

# Schedule: Week 1

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1. TA Introduction: Rachel Wilson, Lindsay Holden
2. Welcome
3. Syllabus
4. Week 1 Lecture
  - Chapter 1: Histology and Its Methods of Study
  - Chapter 2: The Cytoplasm
  - Chapter 3: The Nucleus



# Welcome

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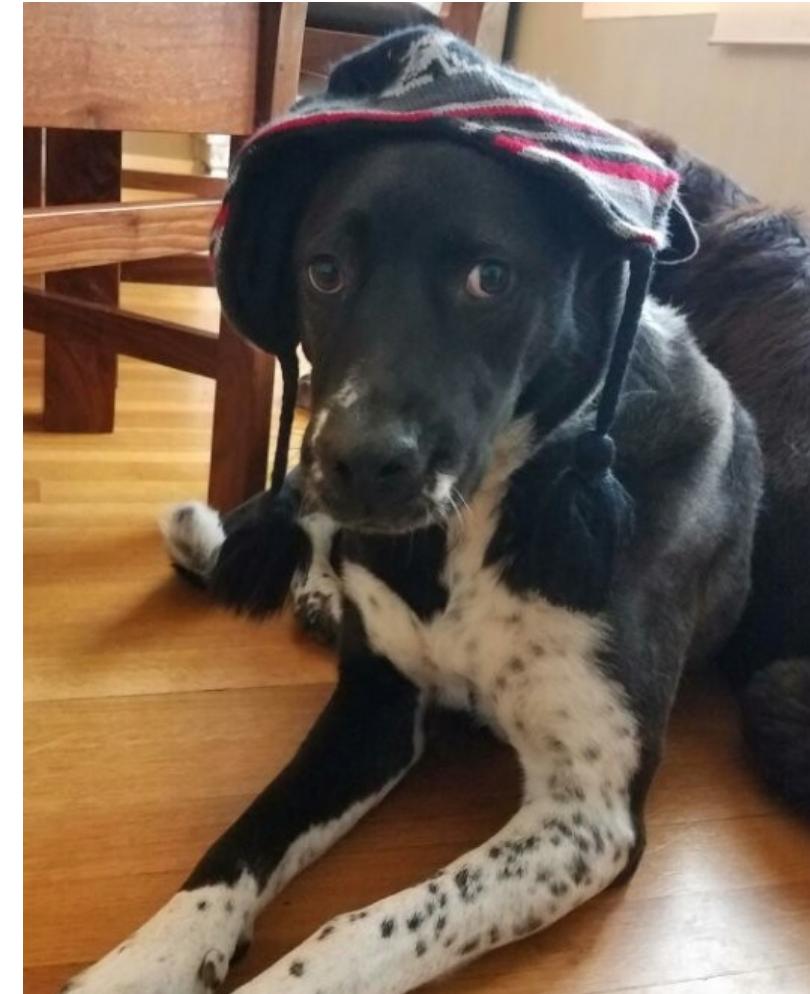
About me: Radhika Reddy

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- Ph.D Neuroscience Johns Hopkins University
- Post Doctoral Fellow New York University
- Peace Corp Volunteer
- Senior Research Associate Oregon Health & Science University
- Instructor PSU present

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Office hours: T/R 8:30-9:30am



# Syllabus

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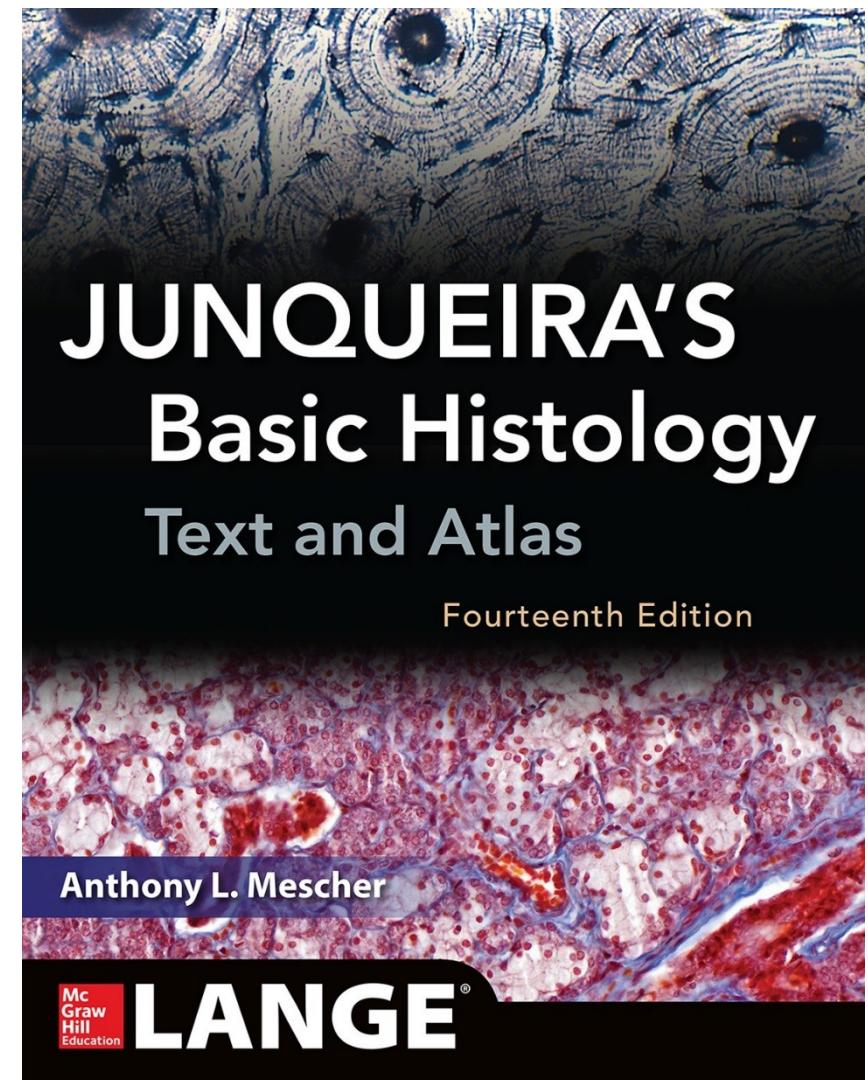


The course syllabus can be found on our D2L webpage. It is your ultimate resources for navigating this course

## **Week 1 Lab**

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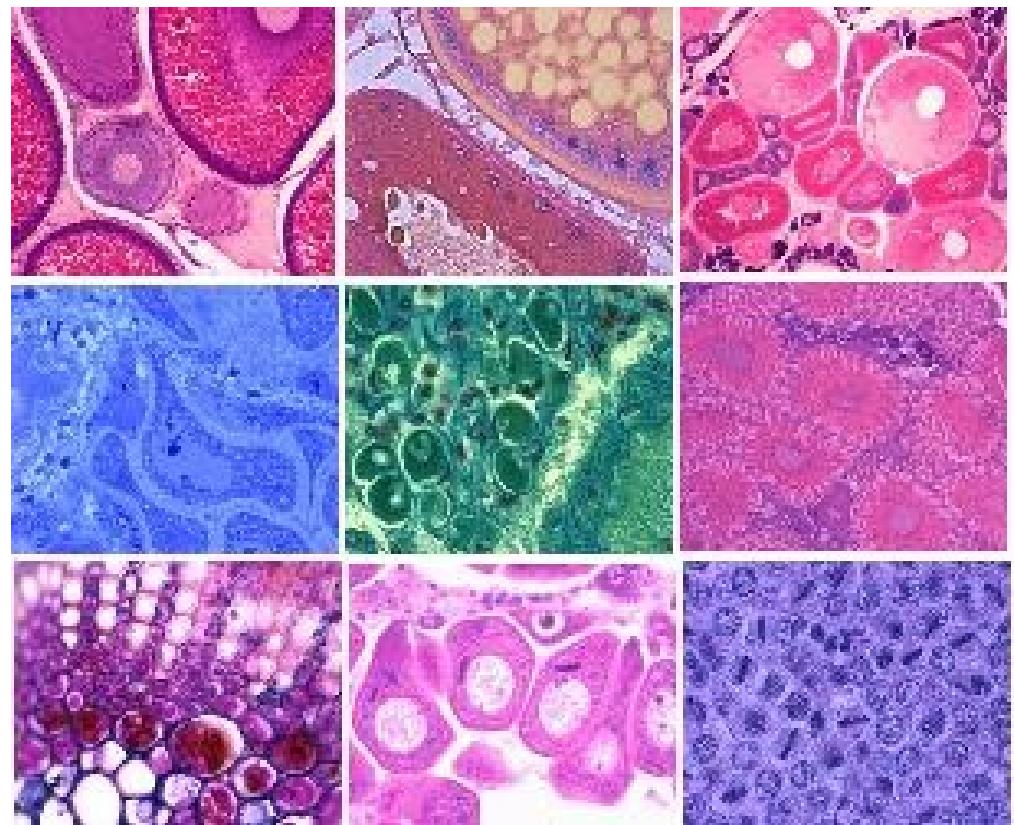
- Always bring the text book to lab!!!
- Day 1: Complete the 1<sup>st</sup> 9 pages of the lab manual
- Day 2: Group cancer activity, complete remainder of lab.



Radhika Reddy, PhD

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# BI 455 CHAPTER 1- 3





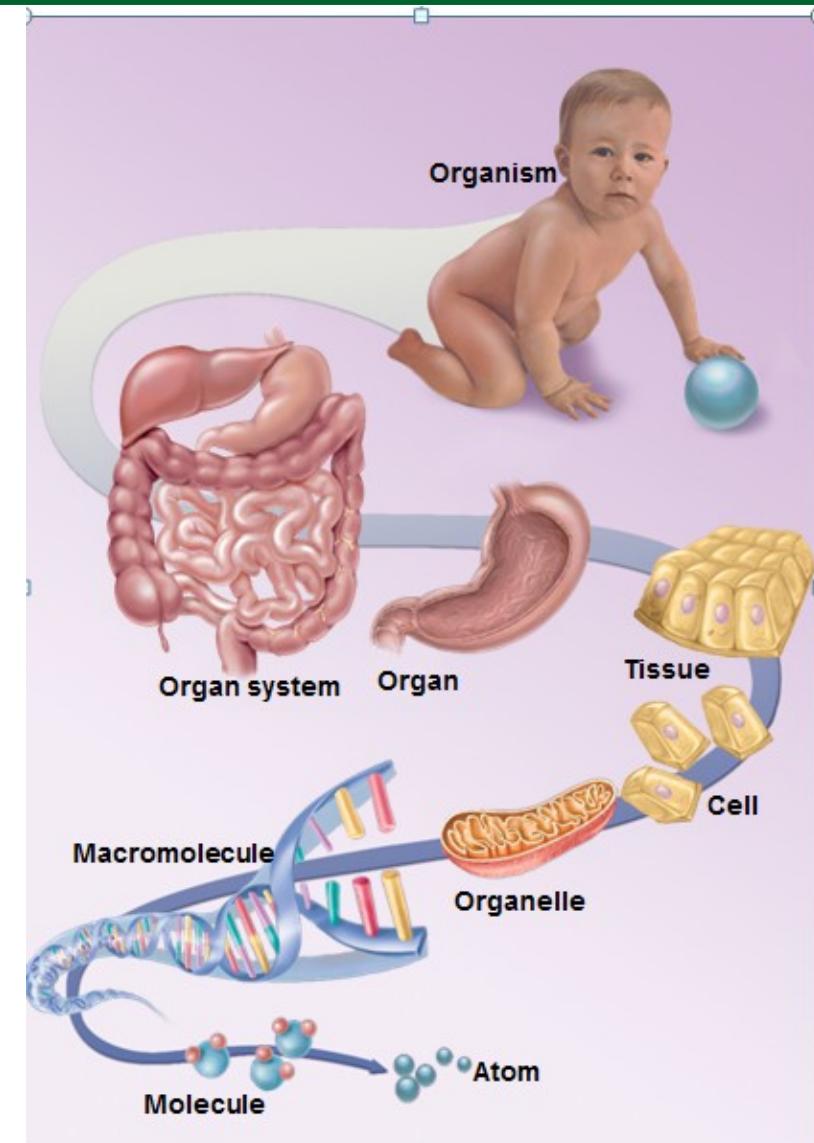
Tissue Preparation, Staining, Microscopy

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# CHAPTER 1: HISTOLOGY AND ITS METHODS OF STUDY

# The Structural Basis of Human Function: The Anatomical Sciences

- Organism is composed of **organ systems**
- **Organ systems** composed of **organs**
- **Organs** composed of **tissues**
- **Tissues** composed of **cells**
- **Cells** composed of **organelles**
- **Organelles** composed of **molecules**
- **Molecules** composed of **atoms**



# The Structural Basis of Human Function: The Anatomical Sciences

## ■ Gross anatomy

- Structure visible to the naked eye
- by surface observation or dissection

## ■ Histology (microscopic anatomy)

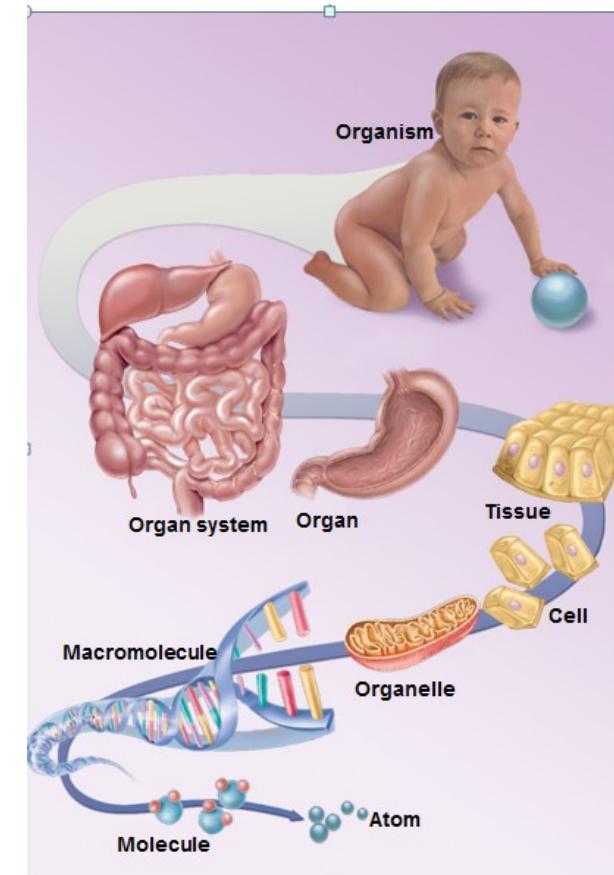
- Tissue specimens thinly sliced and stained
- Observed under a microscope
- Histopathology:** microscopic examination of tissues for disease

## ■ Surface anatomy

- External structure of the body
- Important in conducting physical exam

## ■ Systemic anatomy

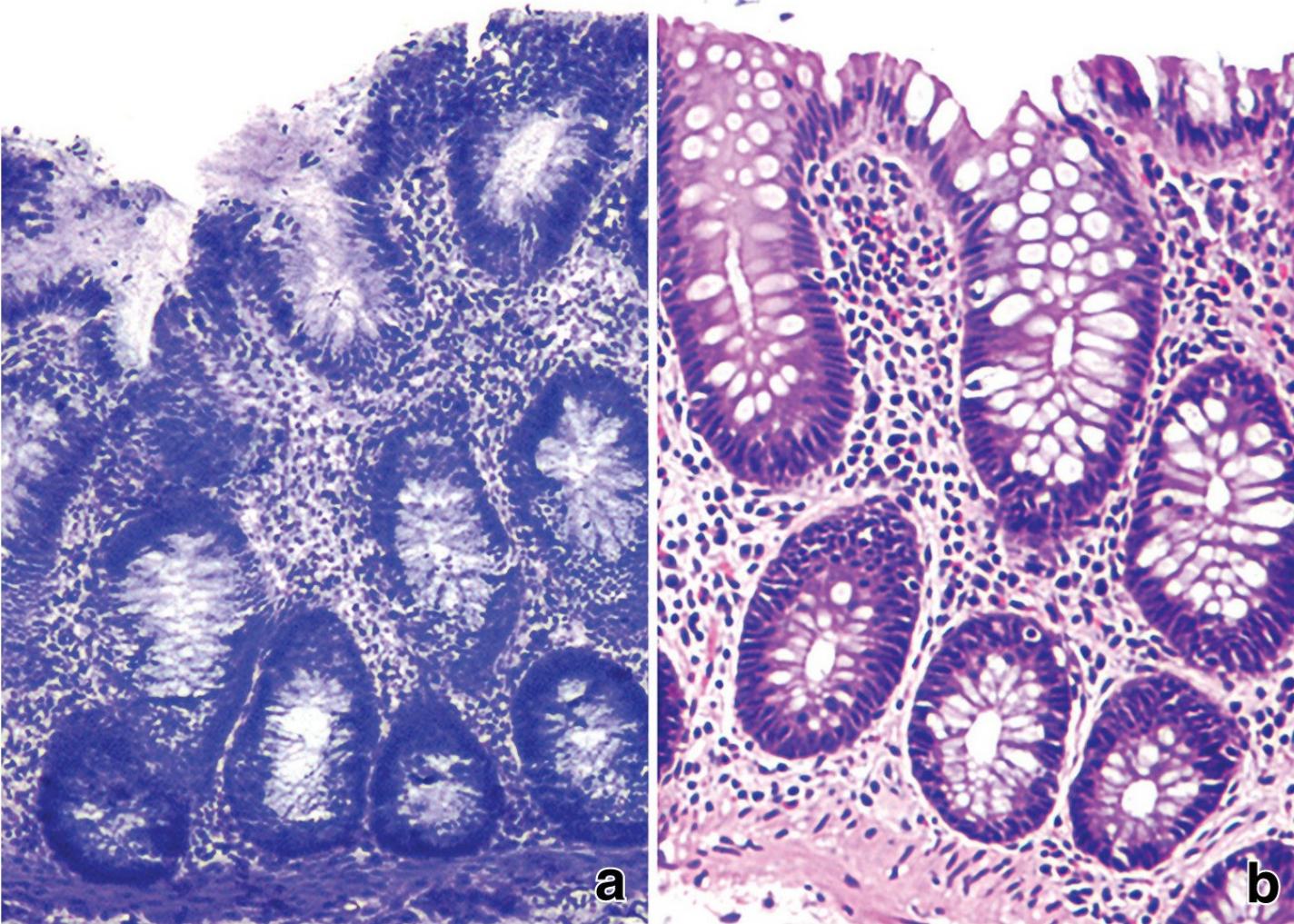
- Study of one organ system at a time



Histology at the University of Bristol:

<https://www.youtube.com/watch?v=PafHxS5bq9A&noredirect=1>

# Clinical Correlation: Frozen sections and stained tissue



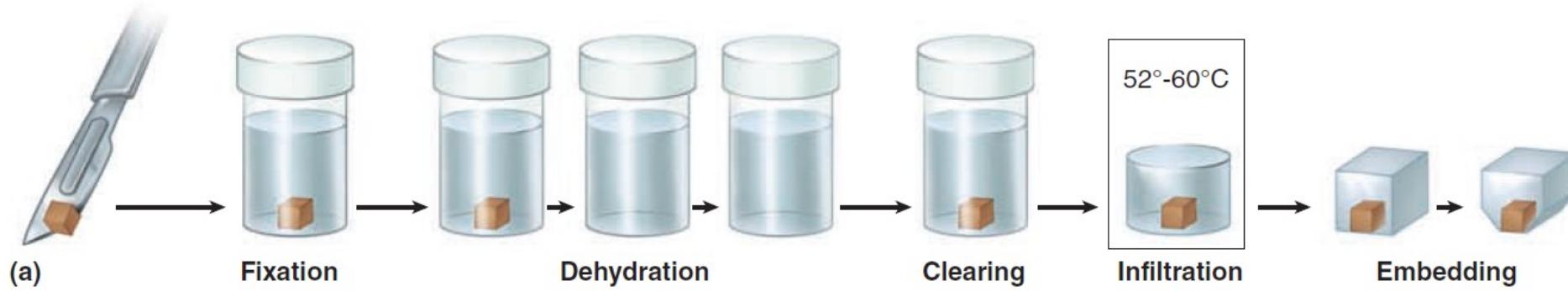
## Evaluation of a specimen obtained during surgery by frozen-section technique.

a. This photomicrograph shows a specimen obtained from the large intestine that was prepared by frozen-section technique and stained with methylene blue.

b. Part of the specimen was fixed in formalin and processed as a routine H&E preparation.

Examination of the frozen section revealed it to be normal. This diagnosis was later confirmed by examining the routinely prepared H&E specimen.

# Most tissues studied histologically are prepared as shown, with this sequence of steps:



- 1. Fixation:** Small pieces of tissue are placed in solutions of chemicals that preserve by cross-linking proteins and inactivating degradative enzymes.
- 2. Dehydration:** The tissue is transferred through a series of increasingly concentrated alcohol solutions, ending in 100%, which removes all water.
- 3. Clearing:** Alcohol is removed in toluene or other agents in which both alcohol and paraffin are miscible.
- 4. Infiltration:** The tissue is then placed in melted paraffin until it becomes completely infiltrated with this substance.
- 5. Embedding:** The paraffin-infiltrated tissue is placed in a small mold with melted paraffin and allowed to harden
6. The resulting paraffin block is trimmed to expose the tissue for sectioning (slicing) on a microtome.

# A microtome is used for sectioning paraffin-embedded tissues for light microscopy

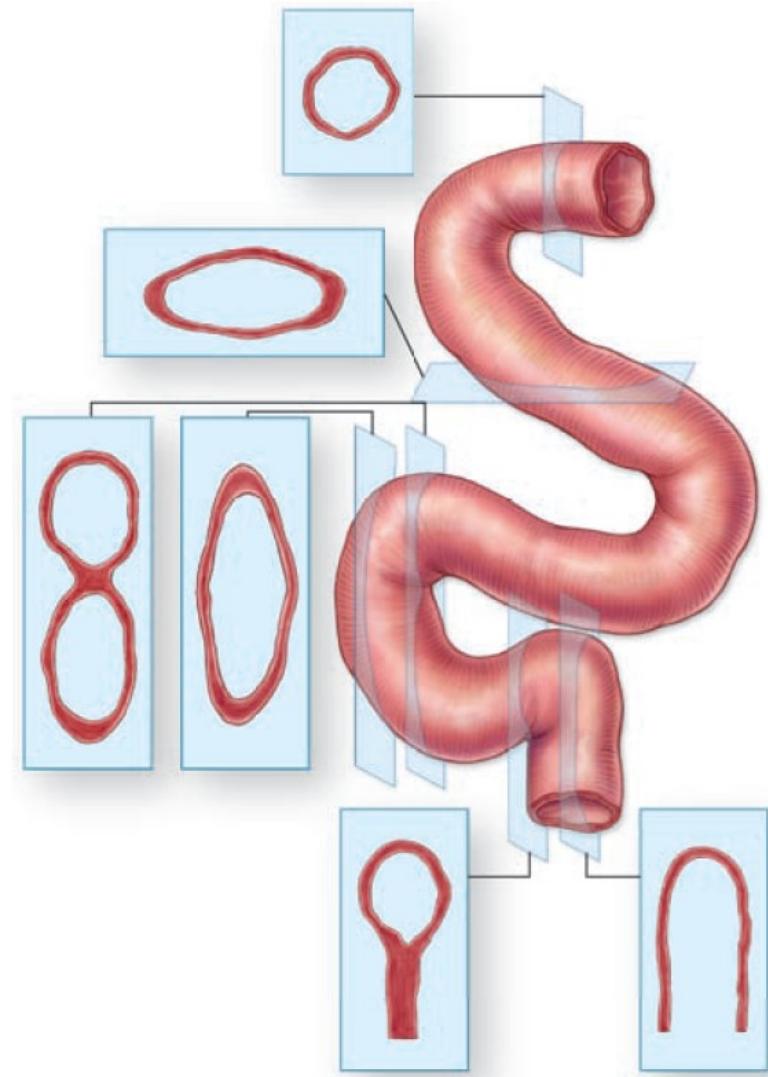


1. The trimmed tissue specimen is mounted in the paraffin block holder, and each turn of the drive wheel by the histologist advances the holder a controlled distance, generally between 1 and 10  $\mu\text{m}$ .
2. After each forward move, the tissue block passes over the steel knife edge and a section is cut at a thickness equal to the distance the lock advanced.
3. The paraffin sections are placed on glass slides and allowed to adhere, deparaffinized, and stained for light microscope study.

# Sectional Planes

FIGURE 1–14 Interpretation of 3D structures in 2D sections.

- When a structure's three-dimensional volume is cut into very thin sections, the sections appear microscopically to have only two dimensions: length and width.
- When examining a section under the microscope, the viewer must always keep in mind that components are missing in front of and behind what is being seen because many tissue structures are thicker than the section.



# Staining

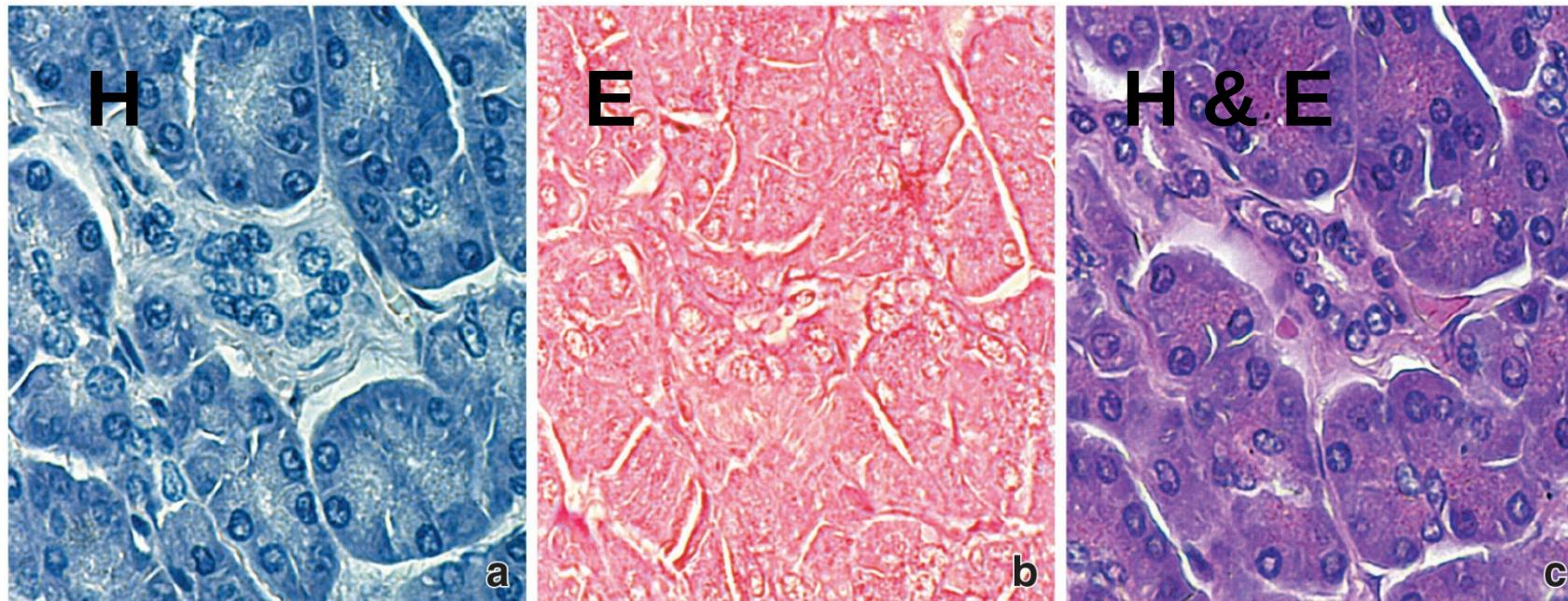
- Most cells and extracellular material are **completely colorless**, and to be studied microscopically sections must typically be **stained (dyed)**.
- Methods of staining have been devised that not only make the various tissue components conspicuous but also permit distinctions to be made between them
- Dyes stain tissue components more or less selectively, with many behaving like acidic or basic compounds and forming electrostatic (salt) linkages with ionizable radicals of molecules in tissues

TABLE	1.2	Some Basic and Acidic Dyes
Dye		Color
<i>Basic dyes</i>		
Methyl green		Green
Methylene blue		Blue
Pyronin G		Red
Toluidine blue		Blue
<i>Acidic dyes</i>		
Acid fuchsin		Red
Aniline blue		Blue
Eosin		Red
Orange G		Orange

# The Hematoxylin and Eosin (H&E) stain is used most commonly

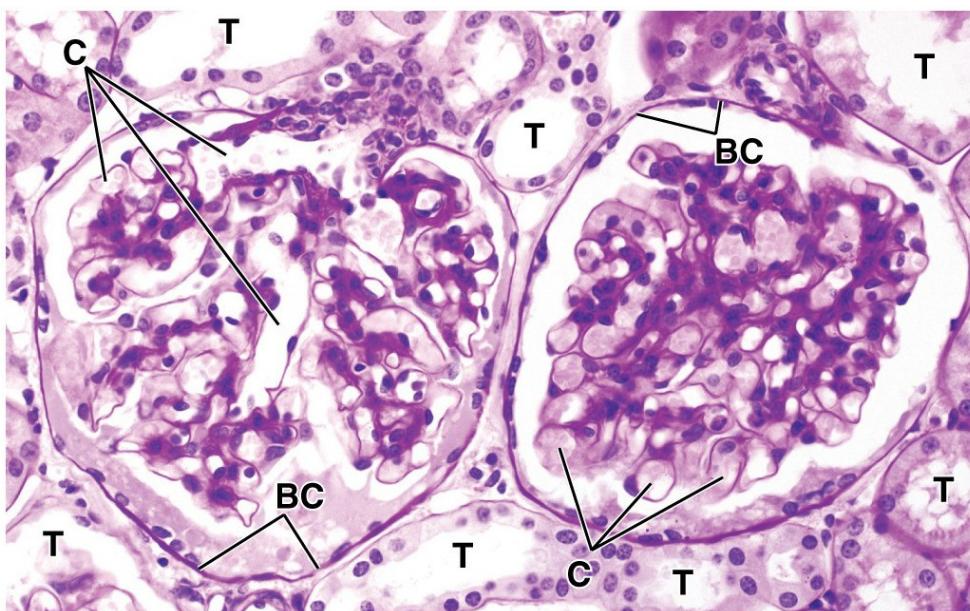
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- **Hematoxylin** (almost basic) produces a dark blue or purple color, staining **DNA** in the cell nucleus and other acidic structures (such as **RNA-rich** portions of the cytoplasm and the **matrix of cartilage**).
- **Eosin** stains other **cytoplasmic components and collagen** pink



# Periodic Acid-Schiff (PAS) reagent.

- The PAS reaction is based on the transformation of 1,2-glycol groups present in sugars into aldehyde residues, which then react with Schiff reagent to produce a purple or magenta color

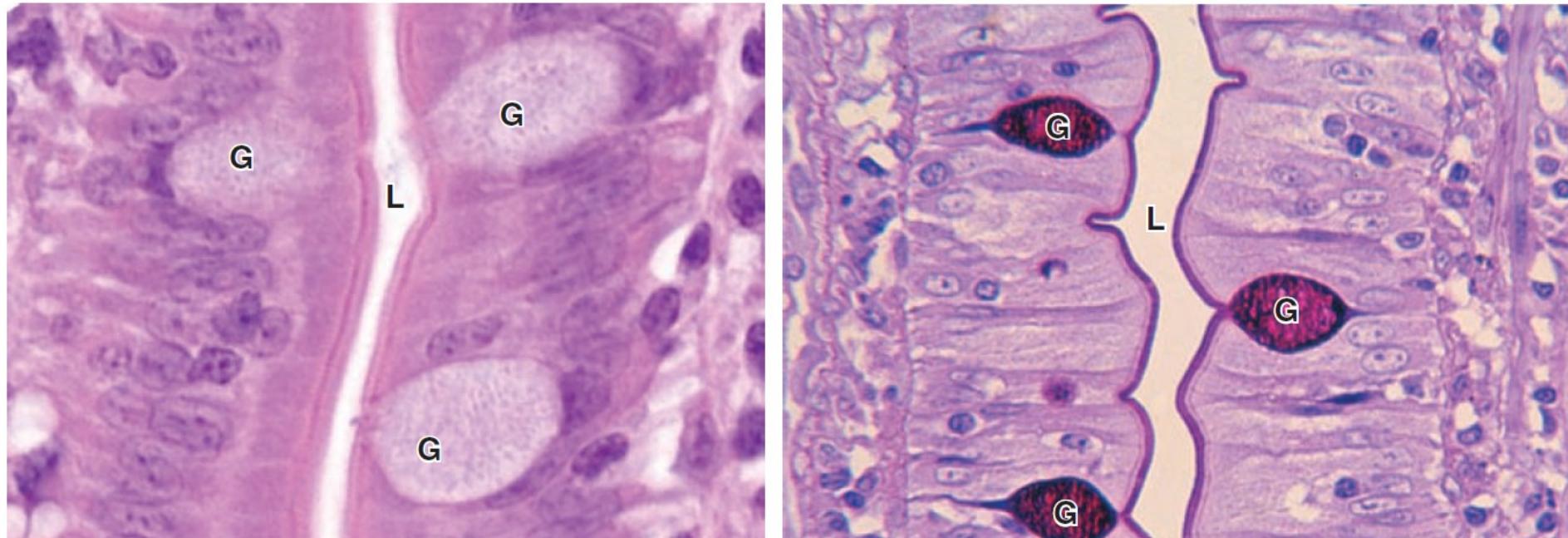


This histochemical method demonstrates and localizes carbohydrates and carbohydrate-rich macromolecules.

The basement membranes in this kidney tissue are PAS positive as evidenced by the magenta staining of these sites. The kidney tubules (T) are sharply delineated by the stained basement membrane surrounding the tubules. The glomerular capillaries (C) and the epithelium of Bowman's capsule (BC) also show PAS-positive basement membranes.

# H & E vs PAS

FIGURE 1–2 Hematoxylin and eosin (H&E) and periodic acid-Schiff (PAS) staining.



Micrograph of epithelium lining the small intestine, (a) stained with H&E, and (b) stained with the PAS reaction for glycoproteins. With H&E, basophilic cell nuclei are stained purple while cytoplasm stains pink. Cell regions with abundant oligosaccharides on glycoproteins, such as the ends of the cells at the lumen (L) or the scattered mucus-secreting goblet cells (G), are poorly stained. With PAS, however, cell staining

is most intense at the lumen, where projecting microvilli have a prominent layer of glycoproteins at the lumen (L) and in the mucin-rich secretory granules of goblet cells. Cell surface glycoproteins and mucin are PAS-positive because of their high content of oligosaccharides and polysaccharides respectively. The PAS-stained tissue was counterstained with hematoxylin to show the cell nuclei. Both X300.

# Enzyme histochemistry (cytochemistry): localizes cellular structures using a specific enzymatic activity present in those structures

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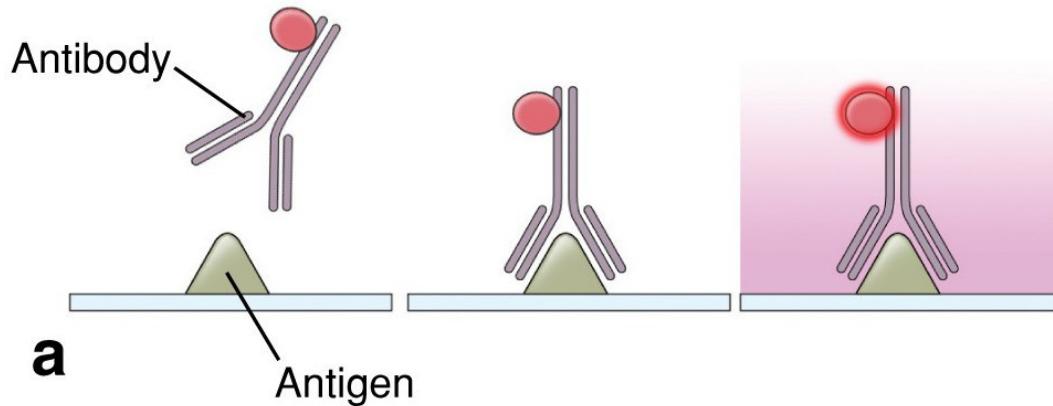


Micrograph of cross sections of kidney tubules treated histochemically to demonstrate alkaline phosphatases shows strong activity of this enzyme at the apical surfaces of the cells at the lumens (L) of the tubules.

- (1) Tissue sections are immersed in a solution containing the substrate of the enzyme to be localized
- (2) The enzyme is allowed to act on its substrate
- (3) The section is put in contact with a marker compound that reacts with a product of the enzymatic action on the substrate
- (4) The final product has color or electron density, and precipitates over the site of the enzymes causing contrast between enzymatically active vs inactive areas

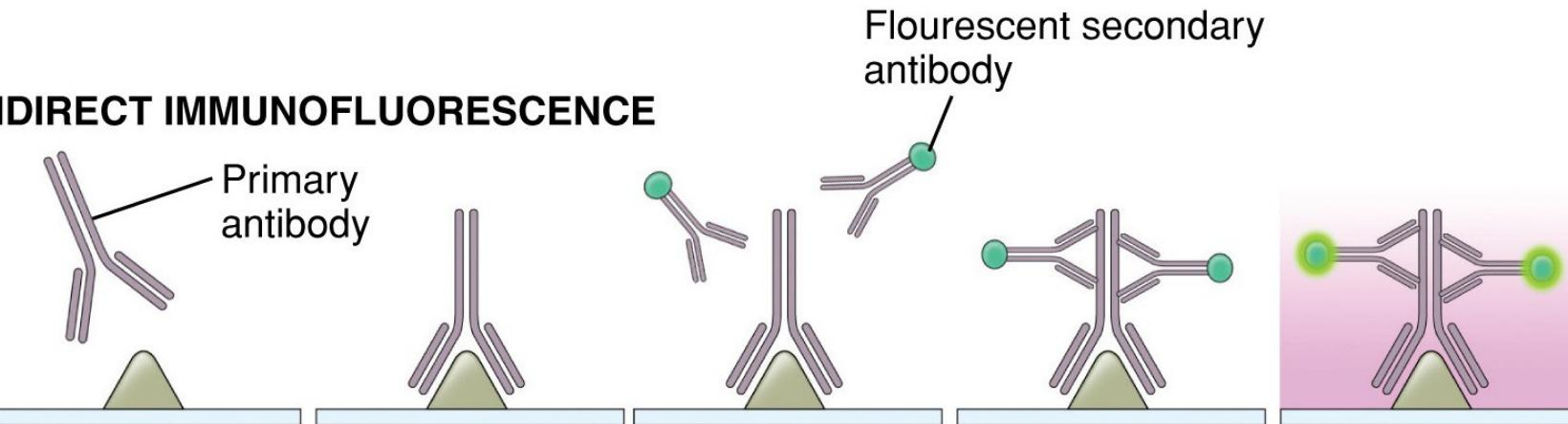
# Immunocytochemistry: uses reaction between an antigen and an antibody to visualize proteins

## DIRECT IMMUNOFLUORESCENCE



**a**

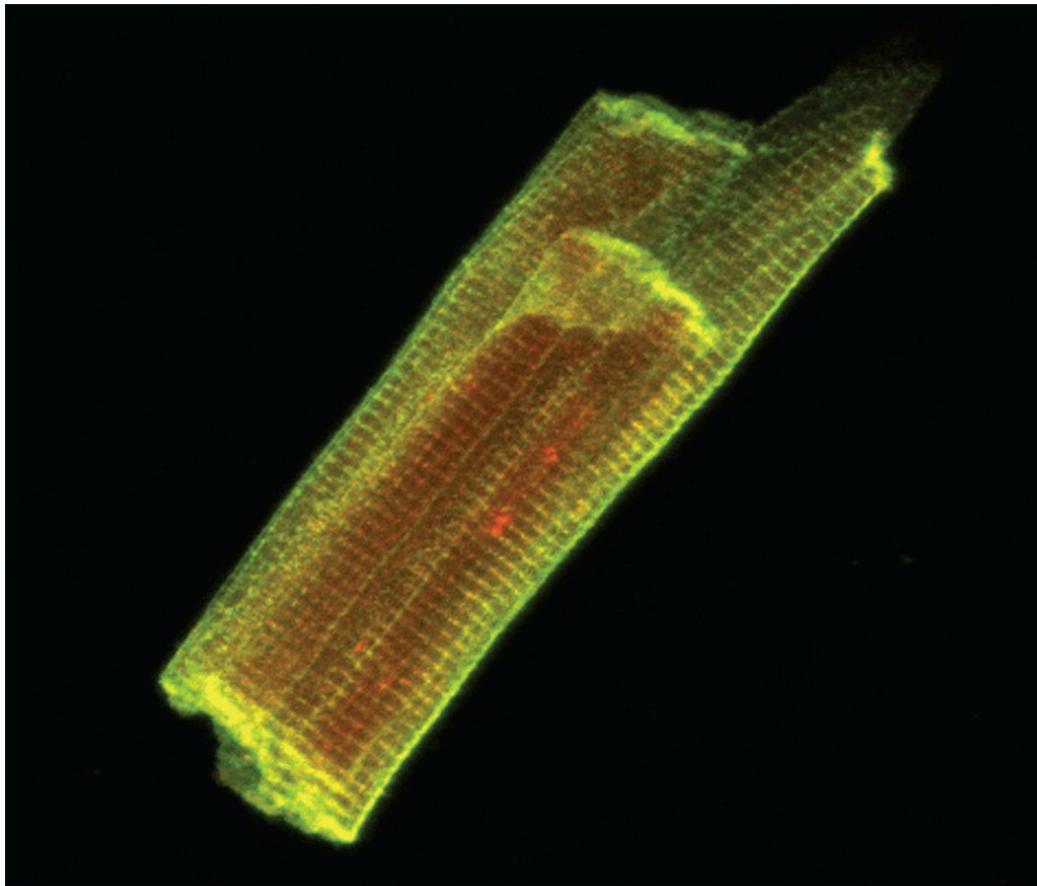
## INDIRECT IMMUNOFLUORESCENCE



**b**

# Immunocytochemistry: uses reaction between an antigen and an antibody to visualize proteins

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Rat Cardiac Muscle Cell:

RED: lactate transporter (MCT1) antibody is detected with a secondary antibody conjugated with rhodamine (red).

GREEN: transmembrane protein CD147 antibody is detected by a secondary antibody labeled with fluorescein (green).

YELLOW: secondary antibodies exactly co-localize within the cardiac muscle cell.

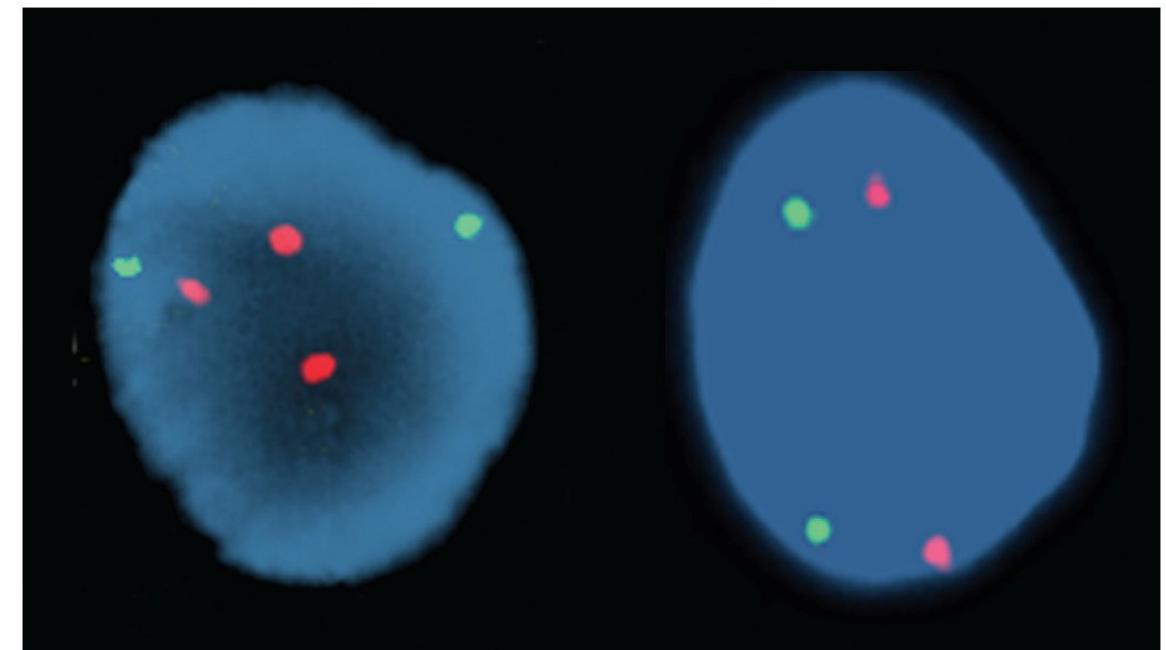
# Hybridization: visualizing gene expression by hybridizing an added nucleotide probe to mRNA in the cell

**Prenatal screening test.** Interphase nuclei of cells obtained from amniotic fluid specimens were hybridized with two specific DNA probes.

ORANGE (LSI 21) chromosome 21 probe  
GREEN (LSI 13) chromosome 13 probe

The right nucleus is from a normal Amniotic fluid specimen

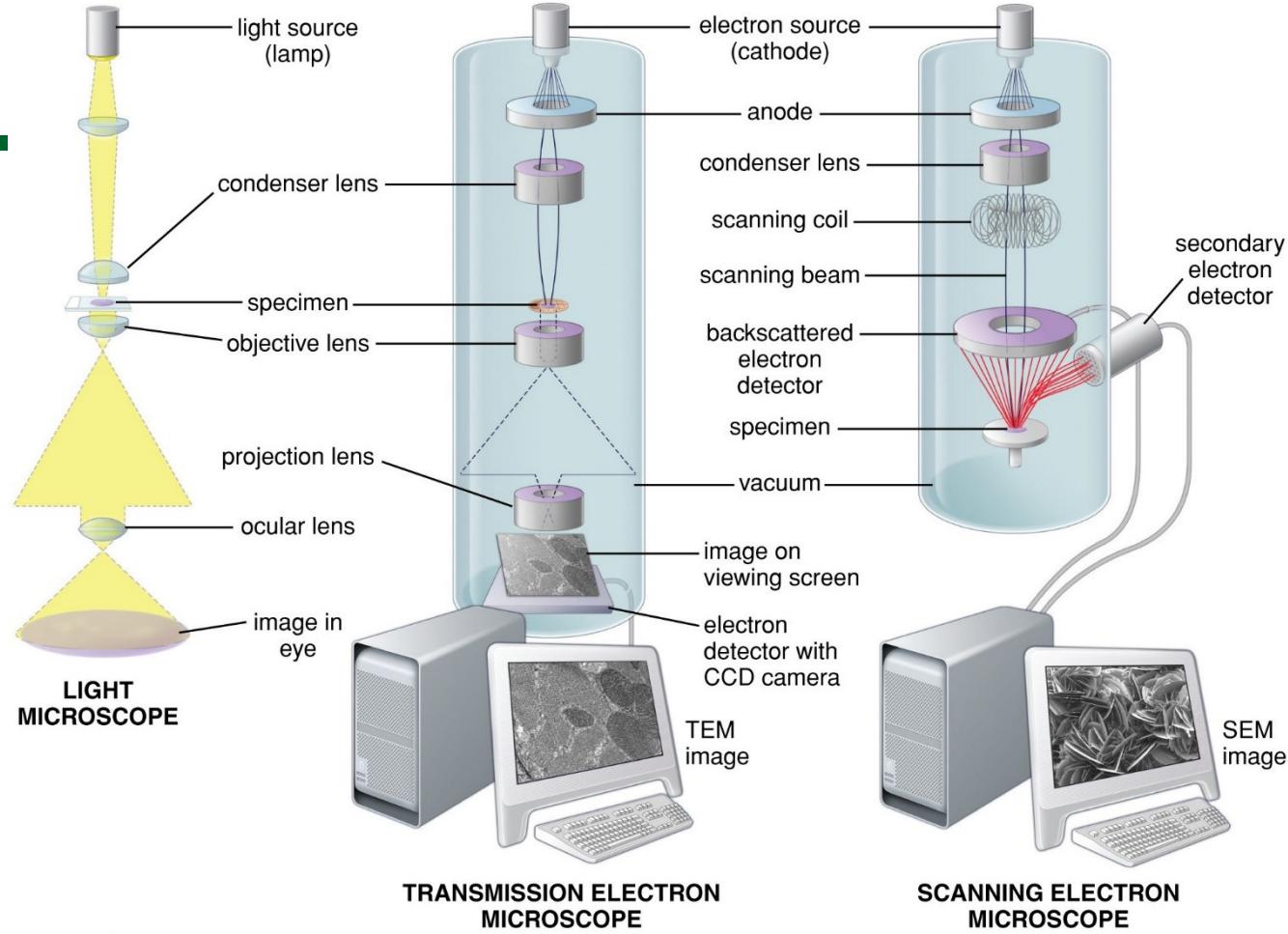
The left nucleus has three orange signals, which indicate trisomy 21 (Down syndrome).



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# Microscopy

1. Light Microscopy
  - a. Bright-field
  - b. Phase Contrast
  - c. Fluorescence
  - d. Confocal
2. Electron Microscopy (EM)
3. Atomic Forces Microscopy
4. Virtual Microscopy



How to focus a microscope:  
<https://www.youtube.com/watch?v=scEhgAiazzU>

# Resolving Power

- The distance by which two objects must be separated to be seen as two objects

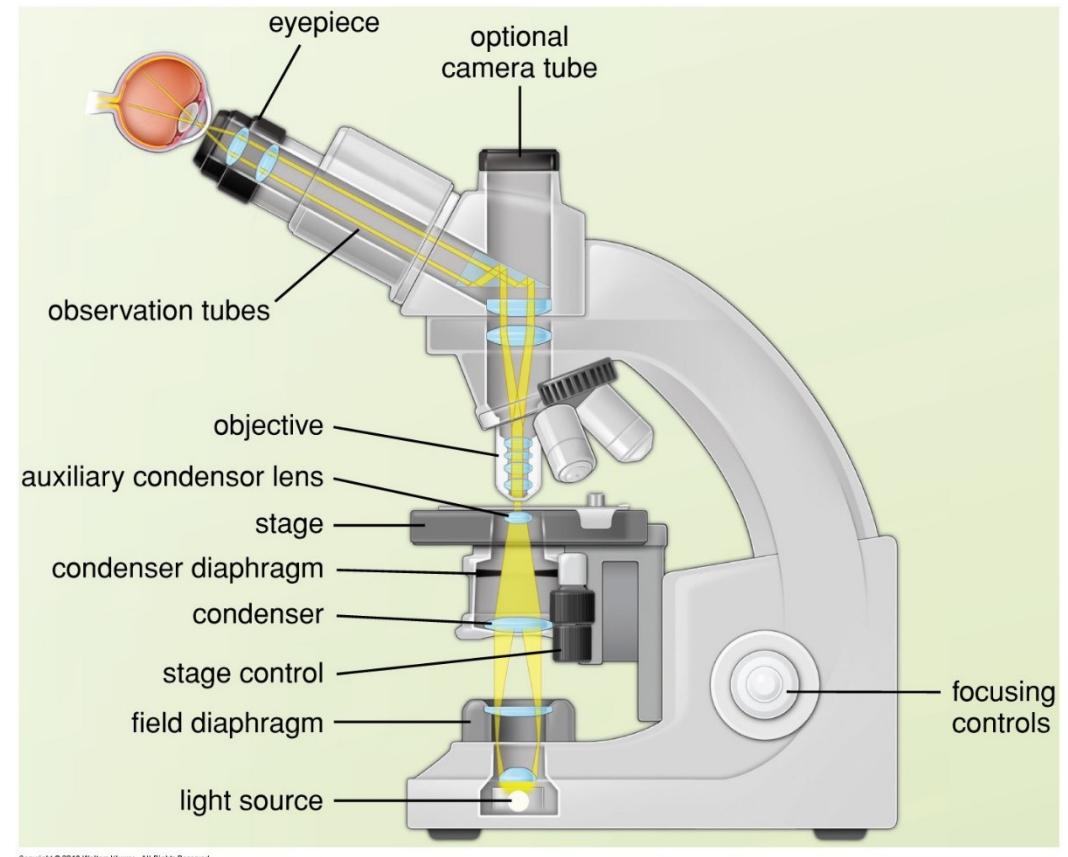
TABLE	1.3	Eye Versus Instrument Resolution
Distance Between Resolvable Points		
Human eye		0.2 mm
Bright-field microscope		0.2 $\mu$ m
SEM		2.5 nm
TEM		
Theoretical		0.05 nm
Tissue section		1.0 nm

# Light Microscopy: interaction of light with tissue components and are used to reveal and study tissue features in different ways

**Bright-field microscopy** (which we will use this term): stained preparations are examined as ordinary light passes through the specimen.

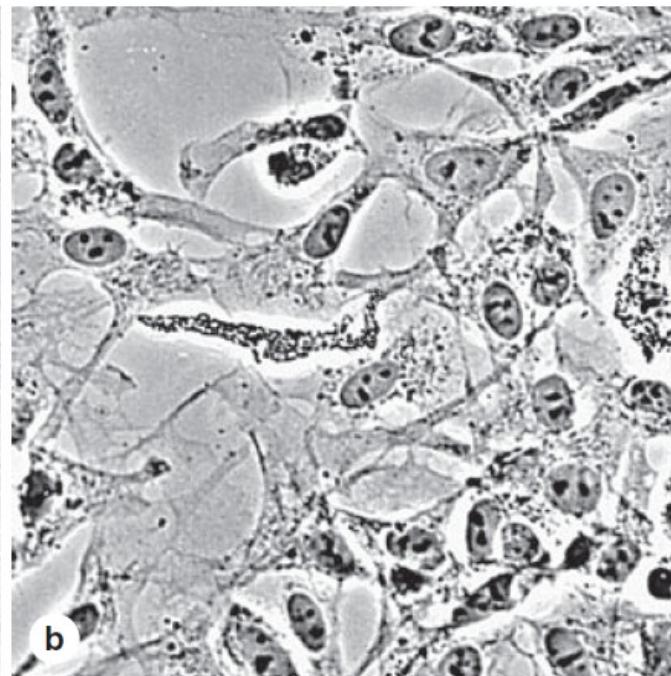
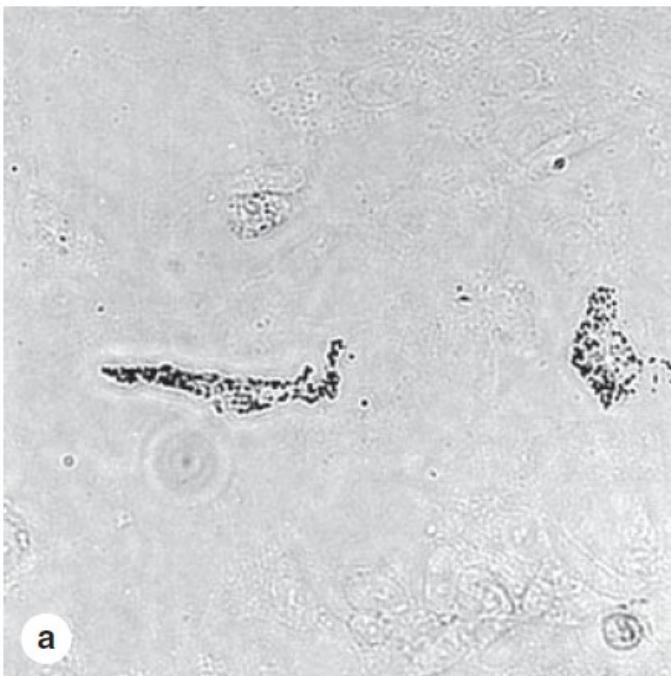
Optical Components:

- **condenser:** collects and focuses light
- **objective lens:** enlarges and projects the image of the object toward eyepiece.
- **ocular lens (eyepiece):** further magnifies image low light levels with a monitor and camera.
- **total magnification:** product of magnifying power of the objective and ocular lenses.



# Other types of light microscopy

- **Phase-contrast microscopy** uses the differences in refractive index of various natural cell and tissue components to produce an image without staining, allowing observation of living cells.

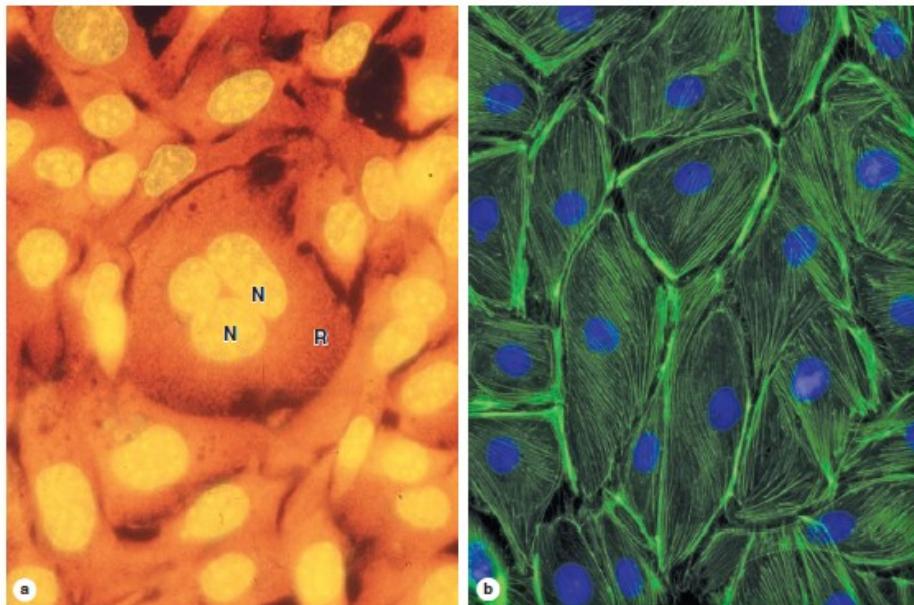


**(a) Bright-field microscopy:** Without fixation and staining, only the two pigment cells can be seen.

**(b) Phase-contrast microscopy:** Cell boundaries, nuclei, and cytoplasmic structures with different refractive indices affect in-phase light differently and produce an image of these features in *all* the cells.

# Other types of light microscopy

- **Fluorescence microscopy** uses ultraviolet light, under which only fluorescent molecules are visible, allowing localization of fluorescent probes which can be much more specific than routine stains.



Components of cells are often stained with compounds visible by fluorescence microscopy.

**(a)** Acridine orange binds nucleic acids and causes DNA in cell nuclei (**N**) to emit yellow light and the RNA-rich cytoplasm (**R**) to appear orange in these cells of a kidney tubule.

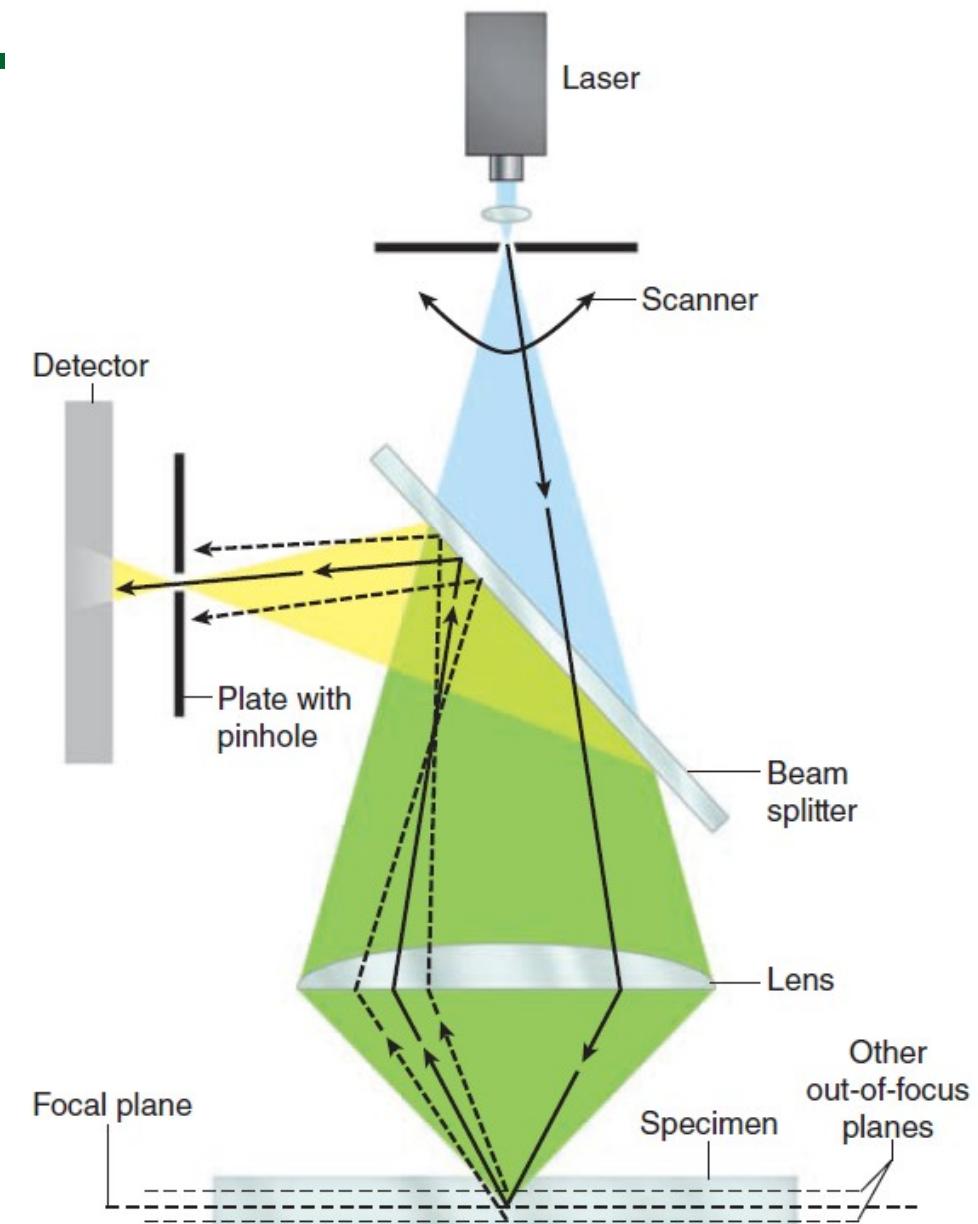
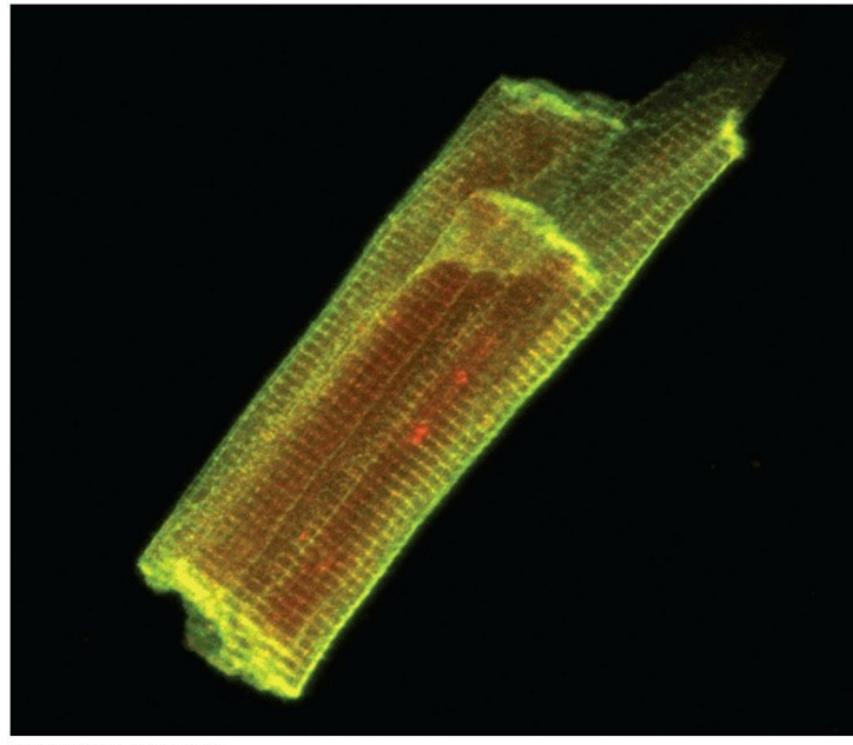
**(b)** Cultured cells stained with DAPI (4',6-diamino-2-phenylindole) that binds DNA and with fluorescein-phalloidin that binds actin filaments show nuclei with blue fluorescence and actin filaments stained green. Important information such as the greater density of microfilaments at the cell periphery is readily apparent. Both X500.

