Volgograd state medical university

Department of histology, embryology, cytology

Lecture:

CONNECTIVE TISSUE

for the 1nd course
English medium students

Volgograd

The objectives:

1. To be able to describe the morphology and to analyze functions of nine or more types of cells and three varieties of fibers, found in loose connective tissue.
2. To compare accurately, histologically and functionally, fibroblasts vs. macrophages, plasma vs. mast cells, and collagenous vs. elastic fibers.
3. To formulate the sequential stages of collagen synthesis and factors that may limit its production.
4. To explain the origin and composition of the amorphous ground substance and explore how it influences the spread of infections and toxic substances in the body.
5. To analyze the roles special types of connective tissues, e.g. mesenchyme, white and brown fat, reticular tissue, play in maintenance of health.
6. To evaluate the benefit of the macrophage system in the promotion of bodily defense mechanisms against infections.

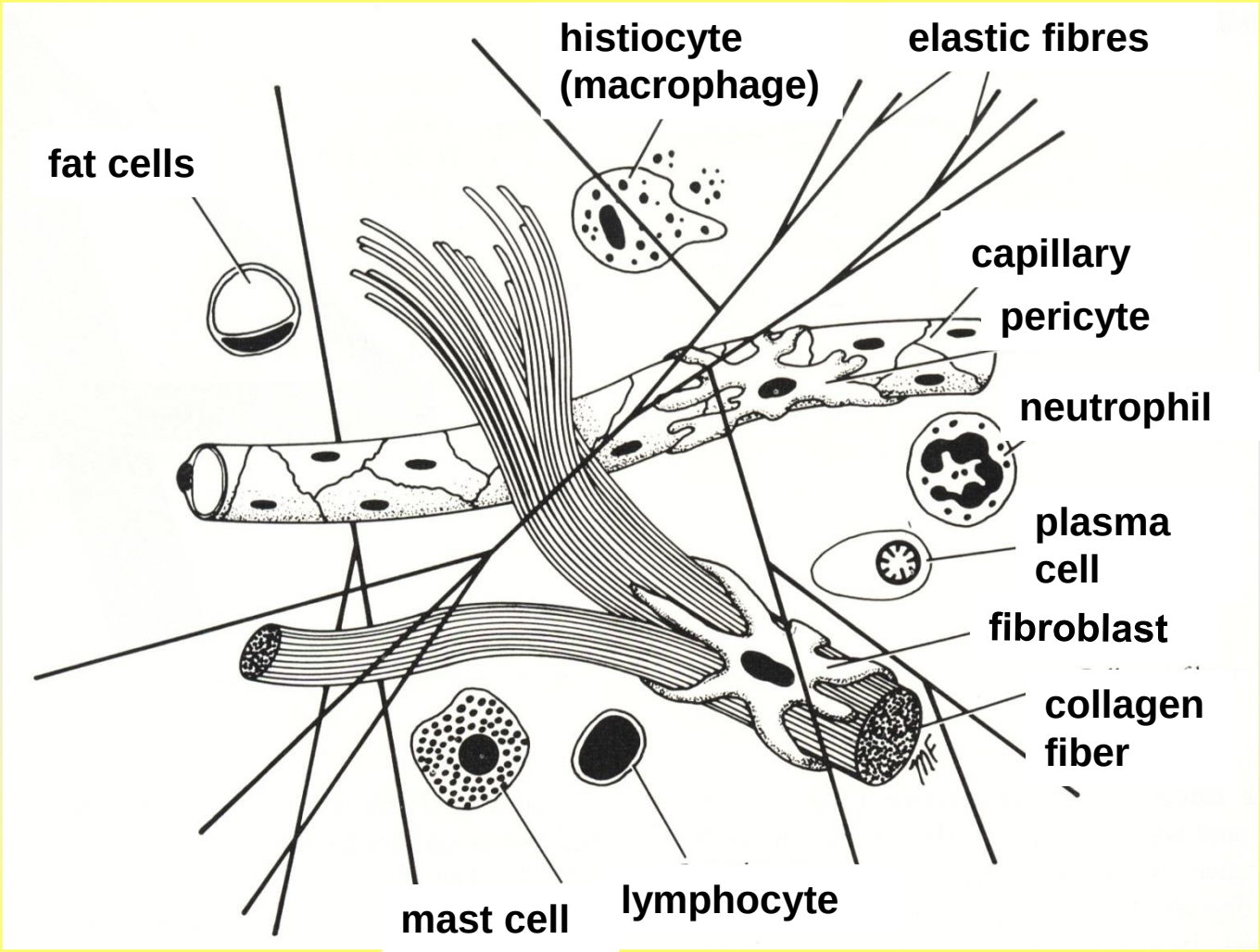
FIBERS:

1. Collagen and elastic fibers, the two major fibrous proteins of connective tissue, have distinct biochemical and mechanical properties as a consequence of their structural characteristics.

2. They provide tensile strength and elasticity to this substance.

3. Classical histologists have described 3 types of fibers although it is now known that reticular fibers are in fact a type of collagen fibers but the term reticular fibers is retained.

II. DEFINITION OF CONNECTIVE TISSUE



Connective tissue is a tissue of mesenchimal origin which connects, holds and supports other body tissue.

III. DISTINCTIVE FEATURES OF CONNECTIVE TISSUES

1. On the contrary to other tissues, connective tissue is composed mostly of extracellular matrix with a limited amount of cells scattered throughout the matrix.

2. Cells maintain their associations with the extracellular matrix by forming specialized junctions that hold them to the surrounding macromolecules.

3. The extracellular matrix of connective tissue is composed of a hydrated gel-like ground substance with fibers embedded in it.

IV. FUNCTIONS OF THE CONNECTIVE TISSUE

- mechanical support (fibers)

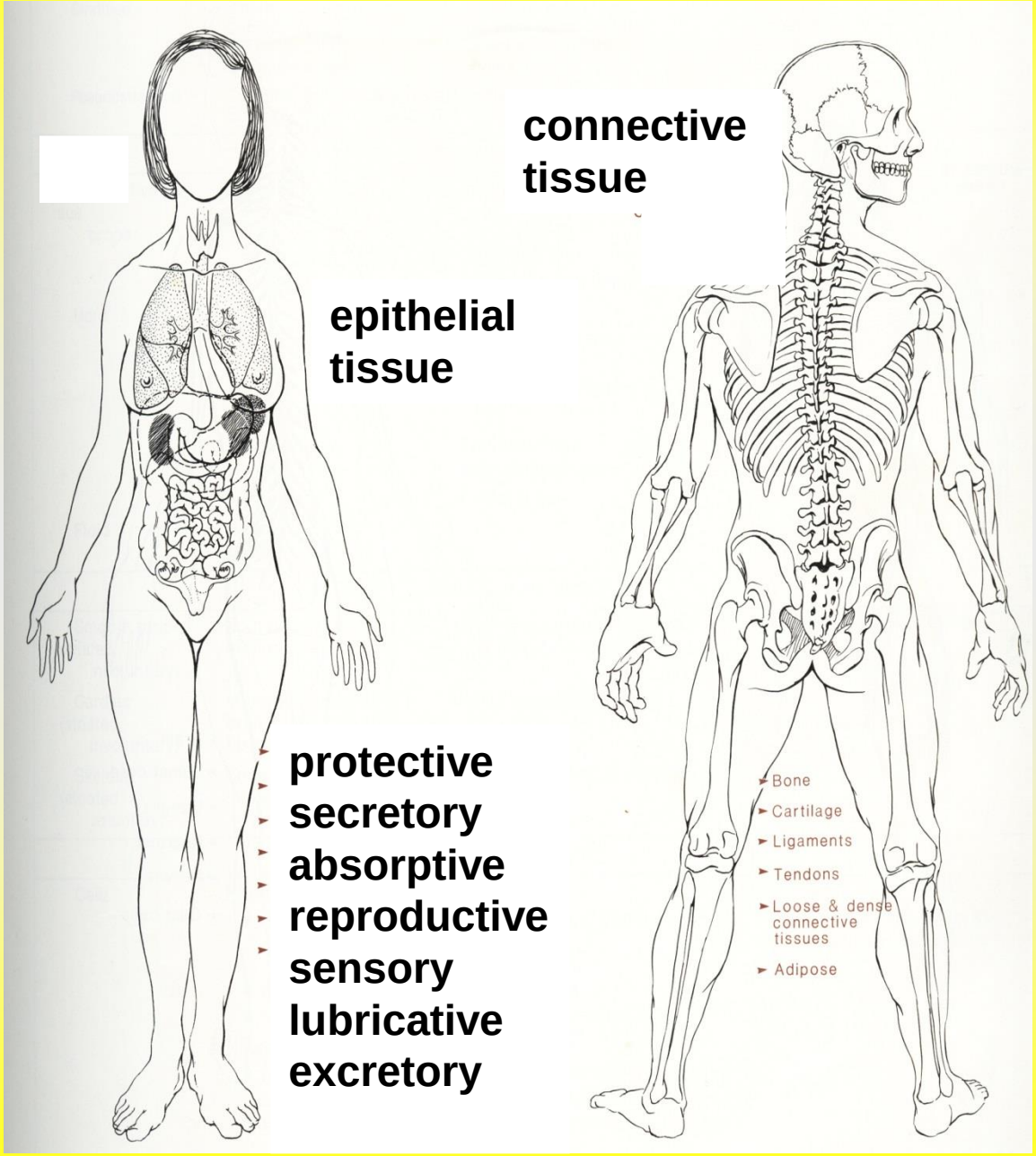
-exchange of metabolites between blood and tissue (ground substance)

-storage of reserve energy material (adipose cells)

- protection against infection and other foreign material (immunocytes)

- - regeneration after injury (fibroblasts)

Localization of Epithelium & Connective Tissue in the Human Body



bone
cartilage
ligaments
tendons
loose and **dense**
connective tissues
adipose

Classification of Connective Tissue by Characteristics of Intercellular Material

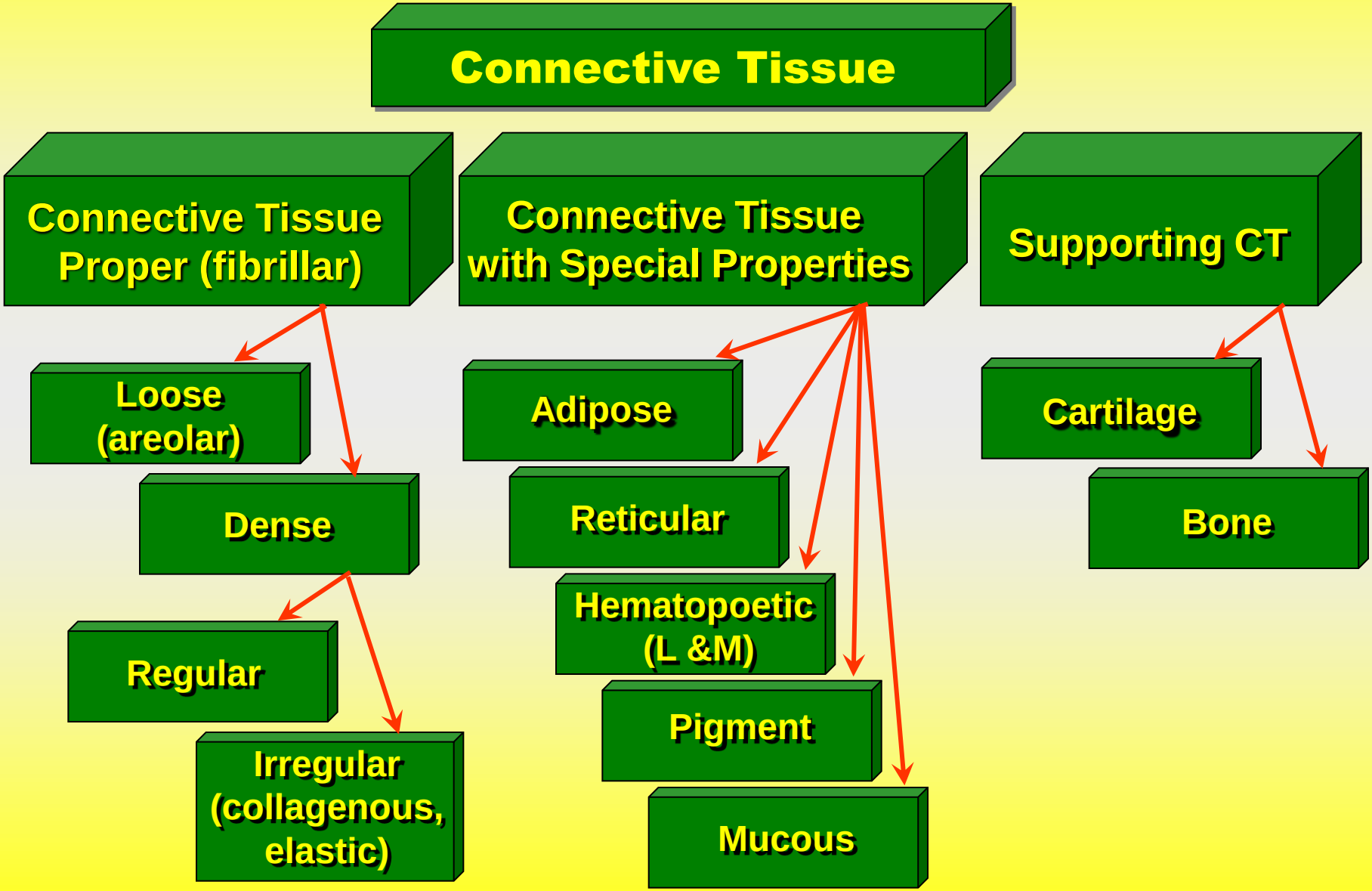
Ground substance
Fiber content
Cell types

