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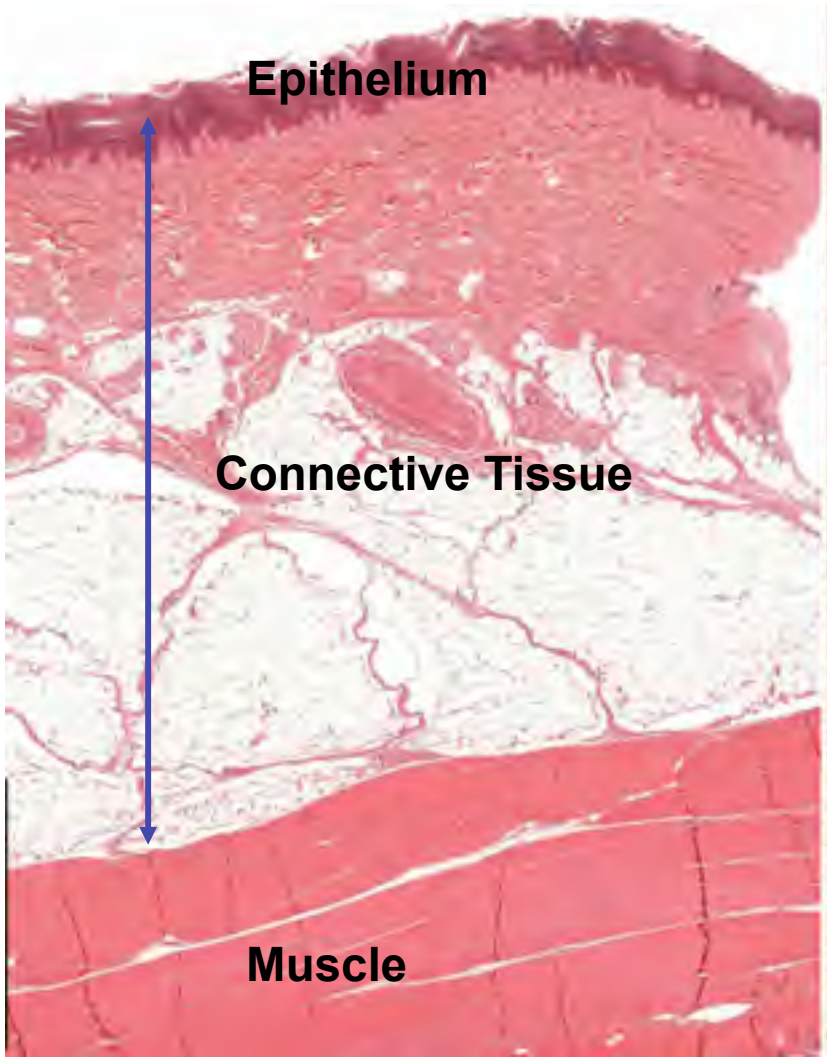
Medical Histology:
Connective Tissue

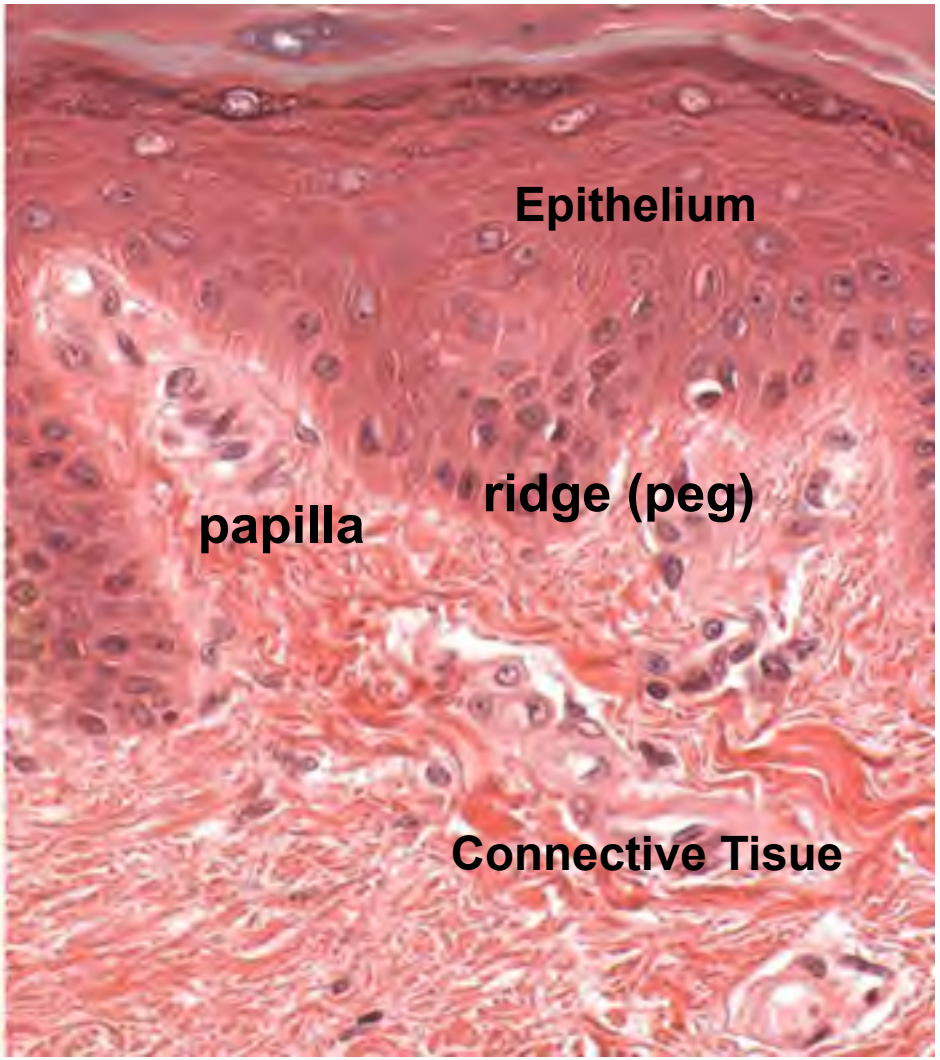
Matt Velkey

Fall 2008

University of Michigan
Medical School

Connective Tissue





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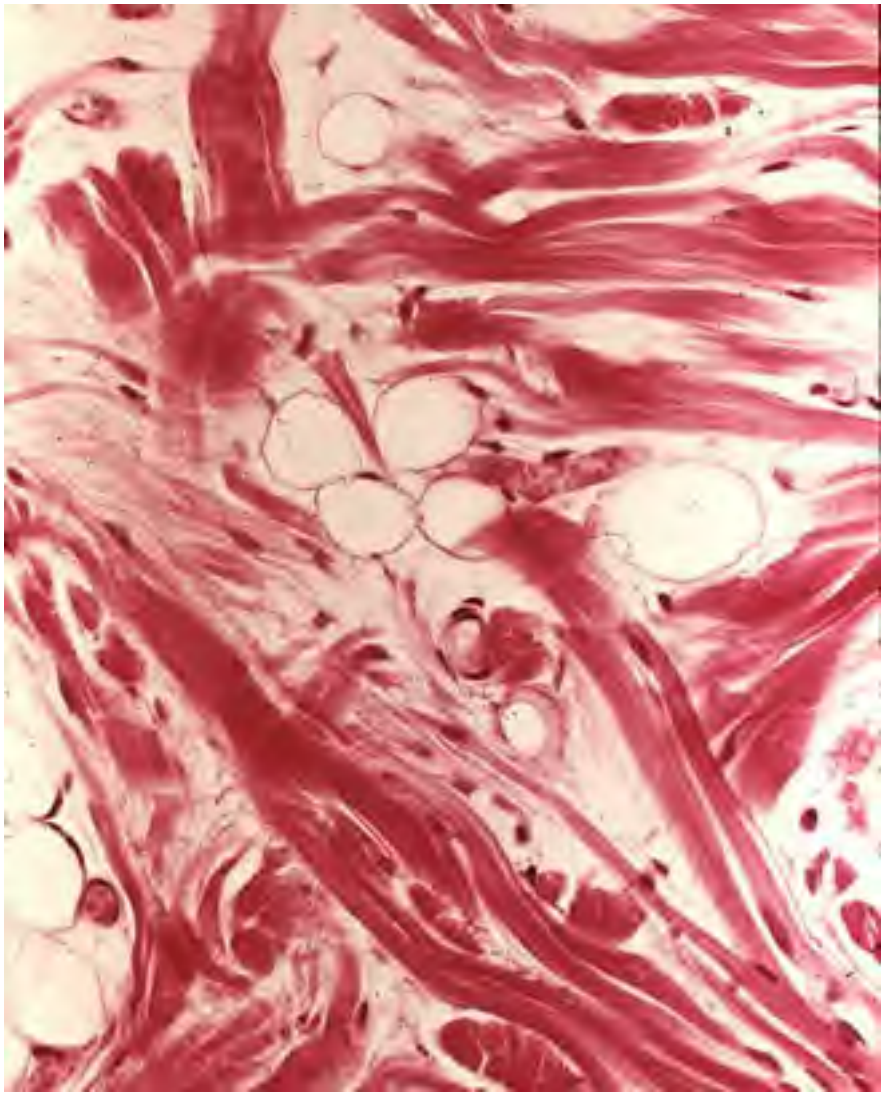
General Properties of Connective Tissue

1. One of the four basic types of tissues (epithelium, connective tissue, muscle, and nervous tissue)
2. Composition:
   - cells (fibroblasts and others),
   - fibers and ground substance (extracellular matrix)
3. Functions:
   - Architectural framework of the body
   - Bind together and provide mechanical support for other tissue (metabolic, defense, transport, storage)
   - Wound repair / inflammatory response

Connective Tissue



- **Extracellular Matrix**
  - **Fibers – collagen & elastic**
  - **"Ground substance"**
- **Cells**
  - Fixed:
    - **Fibroblasts**
    - **Adipocytes**
    - **"Tissue macrophages"**
  - Free:
    - **Immune cells**
      (lymphocytes)
    - **Inflammatory cells**
      (neutrophils & activated macrophages)

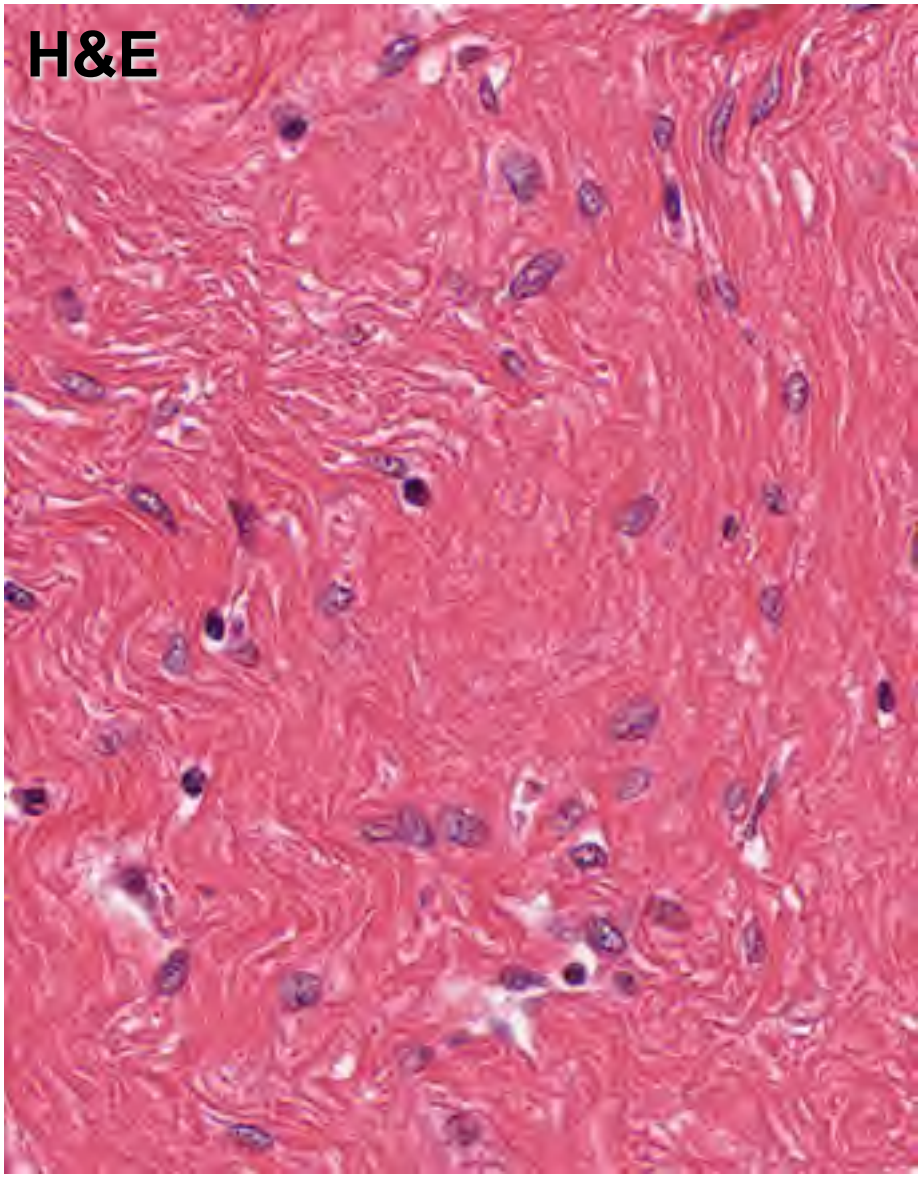
Fibers in Connective Tissue

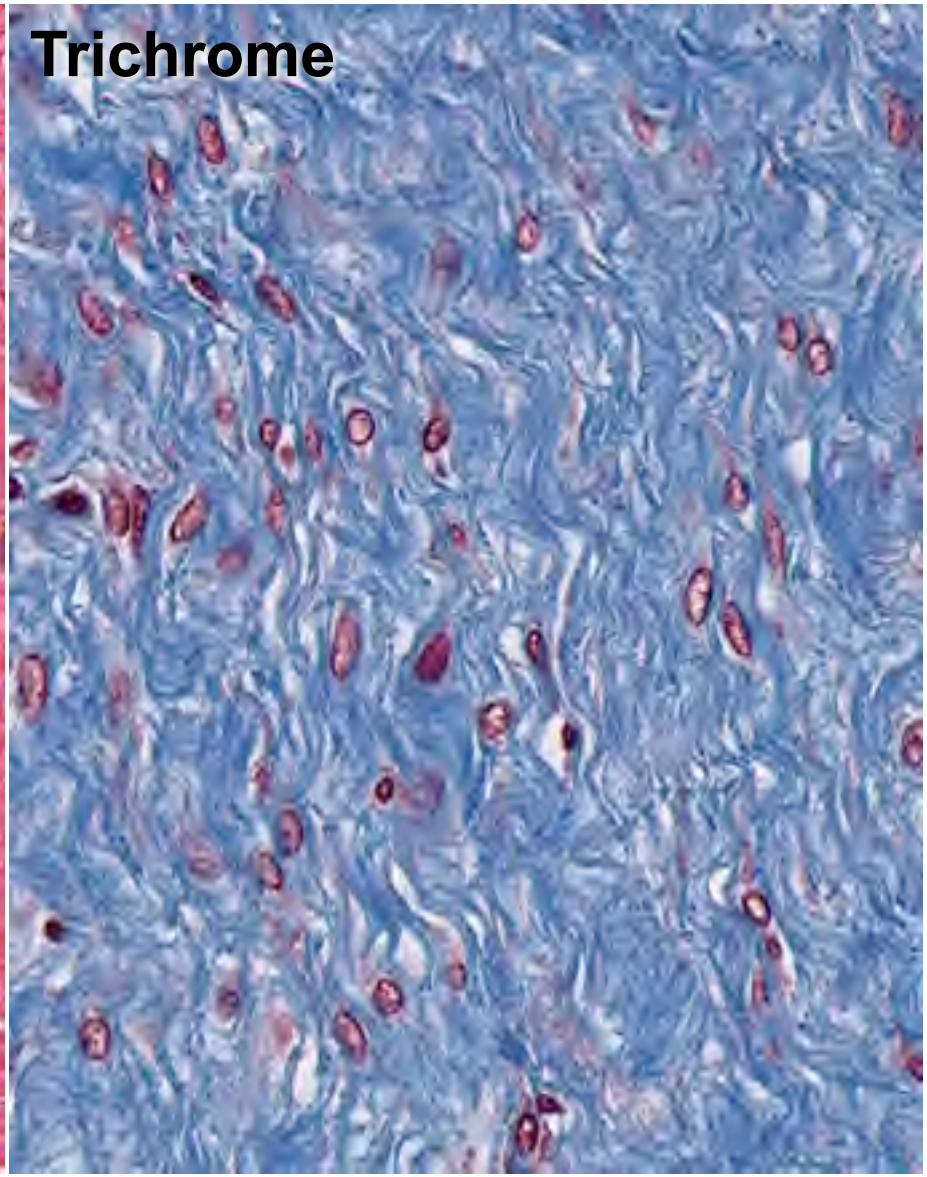
- Collagen
  - most abundant protein in human body (up to 30% dry weight)
  - multiple types: fibril-forming or fibril-associated (in skin, tendon, cartilage, bone, dentin, blood vessels); cross-linked networks (in all basement membranes)
- Reticular Fibers – specialized type of collagen (Type III; reticulin) associated with smooth muscle in organs subjected to changes in volume, forms the stroma in lymphatic and hematopoietic organs
- Elastic Fibers –thin fibers or fenestrated sheets composed of various glycoproteins, including the protein elastin, providing elastic properties to tissues that experience repeated deformation (in skin, blood vessels, lung, bladder)

Major Collagen Fiber Types (out of at least 20)

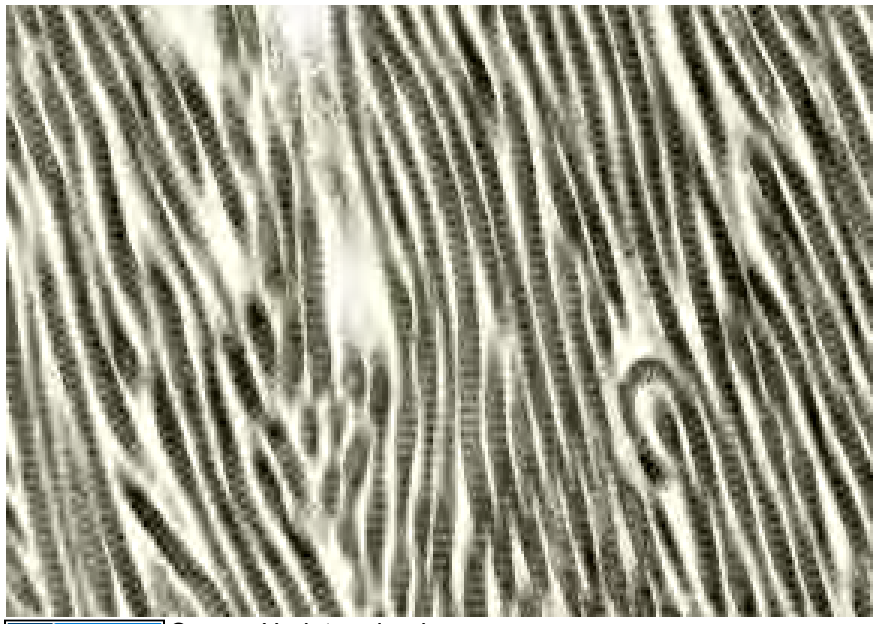
Collagen Type	Tissues	Function
Fibril-forming collagens (these are visible)		
I (most abundant)	Skin, tendon, bone, dentin	Resistance to tension
II	Cartilage, vitreous of eye	Resistance to pressure
III (reticulin)	Skin, muscle, blood vessels, liver, etc.	Structural framework and stability
Network-forming collagens		
IV	All basement membranes	Support and filtration
Fibril-associated collagens with interrupted triple helices (FACIT)		
VI, IX	Assoc. w/ type I and II fibrils	Fibril-fibril / fibril-ECM binding
Anchoring filament collagens		
VII	Epithelia	Epidermis to basal lamina