*(Figure 1–4b, contributed with permission, from Drs Claire E. Walczak and Rania Risk, Indiana University School of Medicine, Bloomington.)*

FIGURE 1–6 Principle of confocal microscopy.

## Other types of light microscopy

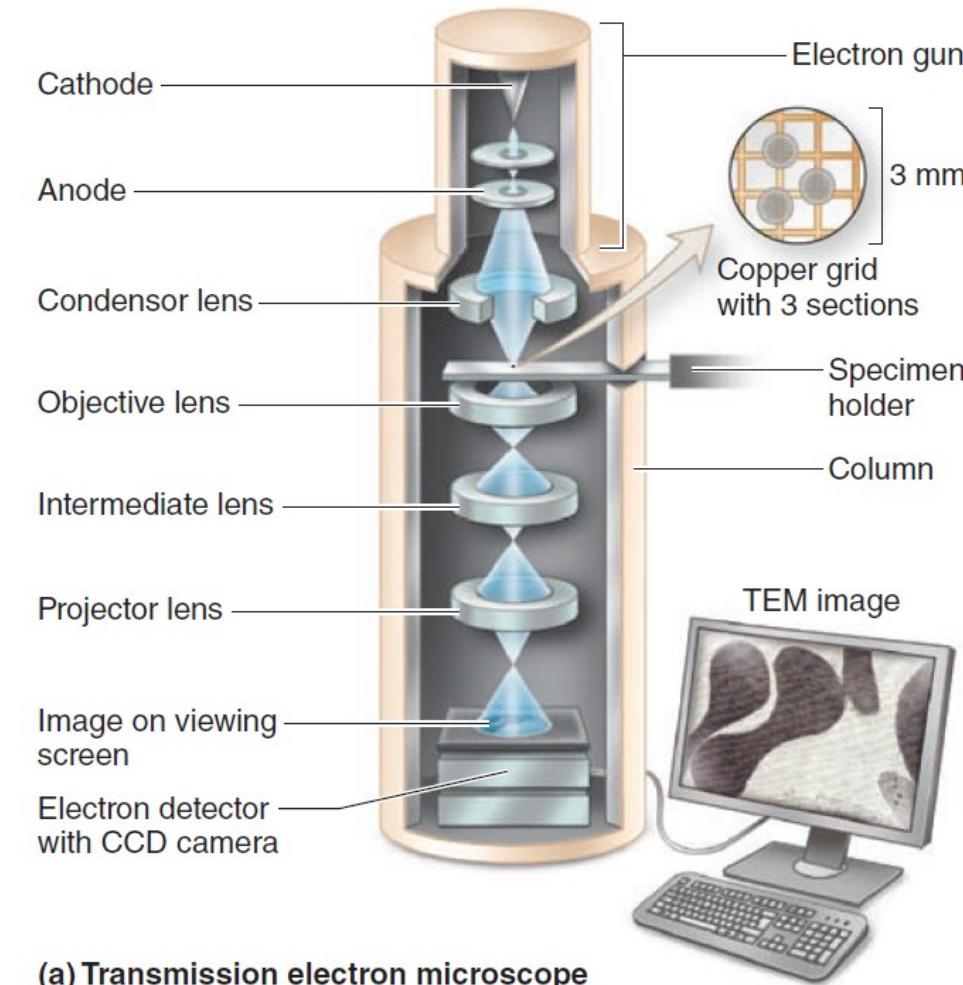
- **Confocal microscopy** involves scanning the specimen at successive focal planes with a focused light beam, often from a laser, and produces a 3D reconstruction from the images.

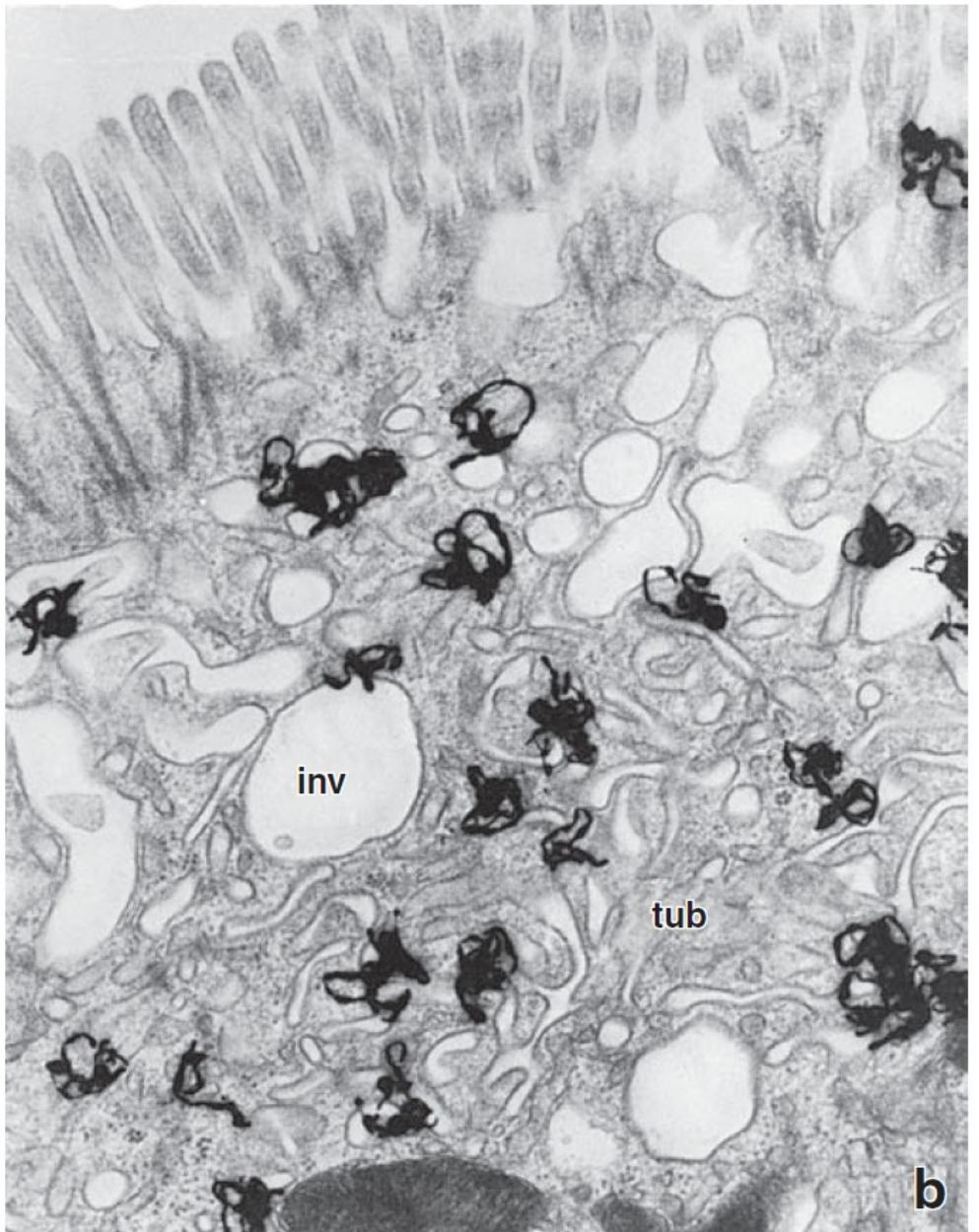


# Electron Microscopy

- Transmission and scanning electron use beams of electrons rather than light. The wavelength in the electron beam is much shorter than that of light, allowing a 1000-fold increase in resolution.
- **Transmission EM** sends an electromagnetically focused beam of electrons at very high voltage through ultrathin sections of tissue.
- Tissue preparation for TEM involves adding **heavy metal ions** that associate at different electron densities with cell and tissue components, improving contrast in the resulting image

FIGURE 1–8 Electron microscopes.



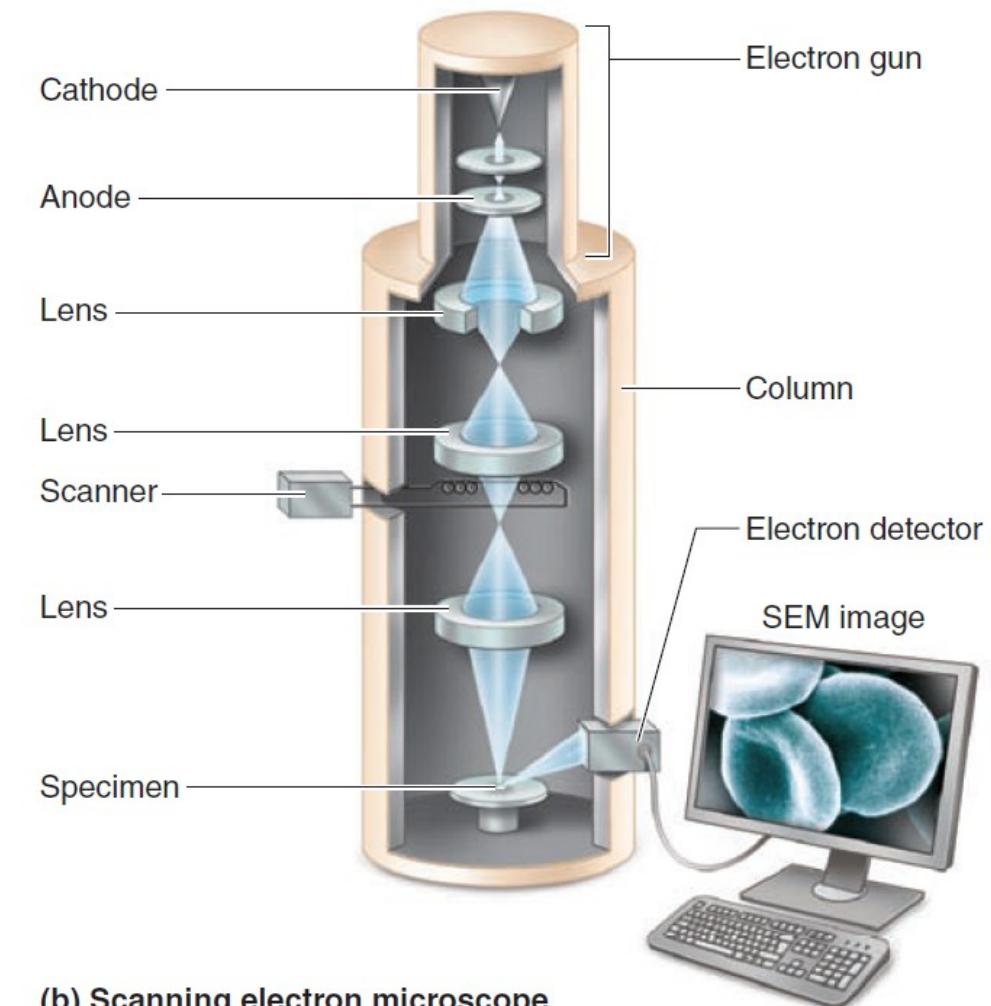


Electron microscopic autoradiograph of the apical region of an intestinal absorptive cell. In this specimen,  $^{125}\text{I}$  bound to nerve growth factor (NGF) was injected into the animal, and the tissue was removed 1 hour later.

The specimen was prepared in a manner similar to that for light microscopy. The relatively small size of the silver grains aids precise localization of the  $^{125}\text{I}$ -NGF complexes. Note that the silver grains are concentrated over apical invaginations (*inv*) and early endosomal tubular profiles (*tub*). 32,000.

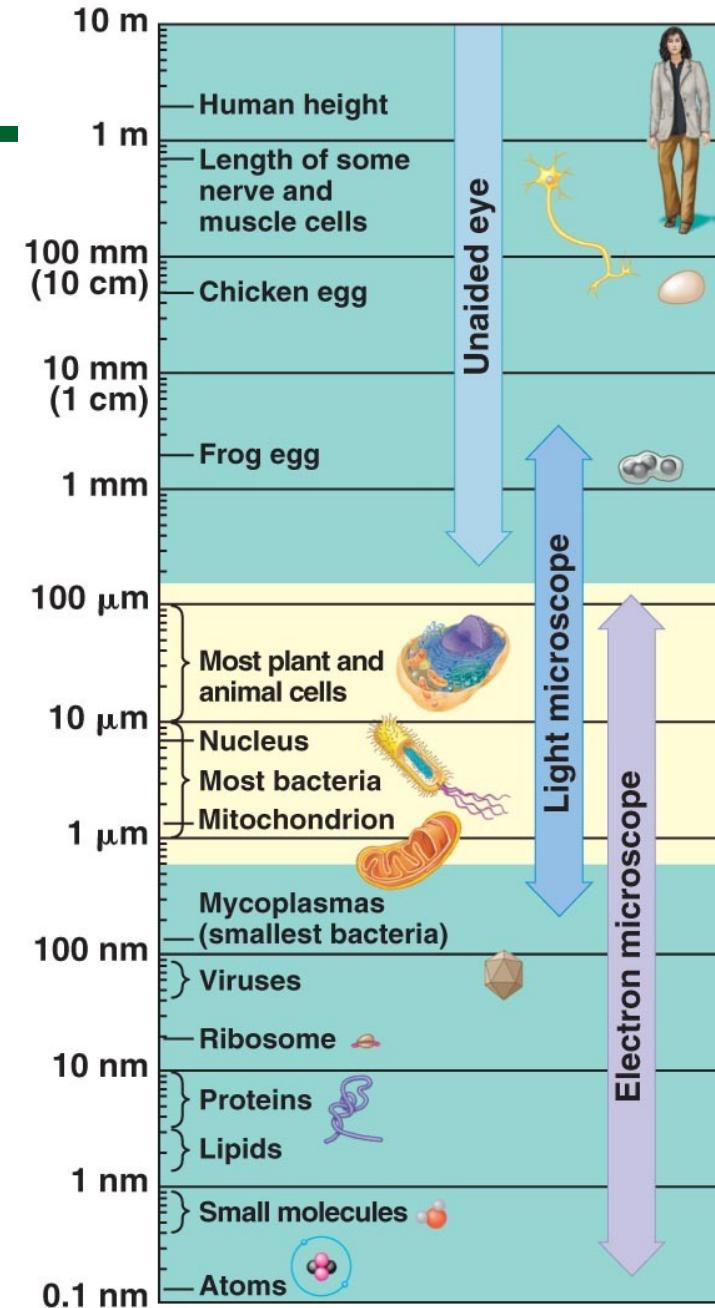
# Electron Microscopy

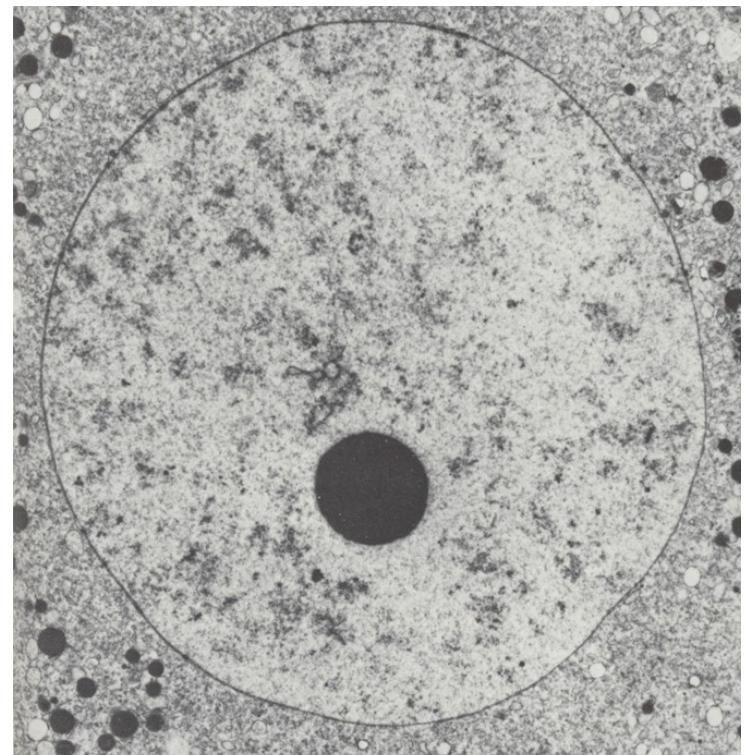
- **Scanning EM** scans an electron beam across a specimen coated with a thin layer of heavy metal; reflected and secondary electrons from the specimen are processed into a 3D ultrastructural image



# Most cells are microscopic

- Most cells cannot be seen without a microscope
  - Bacteria are the smallest of all cells and require magnifications up to 1,000X
  - Plant and animal cells are 10 times larger than most bacteria





Membranous/Non-Membranous Organelles, Inclusions, Cytoplasmic Matrix

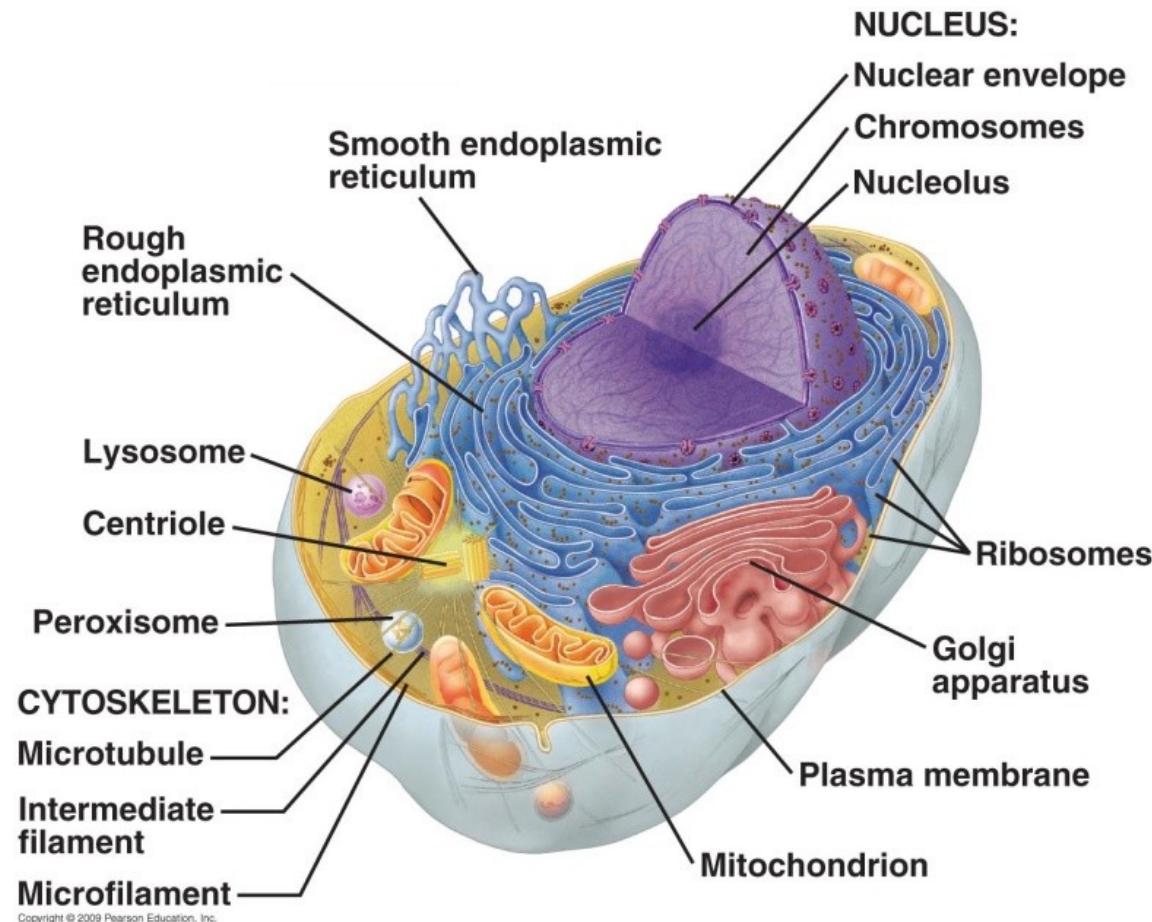
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## CHAPTER 2: CELL CYTOPLASM

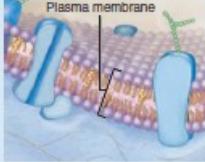
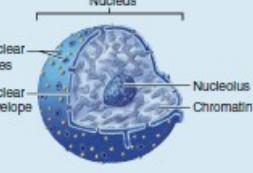
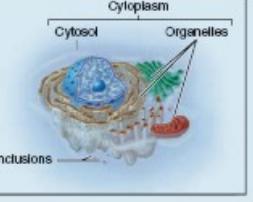
# An Introduction to Cells

The four major life processes in eukaryotic cells & their organelles

1. Manufacturing: nucleus, ribosomes, endoplasmic reticulum, and Golgi apparatus
2. Breakdown of molecules: lysosomes, vacuoles, and peroxisomes
3. Energy processing: mitochondria in animal cells and chloroplasts in plant cells
4. Structural support, movement, and communication: cytoskeleton, plasma membrane, and cell wall



**TABLE 2-6** Summary of cellular structural components.

Component	Structure	Major Function	Appearance
Plasma membrane	Phospholipid bilayer containing cholesterol and proteins (integral and peripheral) and some carbohydrates (externally); forms a selectively permeable boundary of the cell	Acts as a physical barrier to enclose cell contents; regulates material movement into and out of the cell; establishes and maintains an electrical charge difference across the plasma membrane; functions in cell communication	
Cilia	Short, numerous membrane extensions supported by microtubules, which occur on exposed membrane surfaces of some cells	Move substances (eg, mucus, and dissolved materials) over the cell surface	
Flagellum	Long, singular membrane extension supported by microtubules; present on sperm cells	Propels sperm	
Microvilli	Numerous thin membrane folds projecting from the free cell surface; supported by microfilaments	Increase membrane surface area for greater absorption	
Nucleus	Large structure enclosed within a double membrane; contains chromatin, nucleolus, and nucleoplasm	Houses the DNA that serves as the genetic material for directing protein synthesis	
Nuclear envelope	Double membrane boundary between cytoplasm and nuclear contents; continuous with rough endoplasmic reticulum	Separates nucleus from cytoplasm	
Nuclear pores	Openings through the nuclear envelope	Allow passage of materials between the cytoplasm and nucleoplasm, including ribonucleic acid (RNA), protein, ions, and small water-soluble molecules	
Nucleolus	Large, prominent structure within the nucleus	Functions in synthesis of ribosomes	
Cytoplasm	Contents of cells between the plasma membrane and nuclear envelope	Responsible for many cellular processes	
Cytosol	Viscous fluid medium with dissolved solutes (eg, ions, proteins, carbohydrates, lipids)	Provides support for organelles; serves as the viscous fluid medium through which diffusion occurs	
Organelles	Membrane-bound and non-membrane-bound structures	Carry out specific metabolic activities of the cell	
Rough endoplasmic reticulum (rough ER)	Extensive interconnected membrane network that varies in shape (eg, cisternae, tubules); ribosomes attached on cytoplasmic surface	Modifies, transports, and stores proteins produced by attached ribosomes; these proteins are secreted, become components of the plasma membrane, or serve as enzymes of lysosomes	
Smooth endoplasmic reticulum (smooth ER)	Extensive interconnected membrane network lacking ribosomes	Synthesizes, transports, and stores lipids (eg, steroids); metabolizes carbohydrates; detoxifies drugs, alcohol, and poisons; forms vesicles and peroxisomes	

(Continued)

## An excellent summary of chapter 2

### Crash Course Cells

<https://www.khanacademy.org/partner-content/crash-course1/crash-course-biology/v/crash-course-biology-104>

# The membranous organelles: with plasma membranes that separate the internal environment of the organelle from the cytoplasm

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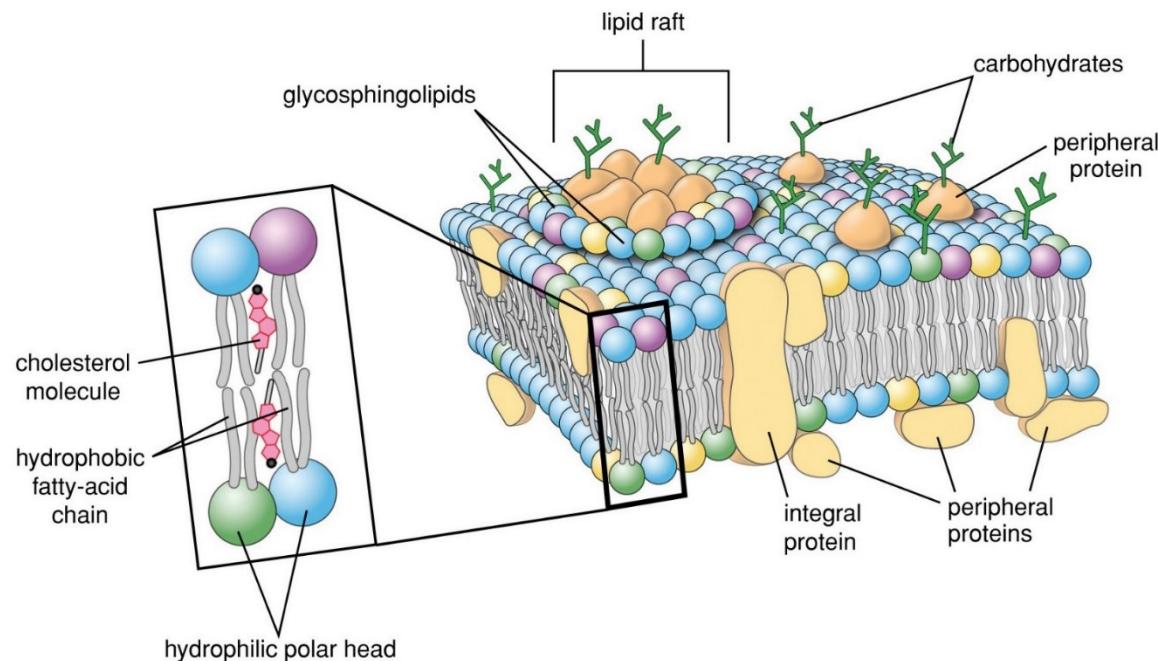
- **plasma (cell) membrane**, a lipid bilayer that forms the cell boundary as well as the boundaries of many organelles within the cell;
- **rough-surfaced endoplasmic reticulum (rER)**, a region of endoplasmic reticulum associated with ribosomes and the site of protein synthesis and modification of newly synthesized proteins;
- **smooth-surfaced endoplasmic reticulum (sER)**, a region of endoplasmic reticulum involved in lipid and steroid synthesis but not associated with ribosomes;
- **Golgi apparatus**, a membranous organelle composed of multiple flattened cisternae responsible for modifying, sorting, and packaging proteins and lipids for intracellular or extracellular transport;

# The membranous organelles: with plasma membranes that separate the internal environment of the organelle from the cytoplasm

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- **Endosomes:** membrane-bounded compartments interposed within endocytotic pathways that have the major function of sorting proteins delivered to them via endocytotic vesicles and redirecting them to different cellular compartments for their final destination;
- **Lysosomes,** small organelles containing digestive enzymes that are formed from endosomes by targeted delivery of unique lysosomal membrane proteins and lysosomal enzymes
- **transport vesicles (pinocytotic, endocytotic, and coated):** involved in both endocytosis and exocytosis and vary in shape and the material that they transport
- **mitochondria,** organelles that provide most of the energy to the cell by producing adenosine triphosphate (ATP) in the process of oxidative phosphorylation; and
- **peroxisomes,** small organelles involved in the production and degradation of H<sub>2</sub>O<sub>2</sub> and degradation of fatty acids.

# The Plasma Membrane

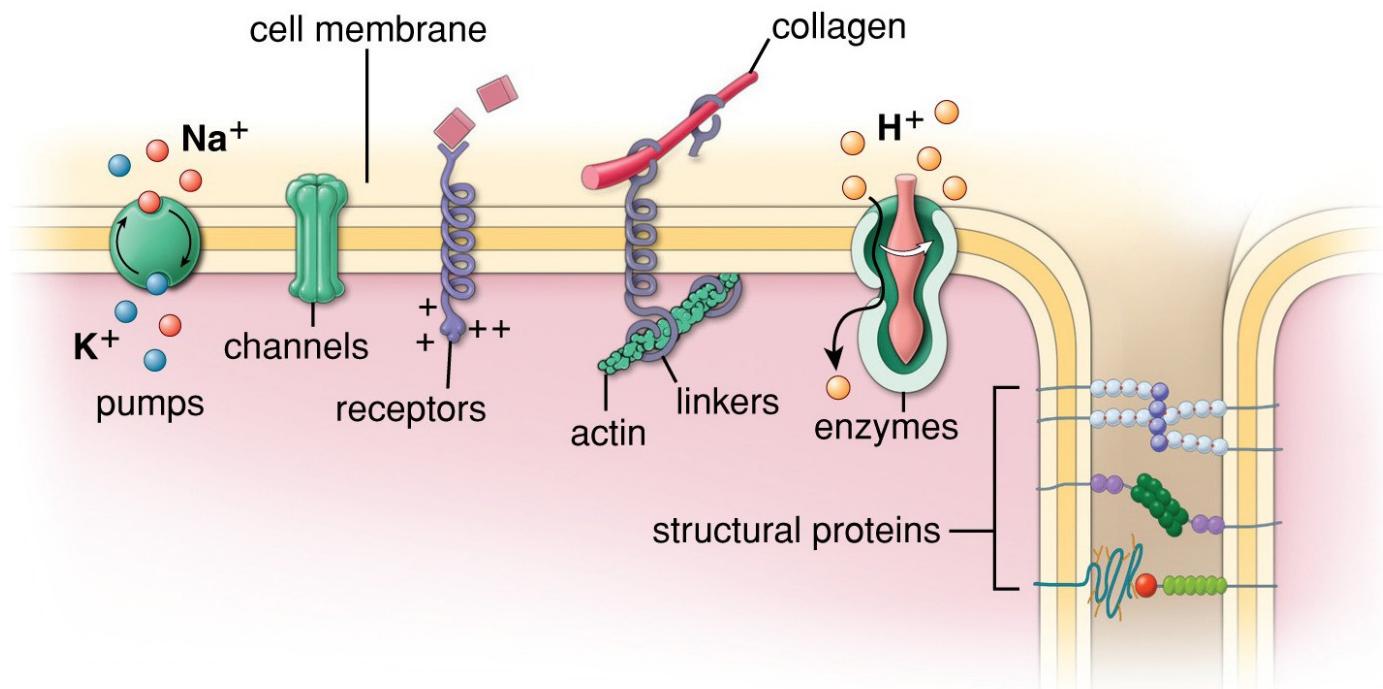


The plasma membrane is a **lipid bilayer** consisting primarily of phospholipid molecules, cholesterol, and protein molecules.

The **hydrophobic fatty-acid chains** of phospholipids face each other to form the inner portion of the membrane, whereas the **hydrophilic polar heads** of the phospholipids form the extracellular and intracellular surfaces of the membrane.

**Cholesterol molecules** are incorporated within the gaps between phospholipids equally on both sides of the membrane.

# Integral Membrane Proteins



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**Different functions of integral membrane proteins.** The six major categories of integral membrane proteins are shown in this diagram:

1. pumps
2. channels
3. receptors
4. linkers
5. enzymes
6. structural proteins.

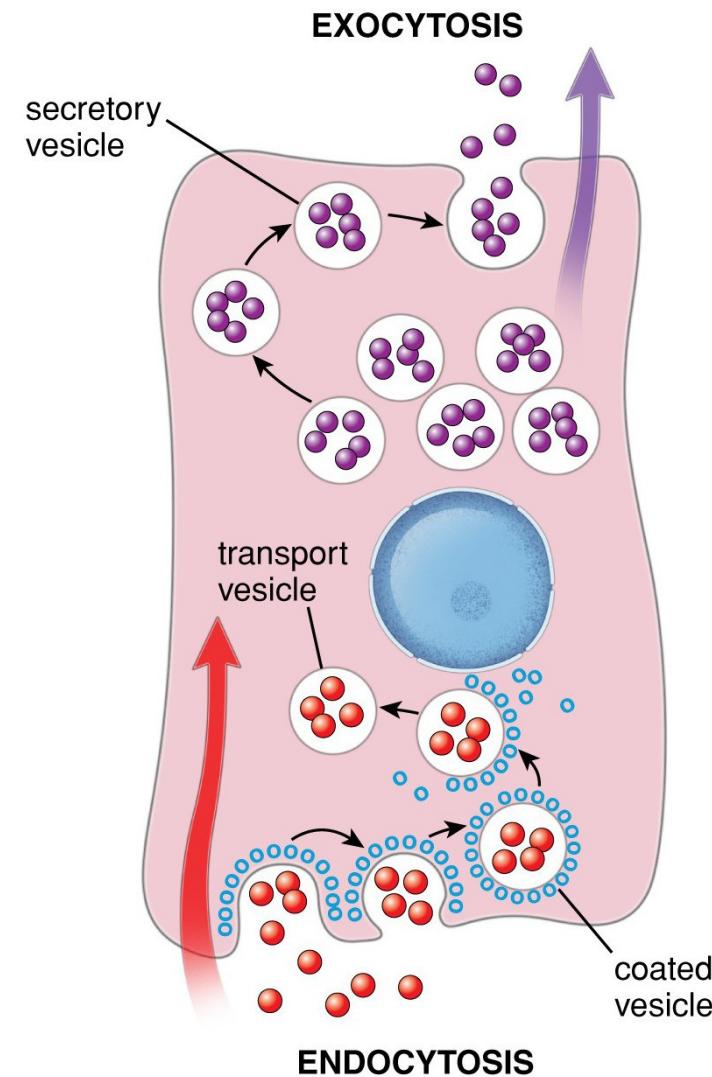
These categories are not mutually exclusive.

A structural membrane protein involved in cell-to-cell junctions might simultaneously serve as a receptor, enzyme, linker, or a combination of these functions.

# Exocytosis and endocytosis transport large molecules across membranes

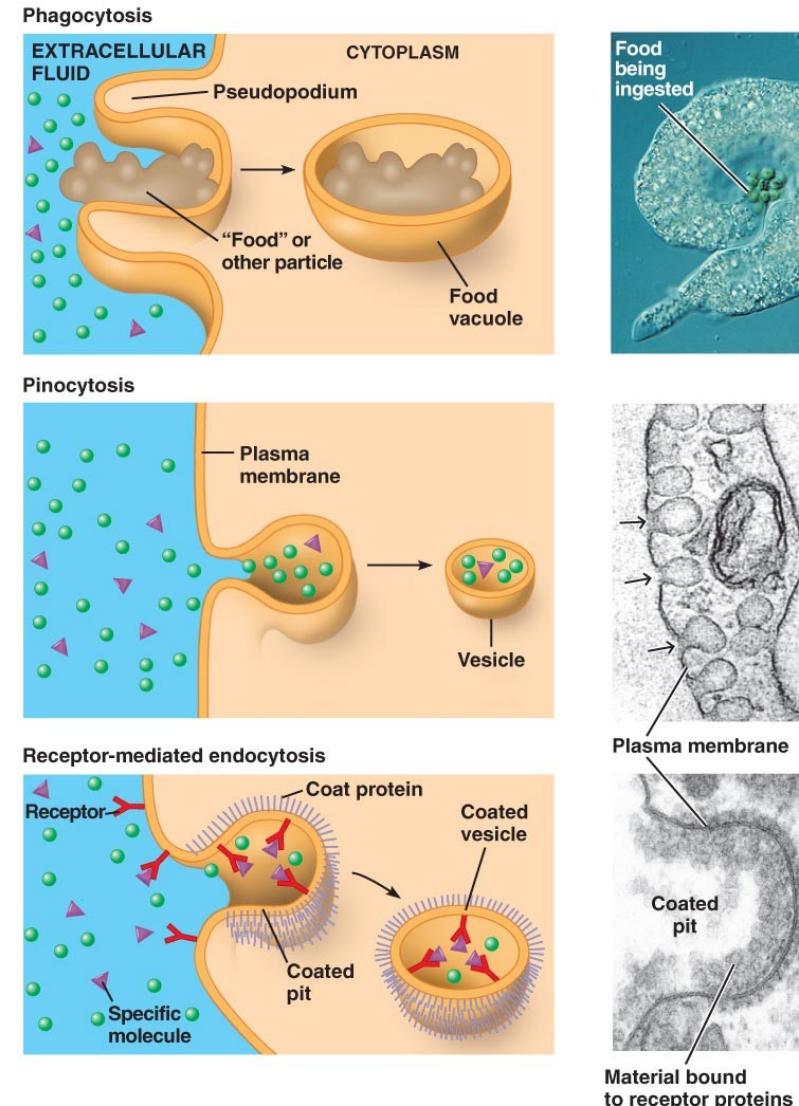
- A cell uses two mechanisms for moving large molecules across membranes
  - **Exocytosis** is used to export bulky molecules, such as proteins or polysaccharides
  - **Endocytosis** is used to import substances useful to the livelihood of the cell
- In both cases, material to be transported is packaged within a vesicle that fuses with the membrane

[http://www.mhhe.com/biosci/ap/ap\\_prep/bioC8.html](http://www.mhhe.com/biosci/ap/ap_prep/bioC8.html)



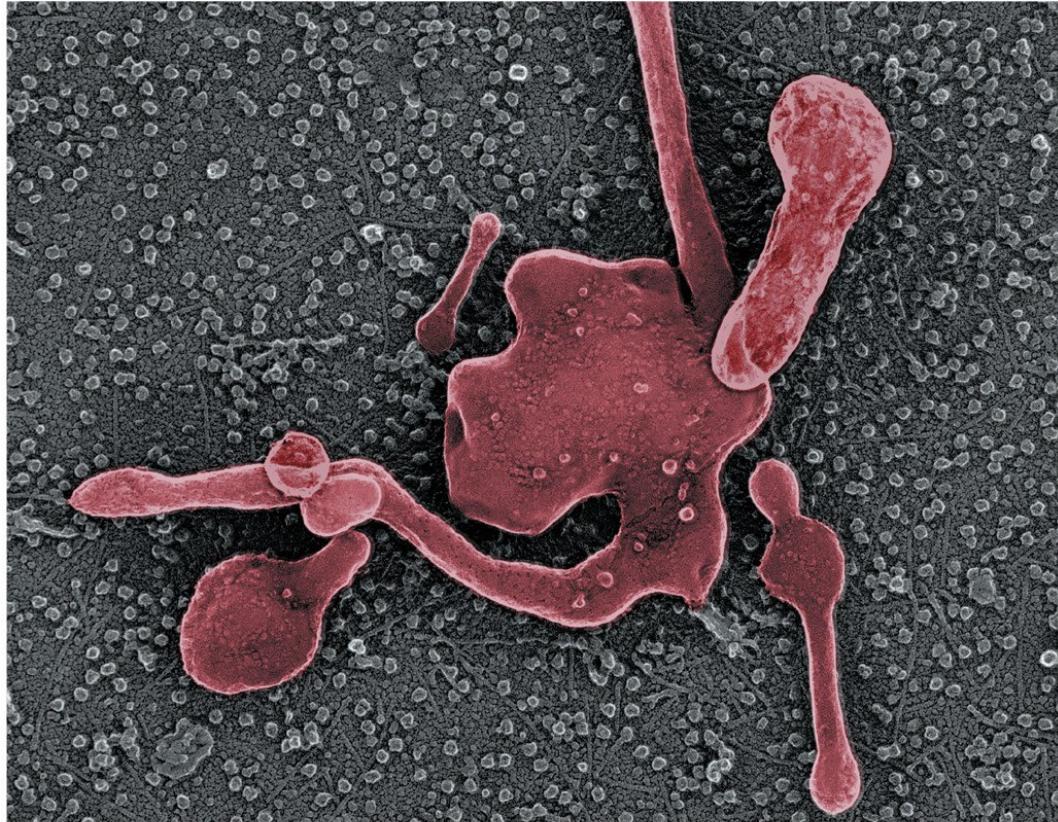
# Exocytosis and endocytosis transport large molecules across membranes

- Three kinds of endocytosis
  - **Phagocytosis** is engulfment of a particle by wrapping cell membrane around it, forming a vacuole
  - **Pinocytosis** is the same thing except that fluids are taken into small vesicles
  - **Receptor-mediated endocytosis** is where receptors in a receptor-coated pit interact with a specific protein, initiating formation of a vesicle



# Endosomes can be viewed either as stable cytoplasmic organelles or as transient structures formed as the result of endocytosis.

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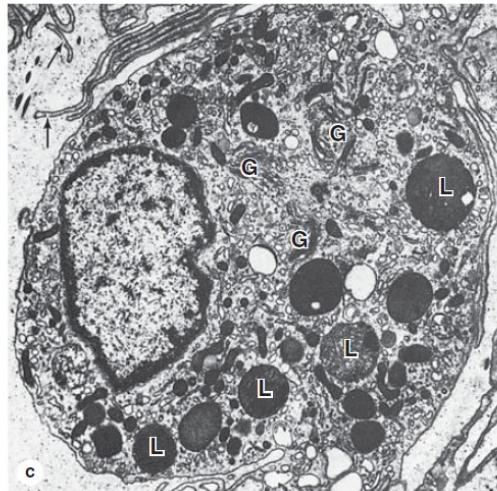
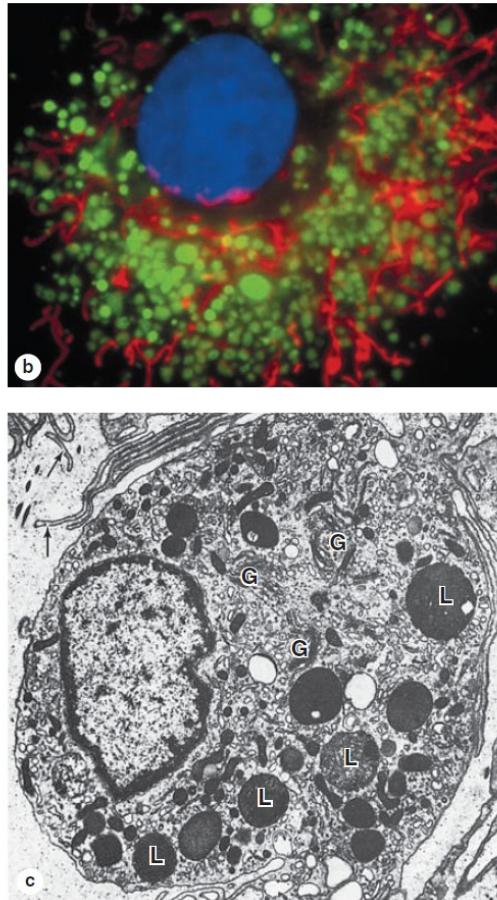
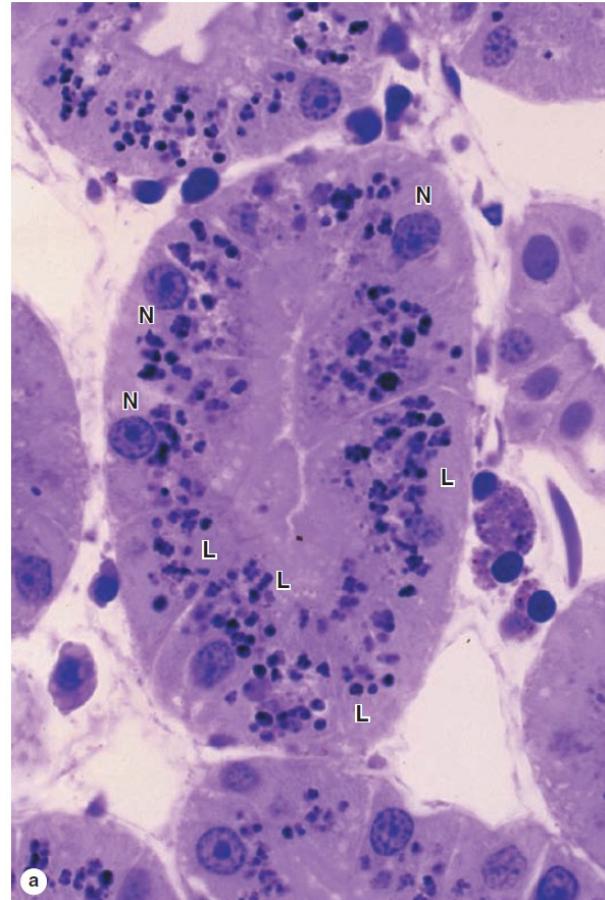


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The TEM reveals the presence in the cytoplasm of membrane enclosed compartments associated with all the endocytotic pathways described above (Fig. 2.15). These compartments, called **early endosomes**, are restricted to a portion of the cytoplasm near the cell membrane where vesicles originating from the cell membrane fuse. From here, many vesicles return to the plasma membrane.

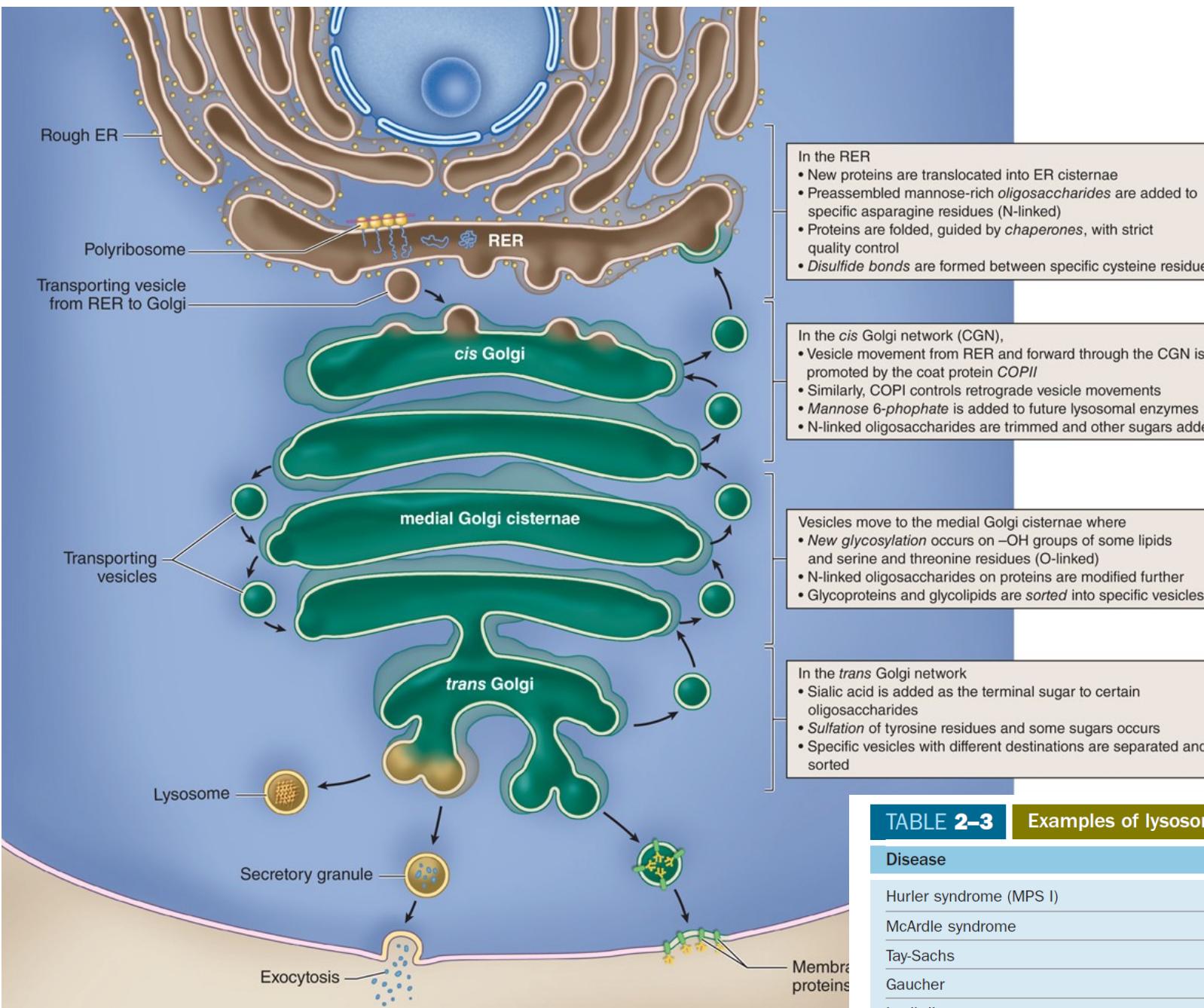
However, large numbers of vesicles originating in early endosomes travel to deeper structures in the cytoplasm called **late endosomes**. The latter typically mature into **lysosomes**.

# Lysosomes are spherical membrane-enclosed vesicles that function as sites of intracellular digestion and are particularly numerous in cells active after the various types of endocytosis.



Lysosomes are not well shown on H&E-stained cells but can be visualized by light microscopy after staining with toluidine blue.

- (a) Cells in a kidney tubule show numerous purple lysosomes
- (b) Lysosomes in cultured vascular endothelial cells can be specifically stained using fluorescent dyes: lysosomes (green), Mitochondria (red) are scattered among the lysosomes.
- (c) In the TEM lysosomes (L) have a characteristic very electron-dense appearance and are shown here near groups of Golgi cisternae (G). The less electron-dense lysosomes represent heterolysosomes in which digestion of the contents is under way.



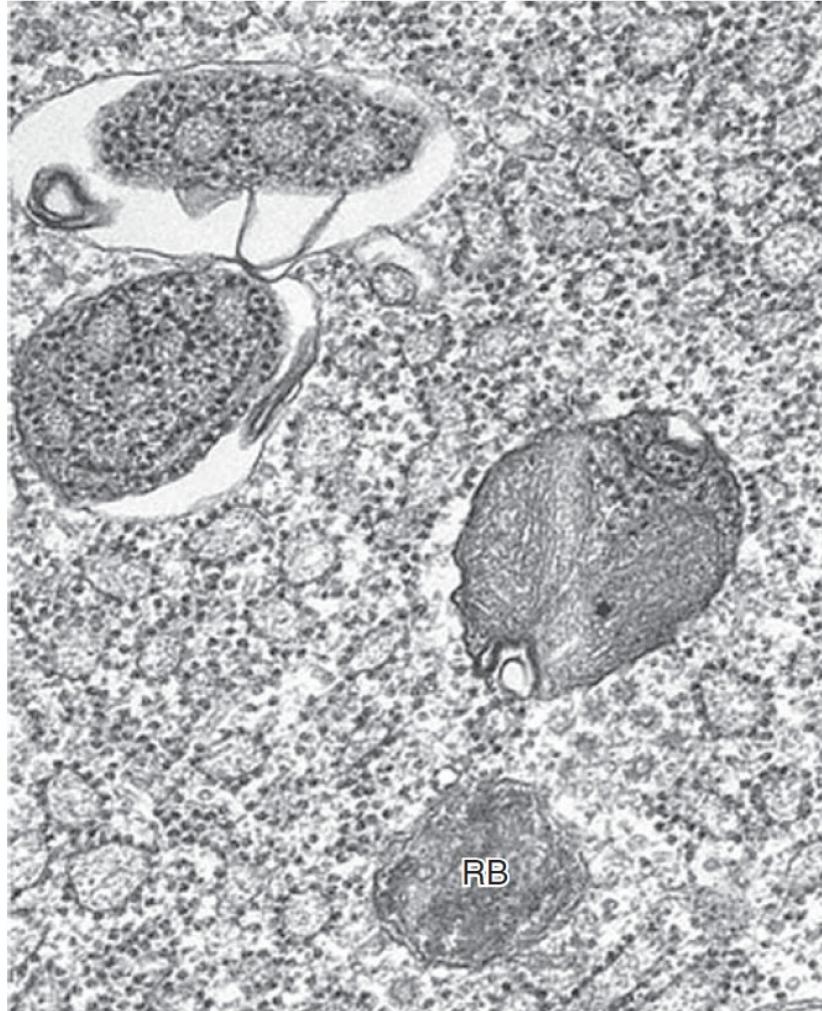
**Lysosomal Storage Diseases, Lysosome Development:**  
<https://www.youtube.com/watch?v=-q8voqiXmF8>

**TABLE 2-3 Examples of lysosomal storage diseases caused by defective lysosomal enzymes.**

Disease	Faulty Enzyme	Main Organs Affected
Hurler syndrome (MPS I)	$\alpha$ -L-Iduronidase	Skeleton and nervous system
McArdle syndrome	Muscle phosphorylase	Skeletal muscles
Tay-Sachs	GM <sub>2</sub> -gangliosidase	Nervous system
Gaucher	Glucocerebrosidase	Liver and spleen
I-cell disease	Phosphotransferase for M6P formation	Skeleton and nervous system

# Autophagy: proteins, organelles, and other cellular structures are degraded in the lysosomal compartment

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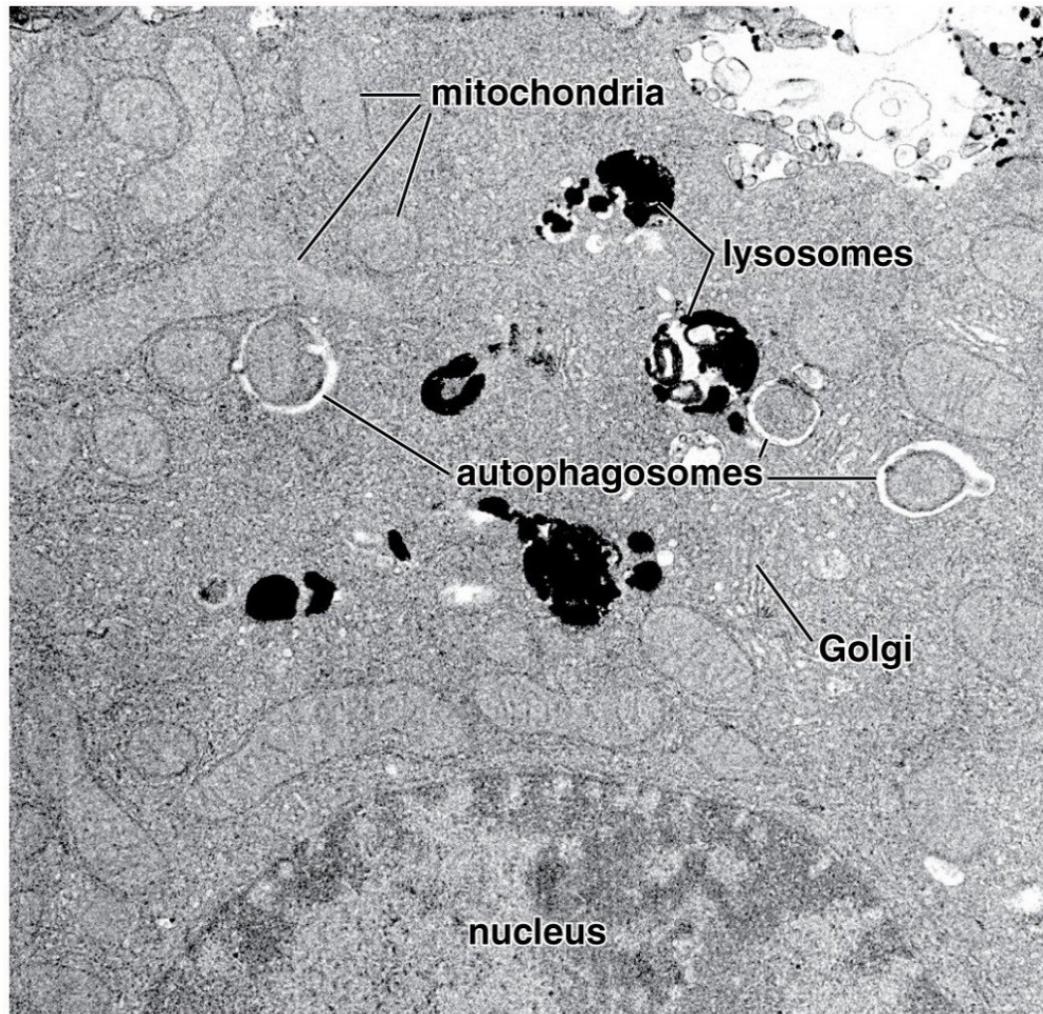
**Autophagy** is a process in which the cell uses lysosomes to dispose of excess or nonfunctioning organelles or membranes.

Membrane that appears to emerge from the SER encloses the organelles to be destroyed, forming an autophagosome that then fuses with a lysosome for digestion of the contents. In this TEM the two autophagosomes at the upper left contain portions of RER more electron dense than the neighboring normal RER and one near the center contains what may be mitochondrial membranes plus RER.

Also shown is a vesicle with features of a residual body (RB).

**Proteasomes are protein complexes that destroy proteins without involvement of lysosomes.**

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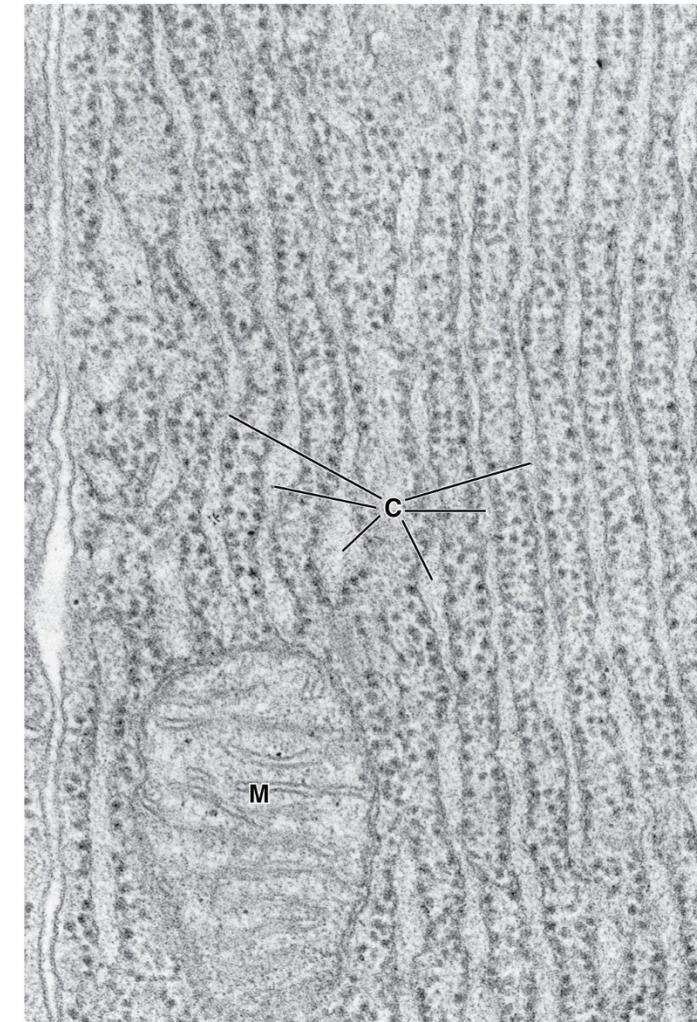


**Electron micrograph of autophagosomes in a hepatocyte**  
shows several autophagosomes containing degenerating mitochondria.  
Note the surrounding lysosomes that have been stained with acid phosphatase

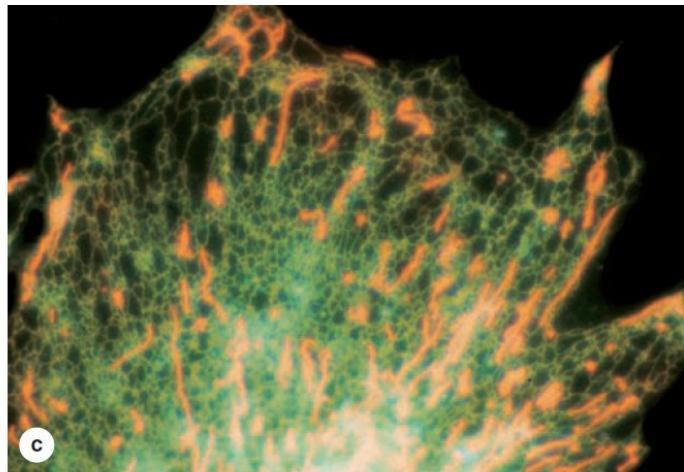
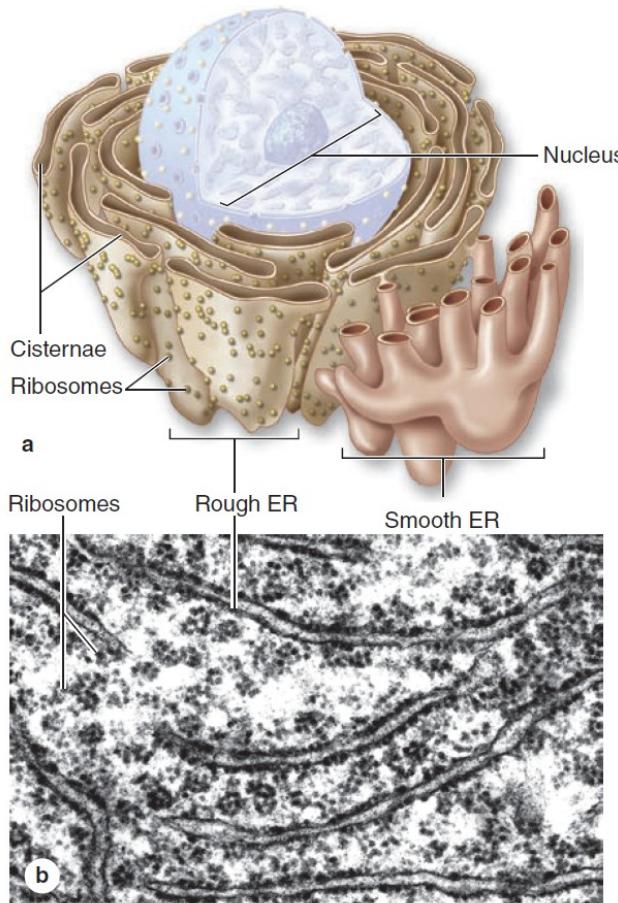
# Rough ER manufactures proteins targeted for secretion or other organelles and membranes

**Electron micrograph of the rER.** This image of the rER in a chief cell of the stomach shows the membranous cisternae (C) closely packed in parallel arrays.

