osteoblasts secrete osteoid in a cyclic manner, producing layers of new matrix (lamellae) with cells (osteocytes) trapped in lacunae. The tunnel becomes constricted with multiple concentric layers of new matrix, and its lumen finally exists as only a narrow central canal with small blood vessels. The dashed lines in (a) indicate the levels of the structures shown in cross-section (b). An x-ray image (c) shows the different degrees of mineralization in osteons and in interstitial lamellae (**I**).

OSTEOBLASTS

- Differentiated bone-forming cell that secretes bone matrix
- Located exclusively at the surfaces of bone matrix
- synthesize and secrete the organic components of bone matrix, which include type I collagen fibers, proteoglycans, and several glycoproteins such as osteonectin

When their synthesizing activity declines, they flatten and basophilia is reduced; inactive osteoblasts represent most of the flattened bone lining cells in both the endosteum and periosteum

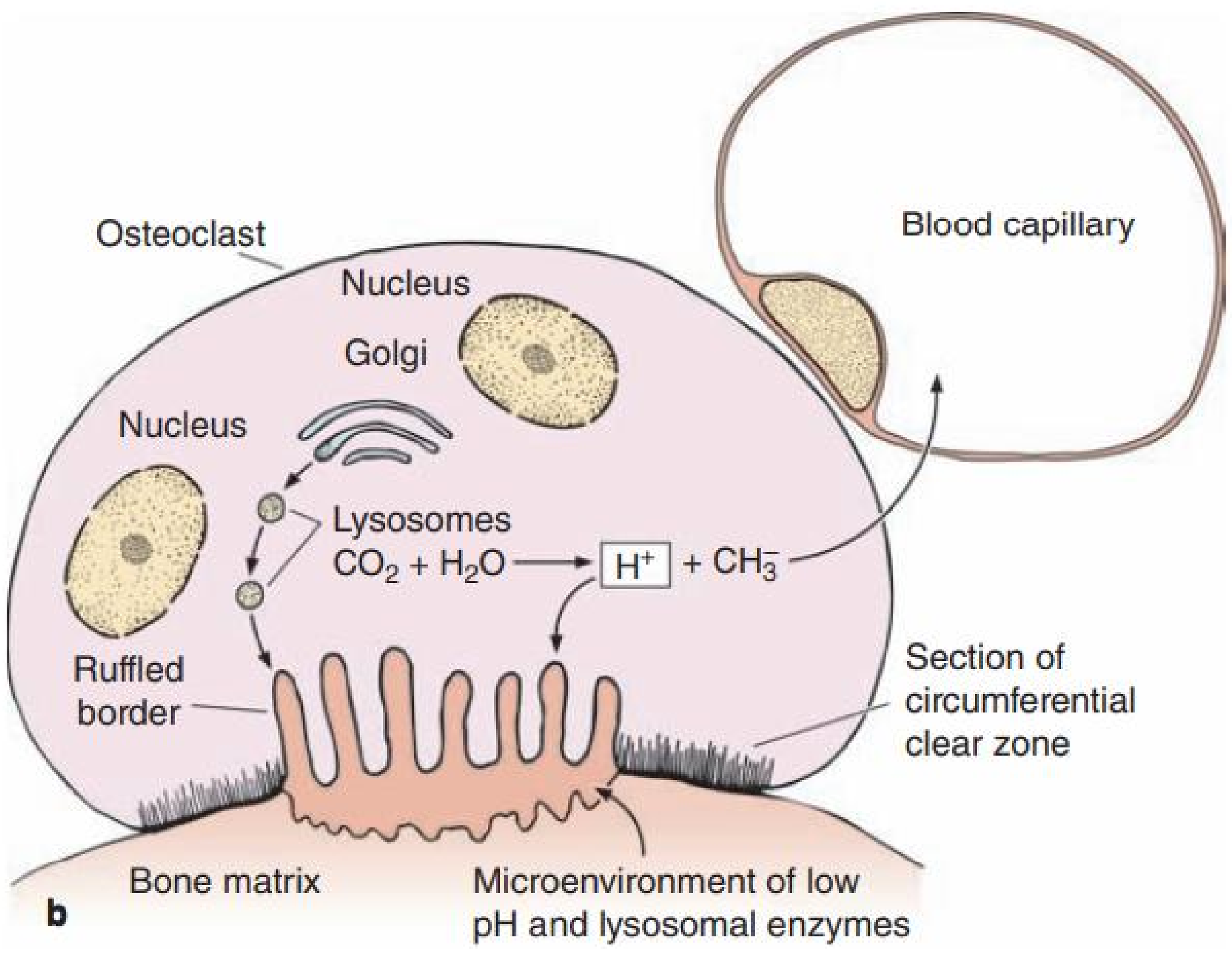
OSTEOCYTES

- Mature bone cell enclosed by bone matrix that it previously secreted as an osteoblast
- enclosed singly within the lacunae that are regularly spaced throughout the mineralized matrix
- communicate with one another via gap junctions on the dendritic processes in the canaliculi and on osteoblasts and bone lining cells
- flat, almond shaped osteocytes exhibit significantly less RER, smaller Golgi complexes, and more condensed nuclear chromatin
- maintain the bony matrix, and their death is followed by rapid matrix resorption
- roles for osteocytes in calcium homeostasis and as sensors for detection of mechanical stresses on bone, which is also important in directing bone remodeling

In the transition from osteoblasts to osteocytes, the cells extend many long dendritic processes, which also become surrounded by calcifying matrix. Osteocytic processes thus come to occupy the many canaliculi.

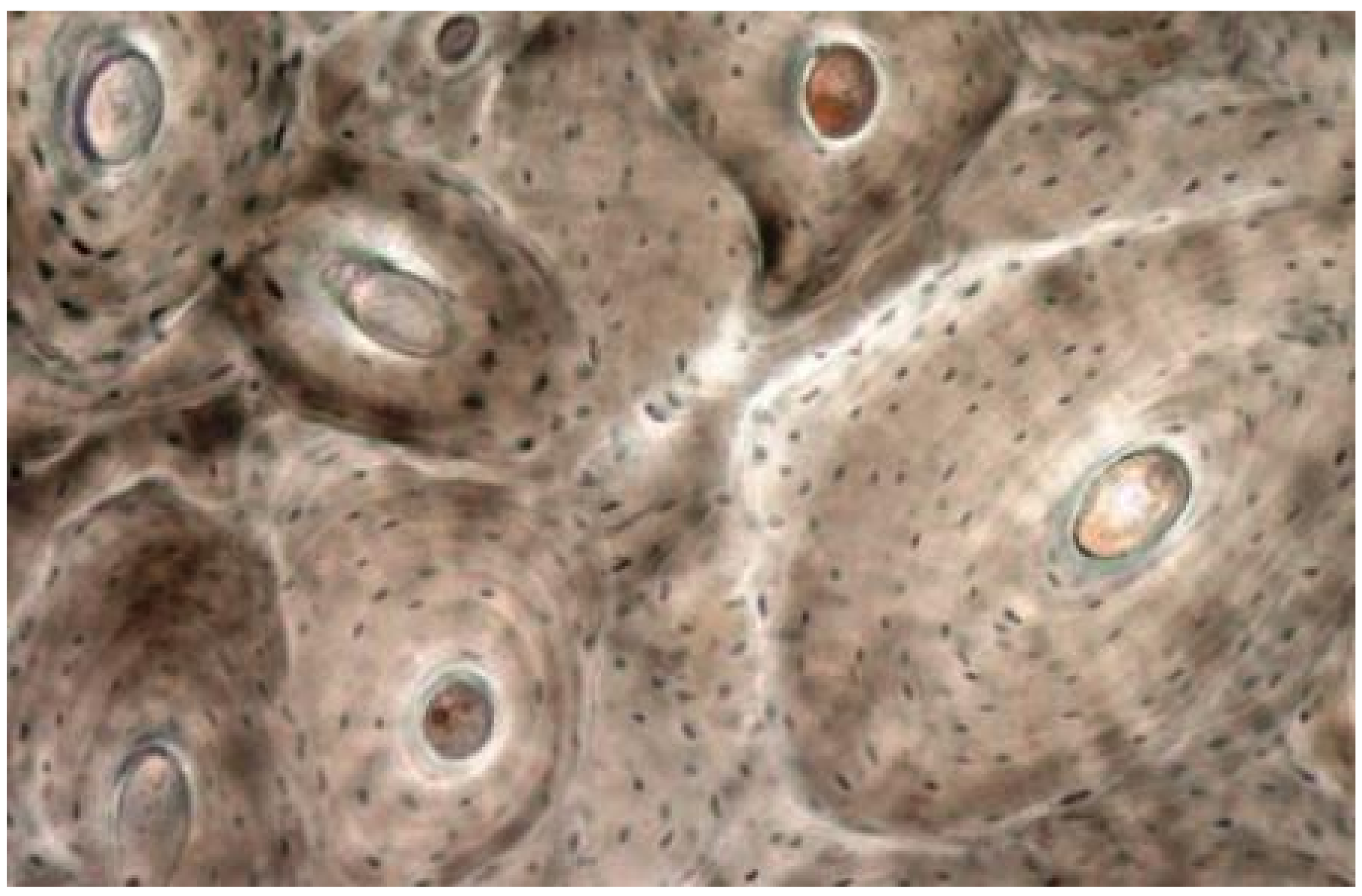
OSTEOCLASTS

- Responsible for bone resorption
- very large, motile cells with multiple nuclei
- play a major role in matrix resorption during bone growth and remodeling
- In areas of bone under going resorption, osteoclasts lie within enzymatically etched depressions or cavities in the matrix known as **resorption cavities** (also called **Howship lacunae**)



TYPE OF BONE

Lamellar Bone



Most bone in adults, compact or cancellous, is organized as lamellar bone, characterized by multiple layers or lamellae of calcified matrix

» MEDICAL APPLICATION

Osteogenesis imperfecta, or "brittle bone disease," refers to a group of related congenital disorders in which the osteoblasts produce deficient amounts of type I collagen or defective type I collagen due to genetic mutations. Such defects lead to a spectrum of disorders, all characterized by significant fragility of the bones. The fragility reflects the deficit in normal collagen, which normally reinforces and adds a degree of resiliency to the mineralized bone matrix.