Collagen fibers viewed by light microscopy





Collagen fibers viewed by TEM*



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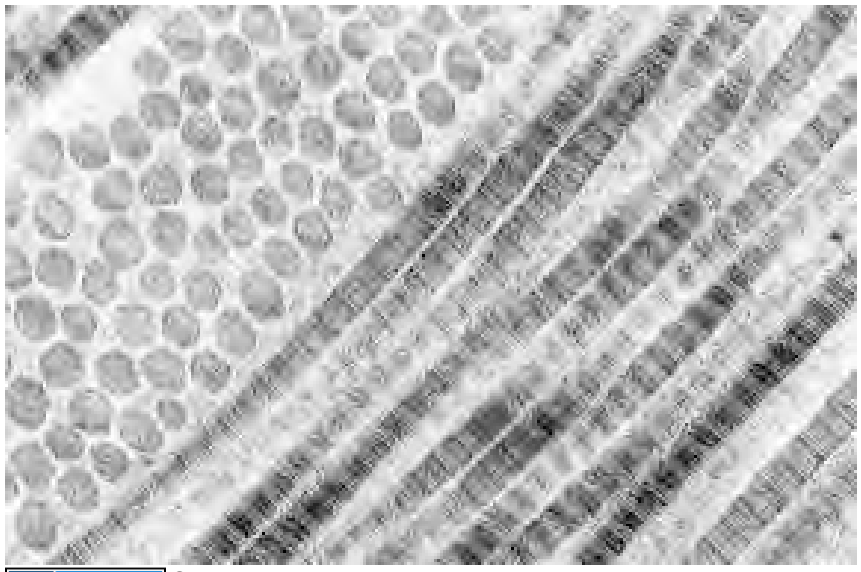
Longitudinal

Transverse



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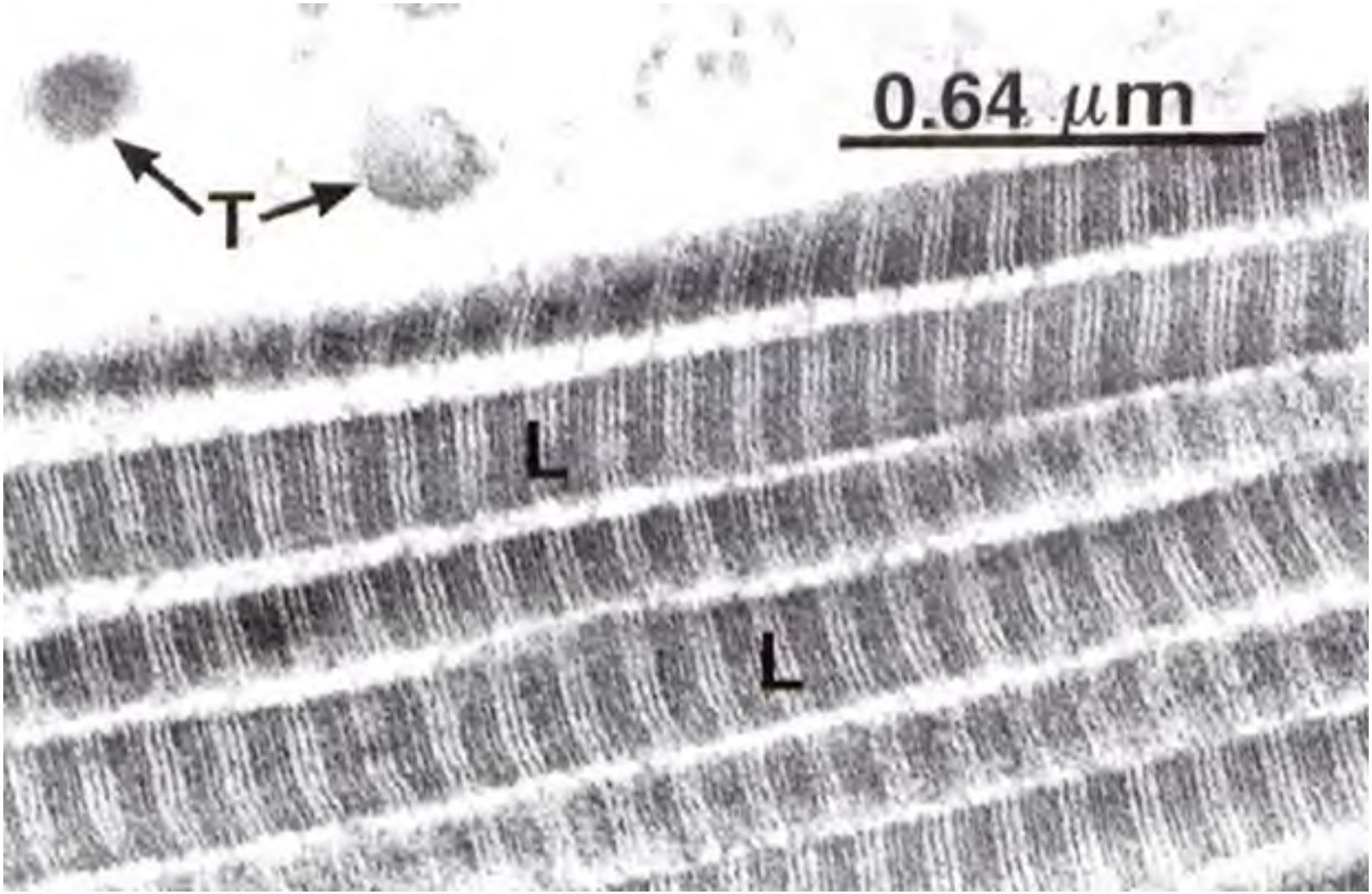
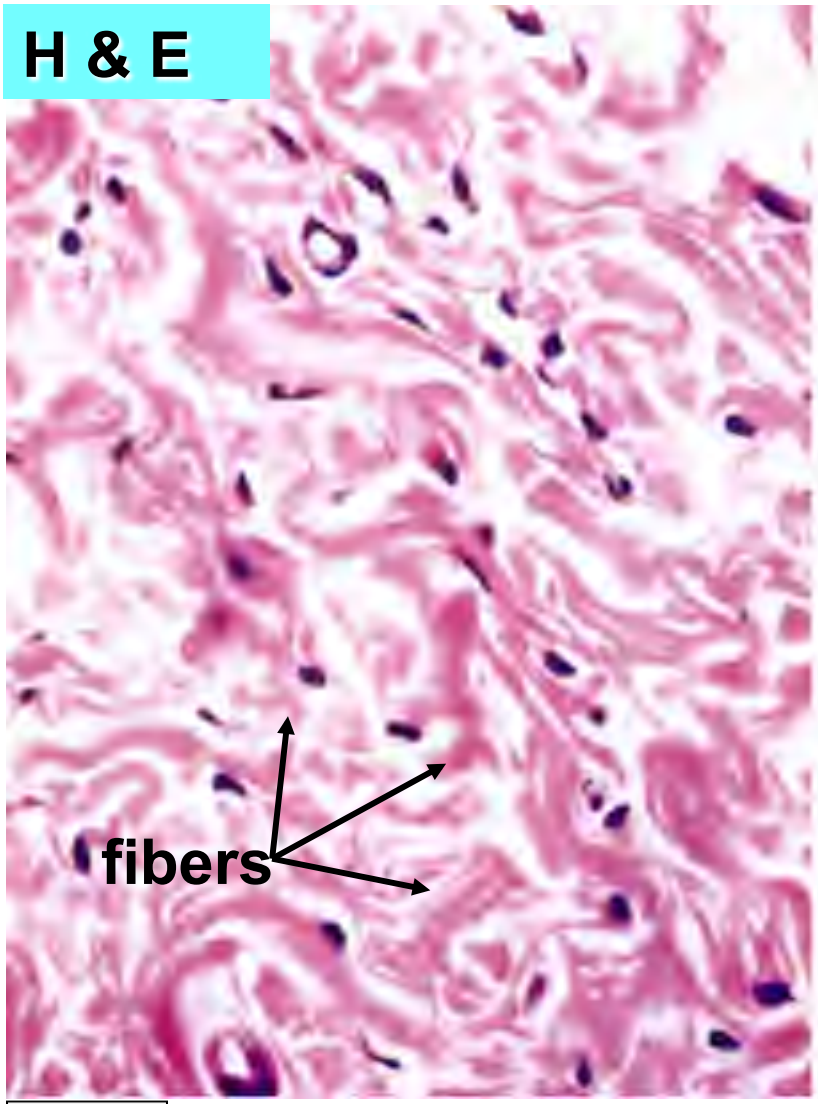
*TEM, transmission electron microscopy

Collagen Fibrils (Type I)



 Ross,M, Pawlina, W. *Wheater's Functional Histology: A Text and Atlas*. Fifth Edition. 2006. Figure 4.2.

Collagen Fibers vs. Fibrils



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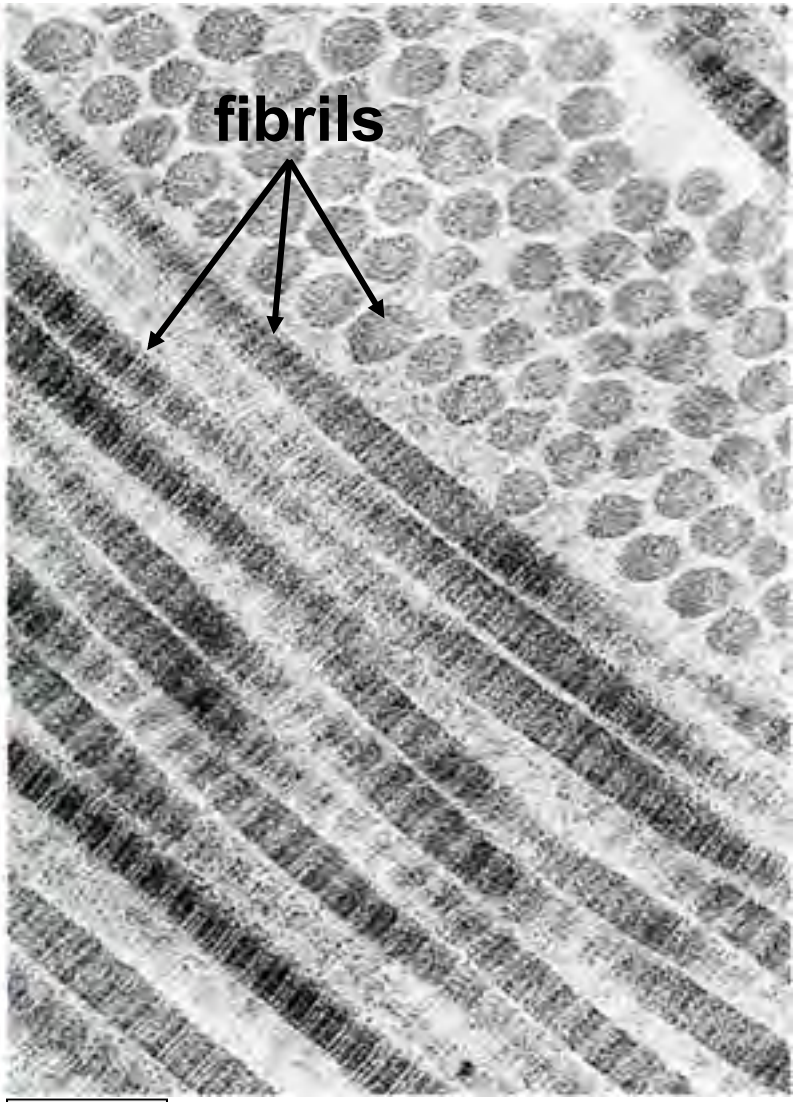
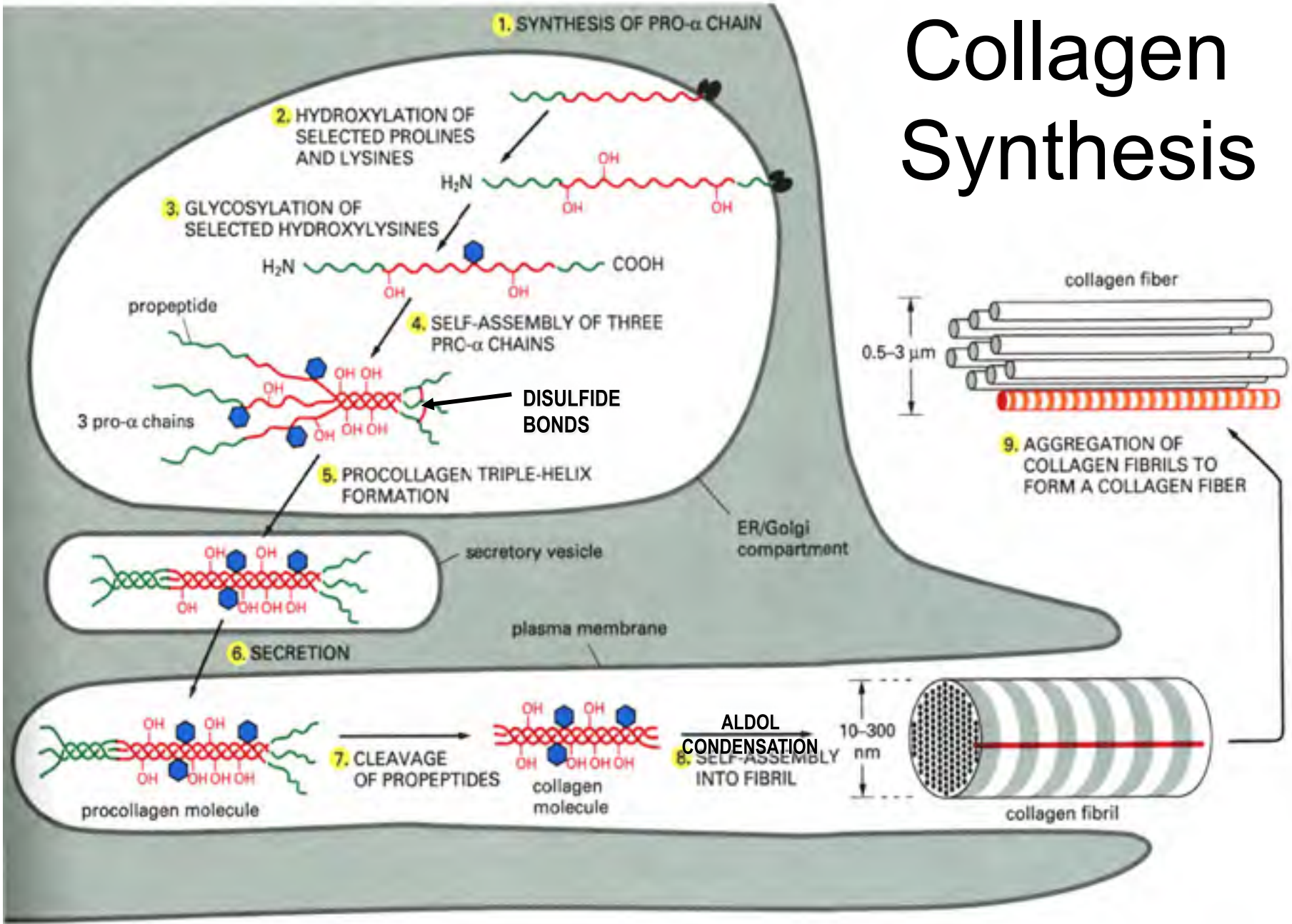


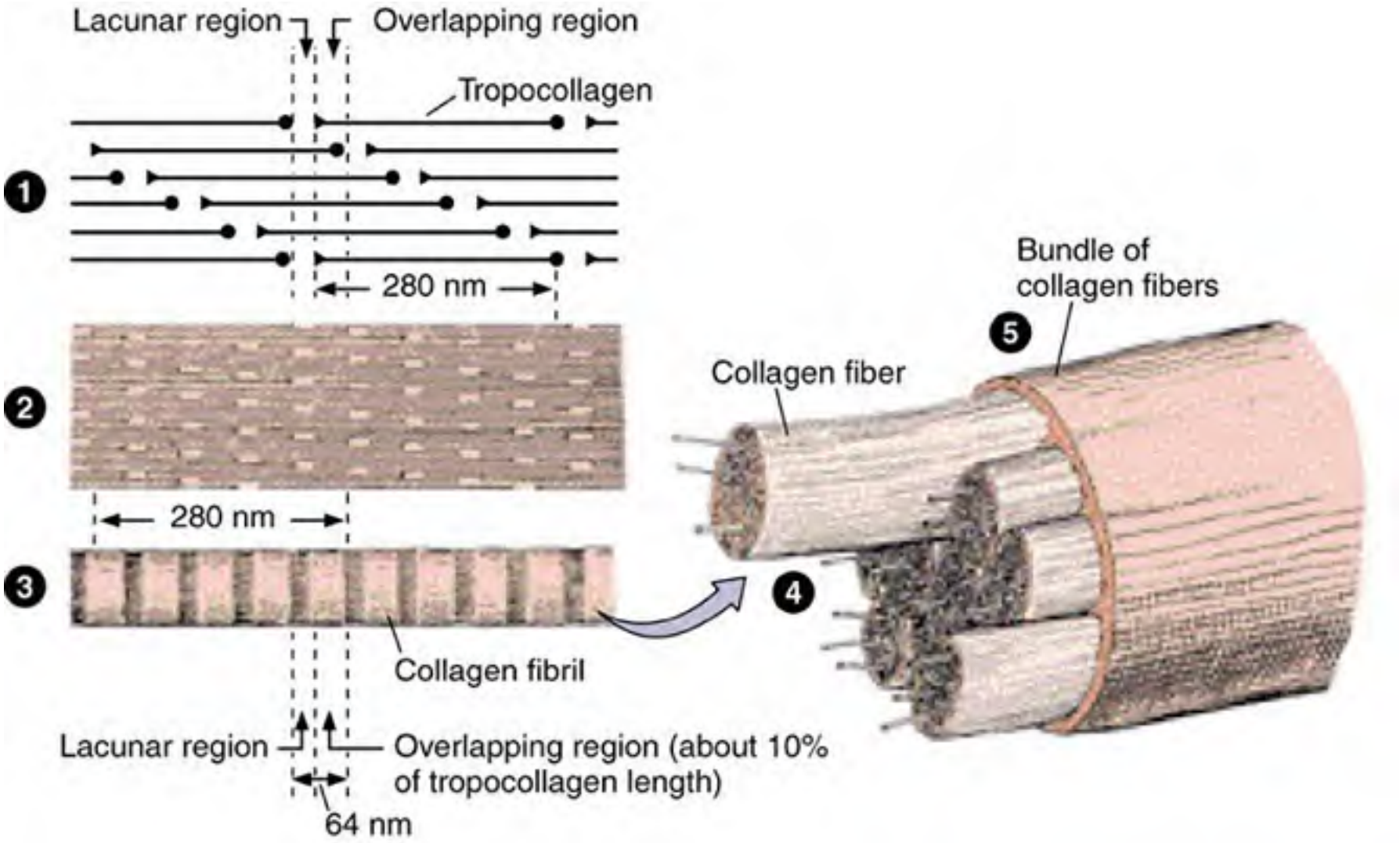
PD-INEL Junquiera and Carneiro. *Basic Histology*. Tenth Edition. 2003.

Collagen Synthesis



 Alberts et. al. *Molecular Biology of the Cell*. Second Edition.