**Polyribosomes** are present on the cytoplasmic surface of the membrane surrounding the cisternae. The image of a ribosome-studded membrane is the origin of the term *rough endoplasmic reticulum*. A few ribosomes are free in the cytoplasm. M, mitochondrion.



# Smooth ER lacks ribosomes and synthesizes lipids



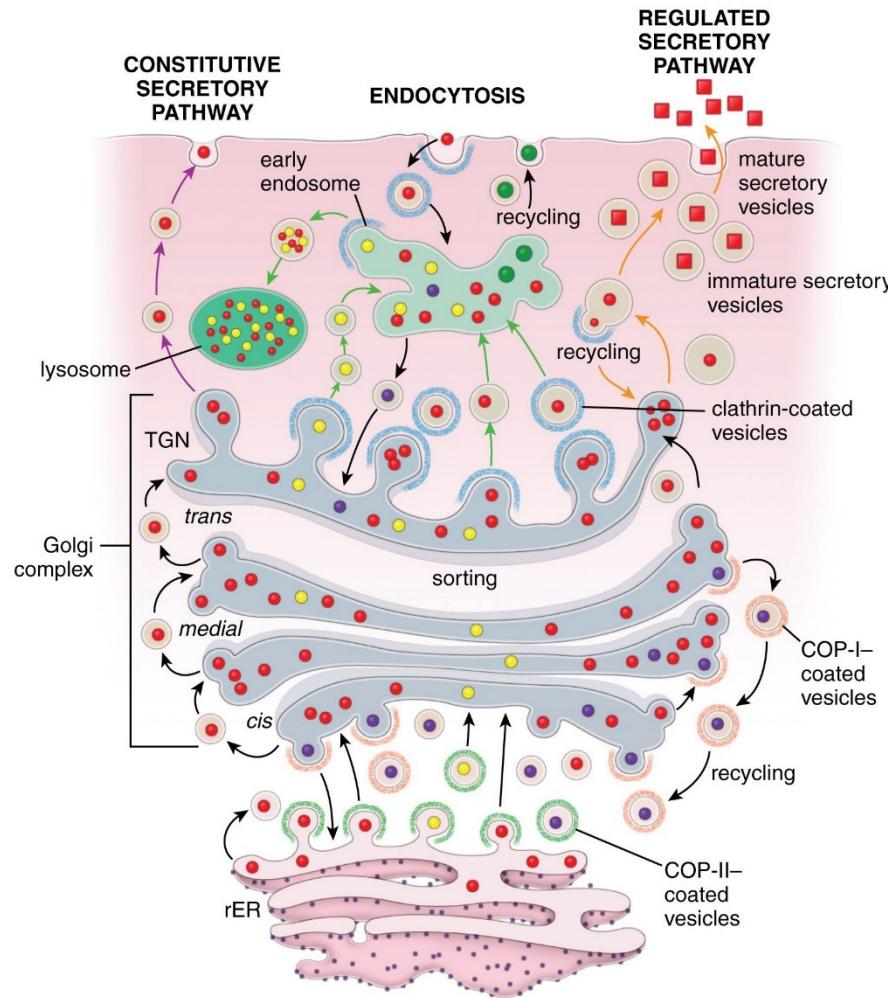
## Functions of Endoplasmic Reticulum

1. **Synthesis:** Provides a place for chemical reactions
  - a. Smooth ER is the site of lipid synthesis and carbohydrate metabolism
  - b. Rough ER synthesizes proteins for secretion, incorporation into the plasma, membrane, and as enzymes within lysosomes
2. **Transport:** Moves molecules through cisternal space from one part of the cell to another, sequestered away from the cytoplasm
3. **Storage:** Stores newly synthesized molecules
4. **Detoxification:** Smooth ER detoxifies both drugs and alcohol

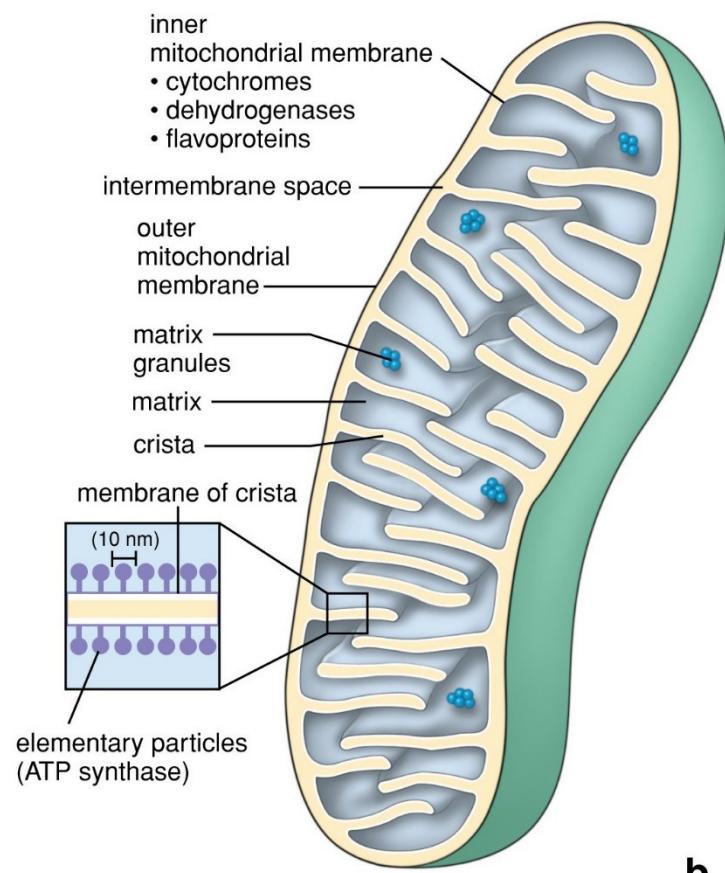
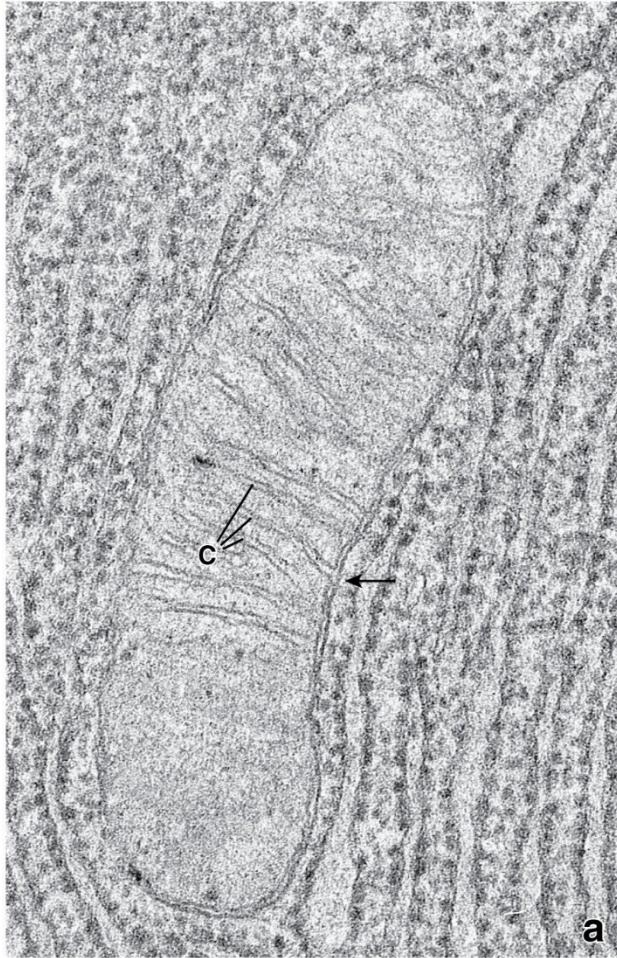
## » MEDICAL APPLICATION

**Jaundice** denotes a yellowish discoloration of the skin and is caused by accumulation in extracellular fluid of bilirubin and other pigmented compounds, which are normally metabolized by SER enzymes in cells of the liver and excreted as bile. A frequent cause of jaundice in newborn infants is an underdeveloped state of SER in liver cells, with failure of bilirubin to be converted to a form that can be readily excreted.

# The Golgi Apparatus and vesicular trafficking



# Mitochondria are abundant in cells that generate and expend large amounts of energy



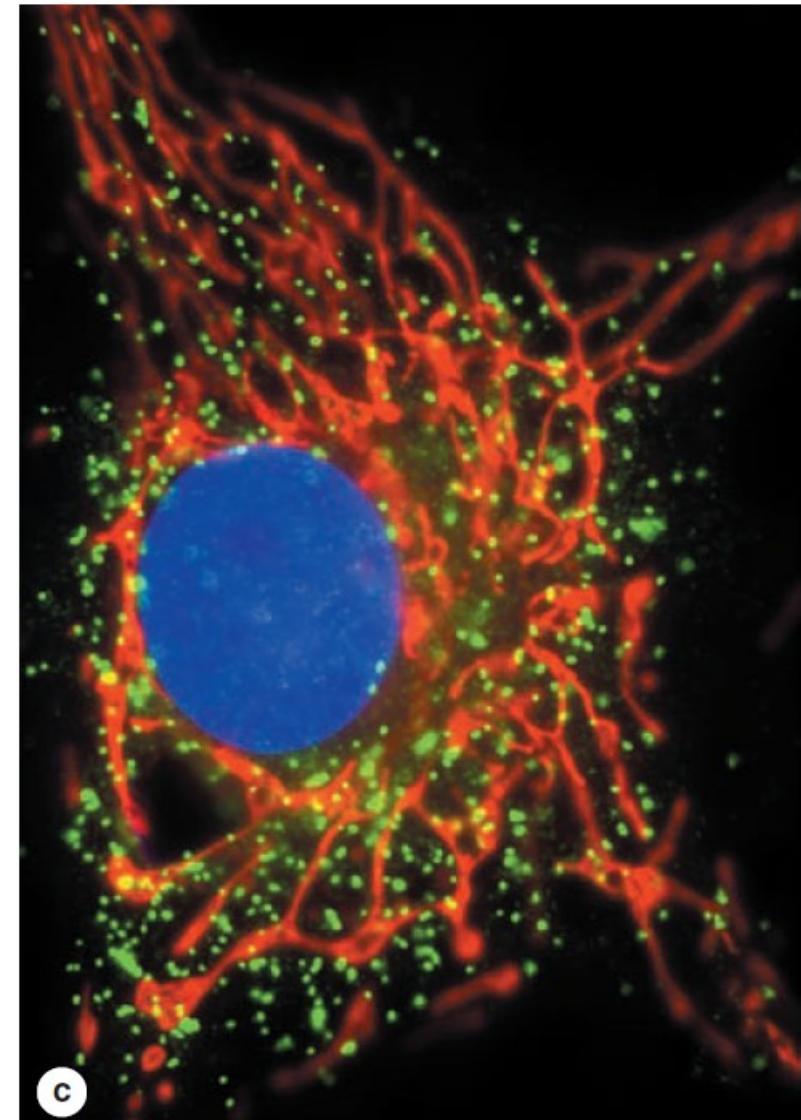
**a.** This electron micrograph shows a mitochondrion in a pancreatic acinar cell. Note that the inner mitochondrial membrane forms the cristae (C) through a series of infoldings, as is evident in the region of the arrow. The outer mitochondrial membrane is a smooth continuous envelope that is separate and distinct from the inner membrane.

**b.** Schematic diagram showing the components of a mitochondrion. Note the location of the elementary particles (inset), the shape of which reflects the three-dimensional structure of ATP synthase.

# Peroxisomes are spherical organelles enclosed by a single membrane

Peroxisomes produce and degrade hydrogen peroxide inactivate various potentially toxic molecules, including some prescription drugs, particularly in the large and abundant peroxisomes of liver and kidney cells

A cultured endothelial cell processed by immunocytochemistry shows many peroxisomes (green) distributed throughout the cytoplasm among the vitally stained elongate mitochondria (red) around the DAPI-stained nucleus (blue). Peroxisomes shown here were specifically stained using an antibody against the membrane protein PMP70.



# Non-membranous organelles

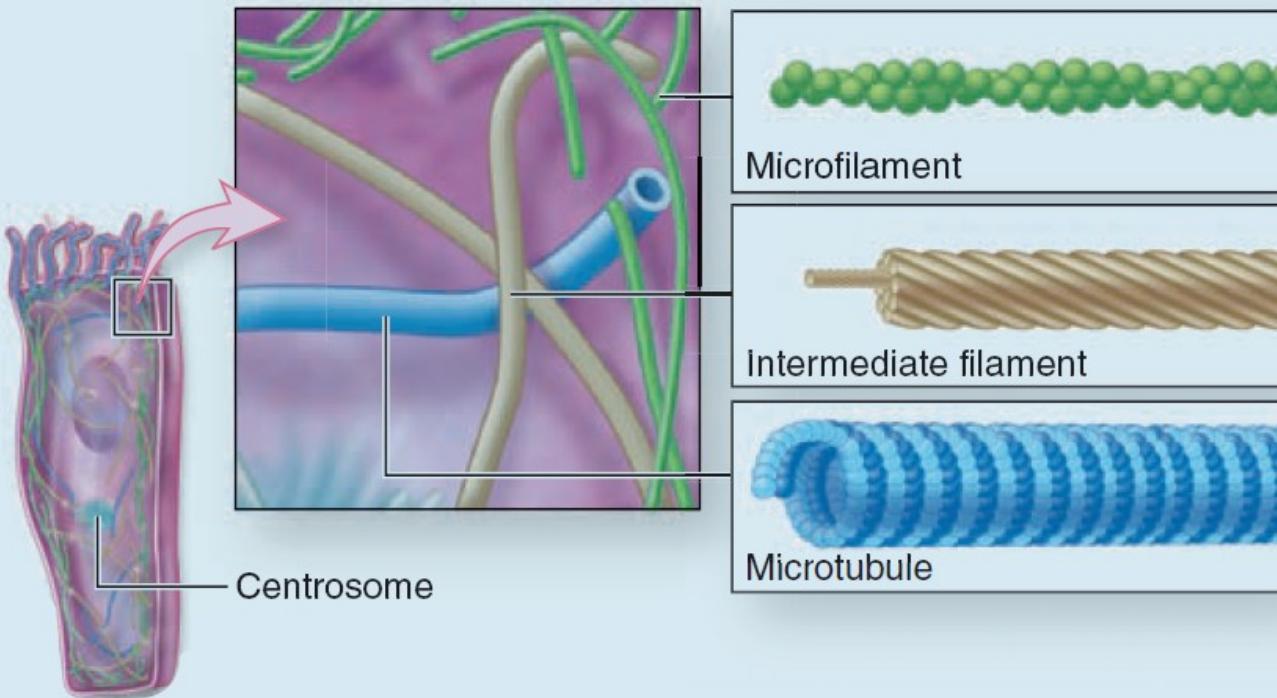
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- **Microtubules:** form elements of the **cytoskeleton** and continuously elongate (by adding tubulin dimers) and shorten (by removing tubulin dimers), a property referred to as **dynamic instability**;
- **Filaments**, which are also part of the cytoskeleton
  - **actin filaments:** flexible chains of actin molecules,
  - **intermediate filaments:** which are ropelike fibers formed from a variety of proteins—both groups providing tensile strength to withstand tension and confer resistance to shearing forces;
- **Centrioles**, or short, paired cylindrical structures found in the center of the **microtubule-organizing center (MTOC)** or **centrosome** and whose derivatives give rise to basal bodies of cilia
- **Ribosomes**, structures essential for protein synthesis and composed of ribosomal RNA (rRNA) and ribosomal proteins (including proteins attached to membranes of the rER and proteins free in the cytoplasm).

# Microtubules & Filaments

TABLE 2-4

Properties of cytoskeletal components (microtubules, microfilaments, and intermediate filaments).



## General Function of Cytoskeleton

- Structural:** Provides structural support to cell; stabilizes junctions between cells
- Movement:** Assists with cytosol streaming and cell motility; helps move organelles and materials throughout cell; helps move chromosomes during cell division

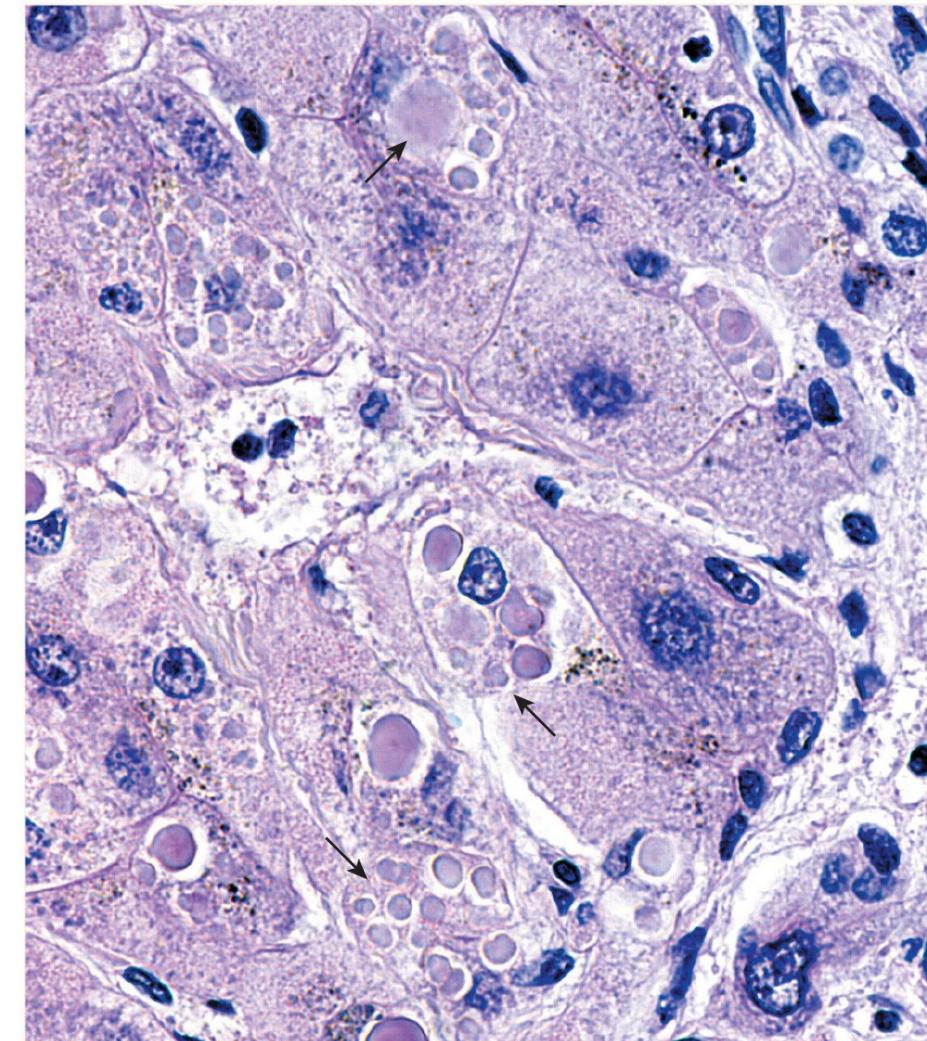
# Abnormalities in microtubules and filaments

## Photomicrograph of Mallory bodies.

Accumulation of keratin intermediate filaments forming intercellular inclusions is frequently associated with specific cell injuries.

In **alcoholic liver cirrhosis**, hepatocytes exhibit such inclusions (arrows), which are known as Mallory bodies.

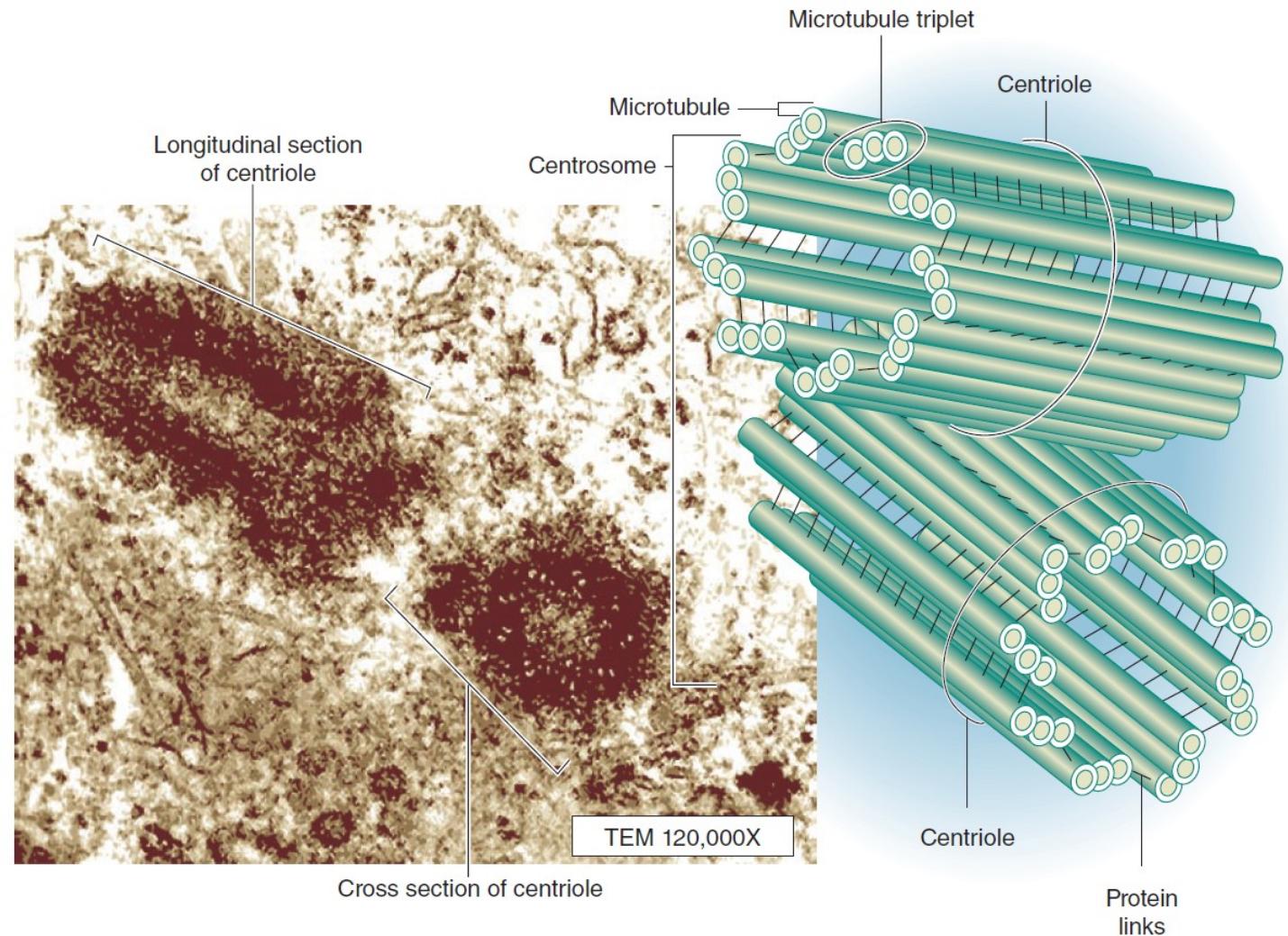
Lymphocytes and macrophages responsible for an intense inflammatory reaction surround cells containing Mallory bodies



# Centrioles

The centrosome is the microtubule-organizing center for the mitotic spindle and consists of paired centrioles. The TEM reveals that the two centrioles in a centrosome exist at right angles to each other in a dense matrix of free tubulin subunits and other proteins

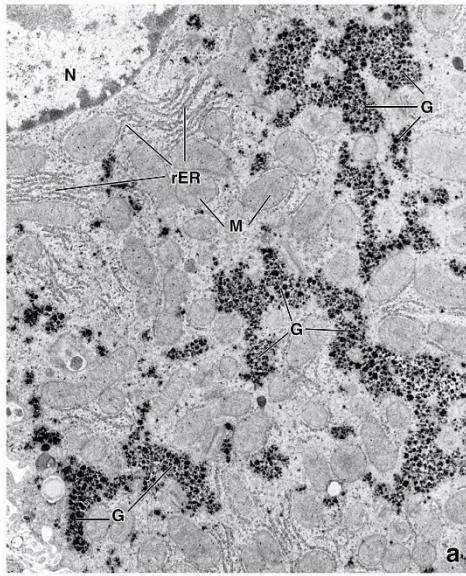
FIGURE 2-24 Centrosome.



# Inclusions contain accumulated metabolites or other substances not enclosed by membrane

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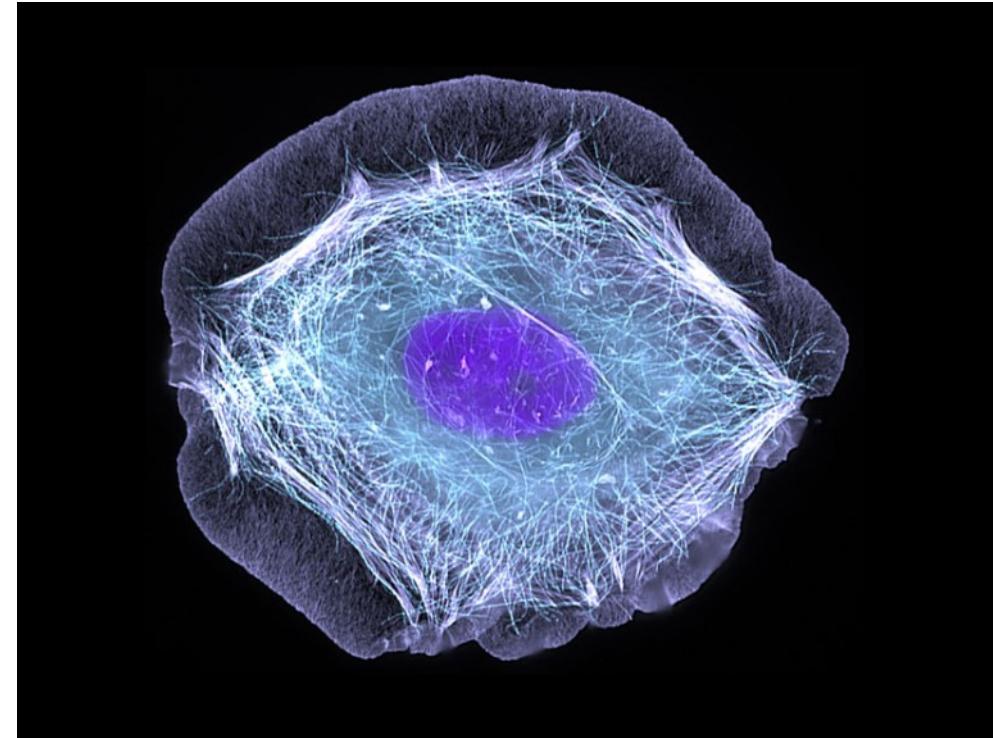
- **Fat droplets:** accumulations of lipid
- **Glycogen granules:** aggregates of glycogen mainly liver cells
- **Lipofuscin:** yellowish-brown pigment found in stable nondividing cells (eg, neurons, cardiac muscle).
- **Hemosiderin:** dense brown aggregate of denatured proteins bound to iron. Found in liver and spleen



## Electron micrographs of a hepatocyte (liver cell) with glycogen inclusions.

- Nucleus (*N, upper left*).
- Glycogen (*G*) appears as irregular electron-dense masses.
- Profiles of rough endoplasmic reticulum (*rER*) and mitochondria (*M*) are also evident.

**A Human Skin Cell.** The purple in the center is the cell's nucleus. Surrounding it are wispy blue and white microtubules and filaments that make up the cell's cytoskeleton



Nuclear Components, Cell Renewal, Cell Cycle, Cell Death

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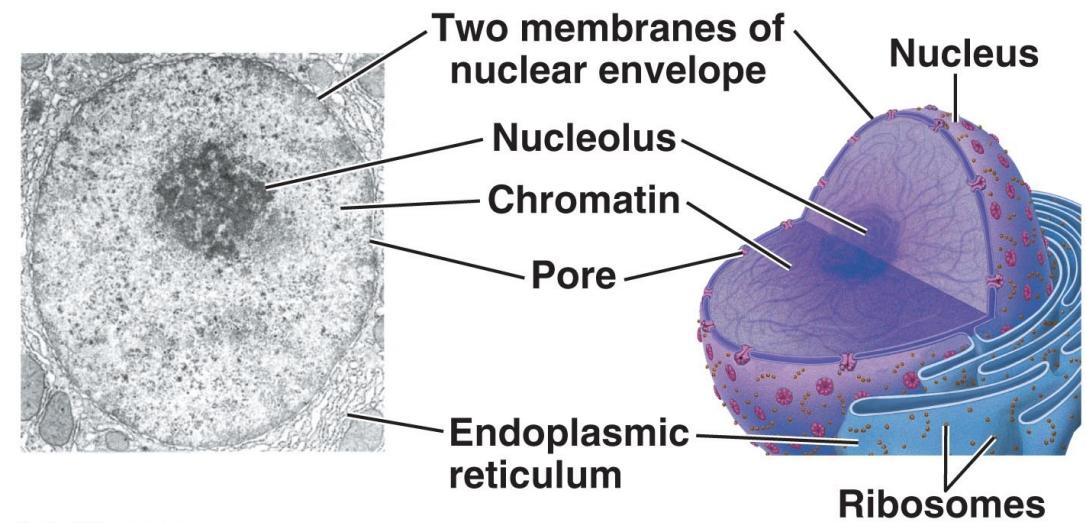
## CHAPTER 3: THE NUCLEUS

# The nucleus is the cell's genetic control center

- The **nucleus** controls the cell's activities and is responsible for inheritance
  - Inside is a complex of proteins and DNA called **chromatin**, which makes up the cell's chromosomes
- The **nuclear envelope** is a double membrane with pores that allow material to flow in and out of the nucleus

**Nucleolus:** contains DNA in the form of transcriptionally active ribosomal RNA (rRNA) genes, RNA, and proteins.

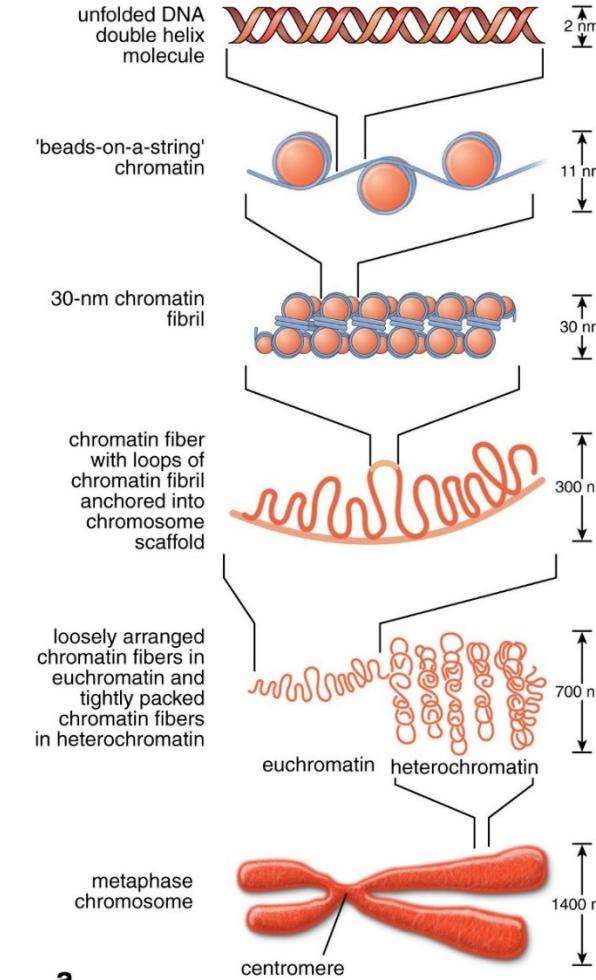
**Nucleoplasm:** nuclear content other than chromatin and nucleolus



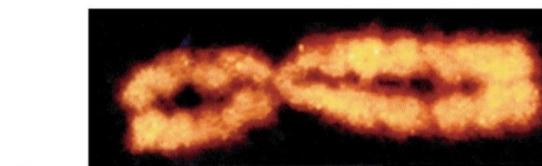
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# Packaging of chromatin into the chromosomal structure

a. Sequential steps in the packaging of nuclear chromatin are shown in this diagram, beginning with the DNA double helix and ending with the highly condensed form found in chromosomes.



b. Structure of human metaphase chromosome 2  
(Courtesy of Dr. Tatsuo Ushiki.)

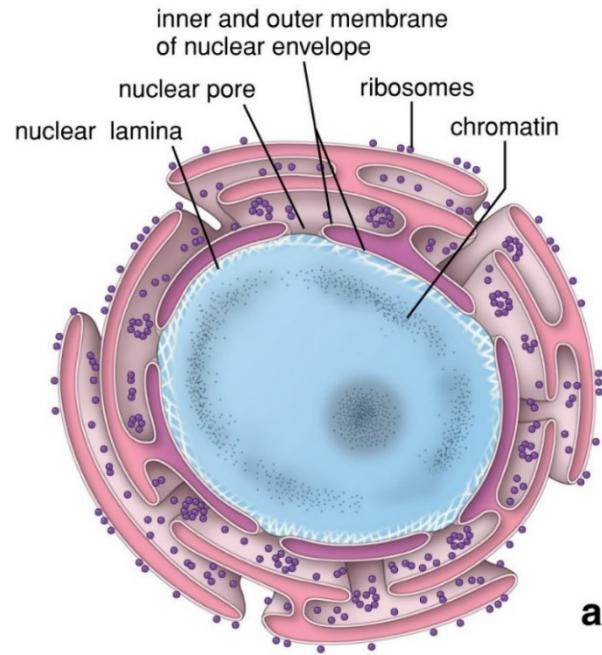


b

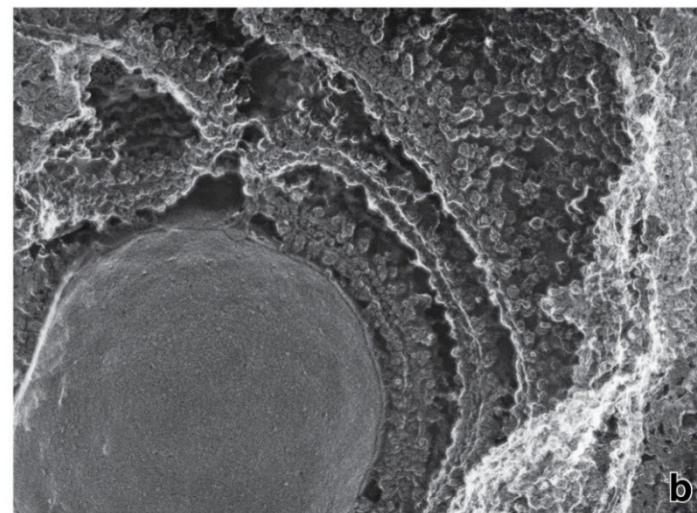
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# Structure of the nuclear envelope and its relationship to the rER

- a. Double membrane envelope surrounds nucleus: outer membrane is continuous with the membranes of the rER; Perinuclear space communicates with the rER lumen. The inner membrane is adjacent to nuclear intermediate filaments that form the nuclear lamina.
- b. Electron micrograph of nucleus surrounded by the nuclear envelope. Note that the outer membrane possesses ribosomes and is continuous with the rER.

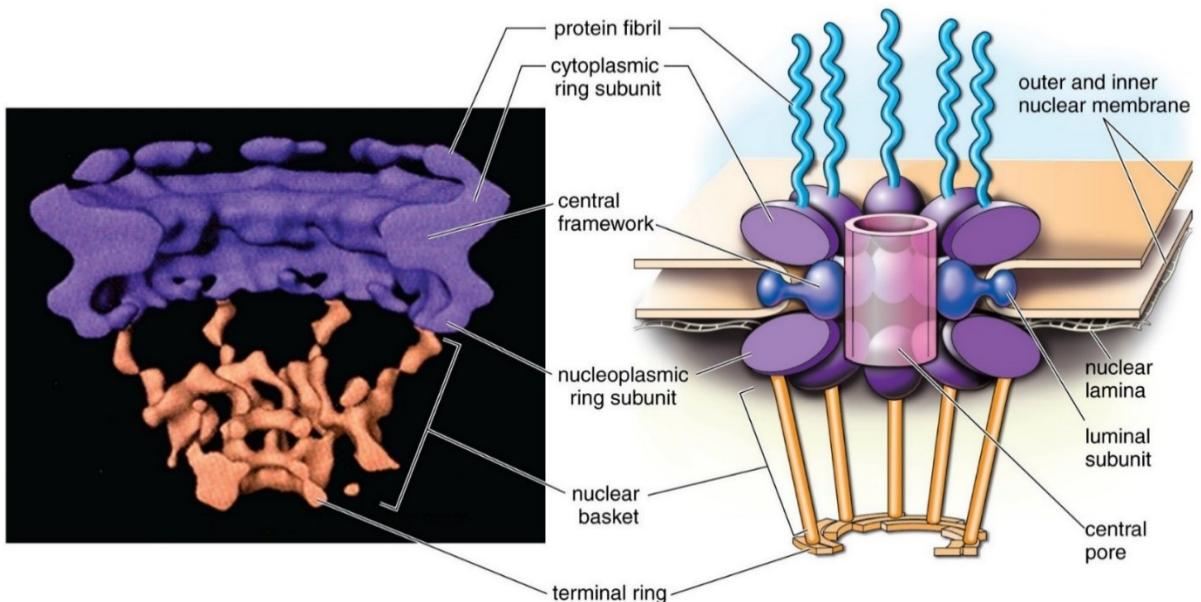


a



b

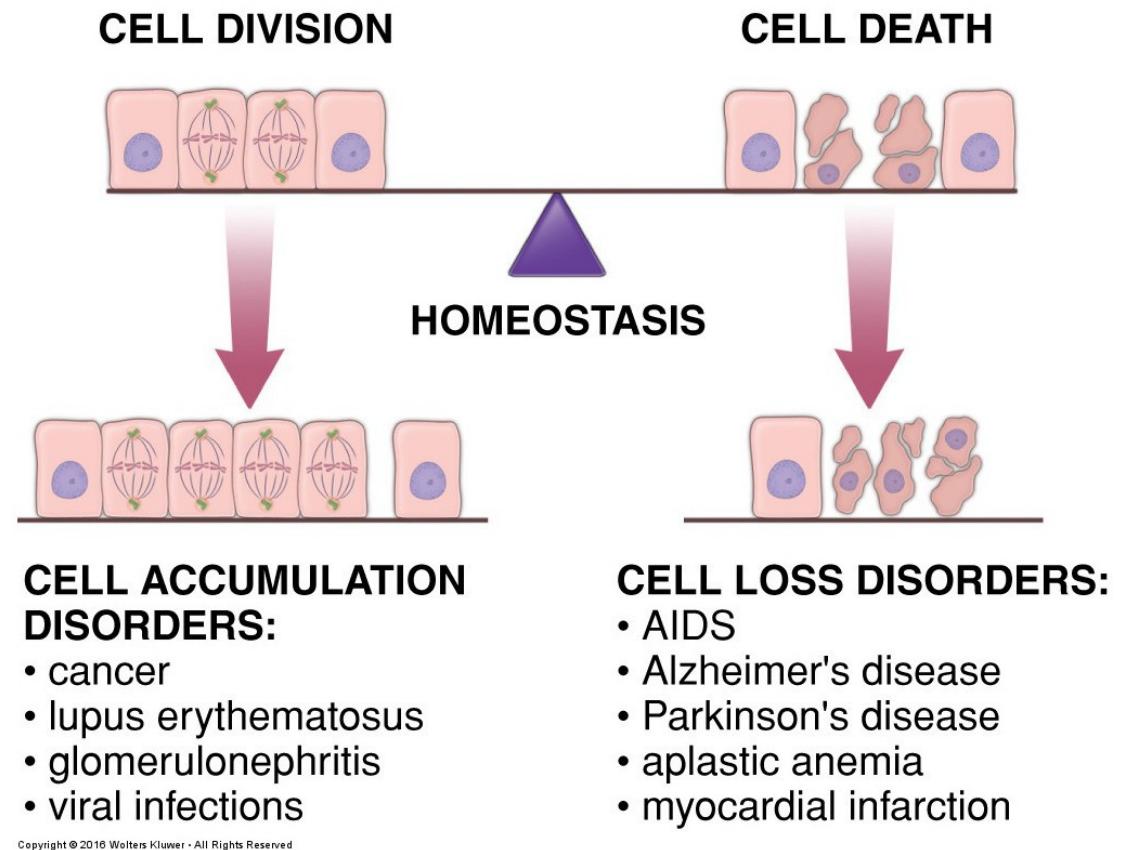
# Nuclear Pore Complex



- Each pore contains eight protein subunits arranged in an octagonal central framework at the periphery of the pore.
- These subunits form a nuclear pore complex that is inserted between two cytoplasmic and nucleoplasmic rings
- The cylindrical central framework encircles the central pore, which acts as a close-fitting diaphragm.

# Cell Division and Cell Death

- Under normal physiologic conditions (homeostasis), the rates of cell division and cell death are similar.
- If the rate of cell death is higher than that of cell division, then a net loss of cell number will occur. Such conditions are categorized as **cell loss disorders**.
- When the situation is reversed and the rate of cell division is higher than the rate of cell death, then the net gain in cell number will be prominent, leading to a variety of disorders of **cell accumulation**.



# Cell Renewal and the Cell Cycle

Somatic cells in the adult organism may be classified according to their mitotic activity

## Interphase:

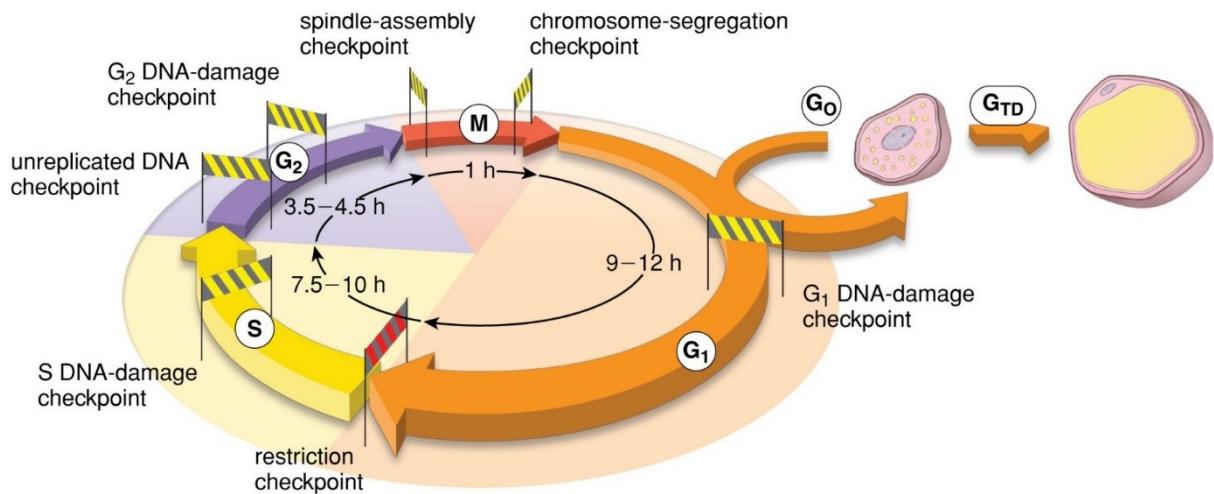
1. **G<sub>1</sub>** (growth phase 1) acquisition of nutrients, growth
2. **S** (DNA synthesis): chromosome replication
3. **G<sub>2</sub>** (growth phase 2) completion of cell growth, preparation for cell division

## Cell division:

4. **Mitosis:** division of the nucleus
5. **Cytokinesis:** cytoplasmic division

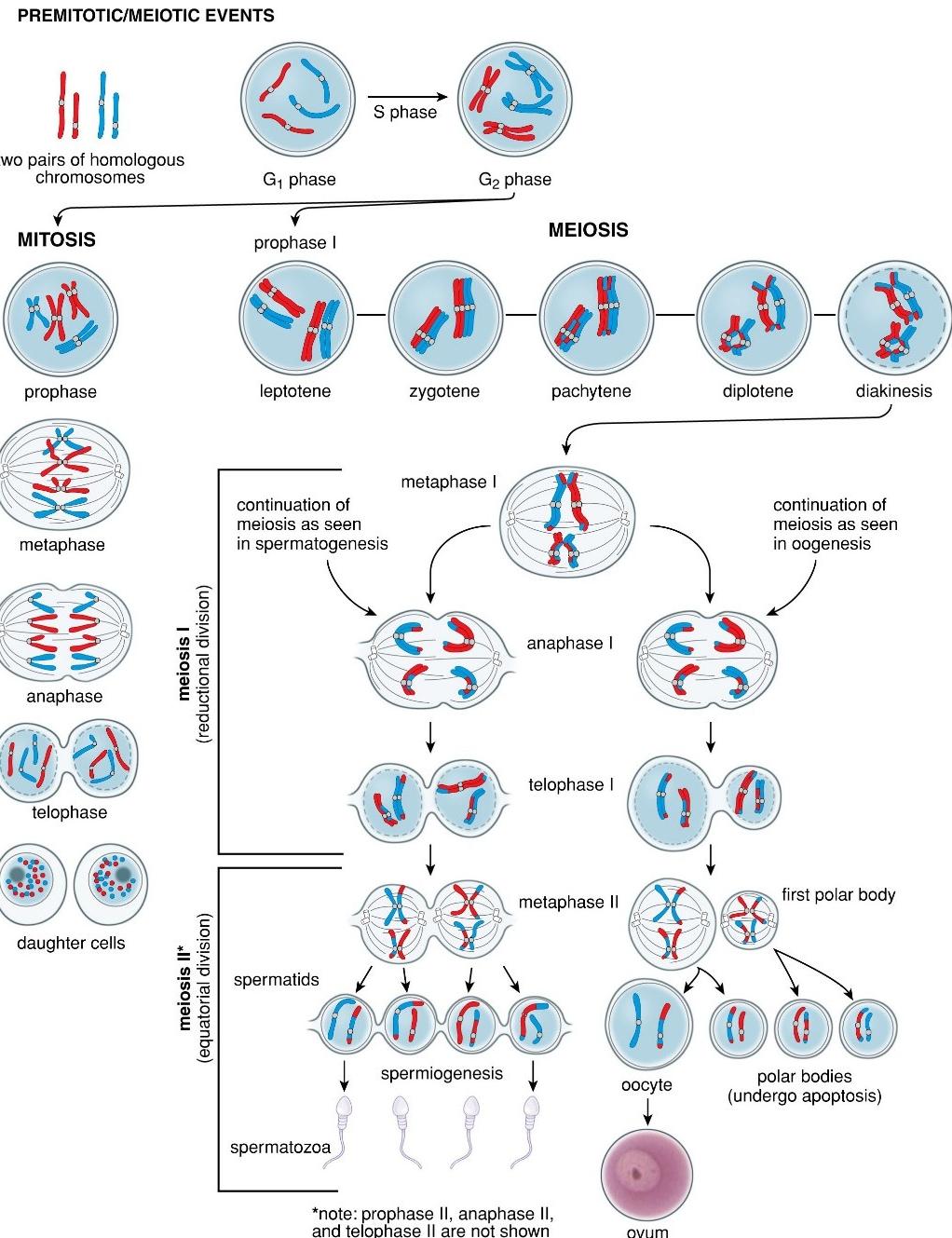
## » MEDICAL APPLICATION

Tissues with either stable or rapidly renewing cell populations can include cells that become transformed to grow at a higher rate and in an uncoordinated manner. Such **neoplastic proliferation** typically follows damage to the DNA of proto-oncogenes and failure of the cells to be eliminated. Neoplastic growth can be either benign (with slow growth and no invasiveness to neighboring organs) or malignant (with rapid growth and great capacity to invade other organs). **Cancer** is the common term for all malignant tumors.



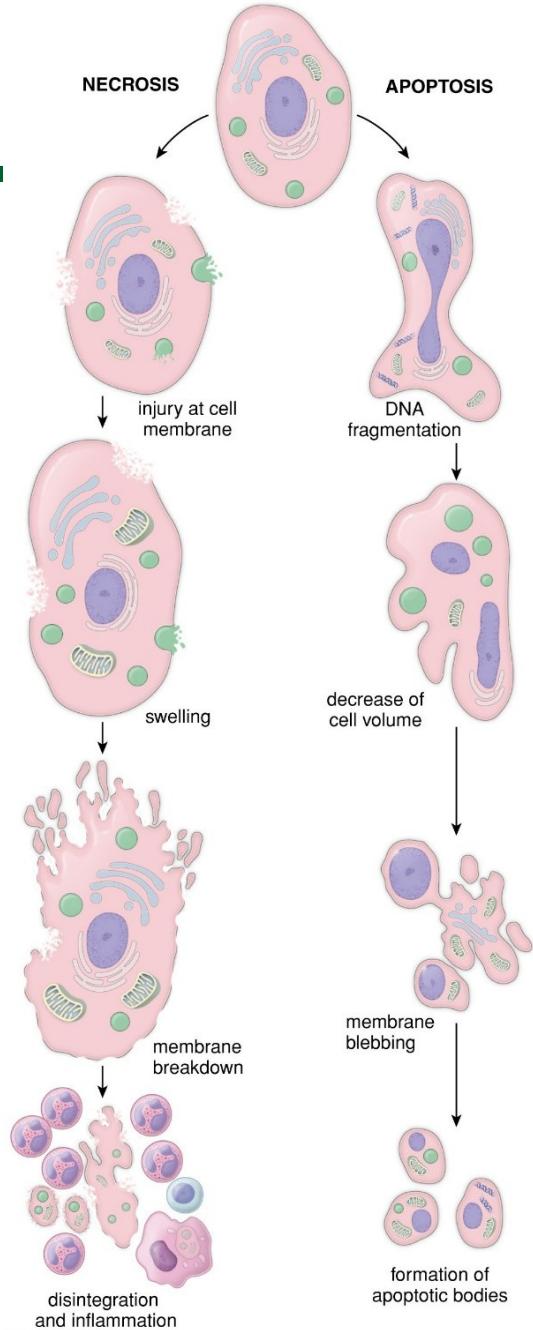
# The Stages of Mitosis

1. Prophase
2. Metaphase
3. Anaphase
4. Telophase

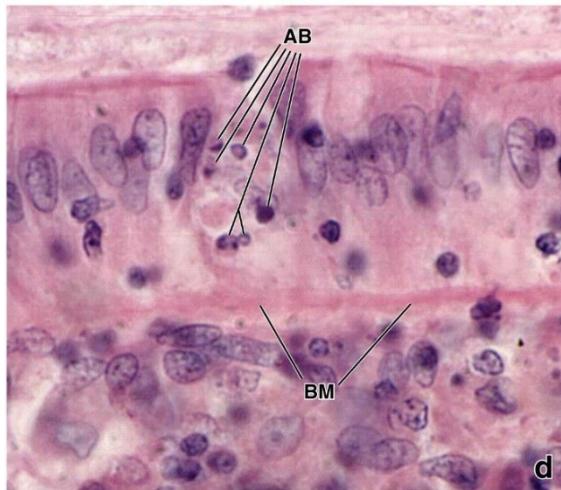
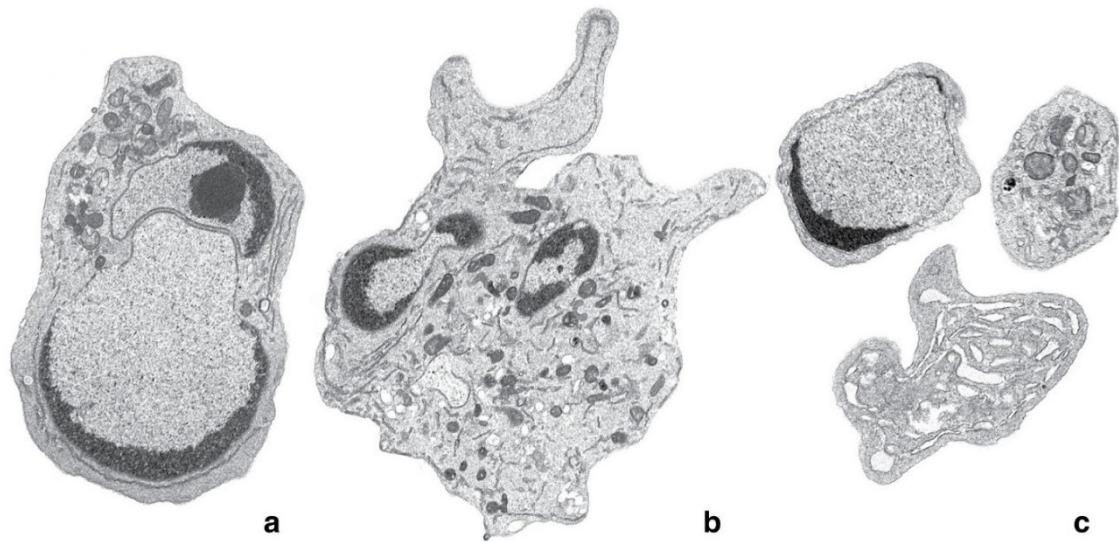


# Apoptosis vs Necrosis

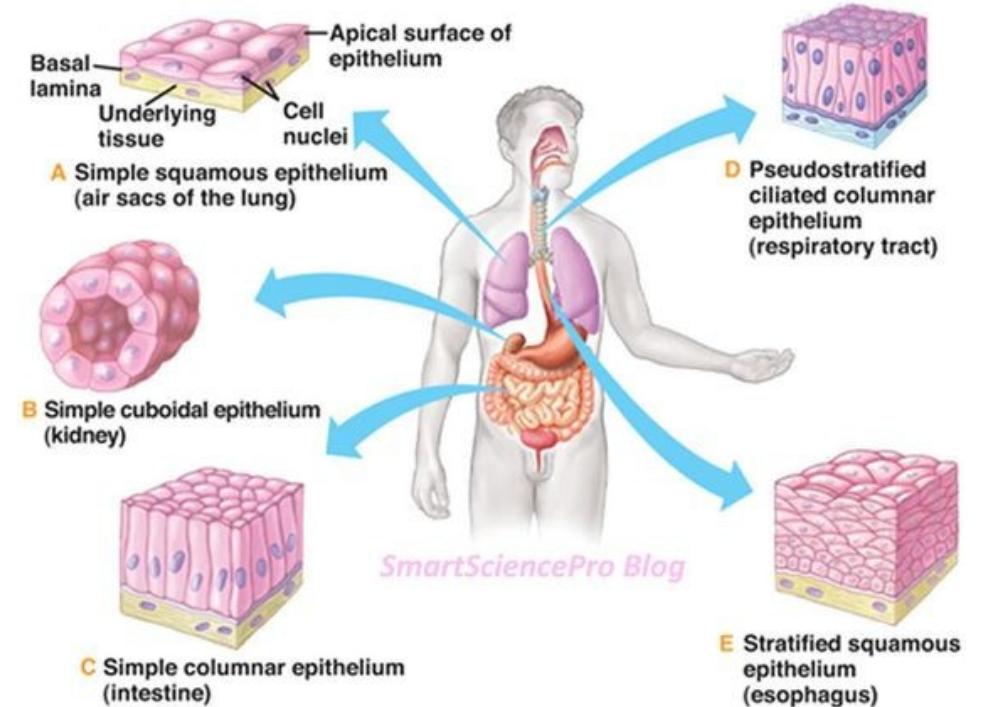
- In **necrosis** (*left side*), breakdown of the cell membrane results in an influx of water and extracellular ions, causing the organelles to undergo irreversible changes. Lysosomal enzymes are released into the extracellular space, causing damage to neighboring tissue and an intense inflammatory response.
- In **apoptosis** (*right side*), the cell shows characteristic morphologic and biochemical features such as DNA fragmentation, decrease in cell volume, membrane blebbing without loss of membrane integrity, and formation of apoptotic bodies, causing cell breakage. Apoptotic bodies are later removed by phagocytotic cells without inflammatory reactions.



# Electron micrographs of apoptotic cells



- a. The nucleus is already fragmented, and the irreversible process of DNA fragmentation is turned on. Note the regions containing condensed heterochromatin adjacent to the nuclear envelope.
- b. Further fragmentation of DNA.
- c. Apoptotic bodies
- d. This photomicrograph taken with light microscopy of intestinal epithelium from the human colon shows apoptotic bodies (AB) within a single layer of absorptive cells. *BM*, basement membrane



Radhika Reddy, PhD

# CHAPTER 4-7: EPITHELIAL, CONNECTIVE, ADIPOSE, CARTILAGE

# Tissues

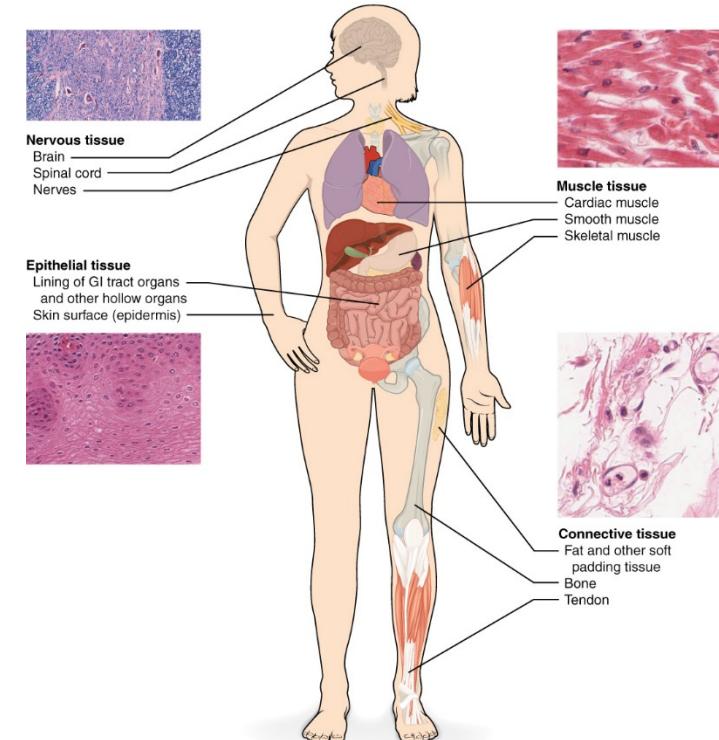
Cells work together in functionally related groups called tissues

Types of tissues:

1. Epithelial – lining and covering
2. Connective – support
3. Muscle – movement
4. Nervous – control

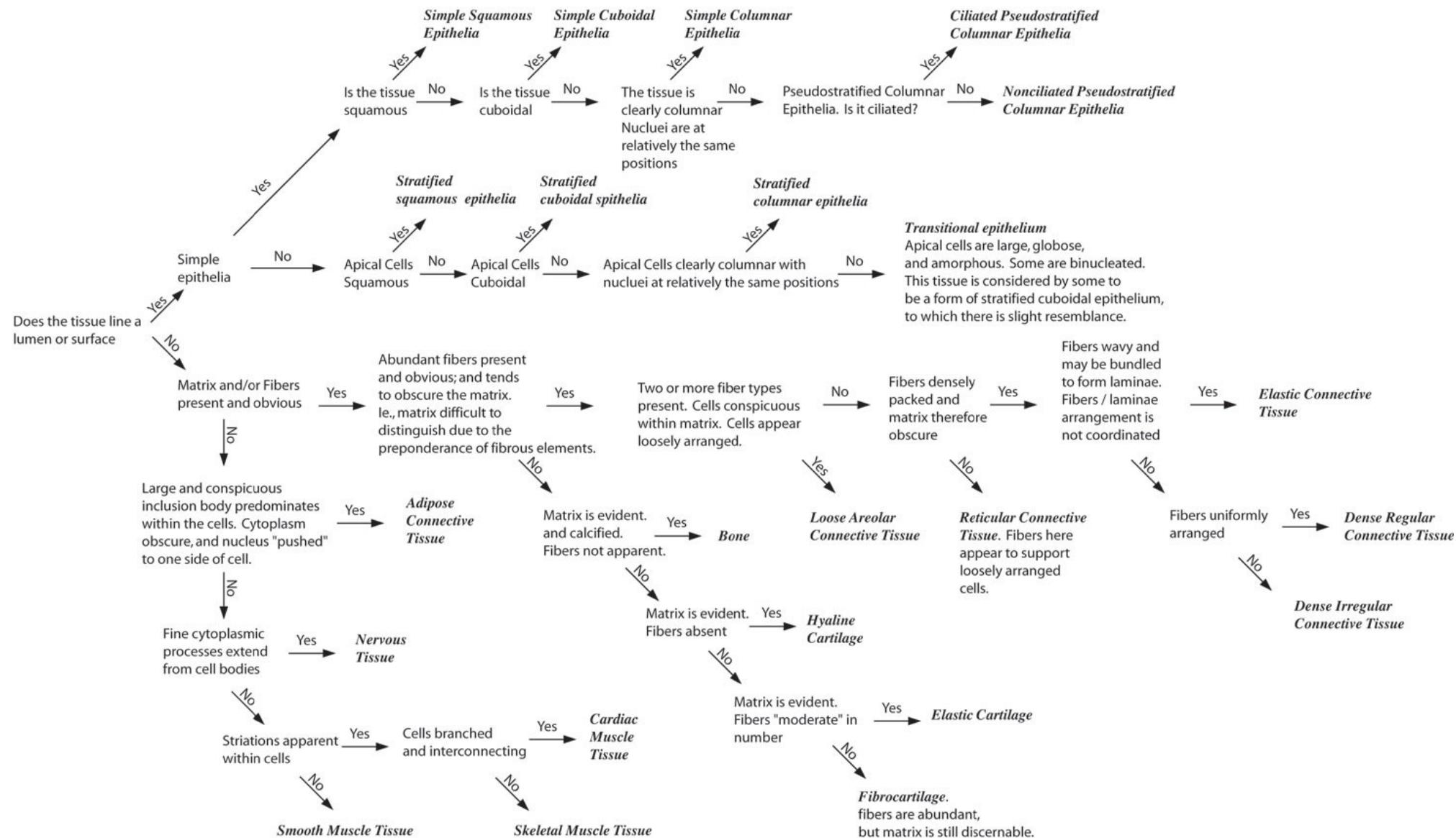
**TABLE 4-1** | Main characteristics of the four basic types of tissues.