Functions

-support	-ancoring
-transport	-insulation
-defense	-tissue repair
-storage	-antibody production
- binding	-packing

Fibrosis repair process
(e. g. wound healing)

CLASSIFICATION OF CONNECTIVE TISSUE



Classification of the Connective Tissue

	Fibers	*Ground Substance*	*Tissue Fluid*	*Cells*	*Location (s)*	*Function (s)*	*Comments*
Embryonic Mesenchyme	Primitive, thin collagenous fibers	Amorphous, jellylike	Abundant	Mesenchymal (early fibroblasts), branching, stellate with many processes	Embryo and early fetus	Precursor of nearly all connective tissue	Very active in mitosis
Mucous	Delicate network of collagenous fibers	Abundant, amorphous, jellylike; gives mucin reaction with PAS; rich in mucopolysaccharides and glycogen	Abundant	Large, branching, stellate early fibroblasts; few macrophages and lymphocytes	Wharton`s jelly in umbilical cord	Support around umbilical vessels	Also found in other parts of the fetus, e.g., beneath the skin

Classification of the Connective Tissue
(continued)

	Fibers	*Ground Substance*	*Tissue Fluid*	*Cells*	*Location (s)*	*Function (s)*	*Comments*
Adult - Connective tissue proper (loose-areolar)	Mostly collagenous, some elastic and a few reticular	Quite fluid, rich in mucopolysac-charides (GAG)	Abundant	Fibroblasts and macrophages; some visitants, e.g., mast and fat cells, leukocytes, etc.	Subcutaneous tissue, mesenteries, fasciae, etc.	Support and padding of tissue; lipid storage	Traversed by blood and lymph vessels, and nerves
-Dense-irregular	Nearly all collagenous fibers with a few elastic and reticular; arranged in disorganized sheets	Limited	Considerable	Flattened, elongated fibroblasts	Dermis, capsules of glands, periosteum	Support	Has considerable tensile strength
-Dense-regular	Parallel collagenous fibers; some elastic fibers in ligaments	Limited	Considerable	Flattened, elongated fibroblasts	Tendons and ligaments	Attachment of muscle to bone (ligaments)	Has great tensile strength; muscle of bone may be fractured by violent contraction, instead of tendon or ligament

Classification of the Connective Tissue (continued)

	Fibers	*Ground Substance*	*Tissue Fluid*	*Cells*	*Location (s)*	*Function (s)*	*Comments*
Special - Adipose-white	Reticular fibers surround cells, some collagenous fibers between cells	Scanty	Negligible	Signet-ring-shaped fat cells with nucleus flattened on periphery of cell by large fat vacuols; few fibroblasts, leukocytes and mast cells	Subcutaneous layer, perirenal areas, and other fat depots	Energy (lipid) storage; insulation against temperature changes	Depleted during starvation and certain discases; not a static tissue; has cycles of deposits and withdrawals; quite vascular
- Adipose-brown	Same as above	Scanty	Negligible	Fat cells smaller, nuclei spherical and centrally located; cytoplasm contains many small fat vacuoles	In man limited amounts in interscapular and inguinal regions; best developed as hibernating gland of certain animals	Source of heat production in newborn and animals in hibernation	More vascular; some pigment present; cells not easily depleted by nutritional deficits; many mitochondria
- Reticular	Reticular	Considerable	Abundant	Primitive reticular cells; often many lymphocytes and other blood cells	Stroma of glands and lymph nodes	Provide supporting frame-work for glands	Probably same as immature collagenous fibers

Classification of the Connective Tissue (continued)

	Fibers	*Ground Substance*	*Tissue Fluid*	*Cells*	*Location (s)*	*Function (s)*	*Comments*
Cartilage - Hyaline	Collagenous fibrils (submicroscopic); about 40% of dry weight is collagen	Dense, semisolid, rich in glycoaminoglycans and collagen	Abundant, is about 75% of wet weight of cartilage	Chondrocytes entrapped in lacunae, random distribution	Articular surfaces; fetal skeleton; tracheal rings	Support	Clear. glassy appearance; avascular, receives nutrients by diffusion; may calcify in old age
- Fibrous- white	Collagenous	Limited except in surrounding cells; heavily laced with entwined collagenous fibers	Limited except in nucleus pulposus of interverteb ral disk	Same as above except cells usually arranged in parallel rows or in small clusters	Intervert ebral disks; symphysis pubis	support, especially where tough, tensile strength is needed	Lacks a perichondrium; is white in fresh state due to abundance of collagenous fibers
- Elastic- yellow	Mostly elastic with some collagenous in subperichondrial region	Limited, filled with branching network of elastic fibers	Limited	Similar to hyaline except cells more abundant and usually occur singly in lacunae	External ear; epiglottis	Support where flexibility and firmness are needed	Yellow color from elastic fibers; fracture healing is often uneven and incomplete, e.g., cauliflower ear

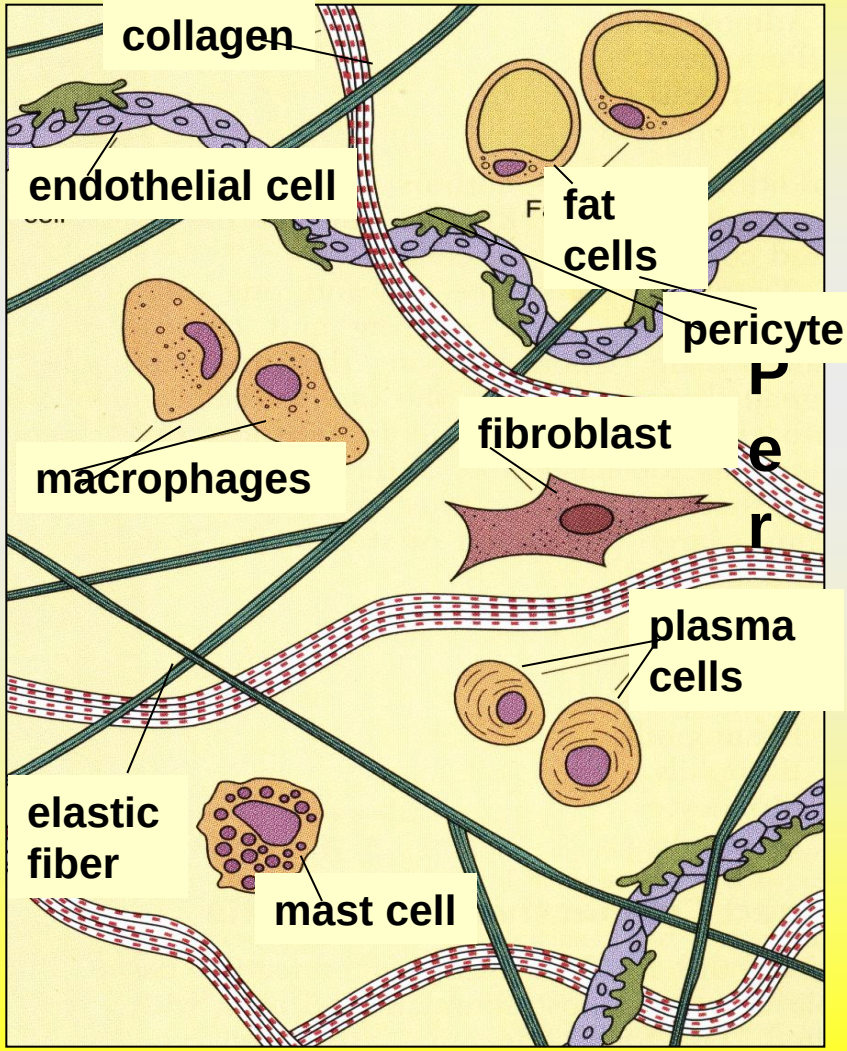
Classification of the Connective Tissue (continued)

	Fibers	*Ground Substance*	*Tissue Fluid*	*Cells*	*Location (s)*	*Function (s)*	*Comments*
Bone - Cancellous	Collagenous fibrils (submicroscopic)	Rigid, calcified	Negligible	Osteocytes, osteoblasts, and osteoclasts	Centers of flat bones; ends of long bones	Support, also houses hemopoietic tissue	Also called spongy bone, forms a lattice work; osteons sparse
- Compact	Same as above	Same	Same	Same	Outer shell of bones	Provides most of support for skeleton	Also called cortical bone; has extensive osteons
Blood	Fibrin strands in clotting	Absent	Greatest amount (plasma)	Erythrocytes, leukocytes, and thrombocytes	Peripheral vascular system; red bone marrow	Erythrocytes for transportation of oxygen; leukocytes for body`s main defense against infection	Also distributes heat; carries nutrients and waste products
Lymph	Same but fibrin forms more slowly		Same; however, composition less stable	Lymphocytes and a few granulocytes	Lymph vessels; lymphoid organs	Largely involved in immune reactions	In intestines, lymph (chyle) has a milky color due to large amount of fat droplets

Subdivisions of Connective Tissue

Type	*Location*
General connective tissue	
Loose connective tissue	
Mesenchyme	Primary in the embryo and developing fetus
Mucoid	Umbilical cord
Areolar	Most organs and tissues
Adipose	Omentum, subcutaneous tissue
Reticular	Lymph nodes, bone marrow
Dense connective tissue	
Irregular	Dermis, capsules of organs, periosteum, perichondrium
Regular	Tendon, ligaments, aponeurosis, cornea
Collagenous	Ligamentum nuchae, ligamenta flava
Elastic	
Special connective tissue	
Cartilage	Costal cartilage, trachea
Hyaline	Symphysis pubis, intervertebral disk
Fibrous	External ear, epiglottis
Elastic	Skeleton
Bone	Cardiovascular system
Blood	Bone marrow, Lymphatic tissue and organs
Hemopoietic	

Classification of the Connective Tissue Cells



CT cells can be characterized as fixed or wandering. The cells that comprise fixed cell population are relatively stable; they normally exhibit little movement and can be regarded as permanent residents of the tissue. They include fibroblasts and a closely related type myofibroblasts, macrophages, adipose cells, mast cells, undifferentiated mesenchimal cells (adventitial cells, pericytes).

The cells that comprise the wandering (transient) population are mostly those that have migrated into the tissue from blood in response to specific stimuli: lymphocytes, plasma cells, neutrophils, eosinophils, basophils, monocytes.

TYPES OF CELLS IN LOOSE AREOLAR TISSUE

1. Resident

-fibroblasts

-macrophages

-mesenchymal cells

-reticular cells

2. Visitant

-fat cells

-plasma cells

-mast cells

-leukocytes

-pigment cells

COMPOSITION OF CONNECTIVE TISSUE

1. CONNECTIVE TISSUE = CELLS + EXTRACELLULAR MATRIX

2. EXTRACELLULAR MATRIX = GROUND SUBSTANCE + FIBERS

3. MACROMOLECULES OF THE GROUND SUBSTANCE = GAG + PROTEOGLYCANS + ADHESIVE GLYCOPROTEINS

COMPOSITION OF GROUND SUBSTANCE

water – mineral salts – glycoproteins – **GAG, proteoglycans**

Nonsulfated group

-Hyaluronic acid (in skin, loose connective tissue, umbilical cord, vitreous body, & synovial fluid } break down with hyaluronidase "speading factor"

-Chondroitin (in cornea & embryonic cartilage)

Sulfated group

-Chondroitin-4-sulfate (in cornea, skin, bone & cartilage)
-Chondroitin-6-sulfate (in tendons, cartilage, umbilical cord & intervertebral disks)
-Dermatan sulfate (in skin, tendons, ligaments & heart velves)
-Keratan sulfate (in bone, cartilage, cornea & intervertebral disks)

Collectively termed "glycosaminoglycans"

Ground substance functions
- controls passage of pathogens
- allows diffusion of O2 & nutrients

GLYCOSAMINOGLYCANS

Glycosaminoglycan	*Sulfation*	*Protein-linked*	*Distribution*
Hyaluronic acid	no	no	cartilage synovial fluid, skin, support tissue
Chondroitin sulfate Dermatan sulfate	yes yes	yes yes	cartilage, bone, skin, support tissue skin, blood vessels, heart
Heparan sulfate Heparin	yes yes	yes yes	basement membrane, lung arteries lung, liver, skin, mast cell granules
Keratan sulfate	yes	yes	cartilage, cornea, vertebral dosk

There are 4 major groups of GAG, which have different tissue distributions. Sulphatation causes the molecules to be highly negatively charged and contributes to their ability to retain Na+ ions and water. With the exception of hyaluronic acid the GAGs become linked to proteins to form proteoglycans. The presence of specific types of GAG in different tissues confers special attributes to the extracellular matrix, particularly with regard to diffusion or binding of other extracellular substances.