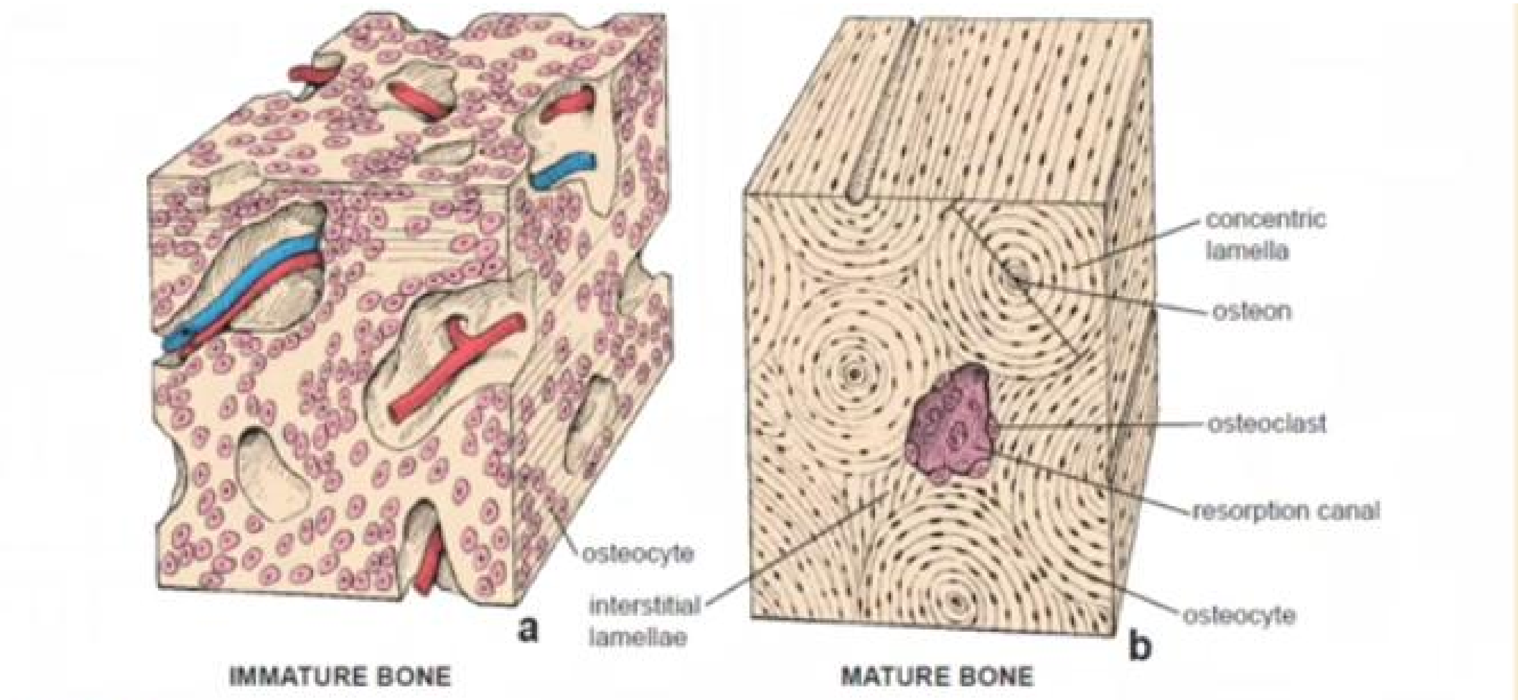


FIGURE 8.5 • **Diagram of immature and mature bone.** Immature bone does not display an organized lamellar appearance because of the interlacing arrangement of the collagen fibers. The cells tend to be randomly arranged, whereas the cells in mature bone are organized in a circular fashion that reflects the lamellar structure of the Haversian system. Resorption canals in mature bone have their long axes in the same direction as the Haversian canals.

Bone remodeling *is continuous throughout life and involves a process of bone resorption and bone formation.*

In compact bone, remodeling resorbs parts of old osteons and produces new ones. Resorption involves the actions of osteoclasts, often working in groups to remove old bone in tunnel-like cavities having the approximate diameter of new osteons.

Woven Bone

- nonlamellar and characterized by random disposition of type I collagen fibers
- first bone tissue to appear in embryonic development and in fracture repair
- usually temporary and is replaced in adults by lamellar bone, except in a very few places in the body, for example, near the sutures of the calvaria and in the insertions of some tendons

BONE FORMATION (OSTEOGENESIS)

The development of a bone is traditionally classified as **endochondral** or **intramembranous**

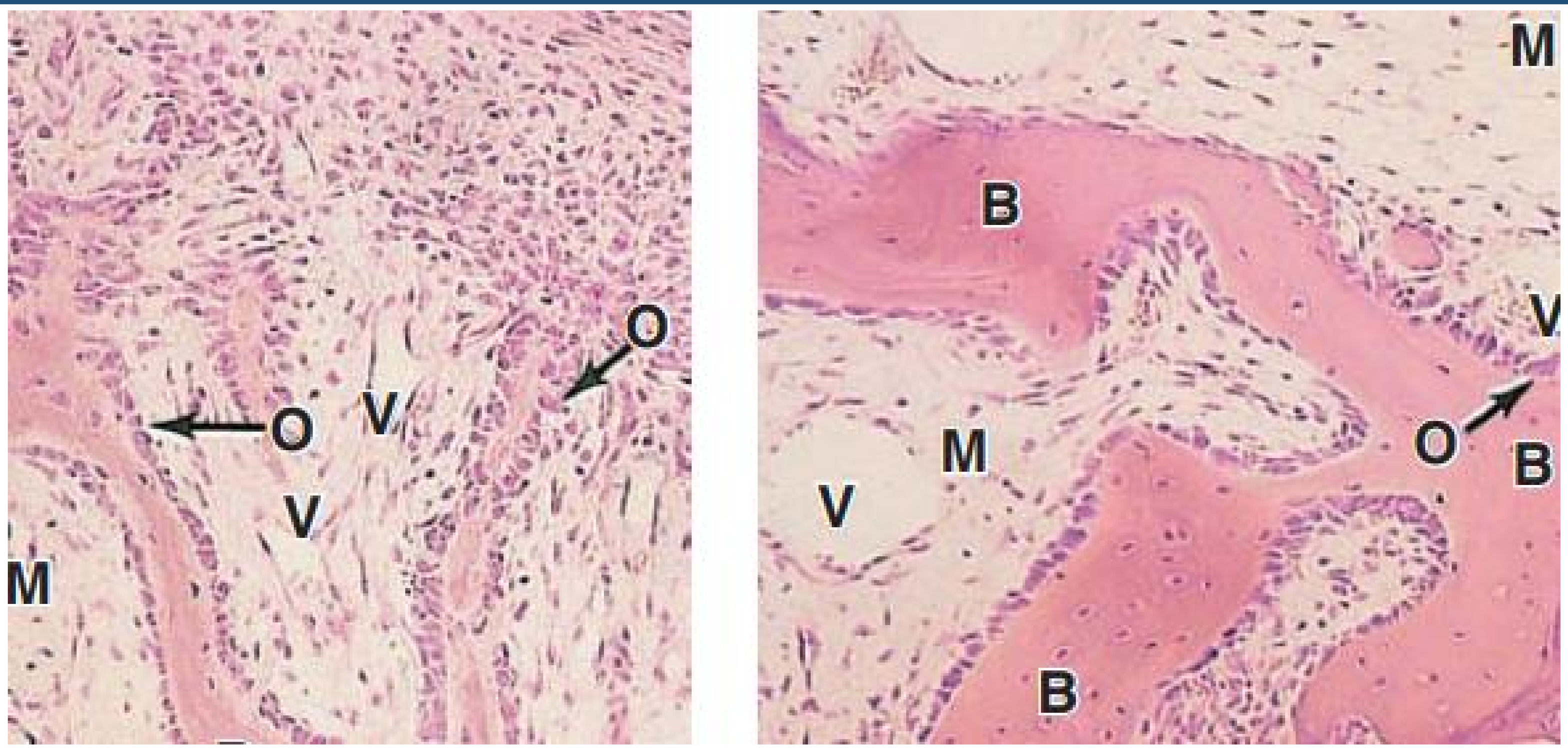
Intramembranous ossification

- In which osteoblasts differentiate directly from mesenchyme and begin secreting osteoid

Endochondral ossification

- in which a preexisting matrix of hyaline cartilage is eroded and invaded by osteoblasts, which then begin osteoid production

The names refer to the mechanisms by which the bone forms initially; in both processes, the bone tissue that appears first is temporary woven bone, which is soon replaced by stronger lamellar bone. During growth of all bones, areas of woven bone, areas of bone resorption, and areas of lamellar bone all exist contiguous to one another.



INTRAMEMBRANOUS OSSIFICATION

which most flat bones begin to form, is so called because it takes place within condensations ("membranes") of embryonic mesenchymal tissue

Within the condensed layer of mesenchyme, the starting points for bone formation are called ossification centers.

In these areas mesenchymal cells differentiate into osteoprogenitor cells which proliferate and form incomplete layers of osteoblasts around a network of developing capillaries.

From their surfaces facing away from these blood vessels, the polarized osteoblasts secrete the osteoid components that calcify as described earlier and form trabeculae of woven bone

Continued matrix secretion, calcification, and trabecular growth lead slowly to the fusion of neighboring ossification centers and gradually produce layers of compact bone that broadly enclose a region of cancellous bone with marrow and larger blood vessels.

The fontanelles or "soft spots" on the heads of newborn infants are areas in the skull that correspond to parts of the connective tissue that are not yet ossified. Regions of the connective tissue that do not undergo ossification give rise to the endosteum and the periosteum of the new bone.

ENDOCHONDRAL OSSIFICATION

(*endon* (within) + *chondros* (cartilage))

- takes place within a piece of hyaline cartilage whose shape resembles a small version, or model, of the bone to be formed
- principally responsible for initiating most bones of the body and is especially well studied in developing long bones

The first bone tissue appears as a collar surrounding the diaphy sis of the cartilage model.

*This **bone collar** is produced by activity of osteoblasts that form within the surrounding perichondrium.*

The collar impedes diffusion of oxygen and nutrients into the underlying cartilage, promoting degenerative changes there.

Blood vessels from the peri chondrium (now the periosteum) penetrate through the bone collar, bringing osteoprogenitor cells to the porous central region.

Next, osteoblasts adhere to the remnants of calcified cartilage matrix and produce woven bone.

The calcified cartilage at this stage appears basophilic, and the new bone is more acidophilic

Primary Ossification Center

The first site where bone begins to form in the diaphysis of a long bone

Secondary Ossification Center

appear later at the epiphyses of the cartilage model and develop in a similar manner

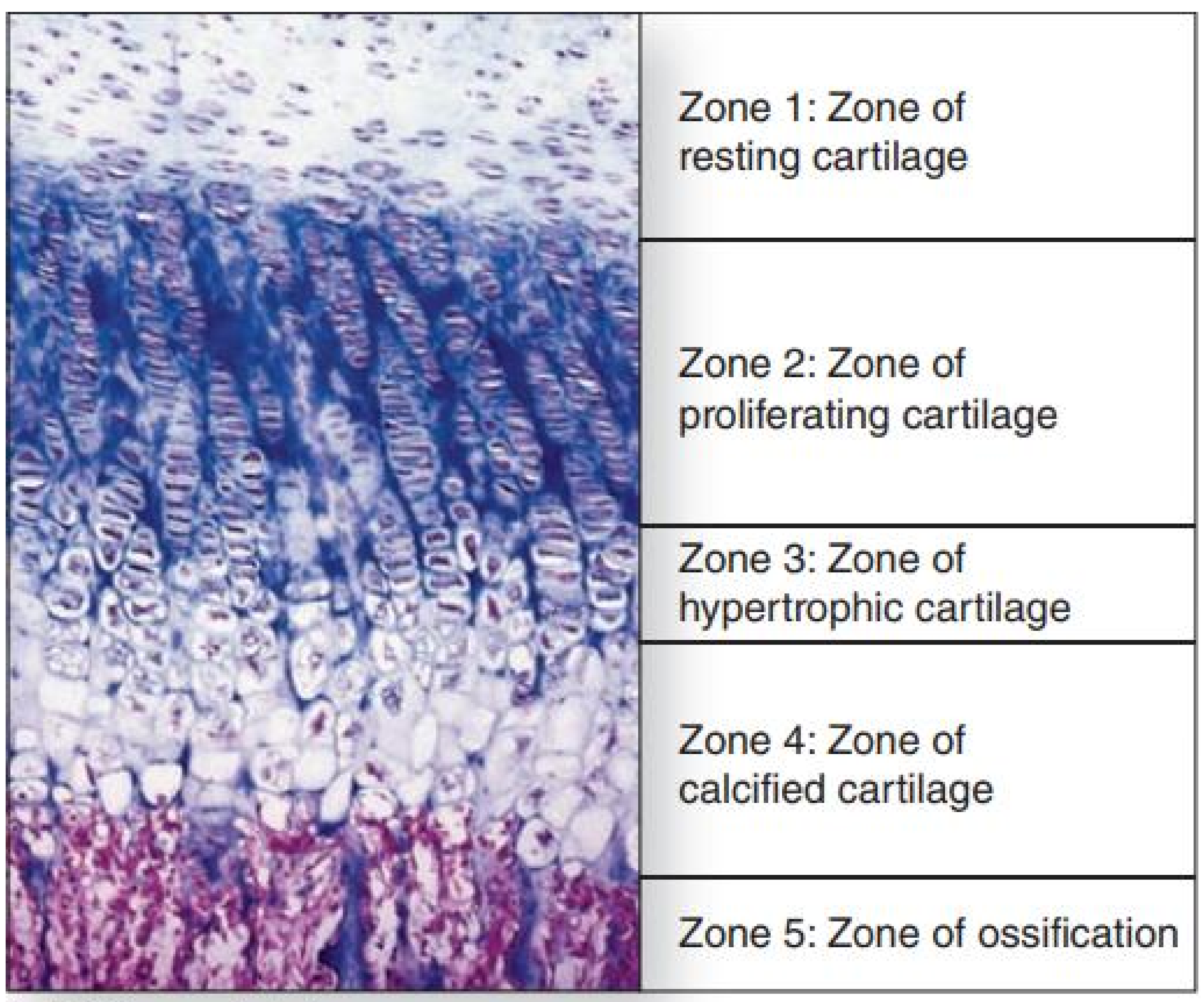
During their expansion and remodeling, the primary and secondary ossification centers produce cavities that are gradually filled with bone marrow and trabeculae of cancellous bone.