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



<http://www.bozemanscience.com/anatomy-and-physiology-introduction>

Watch 3:25-9:25



# Chapter 4 Epithelial Tissues Objectives

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1. General Characteristics of epithelium
2. Basal domain: basement membrane, basal lamina, focal adhesions, hemidesmosomes
3. Lateral Domain: cell junctions and adhesions
4. Apical domain: microvilli and cilia
5. Glands: exocrine and endocrine
6. Classification of epithelium based on shape and complexity

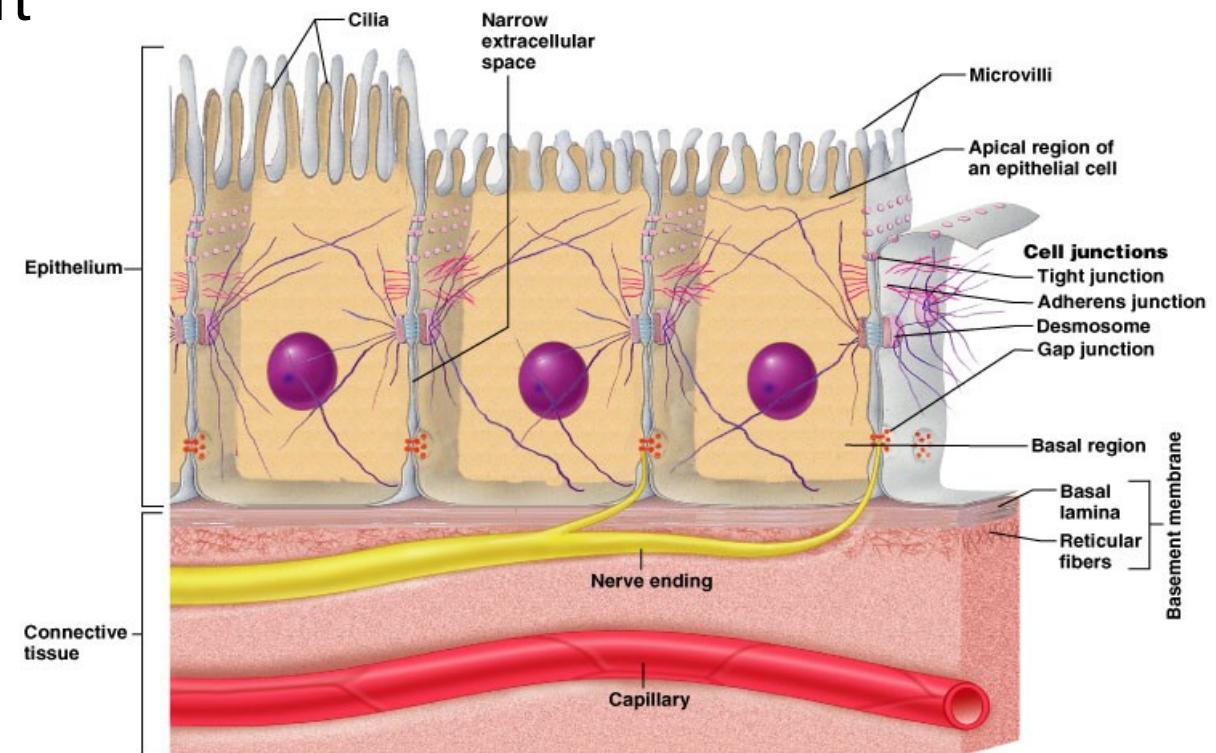
# Epithelial Tissue: General Characteristics & Functions

Covers a body surface or lines a body cavity

Forms most glands

Functions of epithelium

1. Protection
2. Absorption, secretion, and ion transport
3. Filtration
4. Forms slippery surfaces



# Special Characteristics of Epithelia

**Cellularity:** cells are in close contact with each other with little or no intercellular space between them

**Specialized contacts:** may have junctions for both attachment and communication

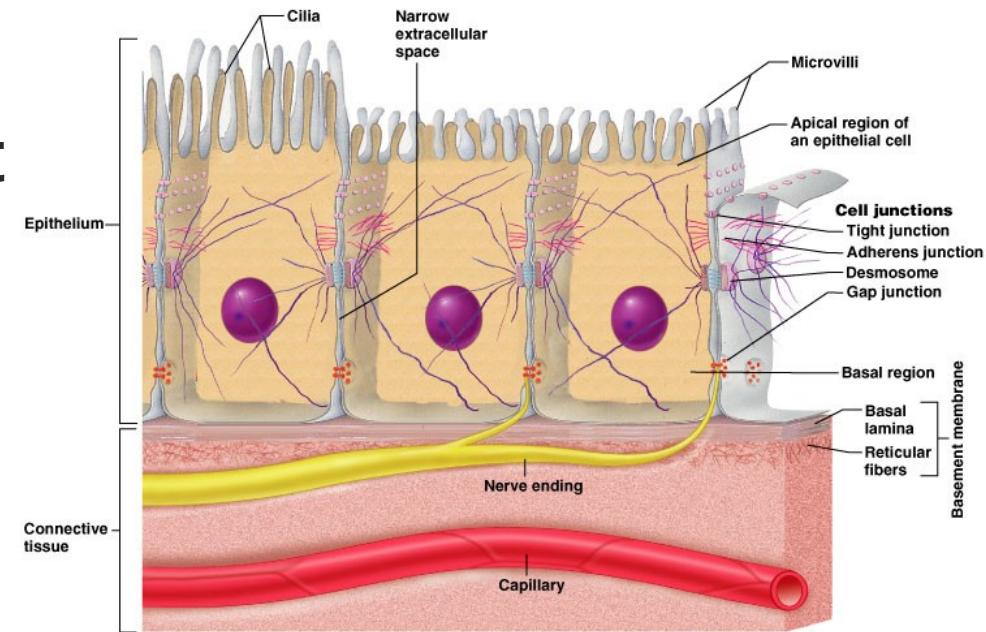
**Polarity:** epithelial tissues always have an **apical** and **basal surface**

**Support by connective tissue:** at the basal surface, both the epithelial tissue and the connective tissue contribute to the **basement membrane**

**Avascular:** nutrients must diffuse

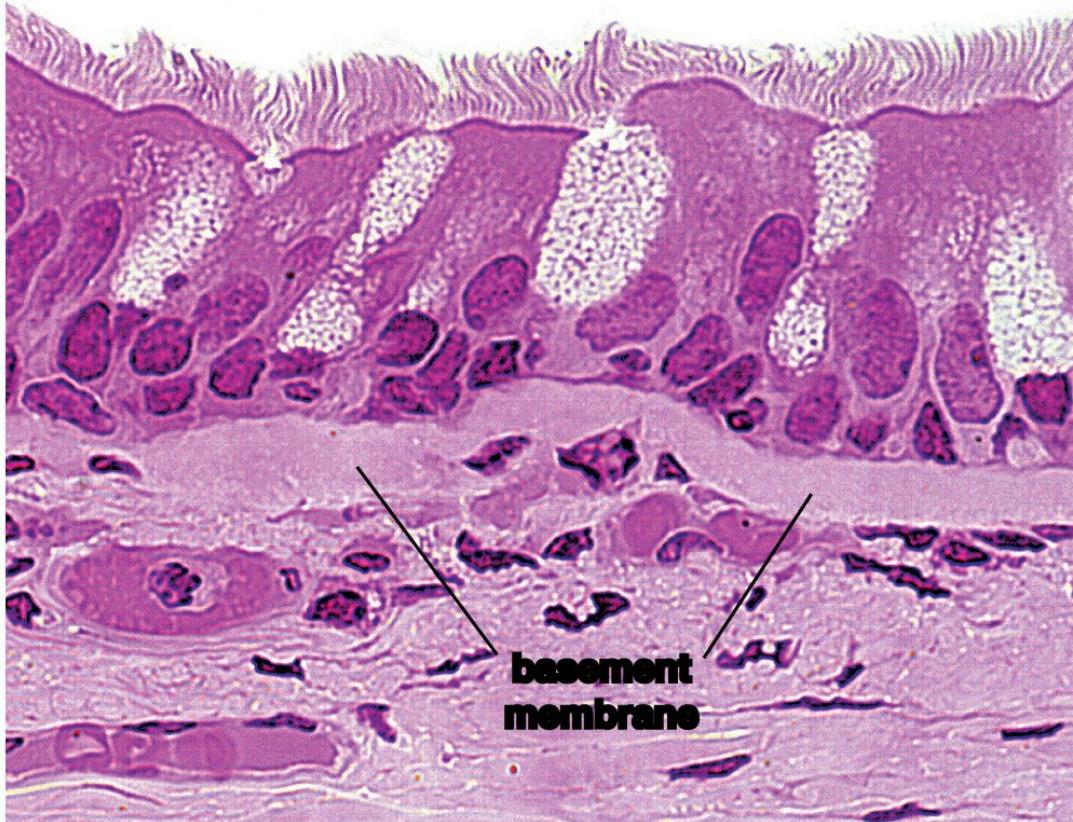
**Innervated**

**Regeneration:** epithelial tissues have a high capacity for regeneration



# The basal domain of epithelial cells

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The **basement membrane** is a specialized structure located next to the basal domain of epithelial cells and the underlying connective tissue stroma.

**Cell-to-extracellular matrix junctions** anchor the cell to the extracellular matrix

**Basal cell membrane infoldings** increase the cell surface area and facilitate morphologic interactions between adjacent cells and extracellular matrix proteins

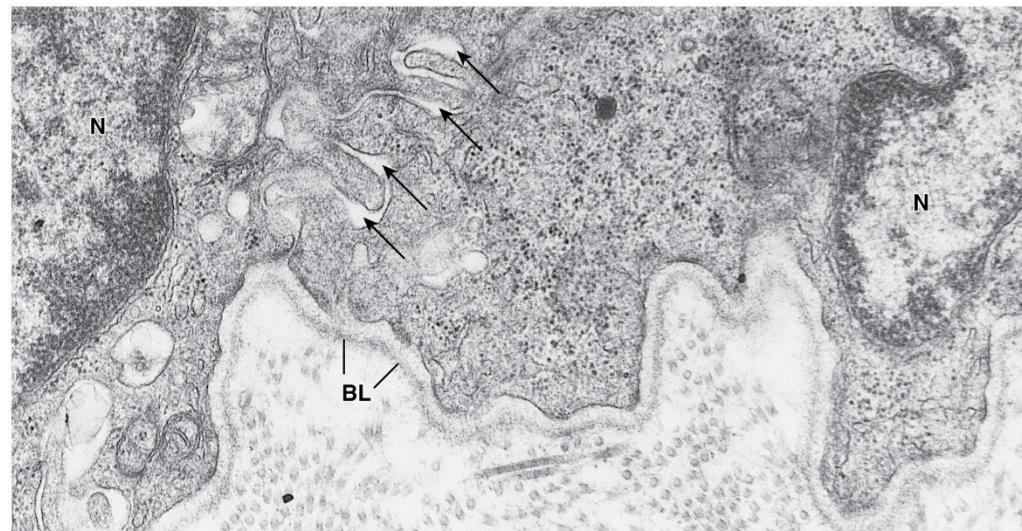
## Basement Membrane = basal lamina + reticular lamina

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**Basal lamina** (also called **lamina densa**): discrete layer of electron-dense matrix material 40- to 60-nm thick between the epithelium and the adjacent connective tissue

Composed of **laminins**, a **type IV collagen molecule**, and various associated **proteoglycans** and **glycoproteins**.

**Reticular lamina**: below basal lamina, more diffuse and fibrous



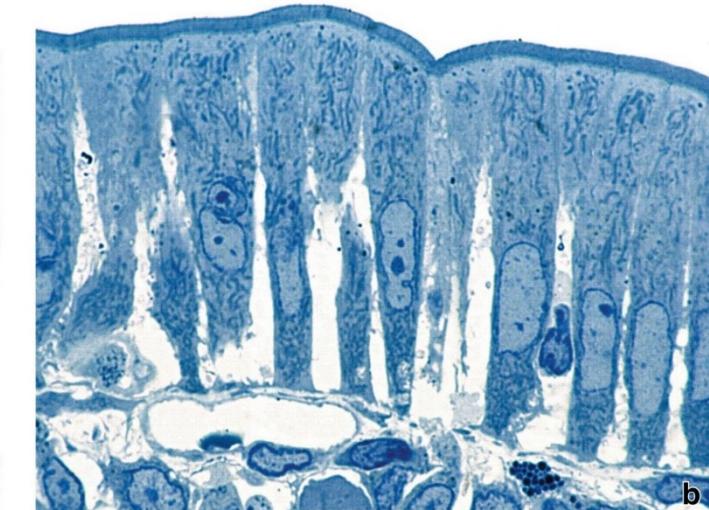
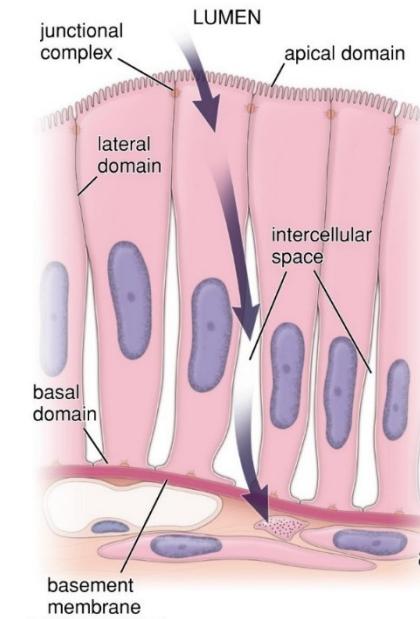
# Cellular domains of epithelia

The **junctional complex** provides adhesion between adjoining cells and separates the luminal space from the intercellular space, limiting the movement of fluid between the lumen and the underlying connective tissue.

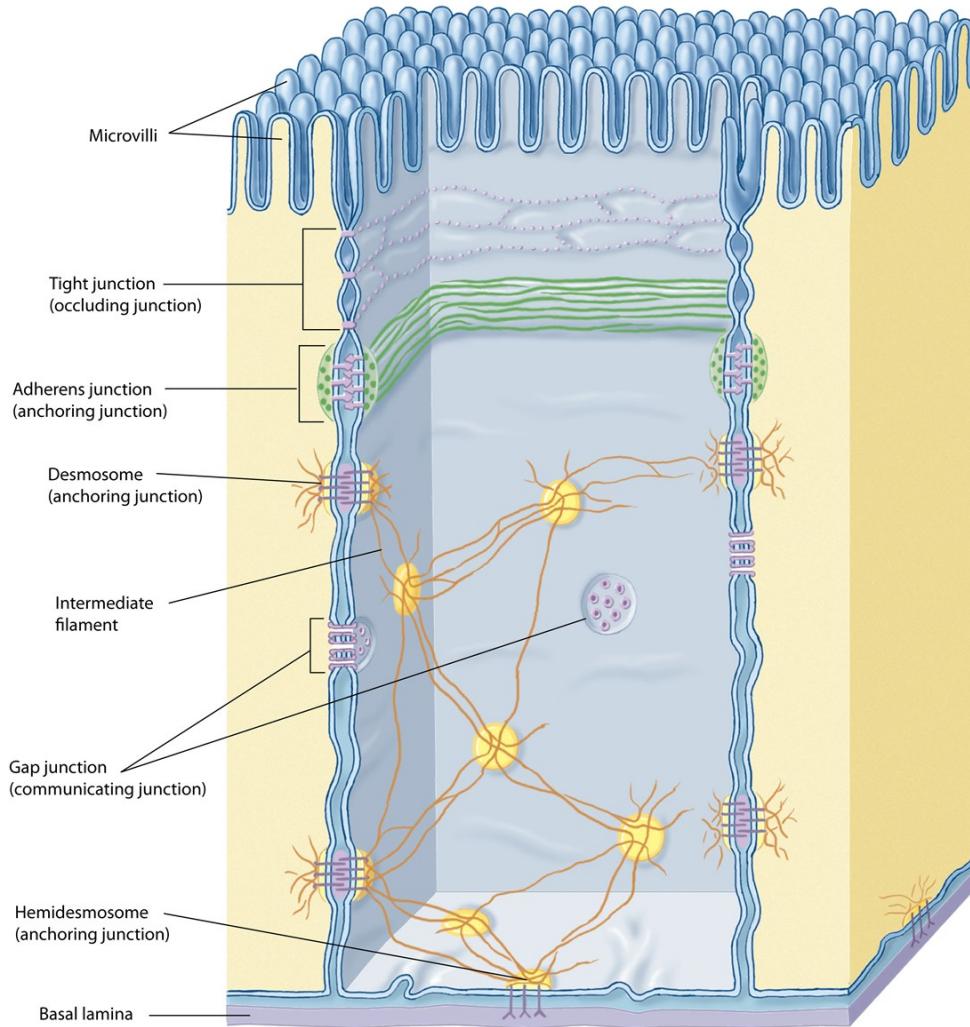
The **intracellular pathway** of fluid movement during absorption (arrows) is from the intestinal lumen into the cell, then across the lateral cell membrane into the intercellular space, and, finally, across the basement membrane to the connective tissue

## » MEDICAL APPLICATION

The enterotoxin secreted by *Clostridium perfringens*, which causes “food poisoning prevents maintenance of tight junctions, and causes loss of tissue fluid into the intestinal lumen via the intracellular pathway.



# Junctional complexes of epithelial cells.



**Tight Junctions:** prevent passive flow of material between the cells

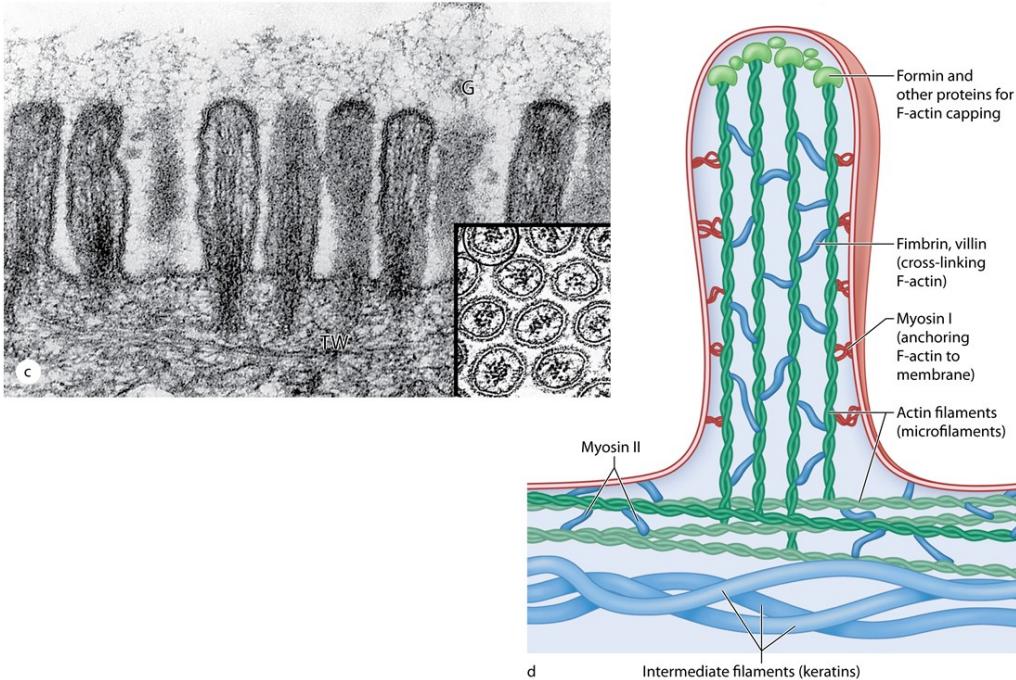
**Adhering junctions:** stabilize and strengthen the circular

**Desmosomes:** form very strong attachment points, play a major role to maintain the integrity of an epithelium.

**Gap junctions:** patch of many **connexons**, serve as intercellular channels for flow of molecules.

**Hemidesmosomes** bind epithelial cells to the underlying basal lamina

# Microvilli are fingerlike cytoplasmic projections on the apical surface of most epithelial cells.



**The internal structure of microvilli contains a core of actin filaments that are cross-linked by several actin bundling proteins. Actin filaments (arrows)**

Actin filament–bundling proteins: fimbrin, espin, and fascin

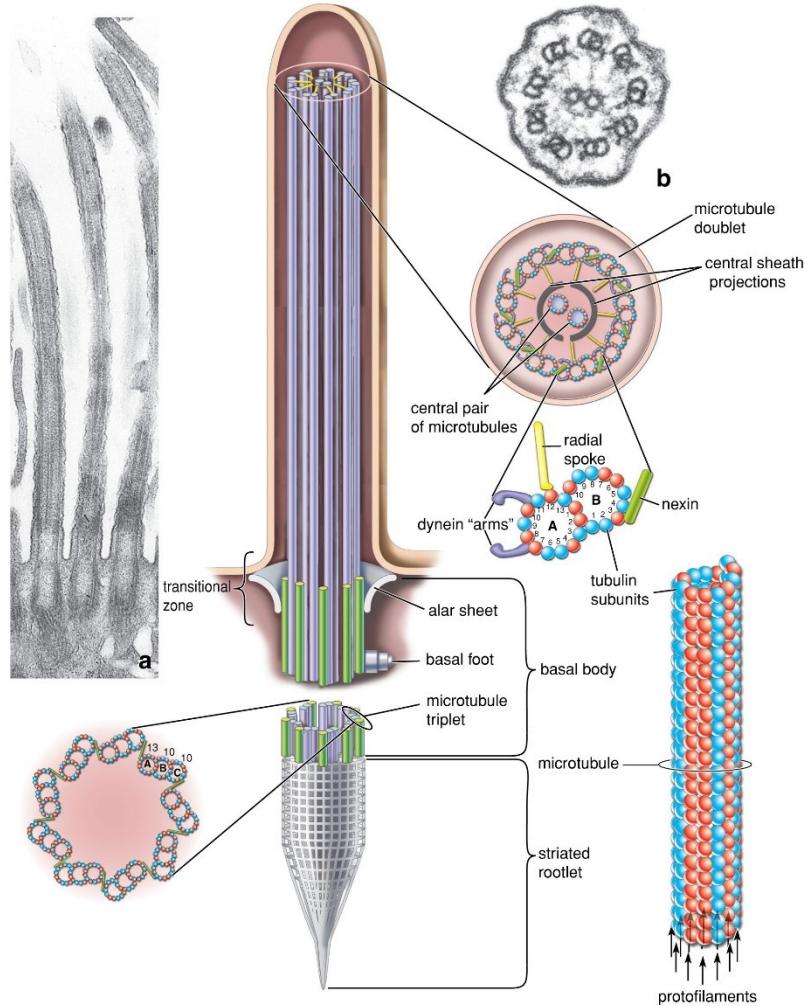
The spectrin molecules stabilize the actin filaments within the terminal web and anchor them into the apical plasma membrane.

Endoscopy of Celiac Disease (0:1:00): <https://www.youtube.com/watch?v=WStdJSqf-LQ>

## » MEDICAL APPLICATION

Celiac disease: loss of microvilli in brush border of the absorptive cells of small intestine, caused by immune reaction against the wheat protein gluten during its digestion, which produces diffuse enteritis (intestinal inflammation), changes to the epithelial cells leading to malabsorption, and eventually to pathologic changes in the intestinal wall.

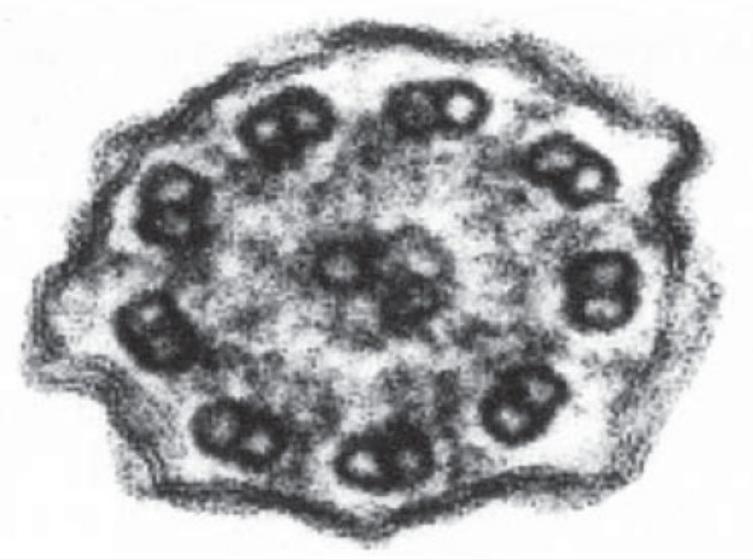
# Cilia are long projecting structures, larger than microvilli, which contain internal arrays of microtubules



Epithelial cilia exhibit rapid beating patterns of movement that propel a current of fluid and suspended matter in one direction over the epithelium

**Axoneme:** The nine doublets form an array around two central microtubules; the  $9 + 2$  assembly of microtubules

# Primary Ciliary Dyskinesia (Immotile Cilia Syndrome)

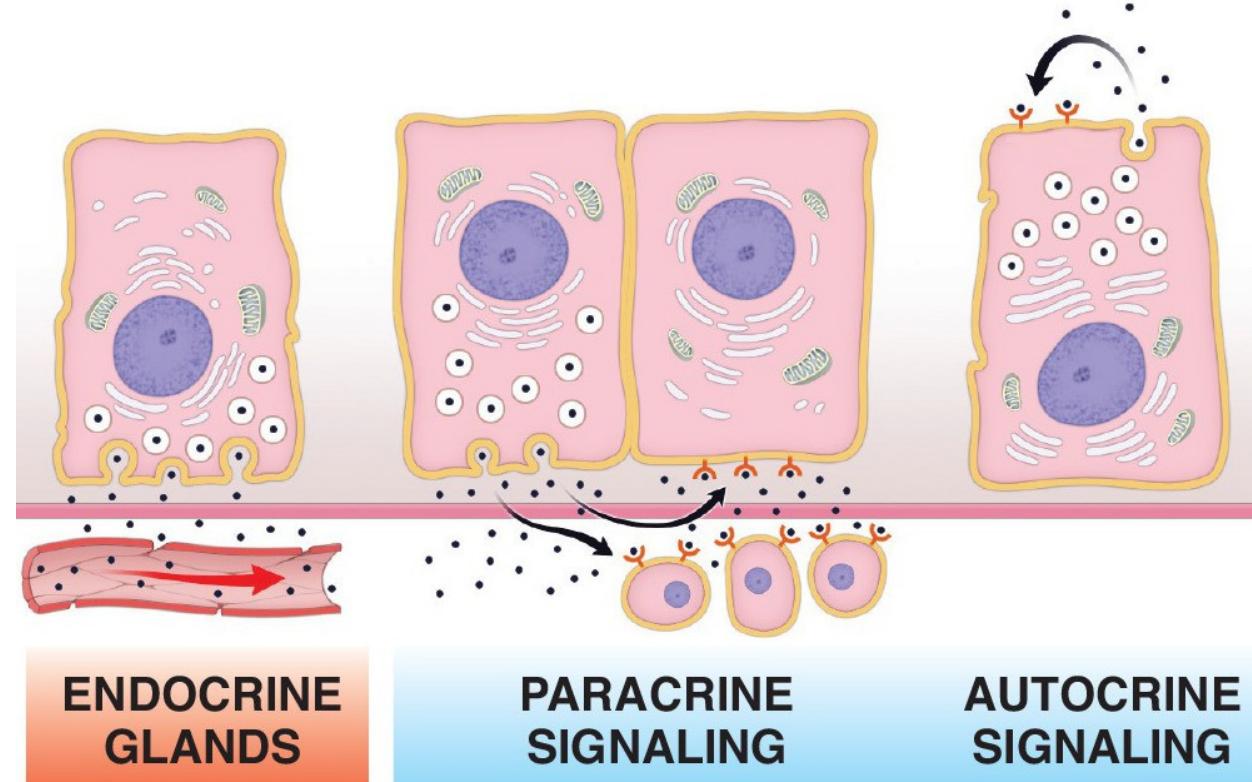


**FIGURE F5.2.1** • Electron micrograph of the cilium from an individual with primary ciliary dyskinesia (PCD). Note the absence of dynein arms on microtubule doublets.  $\times 180,000$ . (Courtesy of Patrice Abell-Aleff.)

## MEDICAL APPLICATION

Kartagener syndrome: mutations in proteins of cilia, whose symptoms are chronic respiratory infections caused by the lack of the cleansing action of cilia in the respiratory tract and immotile spermatozoa, causing male infertility

# Types of glands and their mechanism of secretion



**Endocrine glands** lack a duct system. They secrete their products into the connective tissue, from which they enter the bloodstream to reach their target cells. The products of endocrine glands are called **hormones**.

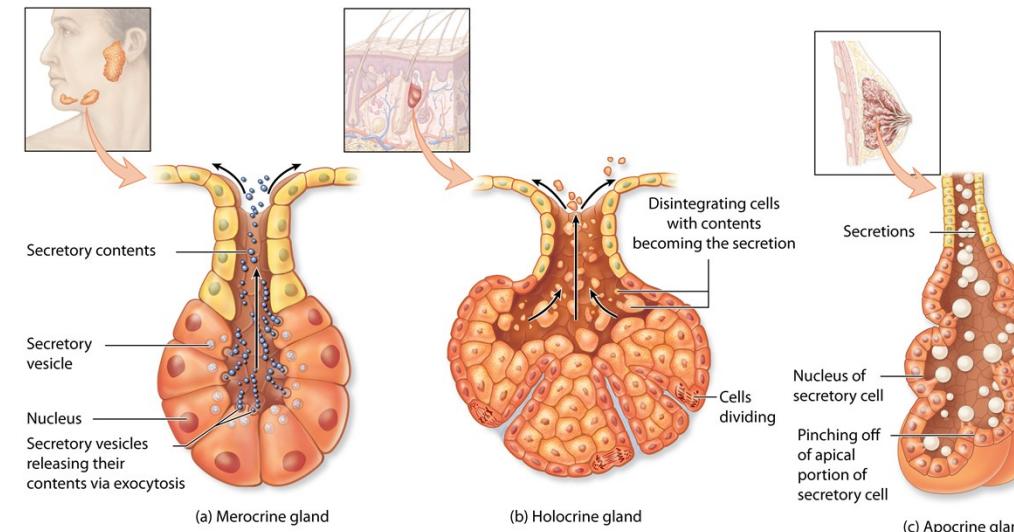
# Types of glands and their mechanism of secretion

**Exocrine glands** secrete their products onto a surface directly or through epithelial ducts or tubes that are connected to a surface.

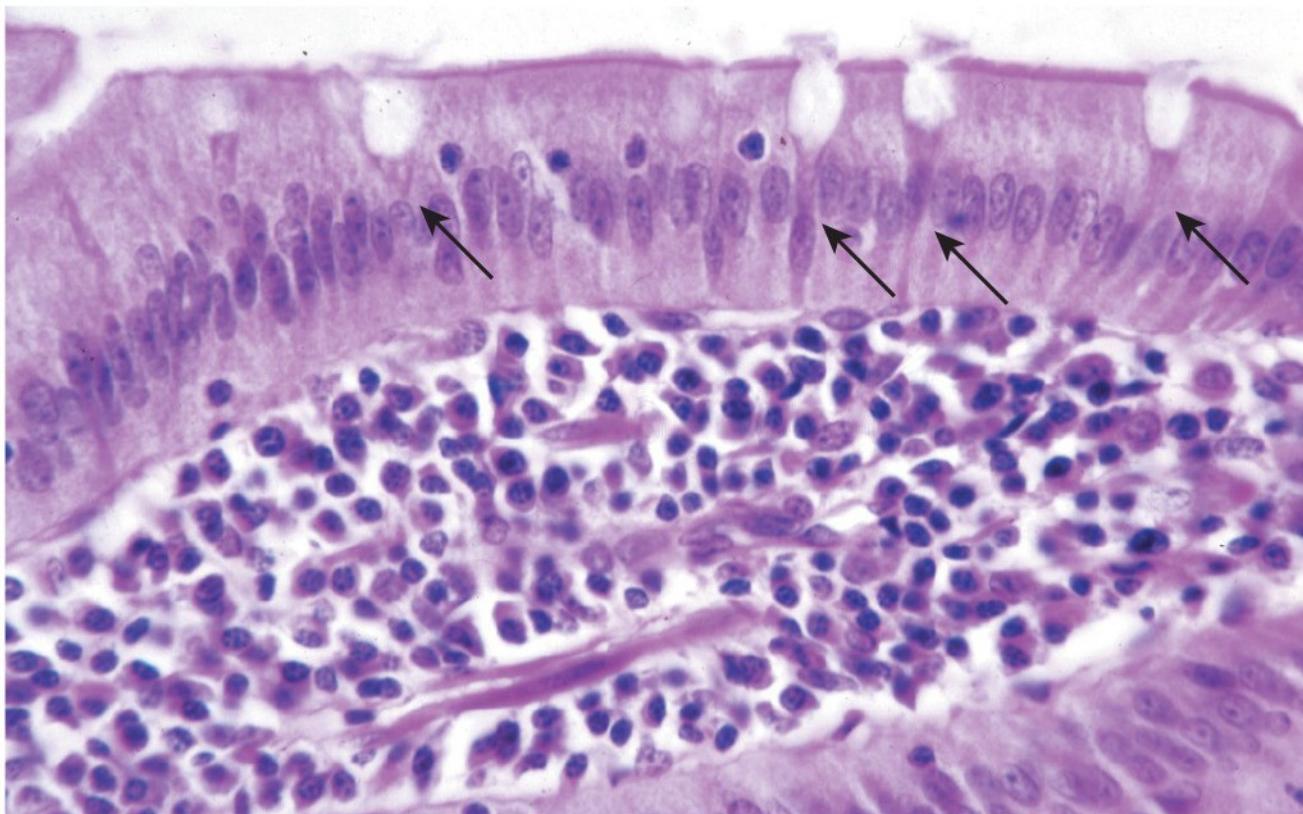
**Merocrine secretion.** This secretory product is delivered in **membrane-bounded vesicles** to the apical surface of the cell and extrude their contents by exocytosis.

**Apocrine secretion.** The secretory product is released in the apical portion of the cell, surrounded by a thin layer of cytoplasm within an envelope of plasma membrane. Ex **mammary gland**, where it is responsible for releasing large lipid droplets into the milk. It also occurs in the **apocrine glands** of skin, **ciliary (Moll's) glands** of the eyelid, and the **ceruminous glands** of the external auditory meatus.

**Holocrine secretion. Programmed cell death.** Both secretory products and cell debris are discharged into the lumen of the gland. This mechanism is found in sebaceous glands of skin and the tarsal (Meibomian) glands of the eyelid.



# Unicellular glands



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**Unicellular glands.** Photomicrograph of intestinal epithelium showing single goblet cells (*arrows*) dispersed among absorptive cells. Each goblet cell may be regarded as a unicellular gland—the simplest exocrine type gland.

## »» MEDICAL APPLICATION

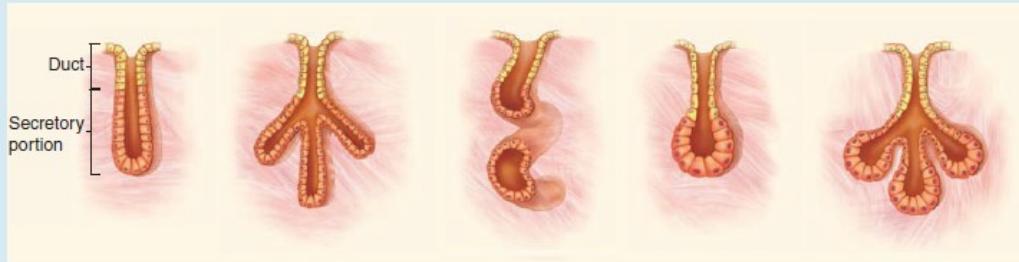
In chronic bronchitis, common among habitual smokers, the number of goblet cells in the lining of airways in the lungs often increases greatly. This leads to excessive mucus production in areas where there are too few ciliated cells for its rapid removal and contributes to obstruction of the airways. The ciliated pseudostratified epithelium lining the bronchi of smokers can also be transformed into stratified squamous epithelium by metaplasia.

TABLE 4-4

Structural classes of exocrine glands, features of each class, and examples.

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

Class	Simple Tubular	Branched Tubular	Coiled Tubular	Acinar (or Alveolar)	Branched Acinar
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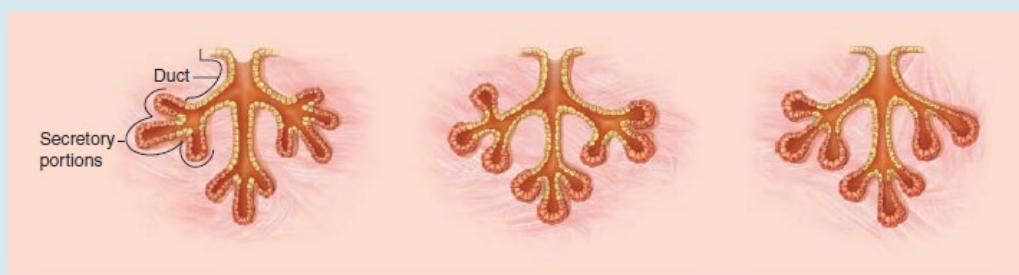


Features	Elongated secretory portion; duct usually short or absent	Several long secretory parts joining to drain into 1 duct	Secretory portion is very long and coiled	Rounded, saclike secretory portion	Multiple saclike secretory parts entering the same duct
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Examples	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
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**COMPOUND Glands (Ducts from Several Secretory Units Converge Into Larger Ducts)**

Class	Tubular	Acinar (Alveolar)	Tubuloacinar
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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
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Examples	Submucosal mucous glands (of Brunner) in the duodenum	Exocrine pancreas	Salivary glands
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**Multicellular glands** subclassification according to the arrangement of the secretory cells (parenchyma) and the presence or absence of branching of the duct elements.

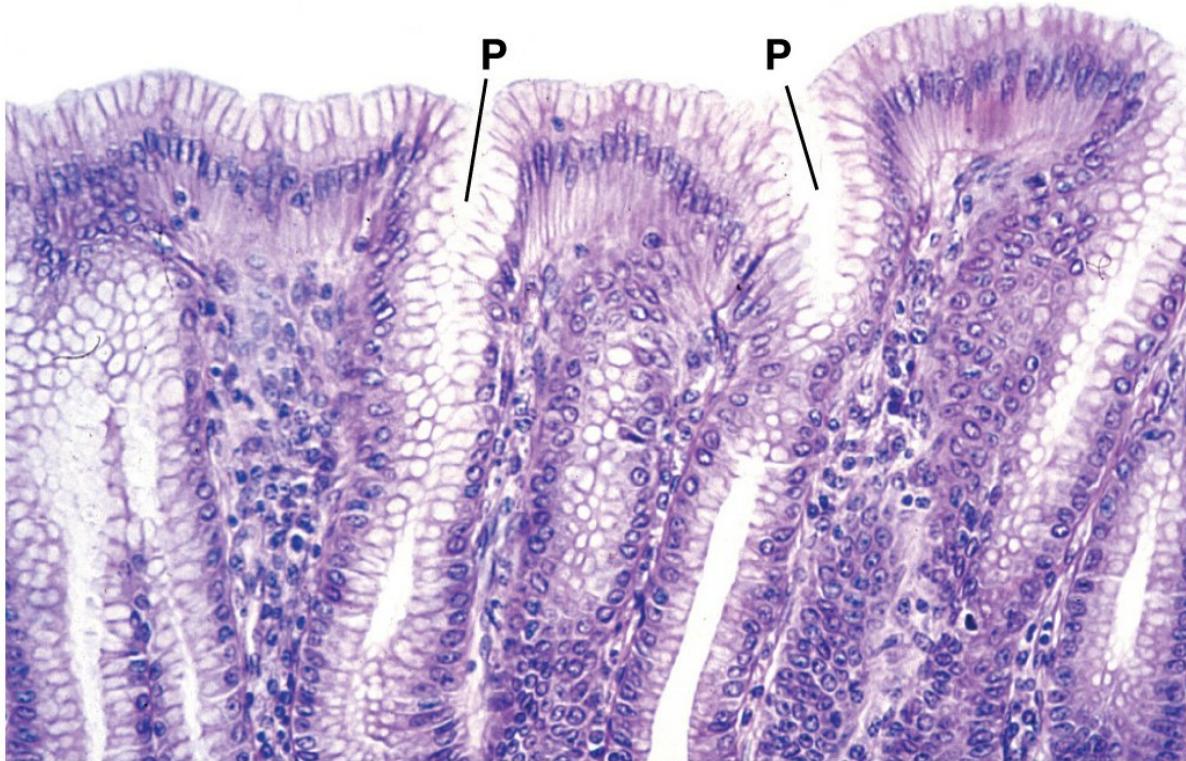
**MEDICAL APPLICATION: Acne** Excessive holocrine secretion of sebum and keratin triggered by the surge of the steroid hormone testosterone. Activity of the normal commensal skin bacterium

*Propionibacterium acnes* within the blocked duct commonly produces localized inflammation.

Is There A Pimple Cure? <https://www.youtube.com/watch?v=CGvx4gl3D7w>

# Mucus-secreting surface cells of stomach.

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## Mucus-secreting surface cells of stomach.

Photomicrograph of stomach surface. The epithelial cells lining the surface are all mucus-secreting cells, as are the cells lining the gastric pits (P). The cells of the gastric pit form simple tubular glands.

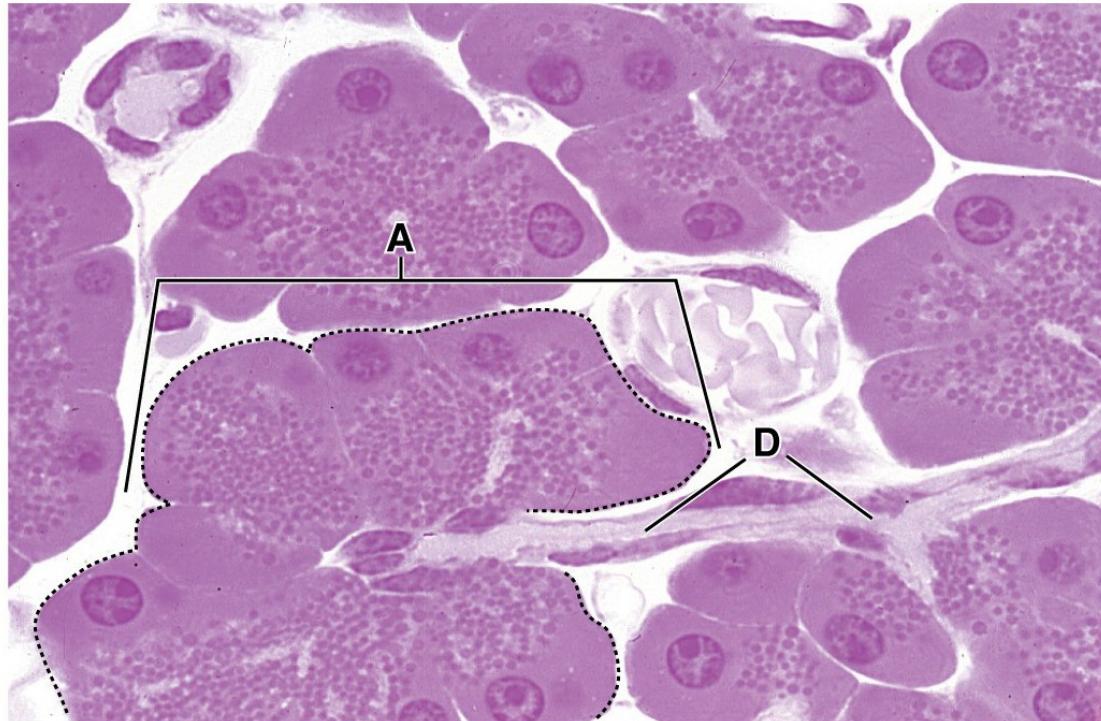
# Mucus-secreting compound gland



**Mucus-secreting compound gland.** Photomicrograph showing two small lobes of a mucus-secreting gland associated with the larynx. Each displays the beginning of a duct (*D*) into which mucin is secreted (*arrows*). The individual secretory cells that form the acinus (*A*) are difficult to define. Their nuclei (*arrowheads*) are flattened and located in the very basal portion of the cell, a feature typical of mucus-secreting glands.

The cytoplasm is filled with mucin that has been retained during preparation of the tissue and appears stained

# Serous-secreting compound gland



**Serous-secreting compound gland.** Photomicrograph of pancreatic acinus (A; outlined by the *dotted line*) with its duct (D). The small round objects within the acinar cells represent the zymogen granules, the stored secretory precursor material.

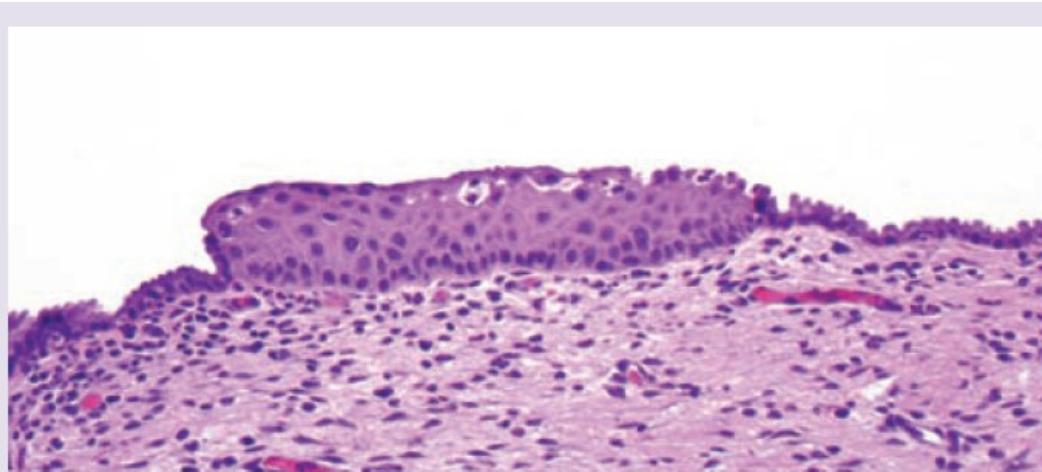
## Classification

The traditional classification of epithelium is descriptive and based on two factors: the number of cell layers and the shape of the surface cells. The terminology, therefore, reflects only structure, not function.

TABLE 5.1 Types of Epithelium

Classification	Some Typical Locations	Major Function
Simple squamous	Vascular system (endothelium) Body cavities (mesothelium) Bowman's capsule (kidney) Respiratory spaces in lung	Exchange, barrier in central nervous system Exchange and lubrication Barrier Exchange
Simple cuboidal	Small ducts of exocrine glands Surface of ovary (germinal epithelium) Kidney tubules Thyroid follicles	Absorption, conduit Barrier Absorption and secretion
Simple columnar	Small intestine and colon Stomach lining and gastric glands Gallbladder	Absorption and secretion Secretion Absorption
Pseudostratified	Trachea and bronchial tree Ductus deferens Efferent ductules of epididymis	Secretion, conduit Absorption, conduit
Stratified squamous	Epidermis Oral cavity and esophagus Vagina	Barrier, protection
Stratified cuboidal	Sweat gland ducts Large ducts of exocrine glands Anorectal junction	Barrier, conduit
Stratified columnar	Largest ducts of exocrine glands Anorectal junction	Barrier, conduit
Transitional (urothelium)	Renal calyces Ureters Bladder Urethra	Barrier, distensible property

# Epithelial metaplasia is a reversible conversion of one mature epithelial cell type to another mature epithelial cell type.



**FIGURE F5.1.1** • **Squamous metaplasia of the uterine cervix.** Photomicrograph of a cervical canal lined by simple columnar epithelium. Note that the center of the image is occupied by an island containing squamous stratified epithelium. This metaplastic epithelium is surrounded on both sides by simple columnar epithelium. Since metaplasia is triggered by reprogramming of stem cells, metaplastic squamous cells have the same characteristics as normal stratified squamous epithelium.  $\times 240$ . (Courtesy of Dr. Fabiola Medeiros.)

Cancers of the lung, cervix, and bladder often originate from squamous metaplastic epithelium. Squamous columnar epithelium may give rise to **glandular adenocarcinomas**.

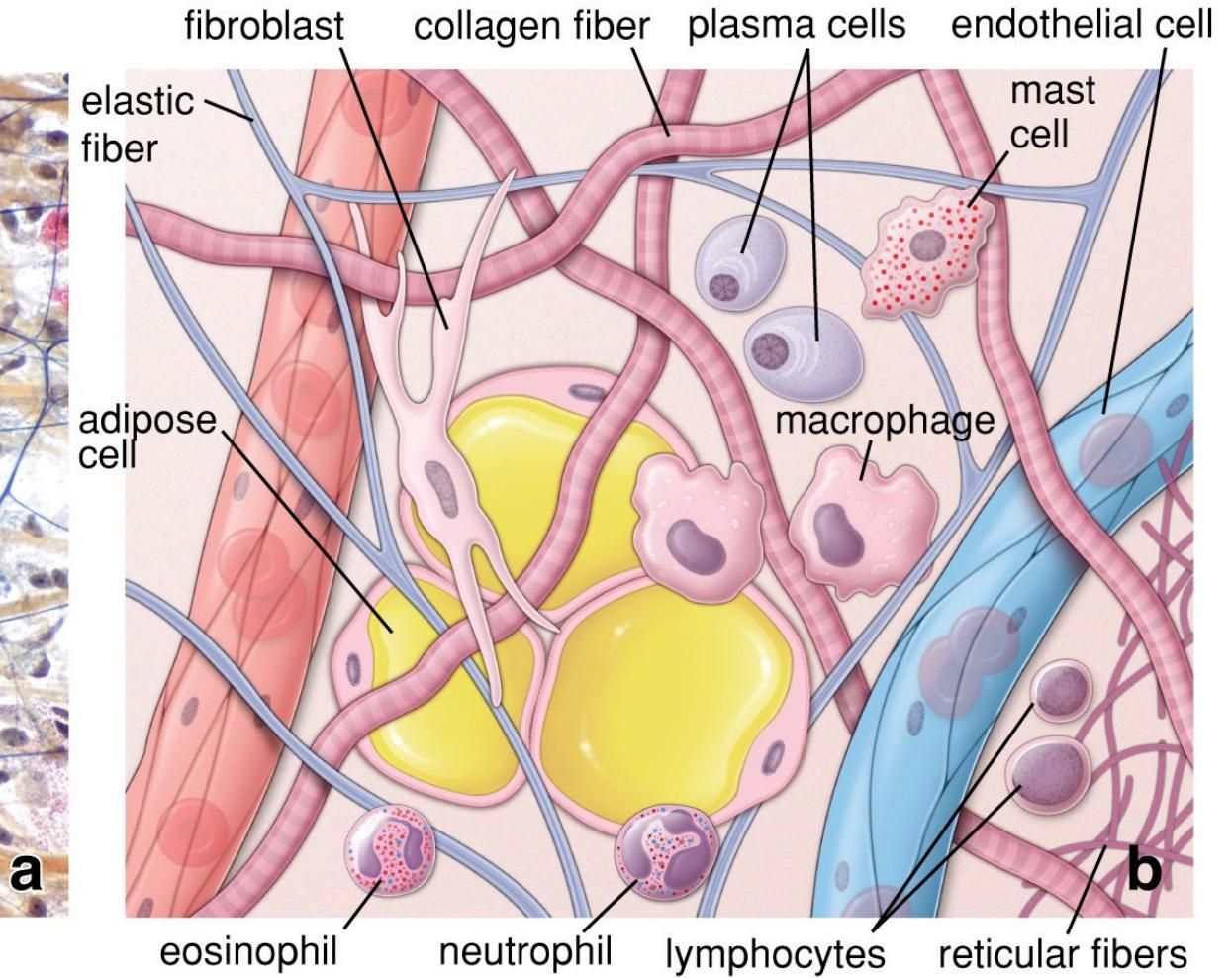
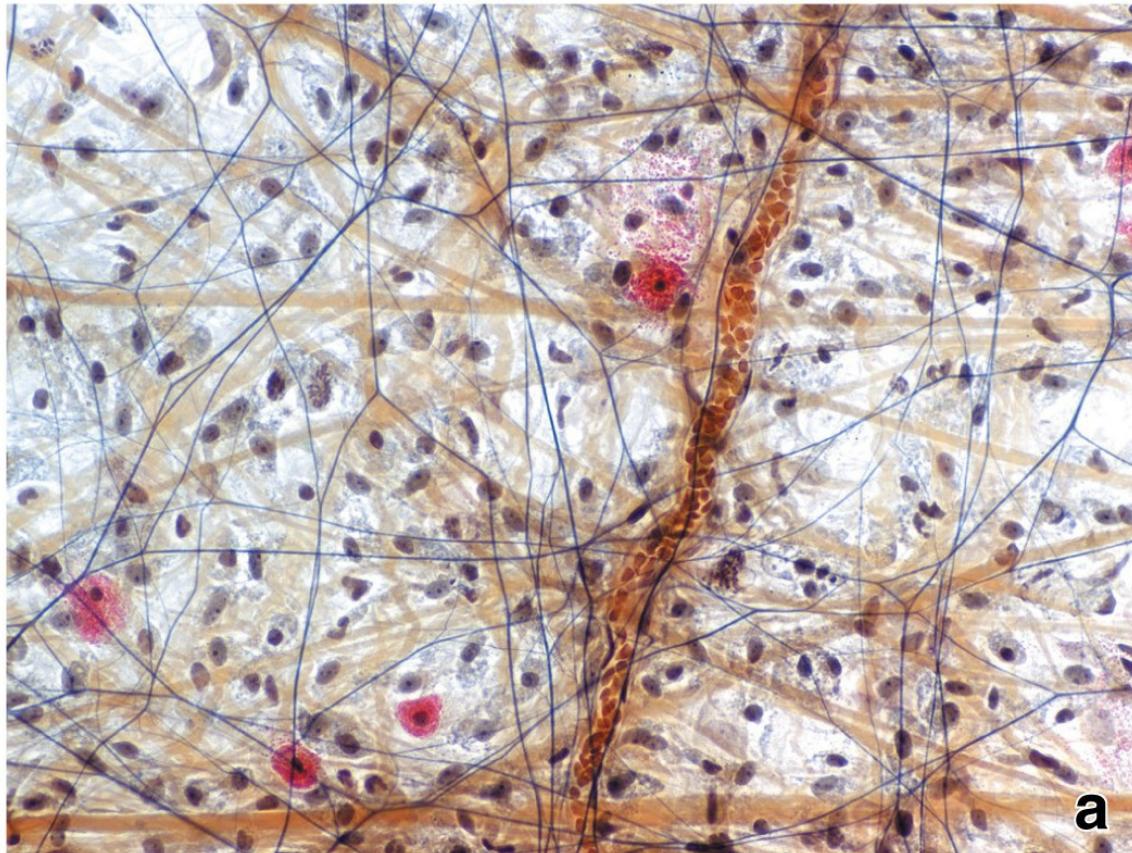
When metaplasia is diagnosed, all efforts should be directed toward removing the pathogenic stimulus (i.e., cessation of smoking, eradication of infectious agents, etc.) and monitoring the metaplastic site to ensure that cancerous changes do not begin to develop.

# Chapter 5 Connective Tissue Objectives

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1. General properties of connective tissue: extracellular matrix, ground substance
2. Connective tissue cells: resident (fibroblasts, macrophages adipocytes, mast cells, stem cells) and wandering (lymphocytes, plasma cells, neutrophils, eosinophils, basophils, monocytes)
3. Connective tissue fibers: collagen, reticular, elastic
4. Extracellular matrix: proteoglycans, glycosaminoglycans, multiadhesive glycoproteins
5. Connective tissue proper: Loose, dense irregular, dense regular
6. Embryonic connective tissue: Mesenchyme, mucous connective tissue

# Loose Connective Tissue: A prototype of cells, fibers, and ECM



# Cells of Fibrous Connective Tissue

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- **Fibroblasts** produce fibers and ground substance
- **Macrophages** phagocytize foreign material and activate immune system when they sense foreign matter (antigen)
  - Arise from white blood cells called monocytes
- **Leukocytes**, or white blood cells
  - Neutrophils wander about attacking bacteria
  - Lymphocytes react against bacteria, toxins, and other foreign material
- **Plasma cells** synthesize disease-fighting antibodies
  - Arise from lymphocytes
- **Mast cells** are found alongside blood vessels
  - Secrete heparin to inhibit clotting
  - Secrete histamine to dilate blood vessels
- **Adipocytes** store triglycerides (fat molecules)

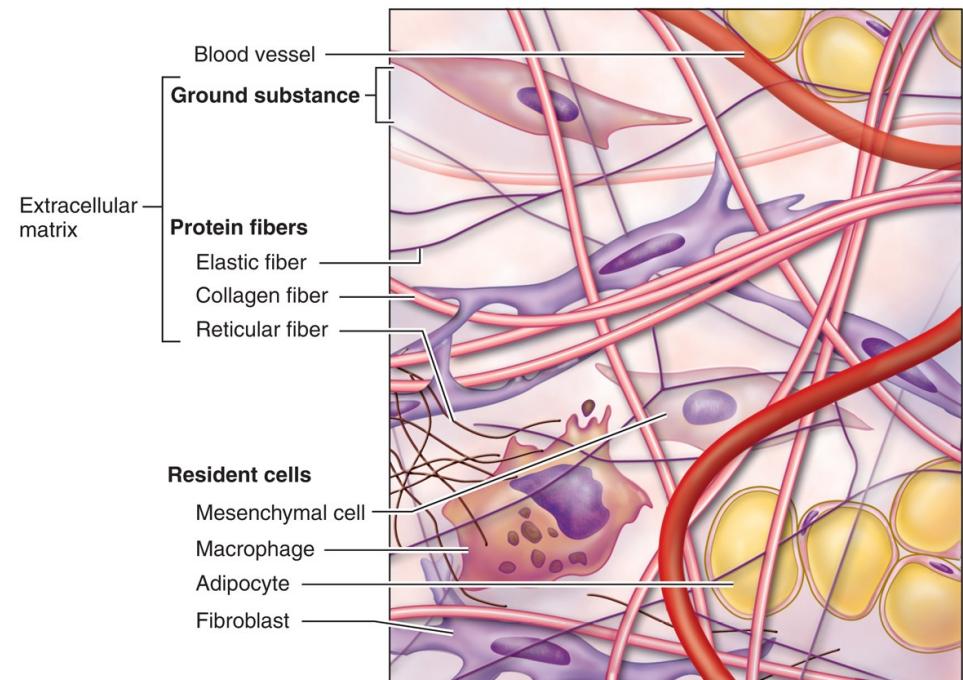
# Connective tissue cells can be resident or wandering.

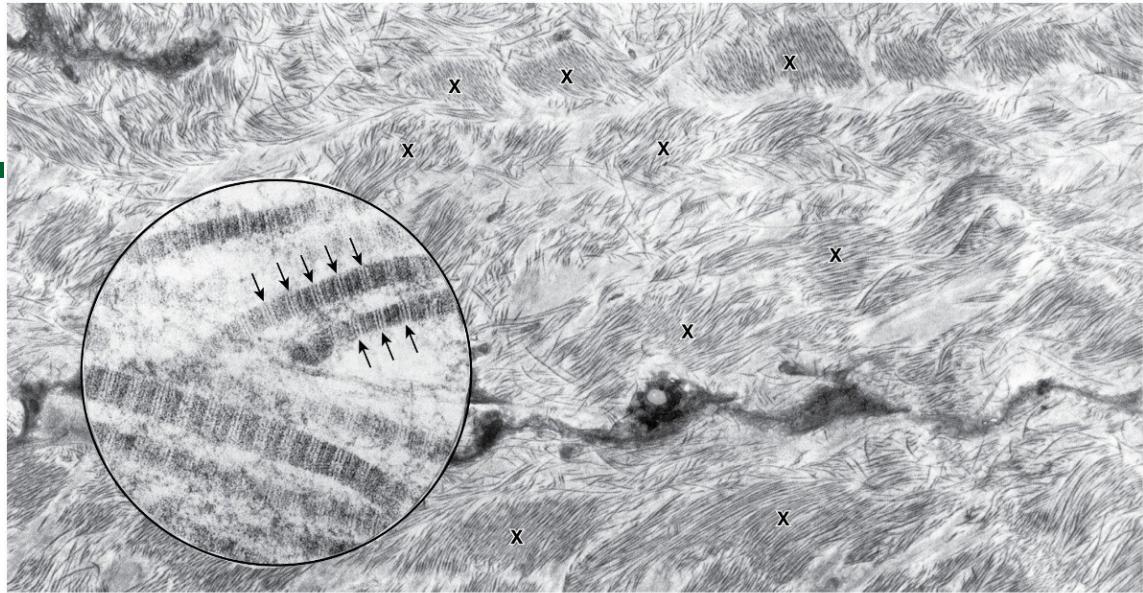
**Resident cell population** are relatively stable; they typically exhibit little movement and can be regarded as permanent residents of the tissue.