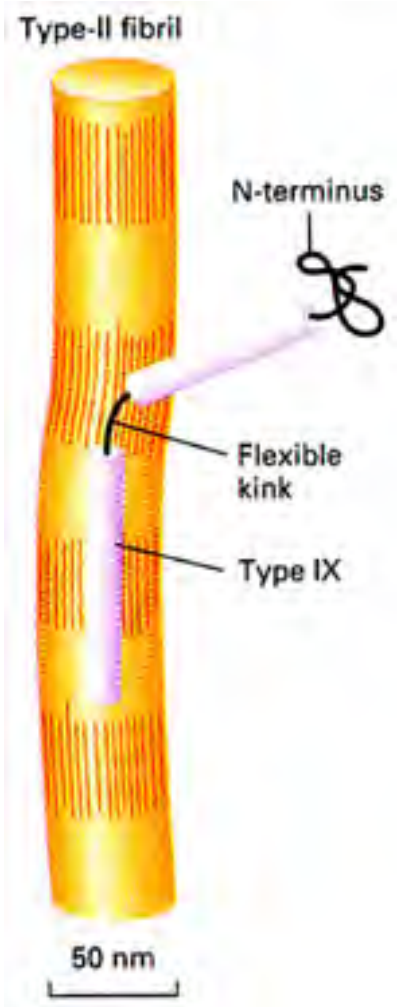
Assembly of collagen fiber bundles



 Junquiera and Carneiro. *Basic Histology*. Tenth Edition. 2003. Figure 5-19.

FACIT: Fibril-Associated Collagens with Interrupted Triple helices

1. Triple helices interrupted by non-helical domains
2. Retain propeptides at ends
3. Do not aggregate into large fibrils
4. Bind collagen fibrils to each other and/or the ECM

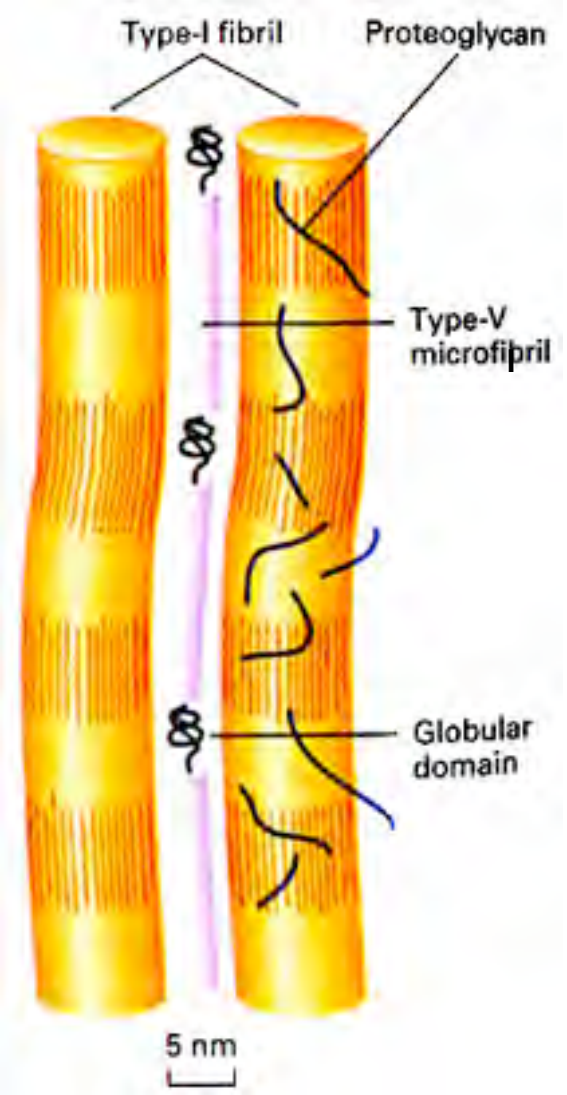


Type IX Collagen (left)

- Binds type II Fibrils to the ECM
- Globular N-terminus interacts with ECM
- Heparin-SO_4 at kink interacts with ECM
- Helical region interacts with type II fibril

Type VI Collagen (right)

Bundles type I fibrils into FIBERS
Binds fibrils via helical domains



 Alberts et. al. *Molecular Biology of the Cell*. Second Edition.

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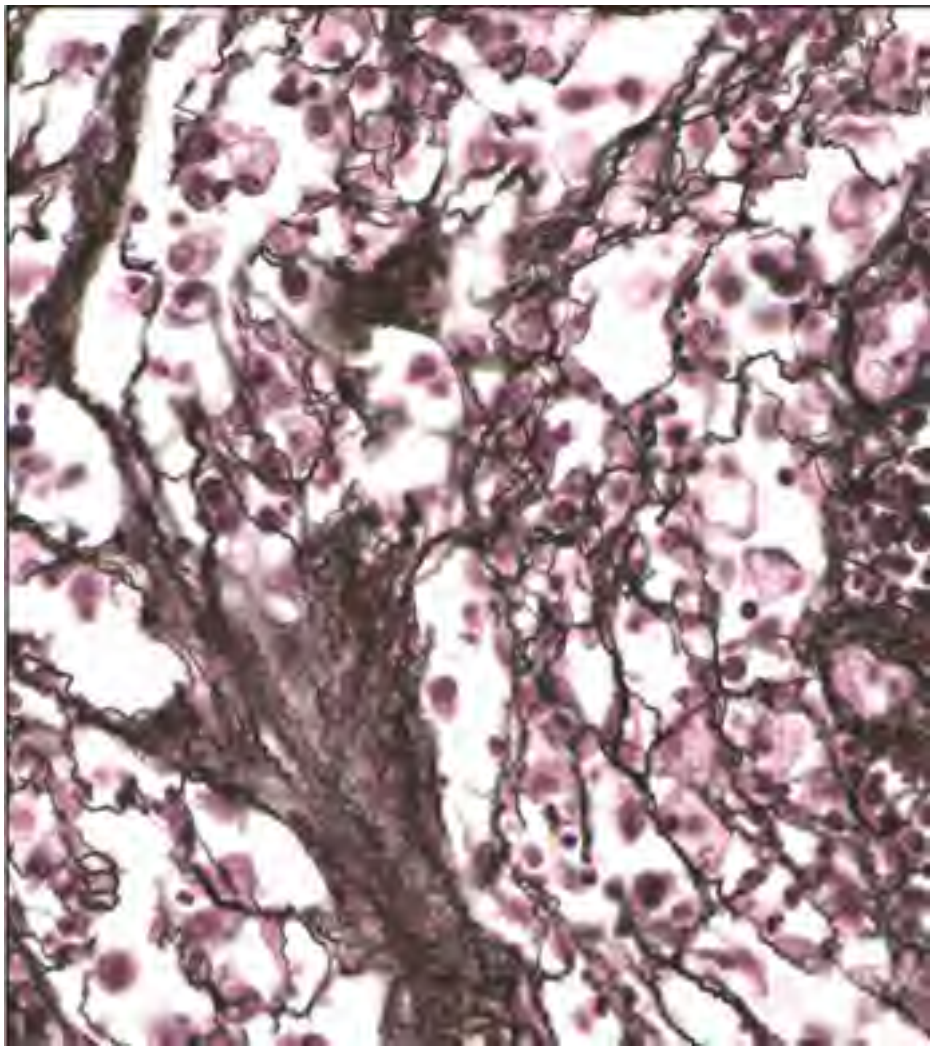
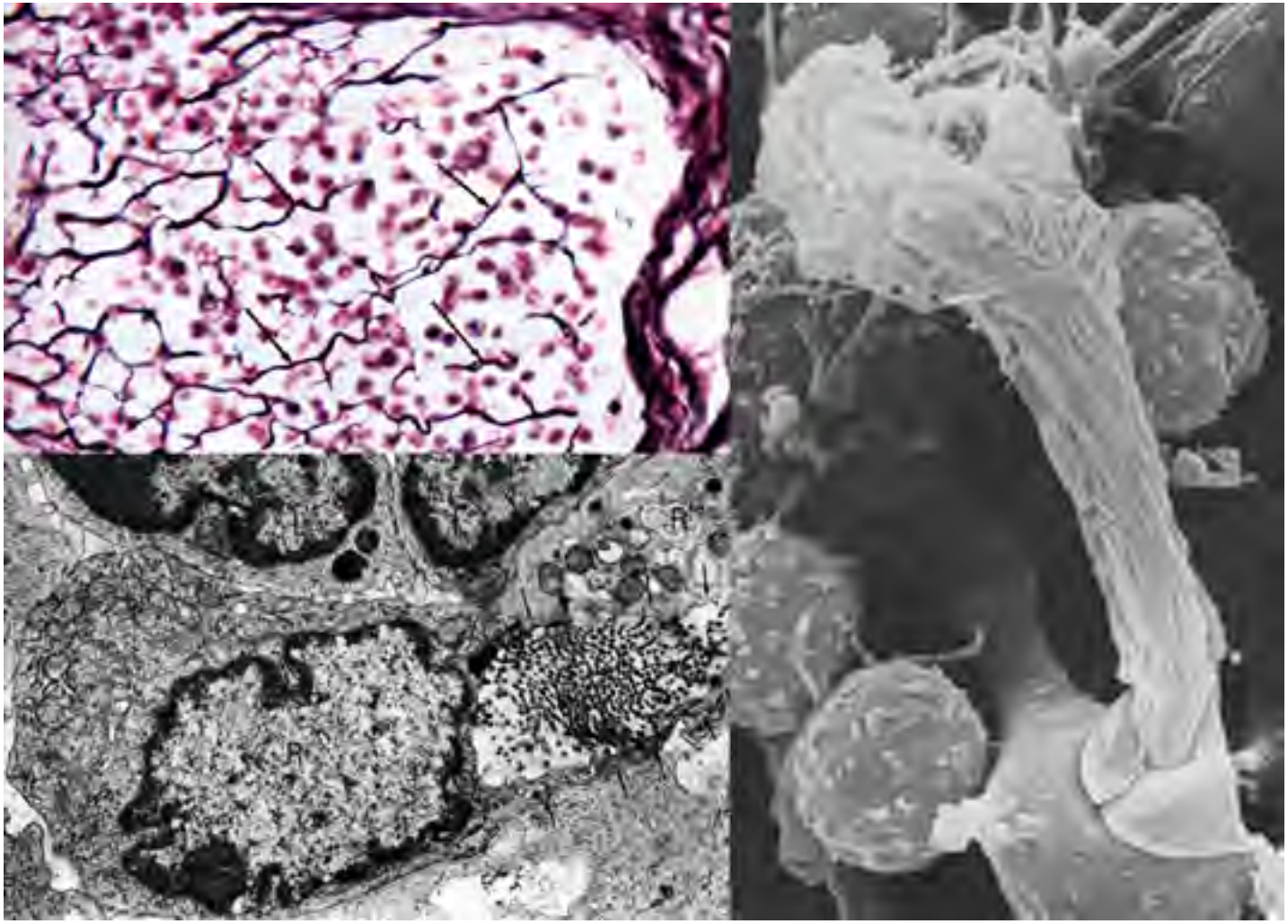
Reticular (Reticulin) Fibers



- Form a delicate supporting framework for highly cellular tissues (endocrine glands, lymph nodes, liver, bone marrow, spleen, smooth muscle).
- Composed mainly of Type III collagen, with a carbohydrate moiety that reduces Ag+ to metallic sliver = argyrophilic
- Special stain: silver impregnation to visualize.
- Thinner than type I collagen
  (Type III fibrils are 30-40 nm diameter; type I fibrils are ~200 nm diameter)

Reticular Fibers (type III collagen)

• made by reticular cells (specialized fibroblasts) and vascular smooth muscle cells

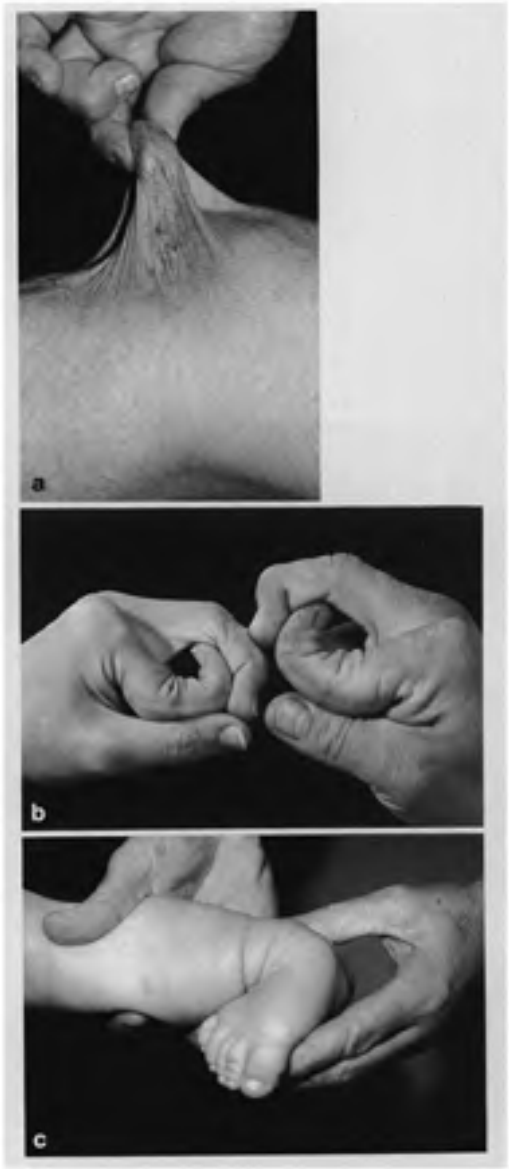


Top left: Ross,M, Pawlina, W. *Wheater's Functional Histology: A Text and Atlas*. Fifth Edition. 2006. Figure 6.12.
Bottom left and Far right: Source Undetermined

Clinical disorders resulting from defects in collagen synthesis

Type	Disease	Symptoms
I	Osteogenesis imperfecta	Spontaneous fractures, progressive hearing loss, cardiac insufficiency
III	Ehlers-Danlos (type IV)	Hypermobility of digits, early morbidity/mortality from rupture of aorta or intestine
multiple	Scurvy (lack of vit. C, a cofactor for prolyl and lysyl hydroxylase)	Ulceration of gums, hemorrhages

Ehlers-Danlos Syndromes



- **A series of genetic diseases with faulty assembly of collagens (lysyl hydroxylase deficiency).**
- **Hyperextensible skin and hypermobile joints**
- **In some forms (*e.g.*, type IV), weakness in blood vessels or intestines are life threatening.**

Noncollagen Components of the Extracellular Matrix

- Elastin
- “Ground substance”
  - Glycosaminoglycans (GAG’s)
  - Proteoglycans
  - Multiadhesive matrix proteins
    - laminin
    - fibronectin

Elastic Fibers

LM: Visualized by selectively staining with **Weigert's** resorcin-fuchsin, or aldehyde-fuchsin

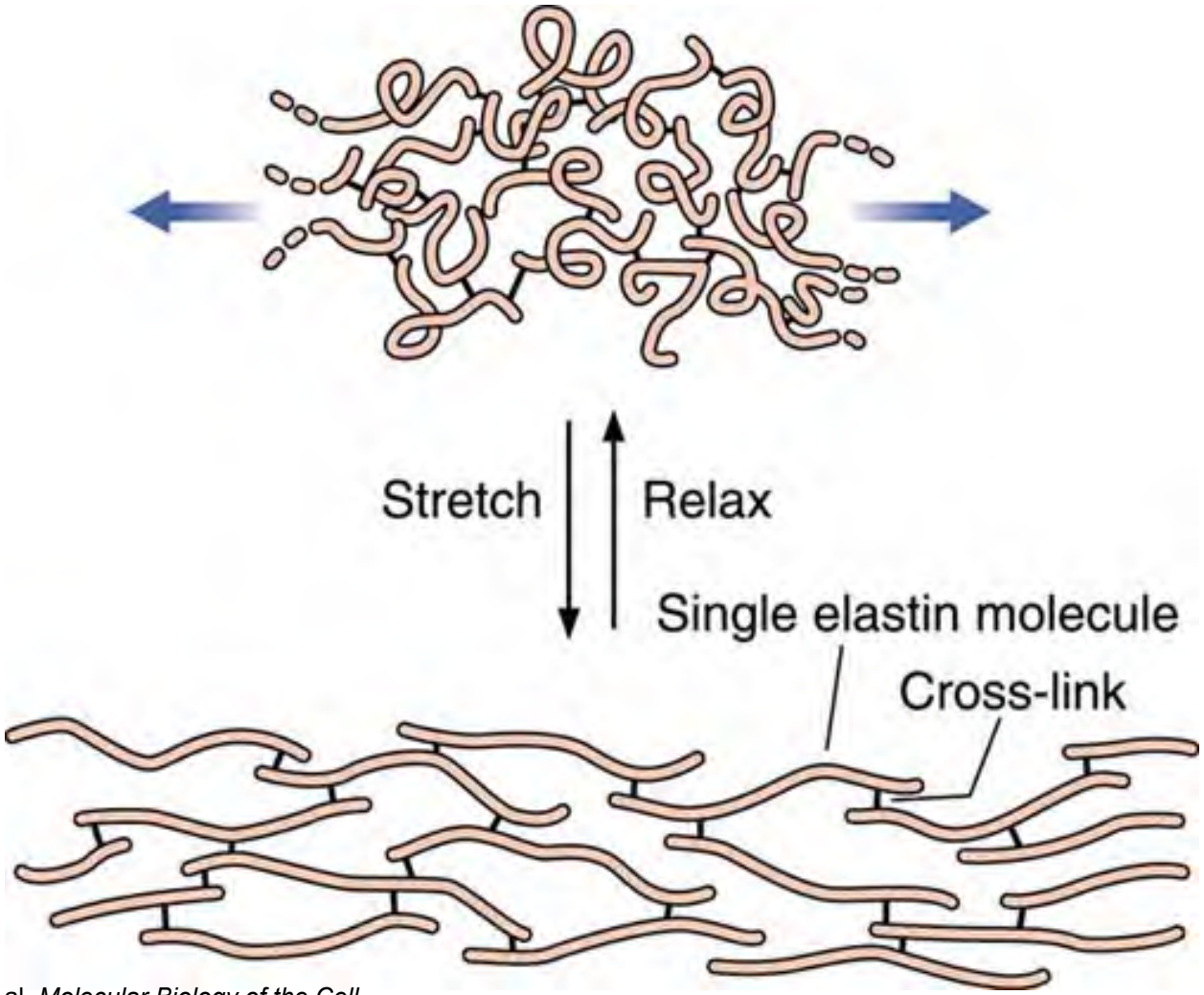
EM: Consist of amorphous core of **elastin** surrounded by microfibrillar glycoprotein, **fibrillin** **(8-10nm)**.

Elastin: is rich in glycine and proline, but it contains little or no hydroxyproline and hydroxylysine . uniquely contains **desmosine** and **isodesmosine**, which are thought to cross-link the molecules into a network of randomly coiled chains. This cross-linking is responsible for its rubber-like properties.