TYPES OF GLYCOSAMINOGLYCANS

GAG	*Molecular Mass (Da)*	*Repeating Disaccharides*	*Sulfated Amino Sugar*	*Covalent Linkage to Protein*	*Location in Body*
Hyaluronic acid	**10^7-10^8**	**Glucuronate and *N*-acetylglucosamine**	**None**	**No**	**Most connective tissue, synovial fluid, cartilage, dermis**
Keratan sulfate	**10,000-30,000**	**Galactose and *N*-acetylglucosamine**	***N*-acetylglucosamine**	**Yes**	**Cartilage, cornea, intervertebral disk**
Heparan sulfate	**15,000-20,000**	**Glucuronate (or iduronate) and *N*-acetylglucosamine**	***N*-acetylglucosamine**	**Yes**	**Blood vessels, lung, basal lamina**
Heparin	**15,000-20,000**	**Glucuronate (or iduronate) and *N*-acetylglucosamine**	***N*-acetylglucosamine**	**No**	**Mast cell granule, liver, lung, skin**
Chondroitin 4-sulfate	**10,000-30,000**	**Glucuronate and *N*-acetylglucosamine**	***N*-acetylglucosamine**	**Yes**	**Cartilage, bone, cornea, blood vessels**
Chondroitin 6-sulfate	**10,000-30,000**	**Glucuronate and *N*-acetylglucosamine**	***N*-acetylglucosamine**	**Yes**	**Cartilage, Wharton`s jelly, blood vessels**
Dermatan sulfate	**10,000-30,000**	**Glucuronate (or iduronate) and *N*-acetylglucosamine**	***N*-acetylglucosamine**	**Yes**	**Heart valves, skin, blood vessels**

CLINICAL CORRELATIONS:

- Many pathogenic bacteria, such as Staphylococcus aureus, secrete hyaluronidase, an enzyme that cleaves hyaluronic acid (it may be up to 20 micrometer long) into numerous small fragments, thus converting gel state of extracellular matrix into a sol state.

- This permits the rapid spread of bacteria through the connective tissue spaces. Permeability of microvessels may increase under certain conditions (inflammation, liberation of the biologically active substances such as histamine and bradykinin).

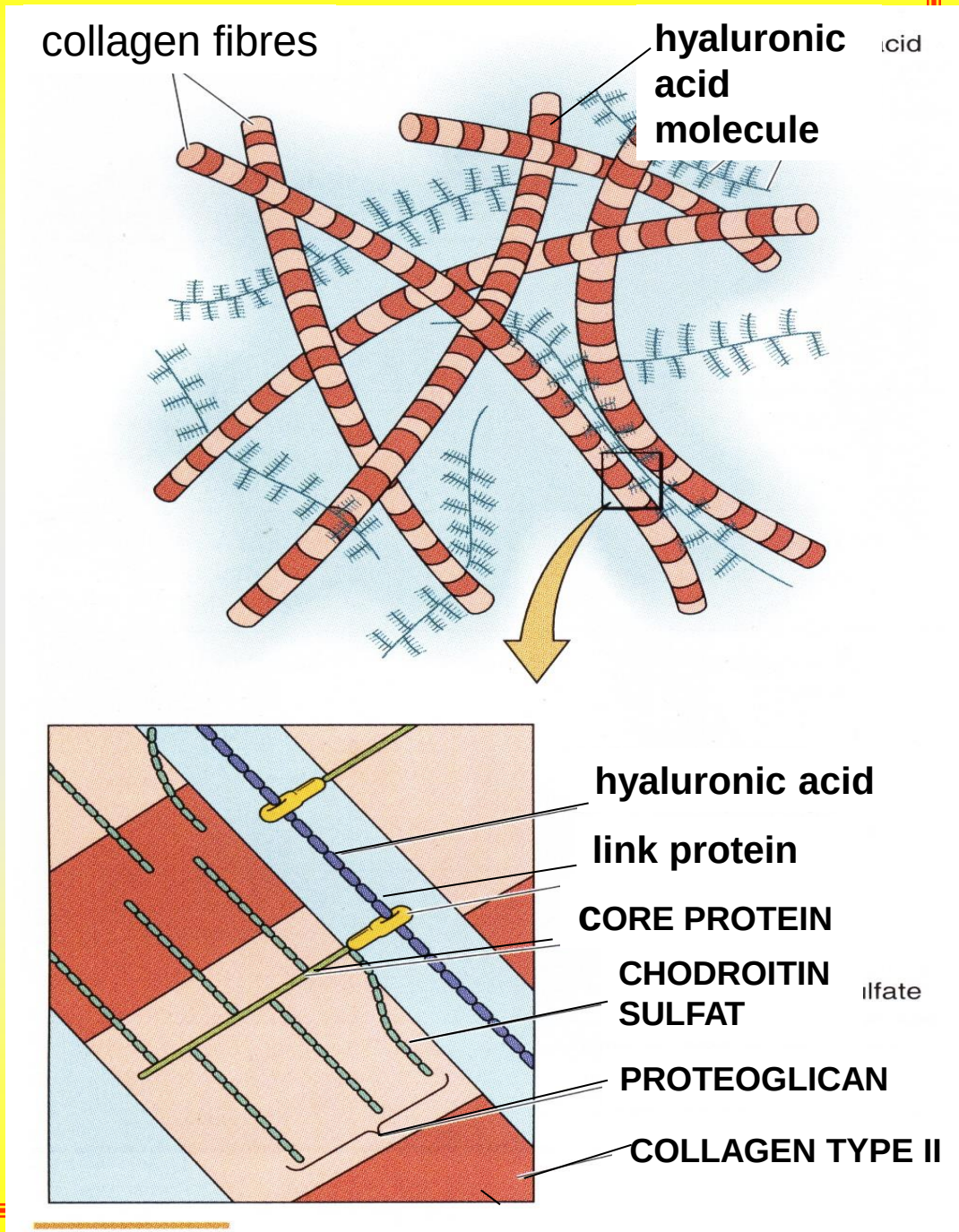
PROTEOGLYCANS:

- Proteoglycans constitute a family of macromolecules; each is composed of a protein core to which glycosaminoglycans are covalently bound.

- These large structures look like a bottle brush, with the protein core resembling the wire stem and the various sulfated GAGs projecting from its surface in three-dimensional space, as do the bristles of the brush. .

Schematic Diagram of Association of Aggrecan Molecules with Collagen Fibers.

Insert displays a higher magnification of the aggrecan molecule indicating the core protein of the proteoglycan molecule to which hyaluronic acid is attached. The core protein is attached to hyaluronic acid by link proteins.



COMMON PROTEOGLYCANS

Name	*Approx. Molecular Weight*	*Type of GAG Monomers*	*Approx. No. of GAG Chain*	*Distribution*	*Function*
Decorin	**40,000**	**Chondroitin sulfate, dermatan sulfate**	**1**	**Wide distribution in connective tissue**	**Binds type I collagen and TGF-β**
Aggrecan	**210,000**	**Chondroitin sulfate, keratan sulfate**	**130**	**Cartilage**	**Aggregates with hyaluronan, supportive function**
Perlecan	**600,000**	**Heparan sulfate**	**2-15**	**Basal laminae**	**Filtering function**
Betaglycan	**36,000**	**Chondroitin sulfate, dermatan sulfate**	**1**	**Cell surface, Extracellular matrix**	**Binds TGF-β**
Syndecan-1	**32,000**	**Chondroitin sulfate, heparan sulfate**	**1-3**	**Surface of fibroblast and epithelial cells**	**Cell adhesion, binds FGF**

GLYCOPROTEINS:

- Cell adhesive glycoproteins have binding sites for several components of the extracellular matrix as well as for integrin molecules of the cell membrane that facilitate attachment of cells to the extracellular matrix.
- The ability of cells to adhere to components of the extracellular matrix is mediated by cell adhesive glycoproteins.
- These large molecules have several domains, at least one of which usually binds to cell surface protein called integrins, one to collagen fibers, and one to proteoglycans.
- In this manner, adhesive glycoproteins fasten the various components of tissues to each other.
- The major types are fibronectin, laminin, entactin, tenascin, chondronectin and osteonectin.

Some Common Proteins in the Extracellular Matrix

Molecule	*Type*	*Common distribution*	*Function*
Aggrecan	Proteoglycan	Cartilage	Hydration, swelling of collagen (type II) framework
Cartilage matrix protein	**Glycoprotein**	**Nonarticular cartilage**	**Bridging for collagen**
Collagen type I	**Fibrils**	**Bone, tendon, ligament, skin**	**Tensile strength**
Collagen type II	**Fibrils**	**Cartilage, vitreous humor**	**Tensile strength, resists compression**
Collagen type III	**“Reticular” fibrils**	**Numerous glands, immune tissue, skin, blood vessels**	**Mesh-like support, compliance**
Collagen type IV	**Network mesh**	**Basal laminae**	**Support, cell behavior**
Collagen type VIII	**Lattice**	**Descemet`s membrane**	**Tensile strength**
Collagen type X	**Lattice**	**Fetal cartilage**	**Early bone formation**
Decorin	**Proteoglycan**	**Bone, tendon, ligament, skin**	**Bridging for collagen**
Elastin	**Fibrillar network**	**Many supporting tissue**	**Elasticity, resilience**
Fibrillins	**Microfibils, glycoprotein**	**With elastic fibers**	**Scaffolding**
Fibrinogen	**Plasma protein**	**Plasma**	**Fibrin clot**
Fibronectin	**Glycoprotein**	**Widespread in extracellular matrix**	**Adhesion, cell migration**
Laminins	**Glycoprotein**	**Basal laminae**	**Development, dofferentiation**
Osteocalcin	**Matrix, protein, glycoprotein**	**Bone, teeth**	**Regulates crystal growth**
von Willebrand factor	**Glycoprotein**	**Plasma**	**Platelet-vascular adhesion**

IRREGULAR DENSE CONNECTIVE TISSUE, SEM

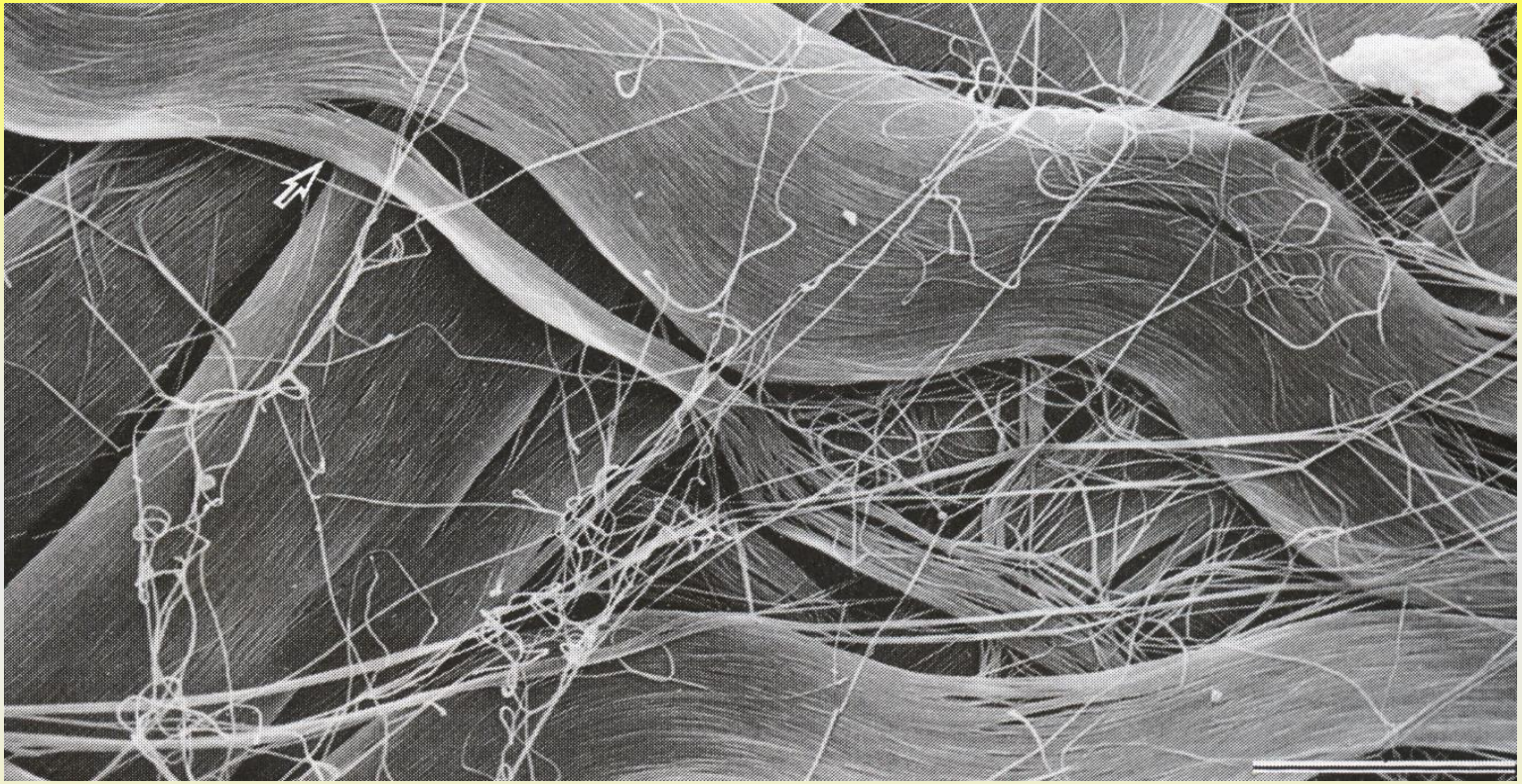
FIBERS:

1. Collagen and elastic fibers, the two major fibrous proteins of connective tissue, have distinct biochemical and mechanical properties as a consequence of their structural characteristics.