- **fibroblasts** and a closely related cell type, the **myofibroblast**
- **macrophages**
- **adipocytes**
- **mast cells**
- **adult stem cells.**

**Wandering cell population or transient cell population:** cells that have migrated into the tissue from the blood in response to specific stimuli.

- **lymphocytes**
- **plasma cells**
- **neutrophils**
- **eosinophils**
- **basophils**





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**Electron micrograph of dense irregular connective tissue** from the capsule of the testis of a young male. The threadlike collagen fibrils are aggregated in some areas (X) to form relatively thick bundles; in other areas, the fibrils are more dispersed.

**Inset.** A longitudinal array of collagen fibrils from the same specimen seen at higher magnification. Note the banding pattern. The spacing of the arrows indicates the 68-nm repeat pattern.

## Connective Tissue Fibers

- Connective tissue fibers are present in varying amounts, depending on the structural needs or function of the connective tissue.
- Produced by fibroblasts
- Composed of protein consisting of long peptide chains.
  - **Collagen fibers**
  - **Reticular fibers**
  - **Elastic fibers**

# Fibers Fibrous Connective Tissue

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- **Collagenous fibers**

- Most abundant of the body's proteins—25%

- Tough, flexible, and resist stretching

- Tendons, ligaments, and deep layer of the skin are mostly collagen

- Less visible in matrix of cartilage and bone

- **Reticular fibers**

- Thin collagen fibers coated with glycoprotein

- Form framework of such organs as spleen and lymph nodes

- **Elastic fibers**

- Thinner than collagenous fibers

- Branch and rejoin each other

- Made of protein called elastin

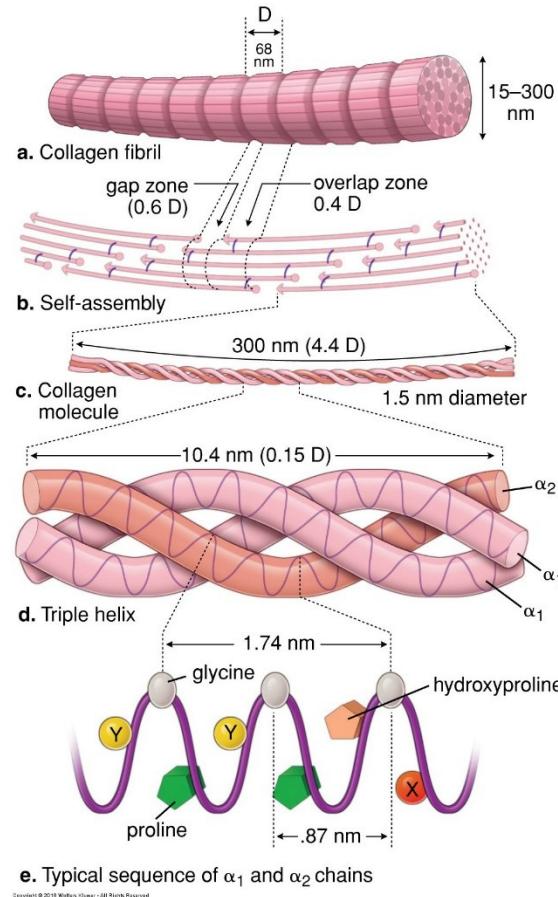
- Allows stretch and recoil

- Yellow fibers—fresh elastic fibers

# Collagen Fibrils in Dense Irregular CT



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## MEDICAL APPLICATION

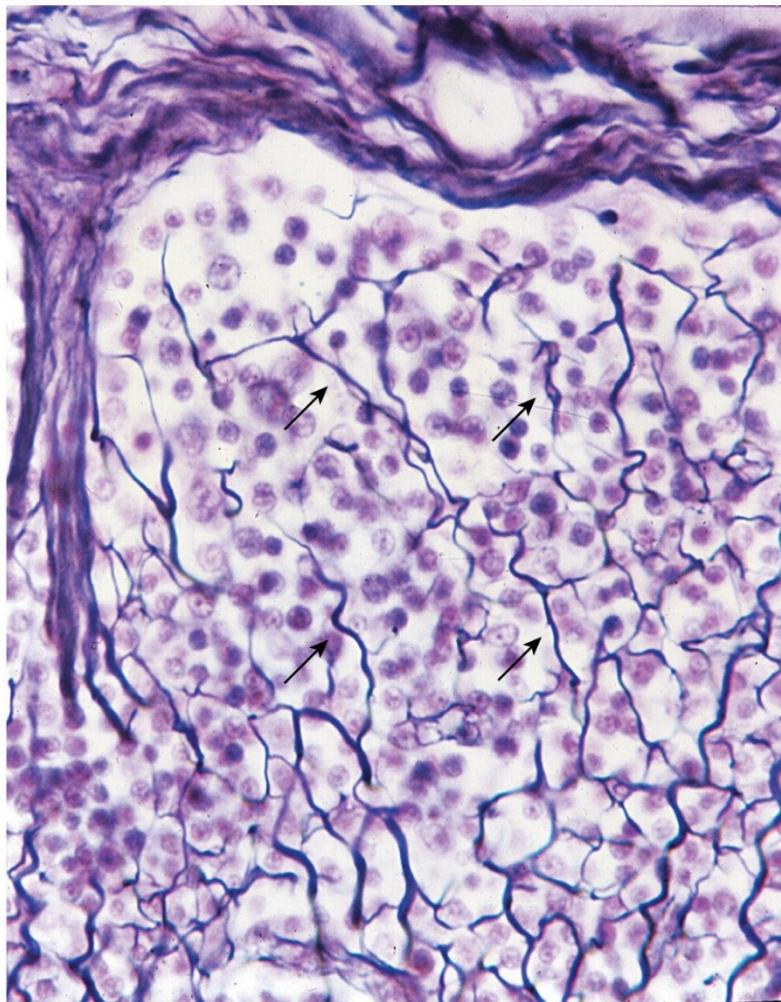
A keloid is a local swelling caused by abnormally large amounts of collagen that form in scars of the skin.  
**Stretch marks**

## MEDICAL APPLICATION

Scurvy Lack of vitamin C, a required cofactor for collagen synthesis results in ulceration of gums, hemorrhages

# Reticular Fibers in the Lymph Node

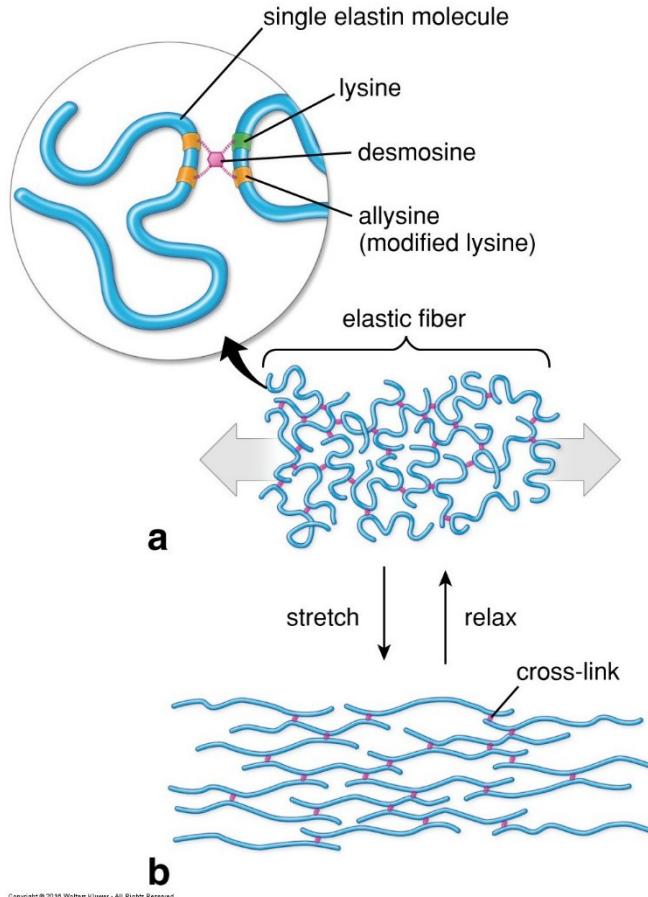
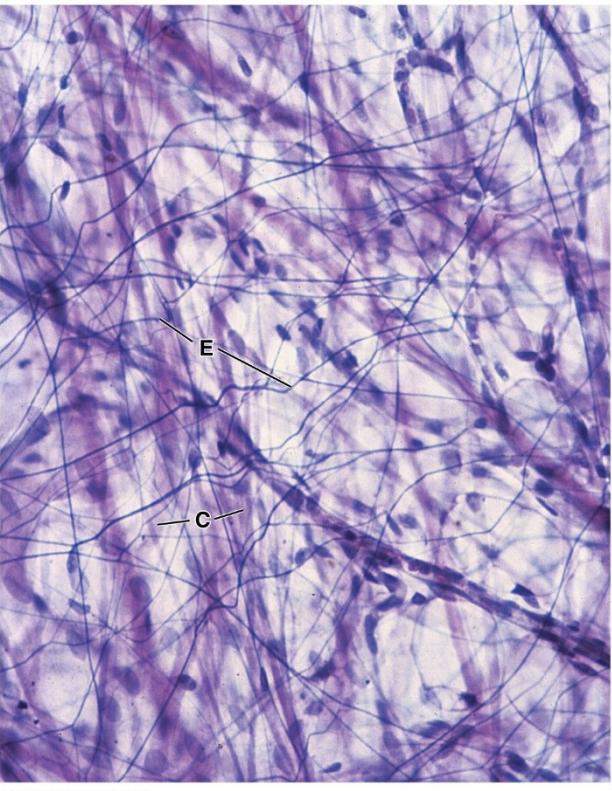
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**Reticular fibers** exhibit a branching pattern, and typically do not bundle to form thick fibers

Photomicrograph of a lymph node silver preparation showing the connective tissue capsule at the top and a trabecula extending from it at the left. The reticular fibers (arrows) form an irregular anastomosing (connection of branching structures) network.

# Elastic Fibers



**Elastic fibers** are typically thinner than collagen fibers, branching pattern. The fibers are interwoven with collagen fibers to limit the distensibility of the tissue and prevent tearing from excessive stretching

## MEDICAL APPLICATION:

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.

# Clinical Correlation: Sun Exposure and Molecular Changes in Photoaged Skin

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**Chronological aging:** changes in stratified squamous epithelium (epidermis) and connective tissue of the dermis.

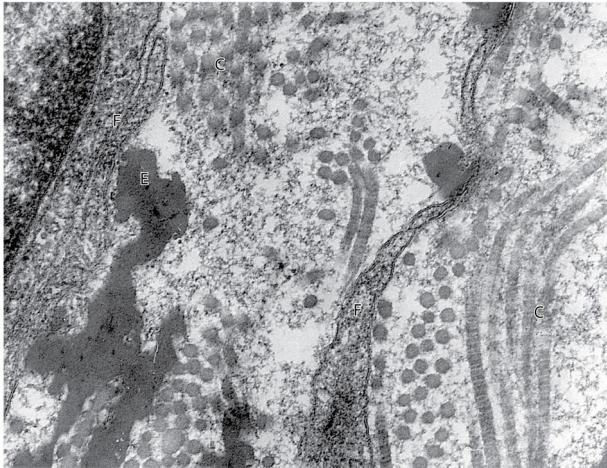
**Photoaging:** Chronic sun exposure leads to decreased production of type I and type III collagen fibers

- Altered crosslinking that occurs between collagen molecules resulting in abnormal stability and decreased resistance to enzymatic degradation.
- number of abnormally thick and nonfunctional elastic fibers increases



# Extracellular Matrix (ECM)

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## Ultrastructure of the extracellular matrix (ECM).

TEM of the connective tissue ECM reveals ground substance as either empty or containing fine granular material that fills spaces between the collagen (**C**) and elastic (**E**) fibers and surrounds fibroblast cells and processes (**F**).

The **extracellular matrix (ECM)** structural network that surrounds and supports cells within the connective tissue.  
**ground substance:**

- **proteoglycans** (e.g., aggrecan, syndecan)
- **multiadhesive glycoproteins** (such as fibronectin and laminin)
- **glycosaminoglycans** (e.g., dermatan sulfate, keratan sulfate, hyaluronan).

**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

# Classification of Connective Tissue

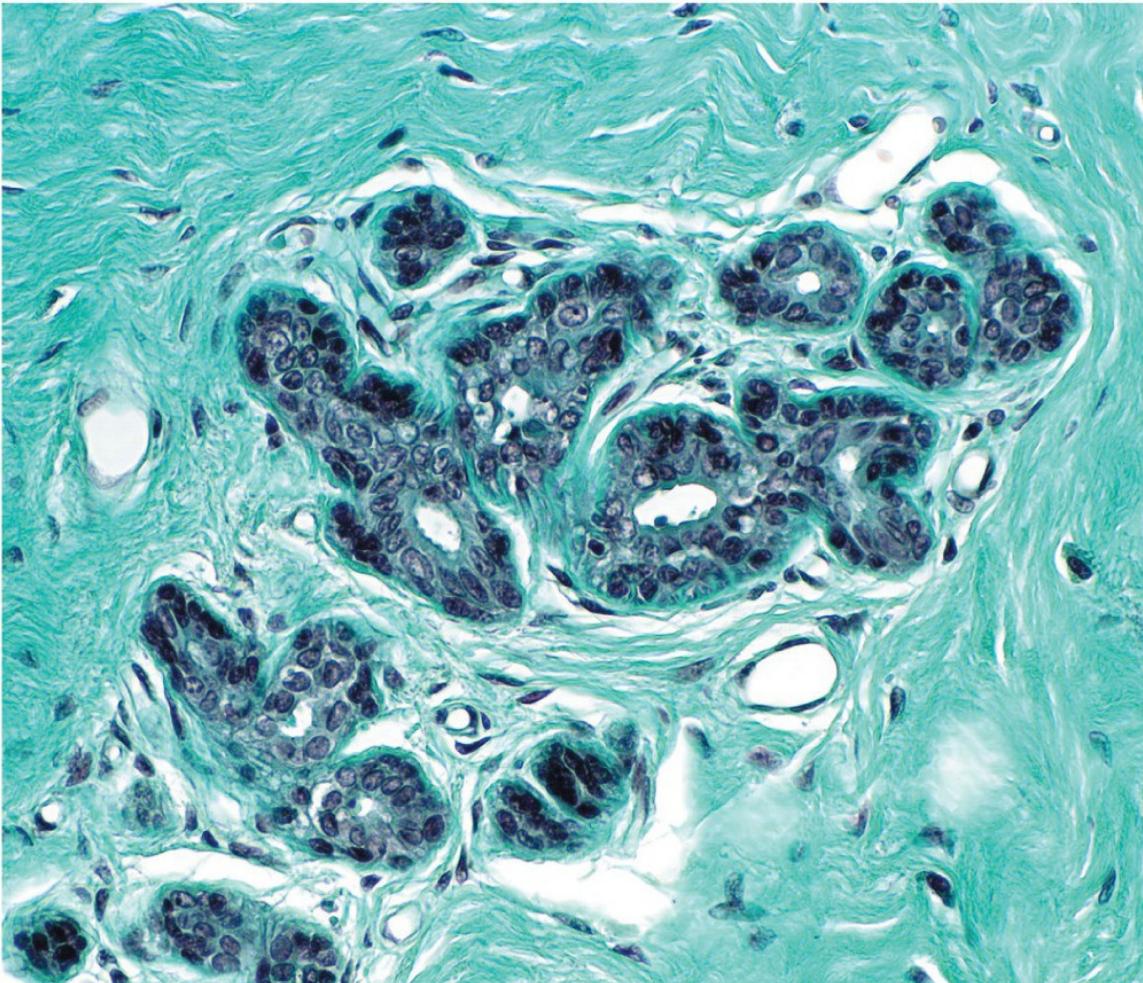
TABLE 5–6 Classification of connective or supporting tissues.

	General Organization	Major Functions	Examples
<b>Connective Tissue Proper</b>			
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
<b>Embryonic Connective Tissues</b>			
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
<b>Specialized Connective Tissues</b>			
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
<b>Adipose Tissue (Chapter 6)</b>			
<b>Cartilage (Chapter 7)</b>			
<b>Bone (Chapter 8)</b>			
<b>Blood (Chapter 12)</b>			

Connective Tissue: Types, Functions & Disorders: <https://www.youtube.com/watch?v=eJ7snAlCaCg>

# Loose and Dense Irregular CT

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## Dense irregular connective tissue

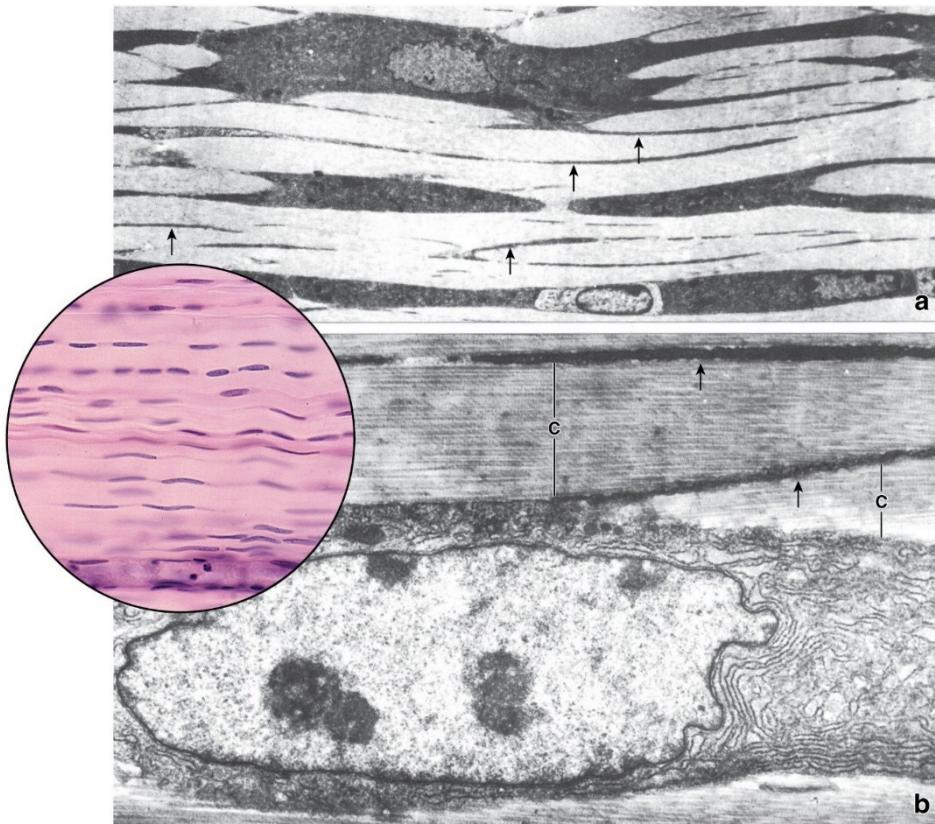
- contains mostly collagen fibers.
- Cells are sparse fibroblasts.
- contains relatively little ground substance

## Mammary gland stained with Masson's trichrome:

- Center: loose connective tissue surrounds the glandular epithelium. Note wispy arrangement of collagen fibers with many cells.
- upper left: dense irregular connective tissue. few nuclei, collagen is considerably more abundant and is composed of very thick fibers

Skin contains dense irregular connective tissue called the **reticular layer** of the dermis, which provides resistance to tearing from stretching forces from different directions

# Dense Regular CT



## Dense regular connective tissue

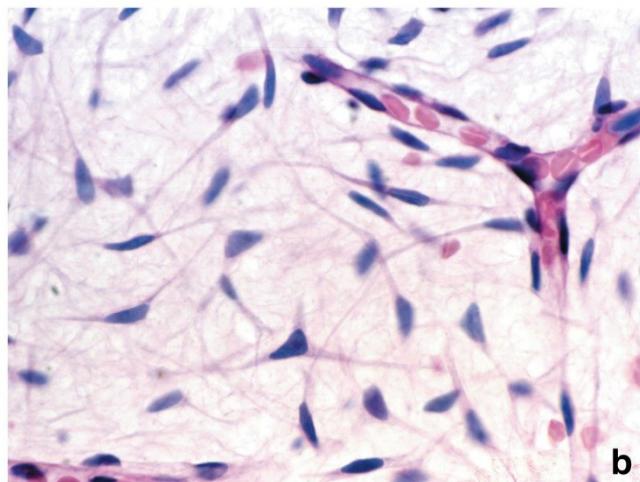
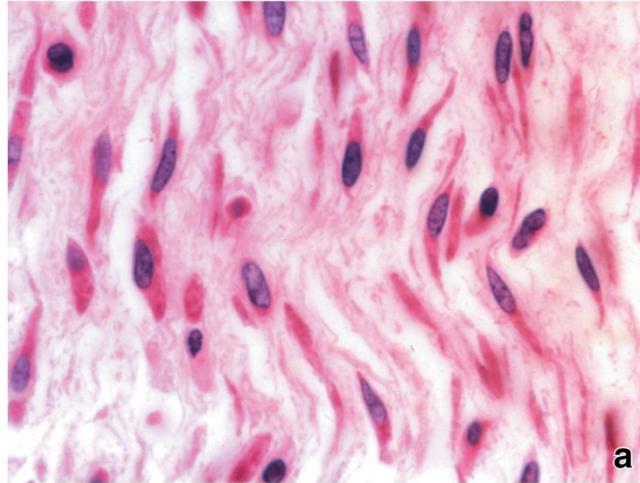
- tendons, ligaments, and aponeuroses.
- fibers are the prominent feature
- little ECM

- a) Electron micrograph of a tendinocytes (fibroblasts) and their thin processes (arrows) lying between the collagen bundles.
- b) higher magnification. The collagen fibers (C). Orderly and regular alignment of the bundles of collagen fibers.

## » MEDICAL APPLICATION

Overuse of tendon-muscle units can result in **tendonitis**, characterized by inflammation of the tendons and their attachments to muscle. Common locations are the elbow, the Achilles tendon of the heel, and the shoulder rotator cuff. The swelling and pain produced by the localized inflammation restricts the affected area's normal range of motion and can be relieved by injections of anti-inflammatory agents such as cortisone. Fibroblasts eventually repair damaged collagen bundles of the area.

# Embryonic Connective Tissue



- a) Although morphologically the mesenchymal cells appear as a homogeneous population, they give rise to cells that will differentiate into various cell types.
- b) Wharton's jelly consists of a specialized, almost gelatin like ground substance that occupies large intercellular spaces located between the spindle-shaped mesenchymal cells

## MEDICAL APPLICATION

Some cells in mesenchyme are multipotent stem cells potentially useful in regenerative medicine after grafting to replace damaged tissue in certain patients.

Stem cells to allow growing new teeth: [https://www.youtube.com/watch?v=\\_Gyv-BVniAw](https://www.youtube.com/watch?v=_Gyv-BVniAw)

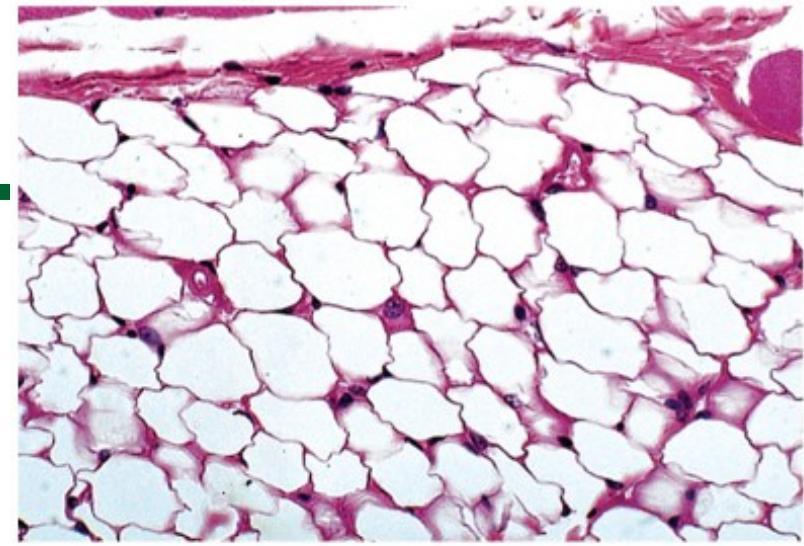
## Chapter 6 Adipose Objectives

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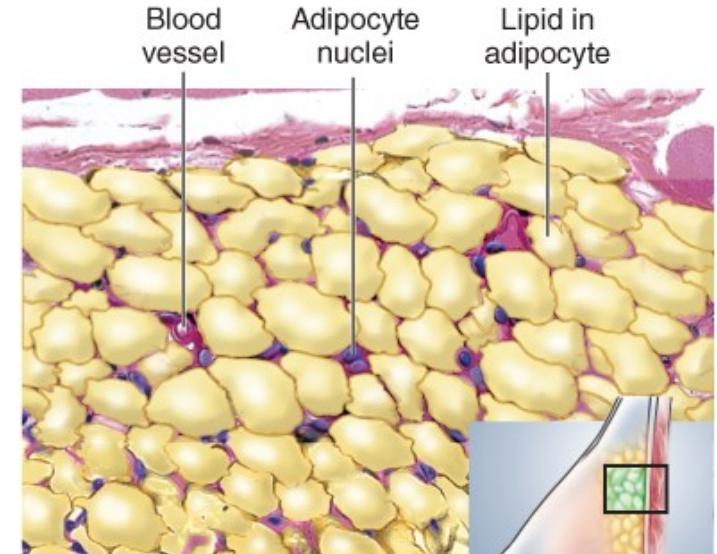
1. Adipose tissue is a specialized connective tissue that plays an important role in energy homeostasis (stores energy in lipid droplets in the form of triglycerides) and hormone production (adipokines).
2. White adipose tissue with supporting collagen and reticular fibers forms the subcutaneous fascia, is concentrated in the mammary fat pads, and surrounds several internal organs.
3. White adipocytes differentiate from mesenchymal stem cells
4. Brown adipose tissue is abundant in newborns (5% of total body mass) but is markedly reduced in adults.
5. Adipocytes are able to undergo white-to-brown and brown-to-white transformation (transdifferentiation) in response to the thermogenic needs of the body.

# Adipose Tissue

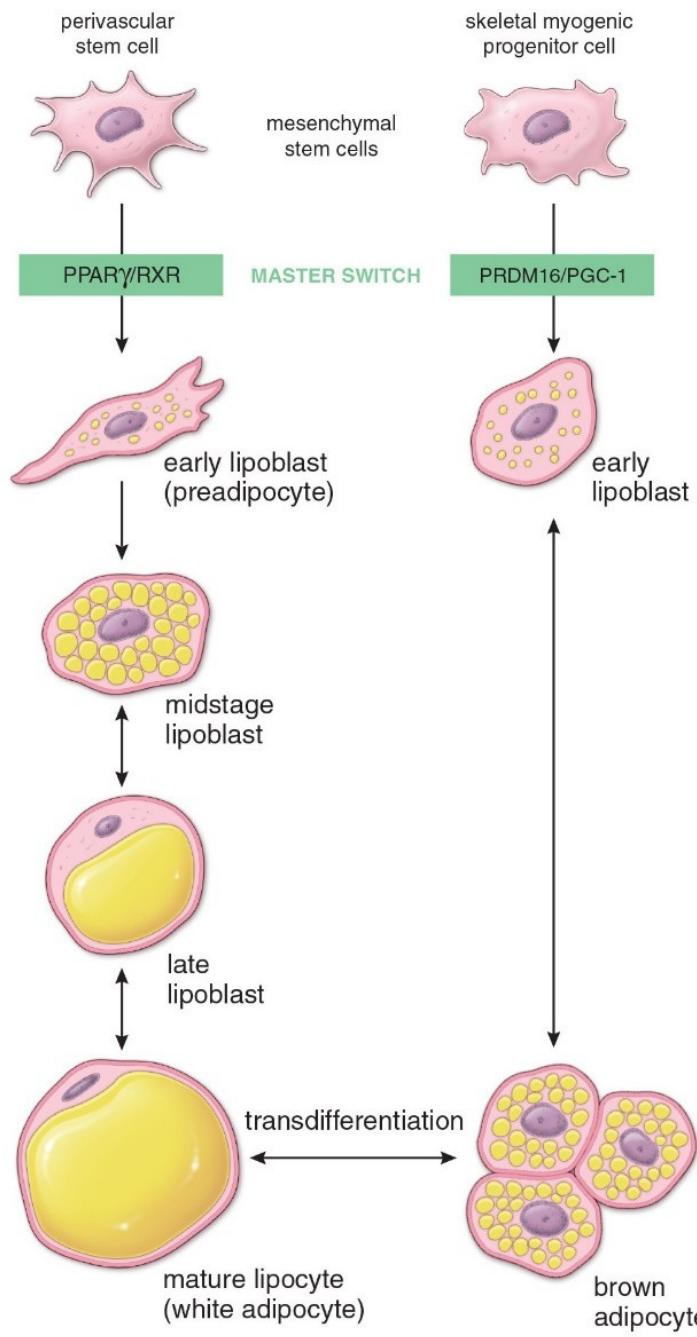
- Description
  - Closely packed adipocytes, nucleus pushed to one side by fat droplet Function
  - Provides reserve food fuel
  - Insulates against heat loss
  - Supports and protects organs
  - Most adult fat is called white fat
  - Brown fat: in fetuses, infants, children. a heat-generating tissue
  - Empty-looking cells with thin margins; nucleus pressed against cell membrane
  - Space between adipocytes is occupied by areolar tissue, reticular tissue, and blood capillaries
- Location: Under skin, around kidneys, Behind eyeballs, within abdomen and in breasts



(a) Permission required for reproduction or display.



(b)



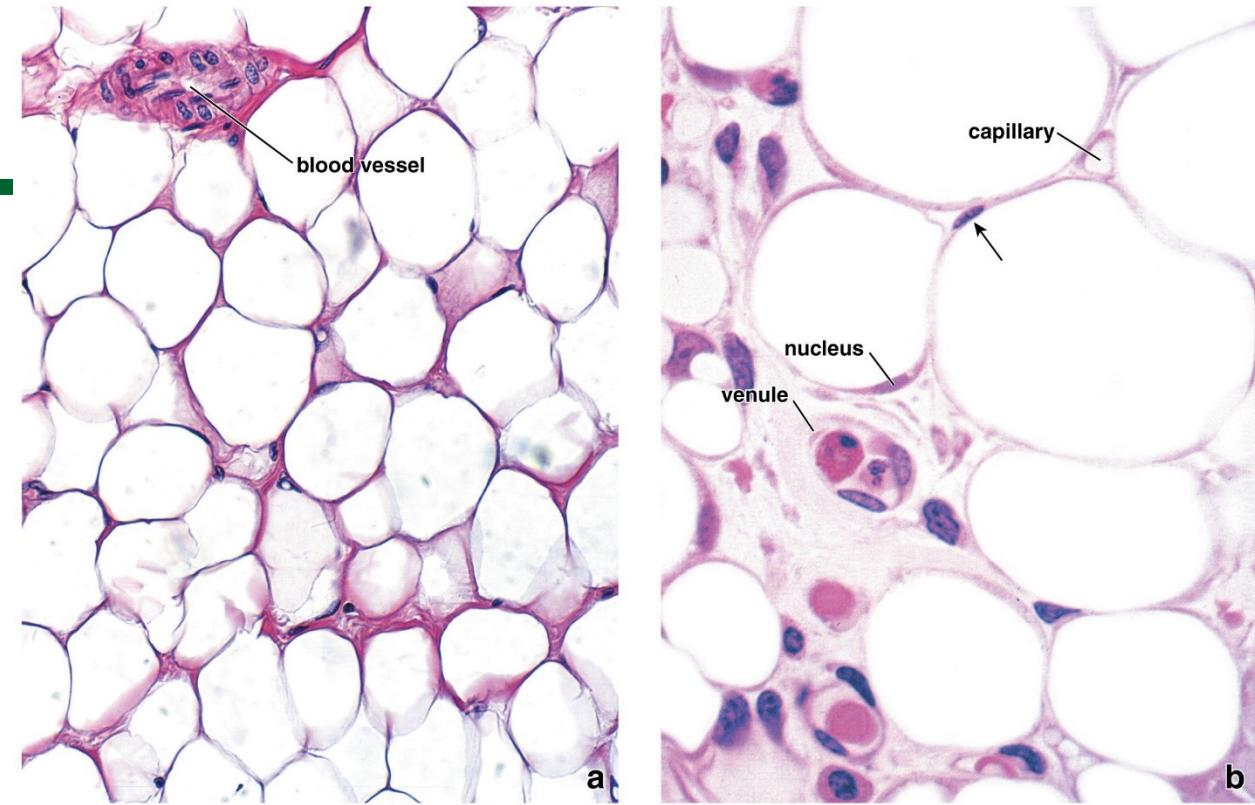
# White adipose tissue begins to form midway through fetal development.

- White adipocytes differentiate from mesenchymal stem cells under the control of **PPARy/RXR** transcription factors (“master switch” for white adipocyte differentiation).
- Brown adipocytes differentiate from mesenchymal stem cells under the control of **PRDM16/PGC-1** transcription factors (“master switch” for brown adipocyte differentiation).
- **Transdifferentiation**: white to brown conversion is induced by cold or physical activity
- **Research application**: Mice with abundant natural or induced brown adipose tissue are resistant to obesity, Genetically modified mice without functional brown adipocytes are prone to obesity and type 2 diabetes.

# White Adipose Tissue

White adipose tissue represents at least 10% of body weight in a normal healthy adult.

- Forms subcutaneous fascia, is concentrated in the mammary fat pads, and surrounds several internal organs.



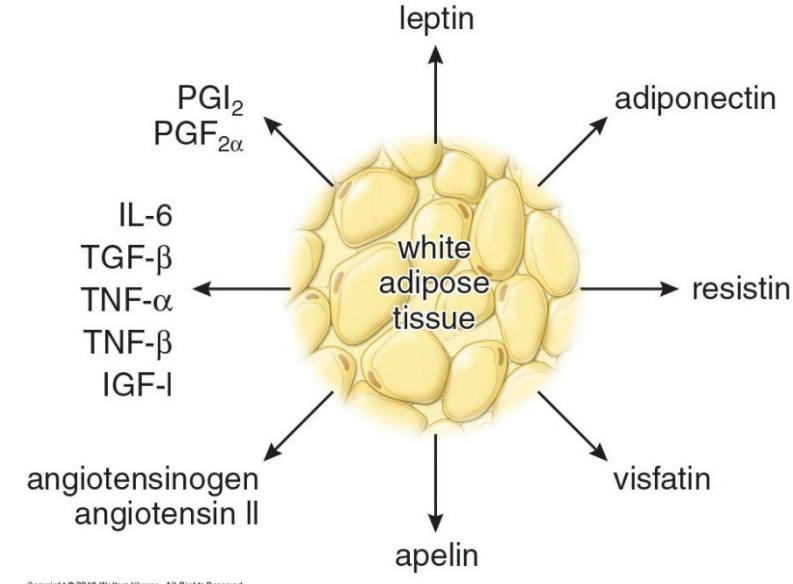
White adipocytes are very large cells (100  $\mu\text{m}$  or more in diameter) with a single, large lipid droplet (unilocular), a thin rim of cytoplasm, and a flattened, peripherally displaced nucleus. A single large lipid droplet within the white adipocyte represents cytoplasmic inclusion and is not membrane bound.

White adipose tissue secretes a variety of adipokines, which include hormones (e.g., leptin), growth factors, and cytokines.

# White adipose tissue produces a variety of hormones, growth factors, and cytokines.

Leptin: **circulating satiety factor** that controls food intake when the body's store of energy is sufficient.

» » **MEDICAL APPLICATION:** In most obese humans adipocytes produce adequate or excess quantities of leptin, but target cells are not responsive due to mechanisms downstream of leptin receptors.

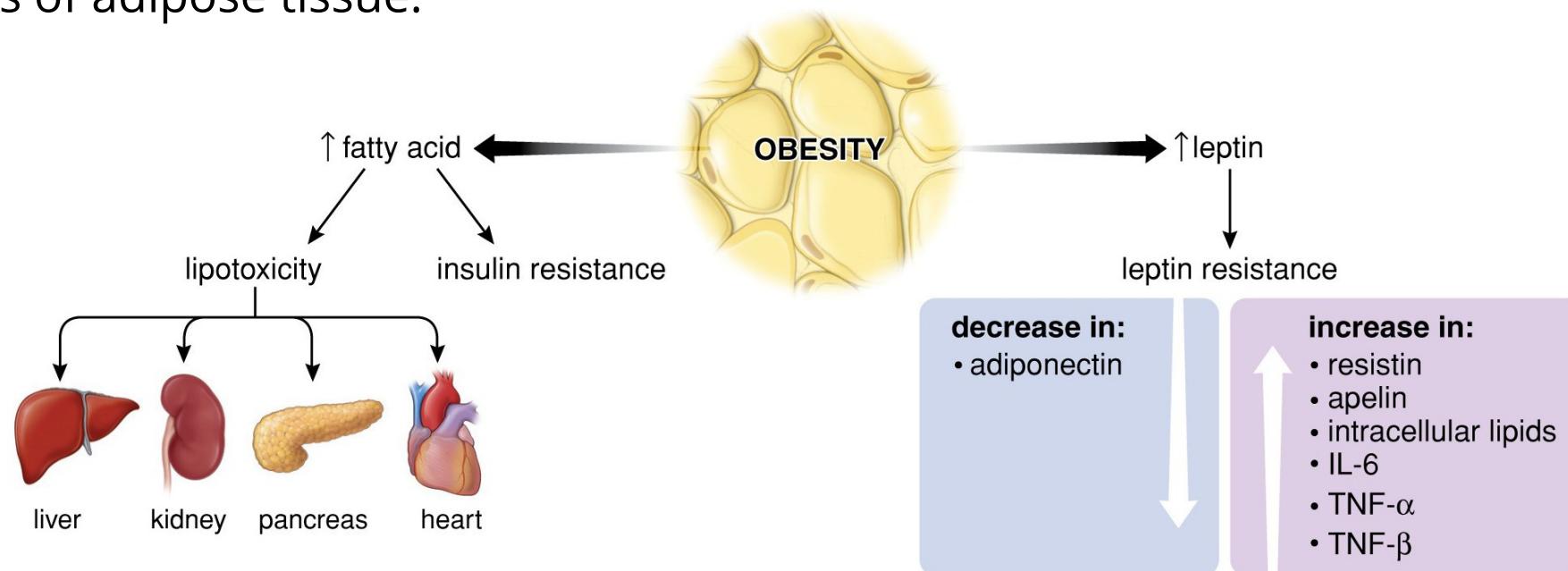


## » » MEDICAL APPLICATION

In addition to leptin, white adipose tissue secretes numerous other cytokines. It is not clear whether these are produced by adipocytes or other cells of the tissue such as macrophages or fibroblasts. With its increased amounts of white adipose tissue, obesity is characterized by a state of chronic mild inflammation and inflammation-related disorders associated with obesity, such as diabetes and heart disease.

# Clinical Correlation: Obesity

Adult-onset obesity is very often associated with age related metabolic changes and may involve reduced activity of the hormone-sensitive lipases of adipocytes, causing less effective fat mobilization out of the cells. The increased number of adipocytes produced during childhood obesity predisposes an individual to obesity in later life. Despite claims of various fad diets, there is no evidence that any particular type of caloric restriction is more effective than others; rather, any intake of calories that is lower than the energy expenditure will result in loss of adipose tissue.



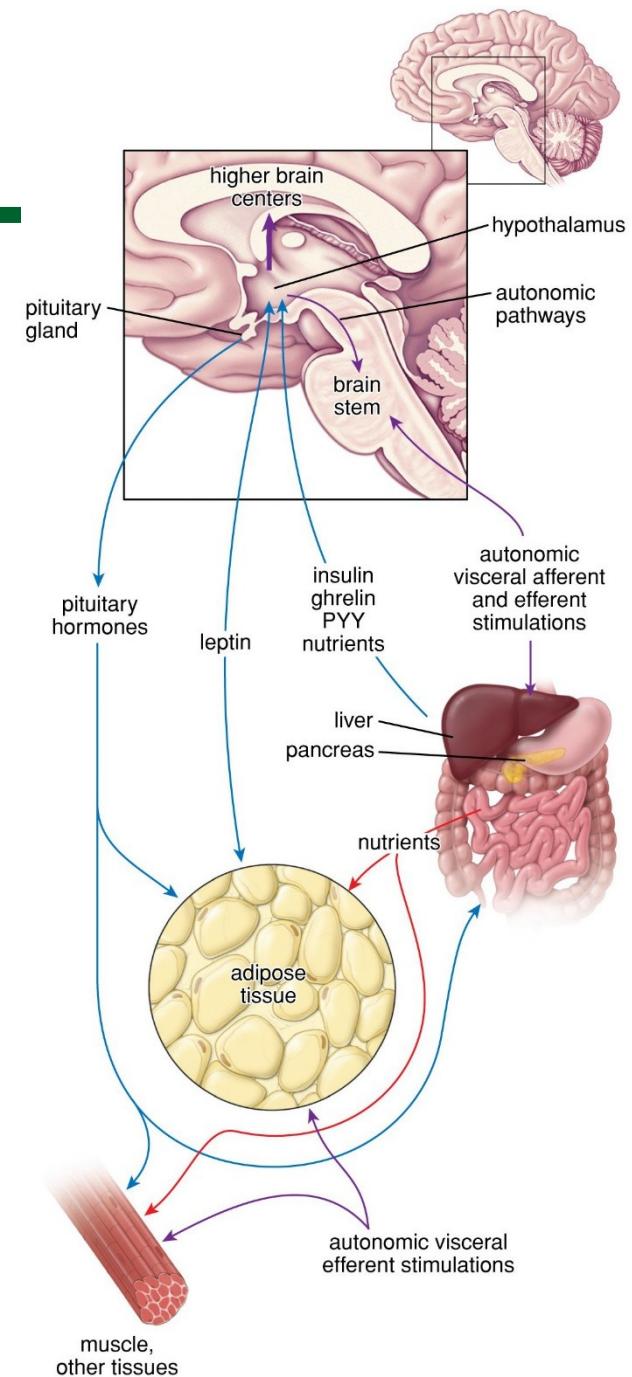
# Regulation of Adipose Tissue: brain-gut-adipose axis

Short-term weight regulation: controls appetite via GI tract hormones **ghrelin** (appetite stimulant) and **peptide YY** (PYY, appetite suppressant)

## Long term weight regulation:

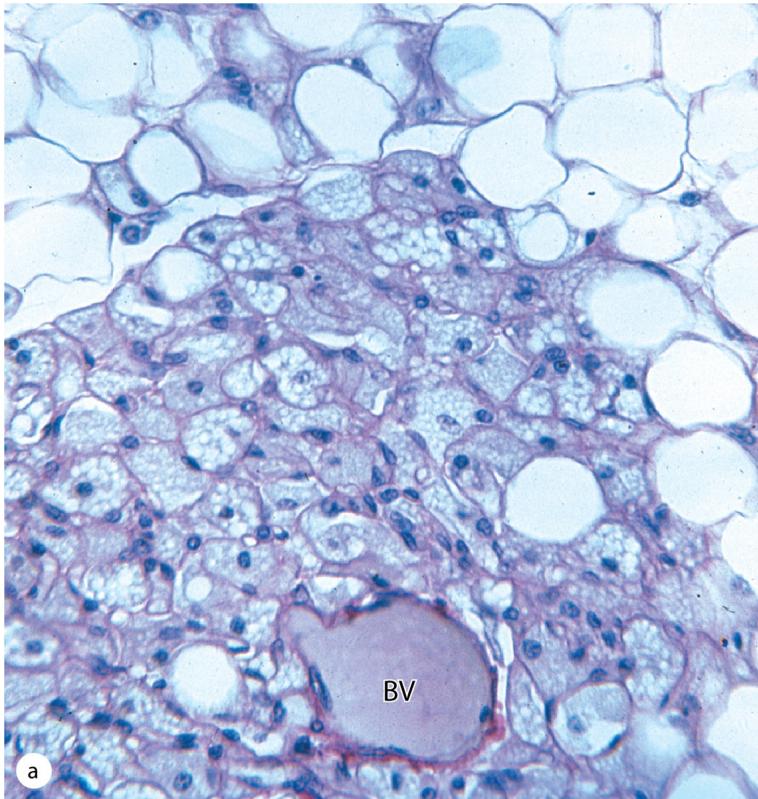
**Leptin**: controls food intake. Mice lacking leptin are obese, however obese humans overexpress leptin. The effect of leptin in satiety may be downstream of the receptor.

**Insulin**: regulates blood glucose levels by encouraging conversion of glucose to triglyceride. It also acts on the hypothalamus.



# Brown adipose tissue, abundant in newborns, is markedly reduced in adults.

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In newborns, brown adipose tissue makes up about 5% of the total body mass which helps to offset the extensive heat loss that results from the newborn's high surface-to-mass ratio and to avoid lethal hypothermia (a major risk of death for premature babies).

Brown (multilocular, multiple fat droplets) adipose tissue cells are smaller than those of white adipose tissue.

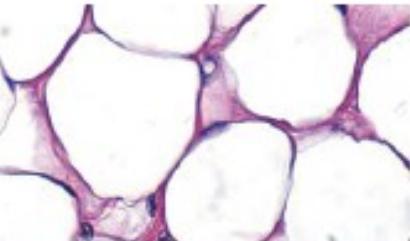
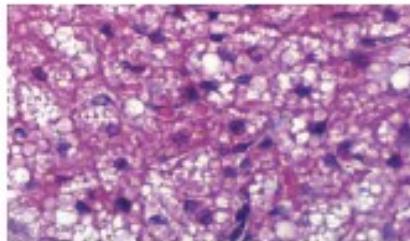
Brown adipose tissue can expand in response to increased blood levels of norepinephrine

**Nonshivering thermogenesis:** Metabolism of lipid in brown adipose for heat, common in hibernating animals. UCP-1 (uncoupling protein 1 in mitochondria) uncouples oxidation of fatty acids from ATP production in favor of heat production.

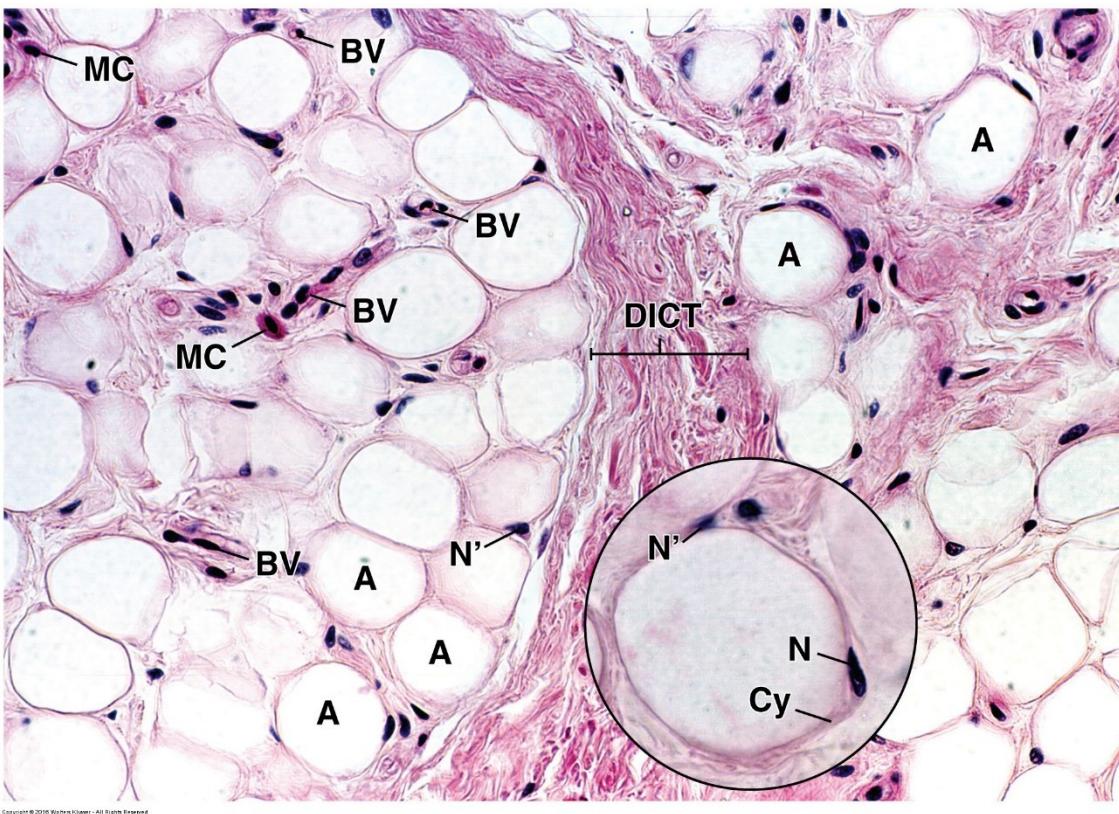
TABLE

9.2

## Summary of Adipose Tissue Features

Features	White Adipose Tissue	Brown Adipose Tissue
		
Location	Subcutaneous layer, mammary gland, greater omentum, mesenteries, retroperitoneal space, visceral pericardium, orbits (eye sockets), bone marrow cavity	Large amounts in newborn Remnants in adults at the retroperitoneal space, deep cervical and supraclavicular regions of the neck, interscapular, paravertebral regions of the back, mediastinum
Function	Metabolic energy storage, insulation, cushioning, hormone production, source of metabolic water	Heat production (thermogenesis)
Adipocyte morphology	Unilocular, spherical, flatten nucleus, rim of cytoplasm Large diameter (15–150 µm)	Multilocular, spherical, round eccentric nucleus Smaller diameter (10–25 µm)
Transcription factors "master switch" in differentiation	PPAR-γ/RXR	PRDM16/PGC-1
UCP-1 genes expression	No	Yes (unique to brown fat)
Mitochondria	Few, poorly developed	Many, well developed
Innervation	Few sympathetic nerve fibers	High density of sympathetic nerve fibers
Vascularization	Few blood vessels	Highly vascularized tissue
Response to environmental stress (cold exposure)	Decreased lipogenesis Increased lipoprotein lipase activity	Increased lipogenesis Decreased lipoprotein lipase activity
Growth and differentiation	Throughout entire life from stromal-vascular cells	Only during fetal period Decreases in adult life (exception: individuals with pheochromocytoma and hibernoma)

# White adipose tissue, human, H&E



Dense irregular connective tissue (DICT) separates the lobules from surrounding structures.

adipocytes (A) with very thin rim of cytoplasm surrounding a single, large fat-containing vacuole fat is lost during tissue preparation

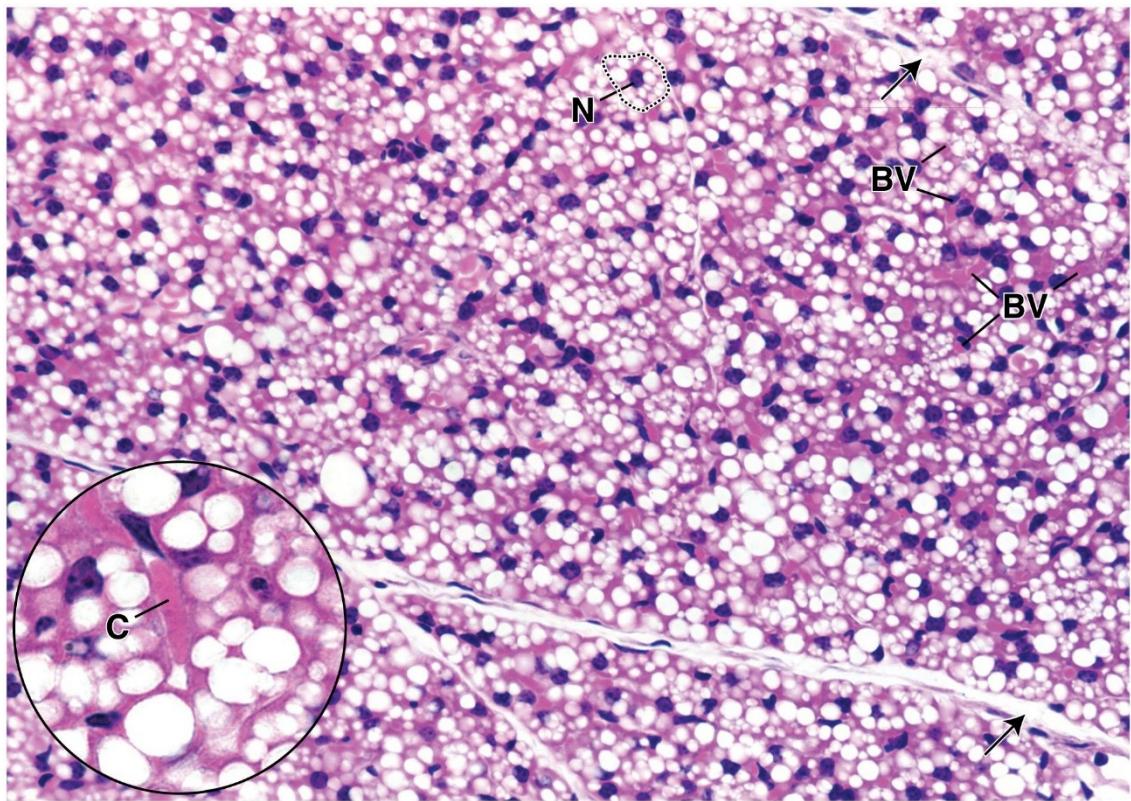
blood vessels (BV), mostly capillaries and venules.

inset shows an adipocyte whose nucleus (N) is relatively easy to identify. It appears to reside within the rim of cytoplasm (Cy), giving the adipocyte the classic “signet ring” appearance.

Because of the relatively large size of the adipocyte, it is very infrequent that the nucleus of the cell is included in the plane of section of a given cell.

Other cells that may be seen within the delicate connective tissue stroma are mast cells (MC) and Nuclei of Fibroblasts (N')

## Brown adipose tissue, human, H&E



Small fat cells that are very closely packed with minimal intercellular space.

Each cell contains many small, fat-containing vacuoles surrounded by cytoplasm. Included in this cell is its nucleus (N).

Brown adipose tissue is highly vascularized

A capillary (C) can be identified in the inset

# Chapter 7 Cartilage Objectives

1. General properties of cartilage: Chondrocytes, lacunae, ECM, avascularity
2. Hyaline cartilage
3. Fibrocartilage
4. Elastic cartilage
5. Formation, growth and repair



# Cartilage is a form of connective tissue composed of cells called chondrocytes and a highly specialized extracellular matrix.

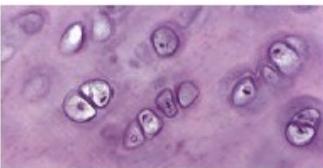
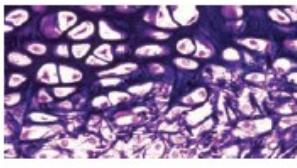
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- Supportive connective tissue with flexible, rubbery matrix that gives shape to ear, tip of nose, and larynx
- **Chondroblasts** produce matrix and surround themselves until they become trapped in little cavities (lacunae)
- **Chondrocytes**: cartilage cells in lacunae
- **Perichondrium**: sheath of dense irregular connective tissue that surrounds elastic and most hyaline cartilage (not articular cartilage)
  - Contains a reserve population of chondroblasts that contribute to cartilage growth throughout life
- **No blood vessels**: Diffusion brings nutrients and removes wastes, heals slowly
- Matrix rich in chondroitin sulfate and contains collagen fibers

TABLE

7.1

## Summary of Cartilage Features

Features	Hyaline Cartilage	Elastic Cartilage	Fibrocartilage
			
Location	Fetal skeletal tissue, epiphyseal plates, articular surface of synovial joints, costal cartilages of rib cage, cartilages of nasal cavity, larynx (thyroid, cricoid, and arytenoids), rings of trachea and plates in bronchi	Pinna of external ear, external acoustic meatus, auditory (Eustachian) tube, cartilages of larynx (epiglottis, corniculate, and cuneiform cartilages)	Intervertebral discs, symphysis publis, articular discs (sternoclavicular and temporomandibular joints), menisci (knee joint), triangular fibrocartilage complex (wrist joint), insertion of tendons
Function	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 and further endochondral bone formation and bone growth	Provides flexible support	Resists deformation under stress
Presence of perichondrium	Yes (except articular cartilage and epiphyseal plates)	Yes	No
Undergoes calcification	Yes (i.e., during endochondral bone formation, during aging process)	No	Yes (i.e., calcification of fibrocartilaginous callus during bone repair)
Main cell types present	Chondroblasts and chondrocytes	Chondroblasts and chondrocytes	Chondrocytes and fibroblasts
Characteristic features of extracellular matrix	Type II collagen fibrils and aggrecan (the most important proteoglycan)	Type II collagen fibrils, elastic fibers, and aggrecan	Types I and II collagen fibers and versican (a proteoglycan secreted by fibroblasts)
Growth	Interstitial and appositional, very limited in adults		
Repair	Very limited capability, commonly forms scar, resulting in fibrocartilage formation		

# Hyaline cartilage is distinguished by a homogeneous, amorphous matrix.

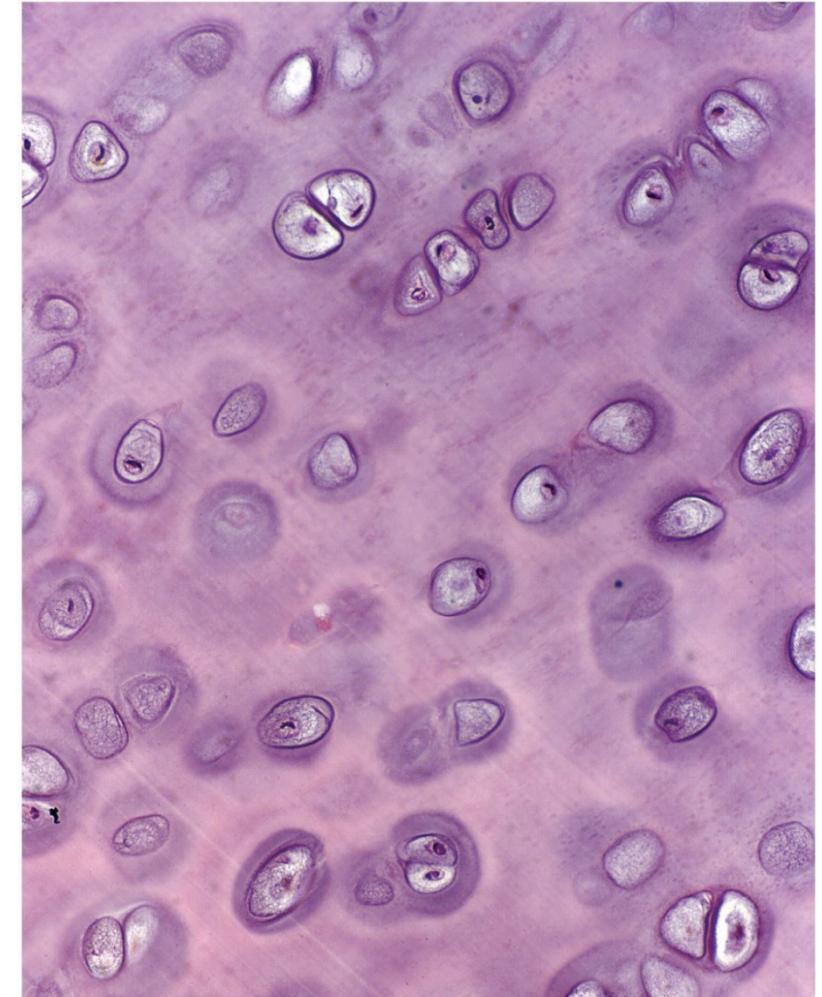
- extensive extracellular matrix
- sparse population of chondrocytes
- Throughout the **cartilage matrix** are spaces called **lacunae**.
- **Chondrocytes** within these lacunae provides a low-friction surface, participates in lubricating synovial joints, and distributes applied forces to the underlying bone.

