Connective Tissue 1

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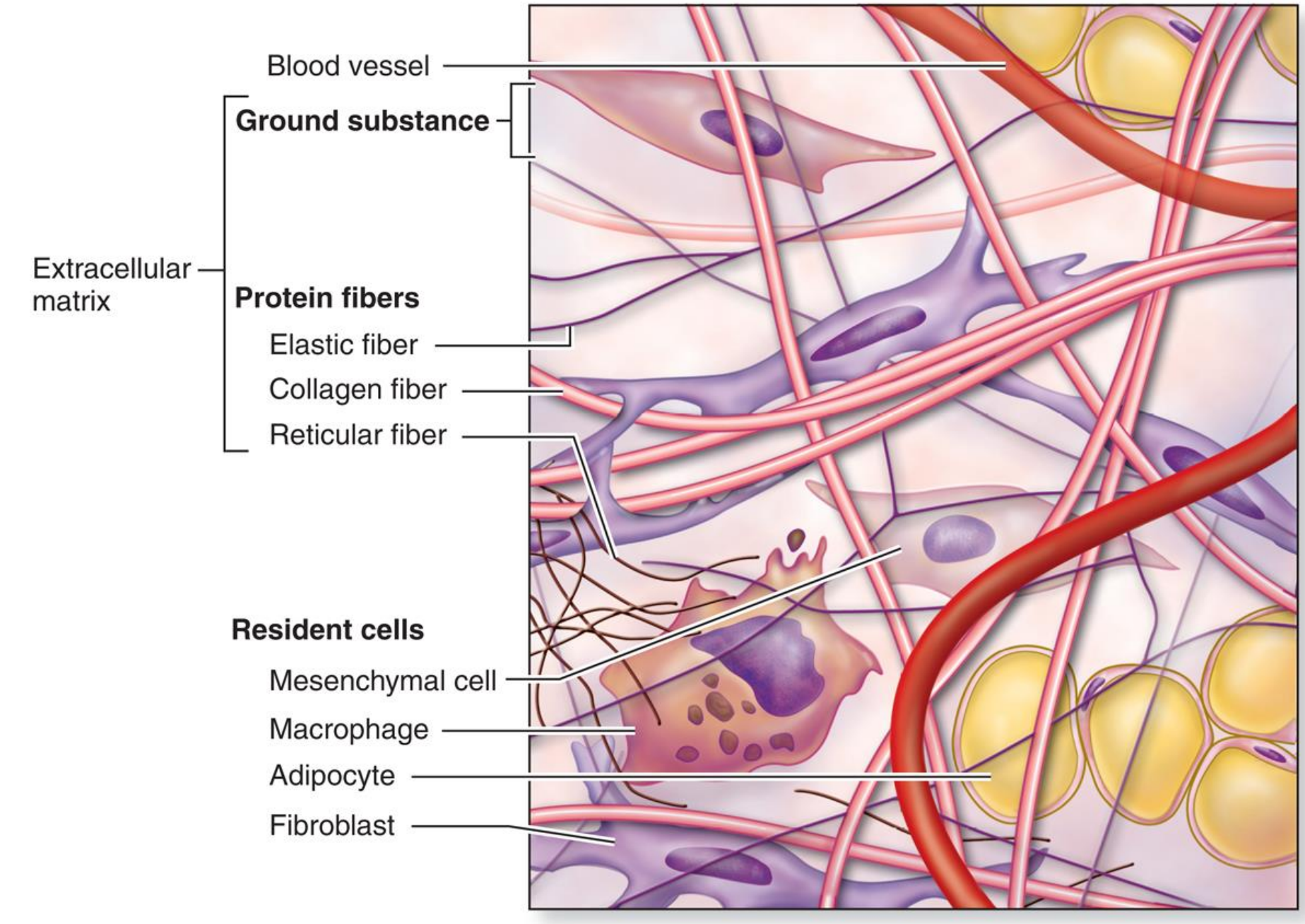
Features

- ✓Composed of cells, fibers and extracellular matrix.
- ✓Highly vascular
- ✓Variable regenerative power
- ✓Originates from the mesenchyme (A tissue derived from mesoderm rich in viscous ground substance)

Components

- Cells
- Protein Fibers
- Ground Substance

Extracellular matrix


Blood vessel
Ground substance
Extracellular matrix
Protein fibers
Elastic fiber
Collagen fiber
Reticular fiber
Resident cells
Mesenchymal cell
Macrophage
Adipocyte
Fibroblast

Functions of Connective Tissue

- Support
- Defense and protection
- Storage
- Transport

Cells of the Connective Tissue

Fixed cells:

- Fibroblasts.
- Adipose cells.
- Pericytes.
- Mast cells.
- Macrophages.

Transient cells:

- Plasma cells.
- White blood cells (Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes).
- Macrophages.

TABLE 5–1 Functions of cells in connective tissue proper.

Cell Type	Major Product or Activity
Fibroblasts (fibrocytes)	Extracellular fibers and ground substance
Plasma cells	Antibodies
Lymphocytes (several types)	Various immune/defense functions
Eosinophilic leukocytes	Modulate allergic/vasoactive reactions and defense against parasites
Neutrophilic leukocytes	Phagocytosis of bacteria
Macrophages	Phagocytosis of ECM components and debris; antigen processing and presentation to immune cells; secretion of growth factors, cytokines, and other agents
Mast cells and basophilic leukocytes	Pharmacologically active molecules (eg, histamine)
Adipocytes	Storage of neutral fats

Fibroblasts

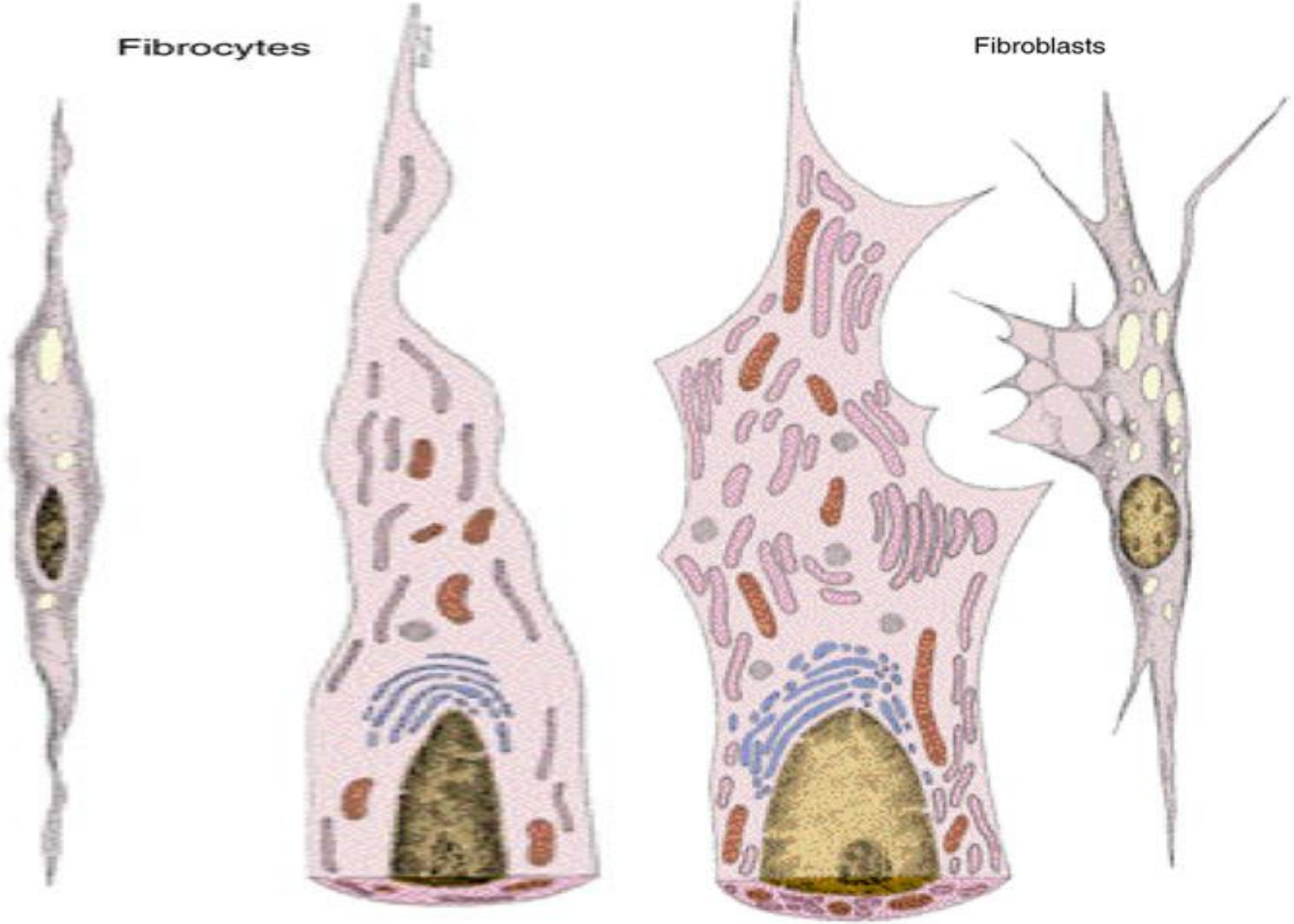
- The most numerous cells of connective tissue.
- Occur in active and inactive forms (fibrocyte).
- Originate from undifferentiated mesenchymal cells.
- Capable of some movement.
- Rarely undergo division (in adults).
- FGF may influence cell growth and differentiation.

Fibroblasts

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

Active fibroblasts

- Closely associated with collagen bundles.
- Elongated, fusiform, and have many processes.
- Cytoplasm is pale and difficult to be differentiated from near by tissue.
- Nucleus is large (ovoid) euchromatic, prominent nucleolus
- E.M: prominent Golgi, mitochondria, rER, actin and myosin.