2. They provide tensile strength and elasticity to this substance.

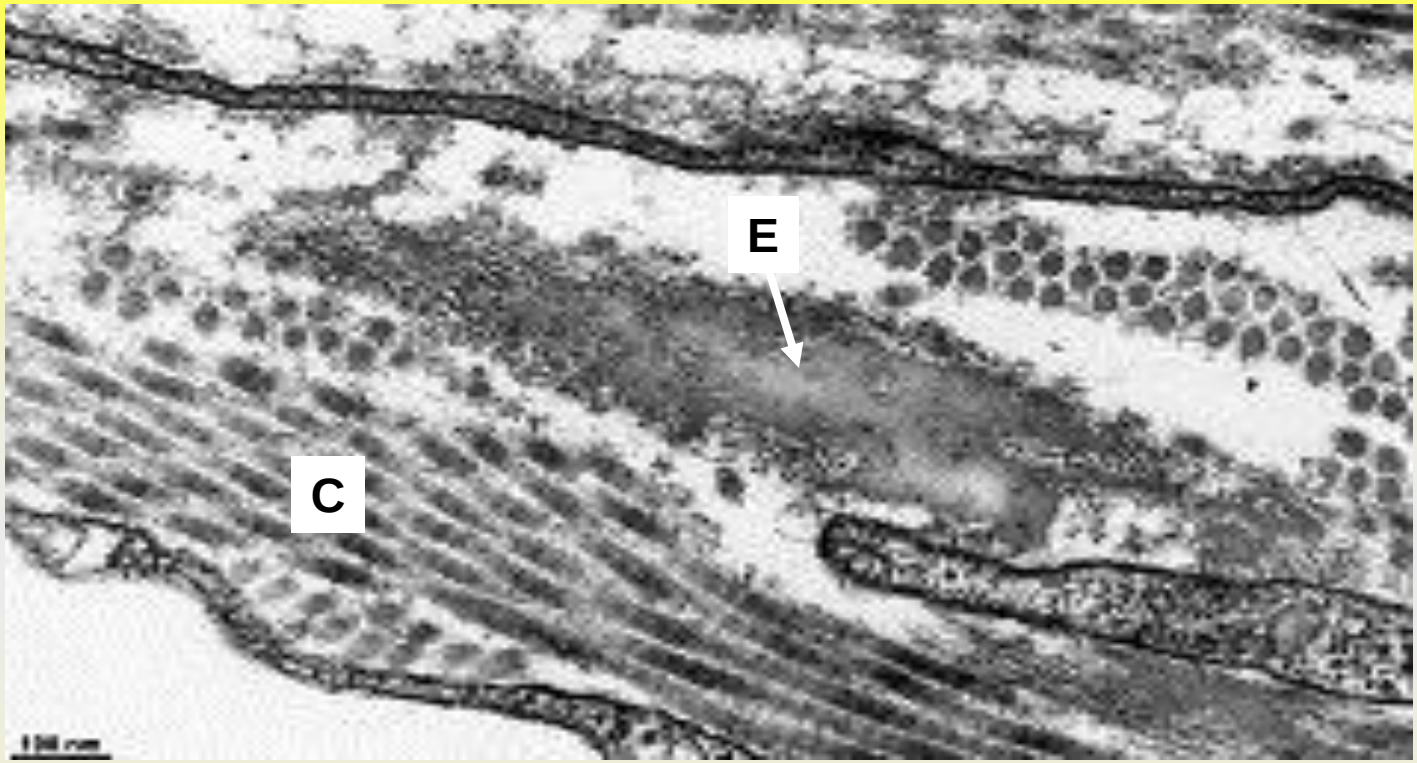
3. Classical histologists have described three types of fibers although it is now known that reticular fibers are in fact a type of collagen fibers but the term reticular fibers is retained.

SEM of Collagen Fiber Bundles in the Epineurium. x 2,000



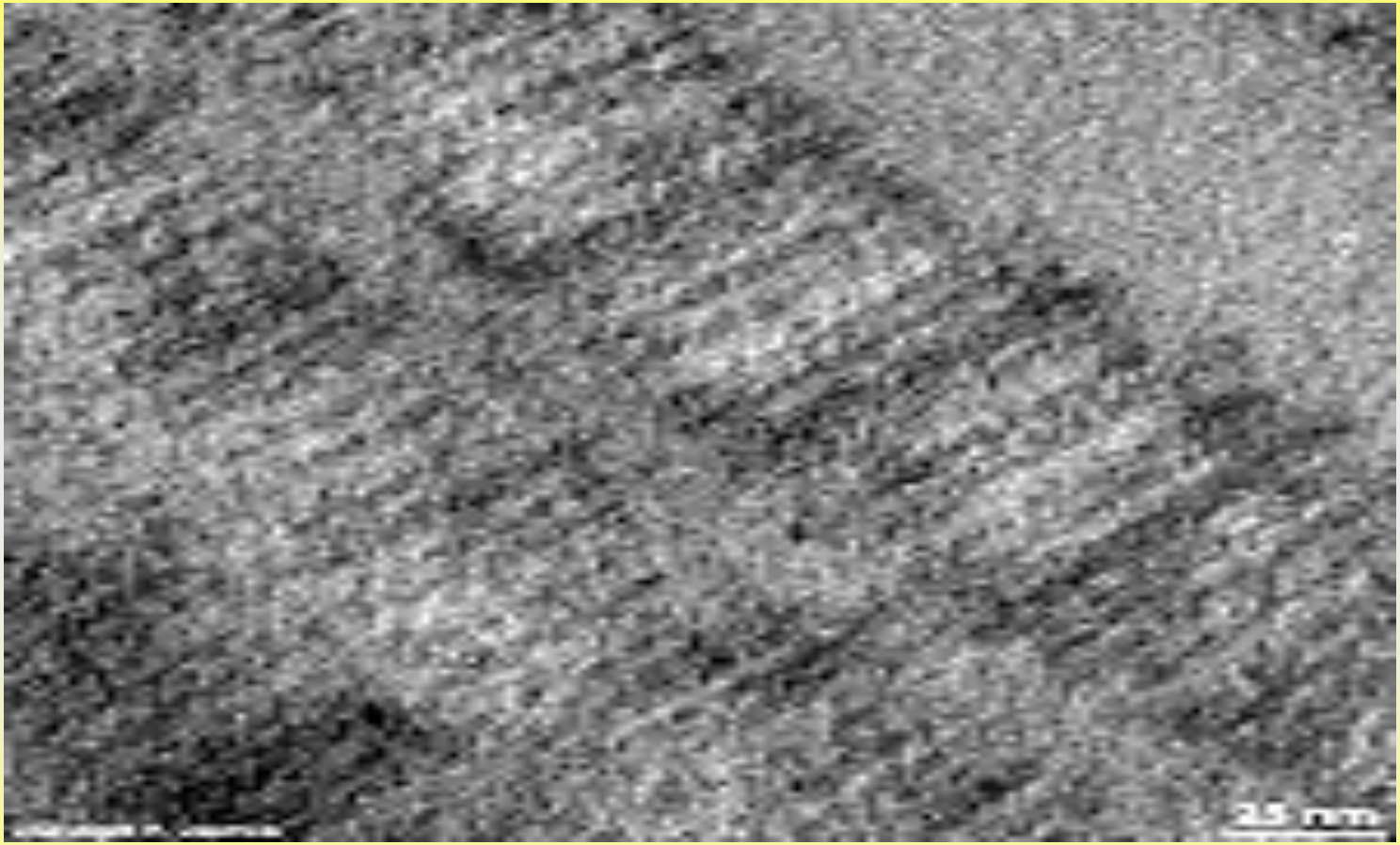
The CT fibers are of three types: collagen, elastic and reticular. The most abundant fiber is collagen, which comprises about 30% of all body proteins. They range from 2 to 10 mcm in diameter and do not branch extensively. Fibers consist of smaller fibrils about 50 nm in width. The fibrils in turn are composed of microfibrils.

Collagen (C) & Elastic (E) Fibers, TEM, 20,000x.



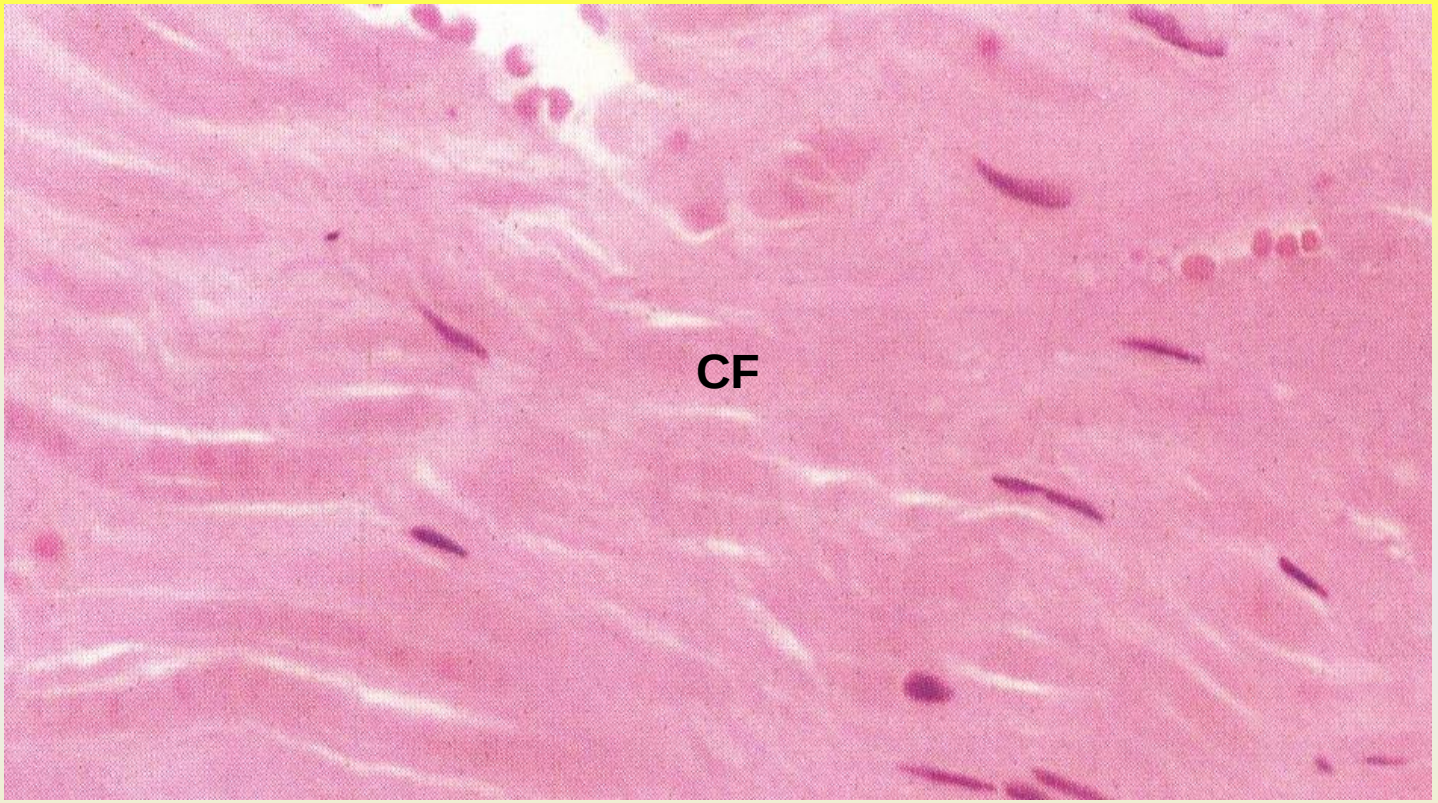
CF are composed of tropocollagen subunits whose alpha-amino acid sequences permit the classification of collagen into at least 15 different fiber types. The capability of extracellular matrix to withstand compressive forces is due to the presence of hydrated matrix formed by GAGs and proteoglycans. Tensile forces are resisted by fibers of the tough, firm, inelastic protein collagen. Collagen forms a flexible fiber whose tensile strength is greater than of stainless steel of comparable diameter.

Collagen Fibrils with 67 nm Periodicity of Striations. TEM, 100,000x.



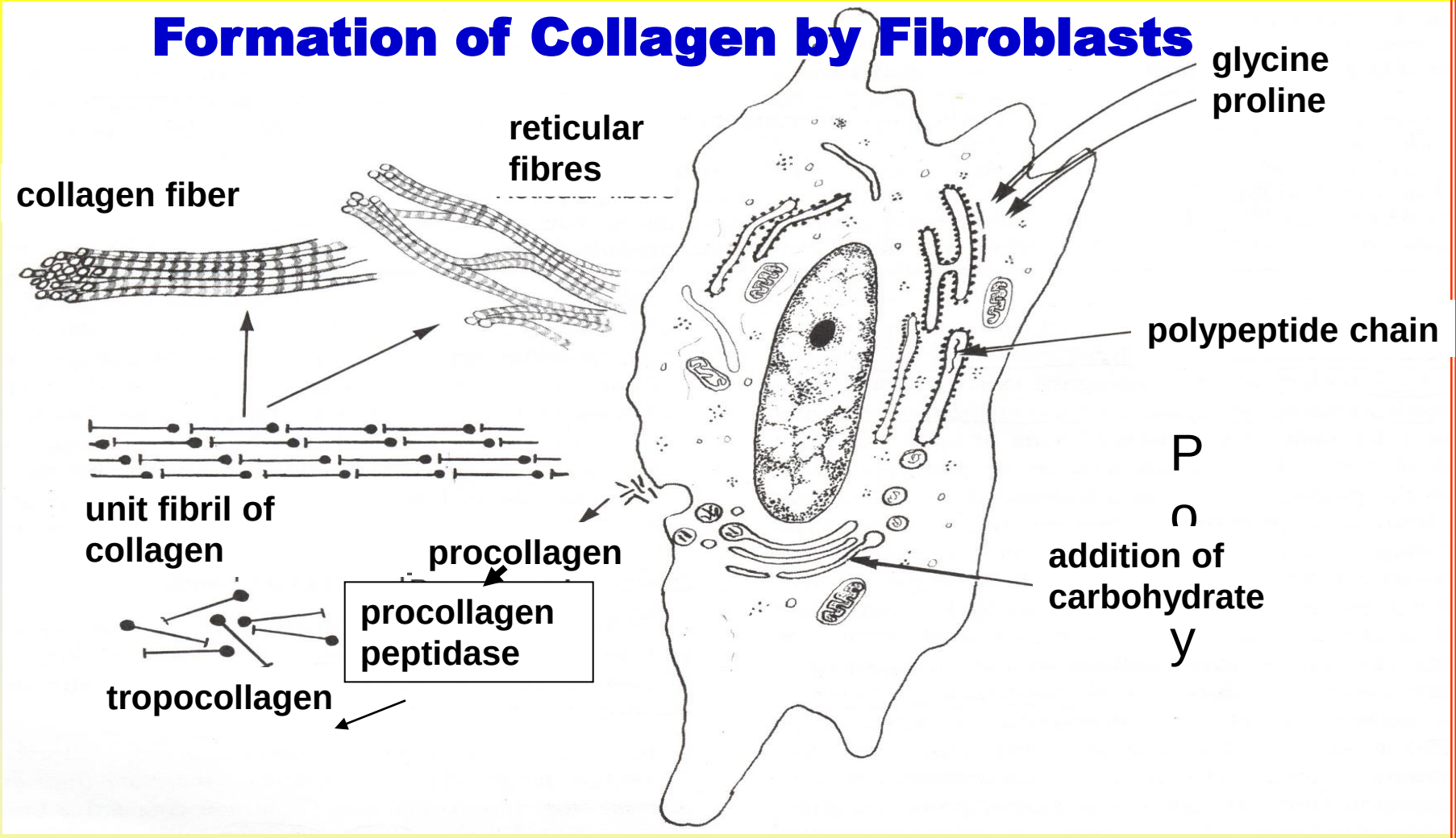
In EM the collagen fibrils exhibit a banding pattern with an axial periodicity of 67 nm. Overlapping of tropocollagen molecules is responsible for banding pattern. Tropocollagen molecules lie parallel to each other overlapping by ¼ of their length.