## 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

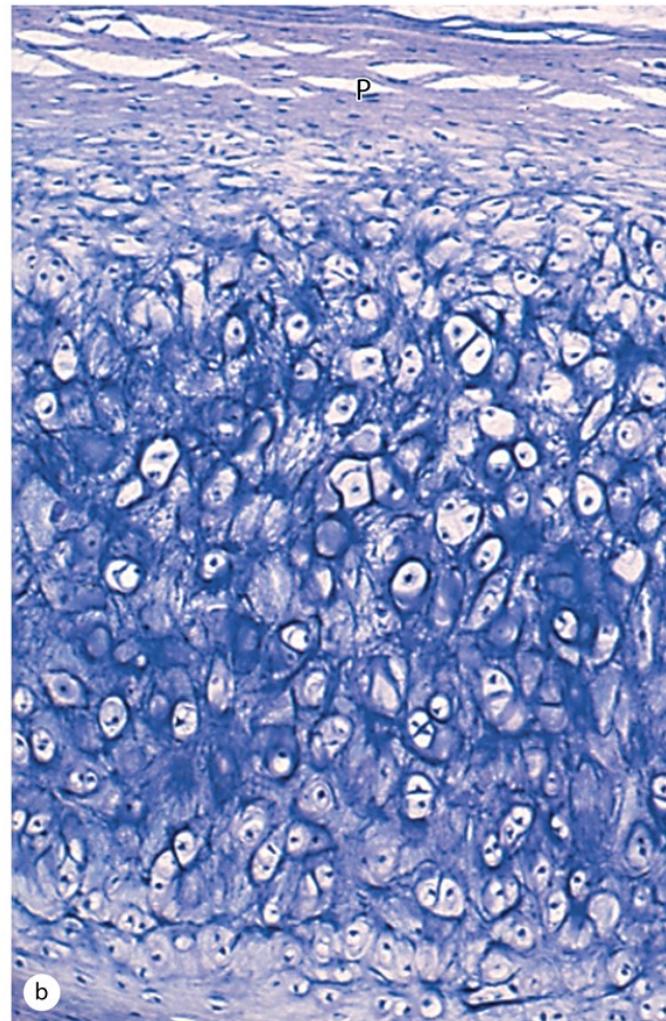
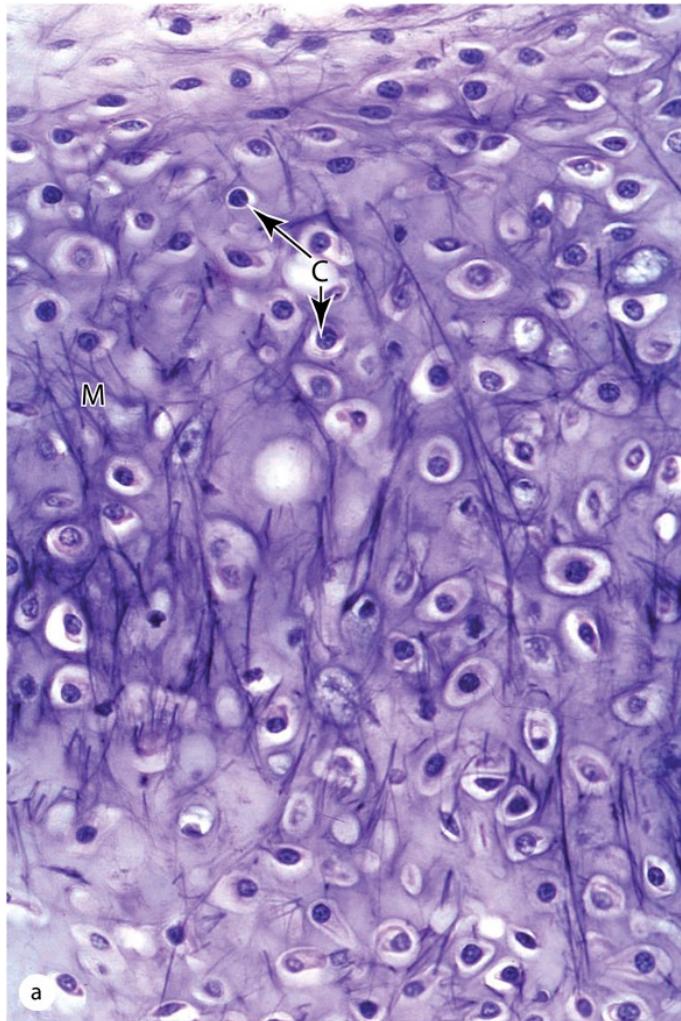
## MEDICAL APPLICATION

Osteoarthritis, a chronic condition that commonly occurs during aging, occurs most in joints that are weightbearing (knees, hips) or heavily used (wrist, fingers) are most prone to cartilage degeneration



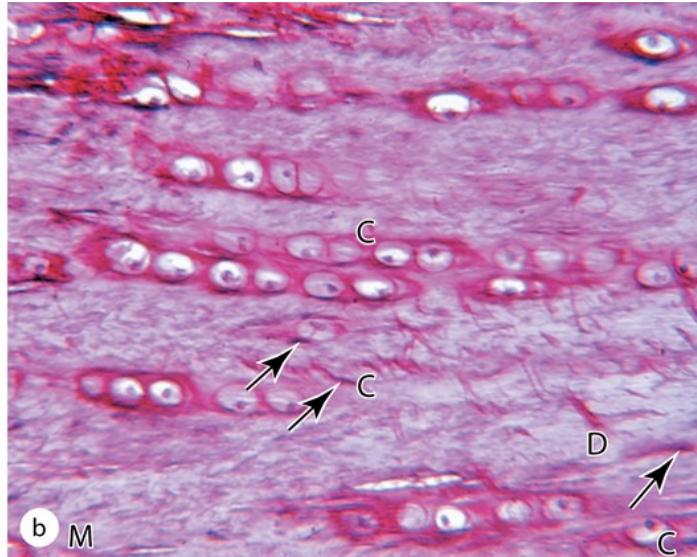
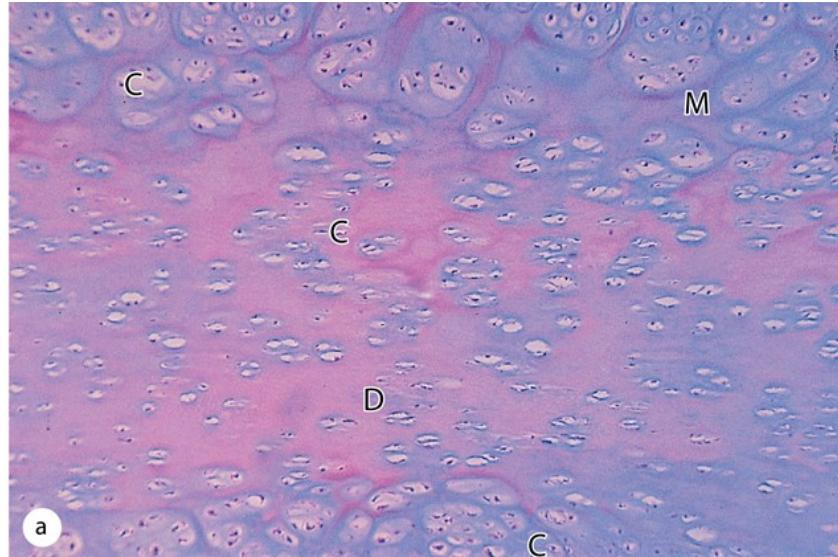
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# The chondrocytes (C) and overall organization of elastic cartilage are similar to those of hyaline cartilage.



Stains for elastin, however, reveal many dark-staining elastic fibers in the matrix (**M**), in addition to the major components found in hyaline matrix. Elastic fibers provide greater flexibility to this form of cartilage. The section in part **b** includes perichondrium (**P**) that is also similar to that of hyaline cartilage. **(a)** X160. Hematoxylin and orcein. **(b)** X100. Weigert resorcin-fuchsin.

# Fibrocartilage varies in different organs, but is essentially a mixture of hyaline cartilage and dense connective tissue.

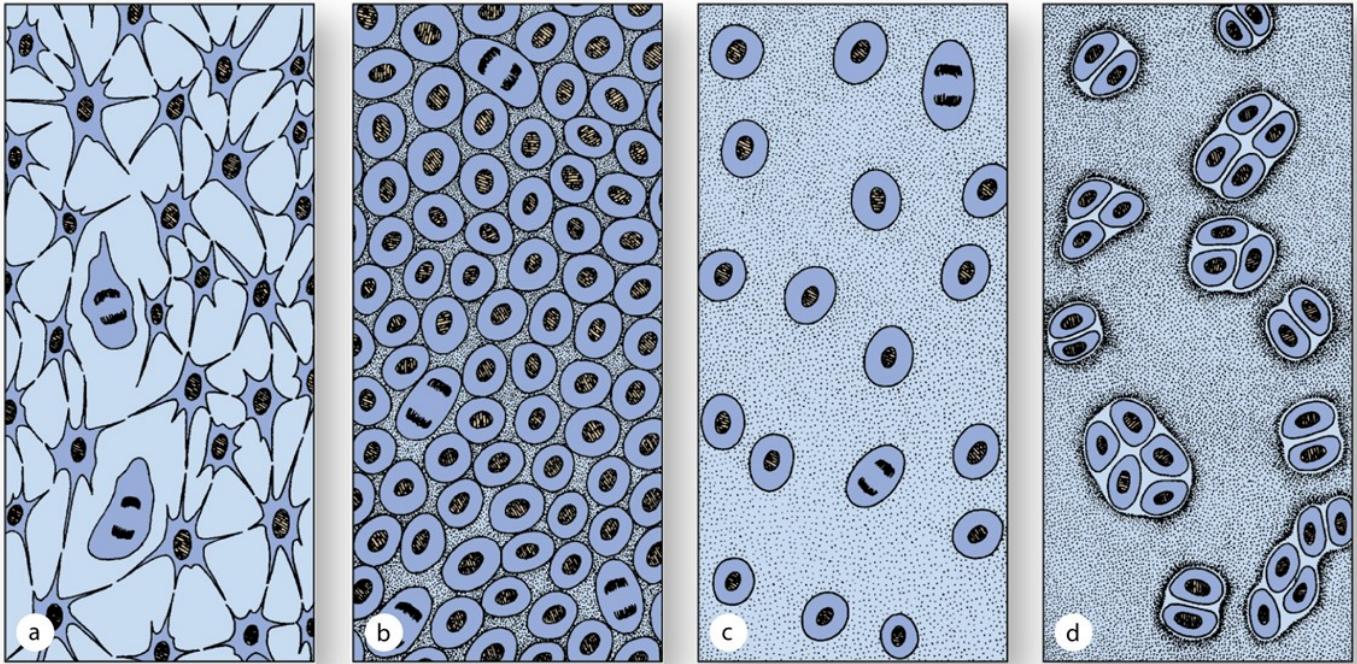


Shotgun Histology Fibro-Cartilage: <https://www.youtube.com/watch?v=mDyTwvgNaQ>

(a) A section of pubic symphysis shows lacunae with isolated and grouped chondrocytes (C) surrounded by matrix (M) and separated in some areas by dense regions (D) containing more concentrated acidophilic type I collagen. No separate perichondrium is present on fibrocartilage. X100. H&E.

(b) At higher magnification in a small region of intervertebral disc, the axially arranged aggregates of chondrocytes (C) are seen to be surrounded by small amounts of matrix and separated by larger regions with dense collagen (D) and a small number of fibroblasts with elongated nuclei (arrows). X250. Picosirius-hematoxylin.

## 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 **chondroblasts**.
- (c) Chondroblasts are then separated from one another again by their production of ECM.
- (d) Multiplication of chondroblasts within the matrix gives rise to **isogenous cell aggregates** surrounded by a condensation of territorial matrix.



Bone, Nervous, Muscle

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## BI 455 CHAPTER 8-10

# Chapter 8 Bone Objectives

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1. Cells and ECM: Osteoblasts, osteocytes, bone matrix
2. Mineralized extracellular matrix
3. General structure of bone tissue: lamellar bone, osteons, perforating canals, lacunae
4. Bone formation: membranous ossification, endochondral ossification
5. Bone growth, remodeling, and repair: interstitial and appositional growth
6. Calcium homeostasis

# Functions of the Skeleton

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- Support: holds up the body, supports muscles, mandible and maxilla support teeth
- Protection: brain, spinal cord, heart, lungs
- Movement: limb movements, breathing, action of muscle on bone
- Electrolyte balance: calcium and phosphate ions
- Acid–base balance: buffers blood against excessive pH changes
- Blood formation: red bone marrow is the chief producer of blood cells



# Bone cells

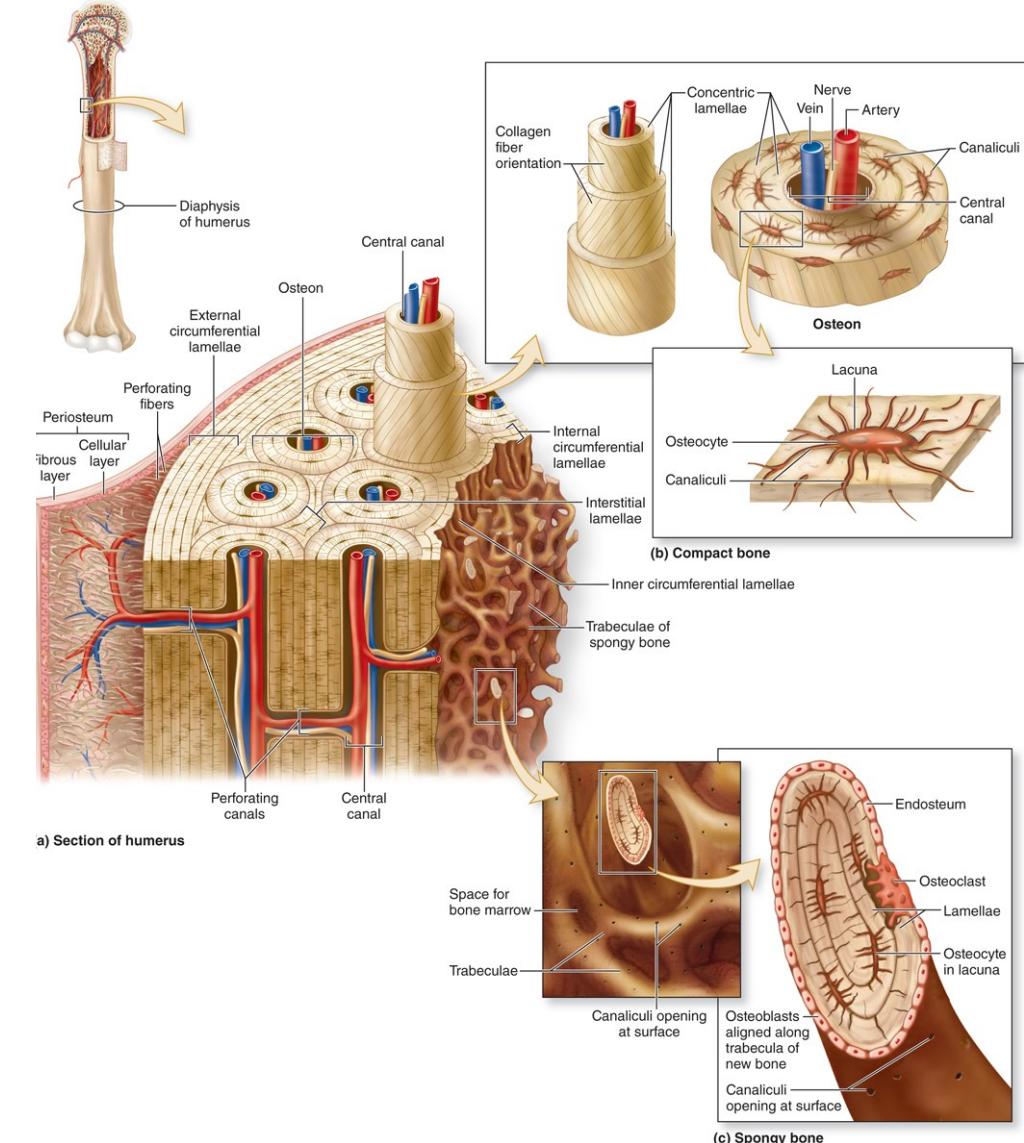
Bone Density Decreases in Space - What to Do? | Video: <https://www.youtube.com/watch?v=nHbj7kqYoVk>

**Osteoprogenitor cells:** derived from mesenchymal stem cells; give rise to osteoblasts.

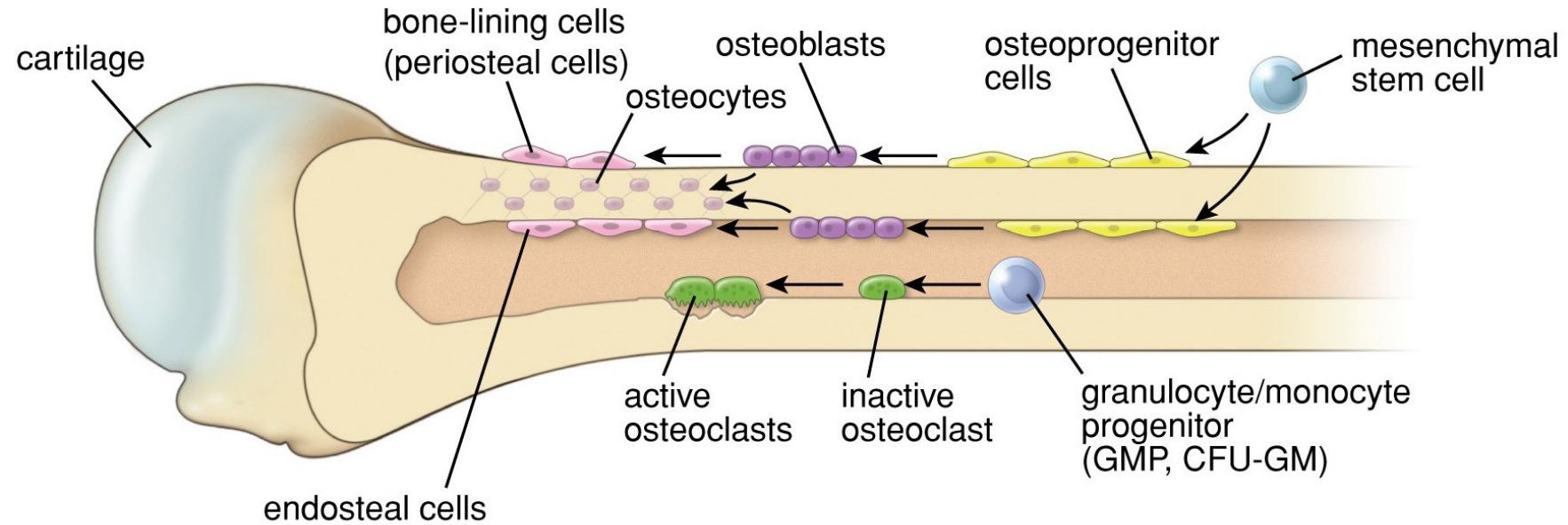
**Osteoblasts:** secrete the extracellular matrix of bone; becomes **osteocyte** once the cell is surrounded with its secreted matrix

**Osteoclasts:** bone-resorbing cells on bone surfaces, for remodeling and repair

**MEDICAL APPLICATION:** dendritic processes of osteocytes detect load and maintain the matrix accordingly. Lack of exercise or the weightlessness experienced by astronauts leads to decreased bone density.

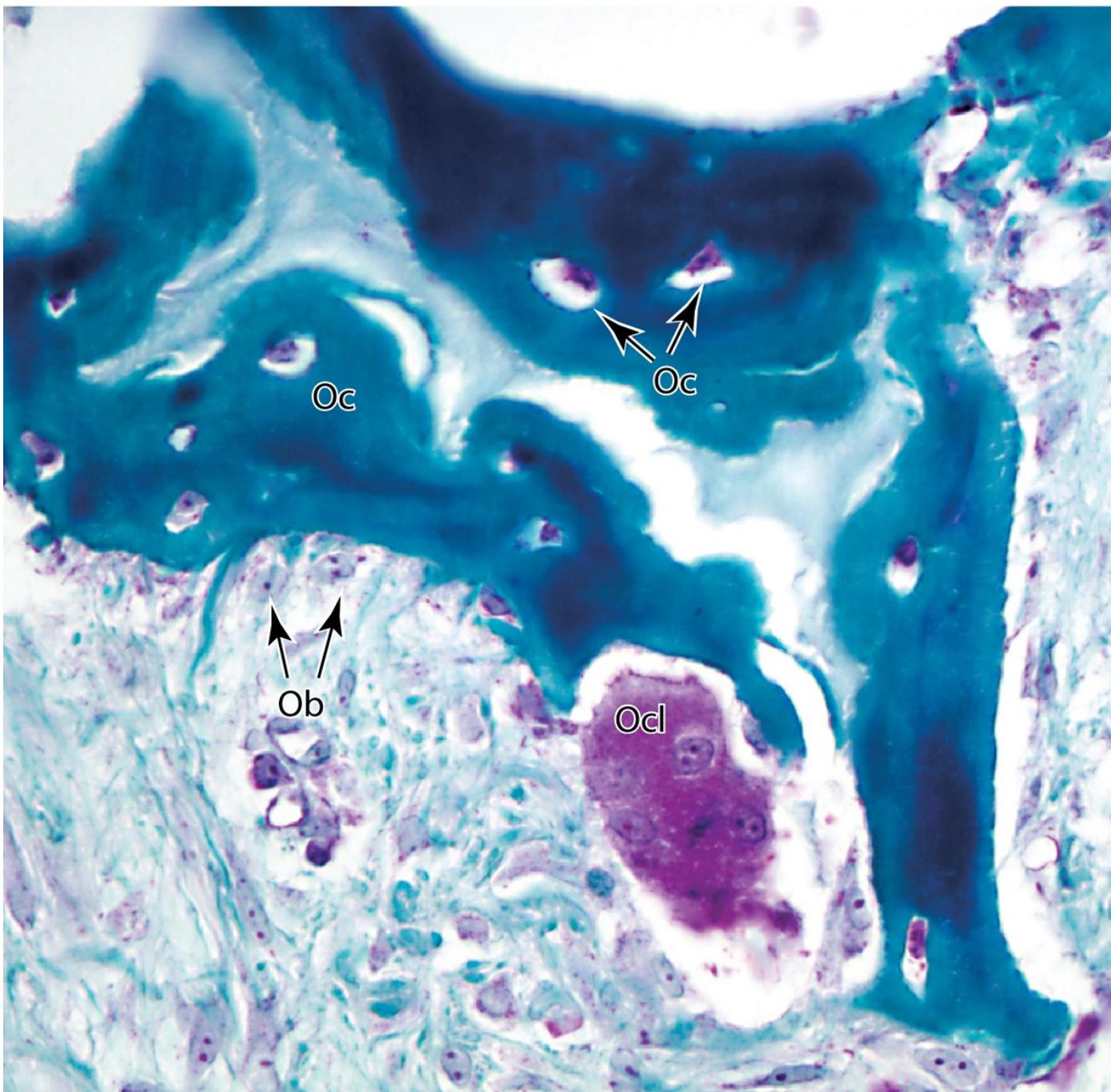


# Bone Cells



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**MEDICAL APPLICATION:** Osteoporosis, frequent in immobilized patients and postmenopausal women, is an imbalance where bone resorption exceeds bone formation. This leads to calcium loss and reduced bone mineral density (BMD).



## Osteoblasts, osteocytes, and an osteoclast (400X Mallory trichrome)

- Bone-forming osteoblasts (**Ob**) differentiate from osteoprogenitor cells in the periosteum and endosteum.
- These cells differentiate further as osteocytes (**Oc**)
- The much less numerous large, multinuclear osteoclasts (**Ocl** reside on bony surfaces

# Bones and Osseous Tissue

- **Bone (osseous tissue):** connective tissue with the matrix hardened by calcium phosphate and other minerals
- **Mineralization or calcification: the hardening process of bone**
  - Continually remodels itself and interacts physiologically with all of the other organ systems of the body
  - Permeated with nerves and blood vessels, which attests to its sensitivity and metabolic activity

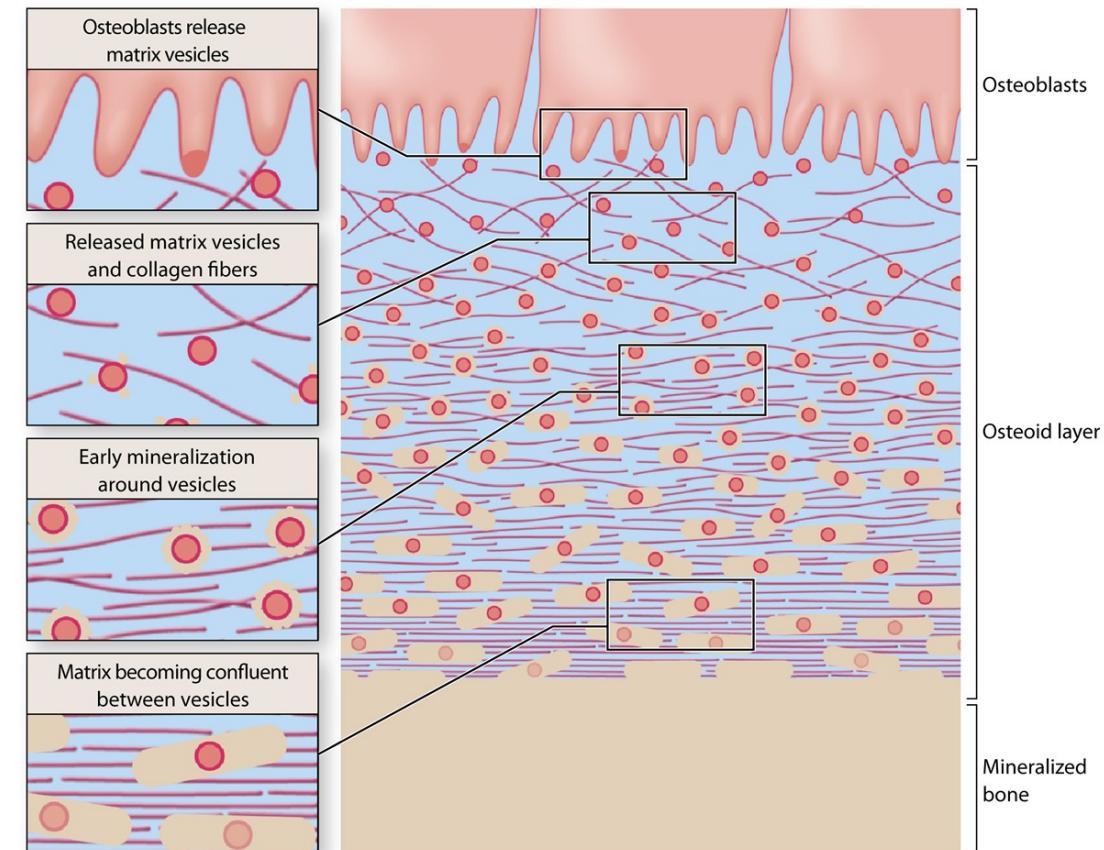
TEM: osteocyte surrounded by matrix, which calcifies around the processes, giving rise to canaliculi (**C**) in the bony matrix.



# Bone matrix contains mainly type I collagen along with other matrix (noncollagenous) proteins.

Osteoblasts secrete type I collagen, several glycoproteins, and proteoglycans.

- Glycoproteins bind  $\text{Ca}^{2+}$  raising its local concentration of these ions.
- Osteoblasts also release very small membrane-enclosed **matrix vesicles**: filled with enzymes that hydrolyze  $\text{PO}_4^-$  ions from various macromolecules,
- Calcified nanocrystals of calcium hydroxyapatite  $[\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2]$  surround the collagen fibers and form bony matrix



# Osteogenesis imperfecta

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.

## Brittle bone disease

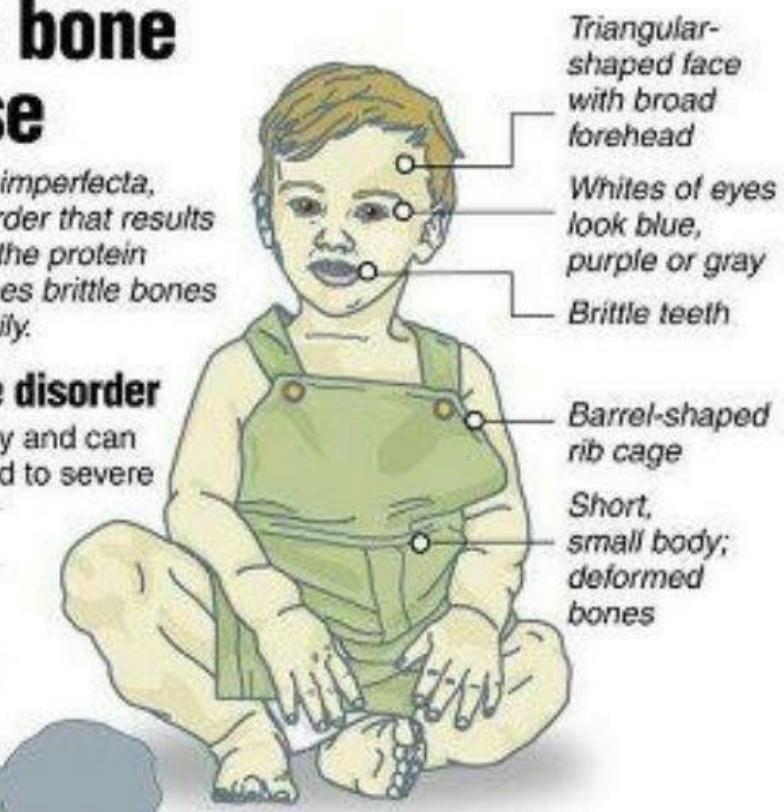
*Osteogenesis imperfecta, a genetic disorder that results from a lack of the protein collagen, causes brittle bones that break easily.*

### Signs of the disorder

Symptoms vary and can range from mild to severe

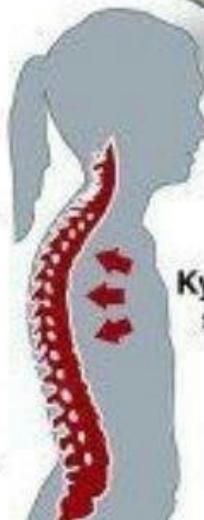
Curved spine

Hearing loss  
(often starts in 20s or 30s)



### Bowing of the back

Can cause spinal curvature called kyphosis, which can lead to a hunchback



Kyphotic spine

### Treatment

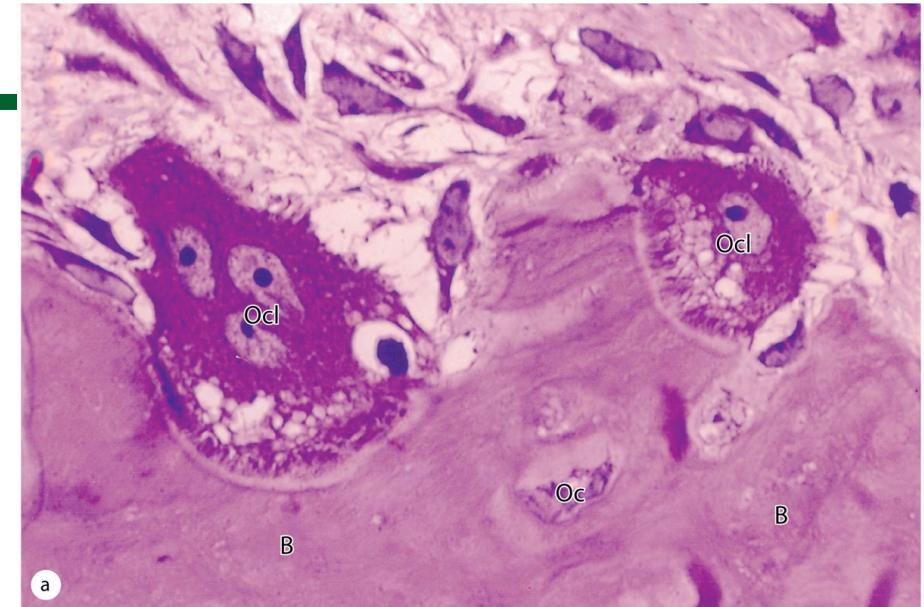
No cure; treatment involves managing symptoms

- Treating broken bones, brittle teeth
- Pain medications, physical therapy, use of assistive tools, such as braces, wheelchairs

# Osteoclasts

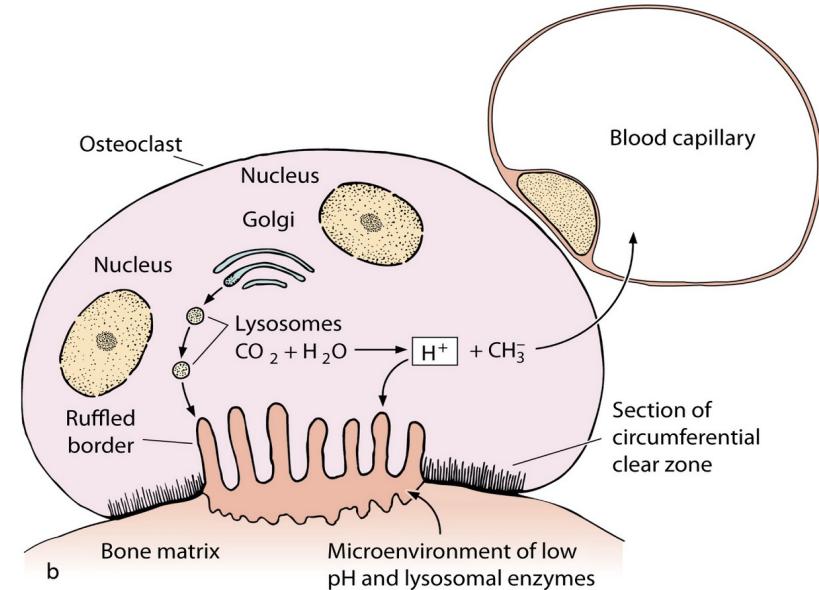
The osteoclast is a large cell with several nuclei derived by the fusion in bone of several blood-derived monocytes.

Osteoclasts (**Ocl**) digest bone matrix (**B**) in resorption cavities on the matrix surface.



## Medical Application

**Osteopetrosis:** dense, heavy bones (“marble bones”). Osteoclasts lack ruffled borders and bone resorption is defective. Most patients with osteopetrosis have mutations in genes for the cells’ proton-ATPase pumps or chloride channels.





A



B

**FIGURE 1:** X-ray of arm prior to (A) and 6 months after (B) bone marrow transplantation. The high bone density, absent medullary

cavity, and abnormal epiphyseal plates of osteopetrosis have largely resolved following bone marrow transplantation.

# An Osteon

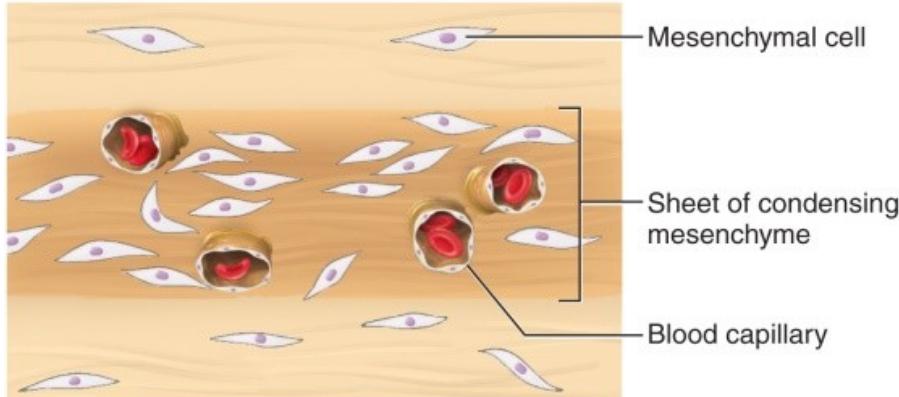
**Osteons (Haversian systems)** constitute most of the compact bone. Shown here is an osteon with four to five concentric lamellae (**L**) surrounding the central canal (**CC**). Osteocytes (**O**) in lacunae are in communication with each other and with the central canal and periphery of the osteon via through hundreds of dendritic processes located within fine canaliculi (**C**). Also shown are the partial, interstitial lamellae (**I**) of an osteon partially eroded when the intact osteon was formed. Ground bone

[http://highered.mheducation.com/sites/0072507470/student\\_view0/chapter\\_6/animation\\_bone\\_growth\\_in\\_width.html](http://highered.mheducation.com/sites/0072507470/student_view0/chapter_6/animation_bone_growth_in_width.html)

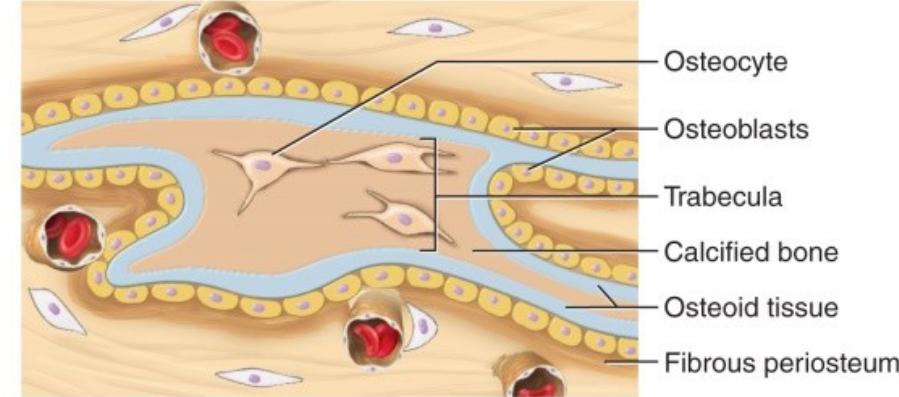


# Intramembranous ossification produces flat bones of skull and clavicle from mesenchymal tissue

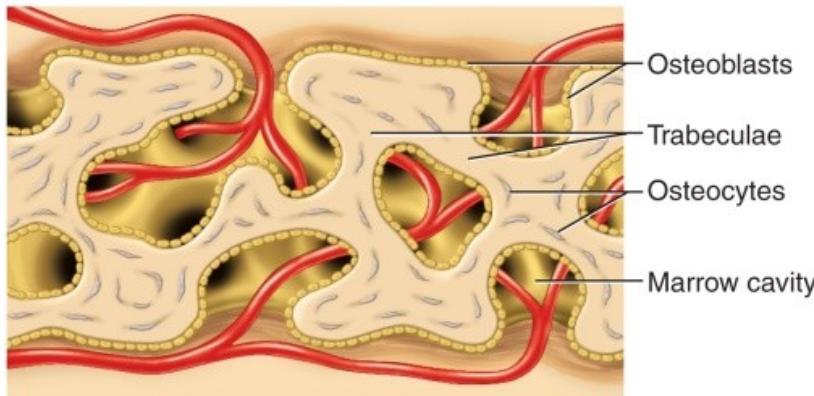
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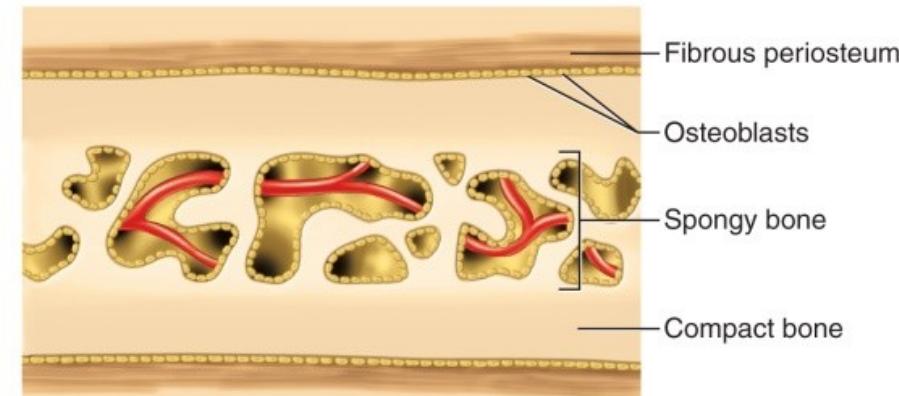
- ① Condensation of mesenchyme into soft sheet permeated with blood capillaries



- ② Deposition of osteoid tissue by osteoblasts on mesenchymal surface; entrapment of first osteocytes; formation of periosteum

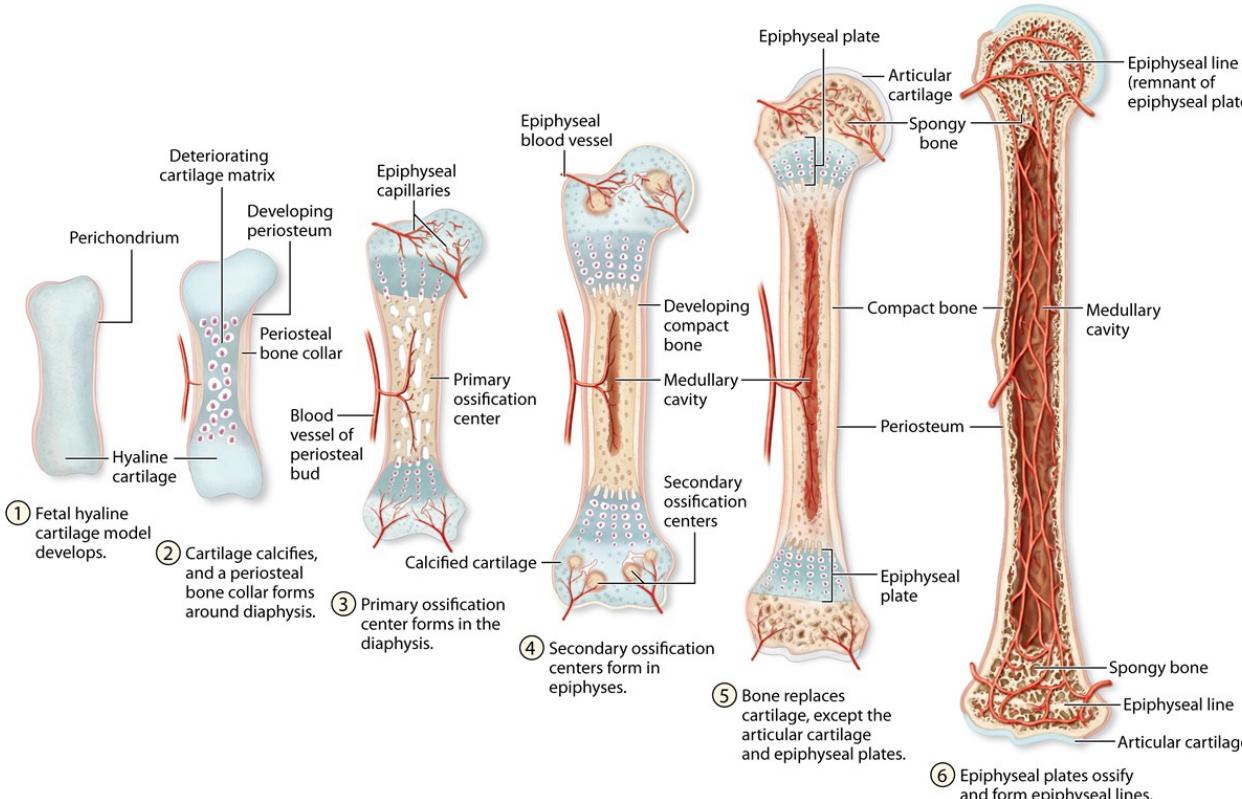


- ③ Honeycomb of bony trabeculae formed by continued mineral deposition; creation of spongy bone



- ④ Surface bone filled in by bone deposition, converting spongy bone to compact bone. Persistence of spongy bone in the middle layer.

# Osteogenesis of long bones by endochondral ossification from hyaline cartilage



(1) Bone collar develops beneath the perichondrium  
(2) Invasion of the degenerating cartilage by capillaries and osteoprogenitor cells to produce a **primary ossification center**  
(3) Osteoid is deposited, calcified into woven bone, and is remodeled as compact bone.

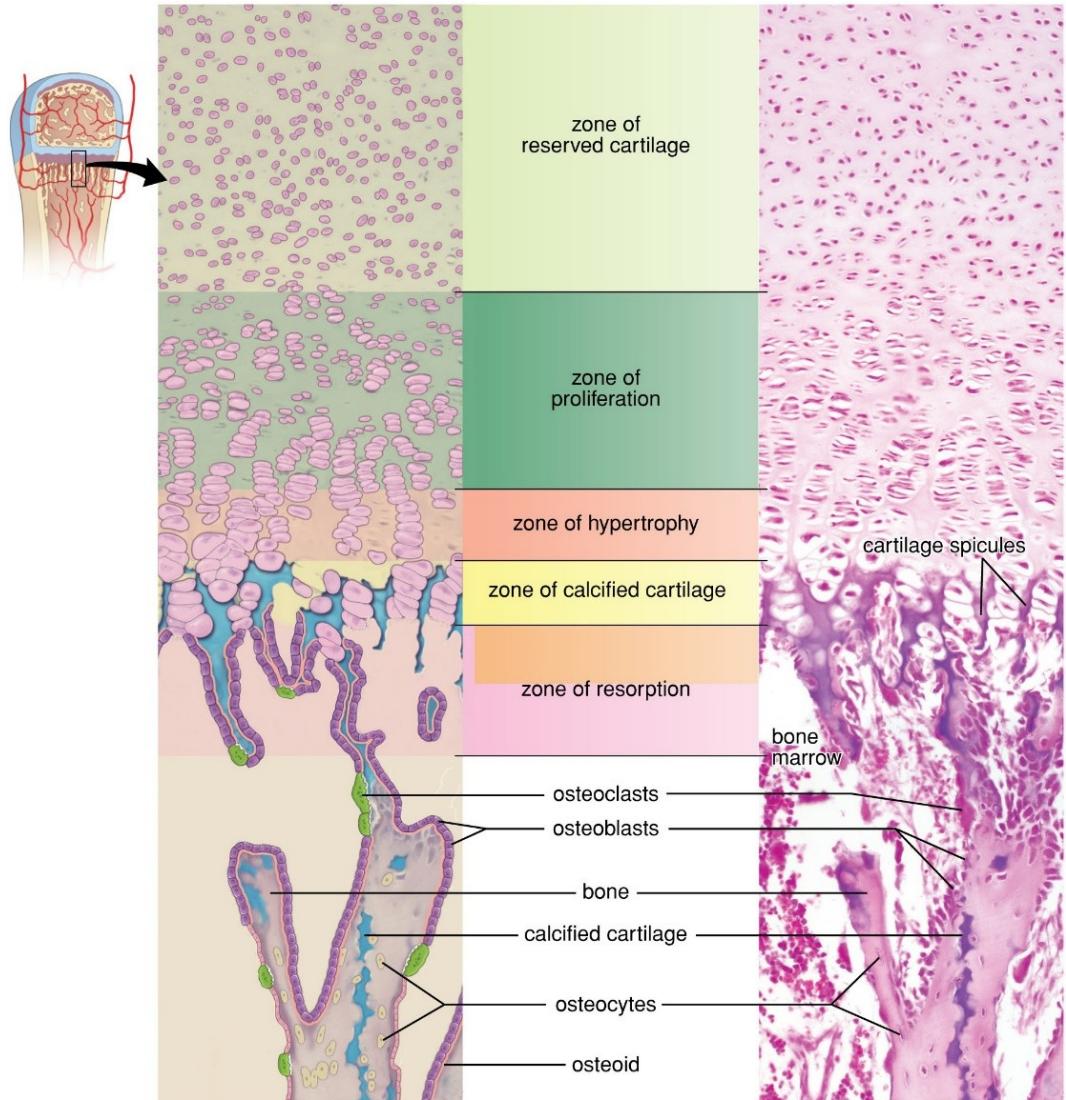
(4) **Secondary ossification centers** develop by a similar process in the epiphyses. Ossification centers gradually come to be separated only by the **epiphyseal plate**.

(5) Continued bone elongation. The two ossification centers do not merge until the epiphyseal plate disappears  
(6) When full stature is achieved, osteoblasts of the periosteum provide for growth in the bone's diameter.

Development of Bone:

<https://www.youtube.com/watch?v=exXgZap0AvL0&nohtml5=false>

# Zones in the Epiphyseal Cartilage



**Zone of reserve cartilage** exhibits no cellular proliferation or active matrix production.

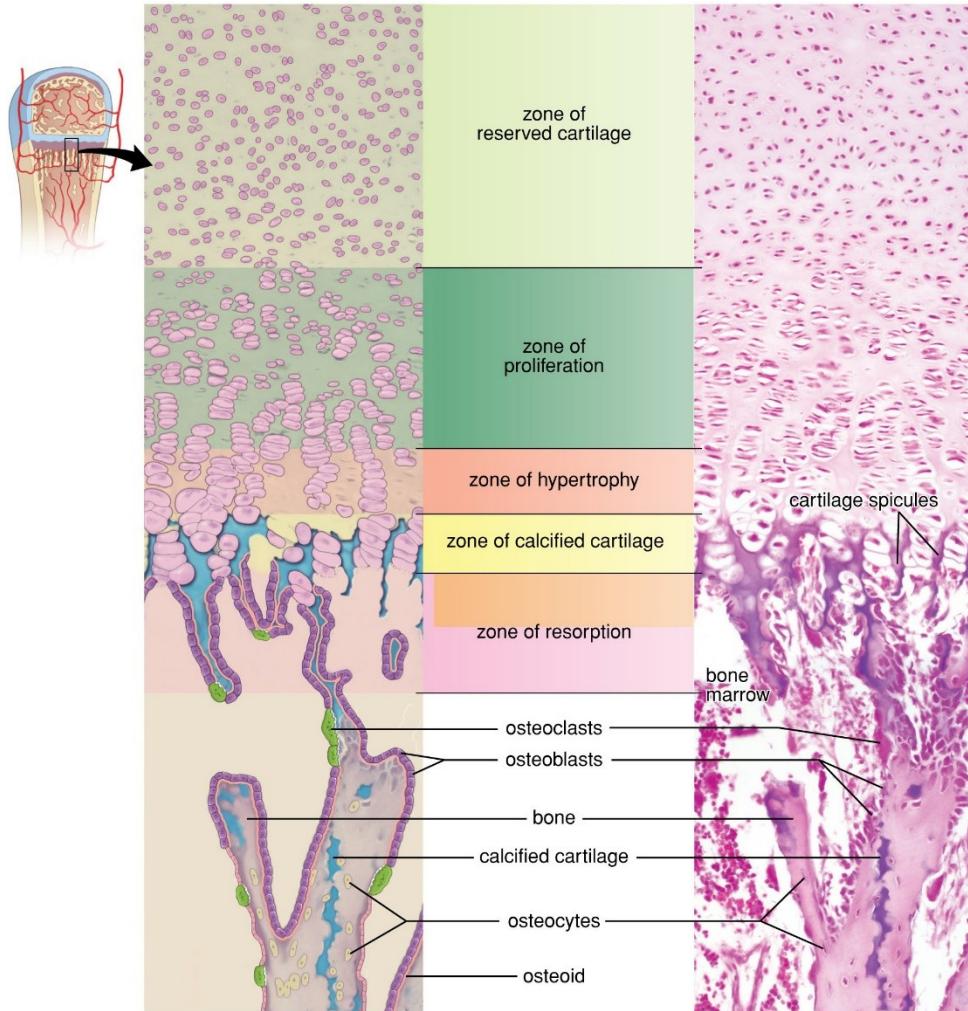
**Zone of proliferation** is adjacent to the zone of reserve cartilage in the direction of the diaphysis. In this zone, the cartilage cells undergo division and organize into distinct columns.

**Zone of hypertrophy** contains greatly enlarged (hypertrophic) cartilage cells.

**Zone of calcified cartilage**, the hypertrophied cells begin to degenerate and the cartilage matrix becomes calcified. The calcified cartilage then serves as an initial scaffold for deposition of new bone.

**Zone of resorption** is the zone nearest the diaphysis. The calcified cartilage here is in direct contact with the connective tissue of the marrow cavity.

# Zones in the Epiphyseal Cartilage



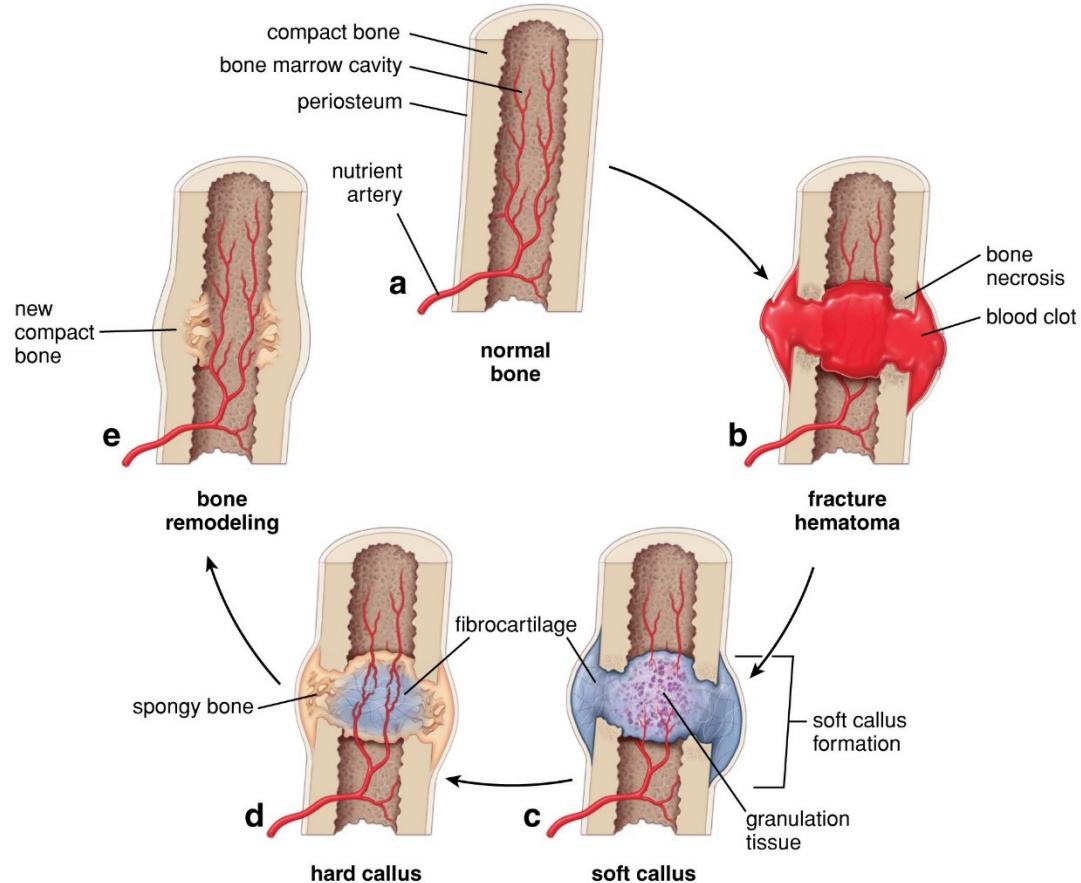
## MEDICAL APPLICATION

Calcium deficiency in children can lead to rickets, a disease in which the bone matrix does not calcify normally and the epiphyseal plate can become distorted by the normal strains of body weight and muscular activity. Ossification processes are consequently impeded

[http://highered.mheducation.com/sites/0072507470/student\\_view0/chapter\\_6/animation\\_osteoporosis.html](http://highered.mheducation.com/sites/0072507470/student_view0/chapter_6/animation_osteoporosis.html)

# Bone fractures and the stages of the bone healing process

## MEDICAL APPLICATION



Bone fractures are repaired by fibrocartilage formation and osteogenic activity of the major bone cells.