Fibrocytes
Fibroblasts

Inactive Fibroblast (Fibrocyte)

- Smaller and simple shaped with acidophylic cytoplasm.
- The nucleus is smaller and darker (heterochromatic).
- Few processes.
- E.M: few rER.
- When stimulated, it may revert to fibroblast.

Myofibroblast

Has features of both smooth muscles and fibroblasts.

Their contraction is responsible for ***wound contraction***.

Adipocyte

specialized for cytoplasmic storage of lipid as neutral fats,

Tissue with a large population of adipocytes, called adipose connective tissue

Macrophage

Macrophages have highly developed phagocytic ability and specialize in turnover of protein fibers and removal of dead cells, tissue debris, or other particulate material, being especially abundant at sites of inflammation. Also called Histiocytes.

When adequately stimulated, macrophages may increase in size and fuse to form multinuclear giant cells, usually found only in pathologic conditions.

Macrophage

Derived from monocyte.

Large cells ~10-30 μm.

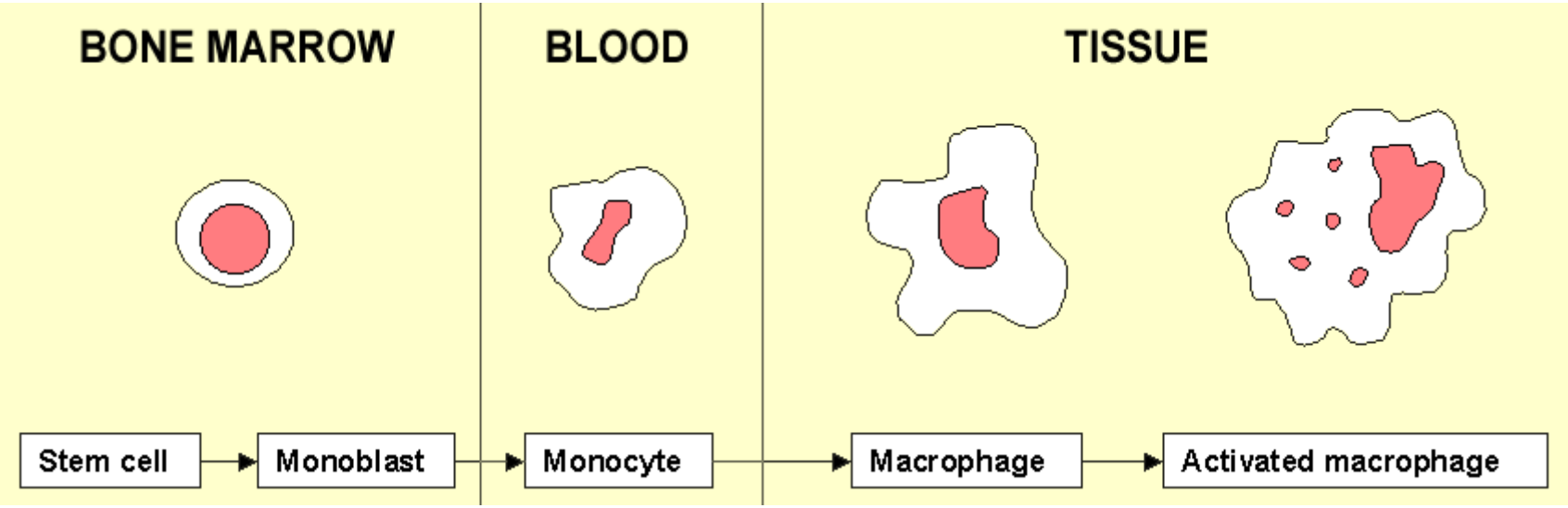
Surface shows many projections.

Nucleus: eccentric, oval or indented (kidney-shaped).

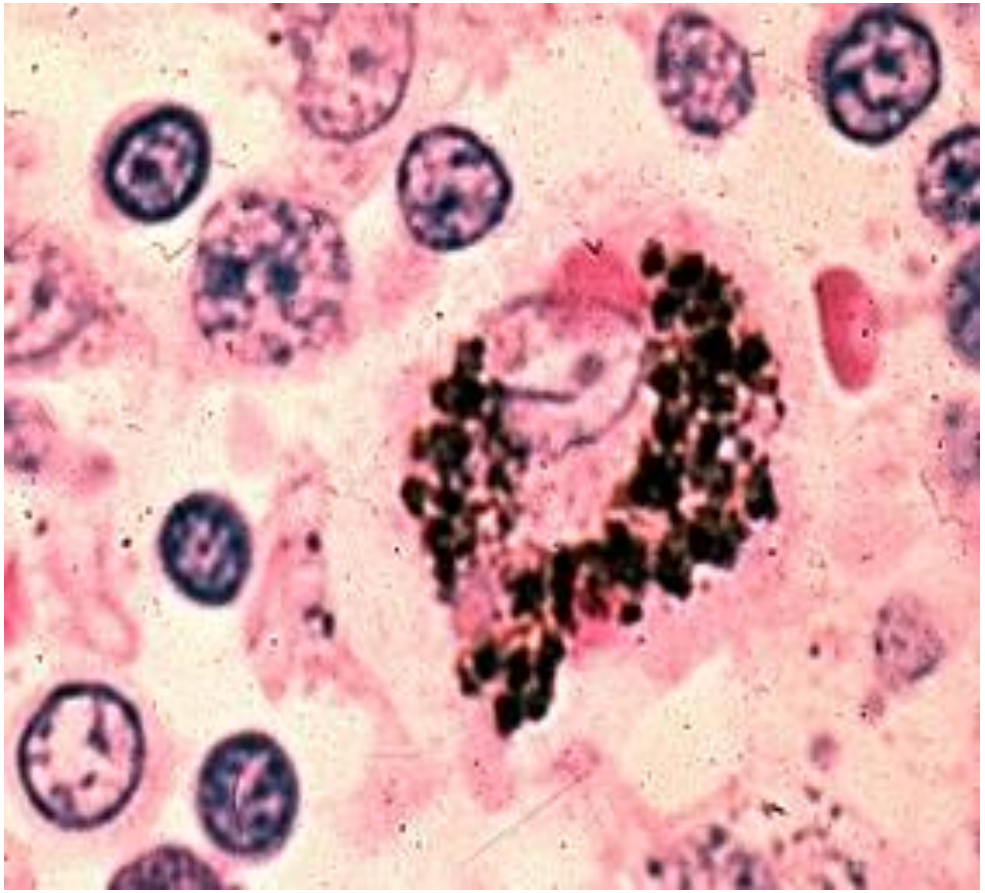
Cytoplasm: basophilic, well developed Golgi, prominent rER, many lysosomes.

They are part of the Mononuclear phagocyte system (MPS).

Monocytes and macrophages are the same cells at different stages of maturation



Macrophage (light micrograph)

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N
Nu

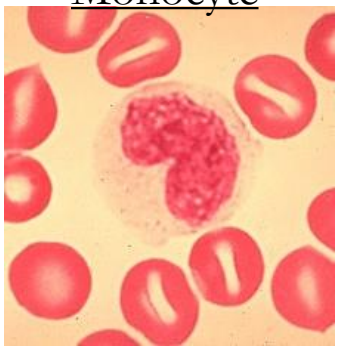
Mononuclear phagocyte system

- Is a part of the immune system that consists of the phagocytic cells
- The macrophage like cells have been given different names in different organs
- also called **Reticuloendothelial System** or Macrophage System

MONONUCLEAR PHAGOCYTIC SYSTEM

(reticuloendothelial system)

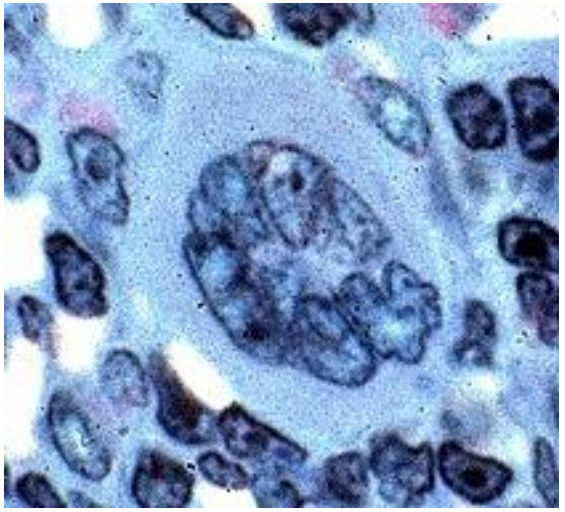
Monocyte



Mononuclear wandering cell

coalescence

Giant Cell



Macrophages

bone marrow
connective tissue

Osteoclasts

bone resorption

Kupffer Cells

liver sinusoids

Microglial Cells

central nervous system

Dendritic cells

Lymph node
spleen

Langerhans cells

epidermis

Dust cells

lung

(all characterized by phagocytic activity)

Mononuclear Phagocyte System

TABLE 5–2 Distribution and main functions of the cells of the mononuclear phagocyte system.