Confers elasticity: **present in large amounts in ligaments, lung, skin, bladder, and walls of blood vessels.**

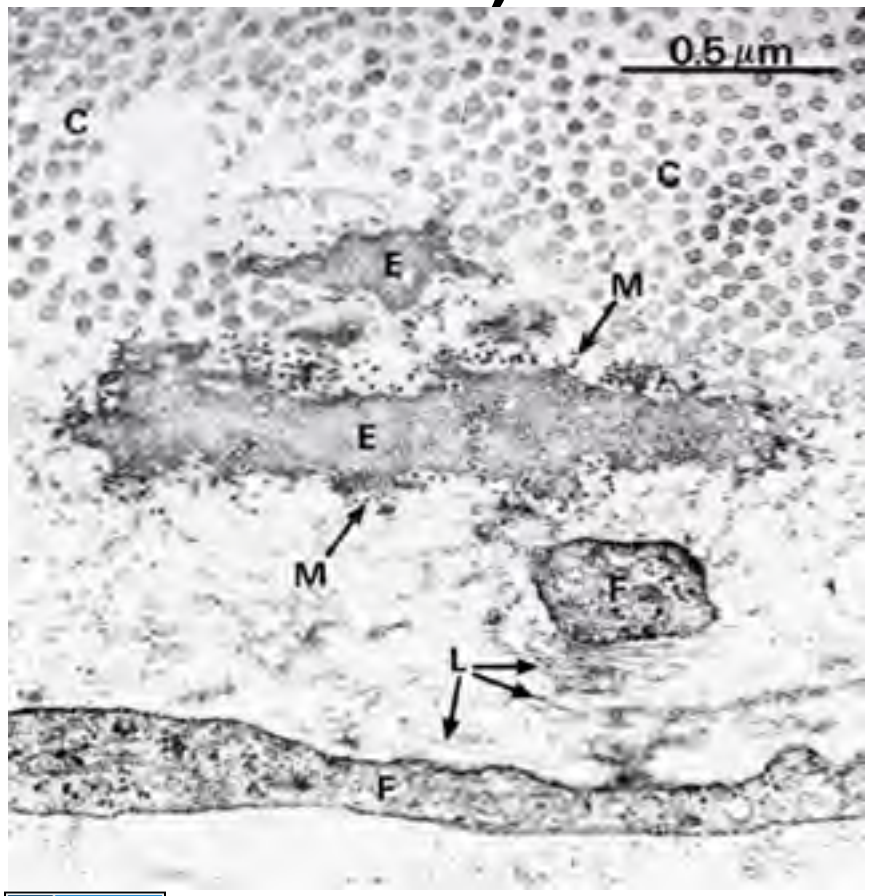
Marfan Syndrome: defect in elastic fiber synthesis; reduced elasticity in skin and lungs, skeletal defects (bones are longer and thinner than usual), cardiovascular complications (aneurism, valve prolapse)

Network of elastin molecules can stretch and recoil like a rubber band

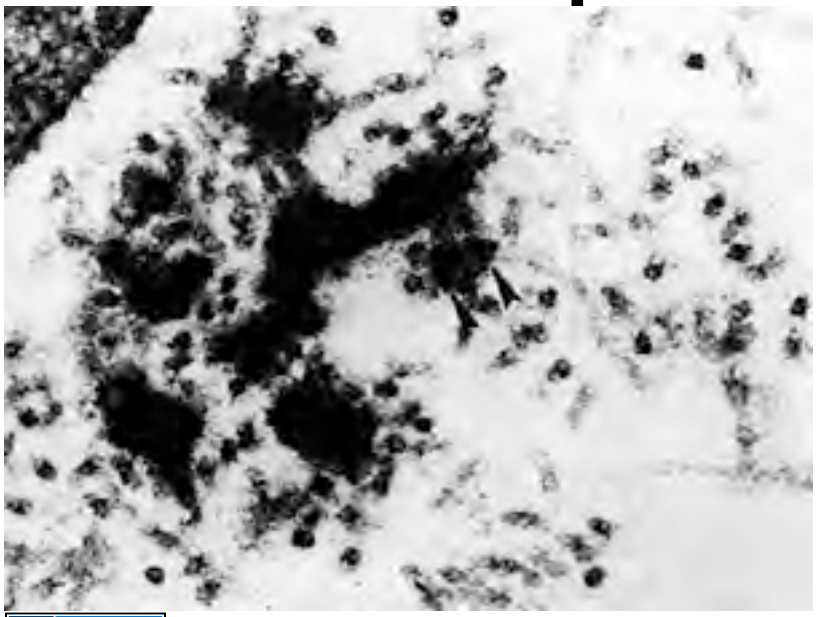


 Alberts et. al. *Molecular Biology of the Cell*.

Elastin appears amorphous (not fibrillar) in the electron microscope



PD-INEL Ross,M, Pawlina, W. *Wheater's Functional Histology: A Text and Atlas*. Fifth Edition. 2006. Figure 4.4.



PD-INEL Source Undetermined

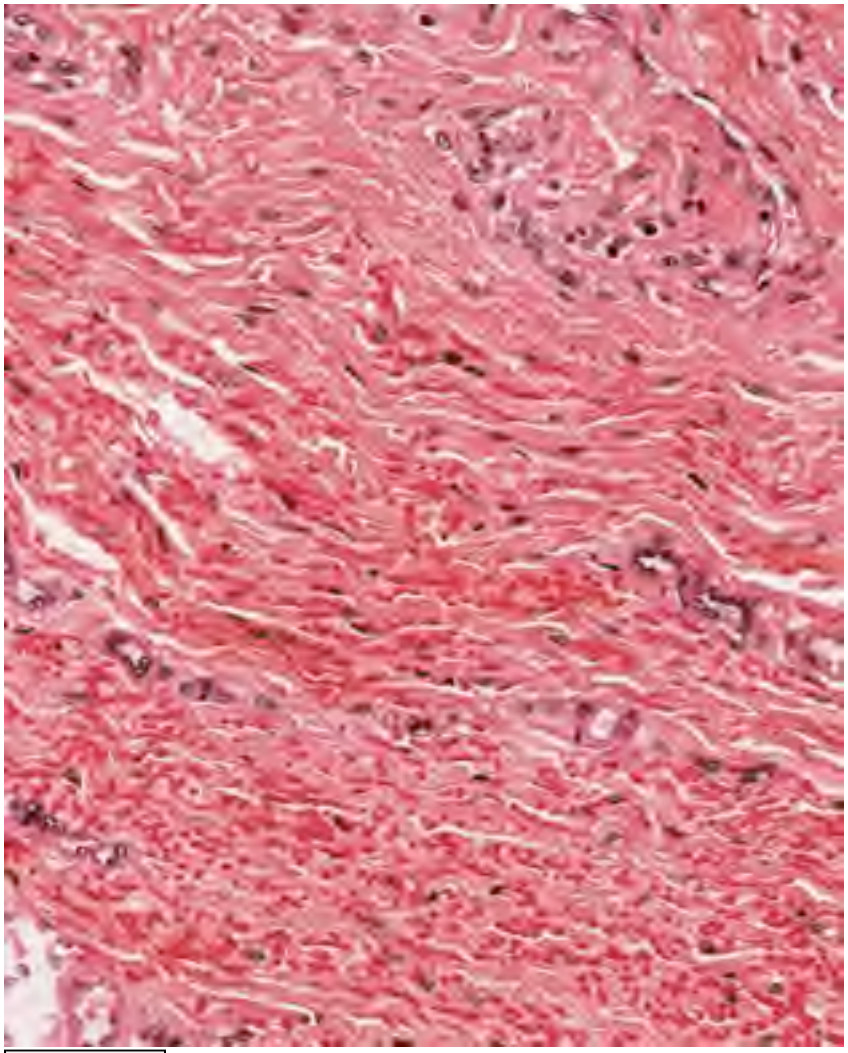
Image of elastin removed

E=elastin C, collagen fibrils

M/L=microfibrils of fibrillin, a scaffolding glycoprotein involved elastin deposition

Marfan Syndrome: defect in fibrillin gene, results in weakened elastic fibers

Elastic and Collagen Fibers



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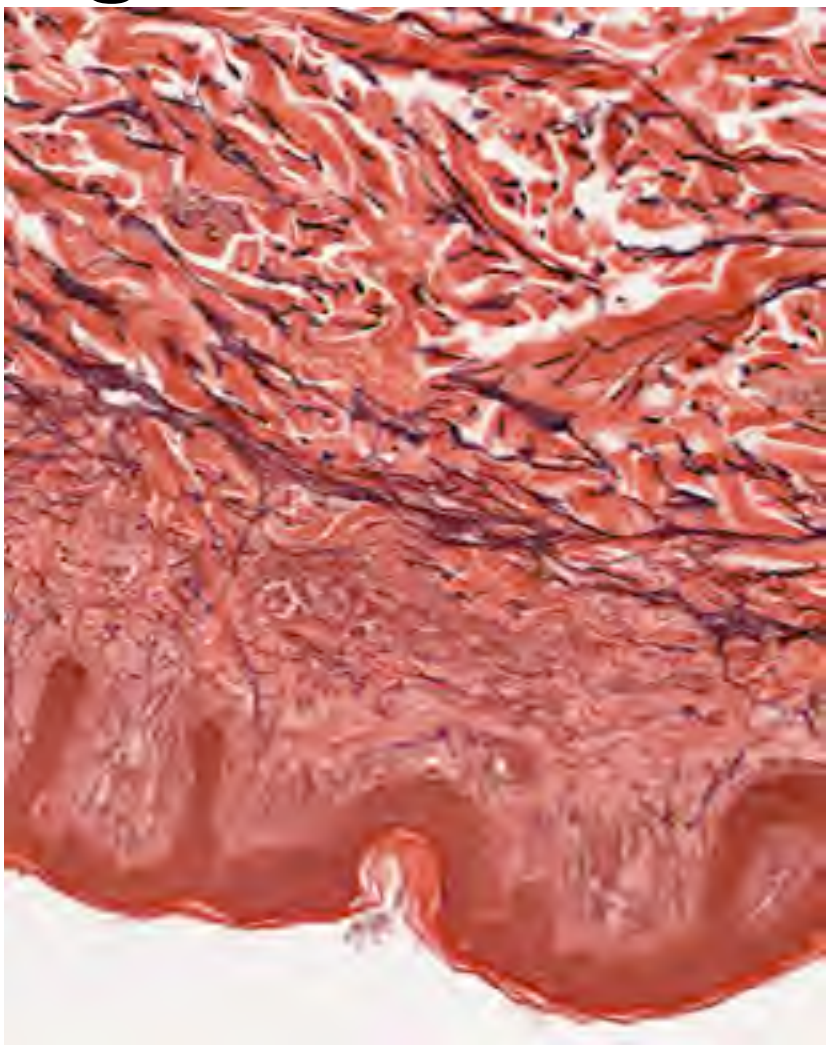
H&E stain: collagen stains *orange/pink*; elastic fibers stain *glassy red* (generally only visible if in HIGH abundance)



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elastin stain ("Weigert's", "aldehyde fuchsin", "Verhoeff"): elastic fibers are *purple/black*

collagen fibers stain *orange/pink* or blue/green depending on other stains used (von Gieson's or trichrome, respectively)

Ground Substance of the Extracellular Matrix (ECM)

1. Glycosaminoglycans (GAG)

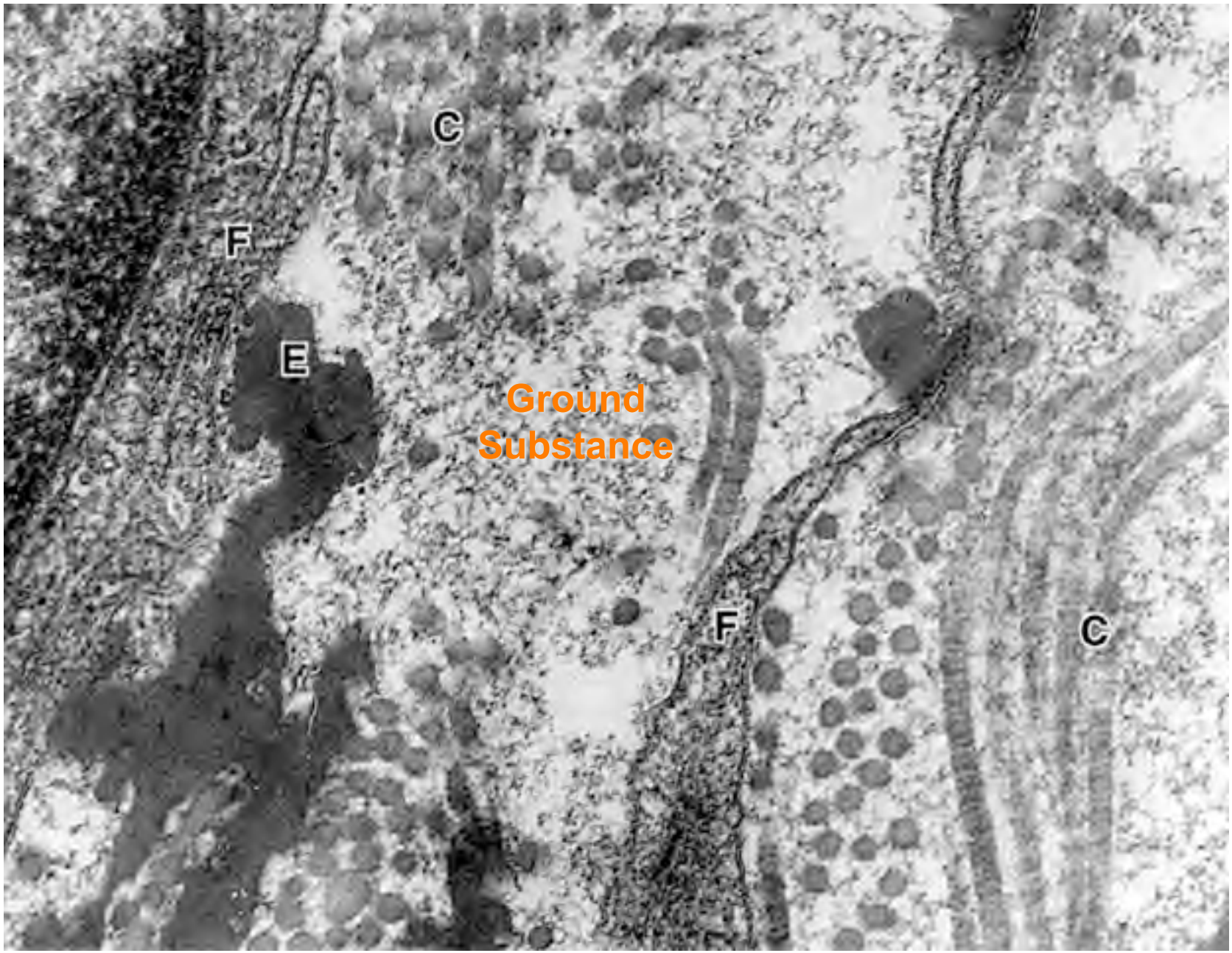
- linear (unbranched) polysaccharides, e.g. heparan sulfate, condroitin sulfate, keratan sulfate, hyaluronic acid
- very hydrophilic due to abundant negative charges (e.g. SO_4^- groups).
- except for hyaluronic acid, are usually bound covalently to protein core as part of a proteoglycan

2. Proteoglycans

- core protein + GAG side chains (like a bottle brush)
- bind cells, other proteins, and/or ECM components

3. Multiadhesive glycoproteins

- small glycosylated proteins containing NUMEROUS binding sites to cells, signaling molecules, and other ECM components
- e.g. fibronectin and laminin: important for adhesion of epithelial cells to the basal lamina via transmembrane integrin receptors.



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Basement Membrane – Collagen Types IV, VII, and III

- **Basement membranes are sheets of extracellular matrix proteins located at the interface of parenchyma (epithelia, endothelia, muscle, nerves, adipocytes) and connective tissue / ECM.**
- **Main constituents are glycosaminoglycans (heparan sulfate), fibrous proteins (collagen types IV, VII, III), structural glycoproteins fibronectin, laminin and entactin.**
- **This is NOT a plasma membrane.**

Basement membranes vary in thickness

Thick

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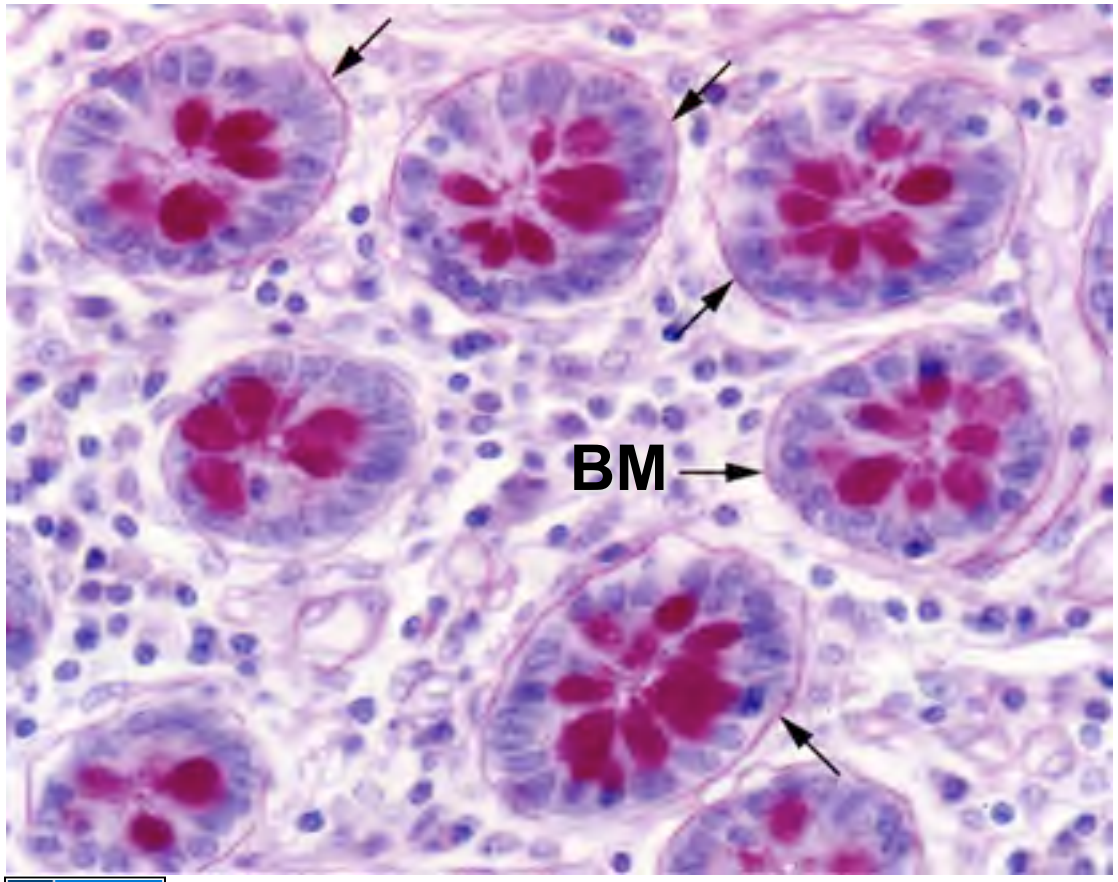
trachea, H&E

Thin -- requires special stain to visualize



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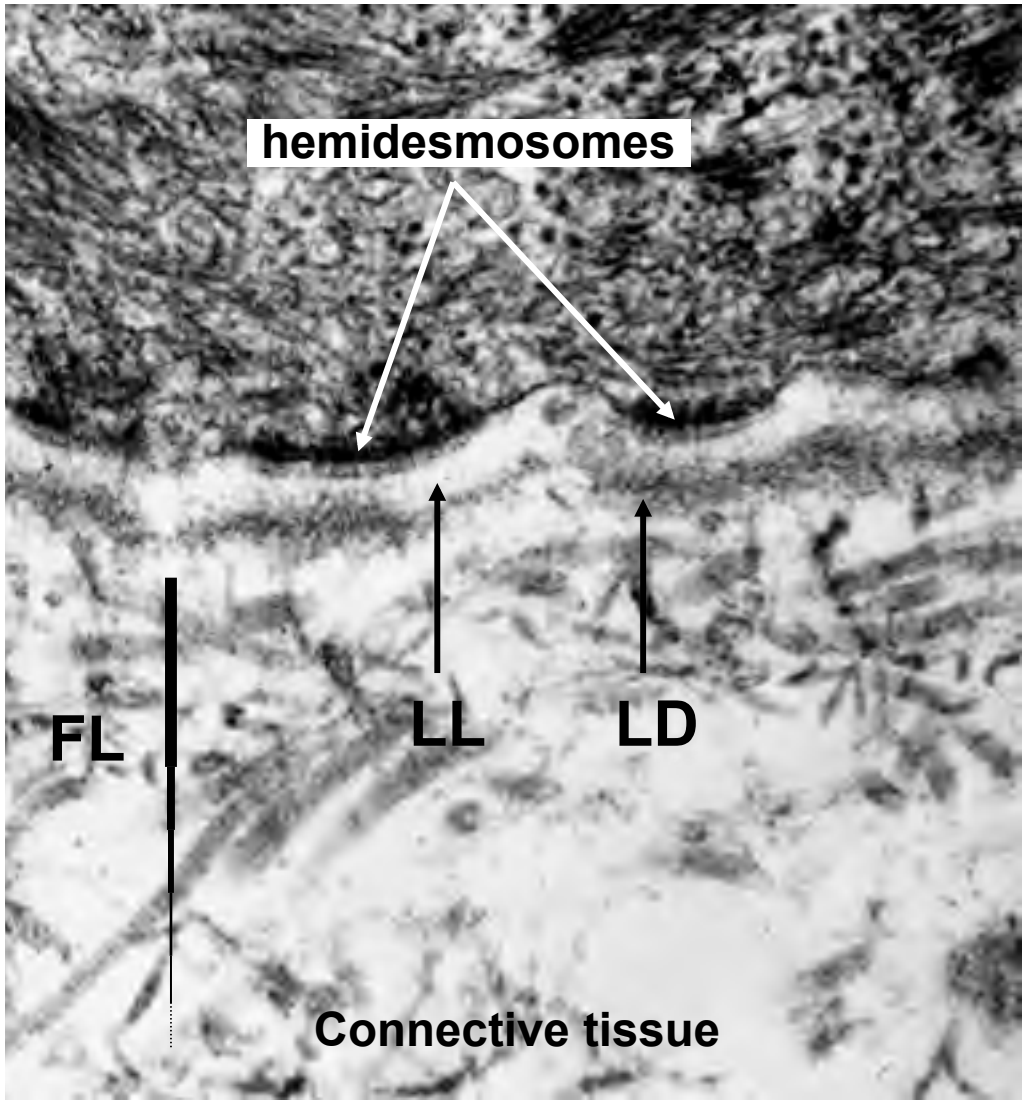
Intestinal glands, PAS

PAS reacts with **carbohydrate-rich molecules** such as perlecan, laminin and type III collagen associated with the basement membrane.