With the primary and secondary ossification centers, two regions of cartilage remain:

- The layer of articular cartilage within joints which usually persists through adult life and does not contribute to bone growth
- The specially organized epiphyseal cartilage (also called epiphyseal plate or growth plate), which connects each epiphysis to the diaphysis

The epiphyseal cartilage is responsible for the growth in length of the bone and disappears at adulthood, causing bone growth to cease.

Once the epiphyses have closed, additional growth in length of bones is no longer possible although bone widening may still occur.



b Epiphyseal plate

1. The **resting zone** consists of hyaline cartilage with typical chondrocytes.

2. In the **proliferative zone**, chondrocytes begin to divide rapidly and form columns of stacked cells parallel to the long axis of the bone.

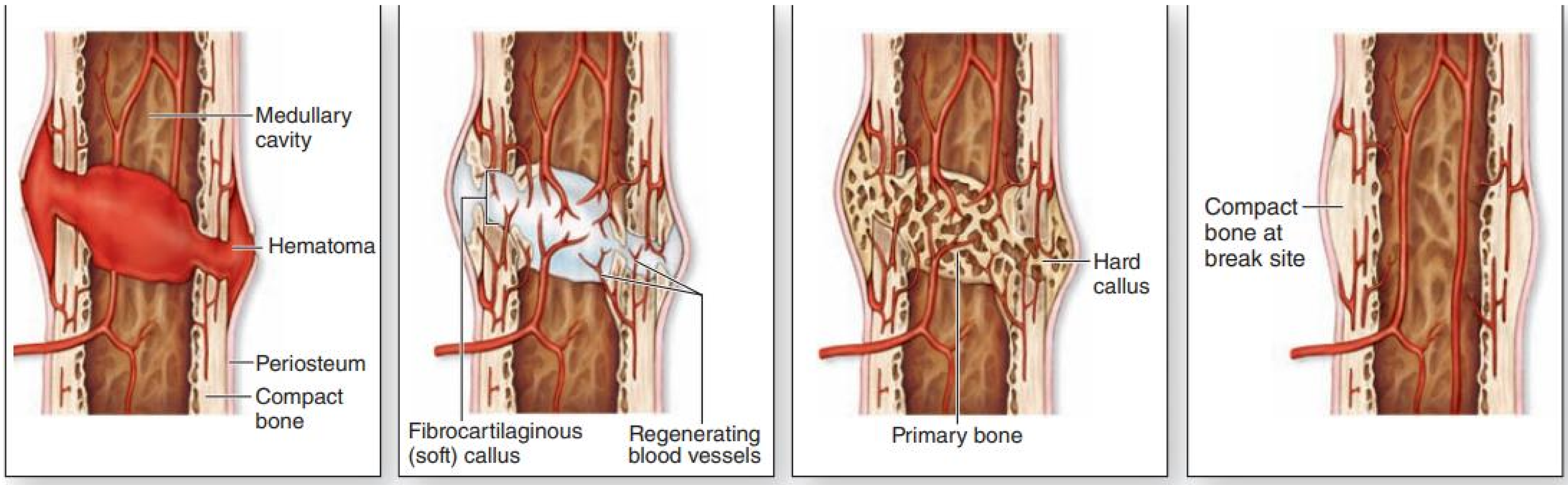
3. The **hypertrophic cartilage** zone contains swollen, degenerative chondrocytes whose cytoplasm has accumulated glycogen. This hypertrophy compresses the matrix into thin septa between the chondrocytes.

4. In the **calcified cartilage zone**, loss of the chondrocytes by apoptosis is accompanied by calcification of the septa of cartilage matrix by the formation of hydroxyapatite crystals

5. In the **ossification zone**, bone tissue first appears. Capillaries and osteoprogenitor cells originally from the periosteum invade the cavities left by the chondrocytes. Many of these cavities will be merged and become the marrow cavity. Osteoblasts settle in a layer over the septa of calcified cartilage matrix and secrete osteoid over these structures, forming woven bone

In summary, growth in length of a long bone occurs by proliferation of chondrocytes in the epiphyseal plate. At the same time, chondrocytes in the diaphyseal side of the plate hypertrophy, their matrix becomes calcified, and the cells die. Osteoblasts lay down a layer of new bone on the calcified cartilage matrix. Because the rates of these two opposing events (proliferation and destruction) are approximately equal, the epiphyseal plate does not change thickness. Instead, it is displaced away from the middle of the diaphysis, resulting in growth in length of the bone.

BONE GROWTH, REMODELING, & REPAIR



(a) A fracture hematoma forms. **(b)** A fibrocartilaginous (soft) callus forms. **(c)** A hard (bony) callus forms. **(d)** The bone is remodeled.

>> MEDICAL APPLICATION

Bone fractures are repaired by a developmental process involving fibrocartilage formation and osteogenic activity of the major bone cells (Figure 8–18). Bone fractures disrupt blood vessels, causing bone cells near the break to die. The damaged blood vessels produce a localized hemorrhage or hematoma. Clotted blood is removed along with tissue debris by macrophages and the matrix of damaged, cell-free bone is resorbed by osteoclasts.

The periosteum and the endosteum at the fracture site respond with intense proliferation and produce a soft callus of fibrocartilage-like tissue that surrounds the fracture and covers the extremities of the fractured bone.

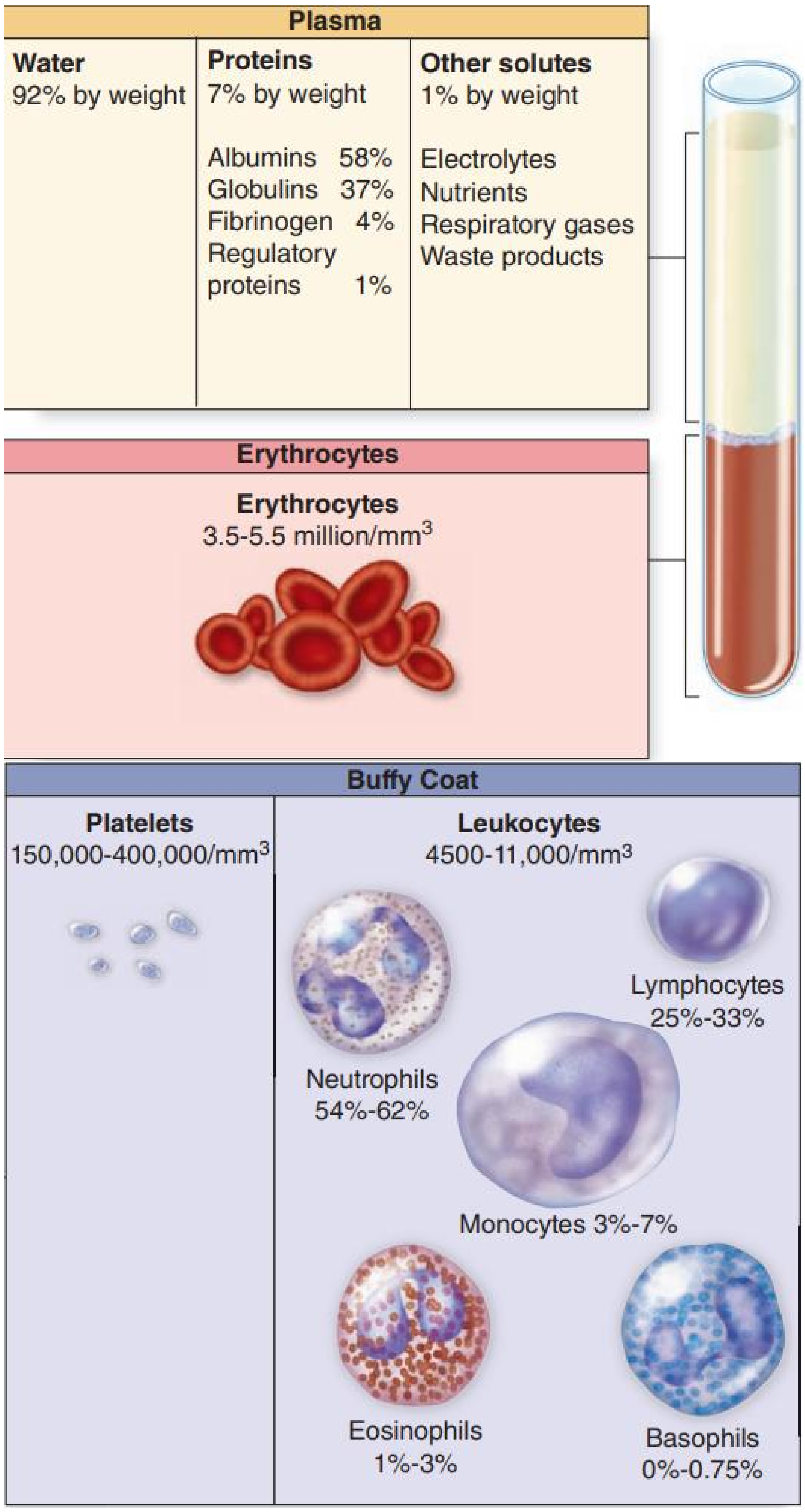
The fibrocartilaginous callus is gradually replaced in a process that resembles a combination of endochondral and intramembranous ossification. This produces a hard callus of woven bone around the fractured ends of bone.

Stresses imposed on the bone during repair and during the patient's gradual return to activity serve to remodel the bone callus. The immature, woven bone of the callus is gradually resorbed and replaced by lamellar bone, remodeling and restoring the original bone structure.

Repair of a fractured bone occurs through several stages but utilizes mechanisms already in place for bone remodeling. **(a)** Blood vessels torn within the fracture release blood that clots to produce a large fracture hematoma. **(b)** This is gradually removed by macrophages and replaced by a soft fibrocartilage-like mass of procallus tissue rich in collagen and fibroblasts. If broken, the periosteum reestablishes continuity over this tissue. **(c)** This soft procallus is invaded by regrowing blood vessels and osteoblasts. In the next few weeks the fibrocartilage is gradually replaced by trabeculae of woven bone, forming a hard callus throughout the original area of fracture. **(d)** The woven bone is then remodeled as compact and cancellous bone in continuity with the adjacent uninjured areas and fully functional vasculature is reestablished.

BLOOD

- The liquid portion of circulating blood is plasma, while the cells and platelets comprised the formed elements; upon clotting, some proteins are removed from plasma & others are released from platelets, forming new liquid termed serum.
- Important protein components of plasma include albumin, diverse alpha- & beta globulins, proteins of the complement system, & fibrinogen, all of which are secreted w/in the liver, as well as the immunoglobulins.