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

Mast Cell

- Derived from precursors in the bone marrow.
- Nucleus: central ovoid.
- Cytoplasm highly granular, metachromatic (which means that they can change the color of some basic dyes (eg, toluidine blue) from blue to purple or red..
- Of two types according to location:
  - Perivascular: Large 10-12um, in skin, granules contain heparin
  - Mucosal: small 5-10um, mucosa of intestines and lungs, granules contain chondroitin sulfate

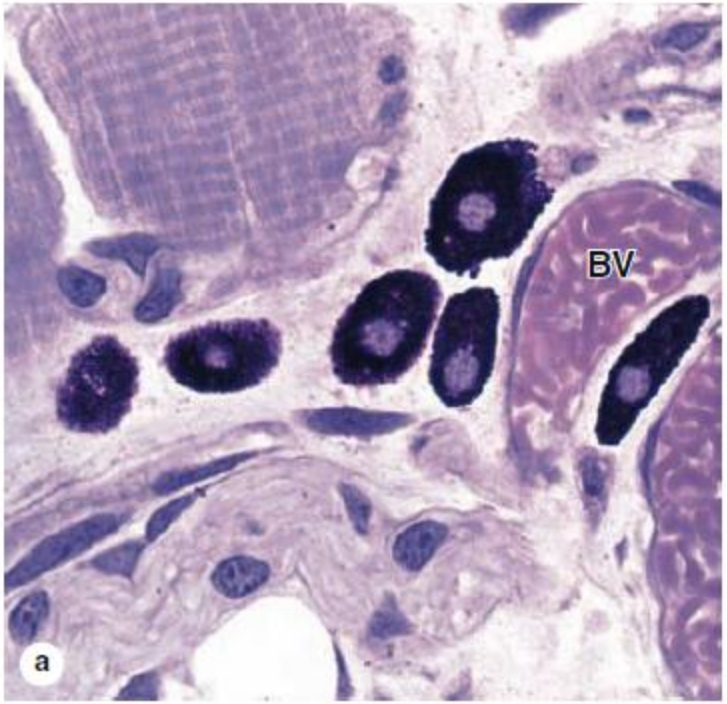
Contents of Mast cell granules

- Heparin (a sulfated GAG that acts locally as an anticoagulant)
- Histamin (promotes increased vascular permeability and smooth muscle contraction)
- Serine proteases
- Eosinophil and Neutrophil chemotactic factors.
- Cytokines
- Phospholipids

Mast cell function

- Release of certain chemical mediators stored in mast cells promotes the allergic reactions known as **immediate hypersensitivity reactions** because they occur within a few minutes after the appearance of an antigen in an individual previously sensitized to that antigen

Mast Cell



Plasma Cell

Derived from B lymphocytes following exposure to an antigen.

Present at portal of entry of organisms and sites of chronic inflammation.

Life span ~ 10-20 days.

Large ovoid cells ~ 20 μm.

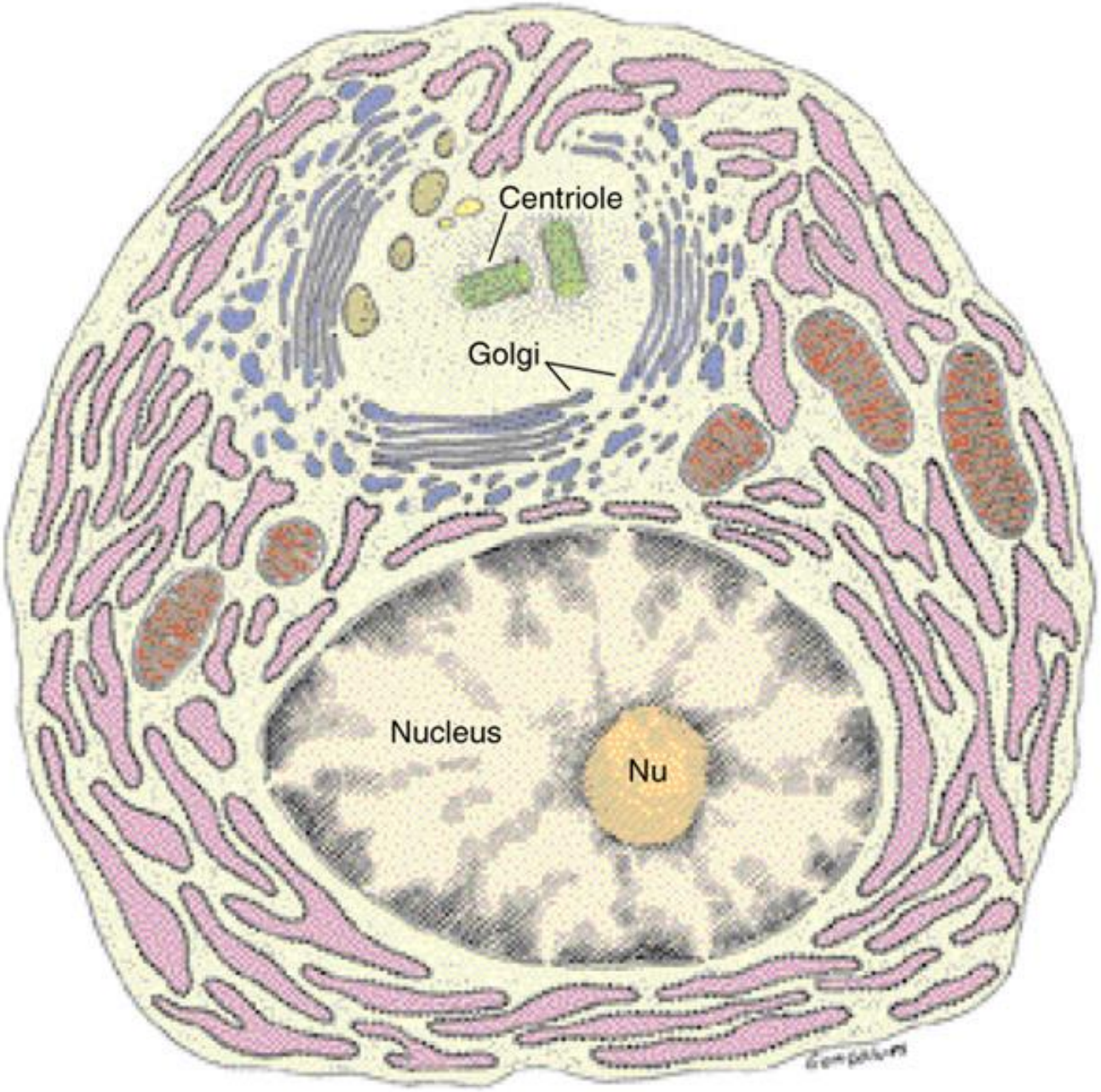
Nucleus: eccentric with clusters of heterochromatin→ cart-wheel or clock-face nucleus.

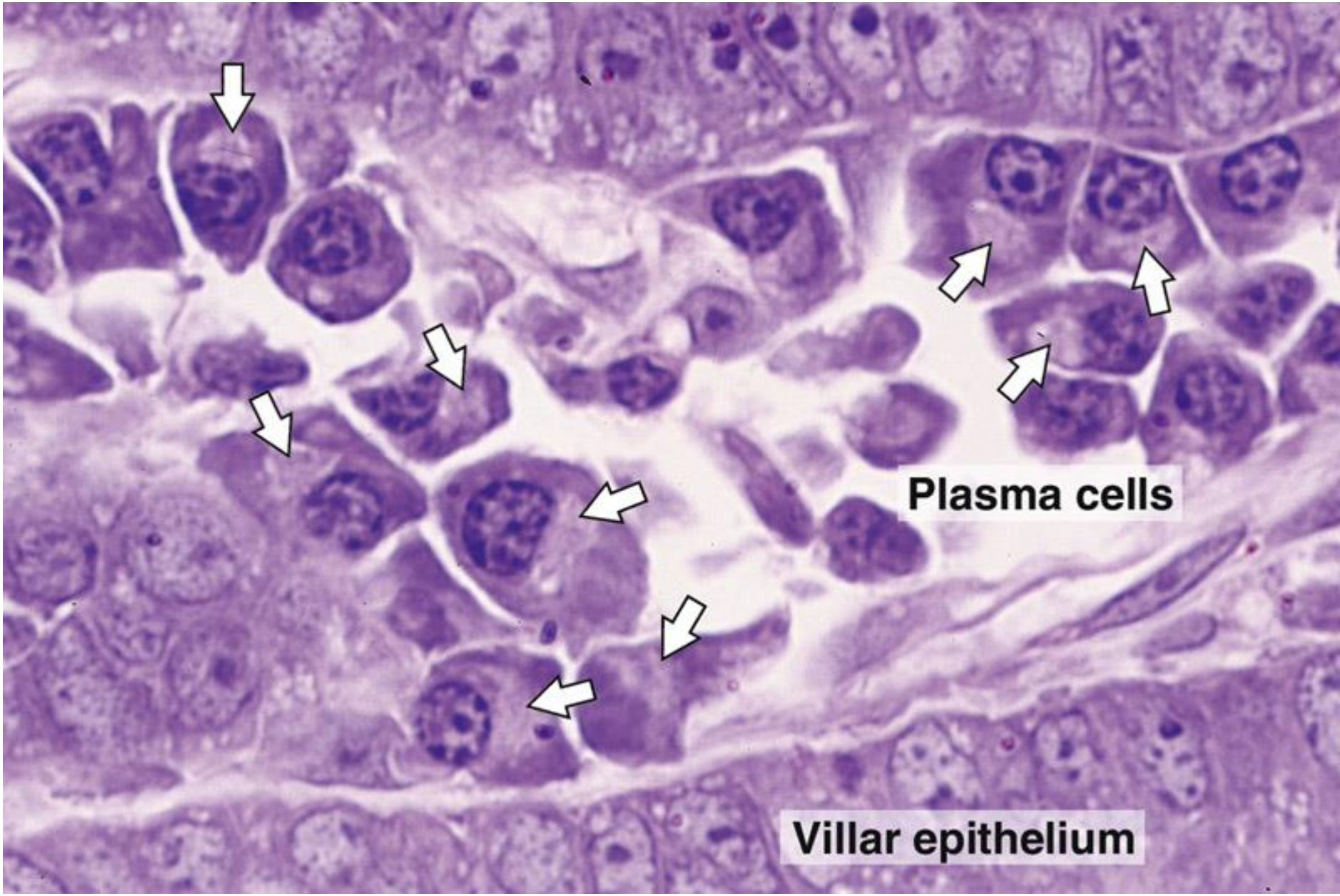
Plasma Cell

Cytoplasm:

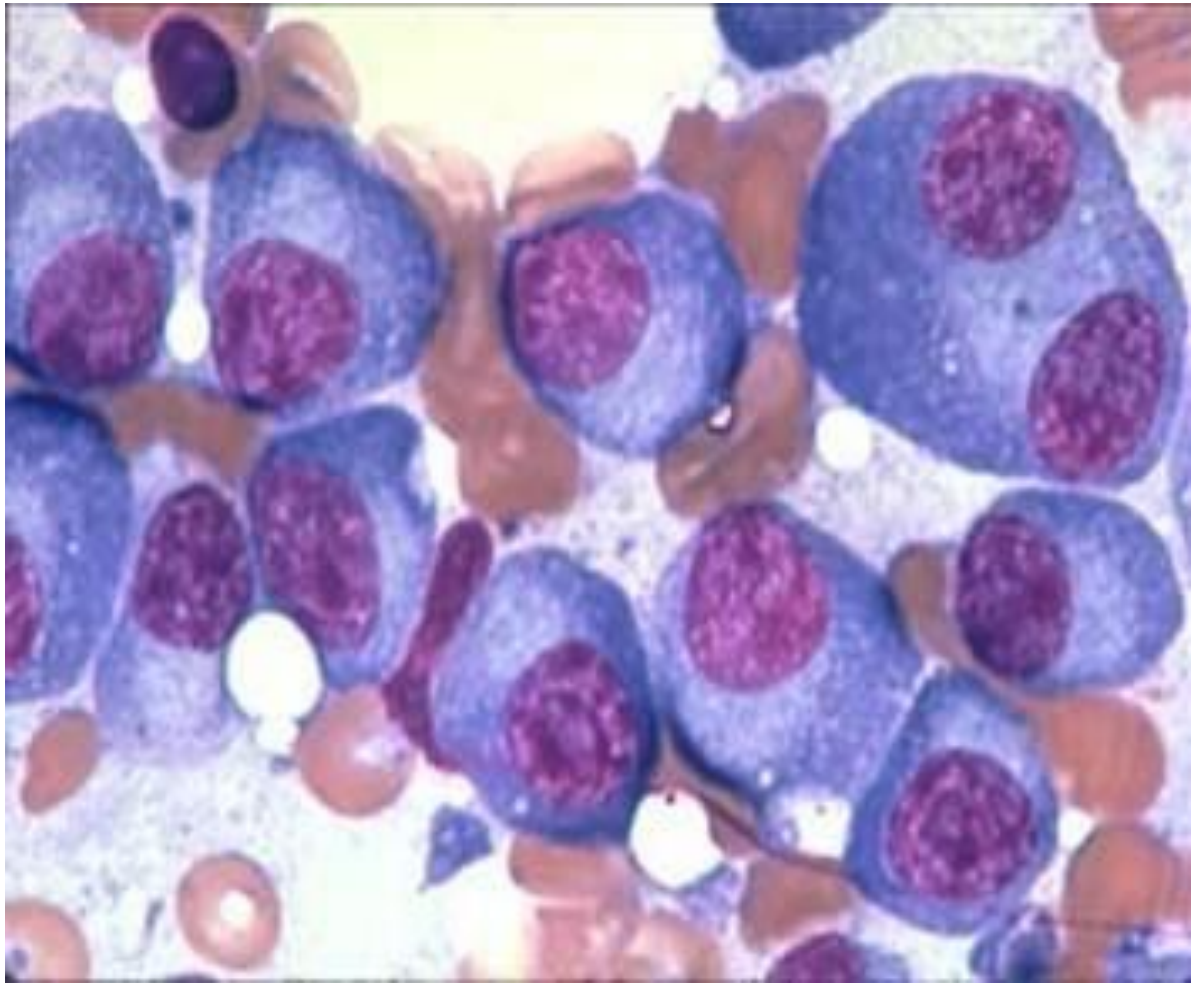
- Intensely basophilic.
- Well developed supranuclear Golgi apparatus (- ve image).
- Well developed rER.

Functions: secretion of specific antibodies.


Centriole
Golgi
Nucleus
Nu


Plasma cells
Villar epithelium

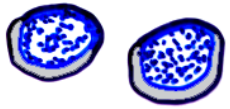
Negative Golgi stain



LYMPHOCYTES AND PLASMA CELLS

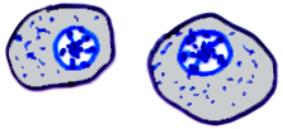
(Agents of the immune response)

Lymphocytes

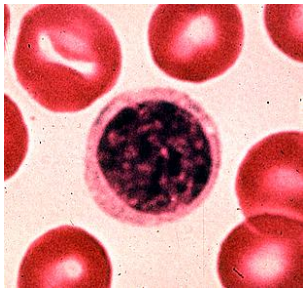


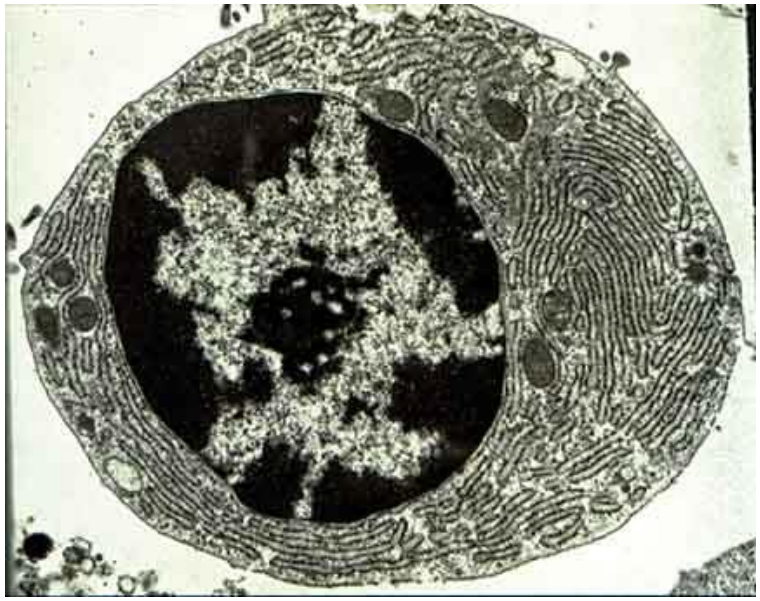
differentiation stimulated by immune activation

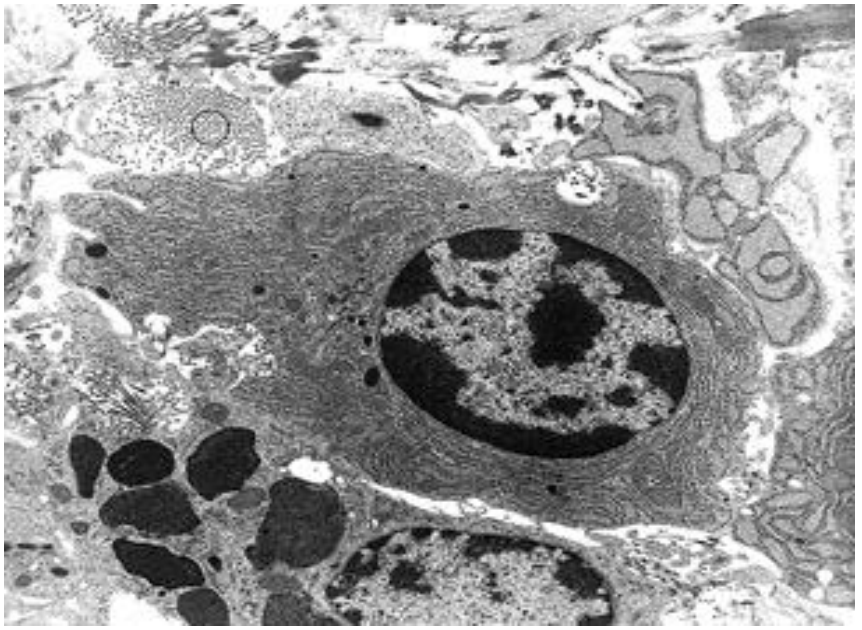
Plasma Cells



(produce immunoglobulins -antibodies)







Extracellular Matrix

- Extracellular Matrix = ground substance + fibers

✓ Resists compression and stretching forces.

✓ The water content allows rapid exchange of metabolites.

Connective Tissue Fibers

Fiber	Properties
Collagen	Undulating course of longitudinally striated bundles, form meshwork of variable texture, stain pink-red in H&E. Nonextensible.
Elastic	Forms sheets or lamina, Unstained in H & E. Reversibly extinsible. Stains brown-black in Orcein or Resorscin Fuchsin.
Reticular	Delicate network, Unstained in H & E. Reversibly extinsible. PAS +ve, stains black in $AgNO_3$ (Argyrophilic).