Basement Membrane(LM): Three layers in the EM



basal lamina

1. lamina lucida (LL) or rara 10-50 nm
2. lamina densa (LD) 20-300 nm (type IV collagen)

fibroreticular lamina

3. Fibroreticular lamina (FL) merges with underlying CT (type III* and type VII collagen fibrils)

**basement membranes can also be visualized with silver stain*

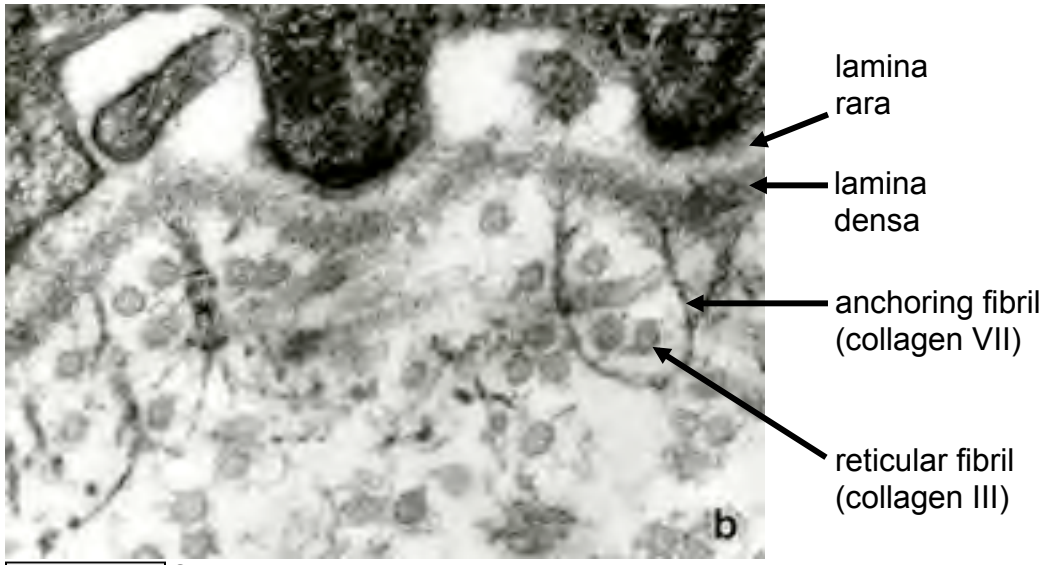
So, the "basement membrane" is the basal lamina + the fibroreticular lamina

Image of cell junctions removed

Tying it all together

Interactions of many proteins tether cell to the underlying connective tissue:

Cell to basal lamina…
- Hemidesmosome
- Type IV collagen
- Integrin/laminin



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Basal lamina to underlying connective tissue:
- Type IV collagen
- Type VIII collagen
- Fibrillin
- Type III collagen

Cells in Connective Tissue

Fixed
(permanent residents)

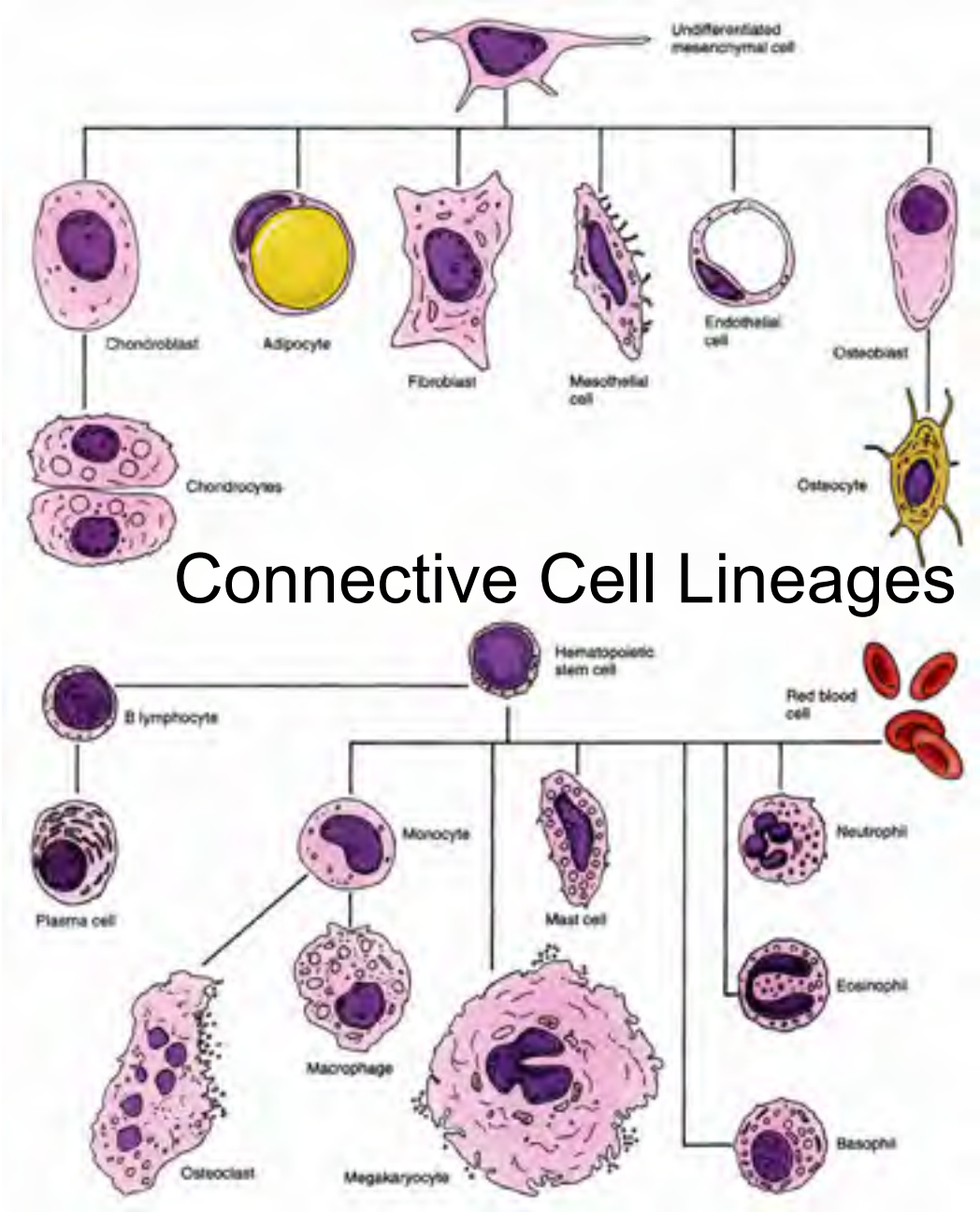
1. **Fibroblasts**
2. **Adipose (fat) cells**
3. **Tissue Macrophages****
4. **Mast cells****

Free
(transient residents)

5. **Lymphocytes & Plasma Cells (differentiated B-cells) ****
6. **"Leukocytes"****

(specifically, neutrophils, eosinophils, & basophils)

**** derived from hematopoietic stem cells and involved in immune function and inflammation**



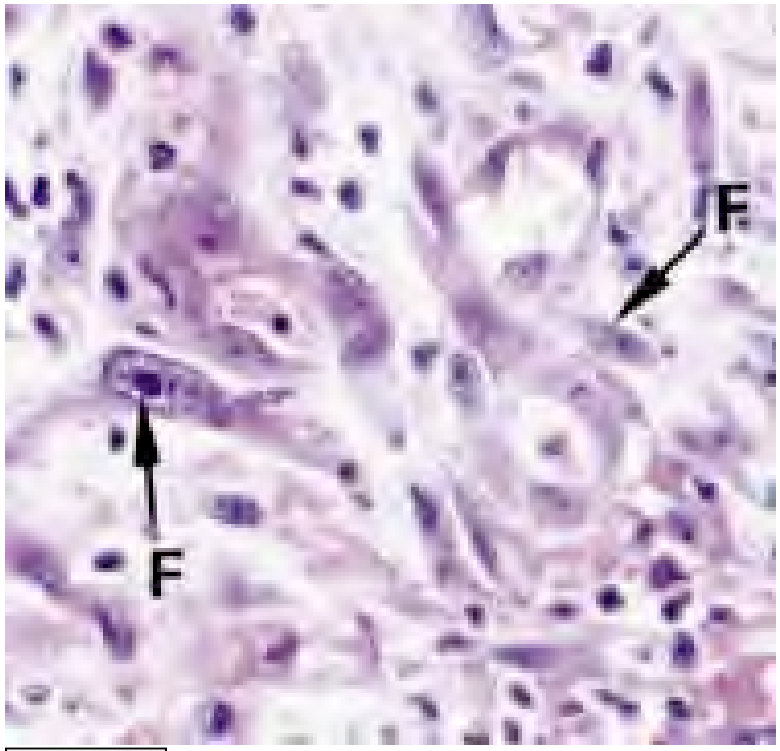
 Junqueira and Carneiro. *Basic Histology.* Tenth Edition. 2003.

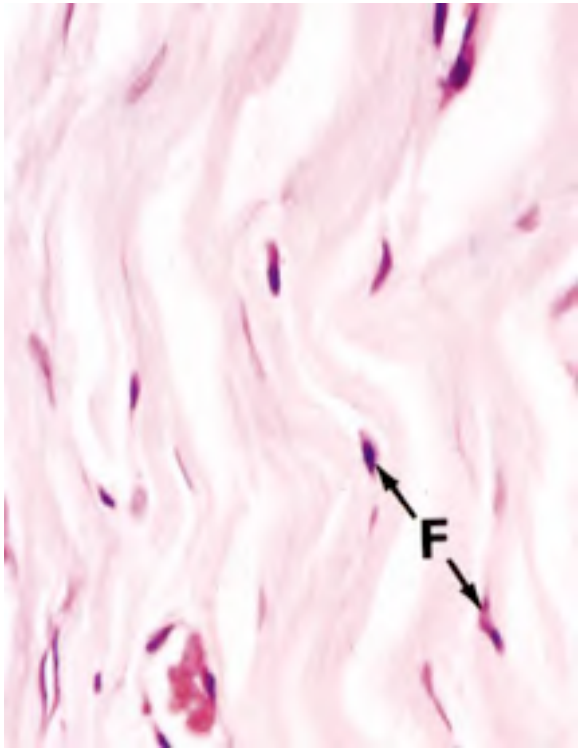
Fibroblasts are the most common cells in connective tissue

- Synthesize and secrete components of the ECM: fibers and ground substance.
- Active and quiescent stages (when quiescent sometimes called fibrocytes or mature fibroblasts).
- Synthesize growth factors.
- Rarely undergo cell division unless tissue is injured, which activates the quiescent cells.
- Play a major role in the process of wound healing and respond to an injury by proliferating and enhanced fiber formation.

Image of active and inactive fibroblasts removed

Active and inactive fibroblasts



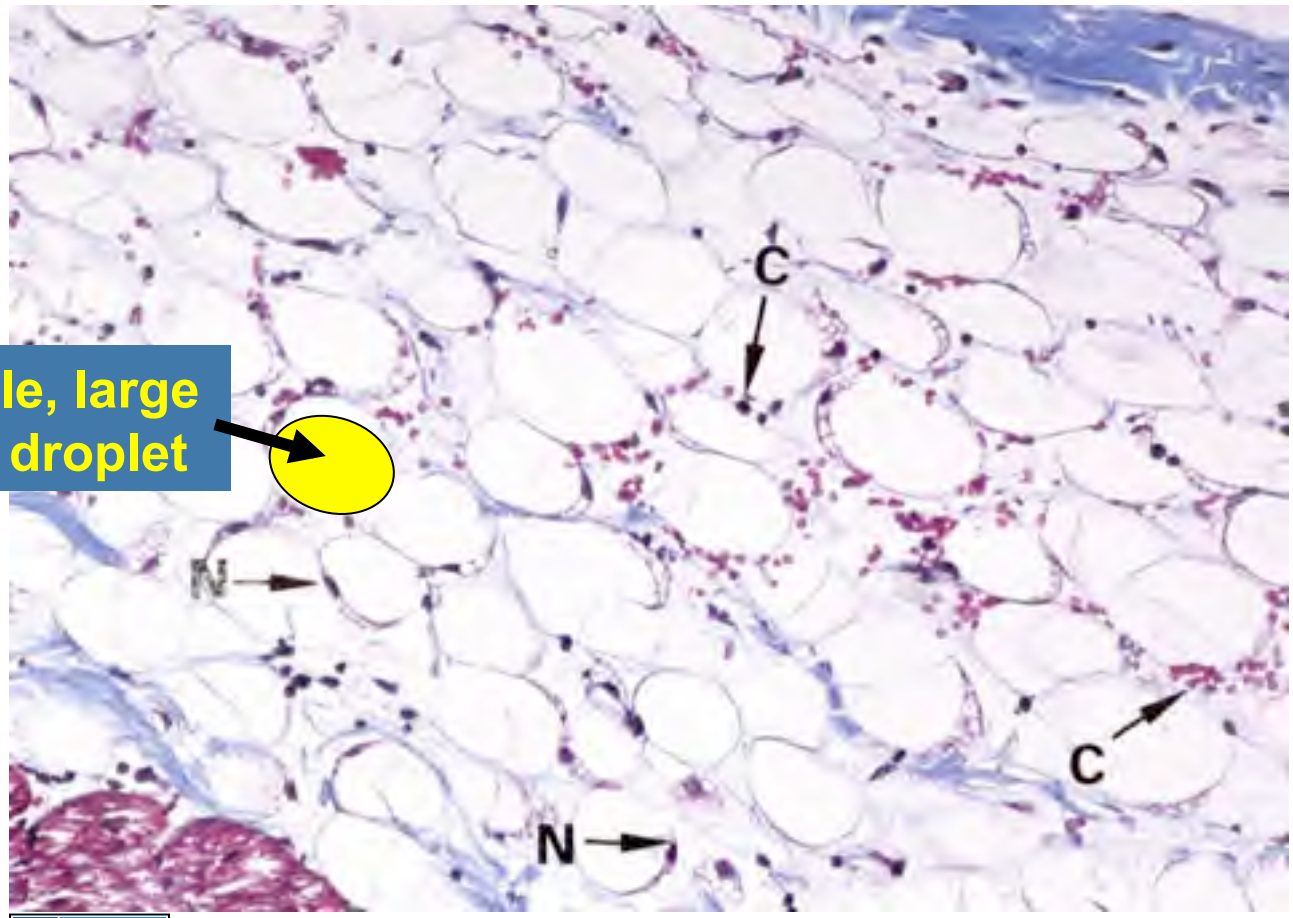


 (Both images) Ross, M. Pawlina, W. *Wheater's Functional Histology: A Text and Atlas*. Fifth Edition. 2006.

Adipocytes predominate in adipose tissue

Very active cells with **many** functions:

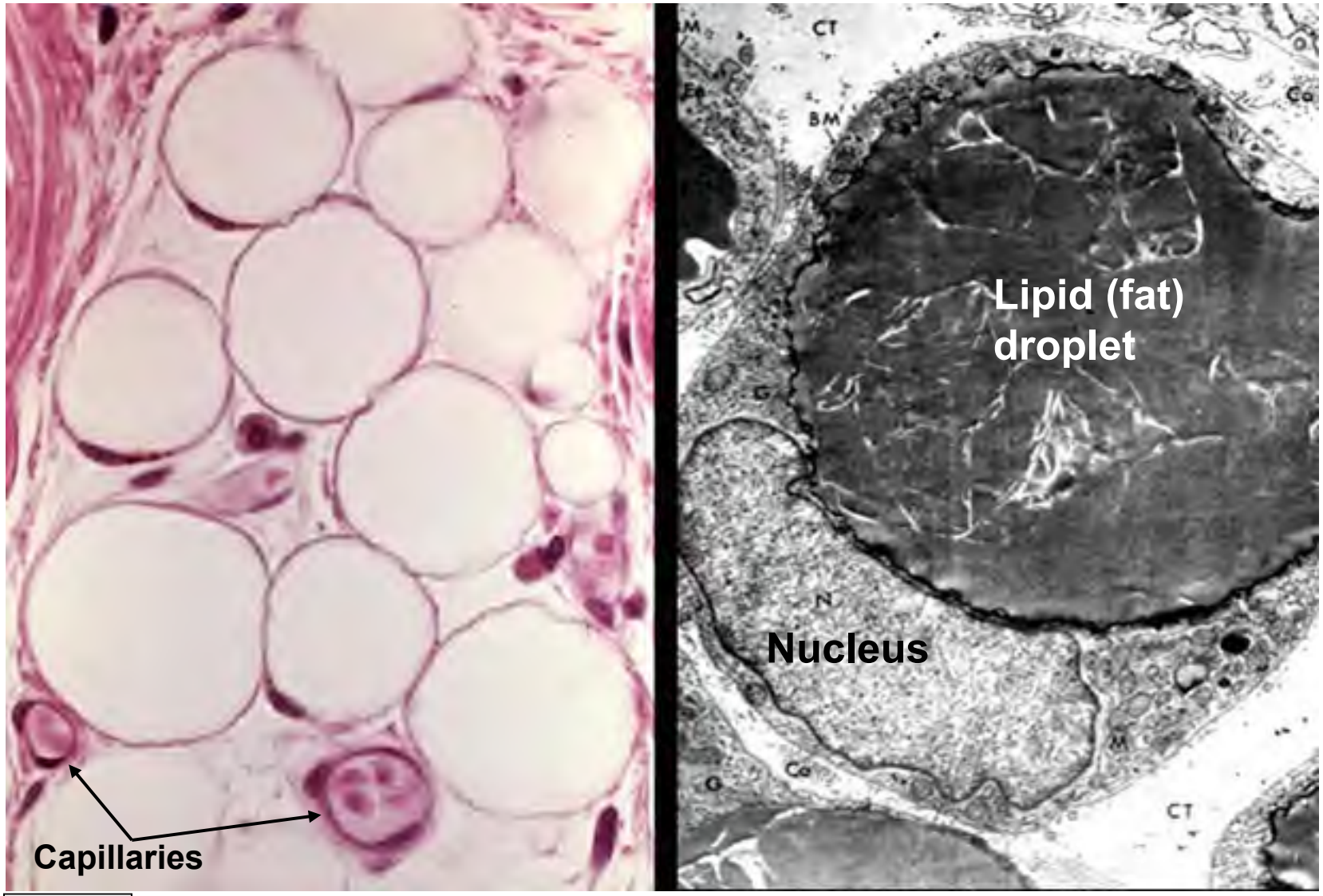
- Triglyceride storage and glucose metabolism (insulin and glucagon receptors)
- Secretion of many bioactive molecules:
  leptin (regulates satiety) **angiotensinogen** (blood pressure) **steroids** (glucocorticoids & sex hormones)
  growth factors (e.g. insulin-like growth factor, tumor necrosis factor α) **cytokines** (e.g. interleukin-6)



 Ross, M. Pawlina, W. *Wheater's Functional Histology: A Text and Atlas*. Fifth Edition. 2006.