BLOOD CELLS

Erythrocytes (RBC)

- Make up the **hematocrit** portion (45%) of a blood sample
- enucleated, flexible biconcave discs
- 7.5 µm in diameter
- Filled w/ hemoglobin for the uptake, transport, & release of Oxygen
- Normal life span of 120 days

Leukocytes (WBC)

- Are broadly grouped as **granulocytes** (neutrophils, eosinophils, basophils) or **agranulocytes** (lymphocytes, moocytes)

Neutrophils

- Most abundant type of WBC
- Have polymorphic, multilobed nuclei
- Faint pink cytoplasmic granules that contain many factors for highly efficient phagolysosomal killing & removal of bacteria
- active phagocytes of bacteria and other small particles and are usually the first leukocytes to arrive at sites of infection, where they actively pursue bacterial cells using chemotaxis

Eosinophils

- Have bilobed nuclei & eosinophilic specific granules containing factors for destruction of helminthic parasites & fr modulating inflammation

Basophils

- Rarest type of circulating WBC
- Have irregular bilobed nuclei & resemble mast cells w/ strongly basophilic specific granules containing factors important in allergies & chronic inflammatory conditions, including **histamines, heparin, chemokines,** and various **hydrolases**

Lymphocytes

- Agranulocytes w/ many functions as T-and B- & Natural killer cell subtypes in the immune system
- Range widely in size depending on their activation state
- Have roughly spherical nuclei w/ little cytoplasm & few organelles
- Also called Robin's egg

Monocytes

- Blood macrophages
- Larger agranulocyte w/ distinctly indented or C-shaped nuclei
- Circulate as precursors of macrophages & other cells of the **mononuclear phagocyte system**

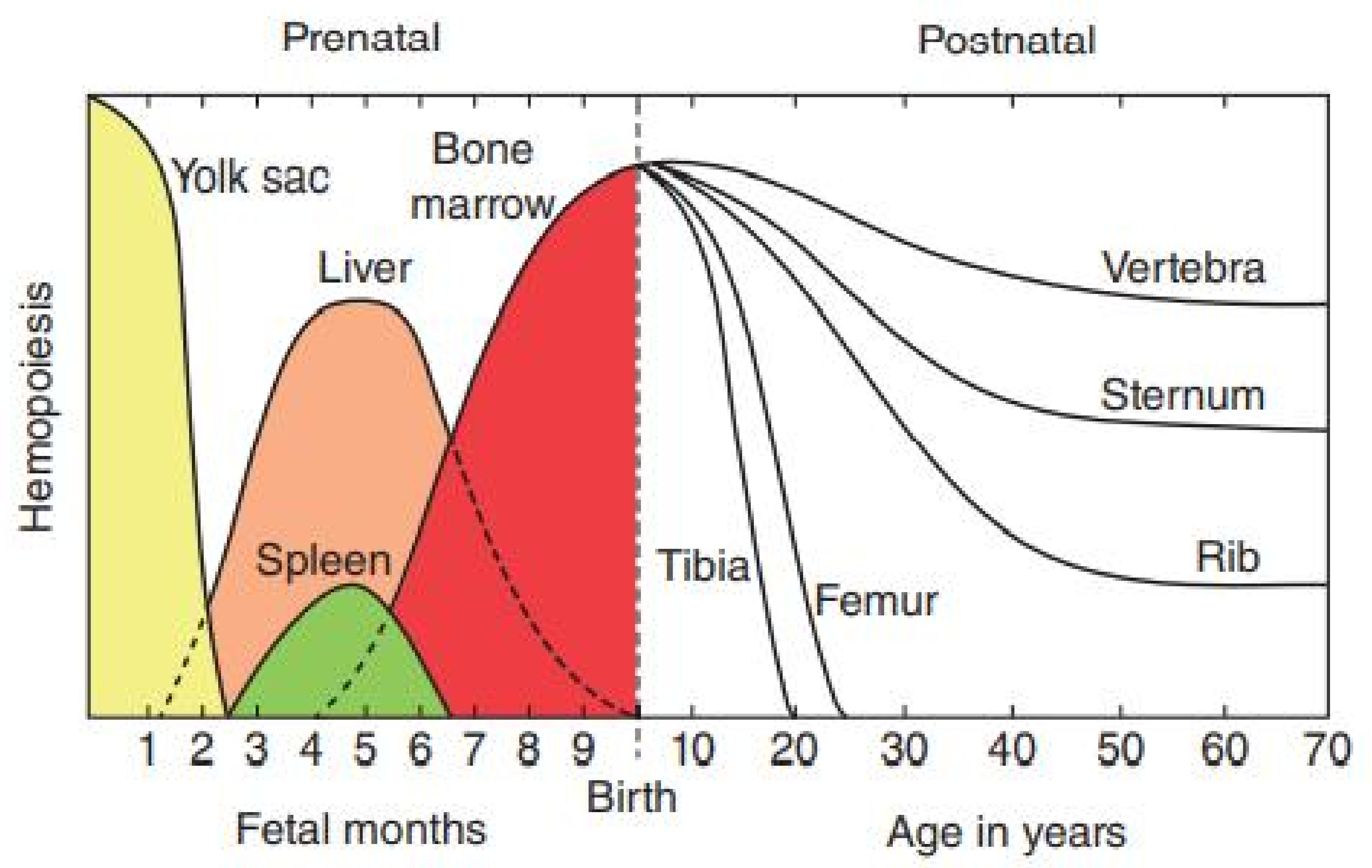
Platelets

- very small non nucleated, membrane-bound cell fragments only 2 to 4 µm in diameter
- Derived from **megakaryocytes** in bone marrow w/ a **marginal bundle** of actin filaments, **alpha granules** and **delta granules,**

and an **open canalicular system** of membranous vesicles;

- Rapid degranulation on contact w/ collagen triggers blood clotting

HEMOPOIESIS



Mature blood cells have a relatively short life span and must be continuously replaced with new cells from precursors developing during hemopoiesis (Gr. haima , blood + poiesis , a making)

In the early embryo (2-8 weeks) these blood cells arise in the **yolk sac** mesoderm.

In the second trimester, hemopoiesis (also called hematopoiesis) occurs primarily in the developing liver , with the spleen playing a more minor role
In the fourth month, skeletal elements begin to ossify and bone marrow develops in their medullary cavities, so that in the third trimester marrow of specifi c bones becomes the major hemopoietic organ

After the fifth fetal month, it becomes the main or primary site of hematopoeisis until postnatal life

HEMOPOIETIC STEM CELLS

*All blood cells arise from a single major type of **pluripotent stem cell** in the bone marrow that can give rise to all the blood cell types*

These pluripotent stem cells are rare, but they proliferate and form two major lineages of progenitor cells with restricted potentials (committed to produce specific blood cells): one for lymphoid cells (lymphocytes) and another for myeloid cells (Gr. myelos , marrow) that develop in bone marrow.

*The progenitor cells for blood cells are commonly called **colony-forming units (CFUs)**, because they give rise to colonies of only one cell type when cultured or injected into a spleen.*

Tabang di nako kasabot

FIGURE **13–2** **Origin and differentiative stages of blood cells.**

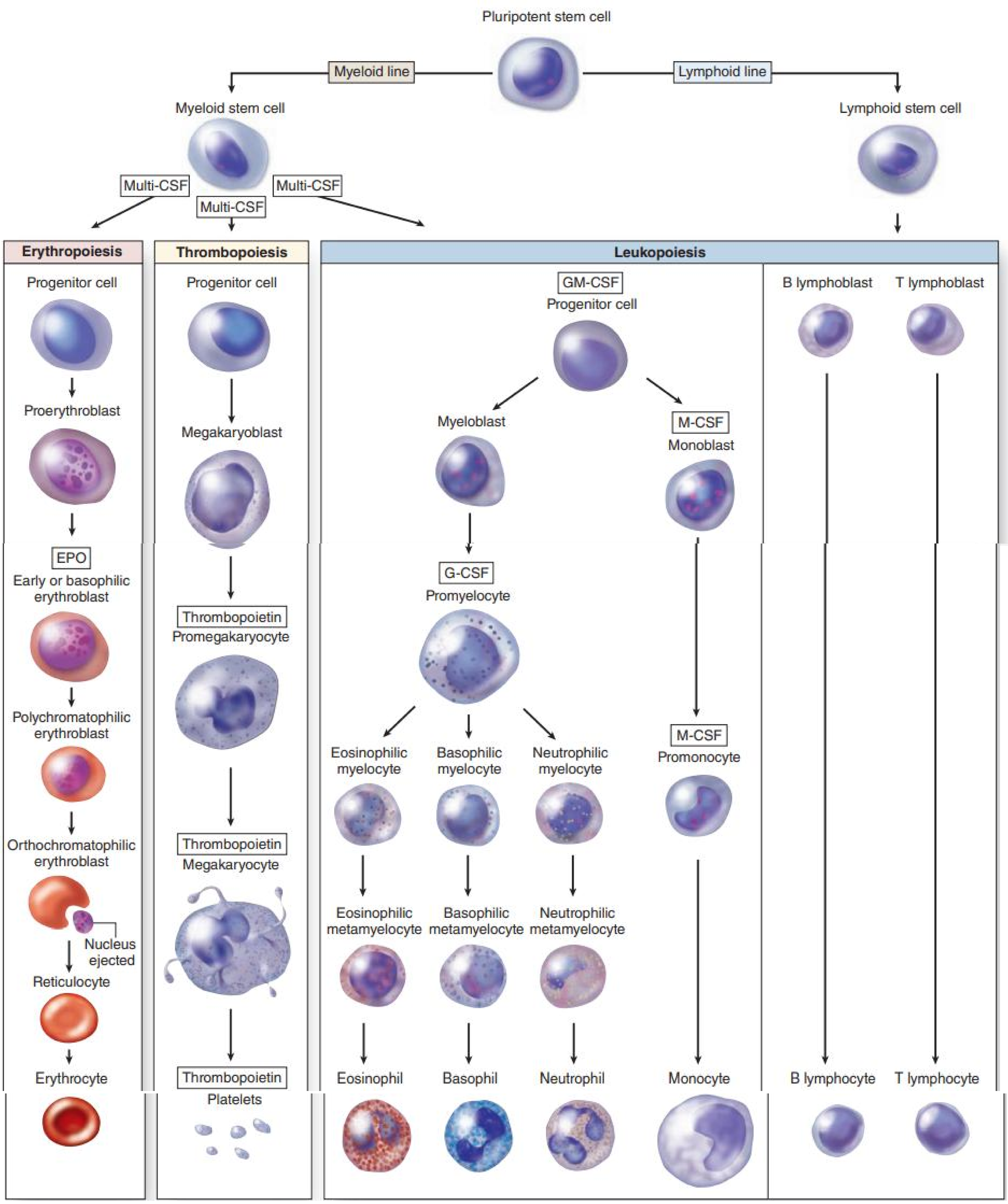


TABLE 4.3 Blood Cell Development Nomenclature of Normal Committed Cell Lines

	Erythrocyte[a]		Megakaryocyte	Granulocyte	Monocyte	Lymphocyte
Immature	Rubriblast	Pronormoblast	Megakaryoblast	Myeloblast	Monoblast	Lymphoblast
	Prorubricyte	Basophilic normoblast	Promegakaryocyte	Promyelocyte	Promonocyte	Prolymphocyte
Bone marrow	Rubricyte	Polychromatophilic normoblast	Megakaryocyte	Myelocyte[b]		
	Metarubricyte	Orthochromatic normoblast or nucleated red blood cell		Metamyelocyte[b]		
Circulating blood	Reticulocyte or polychromatophilic erythrocyte (diffusely basophilic)			Band or stab[b]		
Mature	Erythrocyte		Thrombocyte or platelet	Segmented neutrophil[b]	Monocyte	Lymphocyte
					Macrophage (tissues)	B cell / T cell
						Plasma cell (from B cell)

TABLE 13–1 Major hemopoietic cytokines (growth factors or colony-stimulating factors).