Major Types of Collagen

Type	Synthesizing cell	Function	Location
I	Fibroblast, osteoblast, odontoblast, cementoblast	Resist tension	Dermis, tendons, ligament, capsules, bone, dentin, cementum
II	chondroblasts	Resists pressure	Hyaline and elastic cartilage
III	Fibroblasts, reticular cells, smooth muscle, hepatocytes	Form structural framework of organs	Reticuloendothelial system, lung, skin
IV	Epithelium, muscle, Schwann cells	Meshwork of the lamina densa	Basal lamina
V	Fibroblasts, mesenchymal cells	Associated with type I.	As in type I and placenta
VII	Epidermal cells	Anchoring fibrils between the lamina densa and reticularis	Derma-epidermal junction

Collagen Classification

- **Fibrillar collagen**: forms long fibrils, examples collagen I, II, III
- **Network or sheet-forming collagens**: collagen IV
- **Linking/anchoring collagens**: short, link fibrillar collagen together and to other componenets, collagen VII

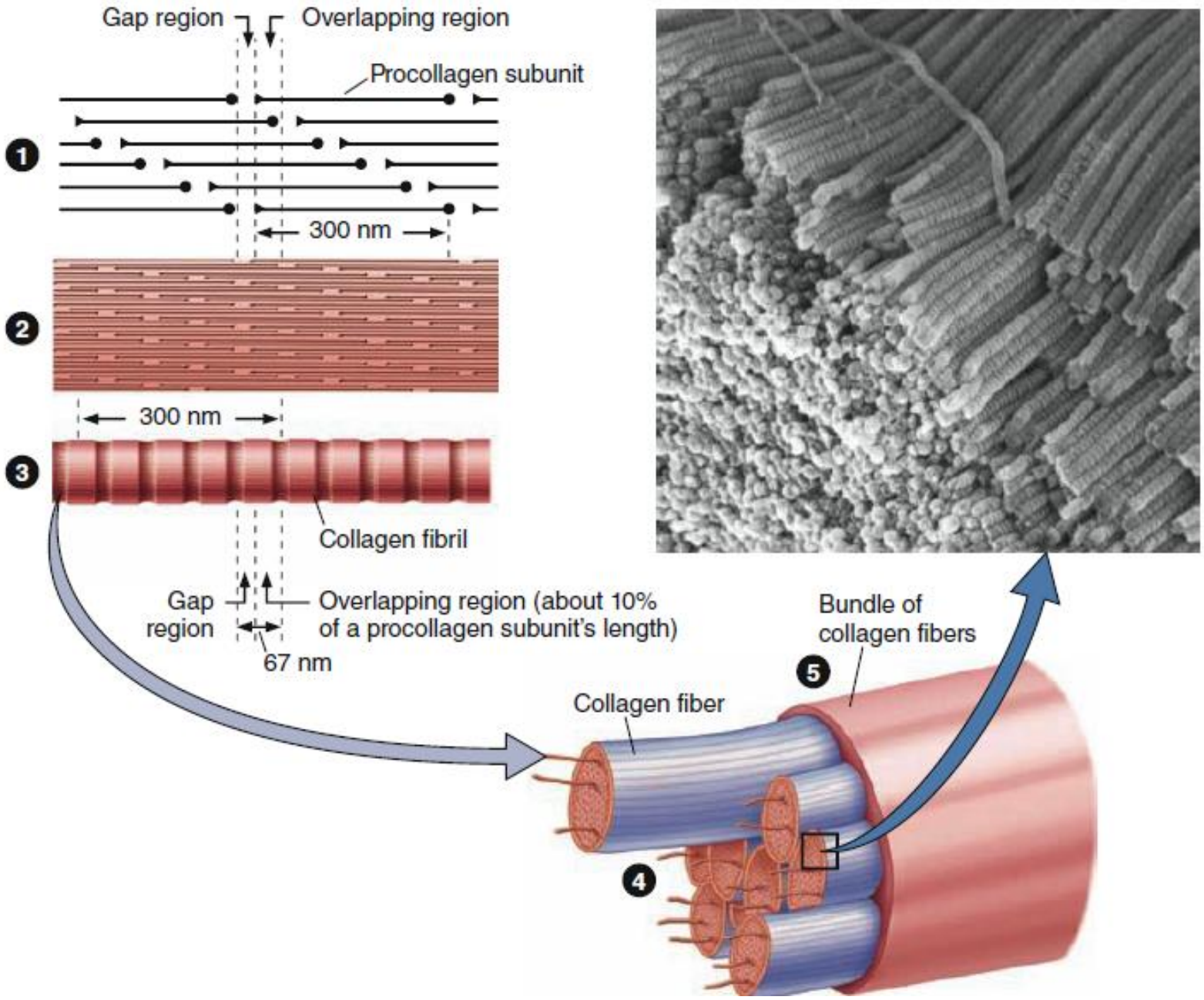
Collagen Fibers (Collagen I)

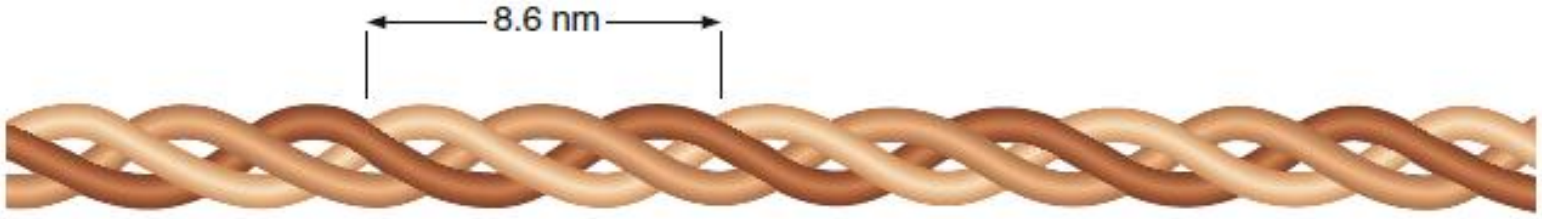
- Subunits of type I collagen, the most abundant collagen, assemble to form extremely strong fibrils, which are then bundled together further by other collagens into much larger structures called collagen fibers

- Gives the extracellular matrix strength to resist tensile forces.

Collagen Fibers (Collagen I)

- H & E: long, wavy pink bundles.
- E.M: cross banding at 67 nm.
- Fibers are formed of aggregation of fibrils.
- Fibrils are formed of procollagen (tropocollagen).
- Procollagen is formed of 3 helical polypeptide chains.


Gap region
Overlapping region
Procollagen subunit
1
300 nm
2
300 nm
3
Collagen fibril
Gap region
Overlapping region (about 10% of a procollagen subunit's length)
67 nm
Bundle of collagen fibers
5
Collagen fiber
4



READ ONLY

Each procollagen molecule or subunit has two α1- and one α2-peptide chains, intertwined in a right-handed helix and held together by hydrogen bonds and hydrophobic interactions. The length of each molecule (sometimes called tropocollagen) is 300 nm, and its width is 1.5 nm. Each complete turn of the helix spans a distance of 8.6 nm.