Collagen Fibers (CF), H & E.



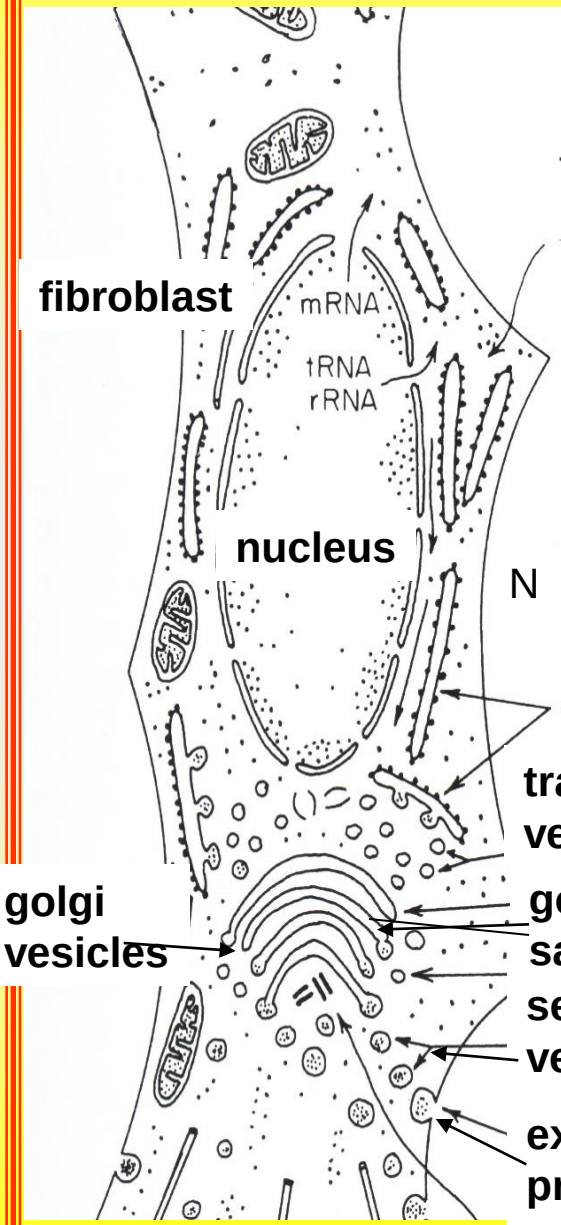
In H & E stained preparations CF appear pink-stained material which is often difficult to delineate from other structures that stain equally pink (e.g. support cells, walls of the blood vessels). Special stains can be used to stain collagen. Immunohistochemical staining can also be performed for different molecular types of collagen, but is seldom used in routine examination of tissues.

Formation of Collagen by Fibroblasts



Molecule of preprocollagen translated in the RER undergoes hydroxylation, glycosylation and formation of procollagen tripple helix in the RER.

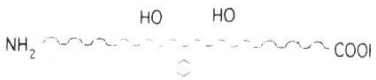
INTRACELLULAR SYNTHESIS OF THE PROCOLLAGEN MOLECULES IN THE CYTOPLASM OF A FIBROBLAST



Intracellular events

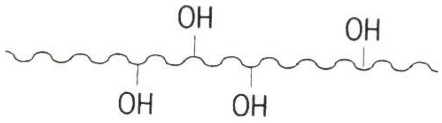
Formation of mRNA for each type of alpha chain

Uptake of proline, lysine,glycine and other amino acids

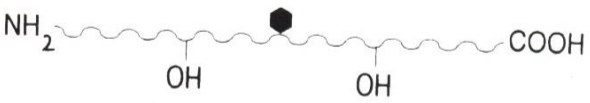


Synthesis pro-a-chains that have extra peptides at both ends of

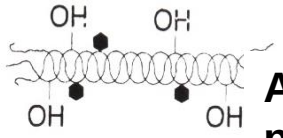
Posttranscriptional modifications include:



Hydroxylation of certain prolyl and lysyl residues (in rER)



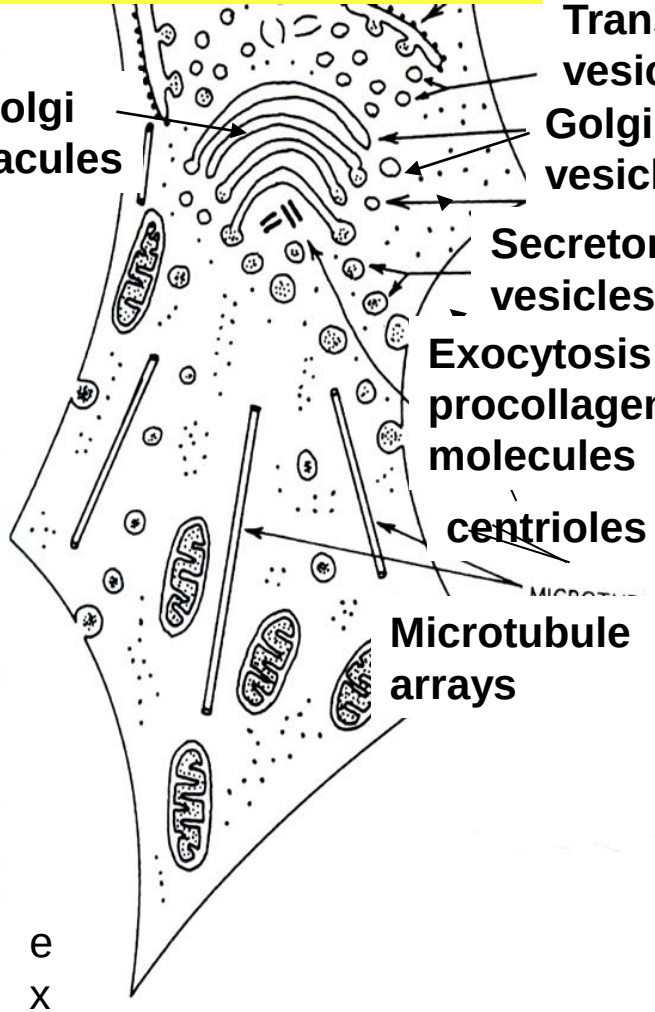
Galactosyl and glucosyl residues are attached to certain hydroxylysyl residues(glycosylation)

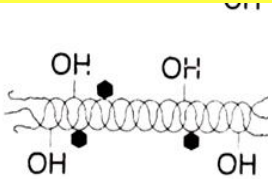


Assembly of a-chains into a procollagen molecule (triple helix)

Procollagen molecules are transported to Golgi complex by transfer of intermediate vesicles (shuttle). Procollagen molecules are transported through Golgi saccules and released in membrane-bound secretory vesicles.

EXTRACELLULAR FORMATION OF THE COLLAGEN FIBRIL



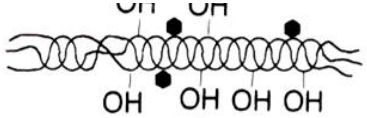


Assembley of a-chains into a procollagen molecule (triple helix)

Procollagen molecules are transported to Goldi complexby transfer of intermediate vesicles (shuttle). Procollagen molecules are transported through Golgi saccules and released in membrane-bound secretory vesicles.

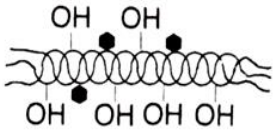
Extracellular events

Exocytosis of procollagen in coves or depressions of fibroblast; procollagen peptidases cleave much of the nonhelical ends of alfa chains, thus converting procollagen into insoluble tropocollagen.