Cytokine	Major Activities and Target Cells[a]	Important Sources
Stem cell factor (SCF)	Mitogen for all hemopoietic progenitor cells	Stromal cells of bone marrow
Erythropoietin (EPO)	Mitogen for all erythroid progenitor and precursor cells, also promoting their differentiation	Peritubular endothelial cells of the kidney; hepatocytes
Thrombopoietin (TPO)	Mitogen for megakaryoblasts and their progenitor cells	Kidney and liver
Granulocyte-macrophage colony-stimulating factor (GM-CSF)	Mitogen for all myeloid progenitor cells	Endothelial cells of bone marrow and T lymphocytes
Granulocyte colony-stimulating factor (G-CSF or filgrastim)	Mitogen for neutrophil precursor cells	Endothelial cells of bone marrow and macrophages
Monocyte colony-stimulating factor (M-CSF)	Mitogen for monocyte precursor cells	Endothelial cells of marrow and macrophages
Interleukin-1 (IL-1)	Regulates activities and cytokine secretion of many leukocytes and other cells	Macrophages and T helper cells
Interleukin-2 (IL-2)	Mitogen for activated T and B cells; promotes differentiation of NK cells	T helper cells
Interleukin-3 (IL-3)	Mitogen for all granulocyte and megakaryocyte progenitor cells	T helper cells

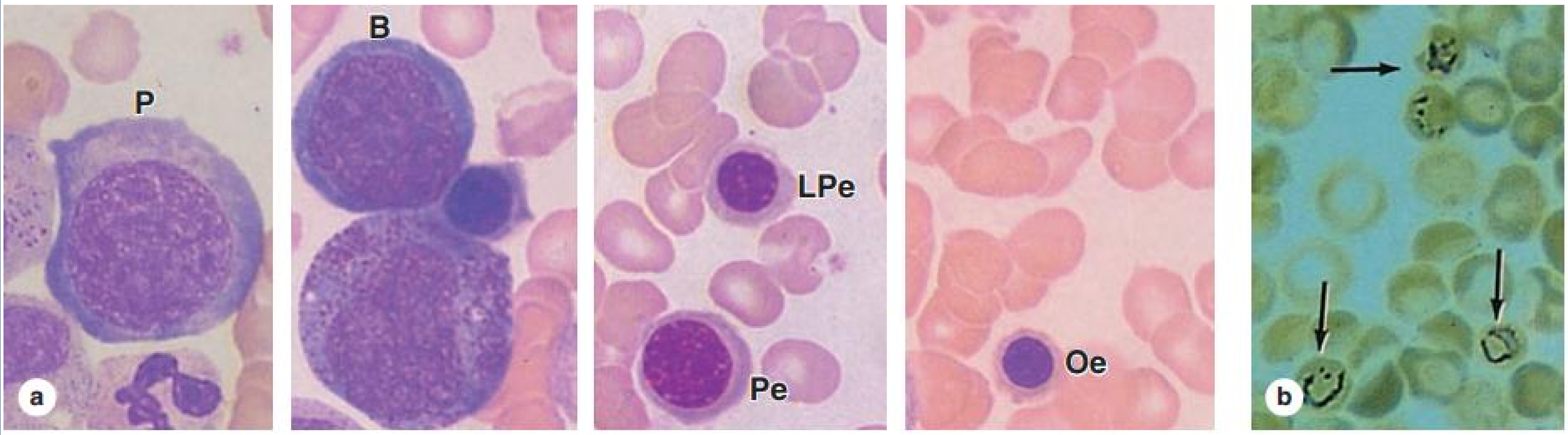
Interleukin-4 (IL-4)	Promotes development of basophils and mast cells and B-lymphocyte activation	T helper cells
Interleukin-5 (IL-5) or eosinophil differentiation factor (EDF)	Promotes development and activation of eosinophils	T helper cells
Interleukin-6 (IL-6)	Mitogen for many leukocytes; promotes activation of B cells and regulatory T cells	Macrophages, neutrophils, local endothelial cells
Interleukin-7 (IL-7)	Major mitogen for all lymphoid stem cells	Stromal cells of bone marrow

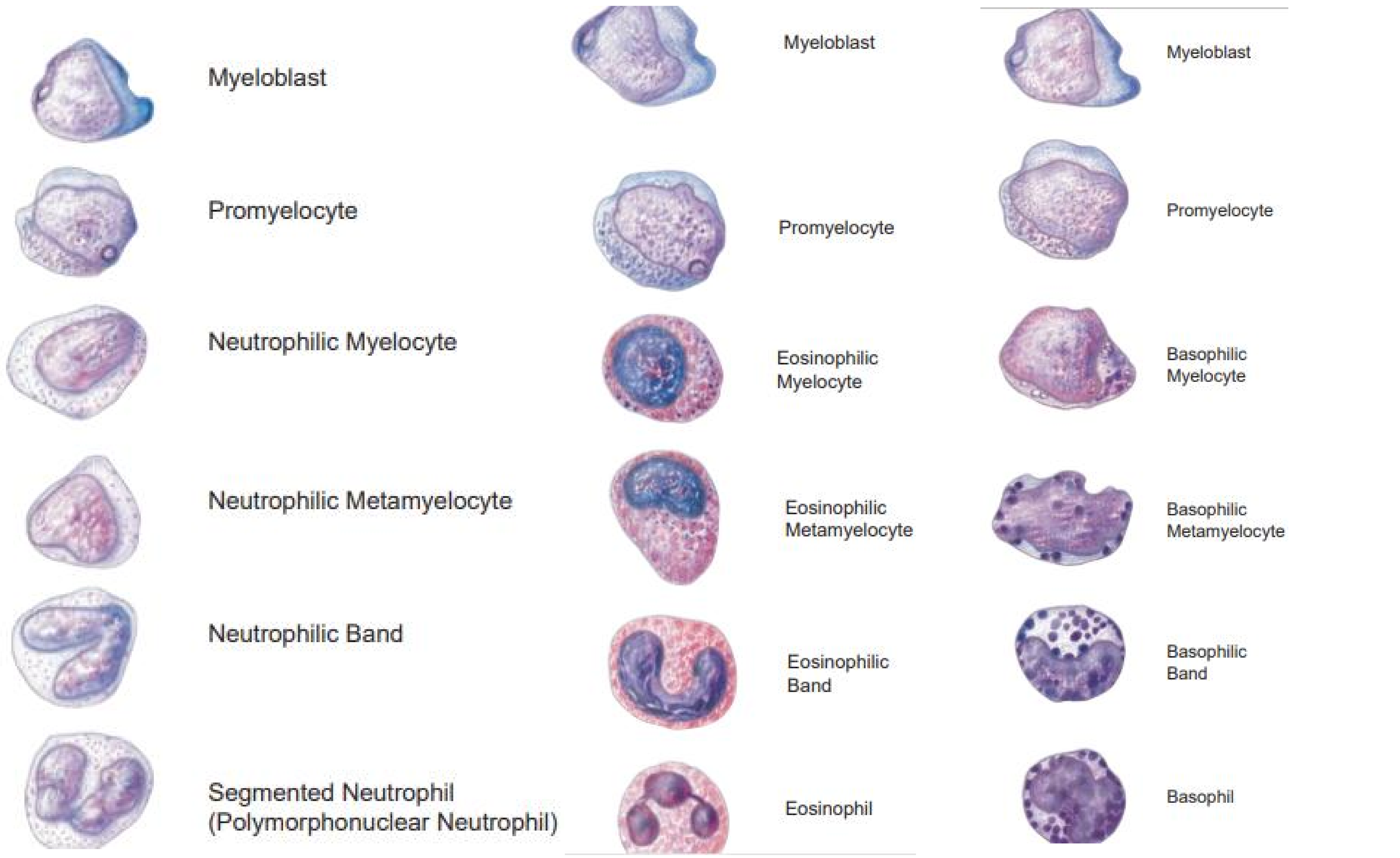
TABLE 8-1 Three Erythroid Precursor Nomenclature Systems

Normoblastic	Rubriblastic	Erythroblastic
Pronormoblast	Rubriblast	Proerythroblast
Basophilic normoblast	Prorubricyte	Basophilic erythroblast
Polychromatic (polychromatophilic) normoblast	Rubricyte	Polychromatic (polychromatophilic) erythroblast
Orthochromic normoblast	Metarubricyte	Orthochromic erythroblast
Polychromatic (polychromatophilic) erythrocyte*	Polychromatic (polychromatophilic) erythrocyte*	Polychromatic (polychromatophilic) erythrocyte*
Erythrocyte	Erythrocyte	Erythrocyte

Erythropoeisis occurs in distinct anatomical sites called **erythropoeitic islands** which are speciliazed niched in which erythroid precursors proliferate, differentiated, and enucleate

RBC basically starts with a very large nucleus then eventually as it matures that nucleus condense and expelled; thus your mature RBC is a nucleotide.

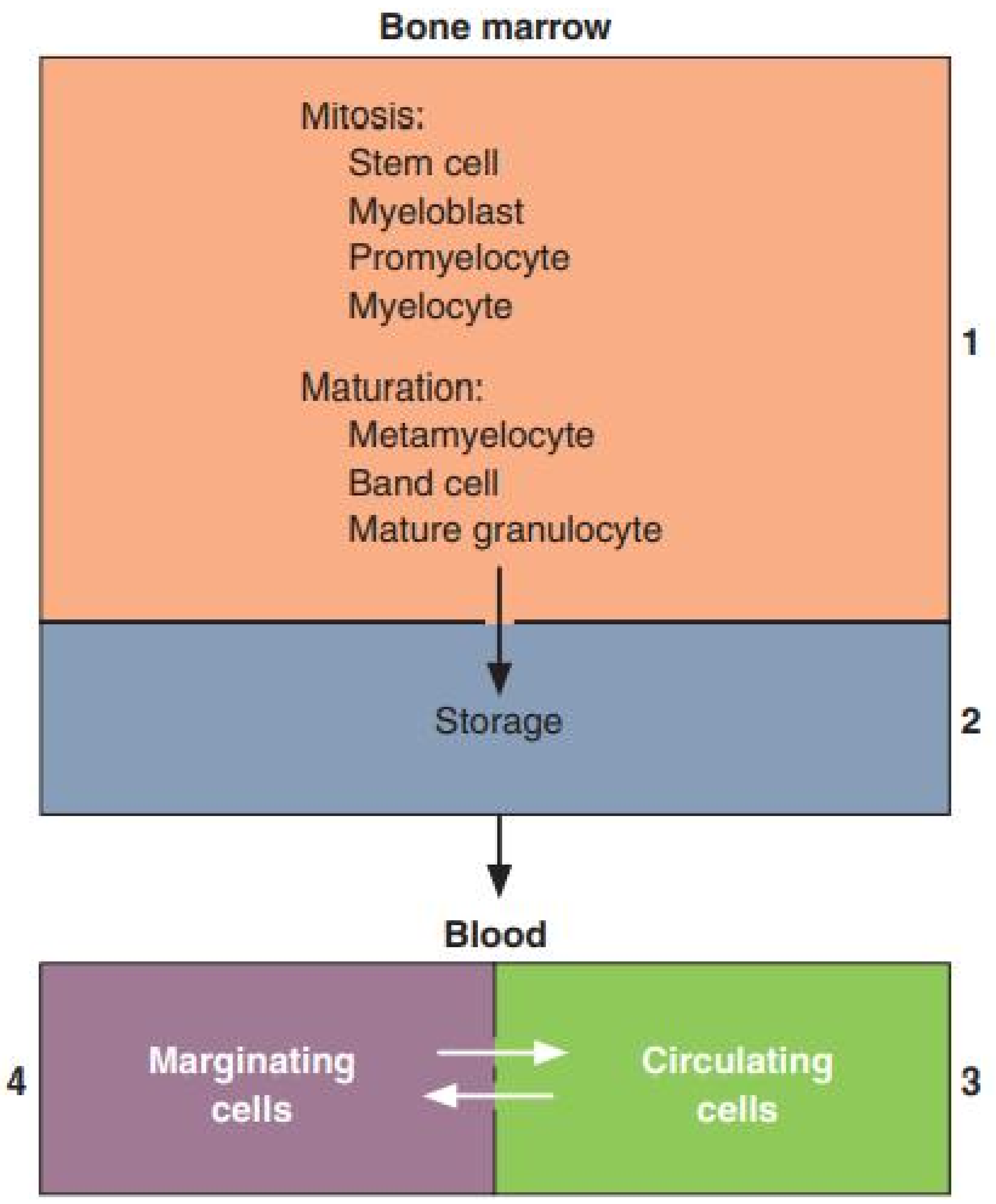




Granulopoeisis can be recognized as a maturational unit.