Collagen bundle

⬇⬇

Fibers

⬇⬇

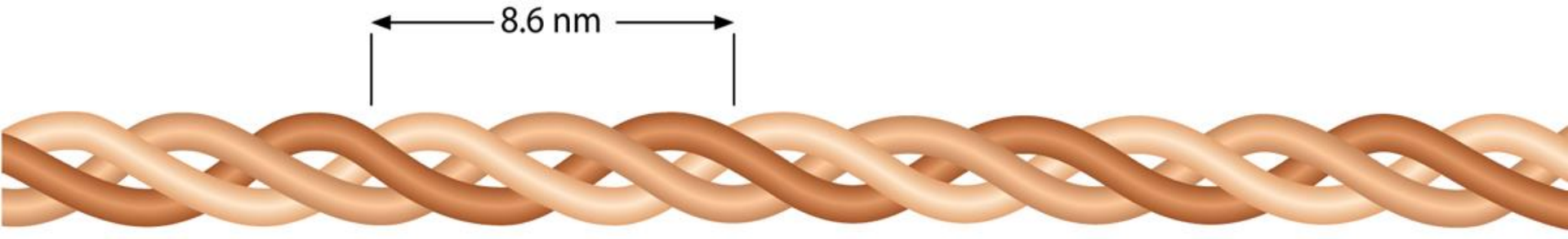
Fibrils

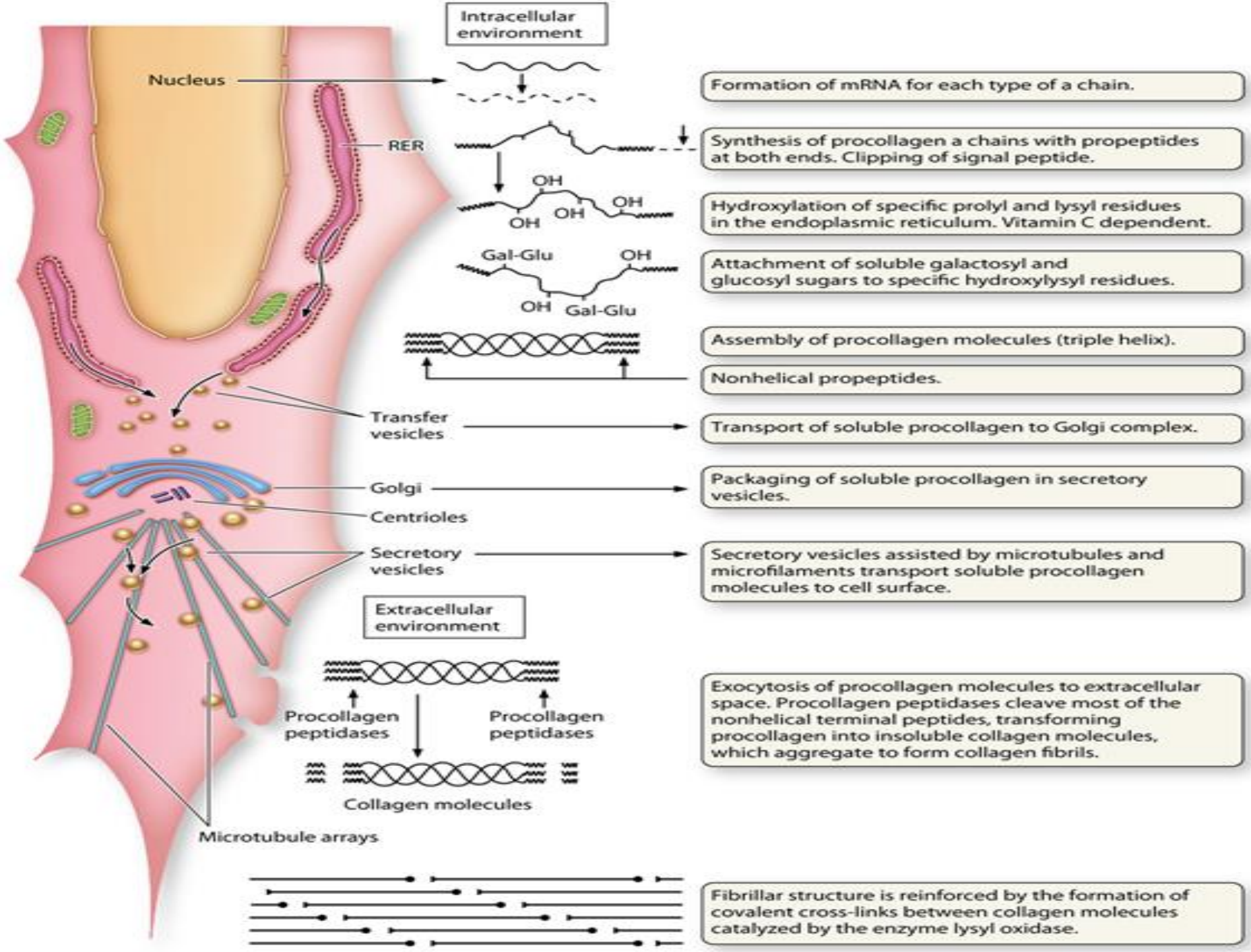
⬇⬇

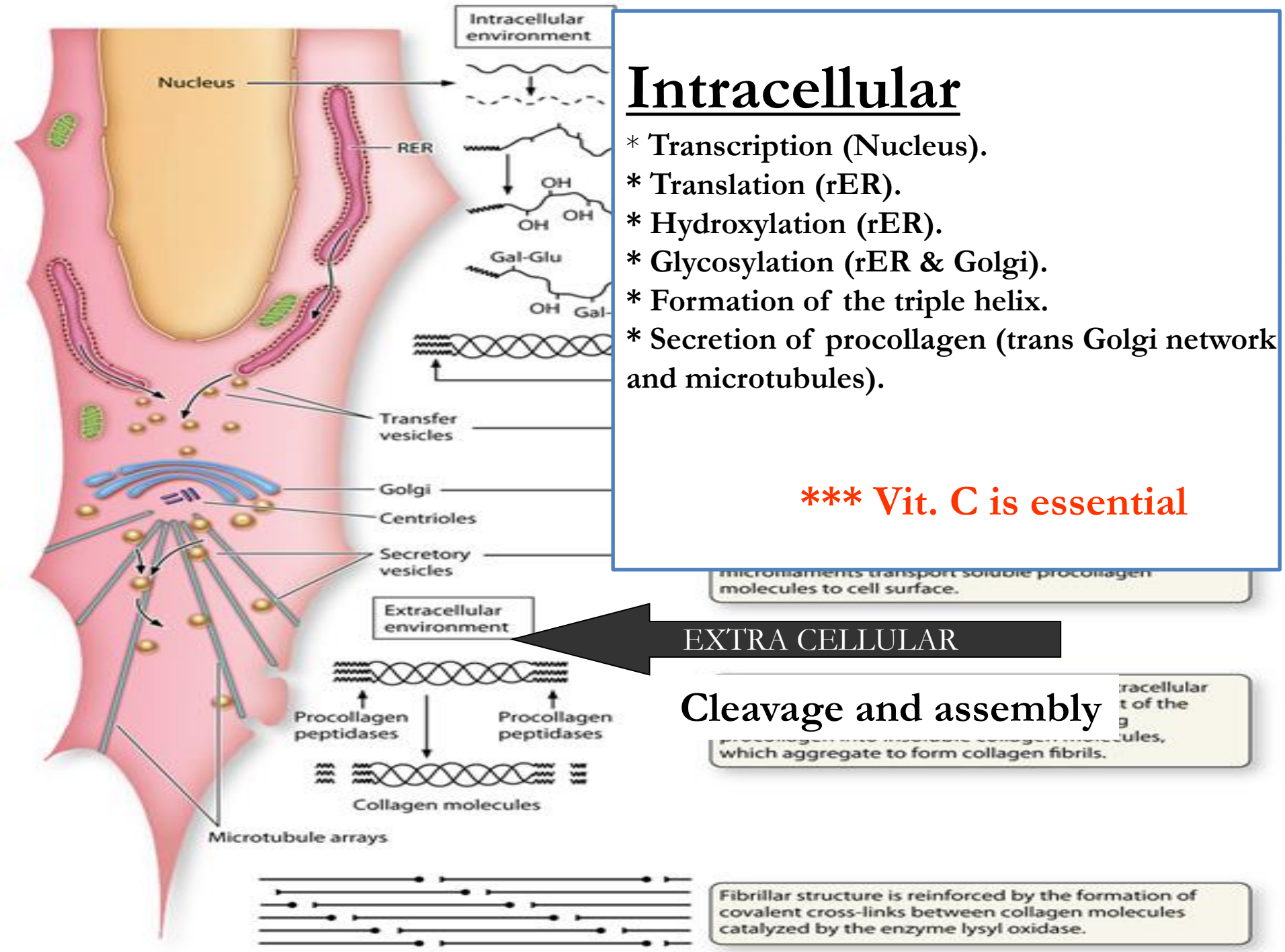
Procollagen

⬇⬇

3 Helical polypeptide chains, α-chains.




Intracellular environment
Nucleus
RER
OH
OH
OH
OH
Gal-Glu
OH
OH
Gal-Glu
Transfer vesicles
Golgi
Centrioles
Secretory vesicles
Extracellular environment
Procollagen peptidases
Procollagen peptidases
Collagen molecules
Microtubule arrays
Formation of mRNA for each type of a chain.
Synthesis of procollagen a chains with propeptides at both ends. Clipping of signal peptide.
Hydroxylation of specific prolyl and lysyl residues in the endoplasmic reticulum. Vitamin C dependent.
Attachment of soluble galactosyl and glucosyl sugars to specific hydroxylysyl residues.
Assembly of procollagen molecules (triple helix).
Nonhelical propeptides.
Transport of soluble procollagen to Golgi complex.
Packaging of soluble procollagen in secretory vesicles.
Secretory vesicles assisted by microtubules and microfilaments transport soluble procollagen molecules to cell surface.
Exocytosis of procollagen molecules to extracellular space. Procollagen peptidases cleave most of the nonhelical terminal peptides, transforming procollagen into insoluble collagen molecules, which aggregate to form collagen fibrils.
Fibrillar structure is reinforced by the formation of covalent cross-links between collagen molecules catalyzed by the enzyme lysyl oxidase.



Intracellular

* Transcription (Nucleus).
* Translation (rER).
* Hydroxylation (rER).
* Glycosylation (rER & Golgi).
* Formation of the triple helix.
* Secretion of procollagen (trans Golgi network and microtubules).

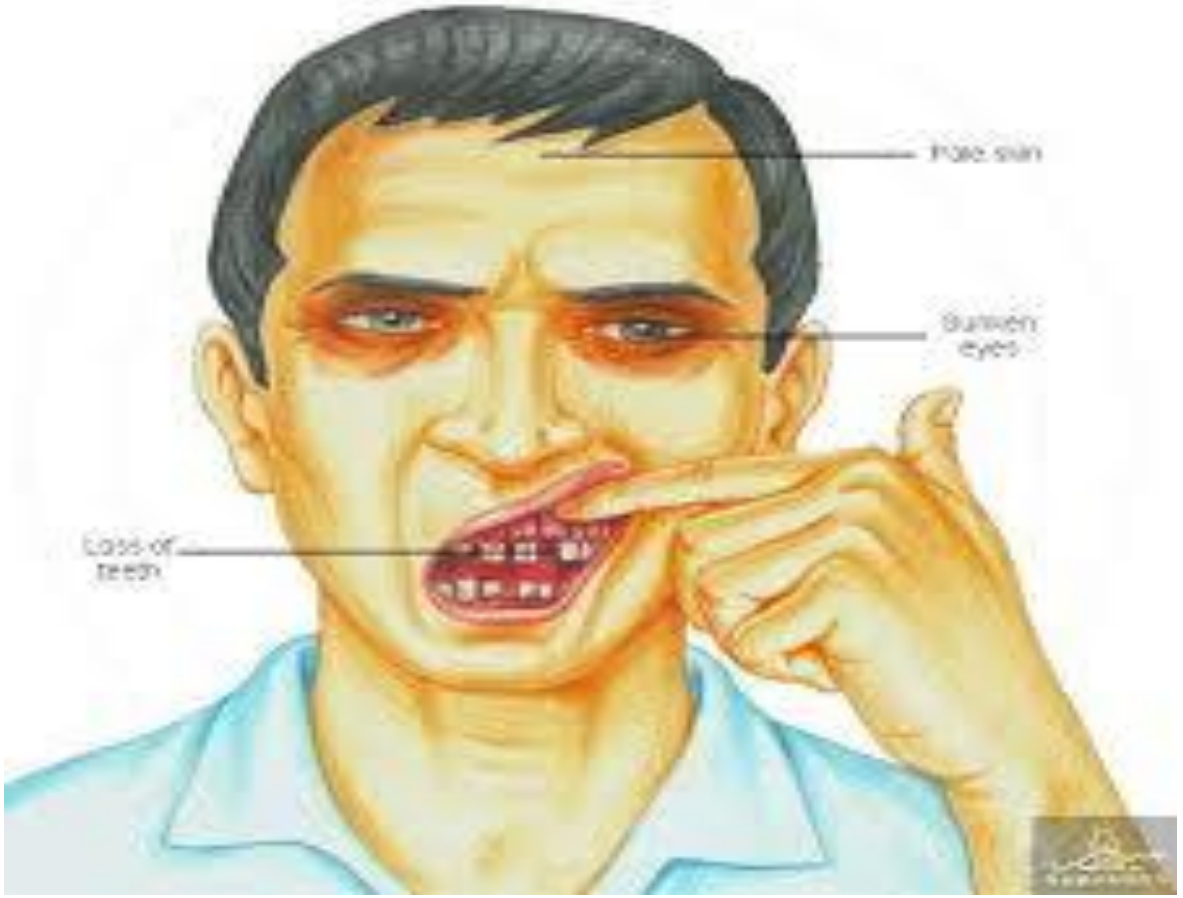
*** Vit. C is essential

Cleavage and assembly

Clinical application

Clinical disorders resulting from defects in collagen synthesis:

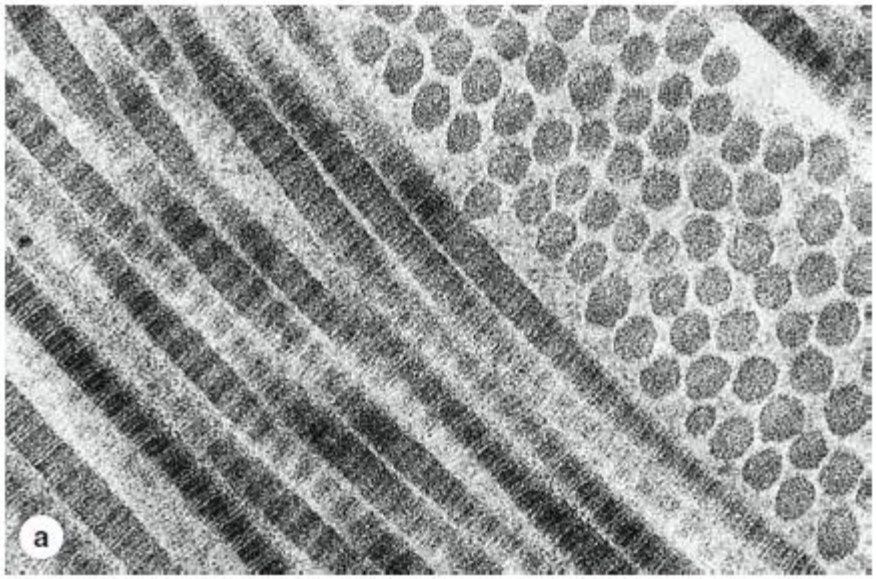
- Vitamin C deficiency (Scurvy)
- Keloid
- Ehlers–Danlos syndrome
- Osteogenesis Imperfecta

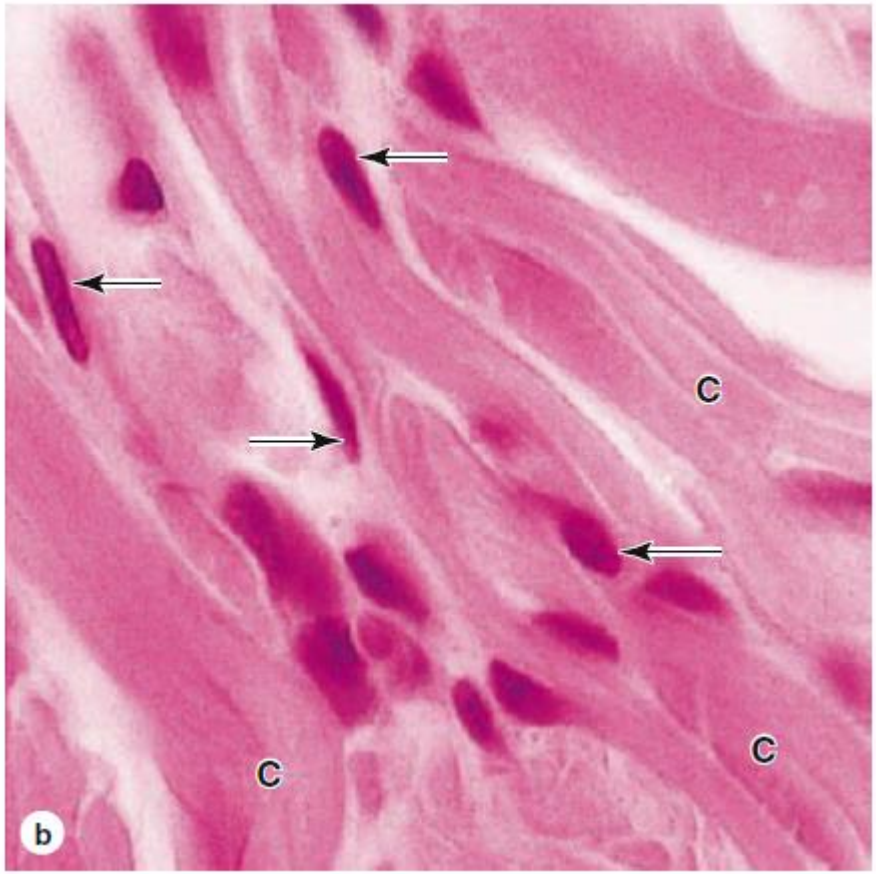

Pale skin
Sunken eyes
Loss of teeth

Keloids

Ehlers–Danlos syndrome – Type with Hypermobility

Collagen Fibers



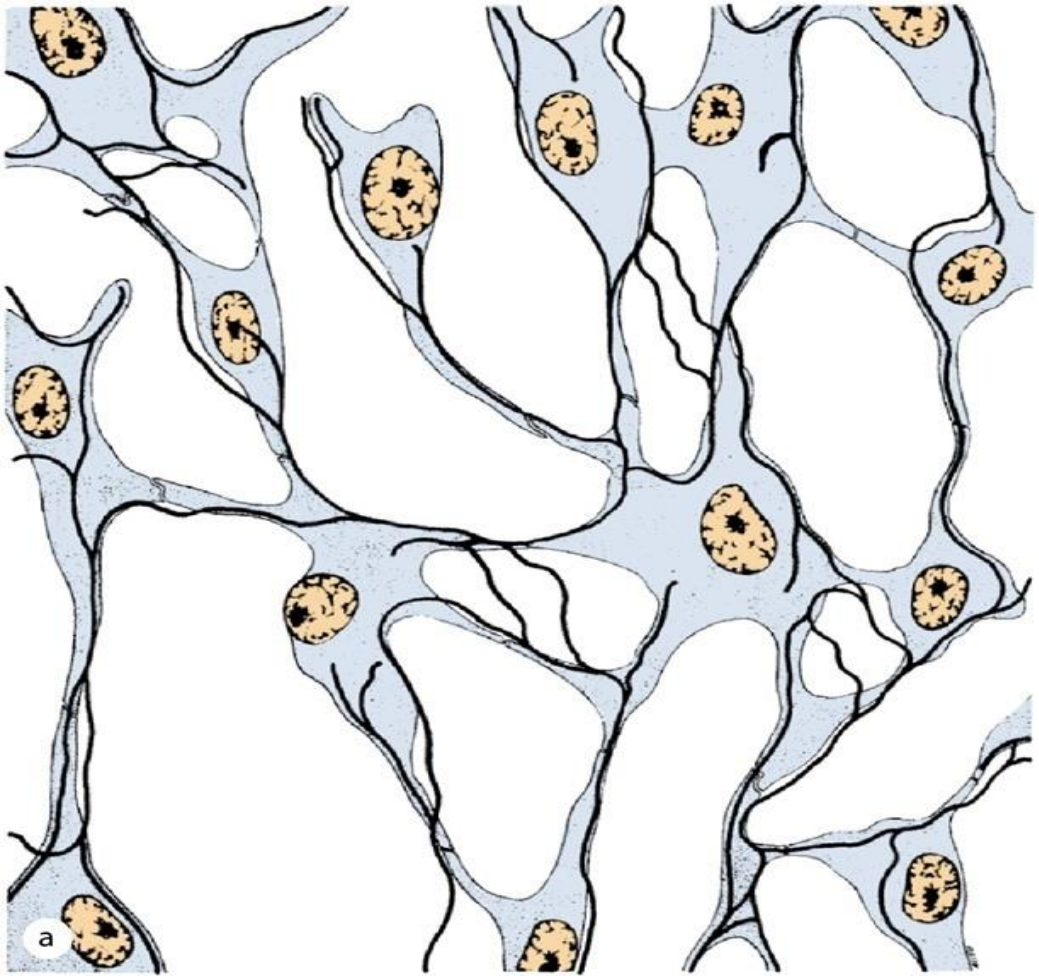


Reticular fibers

- Consist mainly type III collagen.
- Short, thin and branching.
- High sugar content
- Give PAS +ve reaction.
- Stain with Silver Nitrate (***Argyrophylic***).