White (common, yellow, unilocular) adipose tissue stained with Masson's trichrome

Adipocytes



Brown (Multilocular) Adipose Tissue

Present in newborns (and hibernating mammals) and involved in thermoregulation

Mitochondria of brown fat cells express *uncoupling protein* which "short circuits" the electron transport chain producing HEAT rather than ATP.

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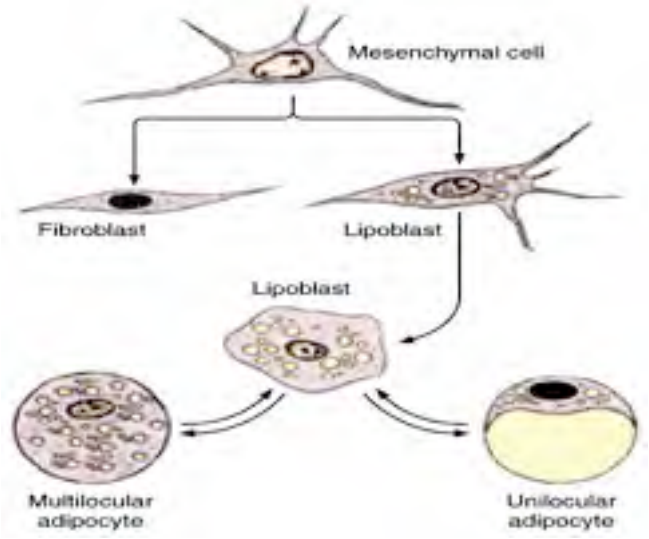

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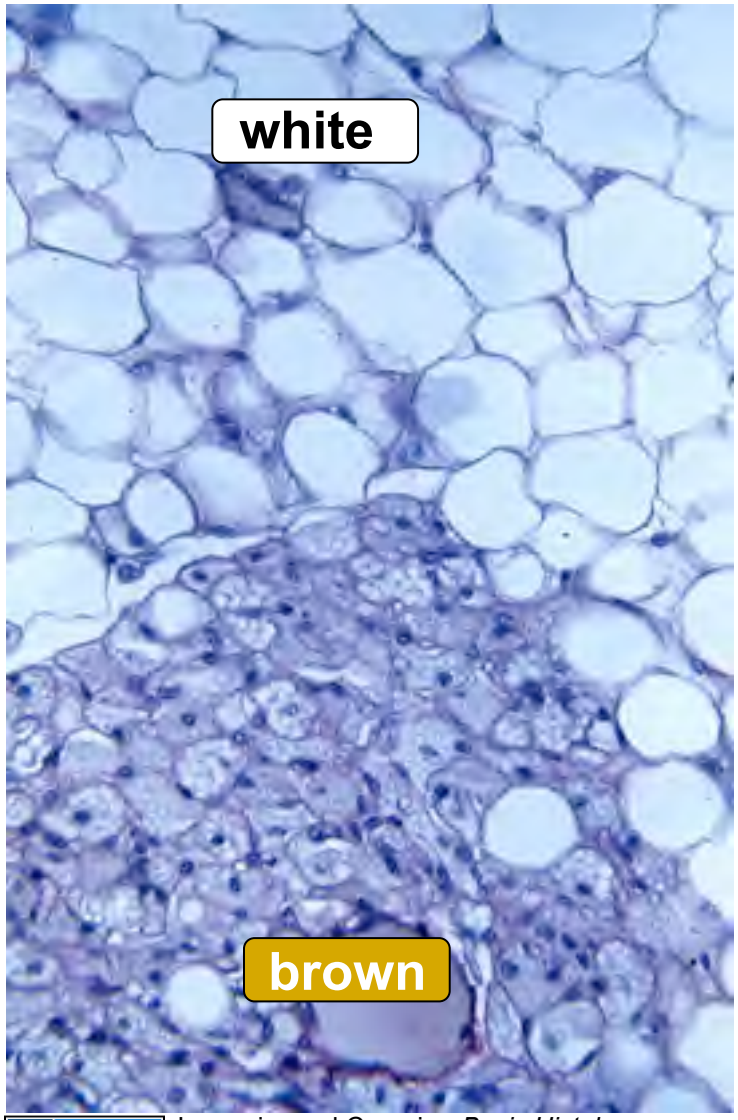

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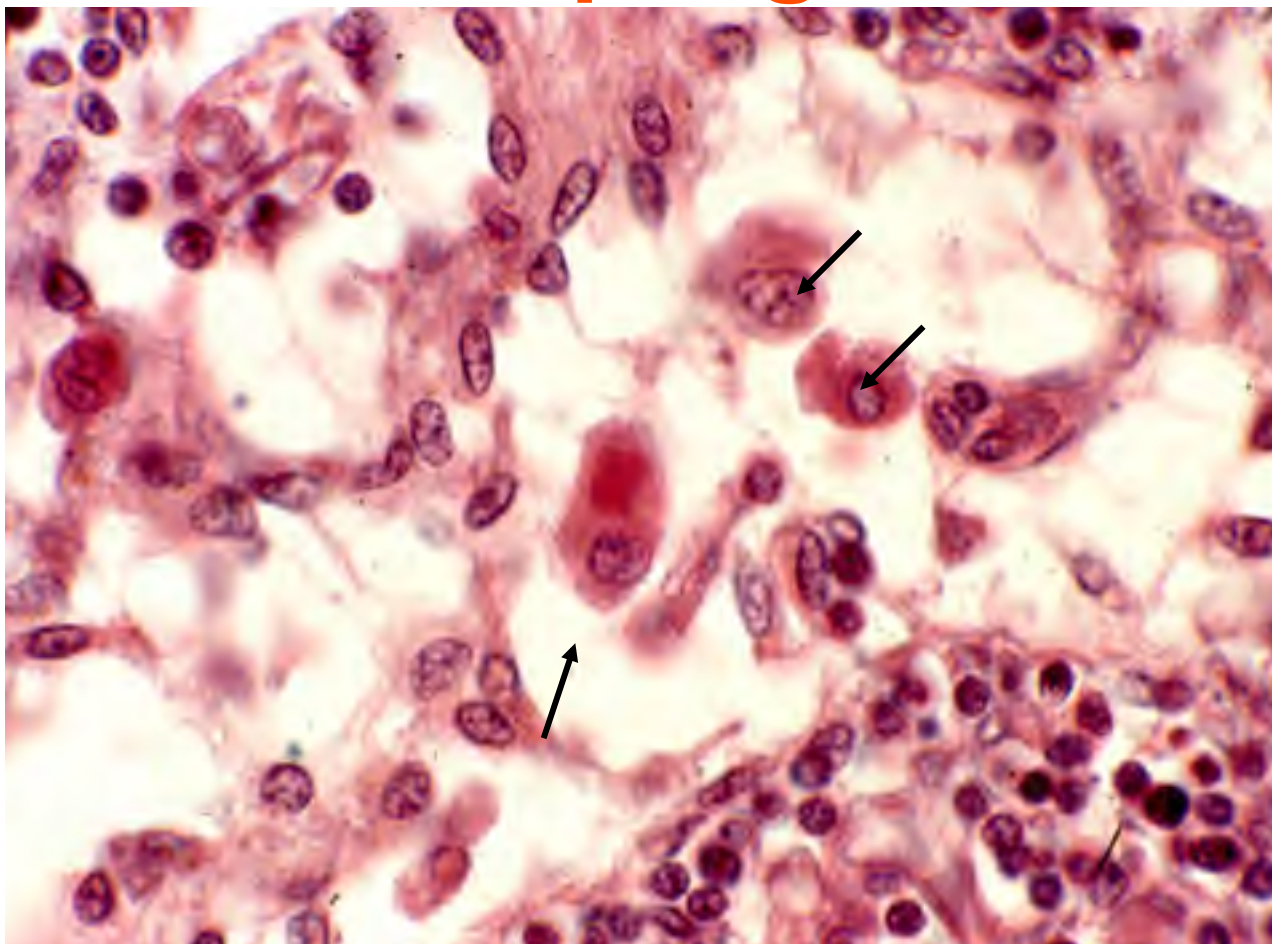
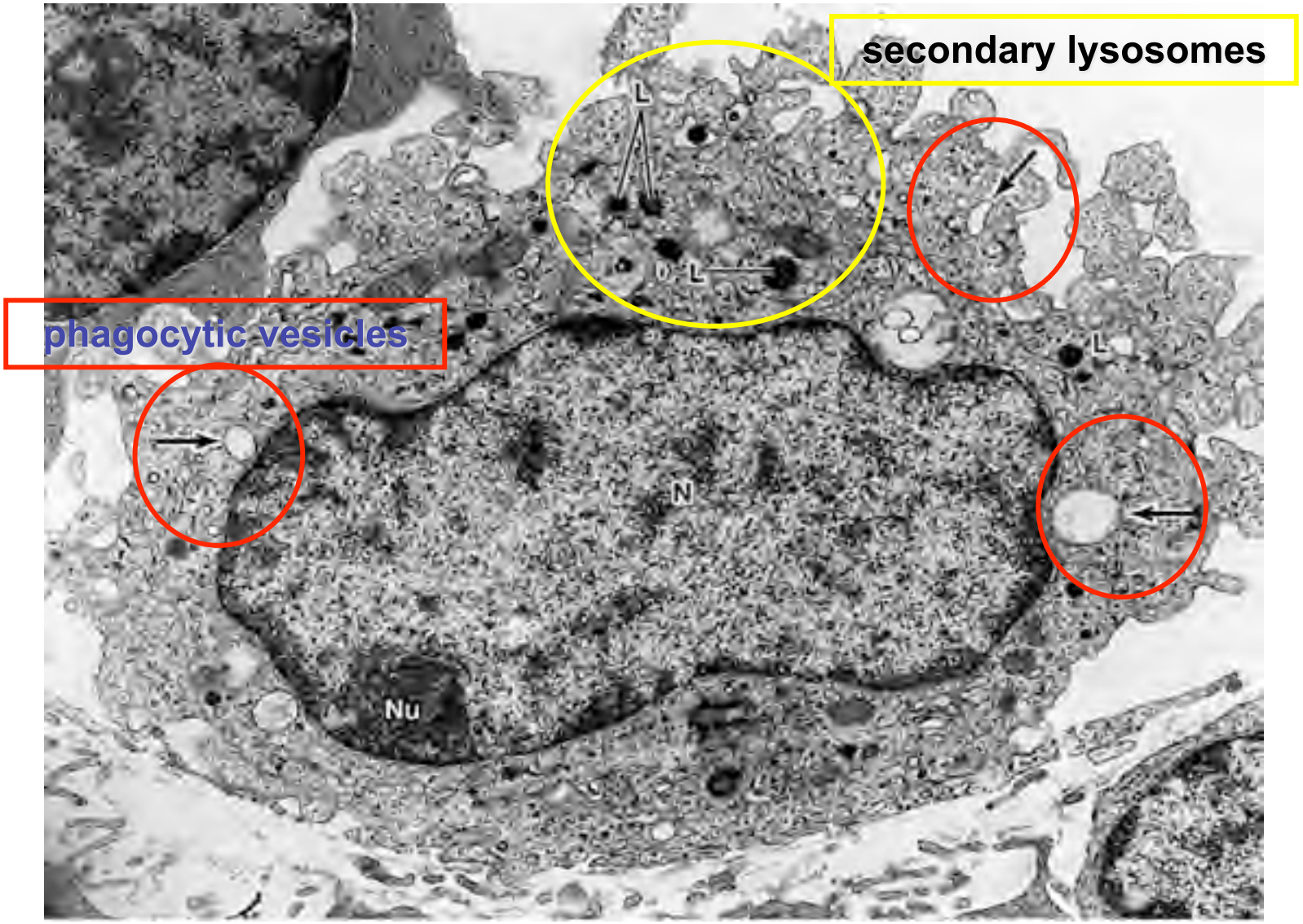
Monocytes escape from blood vessels into connective tissue where they differentiate into

Macrophages



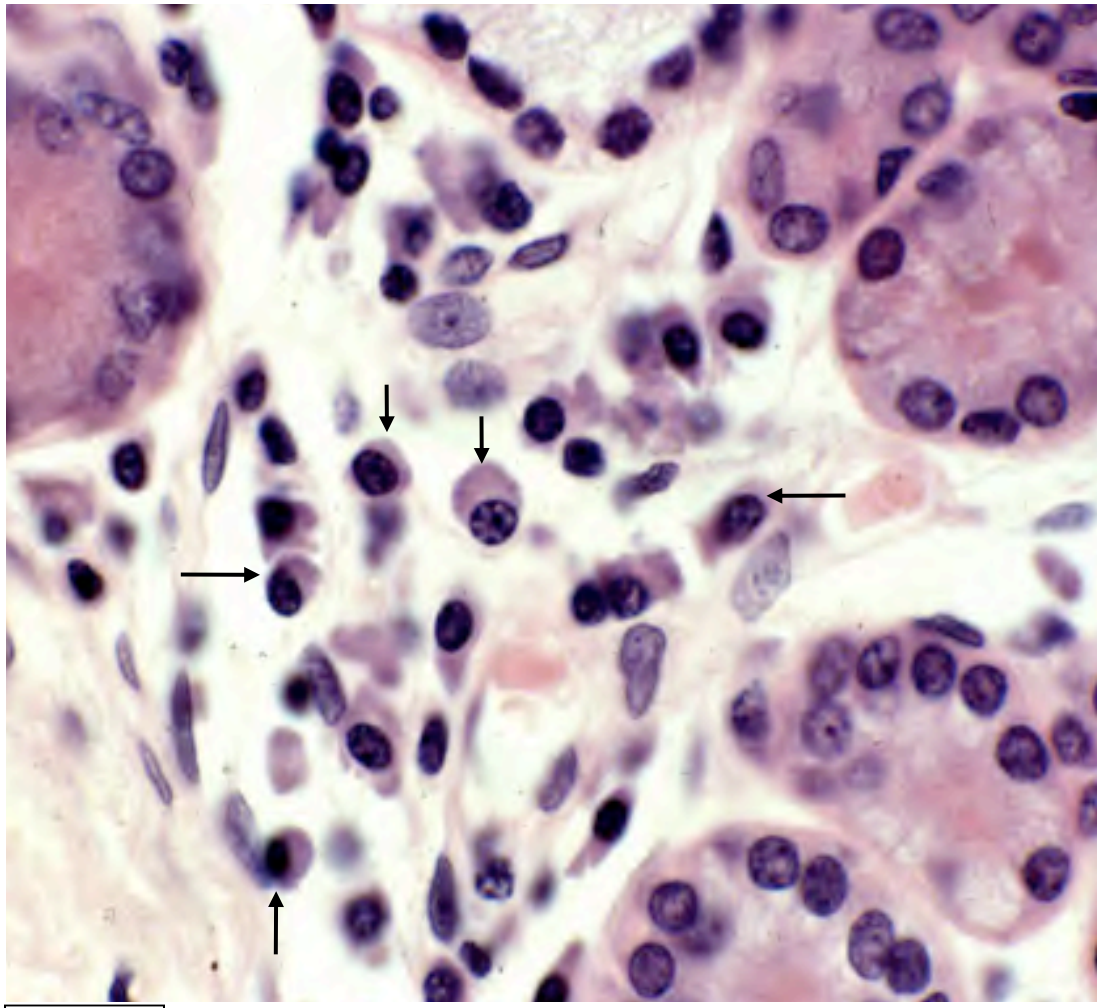
Primary function: phagocytosis and antigen presentation

Ultrastructural features of a Macrophage



 Junqueira and Carneiro. *Basic Histology.* Tenth Edition. 2003. Figure 5.7.

Plasma Cells are mature B lymphocytes that constitutively secrete antibodies



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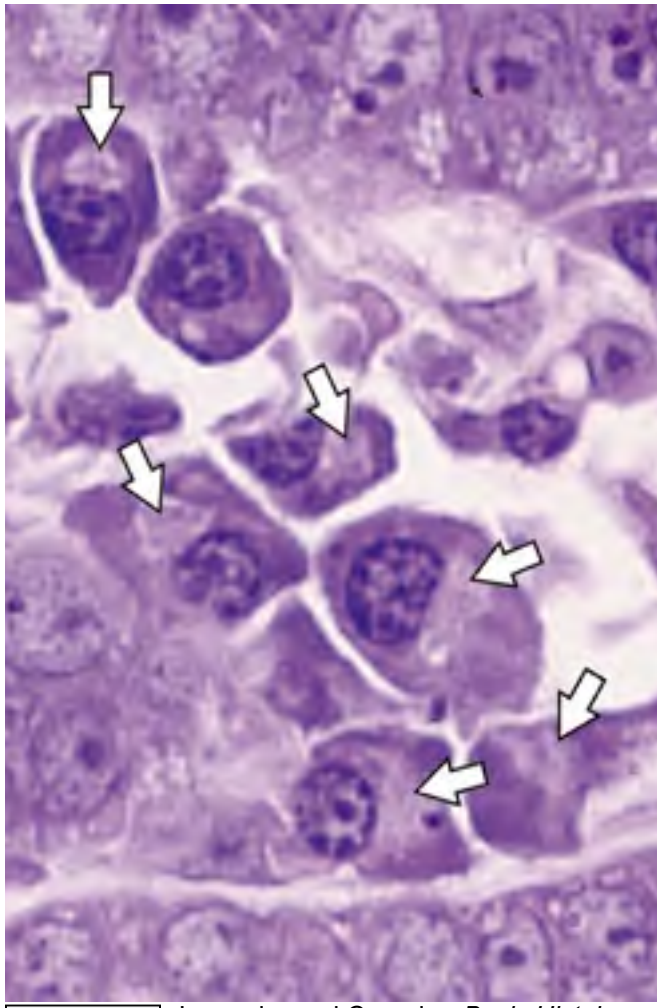
Black arrows indicate several plasma cells