Maturing cells spend an average of 3-6 days in the proliferating pool.

Average lifespan of 6-10 hours in circulation especially for nuetrophils



Neutrophils exist in at least four anatomically and functionally distinct compartments, whose sizes reflect the number of cells:

(1) A **granulopoietic** compartment in bone marrow with developing progenitor cells.

(2) A **storage** (reserve) compartment, also in red marrow, acts as a buffer system, capable of releasing large numbers of mature neutrophils as needed. Trillions of neutrophils typically move from marrow to the bloodstream every day.

(3) A **circulating** compartment throughout the blood.

(4) A **marginating** compartment, in which cells temporarily do not circulate but rather accumulate temporarily at the surface of the endothelium in venules and small veins.

The marginating and circulating compartments are actually of about equal size, and there is a constant interchange of cells between them, with the half-life of cells in these two compartments less than 10 hours. The granulopoietic and storage compartments together include cells in approximately the first 14 days of their existence and are about 10 times larger than the circulating and marginating compartments.

BOX 12-5 Monocyte Destinations

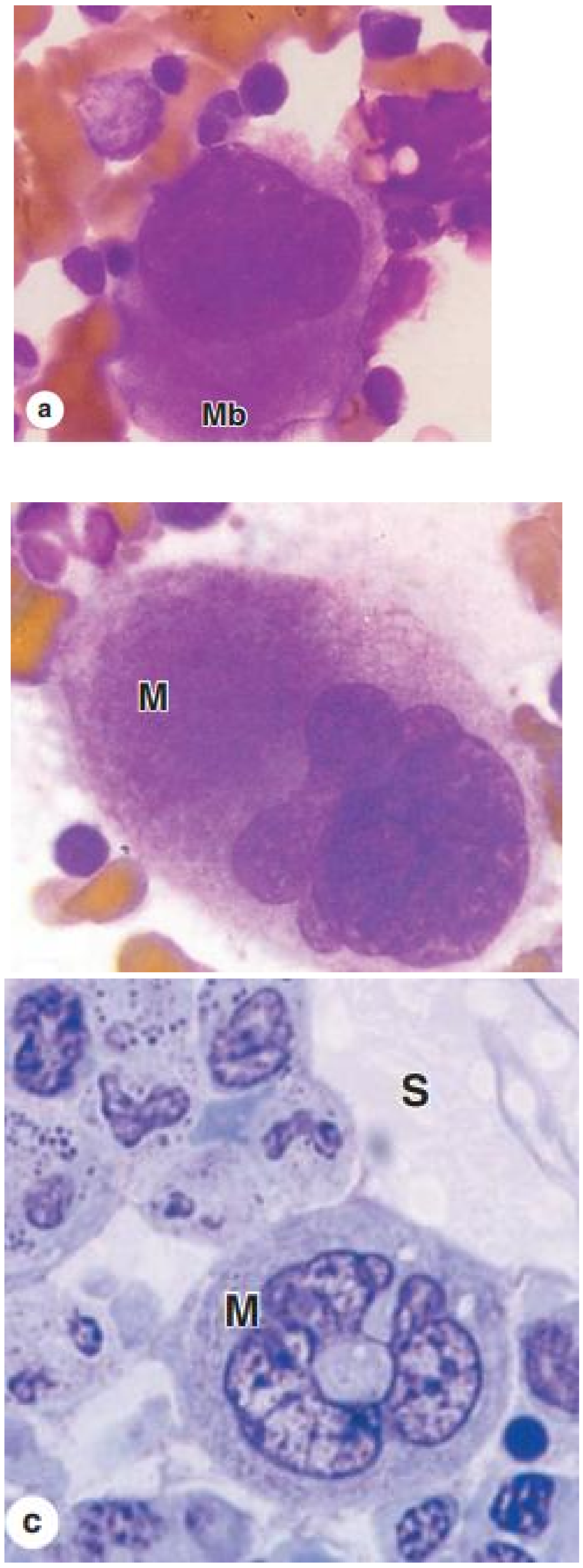
Differentiation into Macrophages

In areas of inflammation or infection (inflammatory macrophages)

As "resident" macrophages in:

- Liver (Kupffer cells)
- Lungs (alveolar macrophages)
- Brain (microglia)
- Skin (Langerhans cells)
- Spleen (splenic macrophages)
- Intestines (intestinal macrophages)
- Peritoneum (peritoneal macrophages)
- Bone (osteoclasts)
- Synovial macrophages (type A cell)
- Kidneys (renal macrophages)
- Reproductive organ macrophages
- Lymph nodes (dendritic cells)

FIGURE **13–13 Megakaryoblast and megakaryocytes.**



(a) Megakaryoblasts (**Mb**) are very large, fairly rare cells in bone marrow, with very basophilic cytoplasm. X1400. Wright. **(b)** Megakaryoblasts undergo endomitosis (DNA replication without intervening cell divisions), becoming polyploid as they differentiate into megakaryocytes (**M**). These cells are even larger but with cytoplasm that is less intensely basophilic. X1400. Wright. **(c)** Micrograph of sectioned bone marrow in which a megakaryocyte (**M**) is shown near sinusoids (**S**). X400. Giemsa. Megakaryocytes produce all the characteristic components of platelets (membrane vesicles, specific granules, marginal microtubule bundles, etc) and in a complex process extend many long, branching pseudopodia-like projections called **proplatelets**, from the ends of which platelets are pinched off almost fully formed.

Megakaryopoeisis takes place adjacent to the sinus endothelium. After 5 days they would then go near the endothelial space and constrict and expand so that its cytoplasm would tear through the endothelial openings and expel the platelet in the process known as **pro platelet process.**

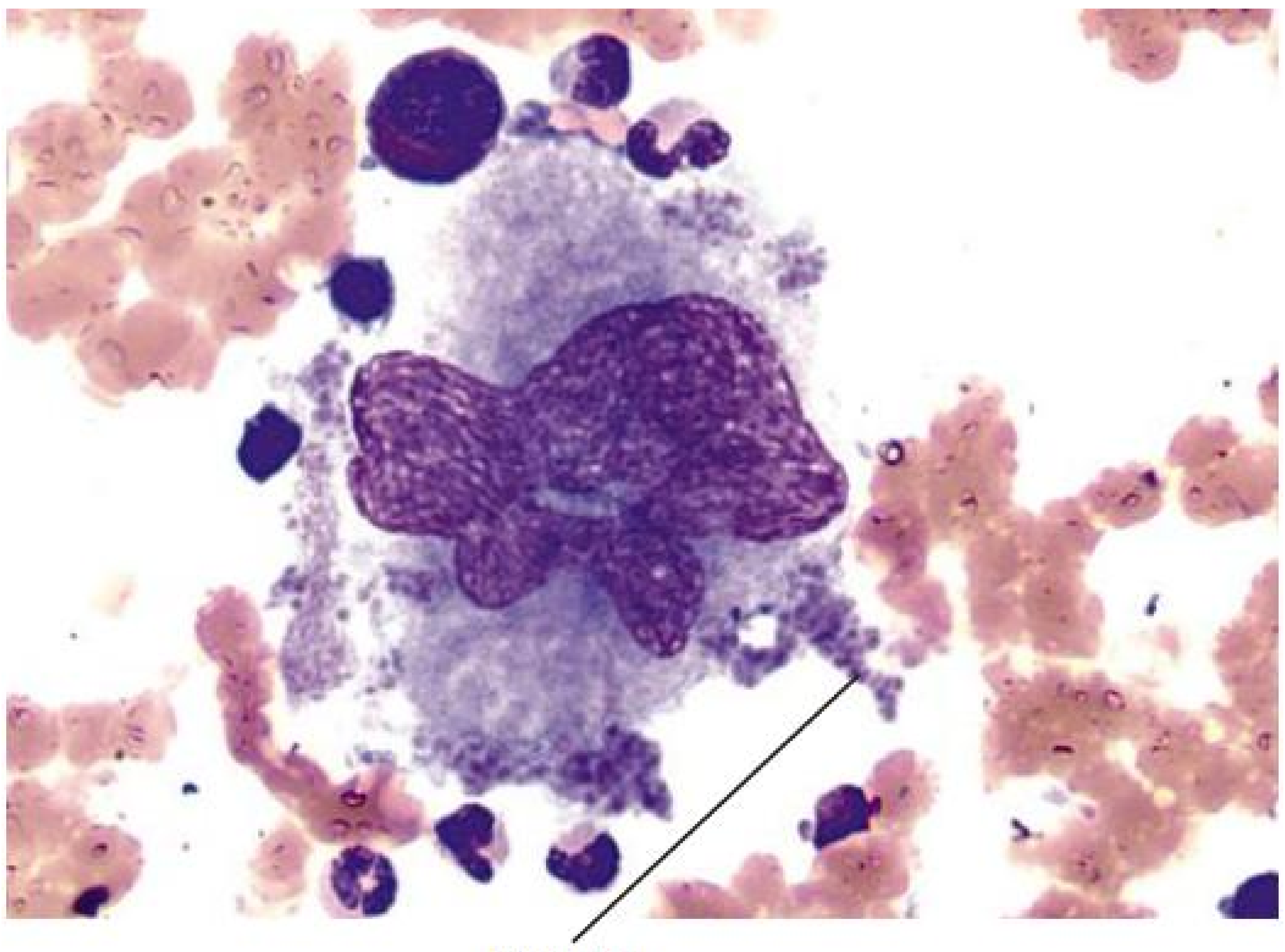


Figure 13-7 This image illustrates a terminal megakaryocyte shedding platelets.