Reticular fibers

- Found mainly in reticular lamina of basement membrane, framework of hematopoietic organs (e.g. spleen, lymph nodes, red bone marrow), network around paranchyma in liver and endocrine glands (supporting stroma)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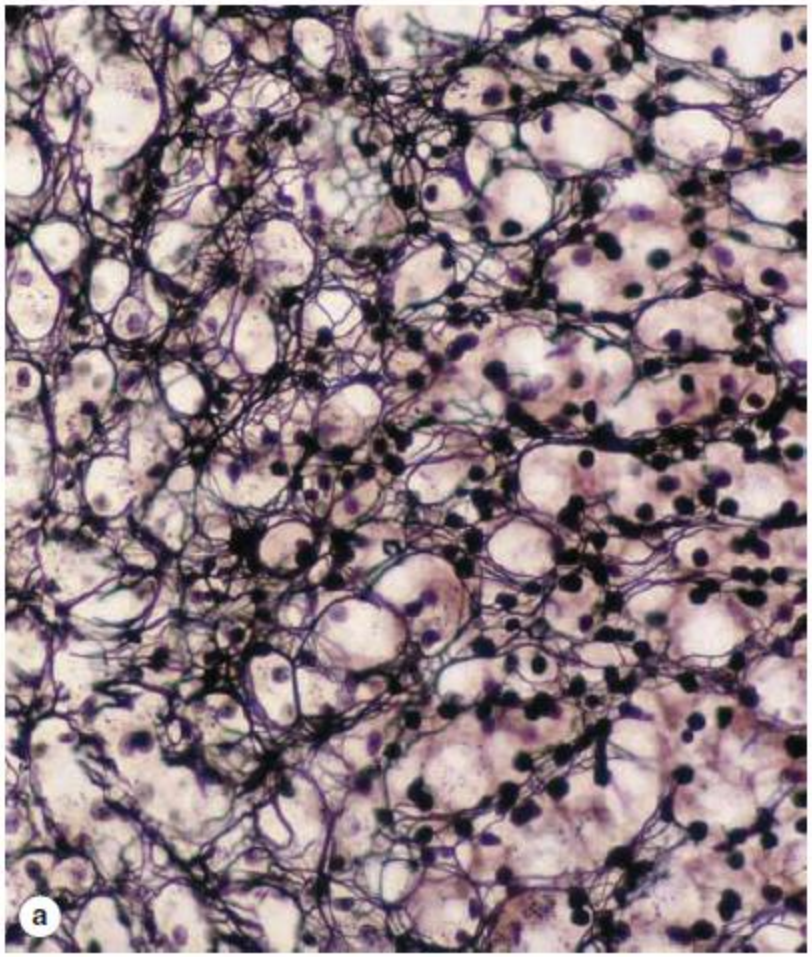
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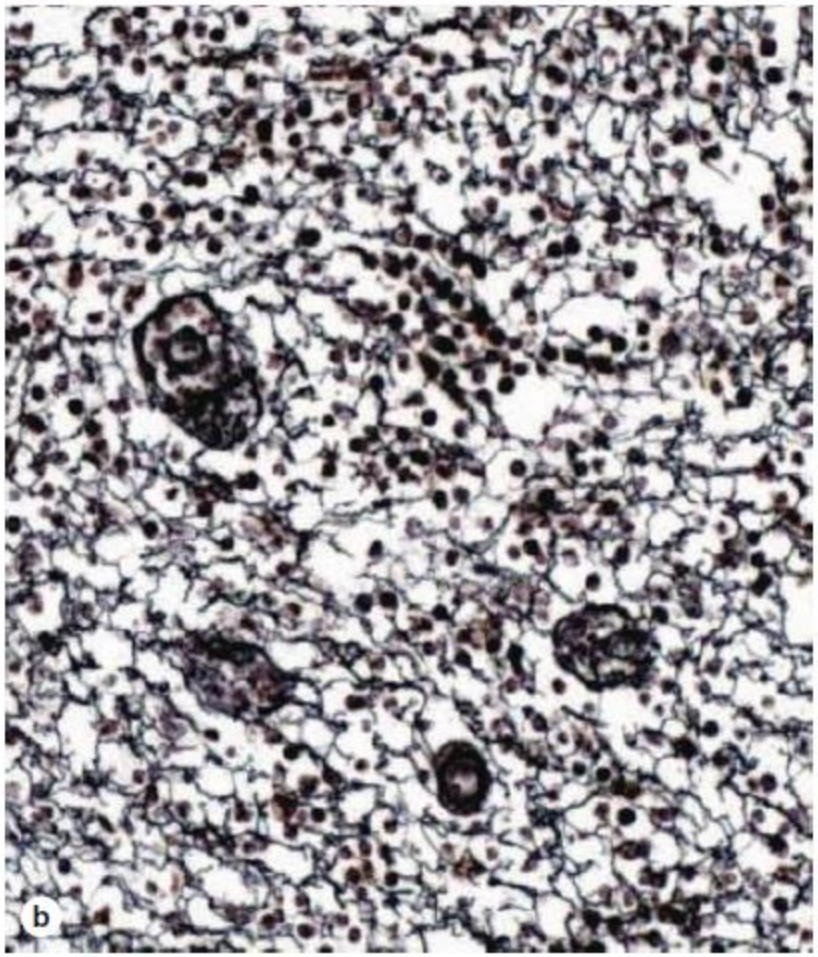
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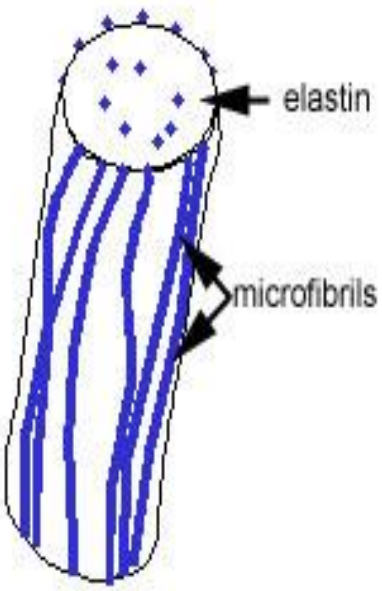
Elastic fibers

Elasticity is due to elastin.

Stability is due to fibrillin microfibrils (resistant to boiling).

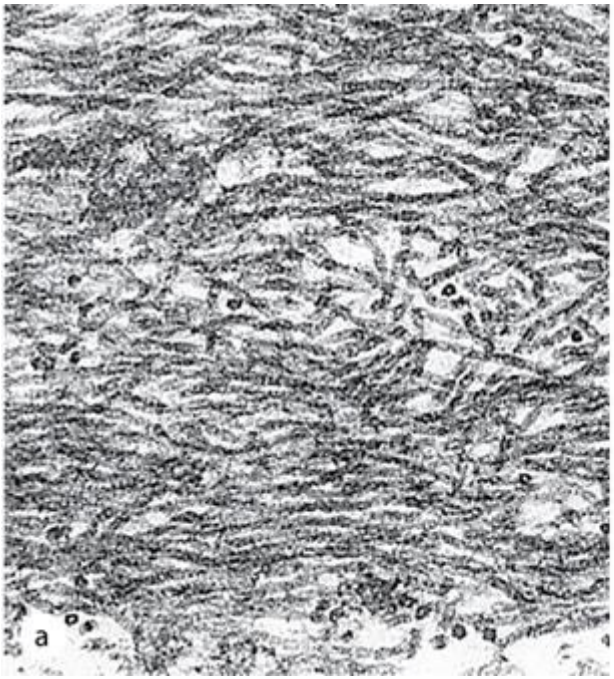
Appears yellow in fresh tissue (if large amount is present)

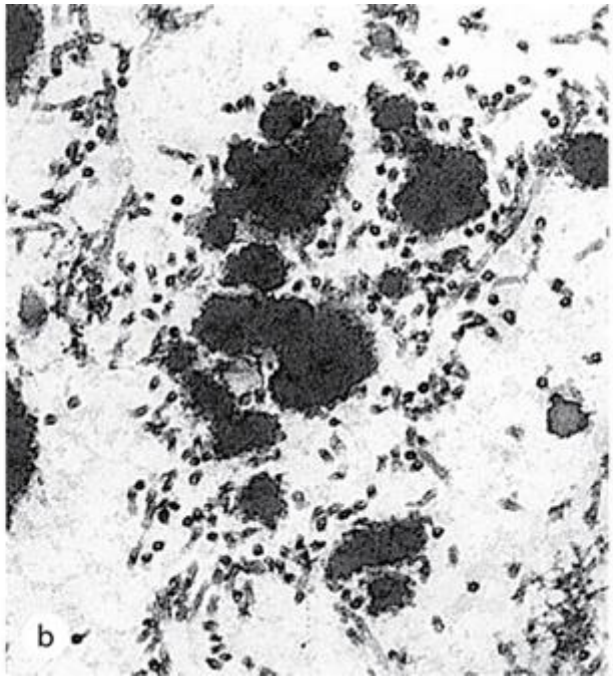
Digested by pancreatic enzyme elastase

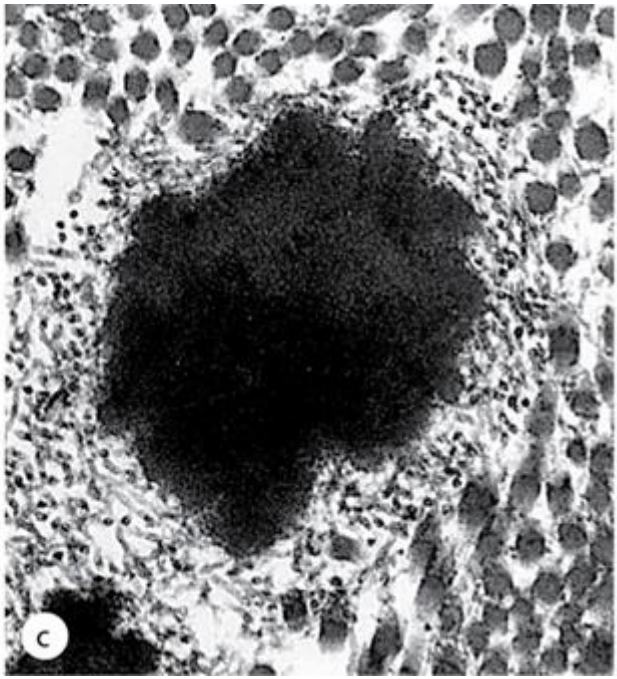


Elastic fibers consist of individual microfibrils(fibrillin) which are embedded in an amorphous matrix (90% of the fiber and composed of elastin)

Elastic material is found in certain ligaments (elastic ligaments), some cartilage (called elastic cartilage) and in large arteries (elastic arteries).







Elastin molecules are crosslinked by desmosine