Procollagen molecule

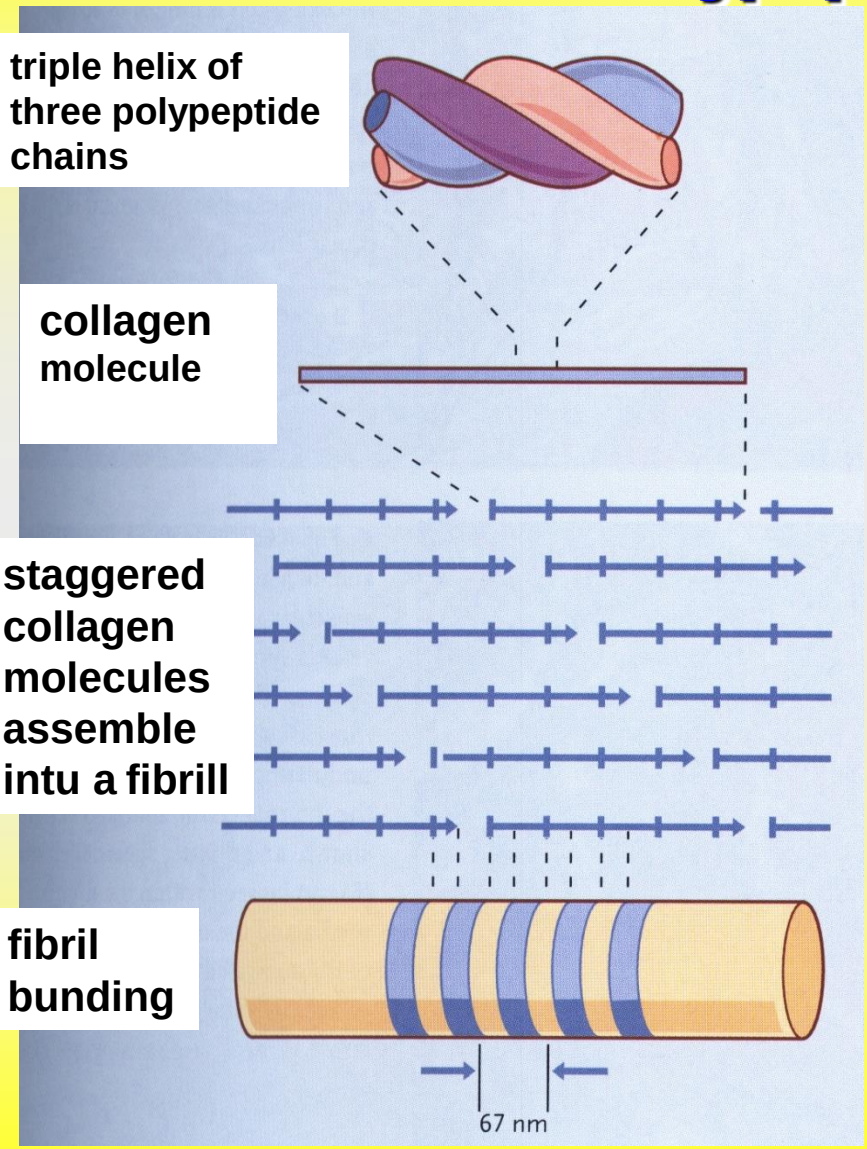
Cleavage of Propeptides



Tropocollagen Molecule

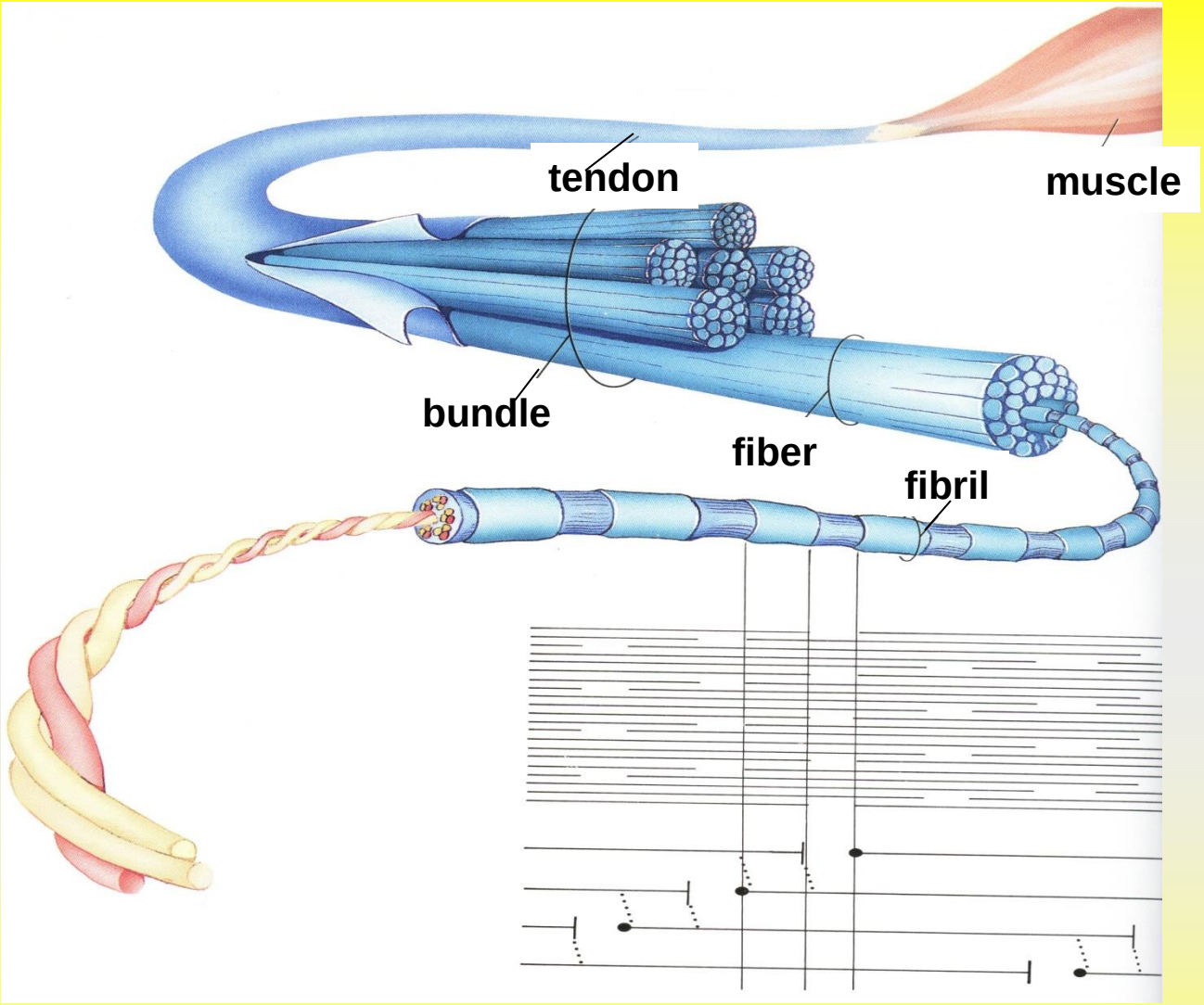
Many procollagen molecules align in a staggered array to form collagen fibrils wich exhibit an axial periodicity with TEM. Adjacent tropocollagen molecules are cross-linced (involves enzyme lysyl oxidase).

The Structure of the Superhelix of Collagen Polypeptide Chain



The composition of the chain determines the type of collagen formed. These collagen molecules (which are also called tropocollagen) self-assemble into protofilaments, which are filaments of 5 nm diameter. These protofibrils have a staggered aggregation pattern that maximizes electrostatic and hydrophobic interactions. Protofibrils link together into larger microfibrils (diameter 10-300 nm), which in turn form fibrils (diameter 0.1-0.5 mcm) which aggregate into fibers (diameter 1-12 mcm), and ultimately into the CF bundles seen in histological section.

Collagen Fibers



Schematic representation of the components of a CF. The ordered arrangement of the tropocollagen molecules gives rise to the gap and overlap regions, responsible for 67nm cross-banding of type I collagen.

Types of Collagen

Collagen Type	*Location*	*Cells Producing*	*Characteristics*
Type I (-90%) (composed of two types of α-chain)	Dermis of skin, tendon. Loose (areolar), dense ordinary connective tissue, collagen fibers. Most widely distributed type of collagen in internal organs. Bone. Dentin (teeth).	Fibroblasts Reticular cells and smooth muscle Osteoblasts Odontoblasts	Low hydroxylysine, low carbohydrate (broad fibrils)
Type II (composed of only one type of α-chain)	Hyaline and elastic cartilage Vitreous body of eye, intervertebral disc	Chondrocytes Retina cells Chondrocytes	High hydroxylysine, high carbohydrate (thinner fibrils than type I)
Type III (composed of only one type of α-chain)	Loose connective tissue; reticular fibers, papillary layer of dermis, (found early in development) Blood vessels	Fibroblasts and reticular cells Smooth muscle cells, endothelial cells	High hydroxyproline, low hydroxylysine, low carbohydrate
Type IV (composed of two types of α-chain)	Basal lamina Lens capsule of eye	Epithelial and endothelial cells Lens epithelium	Very high hydroxylysine, high carbohydrate (retains procollagen extension peptides)
Type V	Fetal membranes (placenta) Basement membranes Bone, Smooth muscle	Fibroblasts Epithelial cells Osteoblasts Smooth muscle cells	

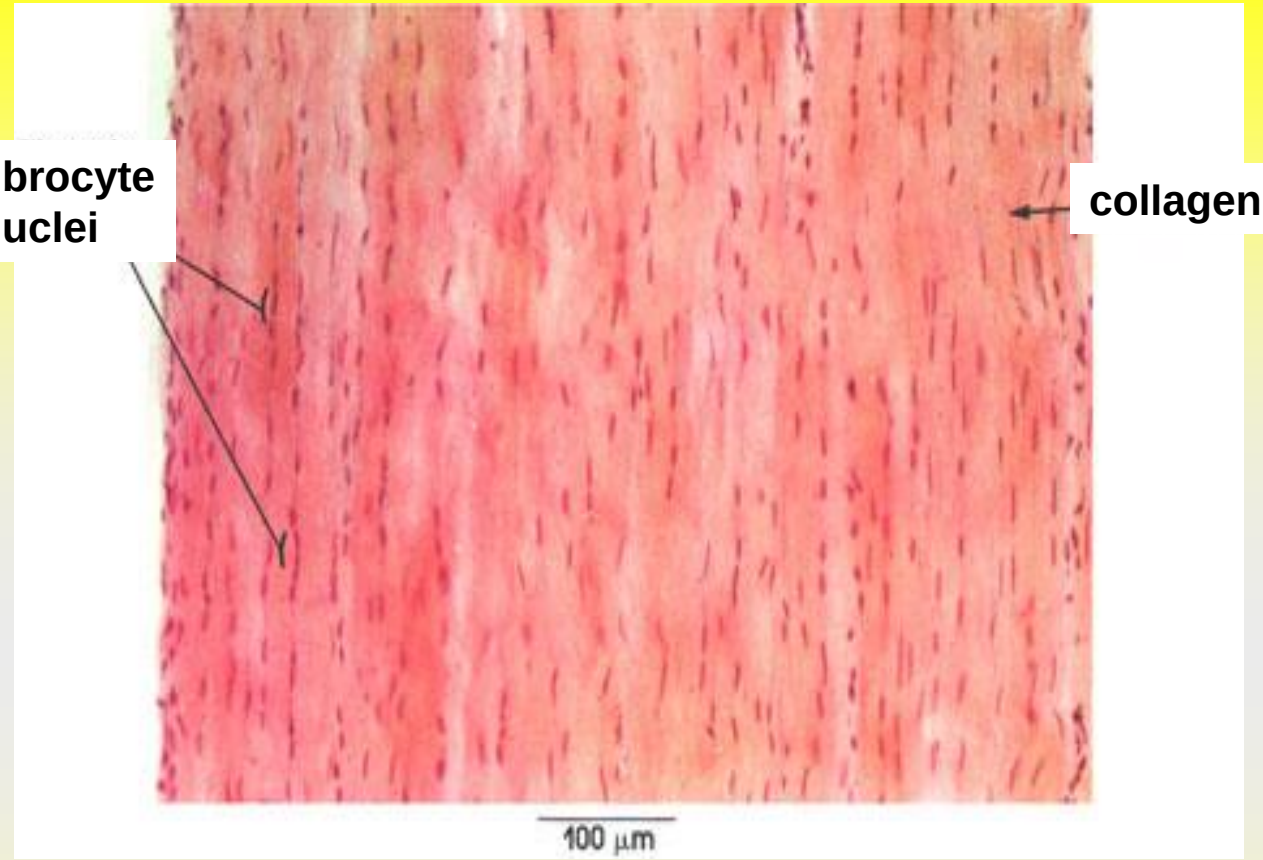
MOLECULAR FORMS OF COLLAGEN

Type	*I*	*II*	*III*	*IV*	*V*	*VI*	*VII*	*VIII*	*IX*	*X*	*XI*
Morpho- logy	large banded collagen fiber	small banded collagen fiber	small banded collagen fibers	sheet-like layers	thin fibers	thin fibers	short striated fibrils	chains and lattices	fibril	short chain	fibril
Distribu-tion	skin dermis, tendon, bone, ligaments, fascia, fibrous cartilage, cornea, loose fibrous tissue	hyaline and elastic cartilage, vertebral disks, vitreous of eye	blood vessels parenchymal organs, bone marrow, lymphoid tissue, smooth muscle, nerves, lung, fetal skin	basement membranes, external laminae, lens capsule	basement membrane of placenta, smooth and skeletal muscle	ubiquitous	anchoring fibrils in basement membrane of skin and amnion	endothe-lium	cartilage	mineral i-zing cartilage	cartilage

Collagen types I-III, V and XI make up fibrils whereas type IV forms a fine meshwork within basement membrane.

Types of Collagen

Type	*Morphologic Features*	*Distribution*
I	Broad, banded fibrils	Widespread; tendon, bone, dermis, dentin, fascia
II	Small-diameter, banded fibrils	Hyaline cartilage, vitreous body, nucleus pulposus, notochord
III	Small-diameter, banded fibrils	Corresponds to reticular fibers; prominent in organs with a major smooth muscle component; uterus, blood vessels
IV	Feltwork of nonbanded fibrils	Basal laminae of epithelial cells, glomerular epithelium
V	Thick nonbanded fibrils	Widespread; pericellular laminae of smooth and striated muscle cells, tendon sheaths
VI	Thin, banded fibrils	Makes up about 25% of collagen in cornea; small amounts where types I and III are found
VII	Small-diameter, banded fibrils	Form anchoring fibrils that link the basal lamina of many epithelia to the underlying connective tissue
VIII	Unknown	A major component of Descemet`s membrane; associated with and produced by endothelial cells
IX	Unknown	Found mainly in cartilage; links type II forms in three-dimensional arrangement
X	Unknown	Cartilage matrix surrounding hypertrophic chondrocytes during endochondral bone formation



COLLA-GENOUS CONNECTIVE TISSUE

Tendo calcaneus (tendon of Achilles) longitudinal section, H & E, x162.

Fibroblasts: Also known in mature tendons as tendon cells, or fibrocytes, they are the only cell type present. They are stellate in shape with cytoplasmic processes extending between and around the collagen bundles.

Collagen: In thick bundles or fascicles, separated by tendon cells and loose connective tissue. Collagenous CT fibers are protein and synthesized by fibroblasts.

CLINICAL CORRELATIONS:

- At the end of surgery, the cut surfaces of skin are carefully sutured; usually a week late the sutures are removed. The tensile strength of the dermis at that point is only about 10% that of normal skin. Within the next 4 weeks, the tensile strength increases to about 80% of normal, but in many cases it never reaches 100%. The initial weakness is attributed to the formation of type three collagen during early wound healing, whereas the later improvement in tensile strength is due to scar maturation, when type III collagen is replaced by type I collagen.

- Some individuals, especially afroamericans, are predisposed to an excessive accumulation of collagen during healing. In these patients the scar forms an elevated growth known as a keloid.

CLINICAL CORRELATIONS:

- Hydroxylation of proline residues requires the presence of vit C. In individuals who suffer from a deficiency of this vitamin, the alpha-chains of the tropocollagen molecules are unable to form stable helices, and the tropocollagen molecules are incapable of aggregating into fibrils. This condition, known as scurvy, first affects connective tissue with high turnover of collagen, such as periodontal ligaments and gingival.

- Because these two structures are responsible for maintaining teeth in their sockets, the symptom of scurvy include bleeding gums and loose teeth. If the vit A deficiency is prolonged, other sites are also affected. These symptoms may be alleviated by eating foods rich in vitamin C.