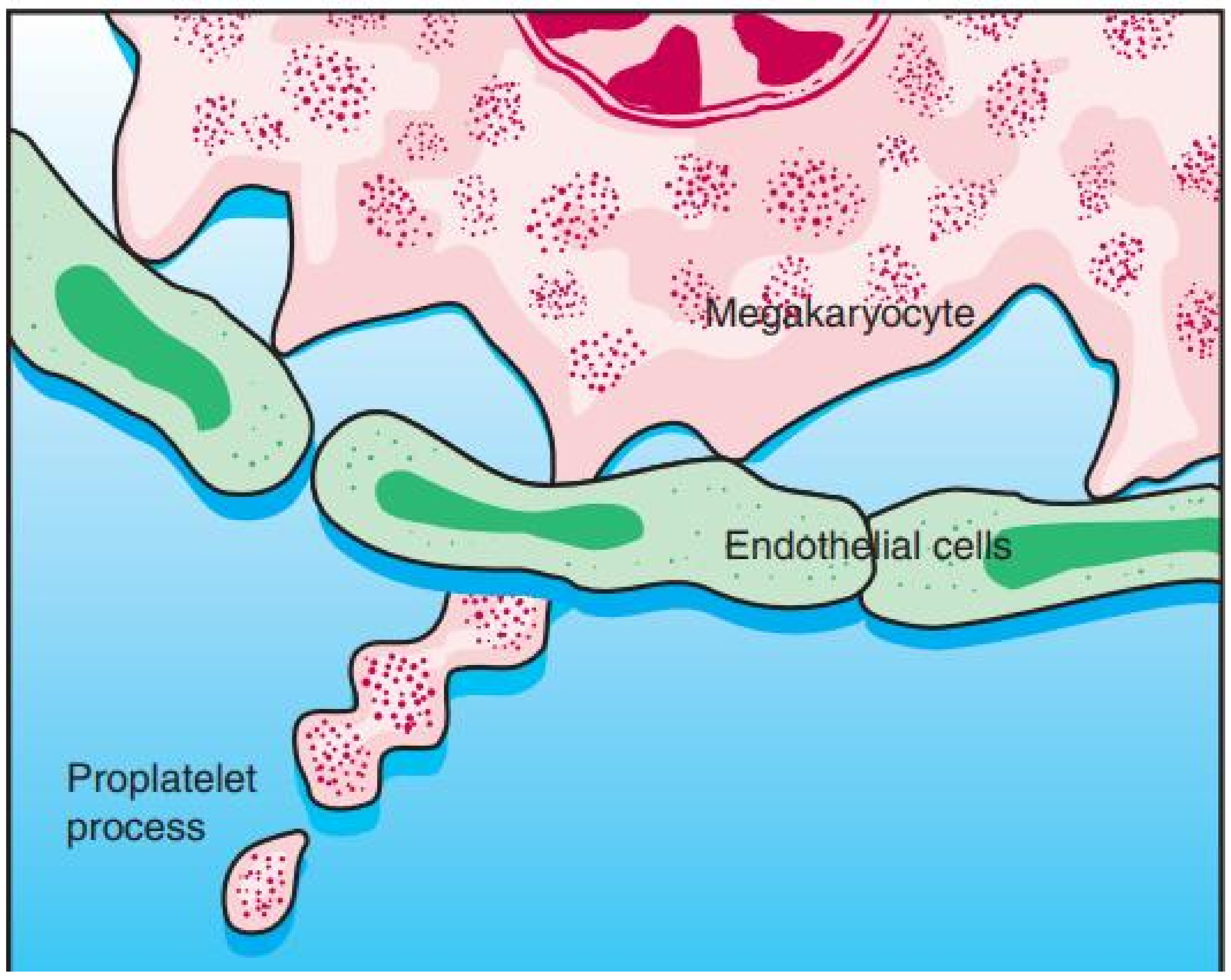


Figure 13-8 Megakaryocyte is adjacent to the abluminal (nonblood) membrane of the sinusoid-lining endothelial cell and extends a proplatelet process through or between the endothelial cells into the vascular sinus.

For platelet formation, megakaryocyte could extend in branching processes called **proplatelets which** would penetrate adjacent microvascular endothelium and are expose in the circulating blood.

PLATELETS

The proplatelet process sheds platelets, cells consisting of granular cytoplasm with a membrane but no nuclear material, into the venous sinus of the bone marrow. Their diameter in the monolayer of a Wright-stained peripheral blood wedge film averages 2.5 µm. MPV, as measured in a buffered isotonic suspension flowing through the impedance-based detector cell of a clinical profiling instrument, ranges from 8 to 10 fL (Figure 1-1). A frequency distribution of platelet volume is log-normal, however, which indicates a subpopulation of large platelets (Figure 15-14). Heterogeneity in the MPV of normal healthy humans reflects random variation in platelet release volume and is not a function of platelet age or vitality, as many authors claim.[22]

FINALLY

Connective Tissue SUMMARY OF KEY POINTS

- Connective tissue is specialized to physically **support** and **connect** other tissues and maintain the water required for metabolite diffusion to and from cells.
- Connective tissues all consist primarily of **extracellular** material rather than cells.
- Within most organs connective tissue proper forms the supportive **stroma**, which supports the organ's unique functional components or **parenchyma**.
- The **extracellular matrix (ECM)** of connective tissue proper usually consists of both large protein **fibers** and nonfibrous areas of unstained **ground substance** rich in various GAGs and water.
- All adult connective tissues are derived from an embryonic form of connective tissue called **mesenchyme**, which contains uniformly undifferentiated cells scattered in a gel-like matrix.

Cells of Connective Tissue

- **Fibroblasts** (fibrocytes), the major cells of connective tissue proper, are elongated, irregularly shaped cells with oval nuclei that synthesize and secrete most components of the ECM.
- **Adipocytes** (fat cells) are very large cells specialized for storage of triglycerides; they predominate in a specialized form of connective tissue called **adipose tissue**.
- **Macrophages** are short-lived cells that differentiate in connective tissue from precursor cells called **monocytes** circulating in the blood; they function in ECM turnover, phagocytosis of dead cells and debris, and antigen presentation to lymphocytes.
- **Mast cells** also originate from blood cell precursors and are filled with granules for the release of various vasoactive agents and other substances during inflammatory and allergic reactions.
- **Plasma cells** are short-lived cells that differentiate from B lymphocytes and are specialized for the abundant secretion of specific antibodies (immunoglobulins).
- Besides macrophages and plasma cells, other **leukocytes** normally wander through all types of connective tissue proper, providing surveillance against bacterial invaders and stimulating tissue repair.

Fibers of Connective Tissue

- The most important and abundant fibers of connective tissue are composed of the protein **collagen**, of which there are some 20 related types.
- Synthesis of collagen by fibroblasts and certain other cells involves posttranslational modifications in the RER, notably **hydroxylation** of the numerous prolines and lysines, and formation of helical trimeric subunits of **procollagen**.
- Upon exocytosis, the nonhelical ends of the procollagen subunits are removed, forming trimeric **collagen molecules** that aggregate and become covalently bound together in large **collagen fibrils**.
- The highly regular assembly of collagens in the fibrils produces a characteristic pattern of **crossbanding** visible ultrastructurally along the fibrils of some collagen types.
- Fibrils of type I collagen are bundled together by other forms of nonfibrillar, linking collagens to produce large **collagen bundles**.
- Collagen fibrils are degraded by collagenase enzymes classified as **matrix metalloproteinases (MMPs)**, produced primarily by macrophages.
- Type III collagen produces a network of delicate **reticular fibers**, which stain very dark with silver stains and are abundant in immune and lymphoid tissues.
- **Elastic fibers**, or sheets called **elastic lamellae**, are composed of the proteins **elastin** and **fibrillin**, which exist in a stretchable conformation that provides elastic properties to connective tissues rich in this material.

Ground Substance

- **Ground substance** is the watery, largely unstained extracellular material that is more abundant than fibers in some types of connective tissue proper.
- Ground substance is rich in **hydrated glycosaminoglycans (GAGs)**, **proteoglycans**, and **multiadhesive glycoproteins**.
- The major types of GAGs are **hyaluronic acid** (HA or hyaluronan), which is a very long polymer of the disaccharide glucosamine-glucuronate, and various shorter chains of **sulfated GAGs** composed of other disaccharide polymers.
- Sulfated GAGs such as **chondroitin sulfate** and **keratan sulfate** have various sizes and compositions, but they are all bound to the core proteins of **proteoglycans** and are produced in the Golgi apparatus before secretion.
- Proteoglycans attach to polymers of HA via **linker proteins** to form huge complexes in ground substance that bind water and other substances, including certain polypeptide growth factors that help regulate fibroblast proliferation.
- **Multiadhesive glycoproteins** such as fibronectin and laminin have binding sites for collagens and for integrin proteins in cell membranes, thus allowing temporary attachments between cells and the ECM required for cell migration and positioning.

Types of Connective Tissue

- **Connective tissue proper** is usually classified as loose or dense according to the amount of collagen and ground substance present.
- **Loose connective tissue** (or **areolar tissue**) has relatively more ground substance than collagen, and it typically surrounds small blood vessels and occupies areas adjacent to other types of epithelia.
- **Dense irregular connective tissue** is filled primarily with randomly distributed bundles of type I collagen, with some elastic fibers, providing resistance to tearing from all directions as well as some elasticity.
- **Dense regular connective tissue**, prominent in tendons and ligaments, features bundles of essentially parallel collagen, providing great strength (but little stretch) in binding together components of the musculoskeletal system.
- **Reticular tissue** consists of delicate networks of type III collagen (reticulin) and is most abundant in certain lymphoid organs where the fibers form attachment sites for lymphocytes and other immune cells.
- **Mucoid tissue** is an embryonic form of gel-like connective tissue with few cells, resembling mesenchyme, and is best seen around blood vessels in the umbilical cord.

Adipose Tissue SUMMARY OF KEY POINTS

- The defining cells of adipose tissue (fat), **adipocytes**, are very large cells derived from mesenchyme and specialized for energy storage in lipid droplet(s) with **triglycerides**.
- Adipocytes store lipids from three sources: from dietary fats packaged as **chylomicrons** in the intestine; from triglycerides produced in the liver and circulating as **very-low-density lipoproteins (VLDLs)**; and from fatty acids synthesized locally.
- Lipids are mobilized from adipocytes by **lipases** that are activated by **hormones** (glucagon, growth hormone) and **norepinephrine** released from sympathetic nerves.
- Cells of adipose tissue are supported by reticular fibers, and connective tissue septa divide the tissue into lobules of various sizes.
- There are two types of adipose tissue: white and brown fat.

White Adipose Tissue

- **White adipose tissue** is found in many organs throughout the body, typically forming about 20% of the body weight in adults.
- Adipocytes of white fat are typically very **large cells**, ranging in diameter from 50 to 150 μm.
- These cells each contain primarily **one large lipid droplet** (they are **unilocular**), causing the nucleus and remaining cytoplasm to be pushed against the plasmalemma.
- Fatty acids are released from white adipocytes when nutrients are needed and carried throughout the body on plasma proteins such as albumin.

Brown Adipose Tissue

- **Brown fat** comprises up to 5% of the newborn body weight but smaller amounts in adults.
- Adipocytes of this tissue are typically smaller than those of white fat and contain primarily **many small lipid droplets** (they are **multilocular**) in cytoplasm containing many mitochondria and a central nucleus.
- Fatty acids released in adipocytes of brown fat are metabolized in mitochondria of these cells for **thermogenesis** rather than ATP synthesis, using **uncoupling protein-1** or thermogenin.

Cartilage SUMMARY OF KEY POINTS

- Cartilage is a **tough**, **resilient** type of connective tissue that structurally supports certain soft tissues, notably in the respiratory tract, and provides cushioned, low-friction surfaces in joints.
- Cells of cartilage, **chondrocytes**, make up a small percentage of the tissue's mass, which is mainly a flexible mass of **extracellular matrix (ECM)**.
- Chondrocytes are embedded within **lacunae** surrounded by the ECM.
- Cartilage ECM typically includes **collagen** as well as abundant **proteoglycans**, notably **aggrecan**, which bind a large amount of **water**.
- Cartilage always **lacks blood vessels**, lymphatics, and nerves, but it is usually surrounded by a dense connective tissue **perichondrium** that is vascularized.
- There are three major forms of cartilage: (1) **hyaline cartilage**, (2) **elastic cartilage**, and (3) **fibrocartilage**.

Hyaline Cartilage

- The ECM of hyaline cartilage is **homogenous and glassy**, rich in fibrils of type II collagen and aggrecan complexes with bound water.
- The ECM has less collagen and more proteoglycan immediately around the lacunae, producing slight staining differences in this **territorial matrix**.
- Chondrocytes occur **singly** or in small, mitotically derived **isogenous groups**.
- **Perichondrium** is usually present, but not at the hyaline cartilage of articular surfaces or the epiphyses of growing long bones.

Elastic Cartilage

- Elastic cartilage generally resembles hyaline cartilage in its chondrocytes and major ECM components, but its matrix includes **abundant elastic fibers**, visible with special stains, which increase the tissue's **flexibility**.
- Elastic cartilage provides flexible support for the external ear as well as certain structures of the middle ear and larynx; it is always surrounded by **perichondrium**.