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

# **Chapter 9 Nerve Tissue & The Nervous System**

## **Objectives**

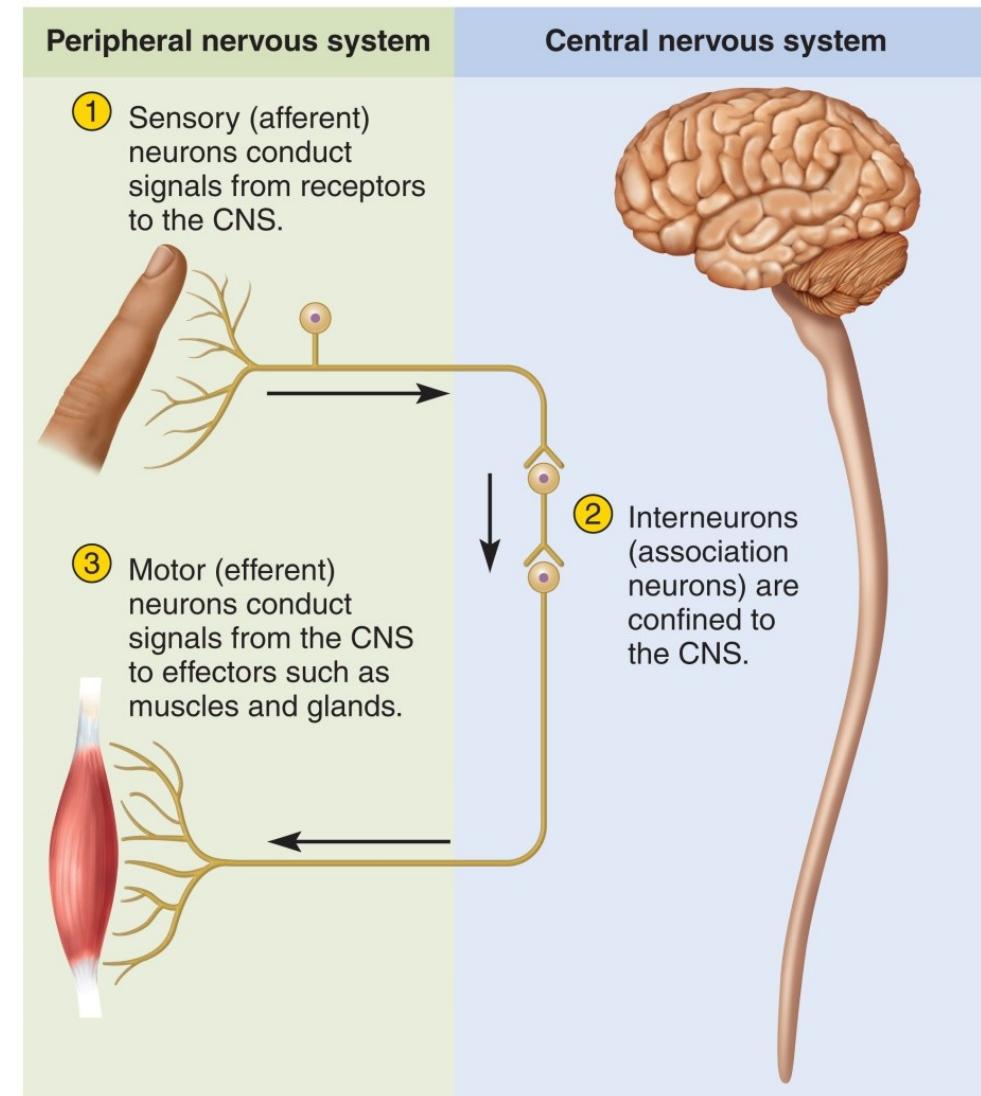
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- 1. Overview of Nervous System**
- 2. Neurons**
- 3. Nerves**
- 4. Glia**
- 5. Meninges**

# Cells and Tissues of the Nervous System: Functions and Divisions

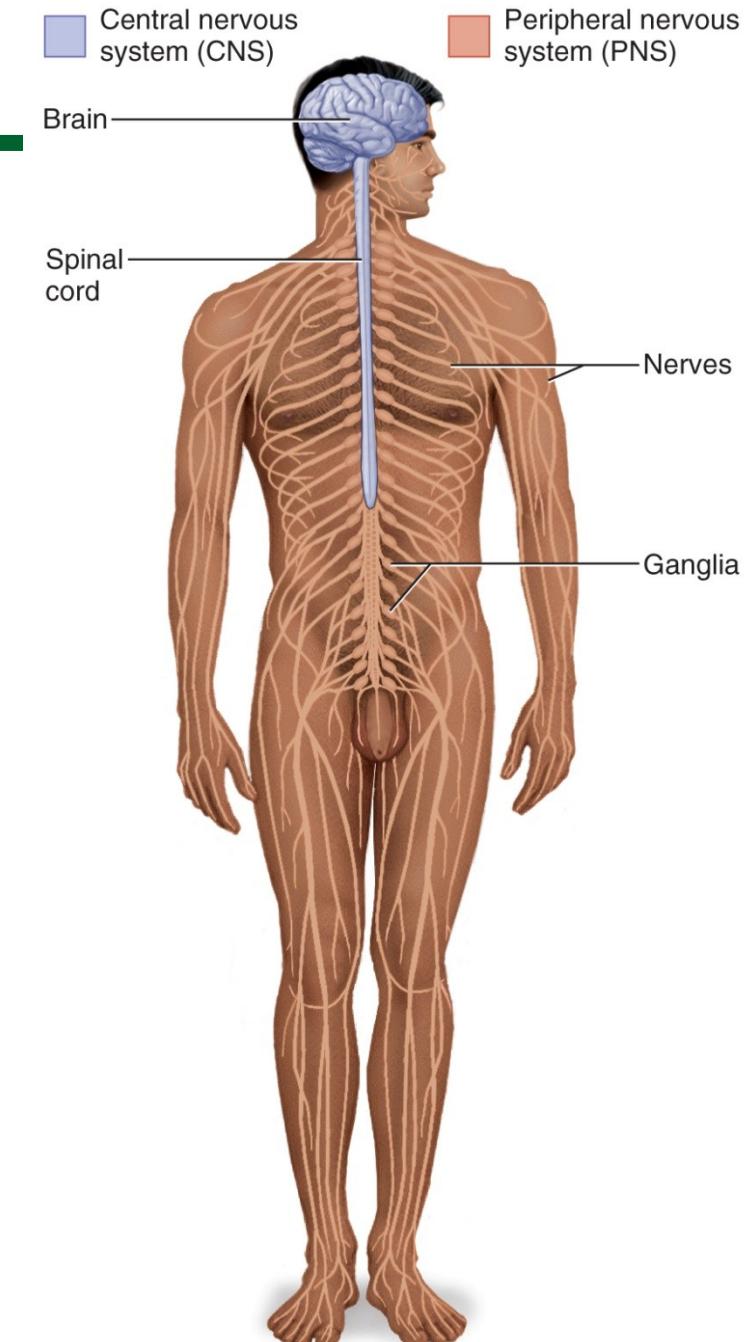
- **Sensory function:** Respond to stimuli
- **Integrative function:** Receive and process information
- **Motor function:** Issue outgoing signals

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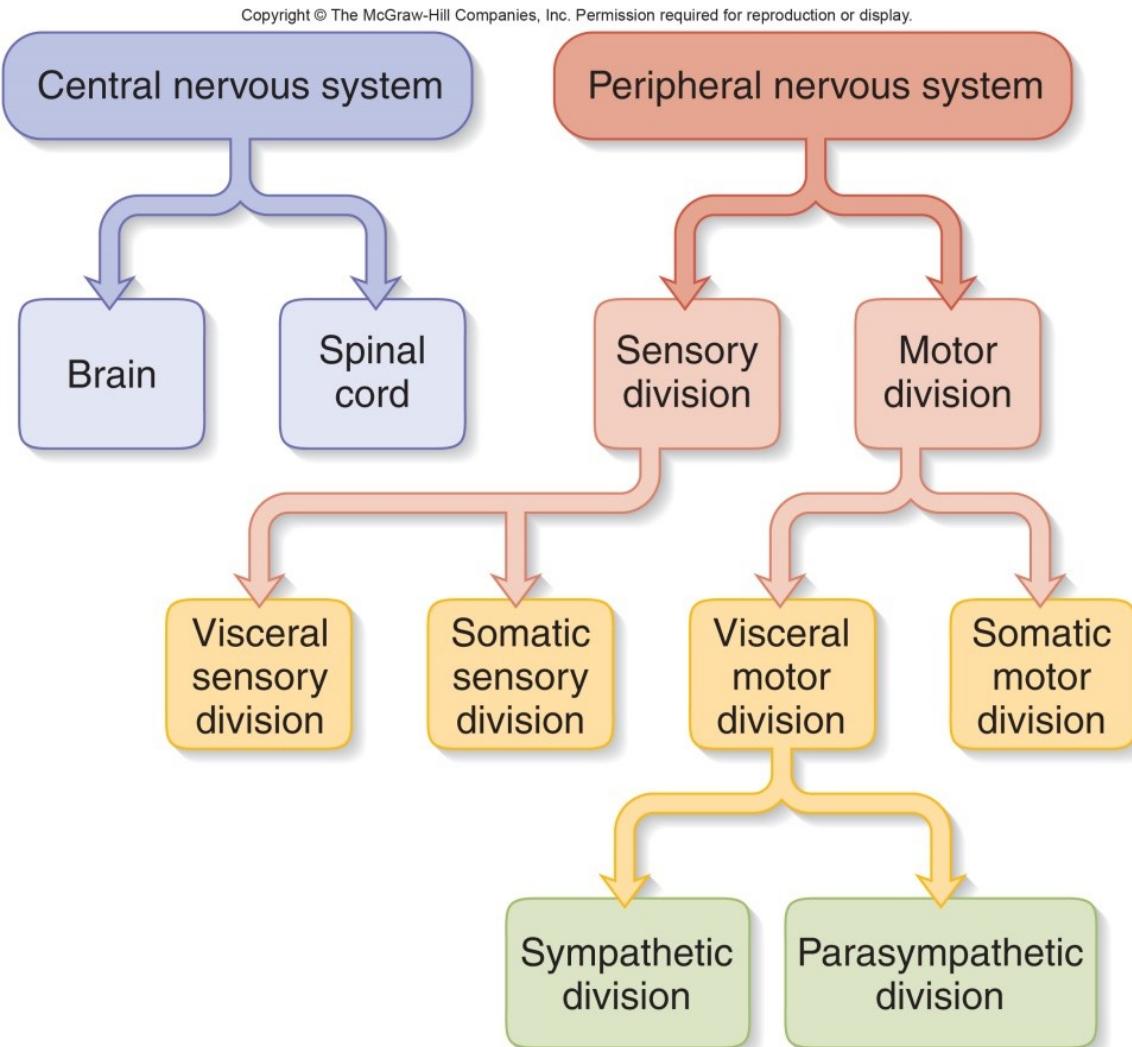
# Two main anatomical subdivisions

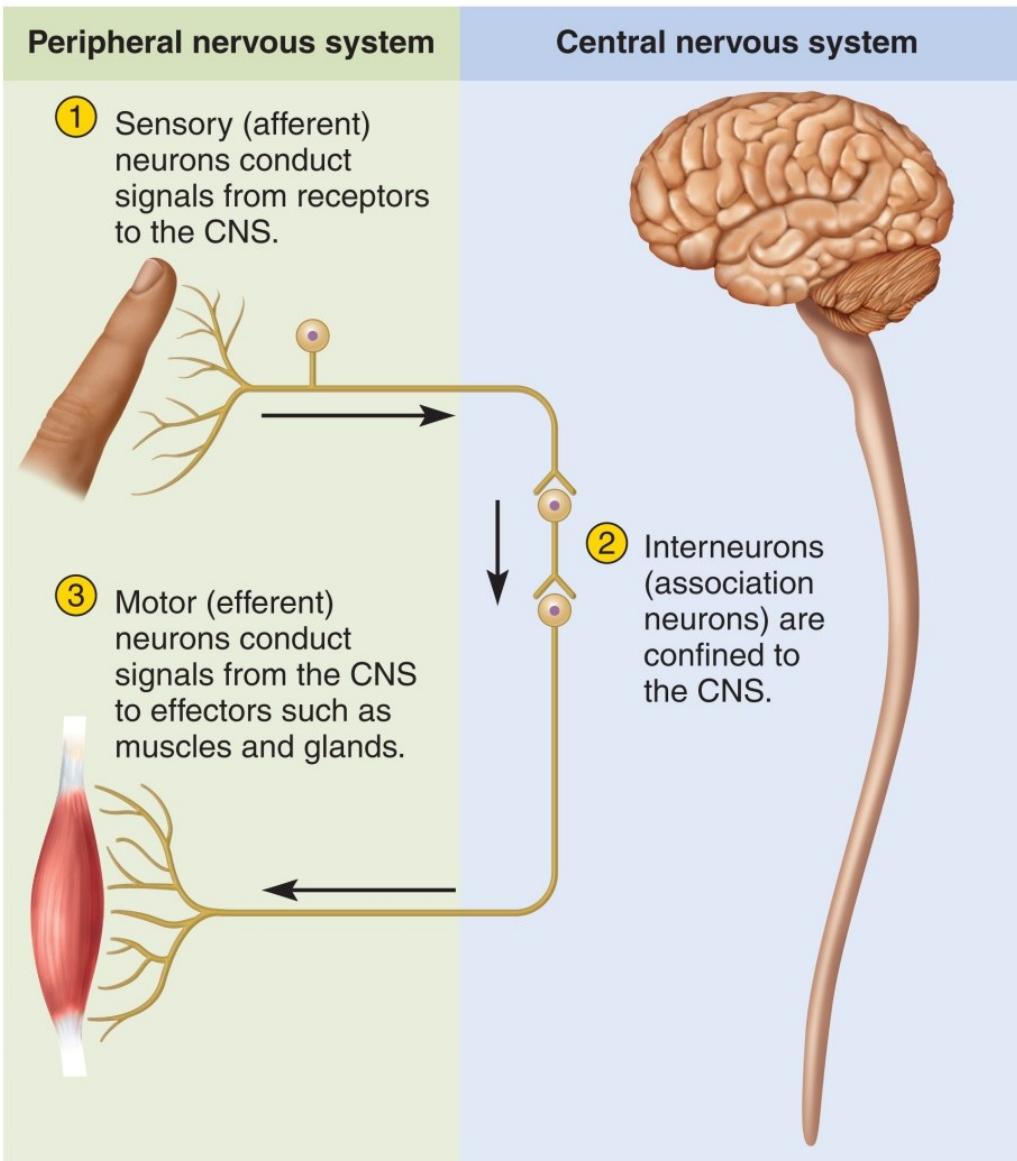
- **Central nervous system (CNS)**
  - Brain and spinal cord
  - Protected by cranium and vertebral column
  - Carries out integrative functions
- **Peripheral nervous system (PNS)**
  - Nerves leading to and from CNS
  - Provides pathway of signal input and output
  - Connects CNS to body's sense organs, muscles, and glands
  - Carries out sensory and motor functions



# Overview of the Nervous System

- Peripheral nervous system has two major functional subdivisions
  - Sensory (afferent) division: carries sensory signals from various receptors to the CNS
    - Informs the CNS of stimuli within or around the body
  - Somatic sensory division: carries signals from receptors in the skin, muscles, bones, and joints
  - Visceral (Autonomic) sensory division: carries signals from the viscera of the thoracic and abdominal cavities
    - Heart, lungs, stomach, and urinary bladder





## >> MEDICAL APPLICATION

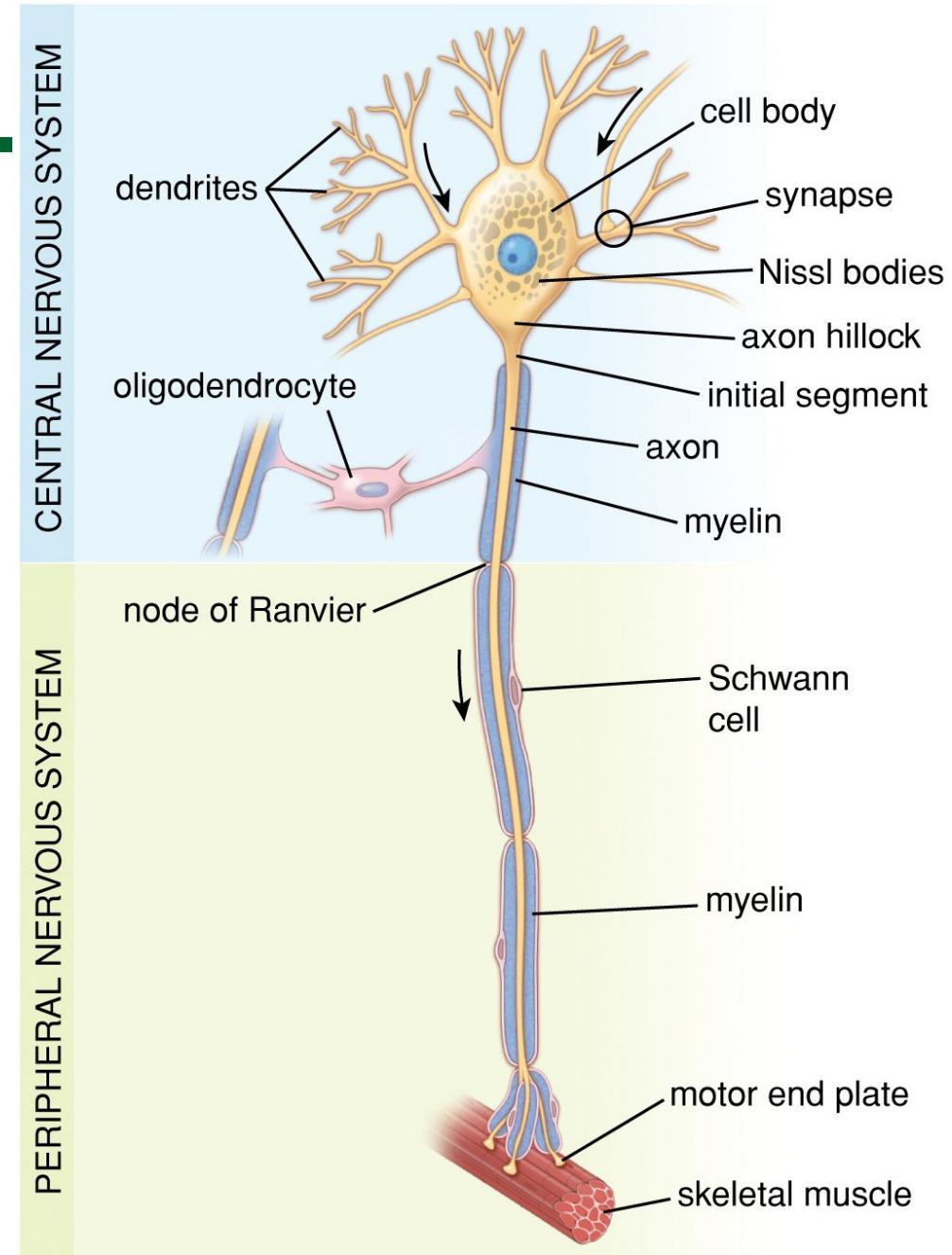
Parkinson disease is characterized by muscle tremors, reduced activity of the facial muscles, loss of balance, and postural stiffness.

It is caused by gradual loss by apoptosis of dopamine-producing neurons whose cell bodies lie within the nuclei of the CNS substantia nigra. Parkinson disease is treated with L-dopa (L-3,4-dihydroxyphenylalanine), a precursor of dopamine which augments the declining production of this neurotransmitter.

<http://abcnews.go.com/Health/video/dr-oliver-sacks-real-life-awakenings-29088197>

# Neuron structure

- **Neurosoma (soma or cell body):** control center of neuron
- **Neurofibrils:** Cytoskeleton of protein bundles
- **Dendrites:** thick arms arising from soma, receives signals from other neurons
- **Axon (nerve fiber):** output pathway for signals to other cells not more than one, sometimes none
- **Synaptic knob:** bulb at terminus of axon
- **Axon hillock:** conical mound on soma side gives rise to axon
- **Axonal transport:** process of carrying substances to and from soma

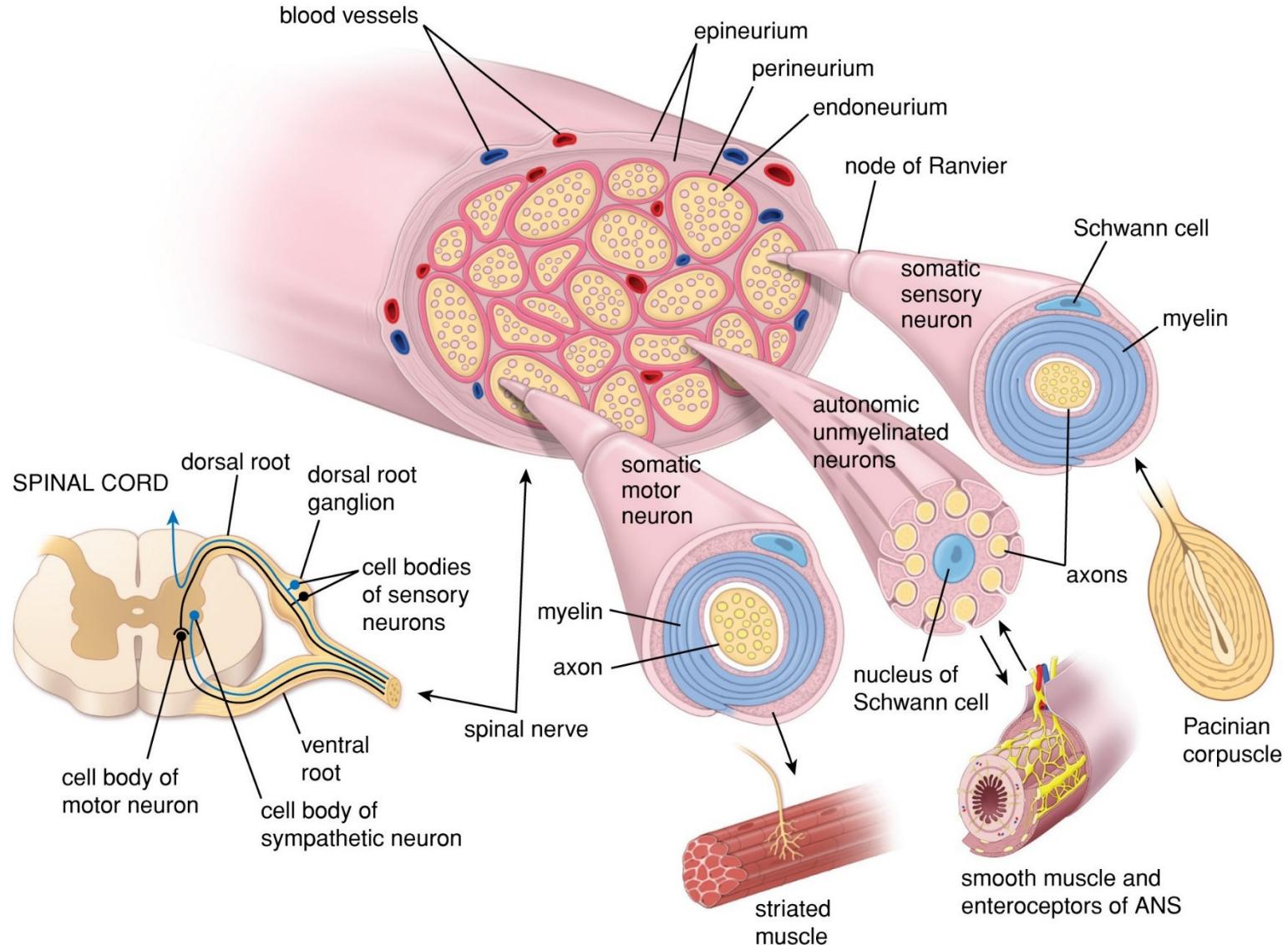


CENTRAL NERVOUS SYSTEM

PERIPHERAL NERVOUS SYSTEM

# Nerve: Bundle of nerve fibers and connective tissue wrappings with internal blood vessels

- **Endoneurium:** thin loose connective tissue covering nerve fiber
- **Perineurium:** epithelium-like cells, wrapped bundles of nerve cells, **fascicles**
- **Epineurium:** fibrous sleeve wrapping several fascicles
- **Ganglion:** Swelling, usually near end of nerve that contains cell bodies of peripheral neurons



# Review of the Synapse

**Presynaptic neuron:** sends signal

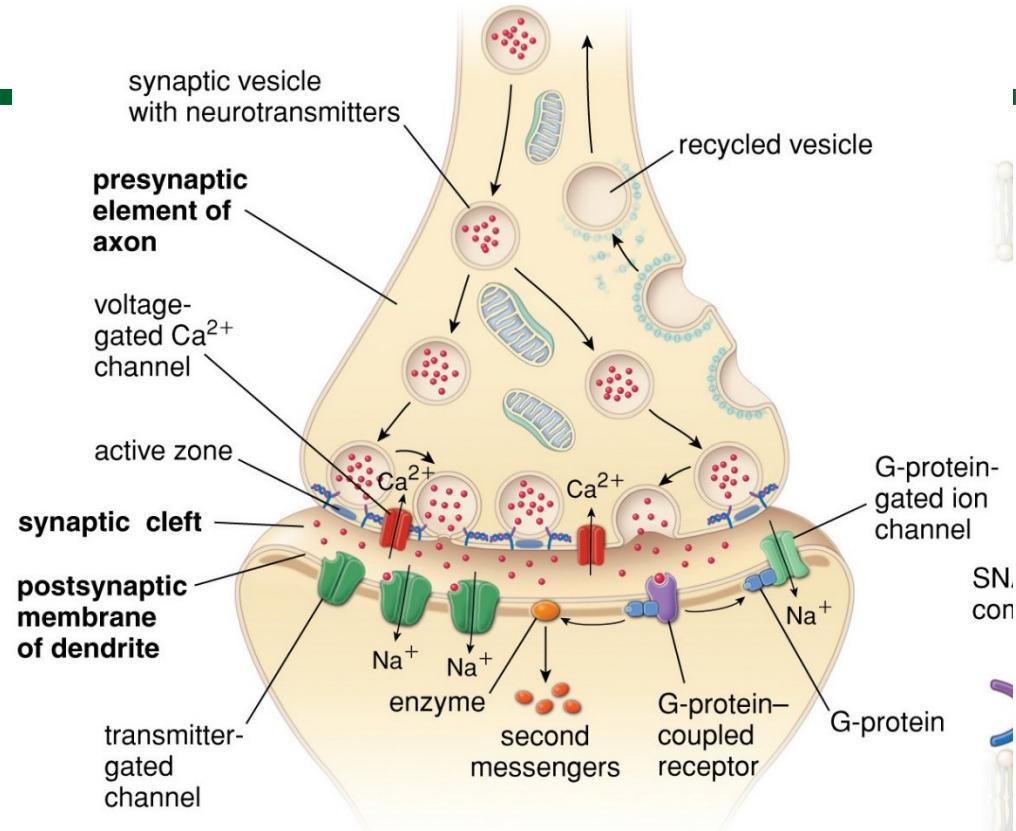
**Postsynaptic neuron:** stimulated neuron

**Synaptic cleft:** gap between two neurons

**Synaptic knob:** Dilated tip of presynaptic neuron

**Synaptic vesicles:** spherical vesicles with

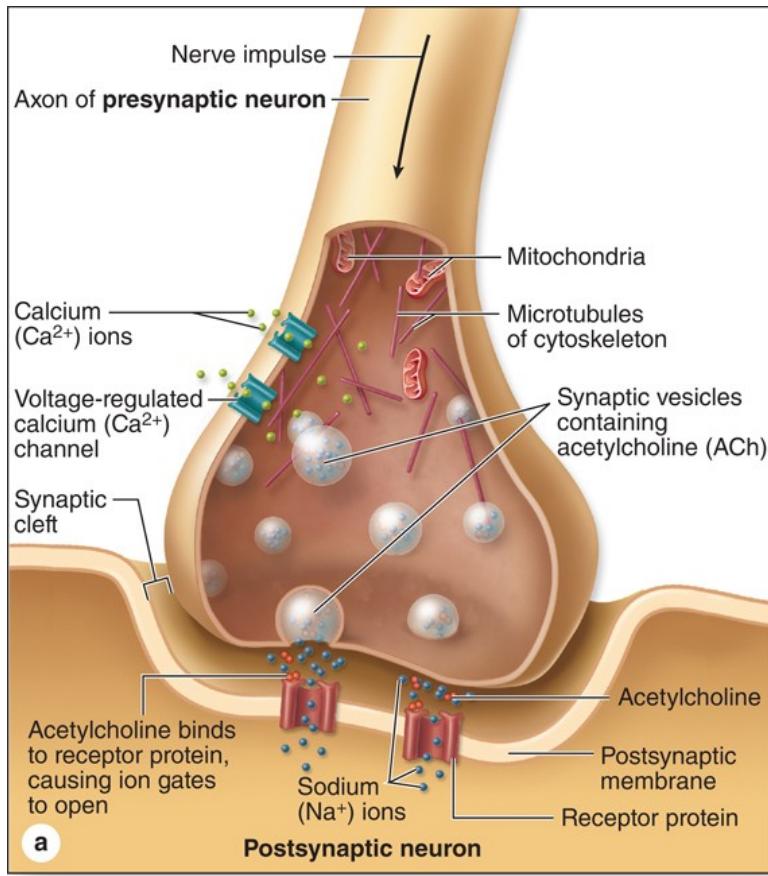
**Neurotransmitters:** chemical signals, undergo exocytosis with arrival of nerve signal



## >> MEDICAL APPLICATION

Most local anesthetics are low-molecular-weight molecules that bind to the voltage-gated sodium channels of the axolemma, interfering with sodium ion influx and, consequently, inhibiting the action potential responsible for the nerve impulse.

[http://highered.mheducation.com/sites/0072495855/student\\_view0/chapter14/animation\\_transmission\\_across\\_a\\_synapse.html](http://highered.mheducation.com/sites/0072495855/student_view0/chapter14/animation_transmission_across_a_synapse.html)



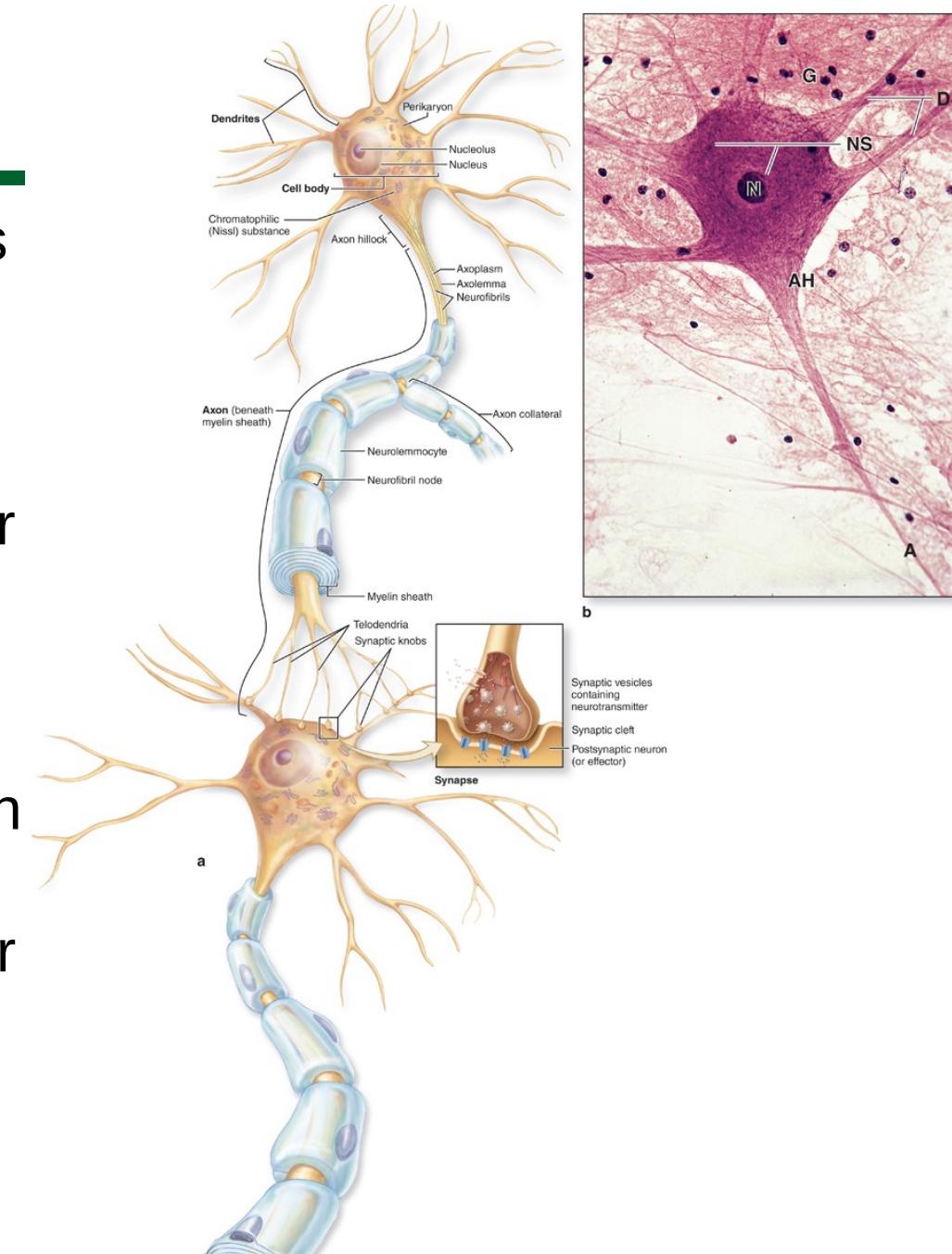
**>> MEDICAL APPLICATION**  
 Alzheimer's disease, a common type of dementia in the elderly, affects both neuronal perikarya and synapses within the cerebrum. Functional defects are due to neurofibrillary tangles, which are accumulations of tau protein associated with microtubules of the neuronal perikaryon and axon hillock regions, and neuritic plaques, which are dense aggregates of  $\beta$ -amyloid protein that form around the outside of these neuronal regions.

## >> MEDICAL APPLICATION

Levels of neurotransmitters in the synaptic cleft and available for binding postsynaptic receptors are normally regulated by several local mechanisms. Selective serotonin reuptake inhibitors (SSRIs), a widely used class of drugs for treatment of depression and anxiety disorders, were designed to augment levels of this neurotransmitter at the postsynaptic membrane of serotonergic CNS synapses by specifically inhibiting its reuptake at the presynaptic membrane.

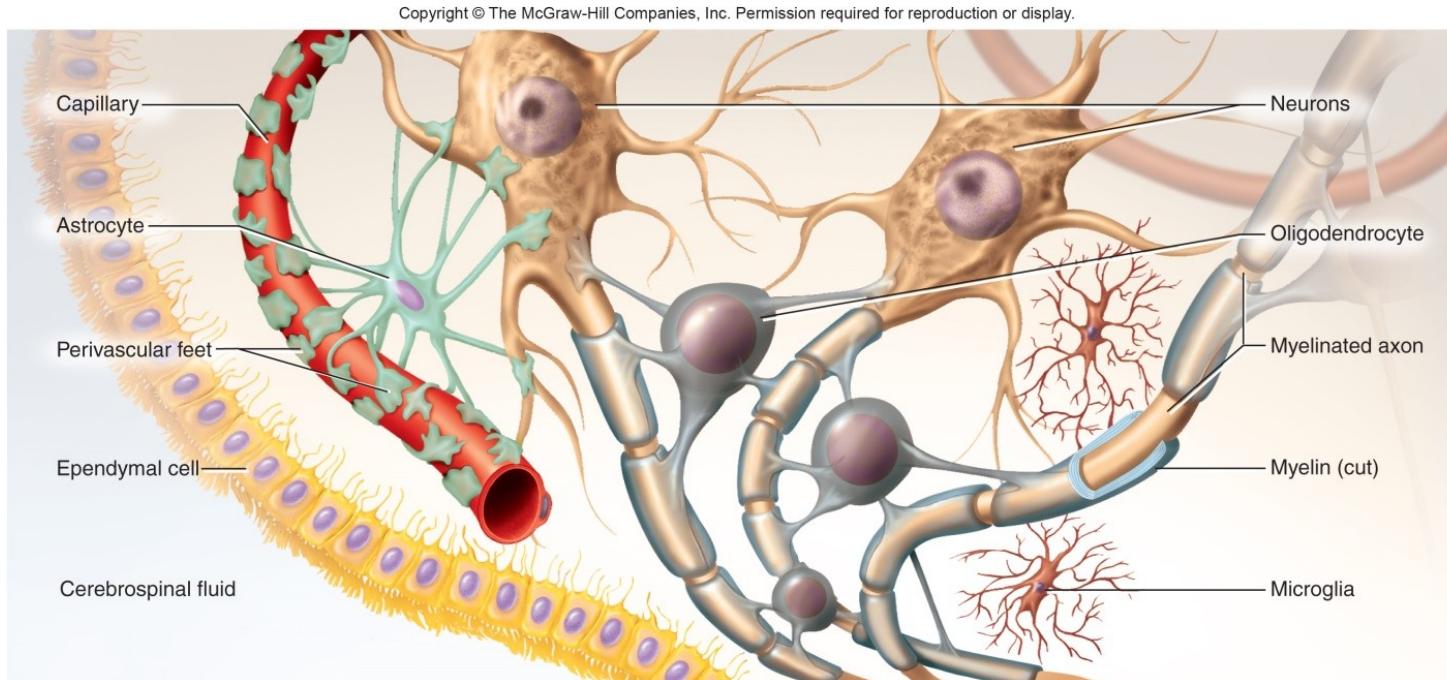
# Supportive Cells (Neuroglia)

- Neuroglia outnumber the neurons by as much as 50 to 1
- Neuroglia or glial cells
  - Support and protect the neurons
  - Bind neurons together and form framework for nervous tissue
  - In fetus, guide migrating neurons to their destination
  - If mature neuron is not in synaptic contact with another neuron it is covered by glial cells
    - Prevents neurons from touching each other
    - Gives precision to conduction pathways



# Types of Neuroglial Cells: CNS

- **Oligodendrocytes** form myelin sheaths in CNS: each wraps around many nerve fibers
- **Ependymal** cells line cavities and produce CSF
- **Microglia** (macrophages) formed from monocytes in areas of infection, trauma or stroke
- **Astrocytes:** contribute to BBB and regulate composition of brain tissue fluid



# Types of Neuroglial Cells

## PNS

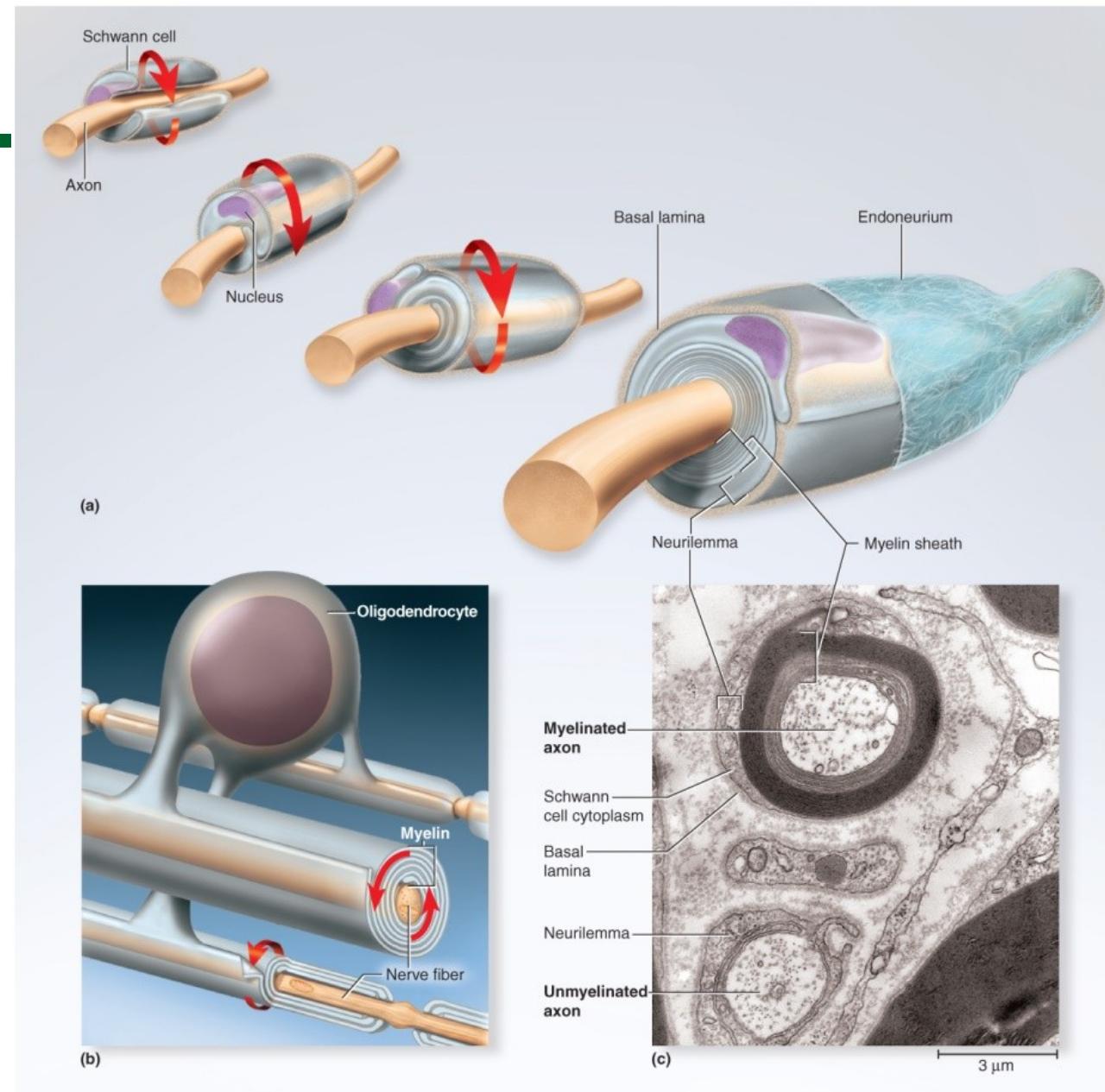
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**Schwann** cells myelinate fibers of PNS  
**Satellite** cells thought to have same function as astrocytes

### »» MEDICAL APPLICATION

In multiple sclerosis (MS) myelin sheaths are damaged by an autoimmune mechanism. T lymphocytes and microglia degrade myelin.

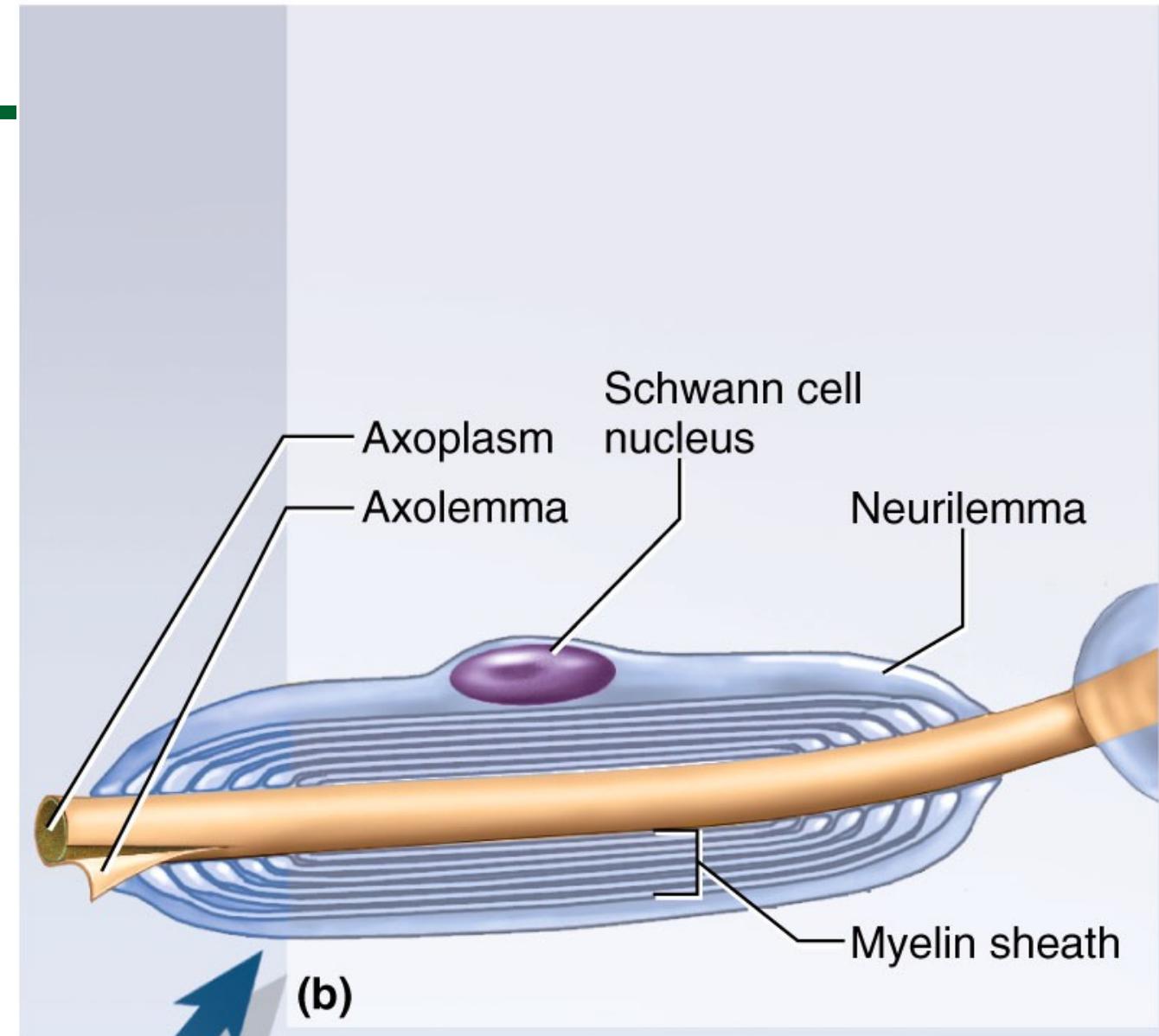
Introduction to Multiple Sclerosis - Medical Animation  
Short: <https://www.youtube.com/watch?v=VloDr8ugbql>



c: © The McGraw-Hill Companies, Inc./Dr. Dennis Emery, Dept. of Zoology and Genetics, Iowa State University, photographer

# The Myelin Sheath

- **Myelin sheath characteristics**
  - Layers wrapped around fiber, insulating it
    - like electrical tape around wire
  - Requires many cells to myelinate one nerve
  - **Nodes of Ranvier**
    - gaps between myelinated segments
  - Myelin covered segments termed **internodes**



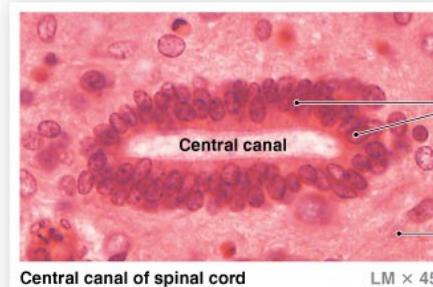
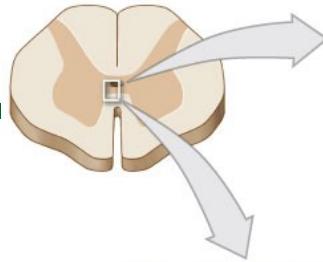
# Myelination

**White matter:** Regions of CNS with many myelinated nerves

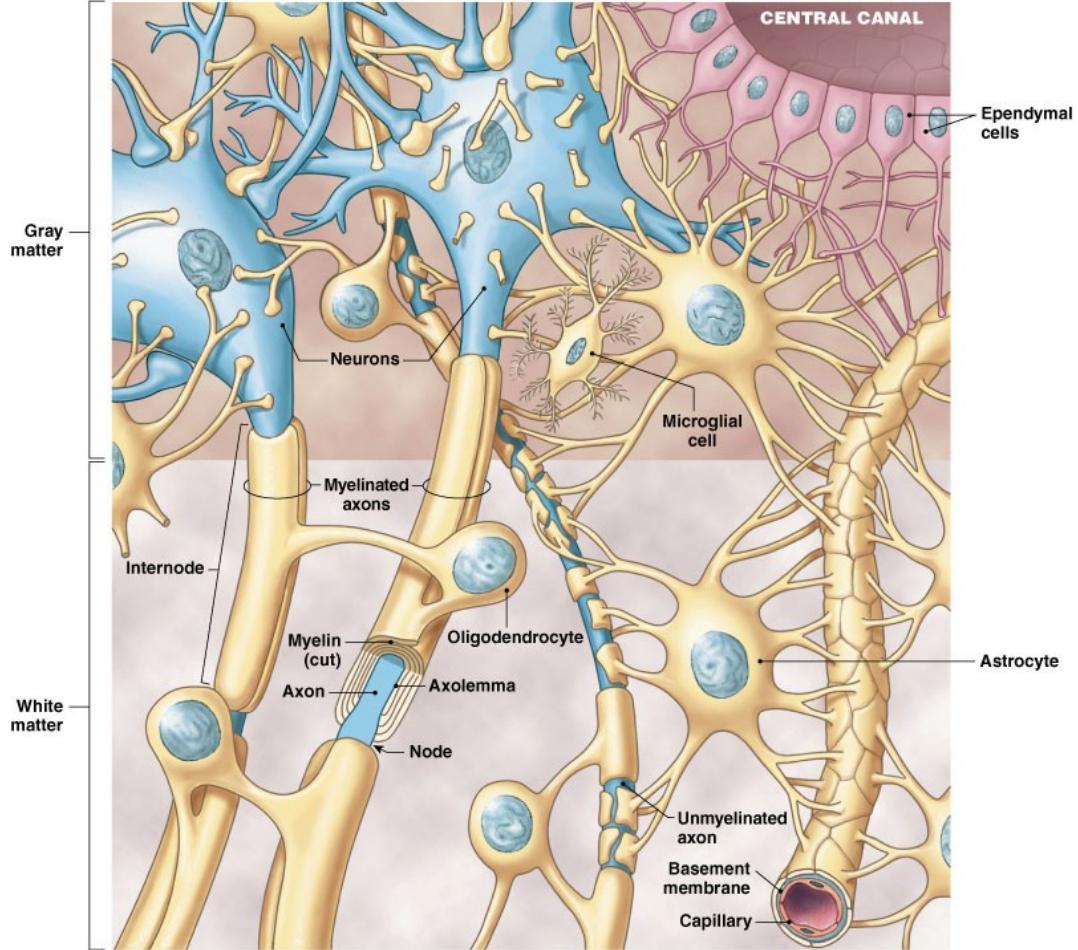
- Bundles of nerve fibers called tracts, each with similar origin, destination, and function
- Myelination giving white color

**Gray matter:** Unmyelinated areas of CNS where neurosomas, dendrites, and synapses are located

- Little myelin, so duller color
- Information-processing part of CNS



a Light micrograph showing the ependymal lining of the central canal of the spinal cord



b A diagrammatic view of neural tissue in the CNS, showing relationships between neuroglia and neurons

# Meninges: Protective Membranes

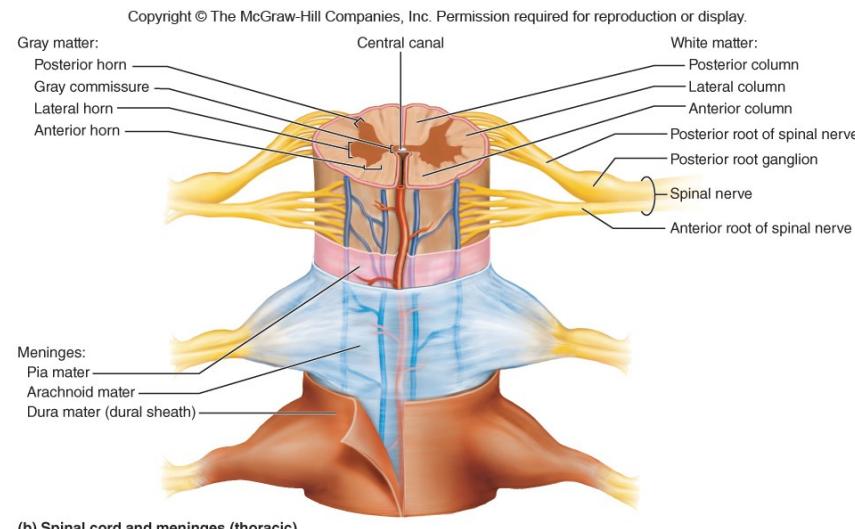
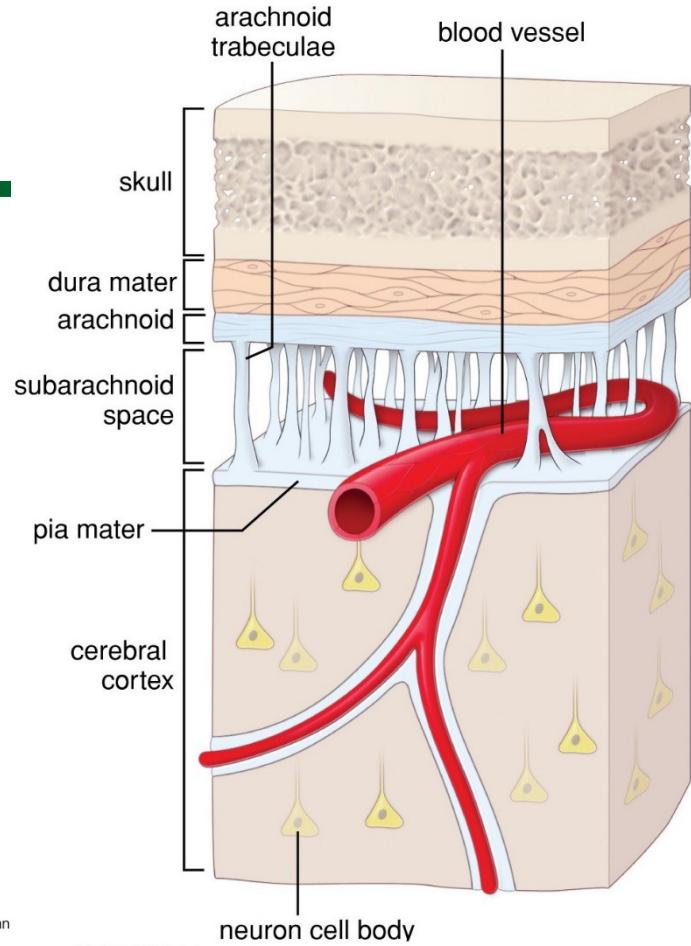
**Meninges:** Fibrous membranes between nervous tissue and bone

**Dura mater:** Tough collagenous outermost membrane

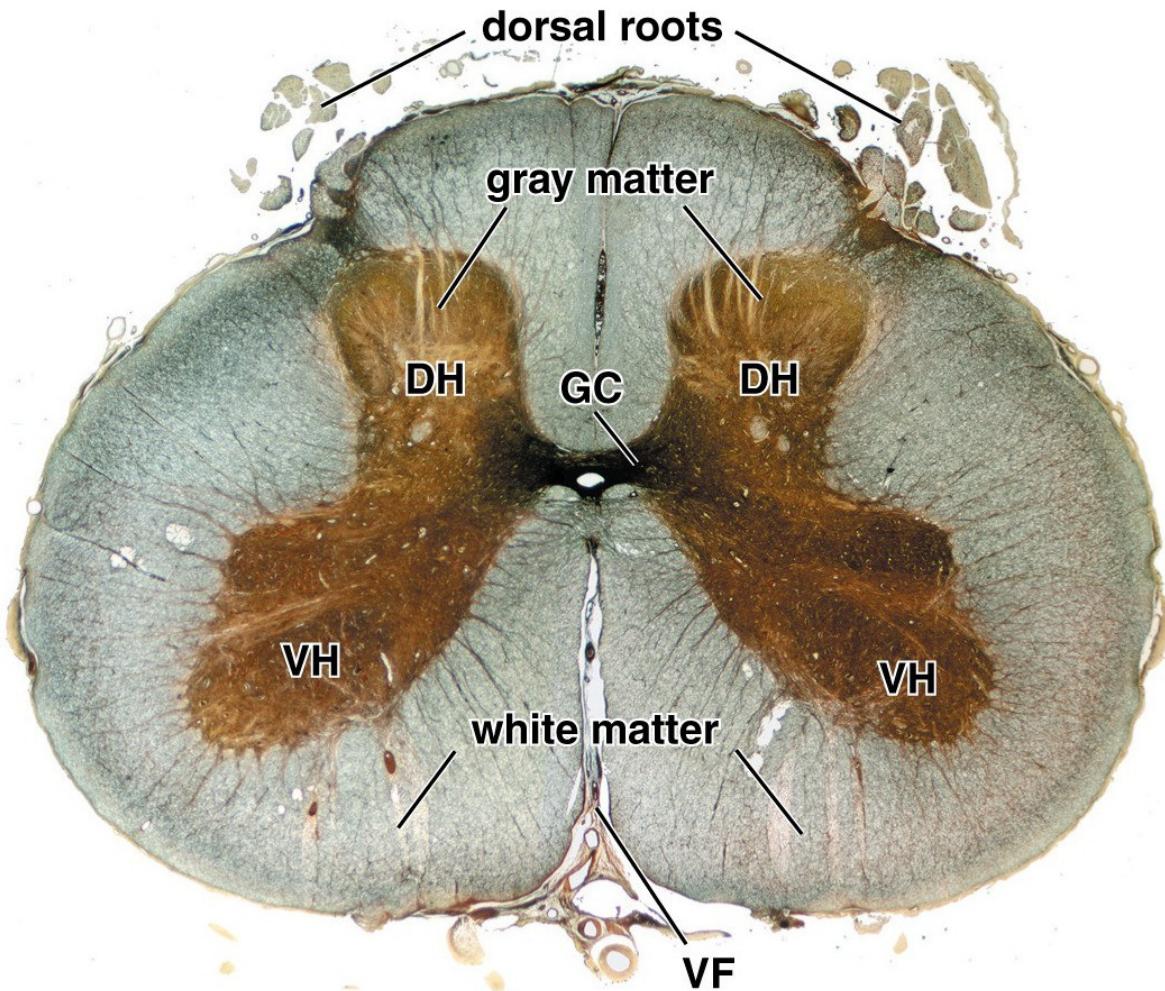
Separated from bone by epidural space, anesthetics often used here

**Arachnoid mater:** Delicate middle layer, Loose webby appearance

**Pia mater:** Innermost thin layer of connective tissue, follows contours of brain and spinal cord



# Cross-section of the human spinal cord



The spinal cord is organized into an outer part, the white matter, and an inner part, the gray matter that contains nerve cell bodies and associated nerve fibers.

The gray matter of the spinal cord appears roughly in the form of a butterfly. The anterior and posterior prongs are referred to as ventral horns (VH) and dorsal horns (DH), respectively. They are connected by the gray commissure (GC).

The white matter contains nerve fibers that form ascending and descending tracts. The outer surface of the spinal cord is surrounded by the pia mater.

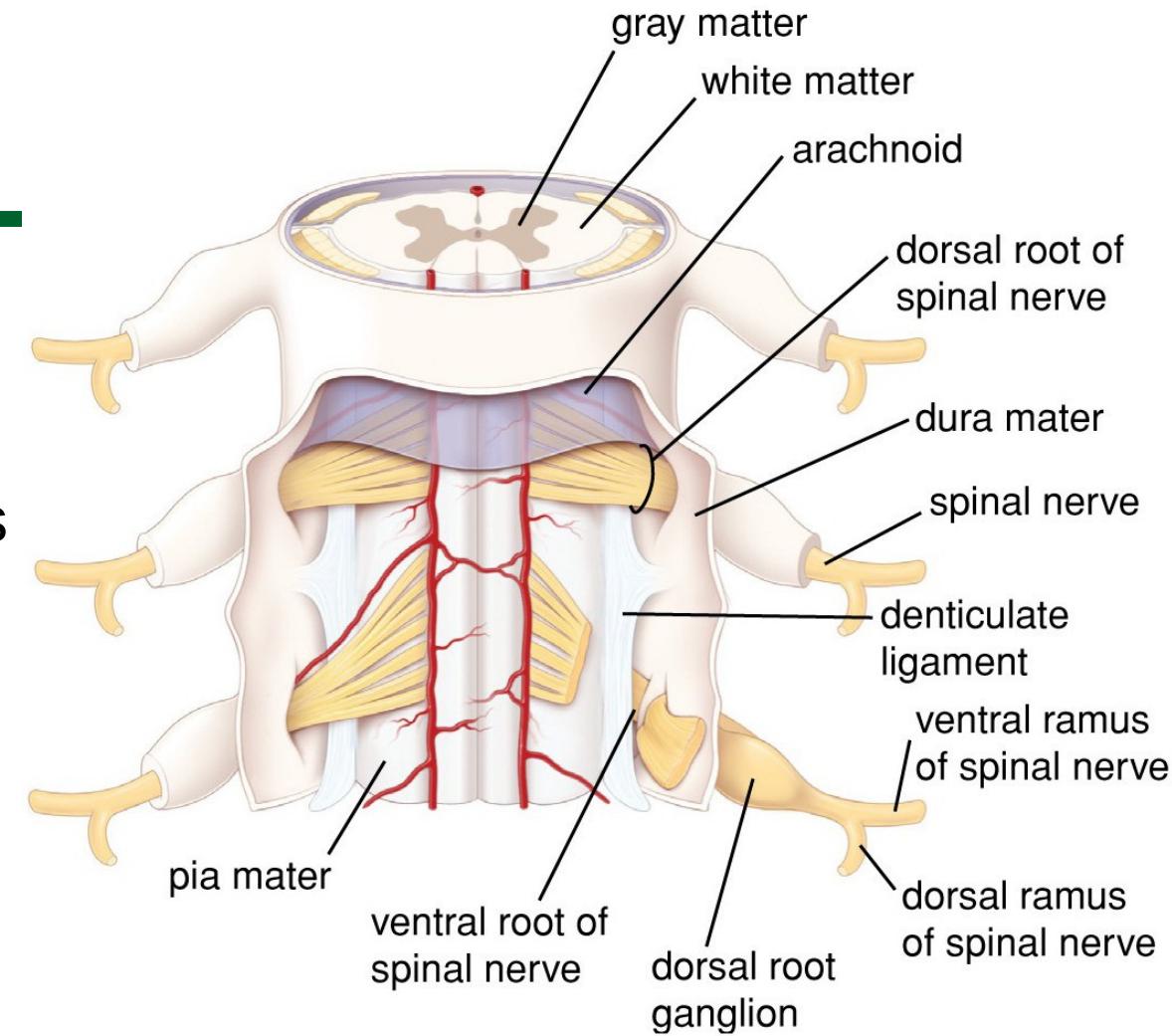
# Cord cross section

**Posterior (dorsal) horns:** sensory reception

**Anterior (ventral) horns:** motor neurons give motor commands through axons/spinal nerve

**Lateral horn:** neurons of sympathetic nervous system

**Gray commissure:** connects right and left halves of cord. May have **central canal** filled with spinal fluid or closed



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» **MEDICAL APPLICATION** regeneration of peripheral nerves is functionally efficient only when the fibers and the columns of Schwann cells are directed properly. In a mixed nerve, if regenerating sensory fibers grow into columns formerly occupied by motor fibers connected to motor end plates, the function of the muscle will not be reestablished.

# Flow of information through the spinal cord

Somatic efferent (motor) system: one neuron conducts the impulses from the CNS to the effector (skeletal muscle).

Visceral (autonomic) efferent system: chain of two neurons conducts the impulses, a presynaptic neuron located within the CNS and a postsynaptic neuron located in the paravertebral or prevertebral ganglia.

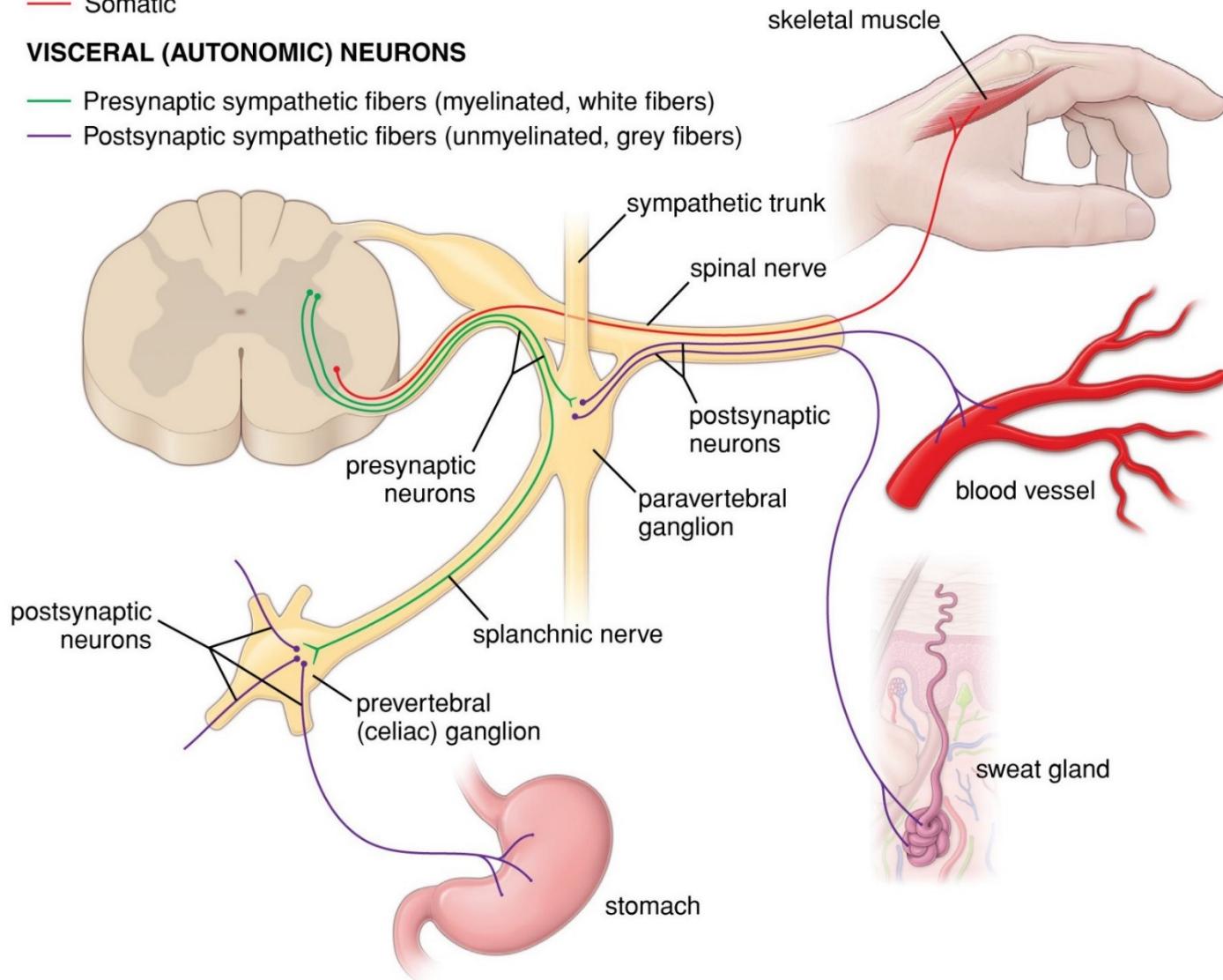
## EFFERENT (MOTOR) NEURONS

— Somatic

## VISCERAL (AUTONOMIC) NEURONS

— Presynaptic sympathetic fibers (myelinated, white fibers)

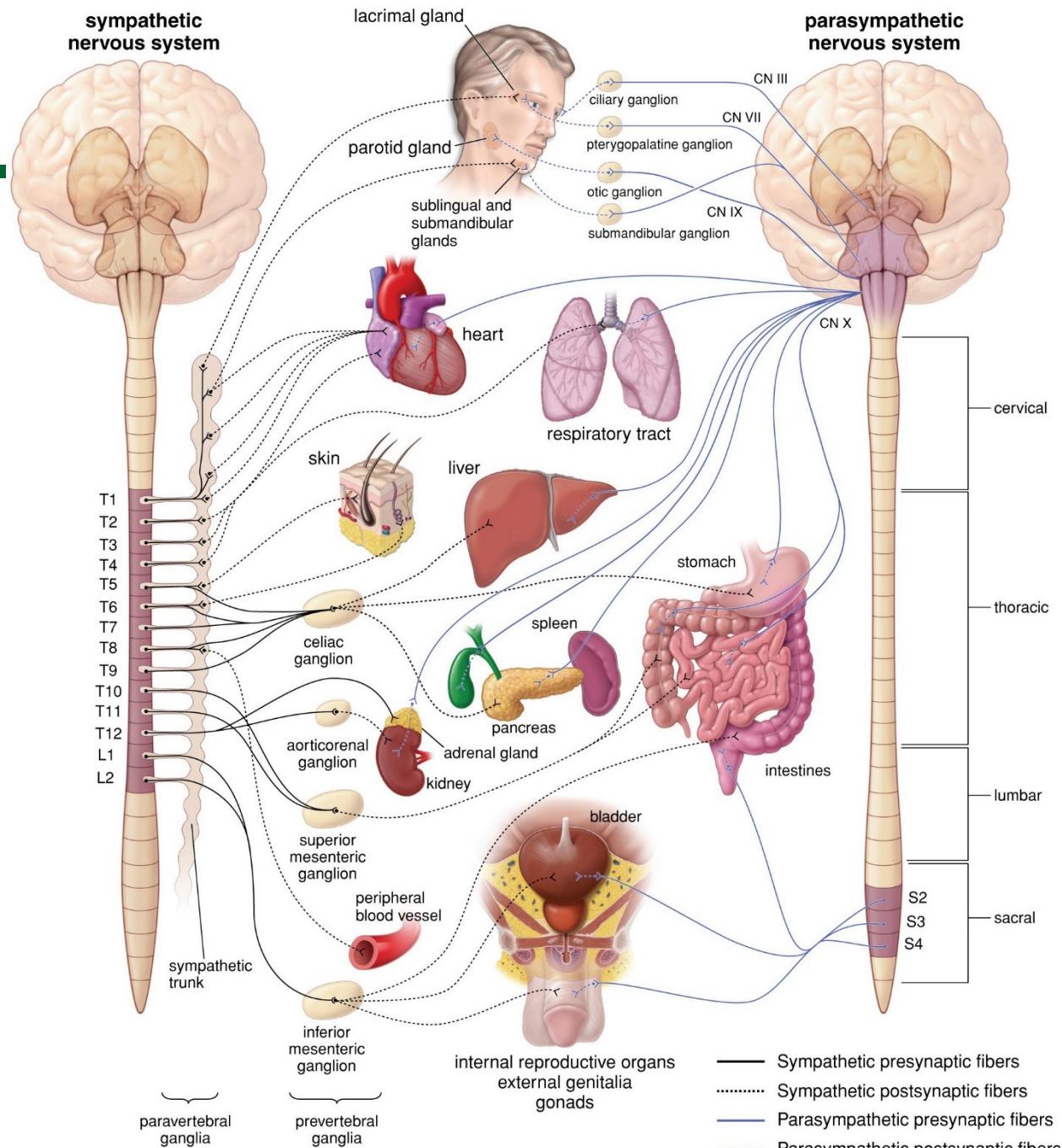
— Postsynaptic sympathetic fibers (unmyelinated, grey fibers)



# Autonomic Nervous System

The sympathetic outflow is shown on the left, the parasympathetic on the right.