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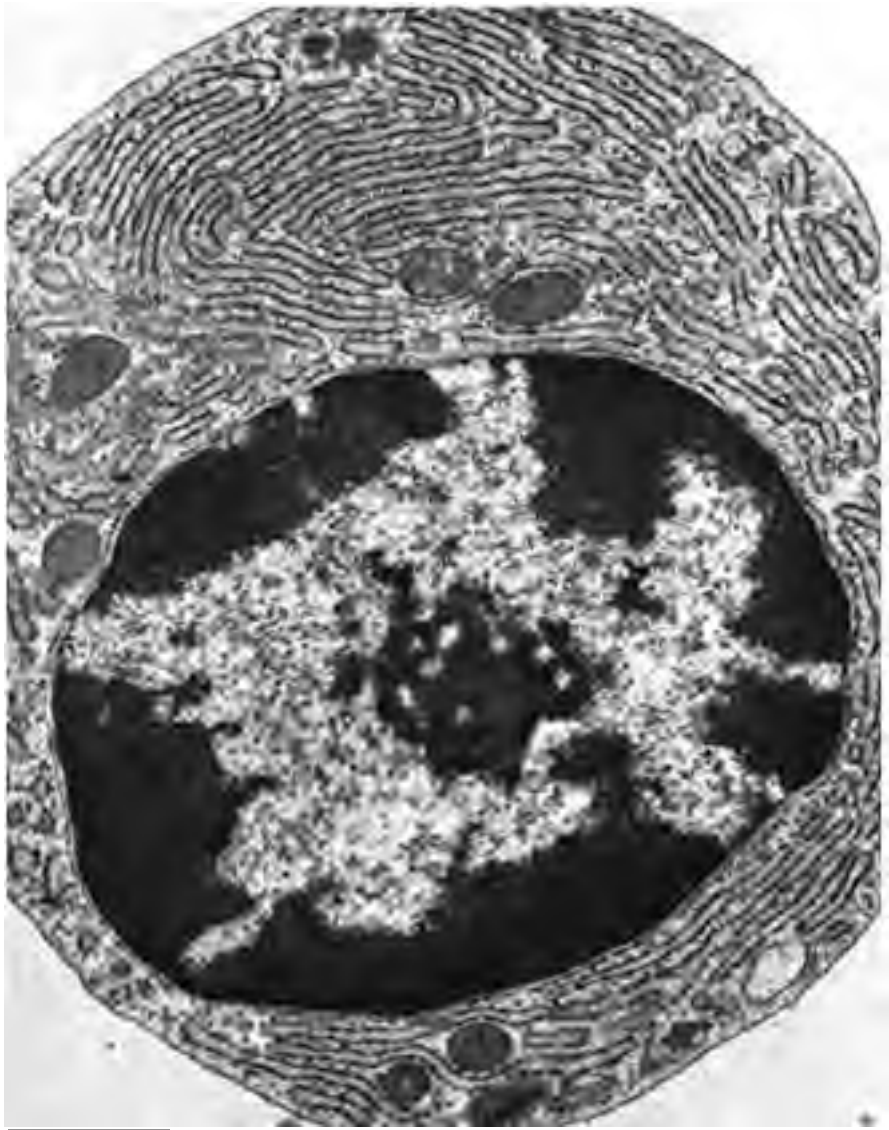
White arrows = Golgi regions

EM of Plasma Cells



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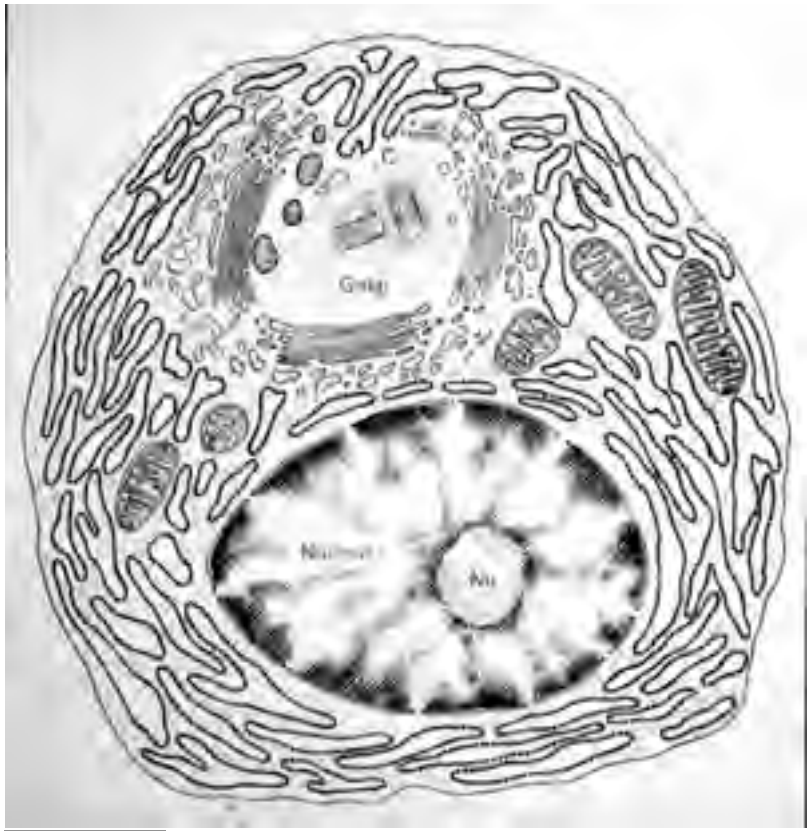

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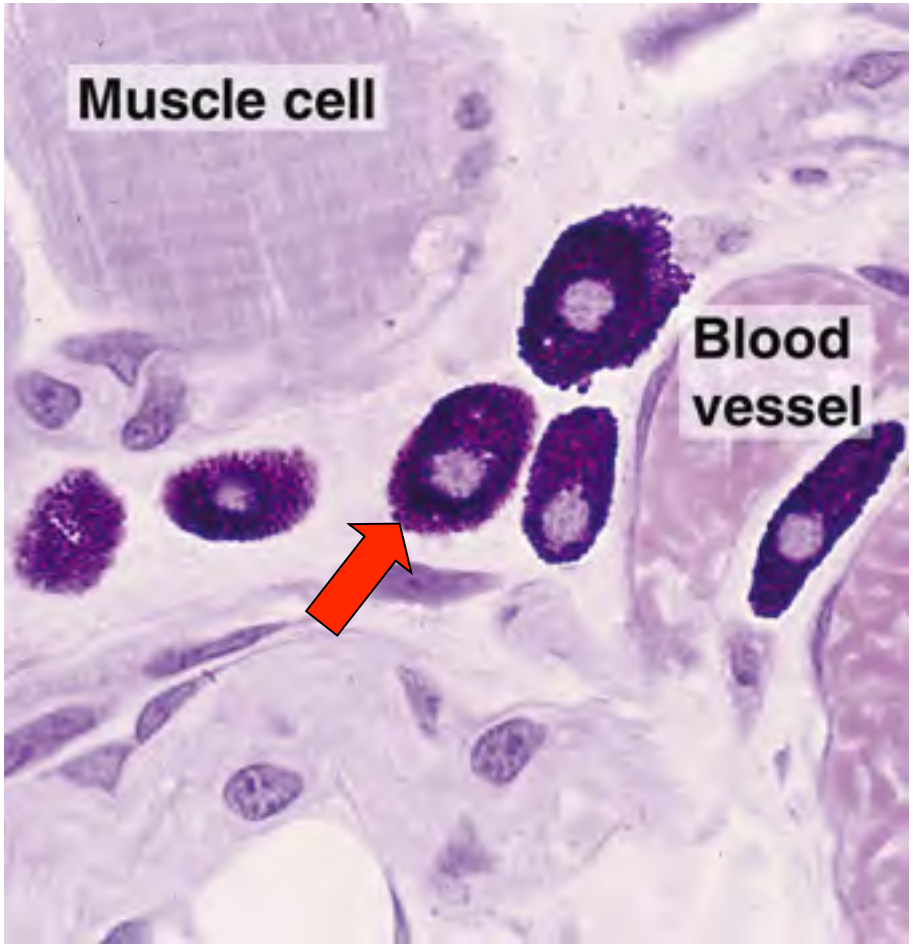
Mast Cells



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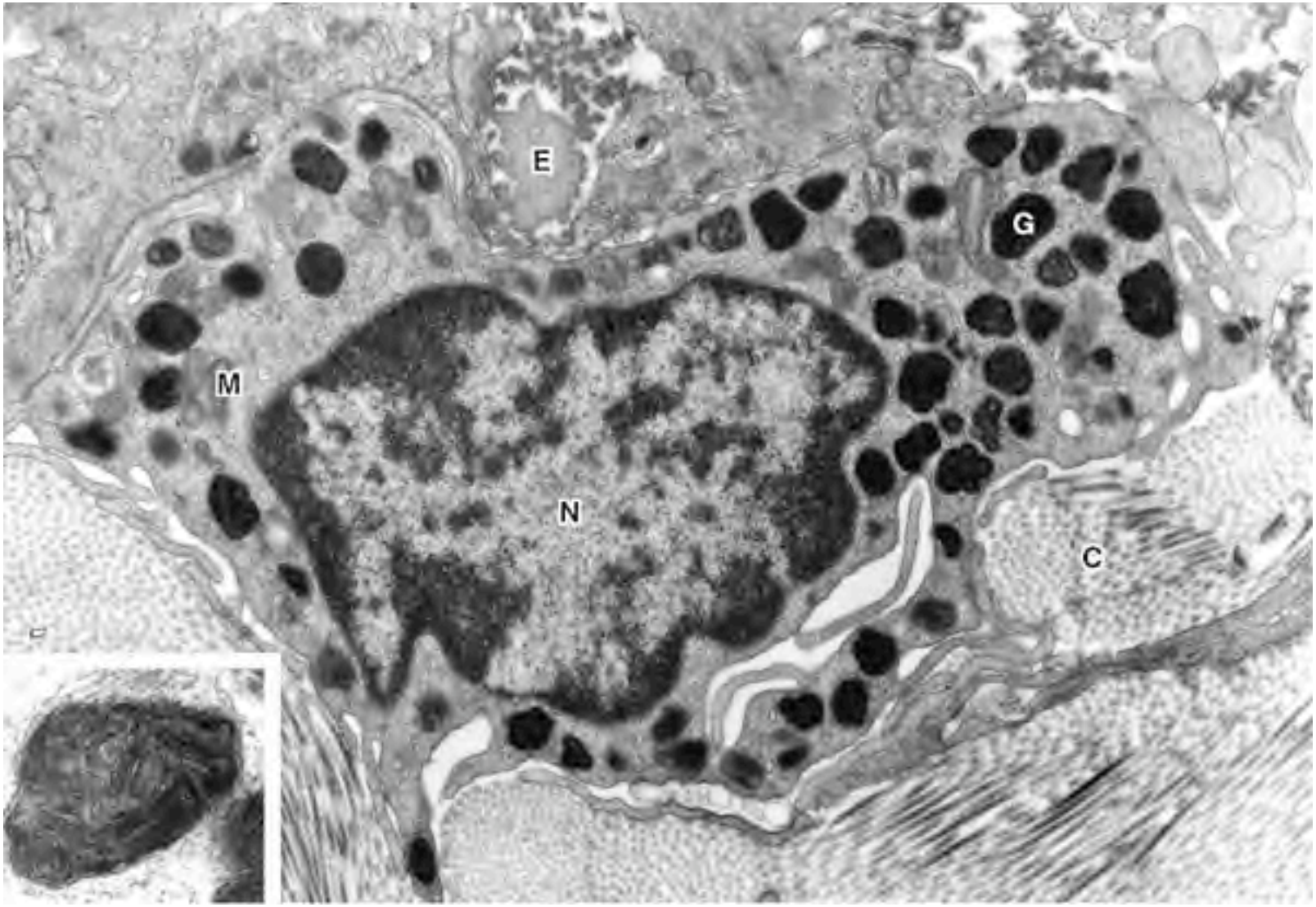
Metachromasia – when stained with toluidine blue, the granules bind the dye and change its color to red.

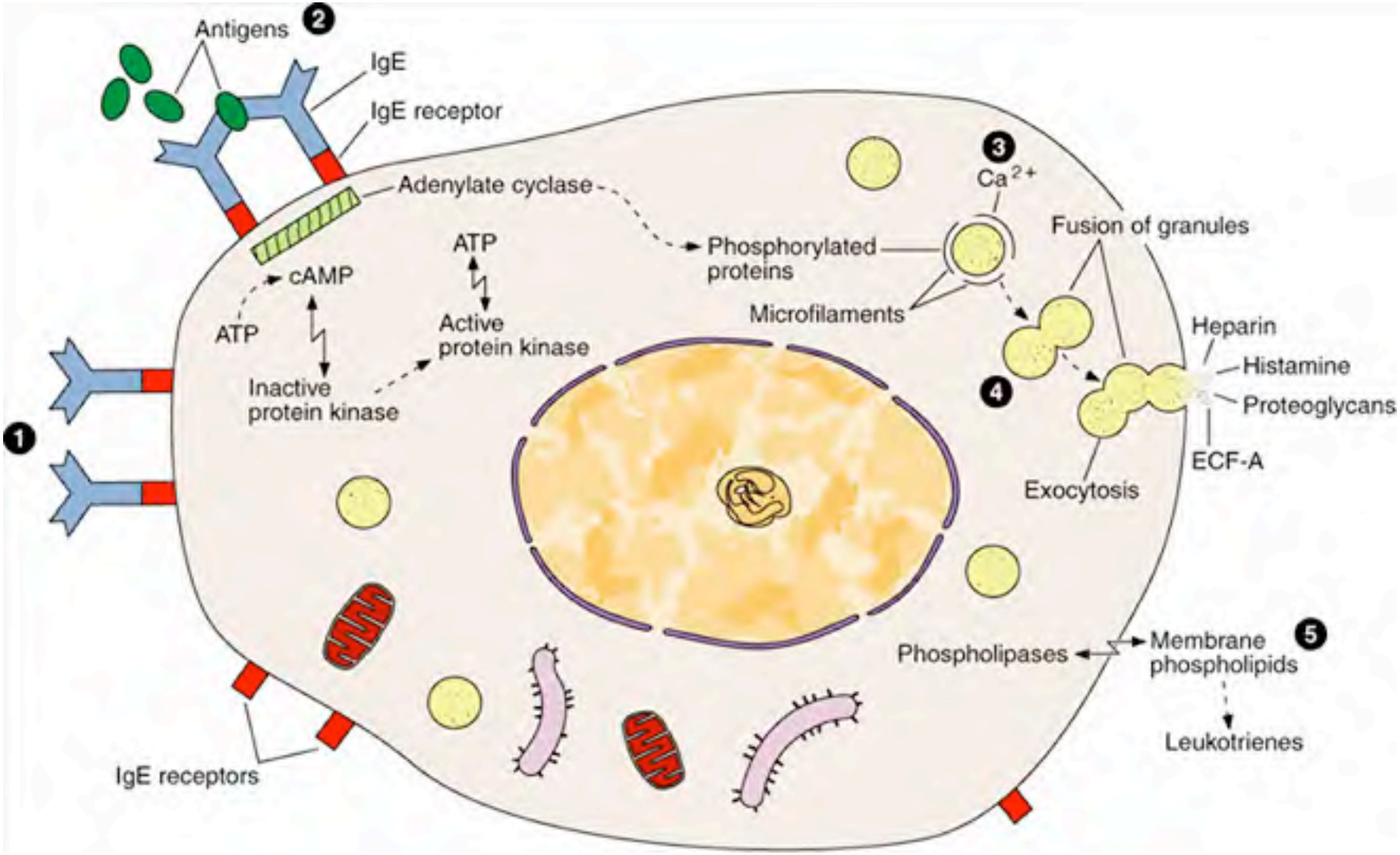
- **Principal function is storage in secretory granules and REGULATED release (degranulation) of histamine and other vasoactive mediators of inflammation.**
- **Responsible for the immediate hypersensitivity response characteristic of allergies, asthma and anaphylactic shock.**
- **Connective tissue mast cells are found in skin (dermis) and peritoneal cavity mucosal mast cells are in the mucosa of the digestive and respiratory tracts.**

EM of a Mast Cell



 Junqueira and Carneiro. *Basic Histology.* Tenth Edition. 2003. Figure 5.11.

Mast Cell Secretion



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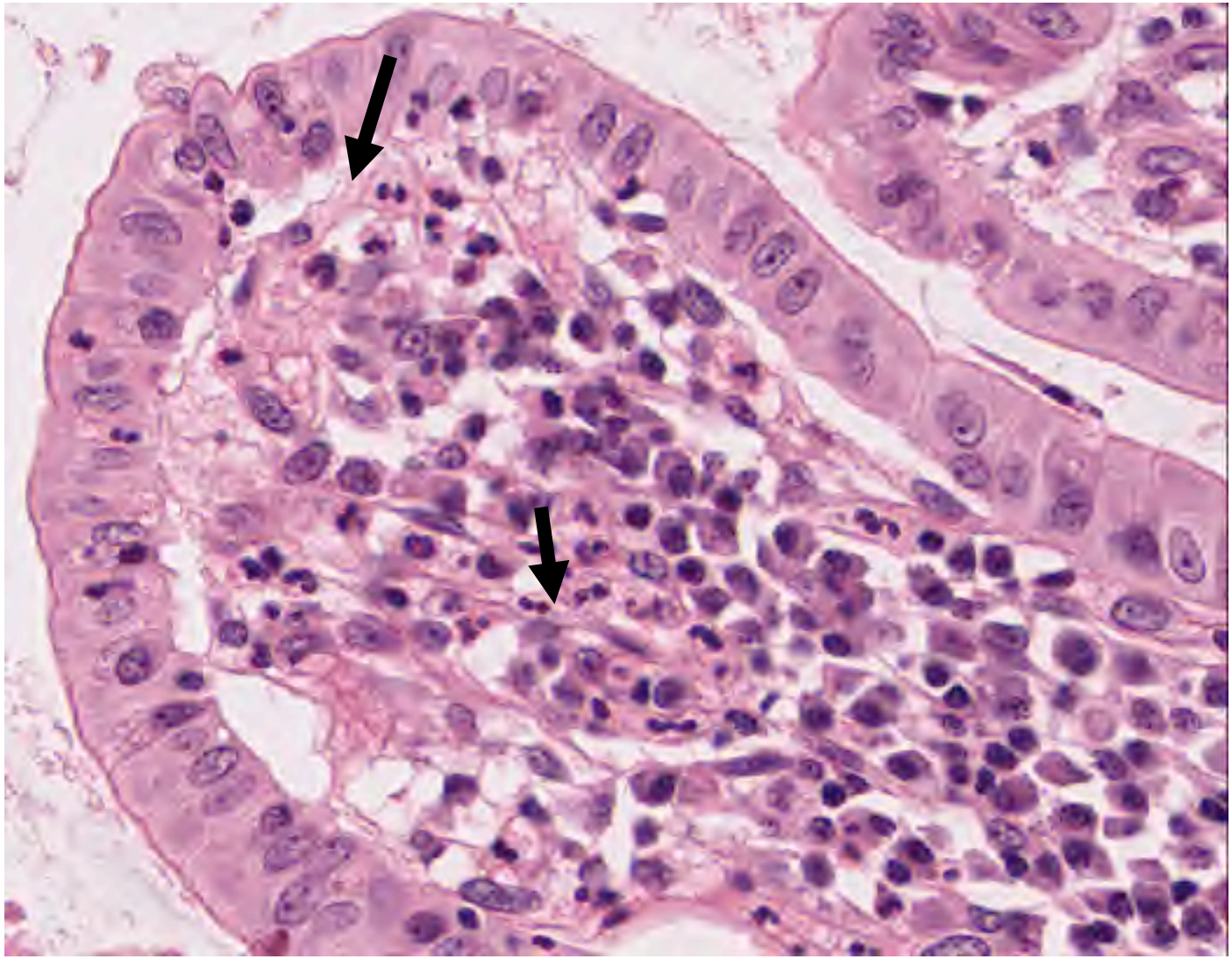
Neutrophils

- Enter connective tissue from blood vessels as the “first wave” in acute inflammatory responses
- Small cells with multi-lobed, heterochromatic nuclei (aka “polymorphonuclear neutrophils”, “PMNs”, “polys”)
- Primary function: anti-bacterial (are phagocytic like mphages, but SHORT-lived and NOT antigen presenting)



Types of Connective Tissue Proper

Loose (areolar) connective tissue – delicate, vascularized, ***cellular***; supports the epithelia of the major organs and glands and fills the space between muscle tissue. - not very resistant to stress