Fibrocartilage

- Fibrocartilage contains varying **combinations of hyaline cartilage** in small amounts of **dense connective tissue**.
- Histologically it consists of small **chondrocytes** in a hyaline matrix, usually layered with larger areas of bundled **type I collagen** with scattered **fibroblasts**.
- Fibrocartilage provides very **tough**, **strong support** at tendon insertions and in **intervertebral discs** and certain other joints.

Cartilage Formation, Growth, & Repair

- All forms of cartilage form from embryonic **mesenchyme**.
- Cartilaginous structures grow by mitosis of existing chondroblasts in lacunae (**interstitial growth**) or formation of new chondroblasts peripherally from progenitor cells in the perichondrium (**appositional growth**).
- Repair or replacement of injured cartilage is very slow and ineffective, due in part to the tissue's **avascularity** and **low metabolic rate**.

Bone SUMMARY OF KEY POINTS

- Bone is a type of connective tissue with a **calcified** extracellular matrix (ECM), specialized to **support** the body, **protect** many internal organs, and act as the body's **Ca^{2+} reservoir**.

Major Cells & Matrix Components of Bone

- **Osteoblasts** differentiate from (stem) osteoprogenitor cells and secrete components of the initial matrix, called **osteoid**, that allow matrix mineralization to occur.
- Important components of osteoid include type I collagen, the protein **osteocalcin**, which binds Ca^{2+} and **matrix vesicles** with enzymes generating PO_4^-.
- High concentrations of Ca^{2+} and PO_4^- ions cause formation of **hydroxyapatite** crystals, whose growth gradually calcifies the entire matrix.
- **Osteocytes** differentiate further from osteoblasts when they become enclosed within matrix **lacunae** and act to maintain the matrix and detect mechanical stresses on bone.
- Osteocytes maintain communication with adjacent cells via a network of long **dendritic processes** that extend through the matrix via narrow **canaliculi** radiating from each lacuna.
- **Osteoclasts** are very large cells, formed by fusion of several blood monocytes, which locally erode bone matrix during osteogenesis and bone remodeling.

Periosteum & Endosteum

- **Periosteum** is a layer of dense connective tissue on the outer surface of bone, bound to bone matrix by bundles of type I collagen called **perforating** (or **Sharpey**) **fibers**.
- Regions of periosteum adjacent to bone are rich in **osteoprogenitor cells** and **osteoblasts** that mediate increases in bone thickness by **appositional growth**.
- The **endosteum** is a thin layer of active and inactive osteoblasts, which lines all the internal surfaces within bone; osteoblasts here are also required for bone growth.

Types & Organization of Bone (Table 8-1)

- Dense bone immediately beneath the periosteum is called **compact bone**; deep to the compact bone are small bony trabeculae or spicules of **cancellous** (or spongy) **bone**.
- In long bones of the limbs these two types of mature bone tissue occur in both the knobby, bulbous ends, called **epiphyses**, and in the intervening shaft or **diaphysis**.
- Immature bone, called **woven bone**, is formed during osteogenesis or repair and has a calcified matrix with randomly arranged collagen fibers.
- By the action of osteoclasts and osteoblasts, woven bone undergoes rapid turnover and is remodeled into **lamellar bone** with new matrix deposited in distinct layers with parallel collagen bundles; both compact and cancellous bone is lamellar bone.
- Most lamellar bone consists of lamellae organized concentrically around small **central canals** containing blood vessels and nerves; this organization is called an **osteon or haversian system**.
- Within each osteon osteocytic lacunae occur between the lamellae, with **canaliculi** radiating through the lamellae, which allow all cells to communicate with the central canal.

Osteogenesis

- Bones of the skull and jaws form initially by **intramembranous ossification**, with osteoblasts differentiating directly from progenitor cells in condensed **"membranes" of mesenchyme**.
- All other bones form by **endochondral ossification**, in which osteoprogenitor cells surround and then invade hyaline **cartilage models** of the skeletal elements in the embryo.
- **Primary ossification centers** in diaphyses of fetal long bones form when chondrocytes die after enclosure of the cartilage within a collar of woven bone, creating an initial cavity that is entered by periosteal osteoblasts and vasculature.
- Later, **secondary ossification centers** develop similarly within the epiphyses, with cartilage of the **epiphyseal growth plate** between the primary and secondary ossification sites.
- The growth plates are the key to **bone elongation** during childhood and are organized as an interrelated series of developing zones.
- Most distally is a **"resting" or reserve zone** of typical hyaline cartilage.
- In an adjacent **proliferative zone**, chondrocytes undergo mitosis and appear stacked within elongated lacunae.
- The most mature chondrocytes in these lacunae swell up, compress the matrix, and undergo apoptosis in a **zone of hypertrophic cartilage** closer to the large primary ossification center.
- Spaces created in the matrix by these events characterize the **zone of cartilage calcification** when they are invaded by osteoblasts, osteoclasts, and vasculature from the primary center.
- In the **ossification zone**, woven bone is laid down initially by osteoblasts and remodeled into lamellae bone.

Bone Growth, Remodeling, & Repair

- **Growth** of bones occurs throughout life, with cells and matrix turning over continuously through activities of osteoblasts and osteoclasts.
- Lamellae and osteons are temporary structures and are replaced and rebuilt continuously in a process of **bone remodeling** by which bones change size and shape according to changes in mechanical stress.
- **Bone repair** after fracture or other injury involves the activation of periosteal fibroblasts to produce an initial **soft, fibrocartilage-like callus**.
- The soft callus is gradually replaced by a **hard callus of woven bone** that is soon remodeled to produce stronger lamellar bone.

Metabolic Role of Bone

- Ca^{2+}, a key ion for all cells, is **stored** in bone when dietary calcium is adequate and **mobilized** from bone when dietary calcium is deficient.
- Maintenance of proper **blood calcium levels** involves activity of all three major bone cells and is largely regulated by subtle paracrine interaction among these and other cells.
- Hormones affecting calcium deposition and removal from bone include **parathyroid hormone (PTH)**, which indirectly stimulates osteoclasts to elevate levels of calcium in blood, and **calcitonin**, which can inhibit osteoclast activity, lowering blood calcium levels.

Joints

- **Joints** are places where bones meet, or articulate, allowing at least the potential for bending or movement in that portion of the skeleton.
- Joints with very limited or no movement are classified collectively as **synarthroses** and freely mobile joints are called **diarthroses**.
- Diarthroses have a **joint cavity** filled with lubricant **synovial fluid**, enclosed within a tough, fibrous **articular capsule**; ends of the bones involved are covered with hyaline **articular cartilage**.
- Specialized connective tissue of the **synovial membrane** lines the capsule, with folds extended into some areas of the joint cavity.
- **Macrophage-like synovial cells** remove wear-and-tear debris from synovial fluid.
- **Fibroblast-like synovial cells** produce hyaluronate that is moved in the synovial fluid with water from local capillaries, forming the synovial fluid that nourishes and lubricates the articular cartilage.
- **Intervertebral discs** allow limited vertebral mobility and consist of large pads of **fibrocartilage** that cushion adjacent vertebrae.
- Each intervertebral disc consists mainly of a thick outer layer of fibrocartilage forming a tough **annulus fibrosus**, and a shock-absorbing inner, gel-like core, the **nucleus pulposus**.

Blood SUMMARY OF KEY POINTS

- The liquid portion of circulating blood is **plasma**, while the cells and platelets comprise the **formed elements**; upon clotting, some proteins are removed from plasma and others are released from platelets, forming a new liquid termed **serum**.
- Important protein components of plasma include **albumin**, diverse **α- and β-globulins**, proteins of the **complement** system, and **fibrinogen**, all of which are secreted within the liver, as well as the **immunoglobulins**.
- **Red blood cells** or **erythrocytes**, which make up the **hematocrit** portion (~45%) of a blood sample, are **enucleated**, **biconcave discs** 7.5 μm in diameter, filled with **hemoglobin** for the uptake, transport, and release of O_2, and with a normal life span of about **120 days**.
- **White blood cells** or **leukocytes** are broadly grouped as **granulocytes** (neutrophils, eosinophils, basophils) or **agranulocytes** (lymphocytes, monocytes).
- All leukocytes become active outside the circulation, specifically leaving the microvasculature in a process involving cytokines, selective adhesion, changes in the endothelium, and **transendothelial migration** or **diapedesis**.
- All granulocytes have specialized lysosomes called **azurophilic granules** and smaller **specific granules** with proteins for various cell-specific functions.
- **Neutrophils**, the most abundant type of leukocyte, have **polymorphic, multilobed nuclei**, and faint pink cytoplasmic granules that contain many factors for highly efficient phagolysosomal killing and removal of bacteria.
- **Eosinophils** have bilobed nuclei and eosinophilic specific granules containing factors for destruction of helminthic parasites and for modulating inflammation.
- **Basophils**, the rarest type of circulating leukocyte, have irregular bilobed nuclei and resemble mast cells with strongly basophilic specific granules containing factors important in allergies and chronic inflammatory conditions, including **histamine**, **heparin**, **chemokines**, and various **hydrolases**.
- **Lymphocytes**, agranulocytes with many functions as T- and B-cell subtypes in the immune system, range widely in size, depending on their activation state, and have roughly spherical nuclei with little cytoplasm and few organelles.
- **Monocytes** are larger agranulocytes with distinctly indented or C-shaped nuclei that circulate as precursors of macrophages and other cells of the **mononuclear phagocyte system**.
- **Platelets** are small (2-4 μm) cell fragments derived from **megakaryocytes** in bone marrow, with a **marginal bundle** of actin filaments, **alpha granules** and **delta granules**, and an **open canalicular system** of membranous vesicles; rapid degranulation on contact with collagen triggers blood clotting.

Hemopoiesis SUMMARY OF KEY POINTS

- **Pluripotent stem cells** for blood cell formation, or **hemopoiesis**, occur in the bone marrow of children and adults.
- **Progenitor cells**, committed to forming each type of mature blood cell, proliferate and differentiate within microenvironmental niches of **stromal cells**, other cells, and ECM with specific growth factors.
- These progenitor cells are also known as **colony-forming units (CFUs)** and the growth factors are also called **colony-stimulating factors (CSFs)** or cytokines.
- **Red bone marrow** is active in hemopoiesis; **yellow bone marrow** consists mostly of adipose tissue.
- **Erythropoietic islands** or cords within marrow contain the red blood cell lineage: **proerythroblasts**, **erythroblasts** with succeeding developmental stages called **basophilic**, **polychromatophilic**, and **orthochromatophilic** that reflect the cytoplasmic transition from RNA-rich to hemoglobin-filled.
- At the last stage of erythropoiesis cell nuclei are extruded, producing **reticulocytes** that still contain some polyribosomes but are released into the circulation.
- **Granulopoiesis** includes **myeloblasts**, which have large nuclei and relatively little cytoplasm; **promyelocytes**, in which lysosomal **azurophilic granules** are produced; **myelocytes**, in which **specific granules** for one of the three types of granulocytes are formed; and **metamyelocytes**, in which the characteristic changes in nuclear morphology occur.
- Immature neutrophilic metamyelocytes called **band (stab) cells** are released prematurely when the compartment of circulating neutrophils is deleted during bacterial infections.
- **Monoblasts** produce **monocytes** in red marrow, but **lymphoblasts** give rise to **lymphocytes** primarily in the lymphoid tissues in processes involving acquired immunity.
- **Megakaryocytes**, large polyploid cells of red bone marrow, produce **platelets**, or **thrombocytes**, by releasing them from the ends of cytoplasmic processes called **proplatelets**.
- All these **formed elements** of blood enter the circulation by crossing the **discontinuous endothelium** of sinusoids in the red marrow.