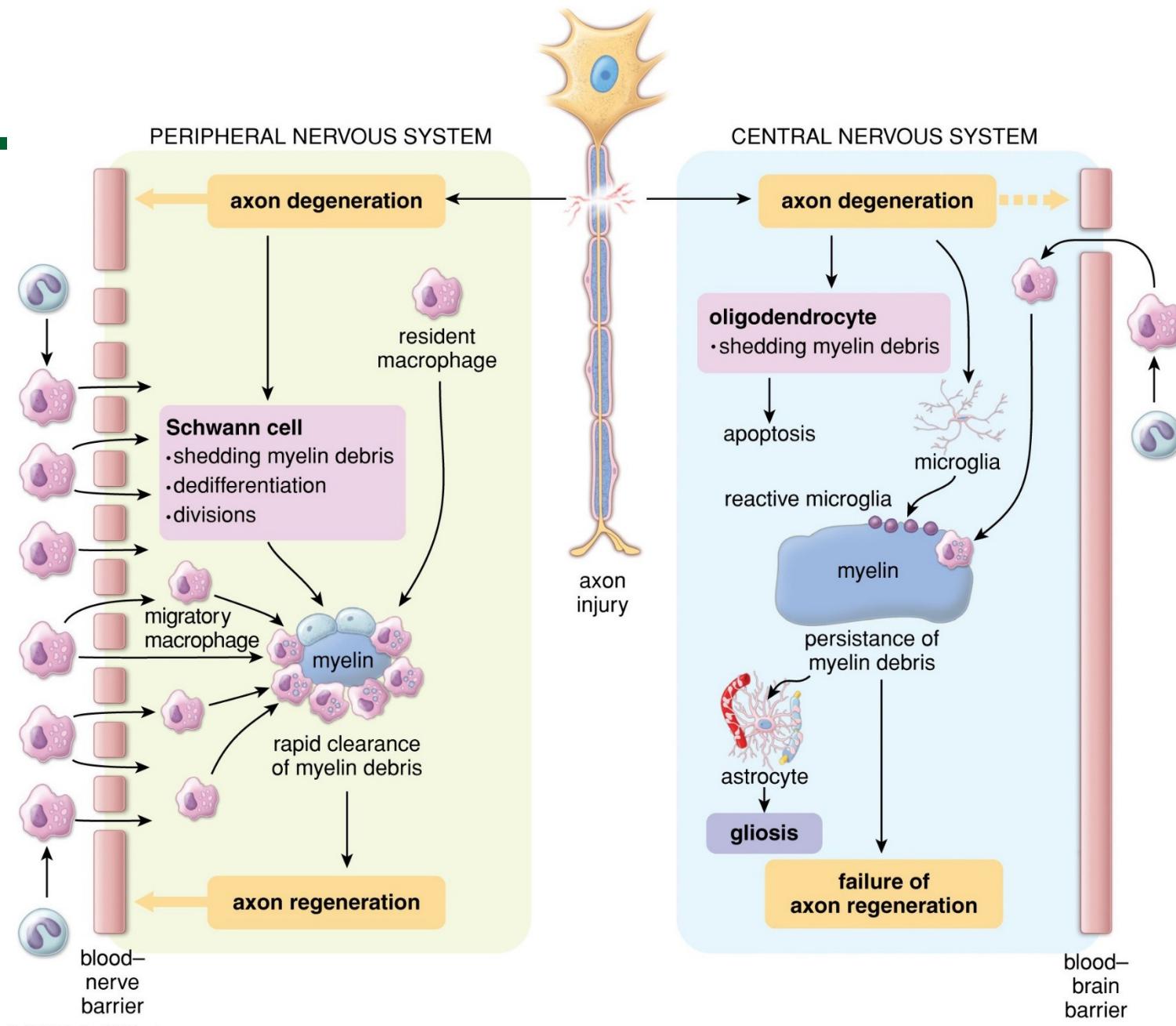
The sympathetic (thoracolumbar) outflow leaves the CNS from the thoracic and upper lumbar segments (T1 to L2) of the spinal cord.



# Response to neuronal injury within peripheral and central nervous systems

Injuries induces axonal degeneration and neural regeneration.

Involves neurons, Schwann cells, oligodendrocytes, macrophages and microglia.



# Chapter 10 Muscle Objectives

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1. Skeletal muscle: Organization and physiology
2. Cardiac Muscle
3. Smooth Muscle

# Functions of the Muscular system

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Muscle is composed of elongated cells that contract

- Converts chemical energy of ATP into mechanical energy

**Movement:** Externally visible movements

- Also internal movements e.g., propulsion of digestive tract and expulsion of urine
- Important roles in communication: speech, writing, etc.

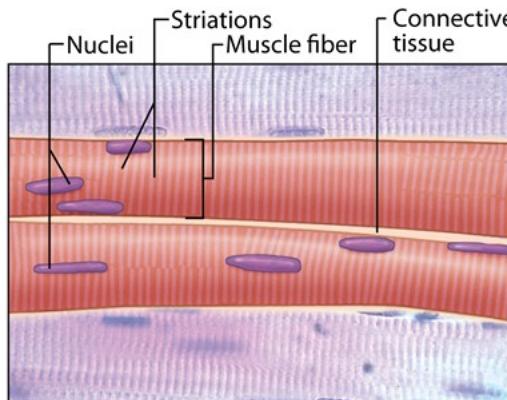
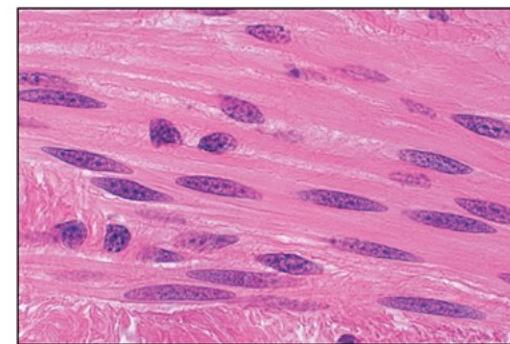
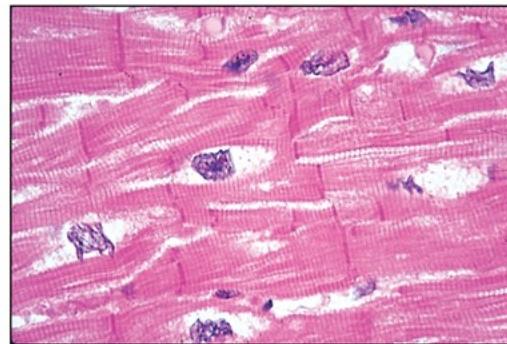
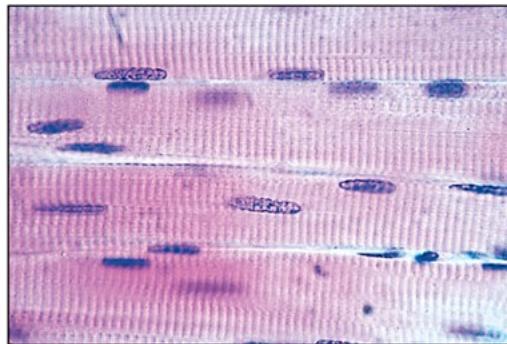
**Stability:** Prevent unwanted movement e.g., posture and holding bones in place

**Control of body openings and passages** E.g., sphincter muscles around eyelids, regulating waste elimination

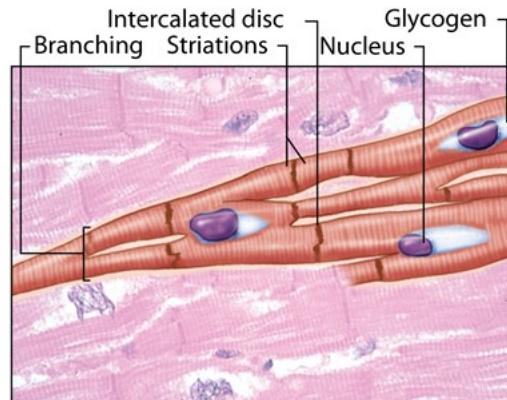
**Heat generation:** Muscles generating 20 to 30% of body heat at rest

**Glycemic control:** Aids regulation of blood glucose

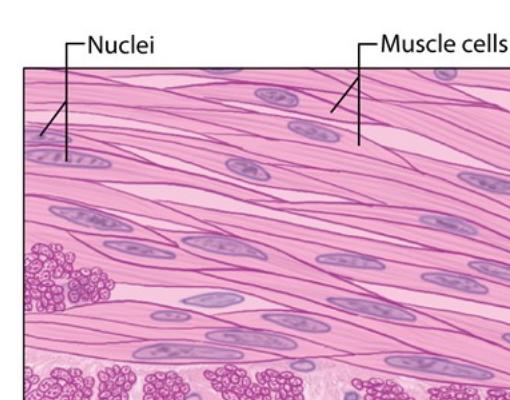




a Skeletal muscle



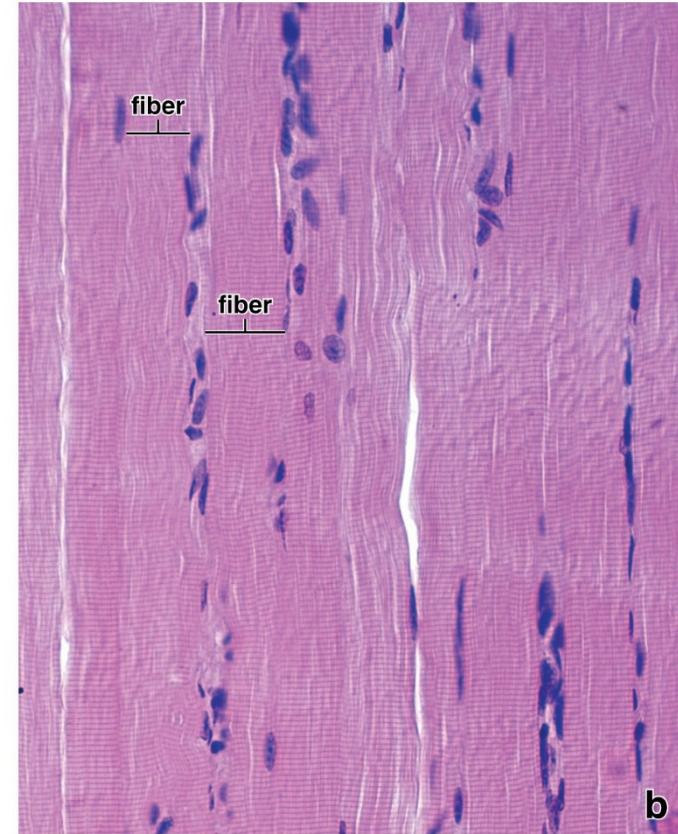
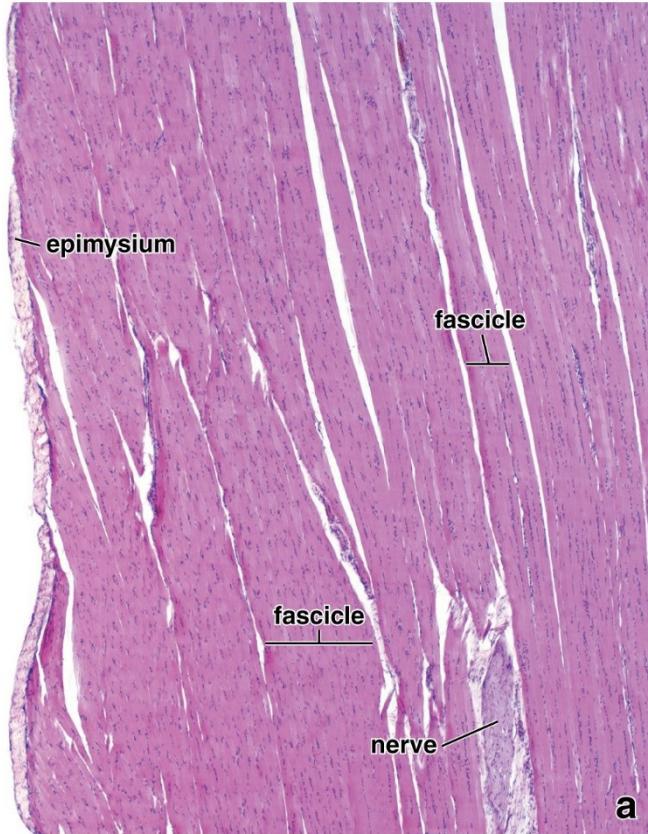
b Cardiac muscle



c Smooth muscle

- (a) **Skeletal muscle:** large, elongated, multinucleated fibers that show strong, quick, voluntary contractions.
- (b) **Cardiac muscle:** irregular branched cells bound together longitudinally by intercalated discs and shows strong, involuntary contractions.
- (c) **Smooth muscle:** grouped, fusiform cells with weak, involuntary contractions.

# Skeletal Muscle Fibers



**Voluntary:** subject to conscious control

**Striated:** alternating light and dark bands, or **striations** reflect overlapping arrangement of internal proteins

Skeletal muscle cells:  
multinucleate termed **muscle fibers** due to long slender shape

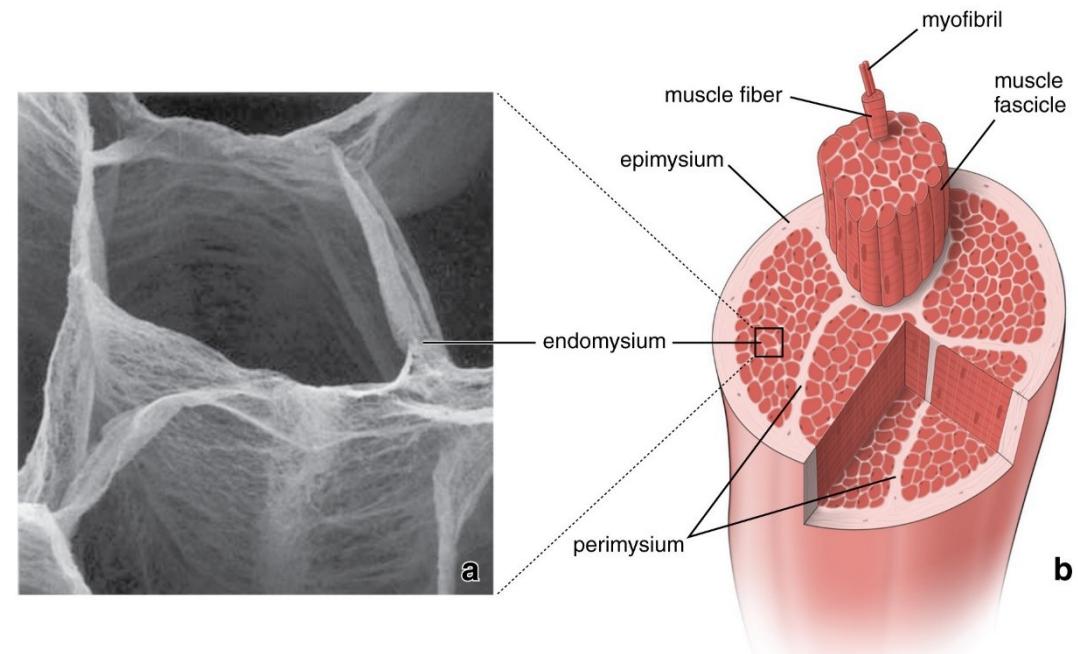
**Endomysium:** thin layer enclosing each muscle fiber, allows room for blood capillaries and nerve fibers. Reticular fibers.

**Perimysium:** layer of thicker connective tissue surrounds bundles of muscle fibers, **fascicles**

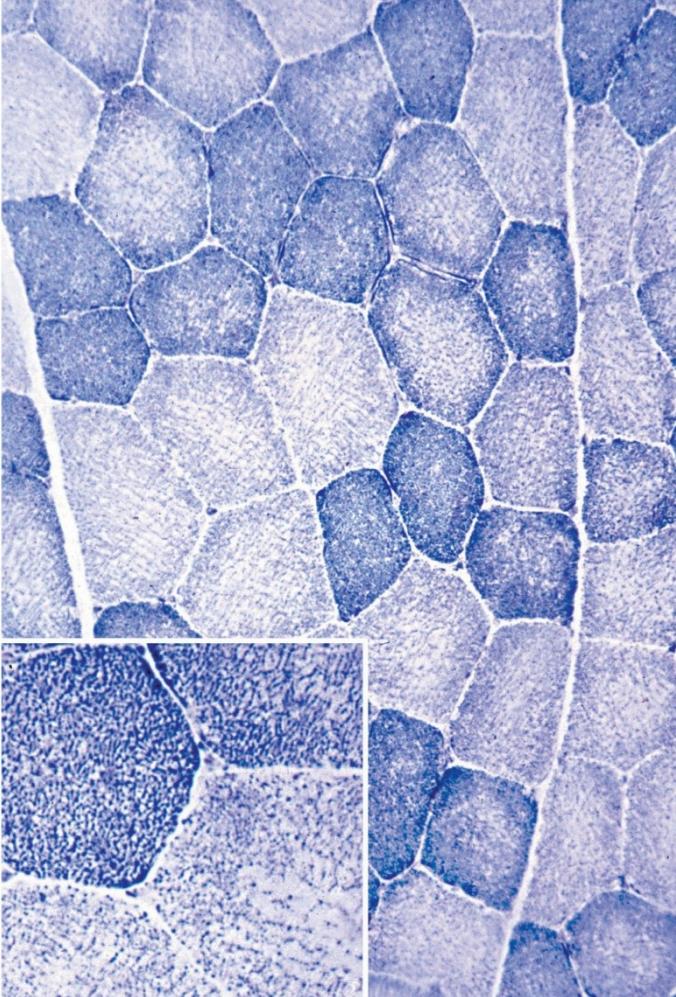
**Epimysium:** layer surrounding muscle as a whole, dense ct

**Fasciae:** fibrous sheets separating muscles from each other, may separate functionally related muscles into **compartments**. Contains nerves and vessels supplying muscle group

## Connective tissue layers in skeletal muscle



# Skeletal Muscle Fiber Types: High levels of mitochondrial oxidative enzymes → strong succinic dehydrogenase and NADH histochemical staining reactions



**Type I fibers (slow oxidative):** slow-twitch, fatigue-resistant motor units  
small, many mitochondria. Postural muscles.

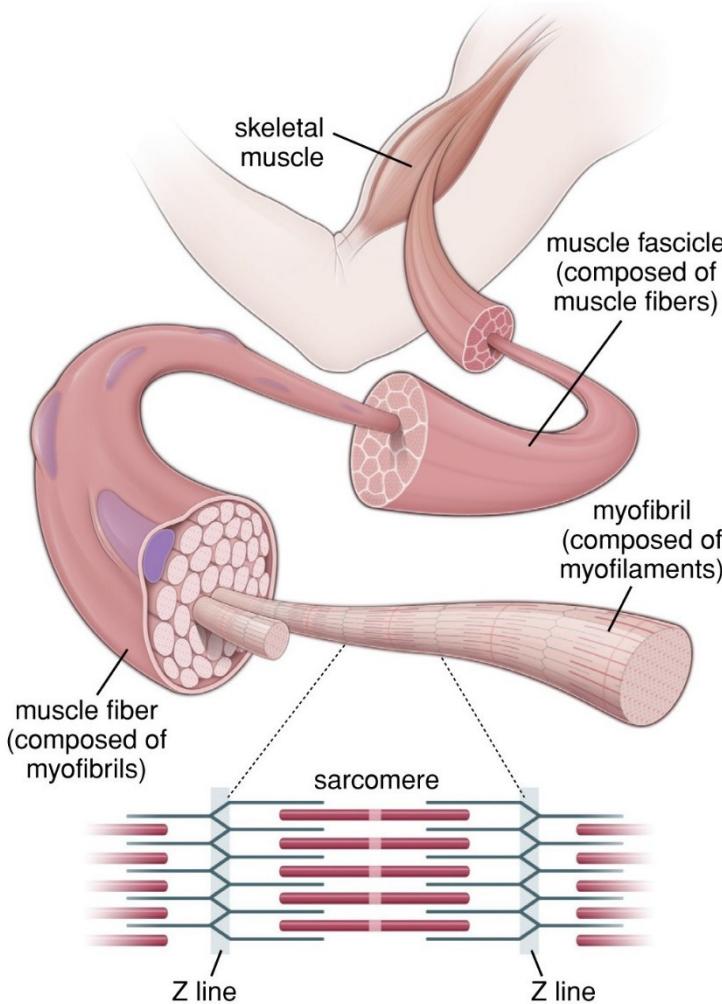
**Type IIa fibers (fast oxidative glycolytic):** fast-twitch, fatigue- resistant motor units that generate high peak muscle tension. 400-800m runners.

**Type IIb fibers (fast glycolytic fibers):** low level of oxidative enzymes, high anaerobic enzyme activity. Eyes and fingers.

## »» MEDICAL APPLICATION

The variation in diameter of muscle fibers depends on factors such as the specific muscle, age, gender, nutritional status, and physical training of the individual. Exercise enlarges the skeletal musculature by stimulating formation of new myofibrils and growth in the diameter of individual muscle fibers. This process, characterized by increased cell volume, is called **hypertrophy** (gr. *hyper*, above + *trophe*, nourishment). Tissue growth by an increase in the number of cells is termed **hyperplasia** (hyper + gr. *plasis*, molding), which takes place very readily in smooth muscle, whose cells have not lost the capacity to divide by mitosis.

# Organization of a skeletal muscle



## Striations:

**A bands:** regions in which thick and thin filaments overlap. Middle part composed of myosin only

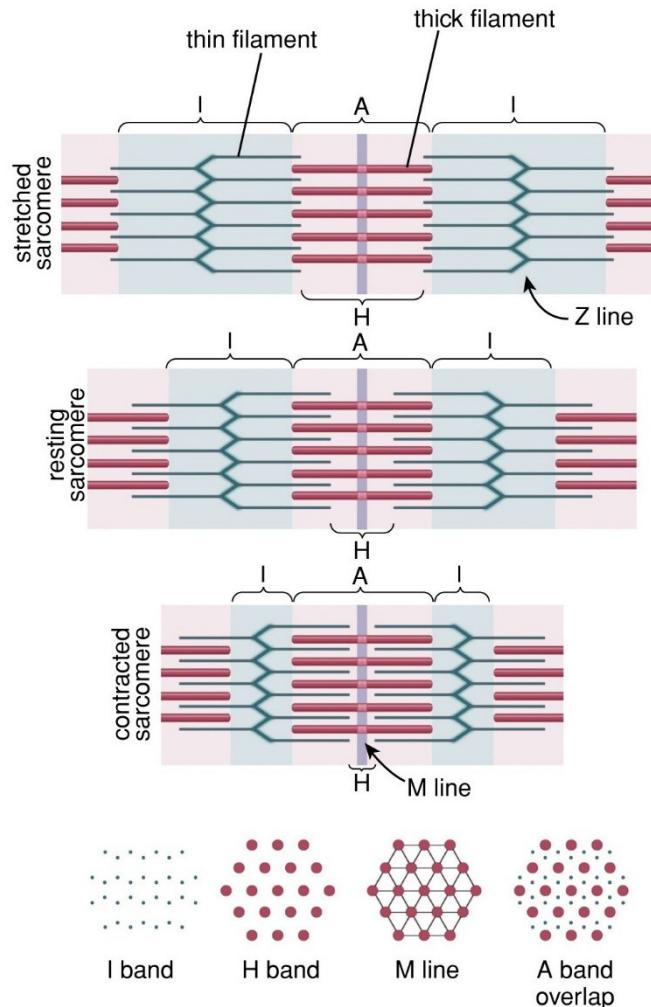
**I bands:** consists only of thin filaments bisected by thin dark line, **Z disc** (protein providing anchorage for thin filaments)

**Sarcomere:** Segment from one Z disc to the next, functional unit of muscle fiber

Muscle shortening due to sarcomeres shortening pull Z discs closer

[http://highered.mheducation.com/sites/0072495855/student\\_view0/chapter\\_10/animation\\_sarcomere\\_contraction.html](http://highered.mheducation.com/sites/0072495855/student_view0/chapter_10/animation_sarcomere_contraction.html)

# The functional unit of the myofibril is the sarcomere, the segment of the myofibril between two adjacent Z lines

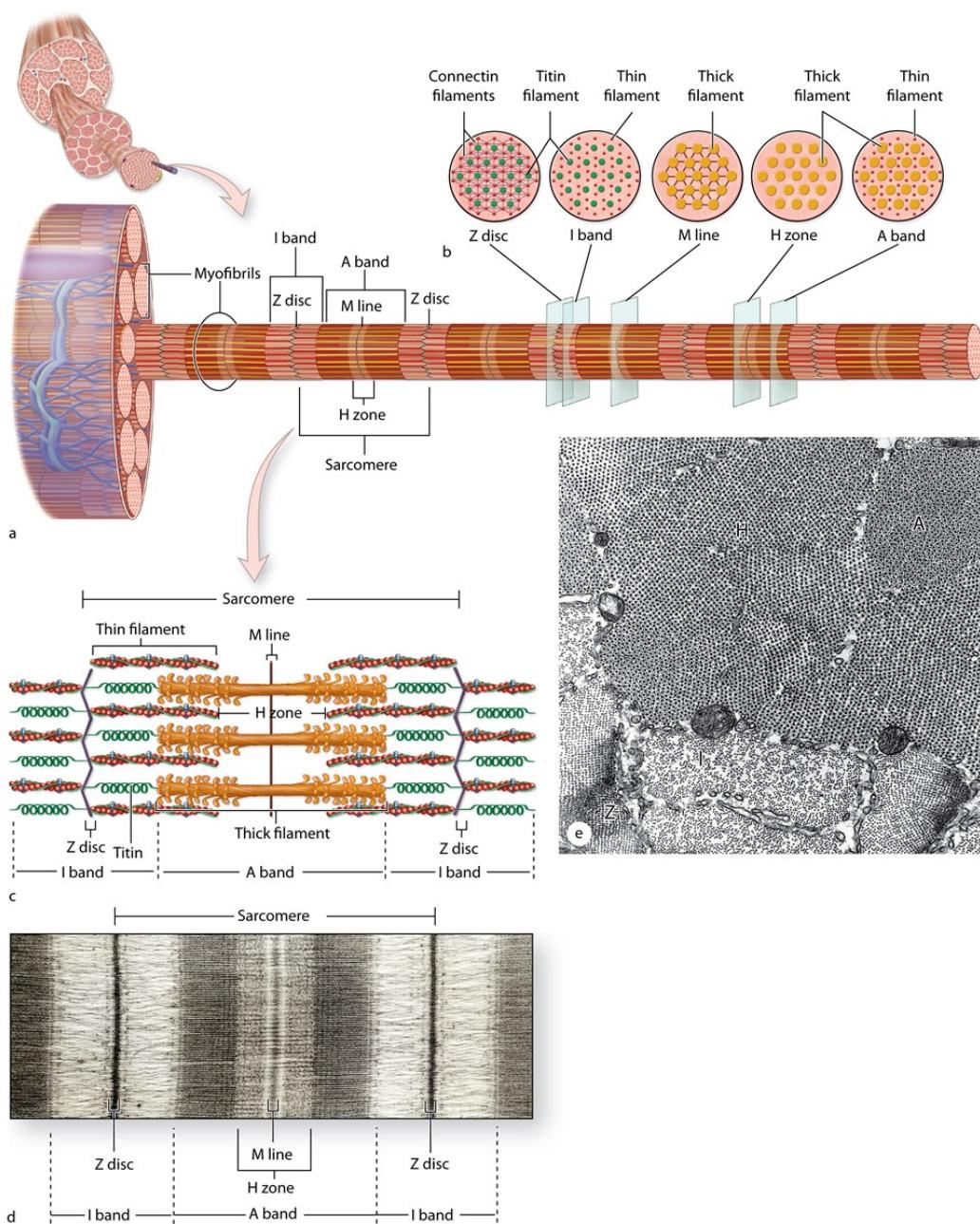


In the resting state (middle), interdigitation of thin (actin) and thick (myosin) filaments is not complete; the H and I bands are relatively wide.

In the contracted state (bottom), the interdigitation of the thin and thick filaments is increased according to the degree of contraction.

In the stretched state (top), the thin and thick filaments do not interact; the H and I bands are very wide. The length of the A band always remains the same and corresponds to the length of the thick filaments; the lengths of the H and I bands change

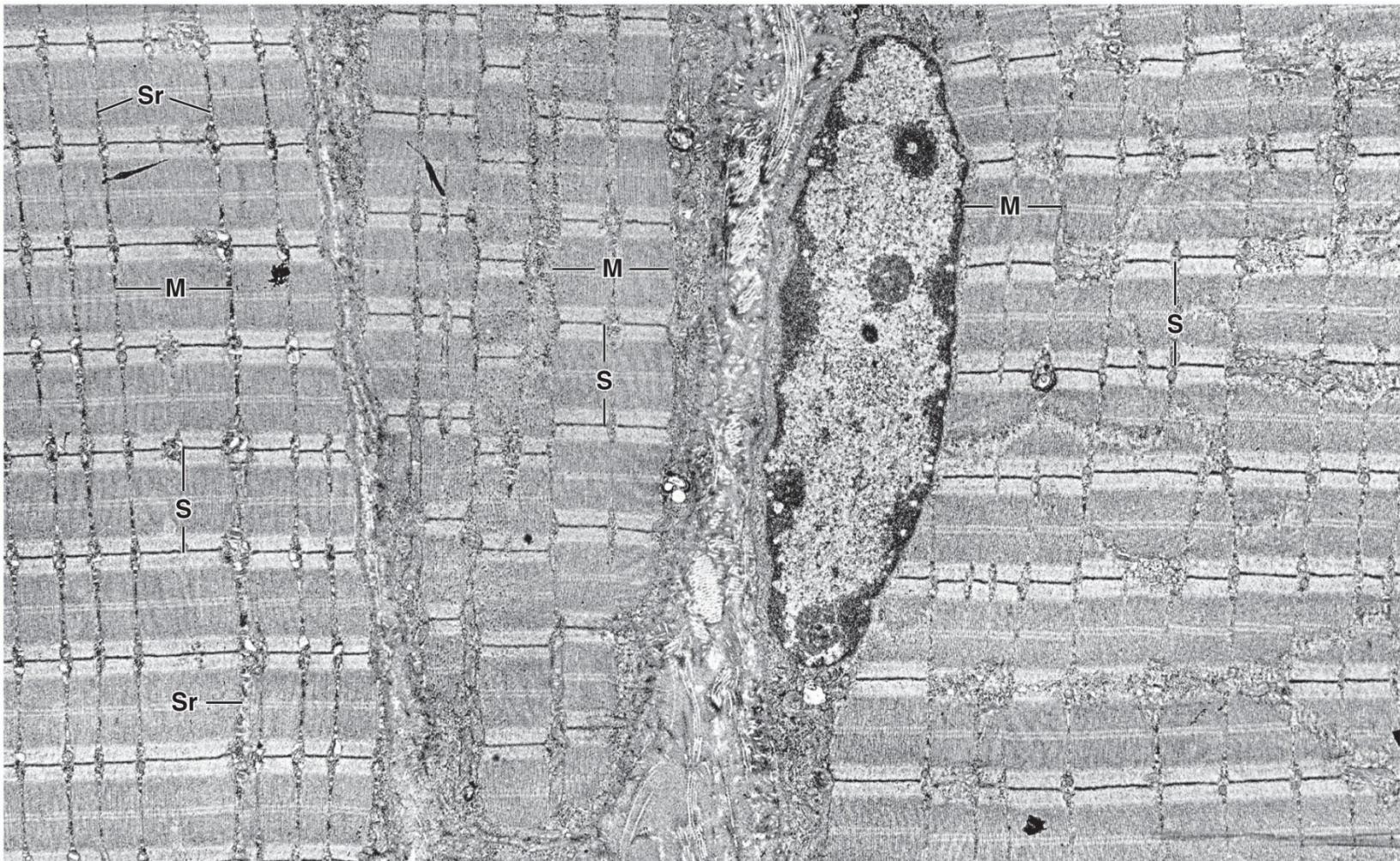
# Structure of a myofibril: A series of sarcomeres.



The myosin-containing thick filaments are restricted to the central portion of the sarcomere (i.e., the A band).

Actin-containing thin filaments attach to the Z line and extend into the A band to the edge of the H band.

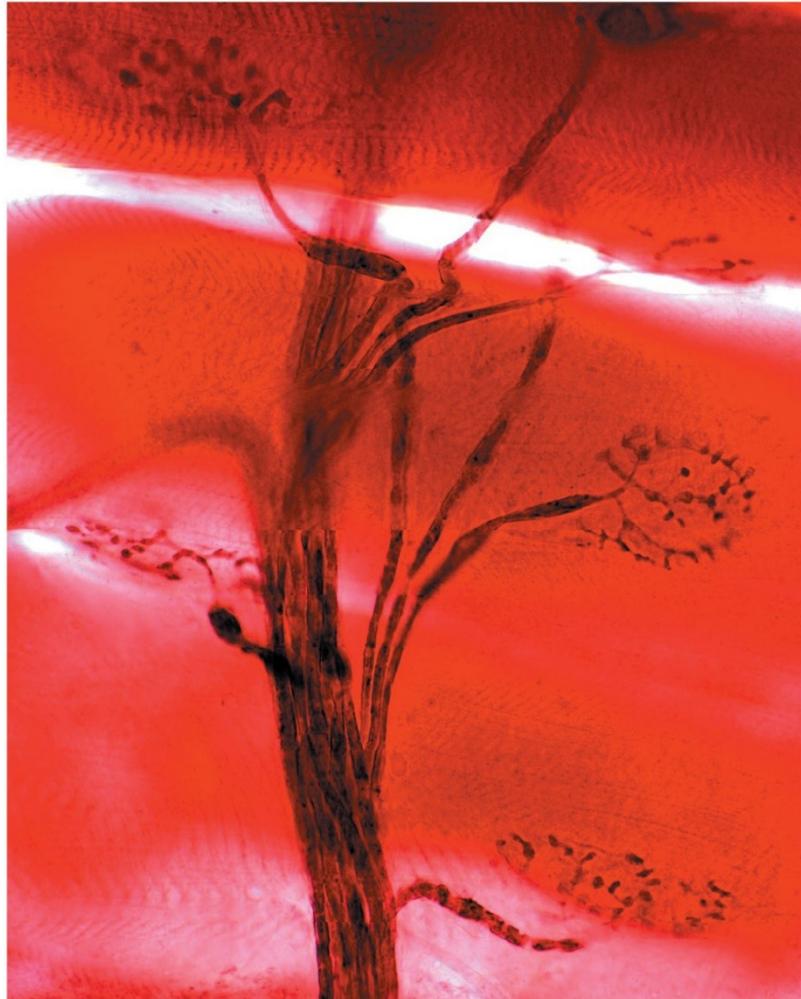
When a muscle contracts, each sarcomere shortens, but the myofilaments remain the same length.



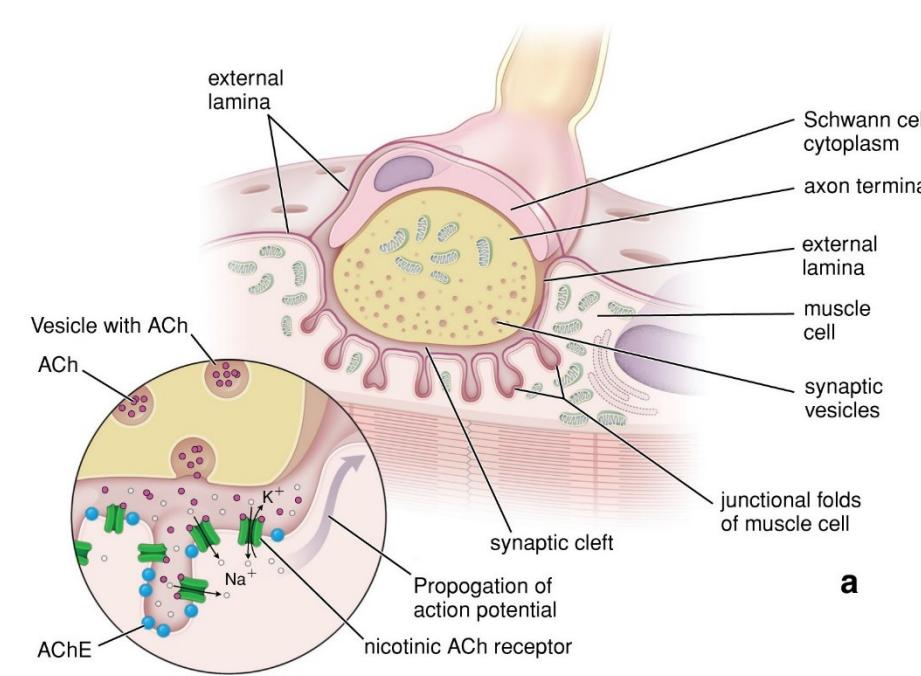
Two fibers—one in the middle and another on the left—exhibit regular profiles of myofibrils separated by a thin layer of surrounding sarcoplasm (Sr). Each repeating part of the myofibril between adjacent Z lines is a sarcomere (S). The cross-banded pattern visible on this micrograph reflects the arrangement, in register, of the individual myofibrils (M); a similar pattern found in the myofibril reflects the arrangement of myofilaments.

# The neuromuscular junction is the contact made by the terminal branches of the axon with the muscle fiber

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A motor nerve and its final branches that lead to the neuromuscular junctions (motor end plates). The skeletal muscle fibers are oriented horizontally in the field and are crossed perpendicularly by the motor nerve fibers. Note that these fibers distally lose their myelin sheath and divide extensively into small swellings, forming a cluster of neuromuscular junctions.

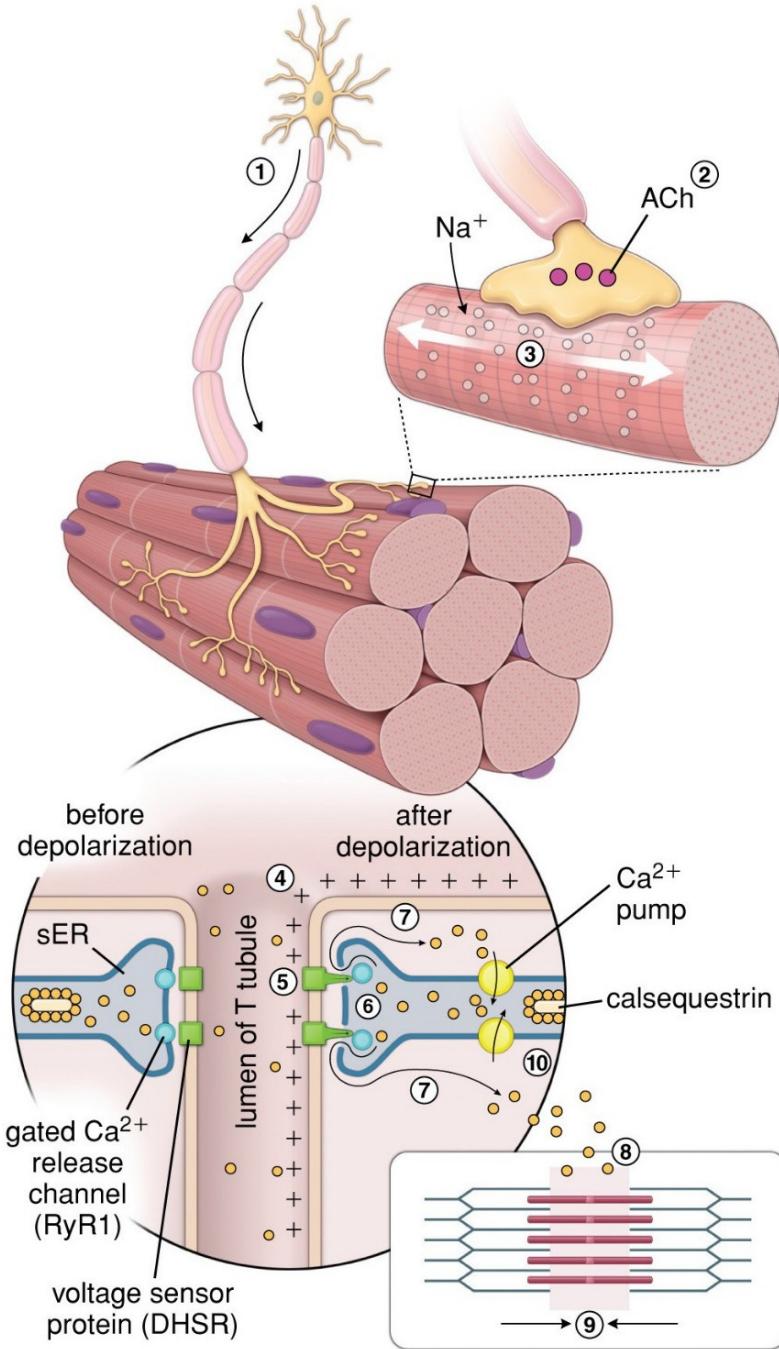


## Release of acetylcholine into the synaptic cleft initiates depolarization of the plasma membrane, which leads to muscle cell contraction.

If the nerve supply to a muscle is disrupted, the muscle cell undergoes regressive changes known as tissue atrophy



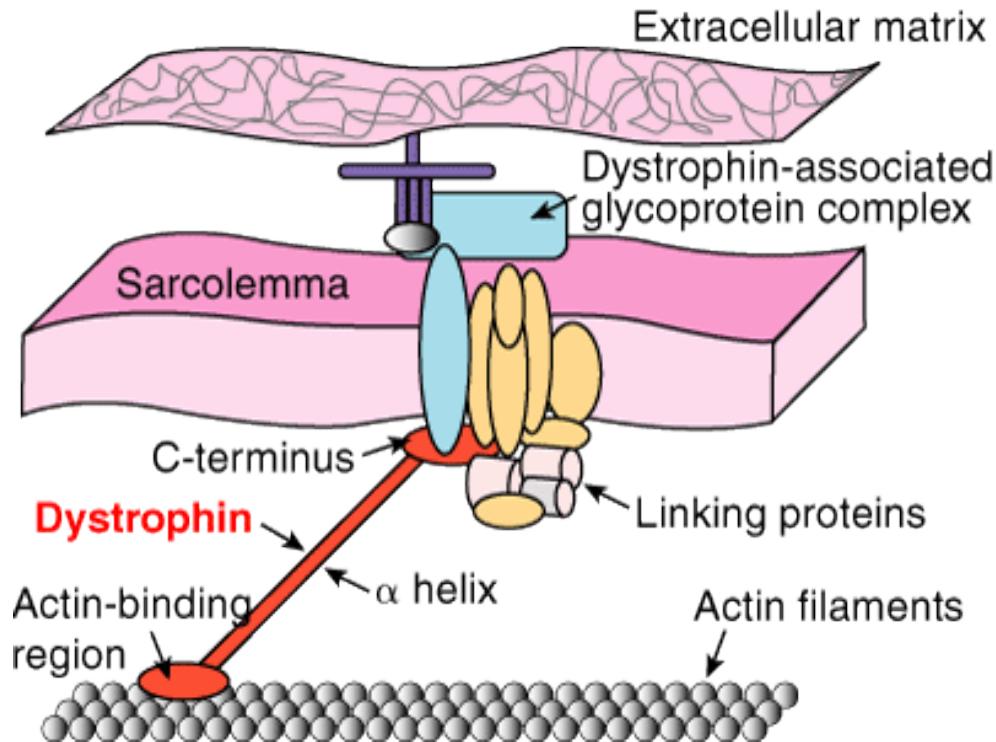
**MEDICAL APPLICATION** Myasthenia gravis is an autoimmune disorder that involves circulating antibodies against proteins of acetylcholine receptors. The disease follows a progressive course. The extraocular muscles of the eyes are commonly the first affected.



# The events leading to contraction of skeletal muscle

1. Nerve impulse.
2. release of acetylcholine into the synaptic cleft, ACh-gated Na channels cause local depolarization of sarcolemma.
3. Voltage-gated Na channels open
4. General depolarization spreads of the muscle cell
5. Voltage sensors in the plasma membrane of T tubules change their conformation.
6. At the muscle cell triads, sarcoplasmic reticulum gated Ca release activated
7. Ca is rapidly released
8. Ca binds troponin complex.
9. Acto-myosin cross-bridge cycle is initiated.
- 10.Ca is returned to the terminal cisternae of the sarcoplasmic reticulum.

# Duchenne muscular dystrophy



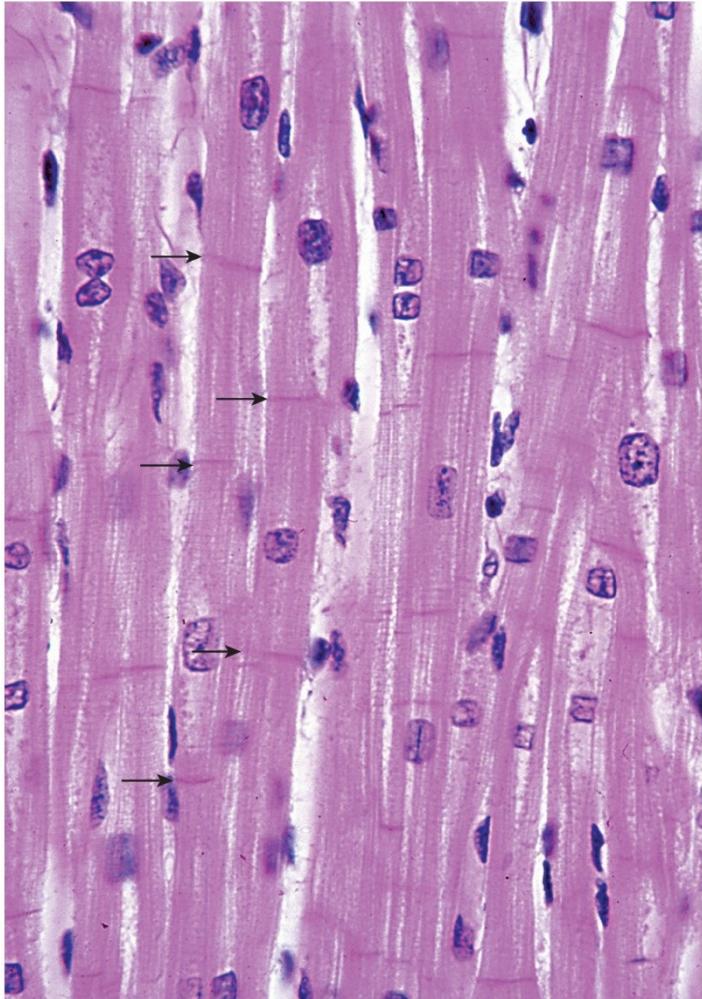
## MEDICAL APPLICATION

Dystrophin is a large actin-binding protein located just inside the sarcolemma of skeletal muscle fibers which is involved in the functional organization of myofibrils.

Research on Duchenne muscular dystrophy revealed that mutations of the dystrophin gene can lead to defective linkages between the cytoskeleton and the extracellular matrix (ECM). Muscle contractions can disrupt these weak linkages, causing the atrophy of muscle fibers typical of this disease.

# Cardiac muscle has the same types and arrangement of contractile filaments as skeletal muscle

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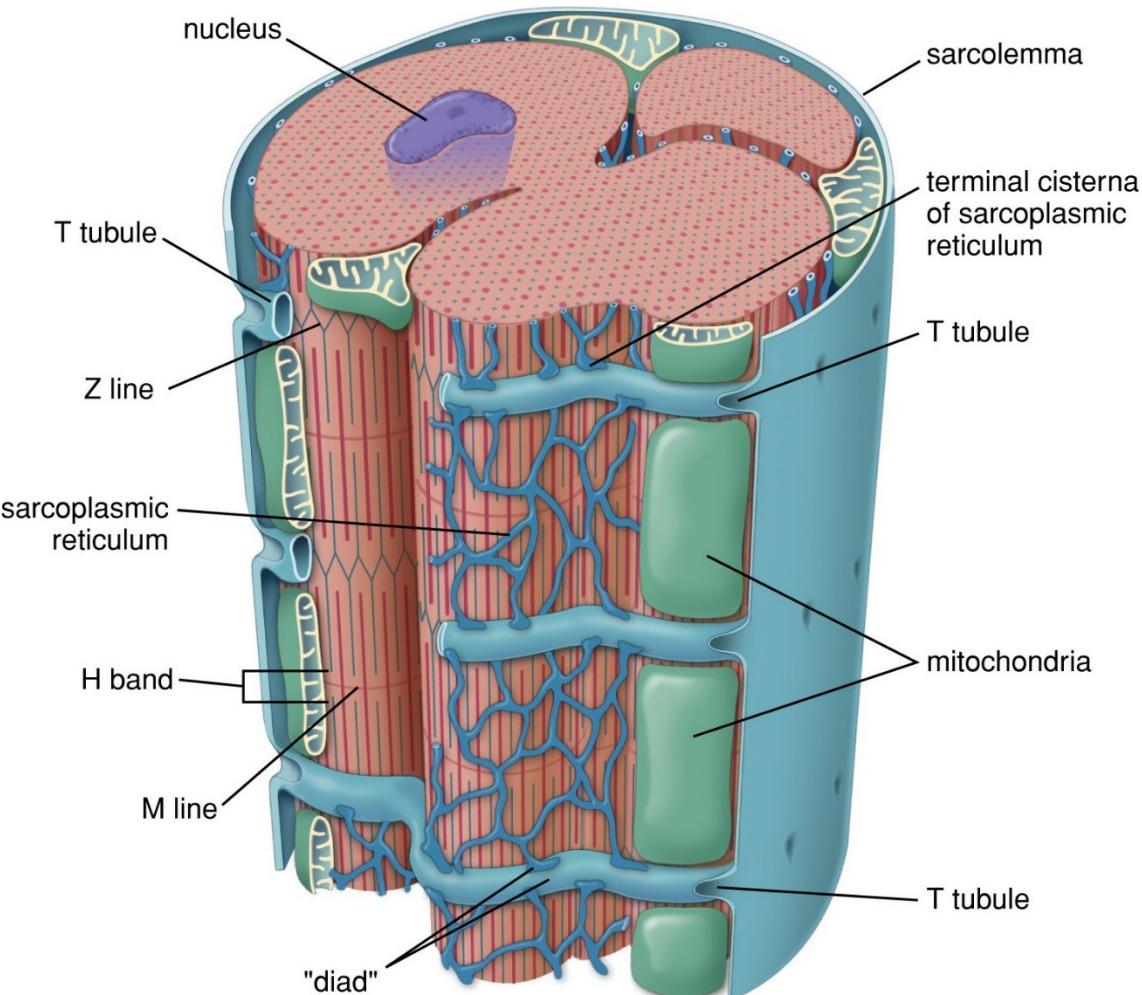
Unlike skeletal and visceral striated muscle fibers that represent multinucleated single cells, cardiac muscle fibers consist of numerous cylindrical cells arranged end to end.

In addition, cardiac muscle fibers exhibit densely staining cross-bands, called **intercalated discs**.

Gap junctions (communicating junctions) constitute the major structural element of the lateral component of the intercalated disc. Gap junctions provide ionic continuity between cells, permitting cardiac muscle fibers to behave as a syncytium while retaining cellular integrity and individuality

The central location of the nucleus in cardiac muscle cells is one feature that helps distinguish them from multinucleated skeletal muscle fibers.

# Organization of cardiac muscle fiber



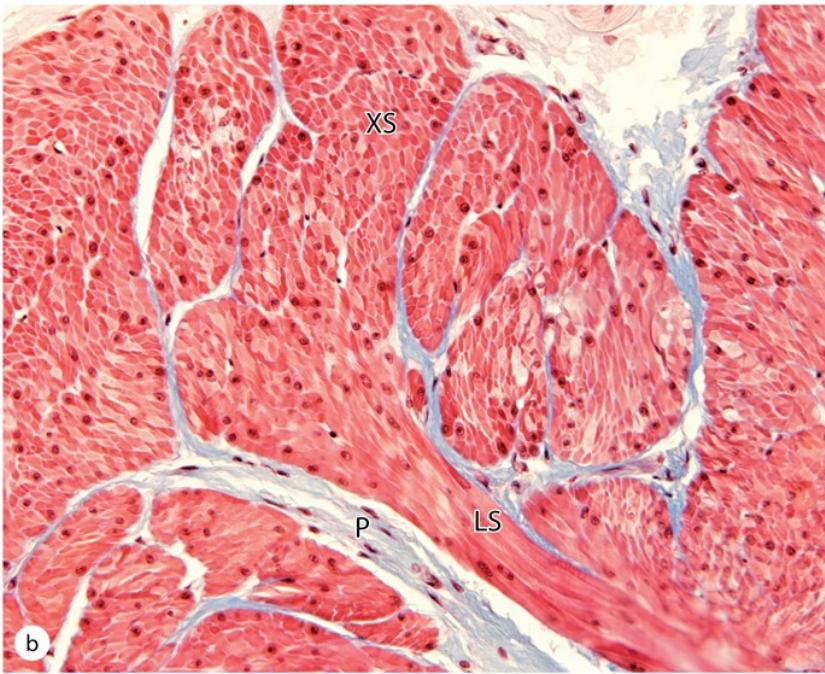
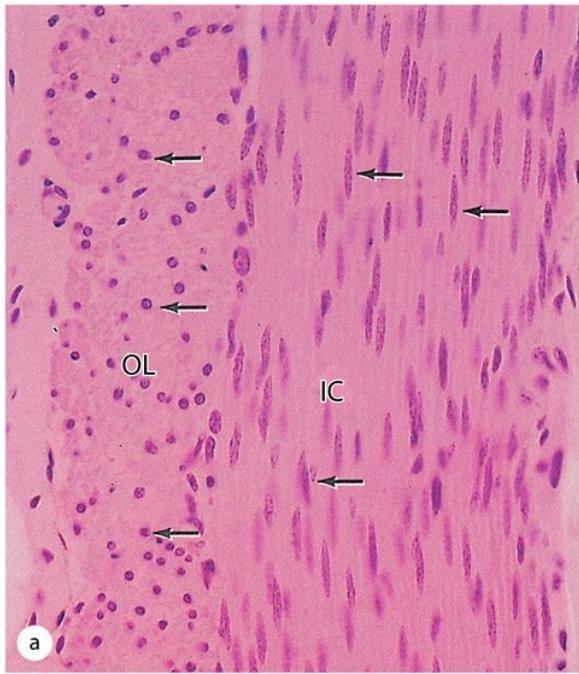
The T tubules of cardiac muscle are much larger than the T tubules of skeletal muscle. They also differ in that they are located at the level of the Z line.

## MEDICAL APPLICATION

Ischemia: tissue damage due to lack of oxygen when coronary arteries are occluded by heart disease.

Adult mammalian cardiac muscle has little potential to regenerate after injury. However, certain fish and amphibians, as well as newborn mice, do form new muscle when the heart is partially removed, despite the lack of satellite cells. Research on the possibility of mammalian heart muscle regeneration builds on work with the animal models, focusing primarily on the potential of mesenchymal stem cells to form new, site-specific muscle.

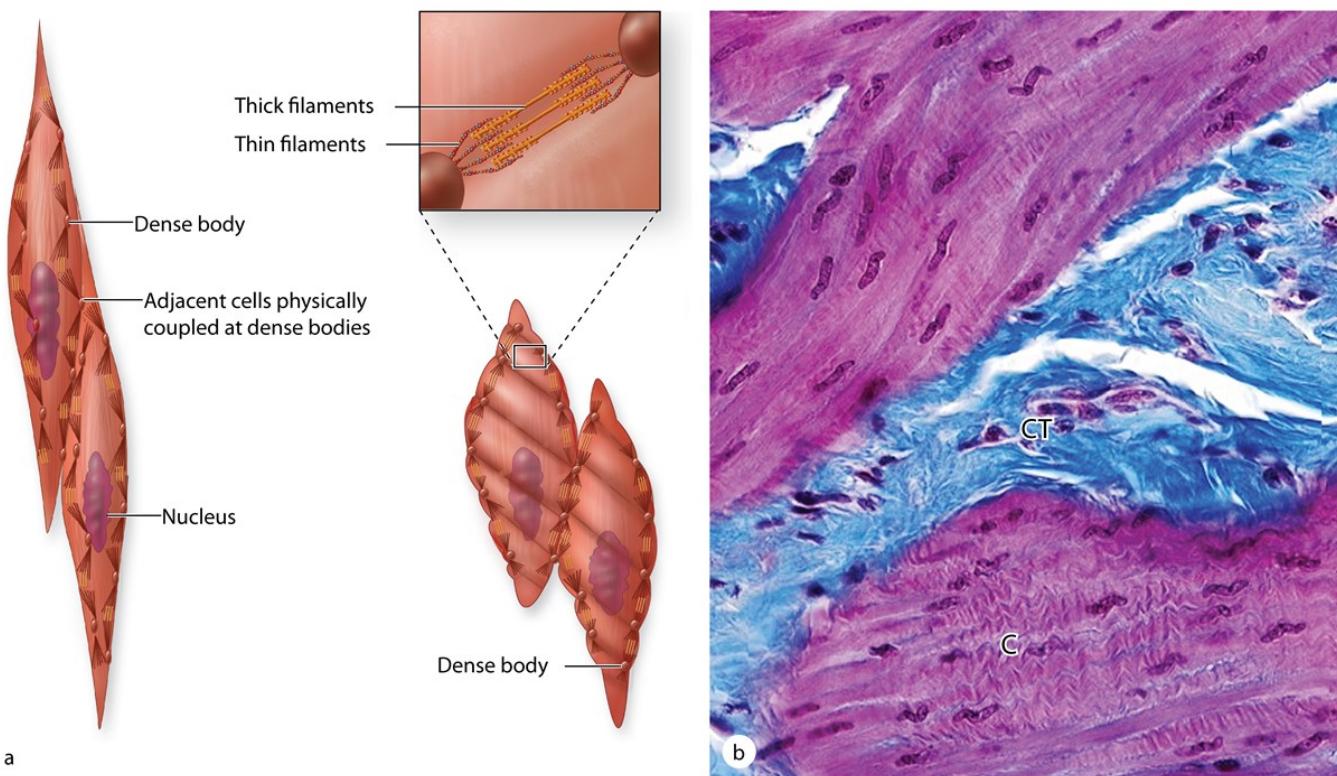
**Cells of smooth muscle are long, tapering structures with elongated nuclei centrally located at the cell's widest part.**



**(a)** wall of the small intestine cells of the inner circular (**IC**) layer are cut lengthwise and cells of the outer longitudinal layer (**L**) are cut transversely.

**(b)** Section of smooth muscle in bladder shows fibers in cross section (**XS**) and longitudinal section (**LS**) with the same fascicle.

# Filaments of smooth muscle are arranged differently and appear less organized.



(a) thin filaments attach to **dense bodies** located at the cell membrane and deep in the cytoplasm. This arrangement of both the cytoskeleton and contractile apparatus allows the multicellular tissue to contract as a unit, providing better efficiency and force.

(b) Contracted (**C**) region of smooth muscle, with contraction decreasing the cell length and deforming the nuclei. The long nuclei of individual fibers assume a cork-screw shape when the fibers contract, reflecting the reduced cell length at contraction. Connective tissue (**CT**) of the perimysium outside the muscle fascicle is stained blue.

	Skeletal	Cardiac	Smooth
<b>Structural features</b>			
Muscle cell	Large, elongate cell, 10–100 µm in diameter, up to 100 cm in length (sartorius m.)	Short, narrow cell, 10–15 µm in diameter, 80–100 µm in length	Short, elongate, fusiform cell, 0.2–2 µm in diameter, 20–200 µm in length
Location	Muscles of skeleton visceral striated (e.g., tongue, esophagus, diaphragm)	Heart, superior and inferior vena cava, pulmonary veins	Vessels, organs, and viscera
Connective tissue components	Epimysium, perimysium, endomysium	Endomyxium (subendothelial and subepicardial connective tissue)	Endomyxium, sheaths, and bundles
Fiber	Single skeletal muscle cell	Linear branched arrangement of several cardiac muscle cells	Single smooth muscle cell
Striation	Present	Present	None
Nucleus	Many peripheral	Single central, surrounded by juxtanuclear region	Single central
T tubules	Present at A-I junction (triad: with two terminal cisternae), two T tubules/sarcomere	Present at Z lines (diad: with small terminal cisternae), one T tubule/sarcomere	None, well-developed sER, many invaginations and vesicles similar to caveolae
Cell-to-cell junctions	None	Intercalated discs containing 1. Fasciae adherentes 2. Macula adherens (desmosome) 3. Gap junctions	Gap junctions (nexus)
Special features	Well-developed sER and T tubules	Intercalated discs	Dense bodies, caveolae, and cytoplasmic vesicles
<b>Functions</b>			
Type of innervation	Voluntary	Involuntary	Involuntary
Efferent innervation	Somatic	Autonomic	Autonomic
Type of contraction	"All or none" (type I and type II fibers)	"All or none" rhythmic (pacemakers, conductive system of the heart)	Slow, partial, rhythmic, spontaneous contractions (pacemakers of stomach)
Regulation of contraction	By binding of Ca <sup>2+</sup> to TnC, causes tropomyosin movement and exposes myosin-binding sites on actin filaments	By binding of Ca <sup>2+</sup> to TnC, causes tropomyosin movement and exposes myosin-binding sites on actin filaments	By phosphorylation of myosin light chain by myosin light chain kinase in the presence of Ca <sup>2+</sup> -calmodulin complex
<b>Growth and regeneration</b>			
Mitosis	None	None (in normal condition)	Present
Response to demand	Hypertrophy	Hypertrophy	Hypertrophy and hyperplasia
Regeneration	Limited (satellite cells and myogenic cells from bone marrow)	None (in normal condition)	Present