Dense connective tissue ***(many more fibers than cells)***

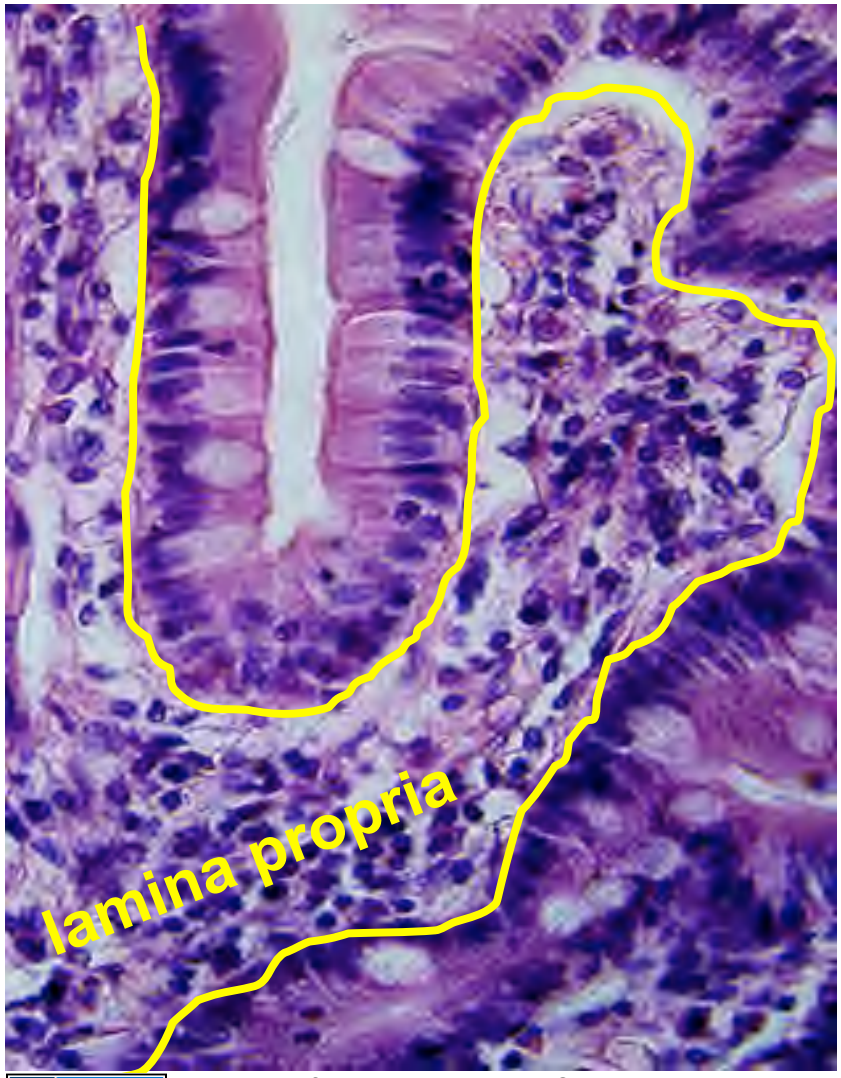
- **Dense irregular**: meshwork of coarse fibers; dermis of skin, organ capsules, fascia - resists multi-directional forces
- **Dense regular**:
  - collagenous: fibers aligned in defined pattern; tendons, ligaments, etc. - resists linear mechanical stresses
  - elastic: elastin and microfibrils (fibrillin) - elasticity

Adipose - fat storage, glucose regulation, satiety

Reticular - argyrophilic fibers of type III collagen - forms stroma of highly cellular organs (e.g. liver, lymph nodes, spleen)

Loose connective tissue:

delicate, vascularized, flexible; facilitates transport of cells and materials (secretion, absorption, immunity)



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small intestine lamina propria

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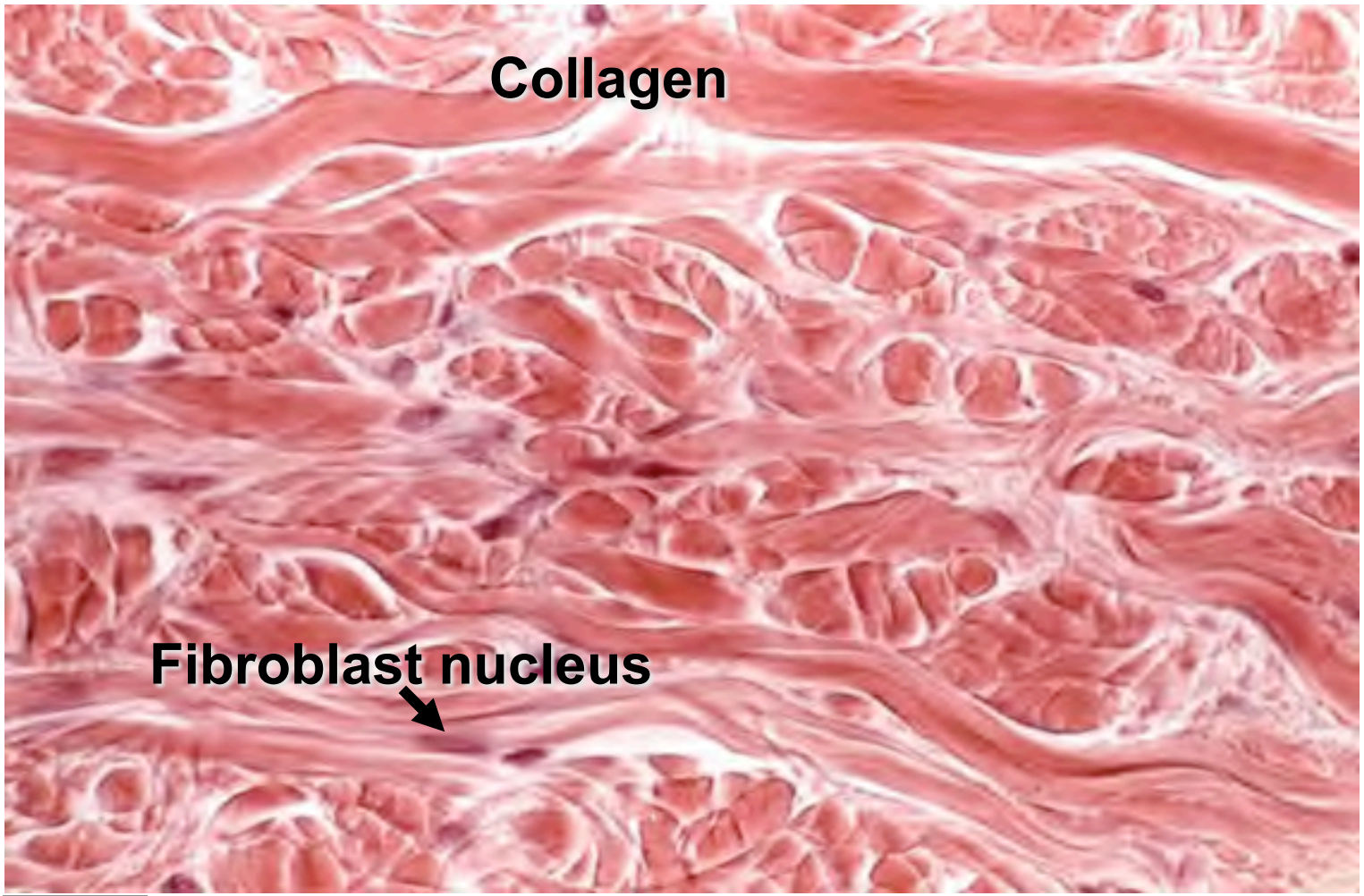
mammary gland intralobular connective tissue

Dense Irregular CT

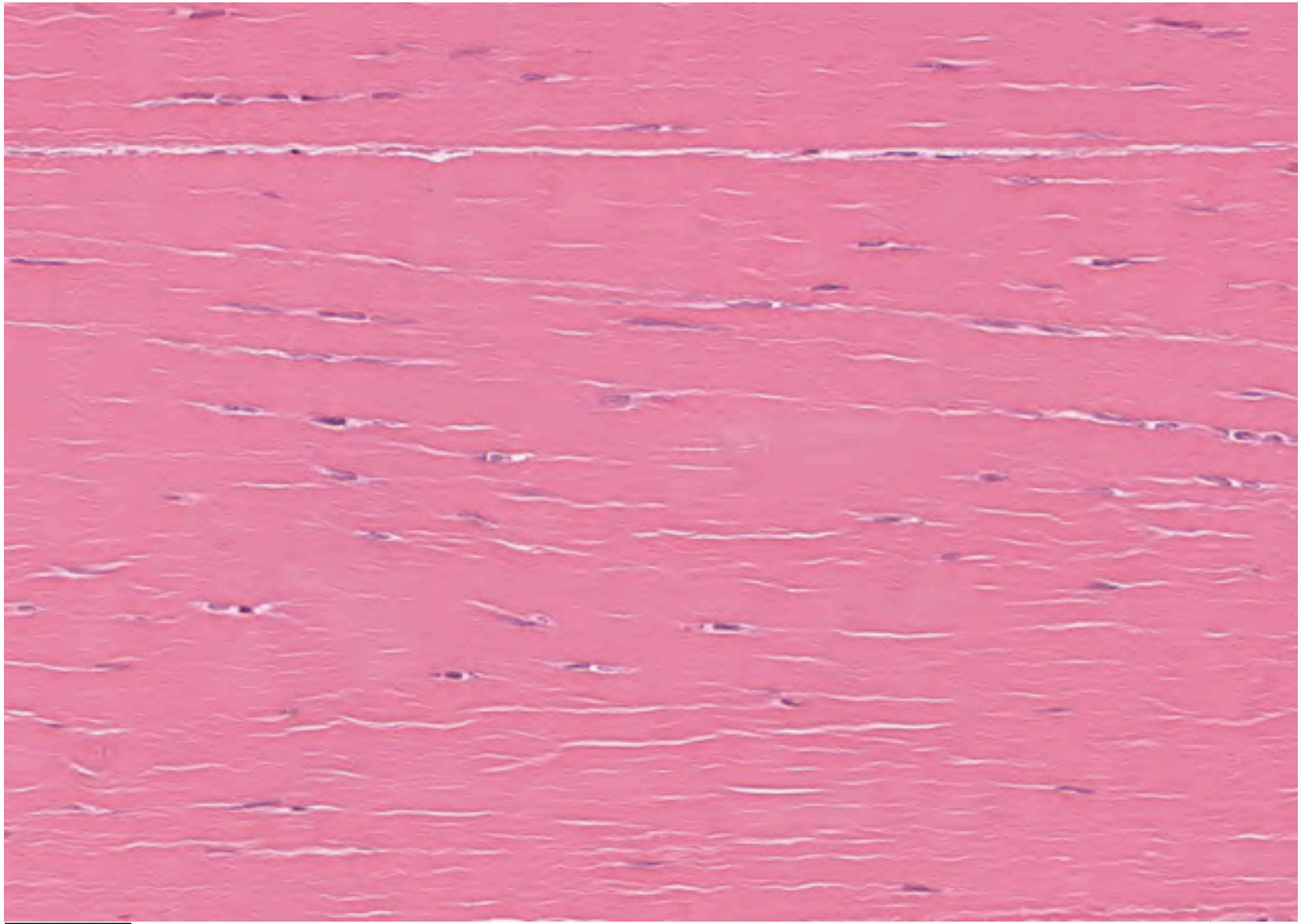
Densely packed collagen fibers, often in perpendicular bundles; resists tension in many directions and provides mechanical support.



Skin dermis, H &E

Dermis of Skin has both Loose and Dense Irregular CT

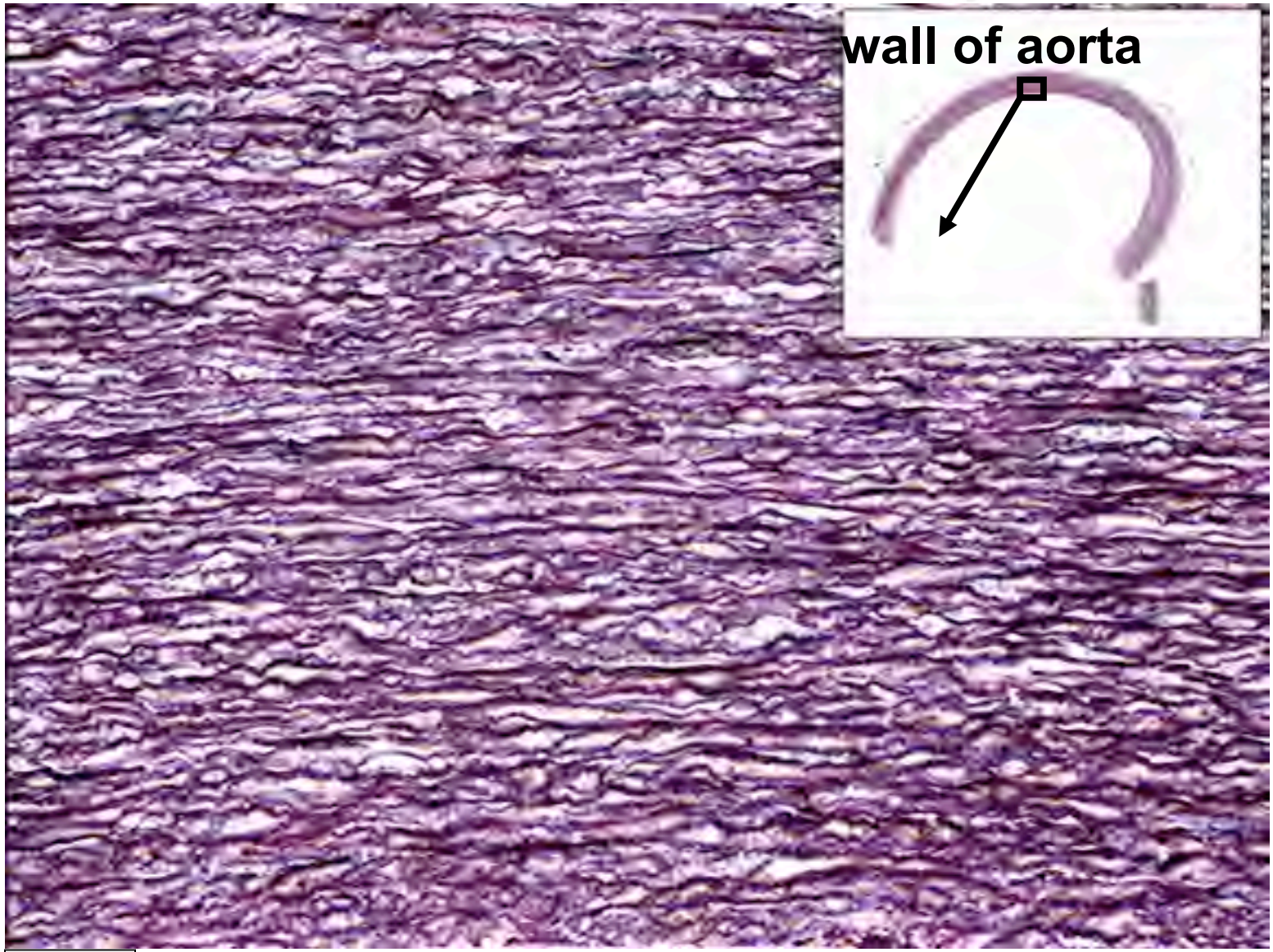
Dense Regular CT (collagenous)



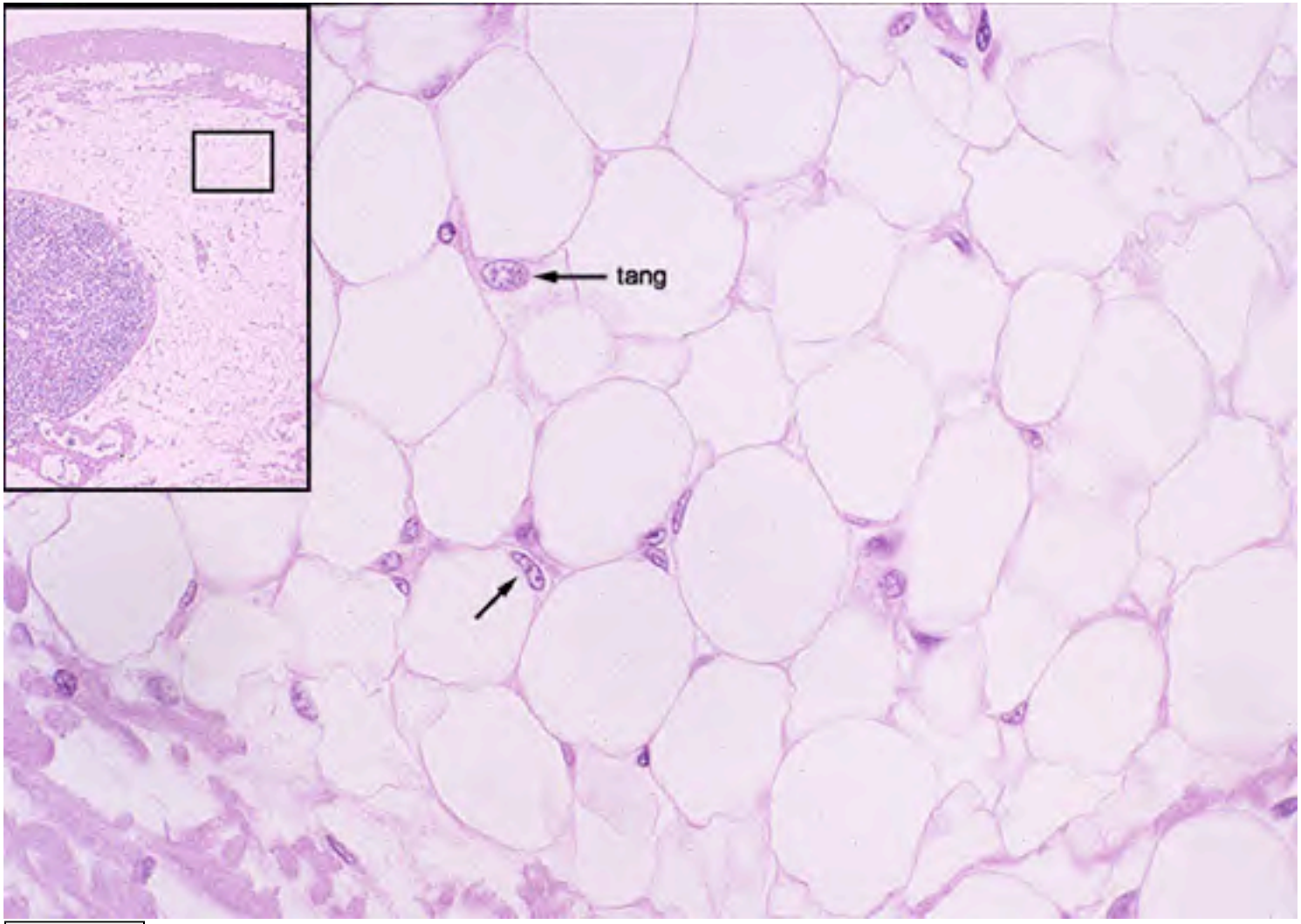
Tendon, H & E

Dense Regular CT (elastic)

Aorta: slide 36 , Weigert stain, 20x obj



Adipose Tissue



Adipose tissue in mesentery; tang=adipocyte sectioned tangentially

Reticular connective tissue

Liver: slide 198 odd, silver stain, 40x obj

Learning Objectives

At the end of this session, you should be able to:

1. Describe the functions and identify the cells commonly found in connective tissue.
2. Recognize interstitial (fibrillar) collagens and elastic fibers at the light and electron microscopic levels.
4. Distinguish between elastic, type I collagen, type III (reticular) collagen, and elastic fibers when appropriately stained material is presented.
6. Use knowledge about the physical characteristics of collagen and elastin in explaining the functions of tissue where these molecules occur in large quantities (*e.g.*, coarse type I collagen fibrils present in dense connective tissue compared to more delicate type III fibers found closer to the interface of cells and the extracellular matrix).
8. Recognize types of connective tissue (*e.g.*, dense irregular, dense regular, loose, adipose) and provide examples where different types of connective tissue are found in the body.
10. Recognize a basement membrane (or basal lamina) in sections or micrographs where the structure is conspicuously present and understand its functions.

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for more information see: http://open.umich.edu/wiki/CitationPolicy

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Slide 23: Ross,M, Pawlina, W. *Wheater's Functional Histology: A Text and Atlas*. Fifth Edition. 2006. Figure 4.4; Source Undetermined
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