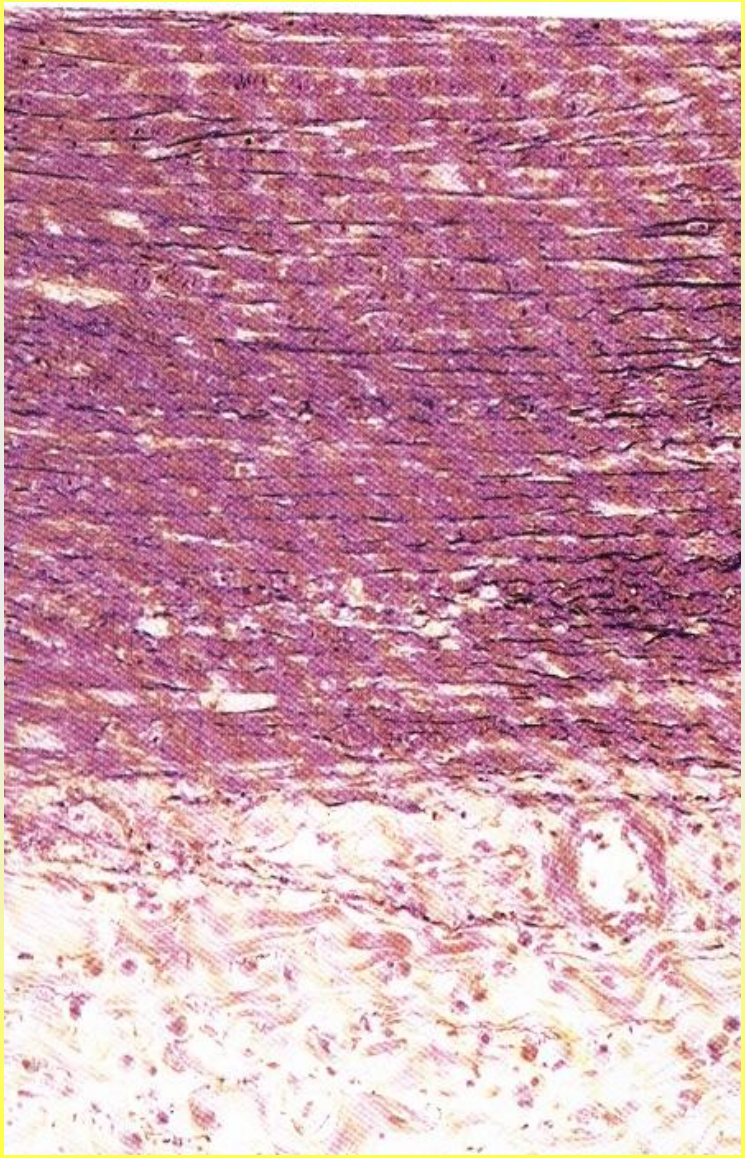
CLINICAL CORRELATIONS:

- Deficiency of the enzyme lysyl hydrolase (this enzyme forms transverse bonds in microfibril formation), a genetic order known as Ehlers-Danlos syndrome, results in abnormal cross-links among tropocollagen molecules (tropocollagen molecules spontaneously self-assemble in specific head-to tail direction into a regularly staggered array – end-to-end and side-to-side).

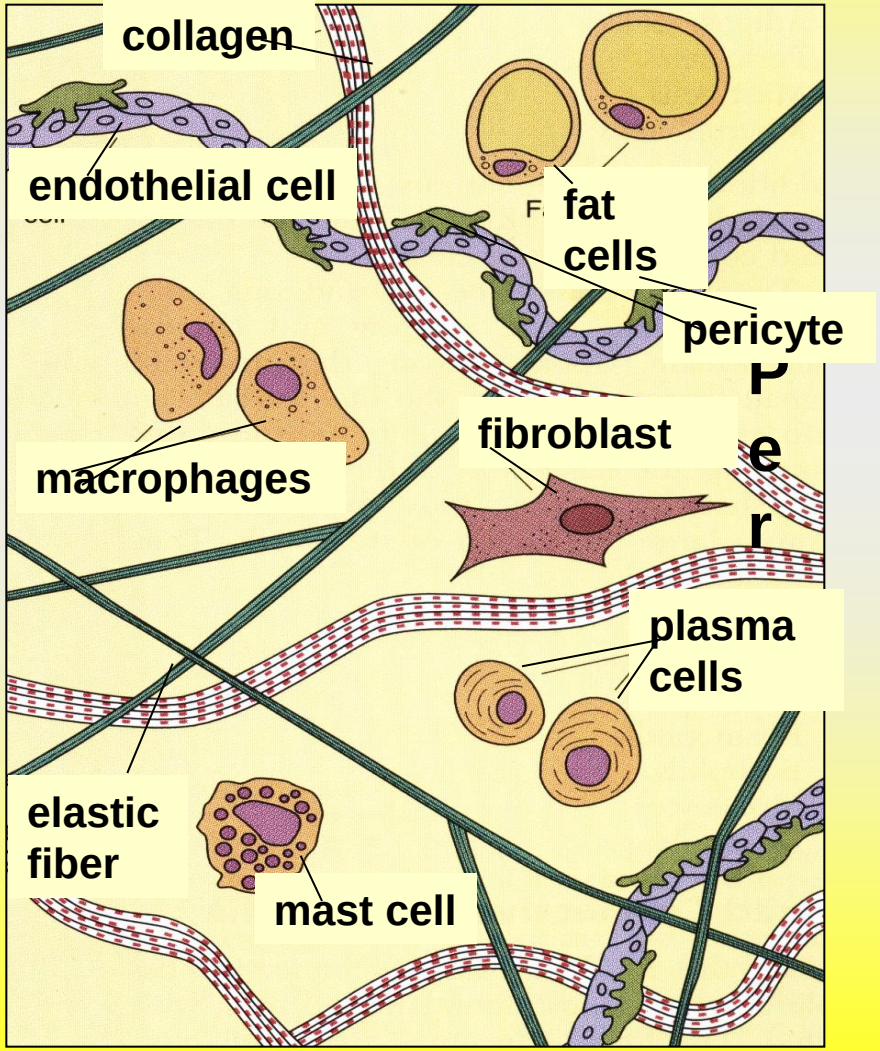
- Individuals afflicted with this anomalous condition possess abnormal collagen fibers that result in hypermobile joints and hyperextensive skin. In many instances, the skin of affected patients is readily traumatized and the patients is subject to dislocation of the affected joints.

Elastic Artery, Orcein, x 132

Elastic fibers, unlike collagen, are highly accommodating and may be stretched one and a half times their resting length without breaking. When the force is released, elastic fibers return to their resting length.



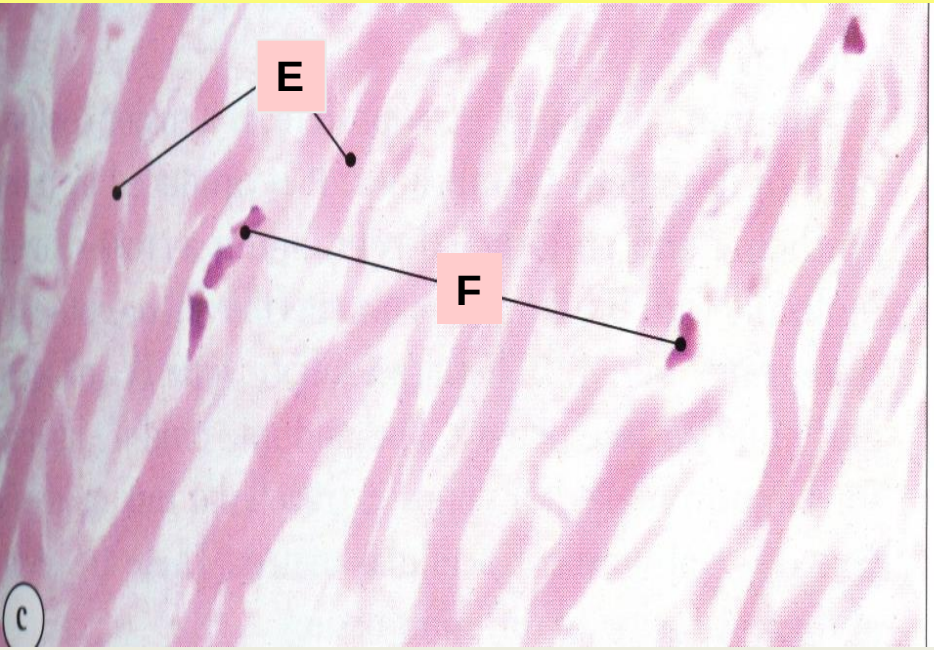
Elastic Fibers

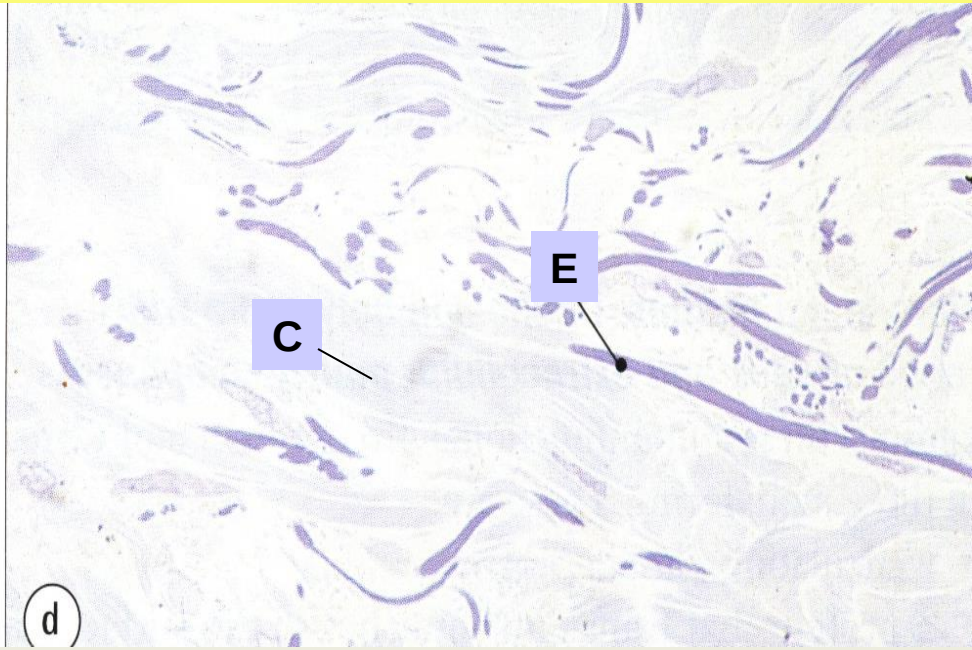


The elasticity of CT is due, in great part, to the presence of elastic fibers in the extracellular matrix. These are usually slender, long, branching in loose CT.

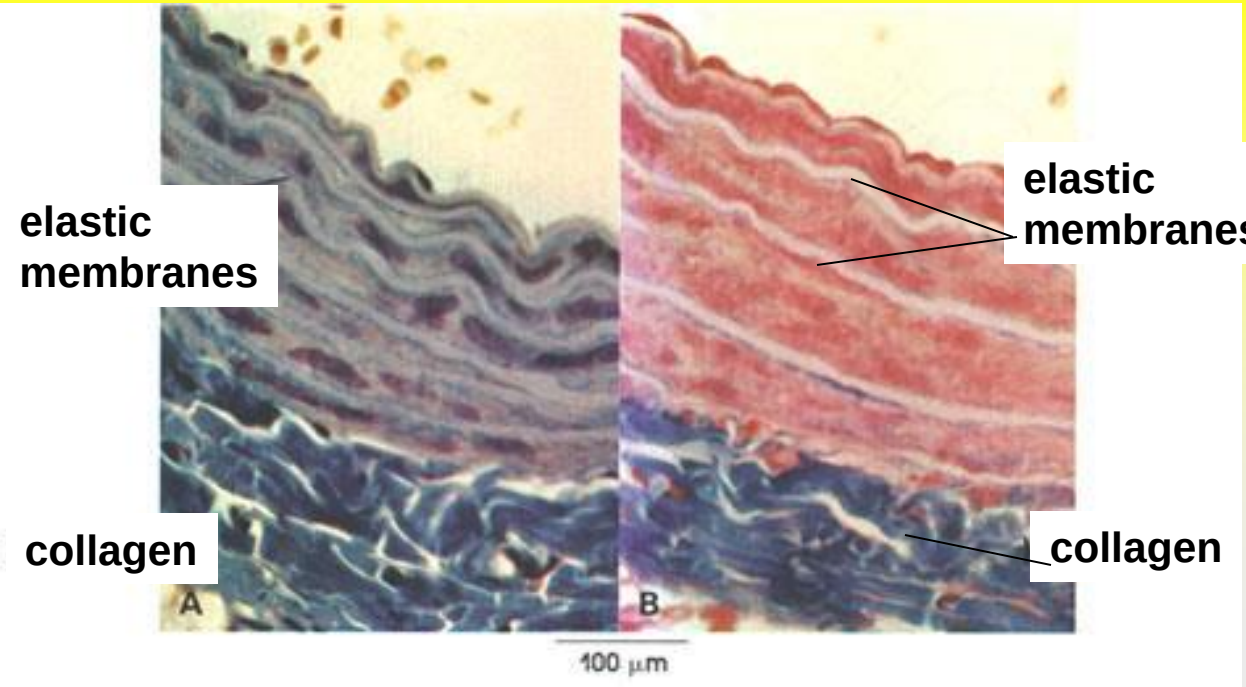
They are manufactured by fibroblasts of connective tissue and by smooth muscle cell of blood vessels. They are composed of elastin, a protein rich in glycine and lysine.

ELASTIC FIBERS





In H & E stained tissues, elastic fibers (E) stand out as glassy bright pink-stained structures, taking up acidic dyes such as eosin with much greater avidity than CF (F, fibroblsts).
EF can be stained by special techniques. In this example, EF (E) in the dermis of the skin are stained blue by toluidine blue and contrast with pale-staining collagen.



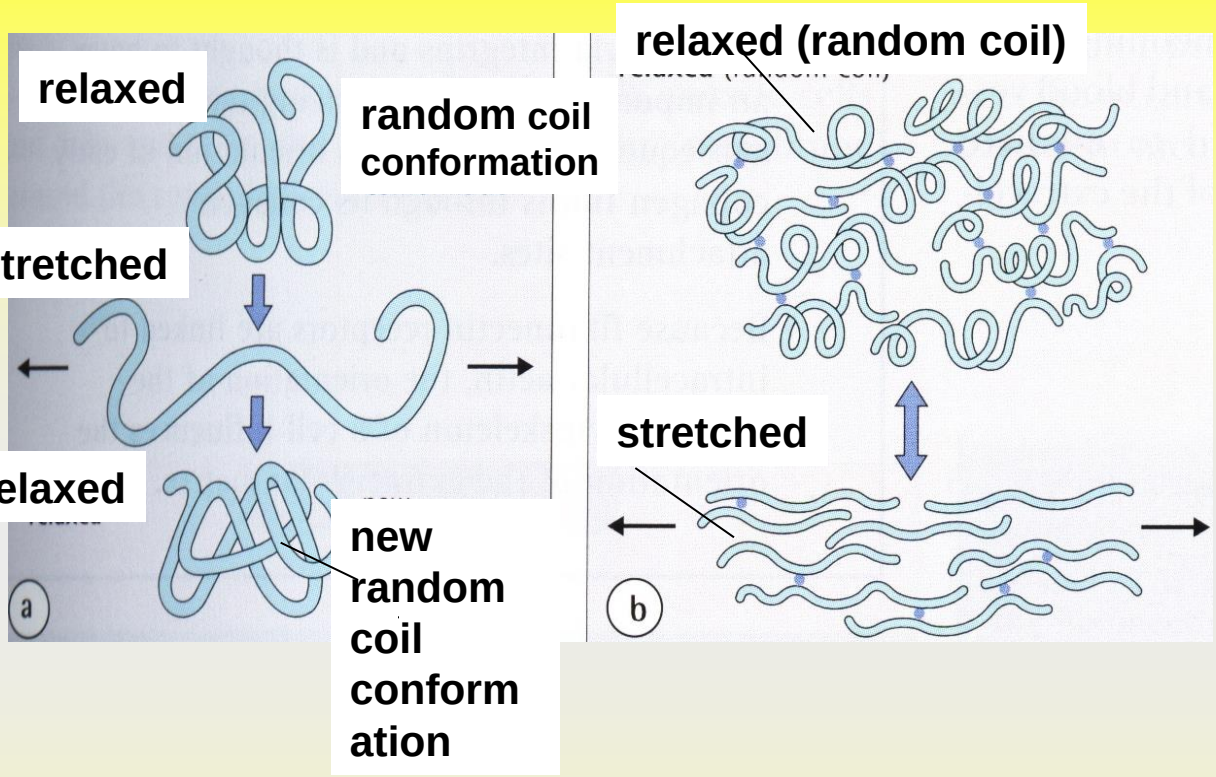
ELASTIC MEMBRANES COLLAGENOUS FIBERS

Aorta, Rat, Mallory's stain (A), Mallory-azan stain (B), 162 x.

Elastic membranes are a striking feature of the aorta. Located within the tunica media of the vessel wall, they serve as "shock absorbers." Elastic arteries are subject to the greatest and most rapid changes in blood pressure. The elastic membranes or laminae are separated from each other by smooth muscle fibers, fibroblasts, and collagenous and reticular CT fibers. Note that the elastic laminae are unstained by the methods used here.

Collagen: Primarily located external to the outermost elastic lamina, it stains a bright blue with Mallory and Mallory-azan stains. Note the collagenous CT immediately adjacent to the elastic laminae.

ELASTIN

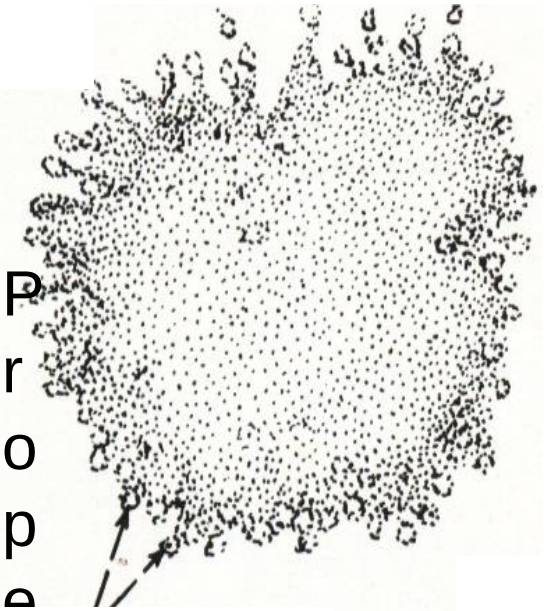


Elastin is a protein which assembles into stretchable and resilient fibers and sheets & is the main component of EF.

a)Elastin has a random coil structure in the relaxed state that can stretch, but reforms as a different random coil on relaxation.
b)Elastin molecules are covalently linked into arrays which can reversibly stretch & recoil, and may be arranged as fibers or sheets.

EXTRACELLULAR MATRIX OF THE CONNECTIVE TISSUE

Cross-section of elastic fiber



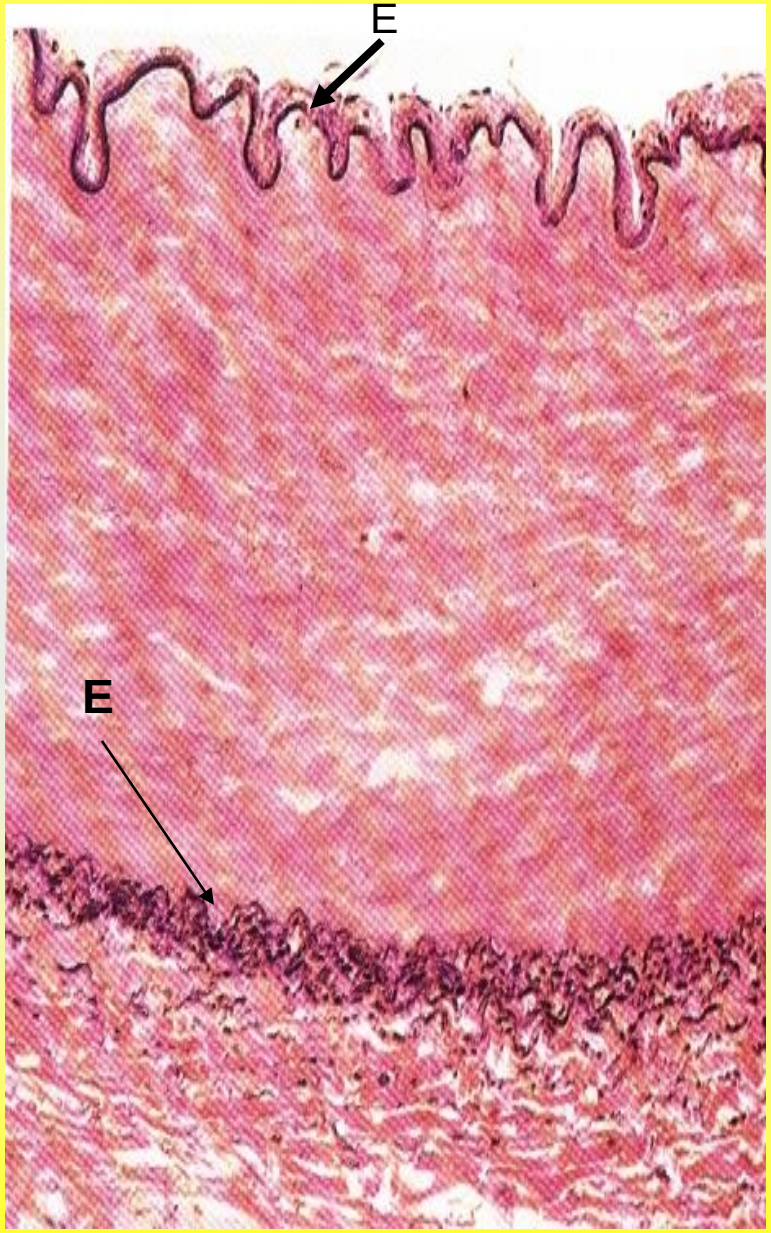
Properties of ground substance (lies between cells and fibers)

- -amorphous gel-like
- -binds water
- -acts as molecular sieve
- -homogenous & transparent
- -mixture of H_2O, minerals,glyco-proteins & mucopolysacchrides
- -altered by hyaluronidase

Elastin chains are held together in such a fashion that four lysine molecules, each belonging to a different elastin chain, form covalent bonds with each other to form desmosine cross-links.

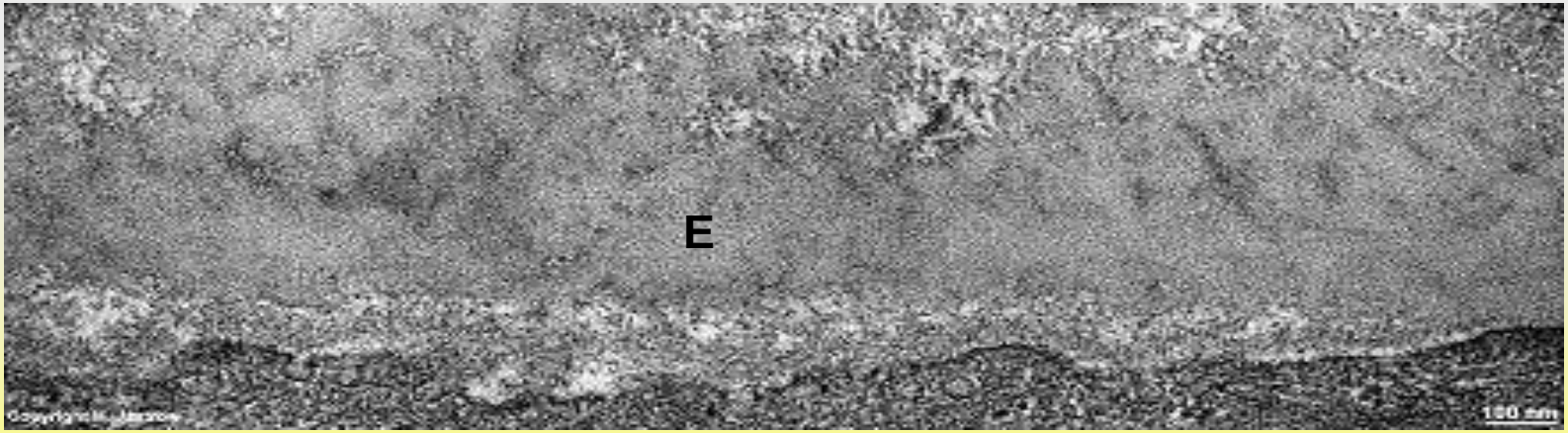
MUSCULAR ARTERY, x 132

These desmosine residues are highly deformable and they impart a high degree of elasticity to elastic fibers (E) to such an extent that theses fibers may be stretched to about 150% of their length before breaking. After being stretched they return to their resting length.



As their name implies, EF confer elasticity to tissues & allow them to recoil after stretching. EF are important constituents of many supported tissues. EF are formed by the interaction of elastin & fibrillin.

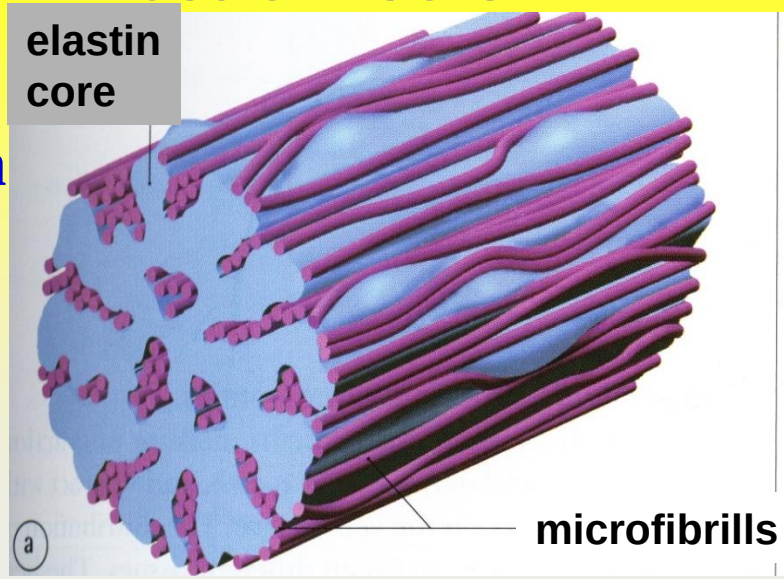
The microfilaments of fibrillin are prominent in early formed elastic tissue, and decrease in number with aging. Fibrillin, a recently characterized fibril-forming glycoprotein, is the main component of extracellular microfibrils.

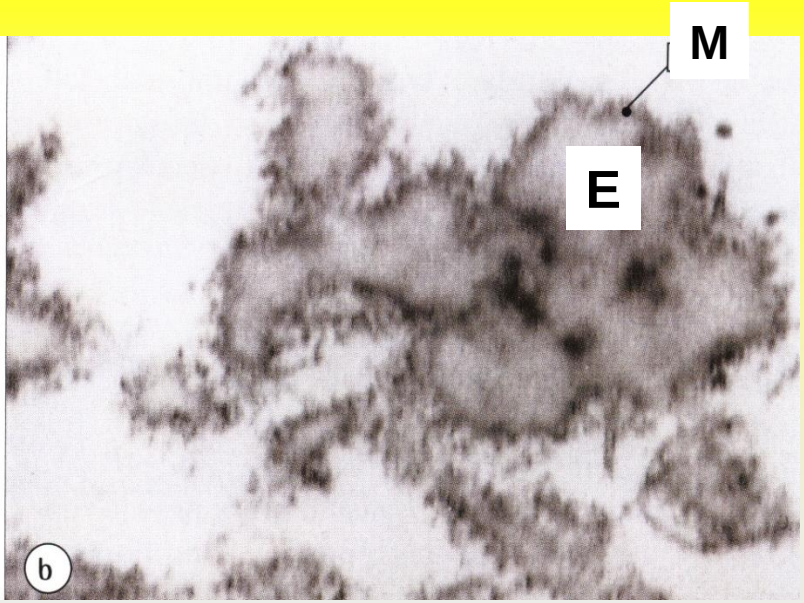


Elastic Fibers of the Internal Elastic membrane of the Arteriole in the Connective Tissue of the ovary. TEM, 100,000x.

Elastic Fibers

Dia-gram

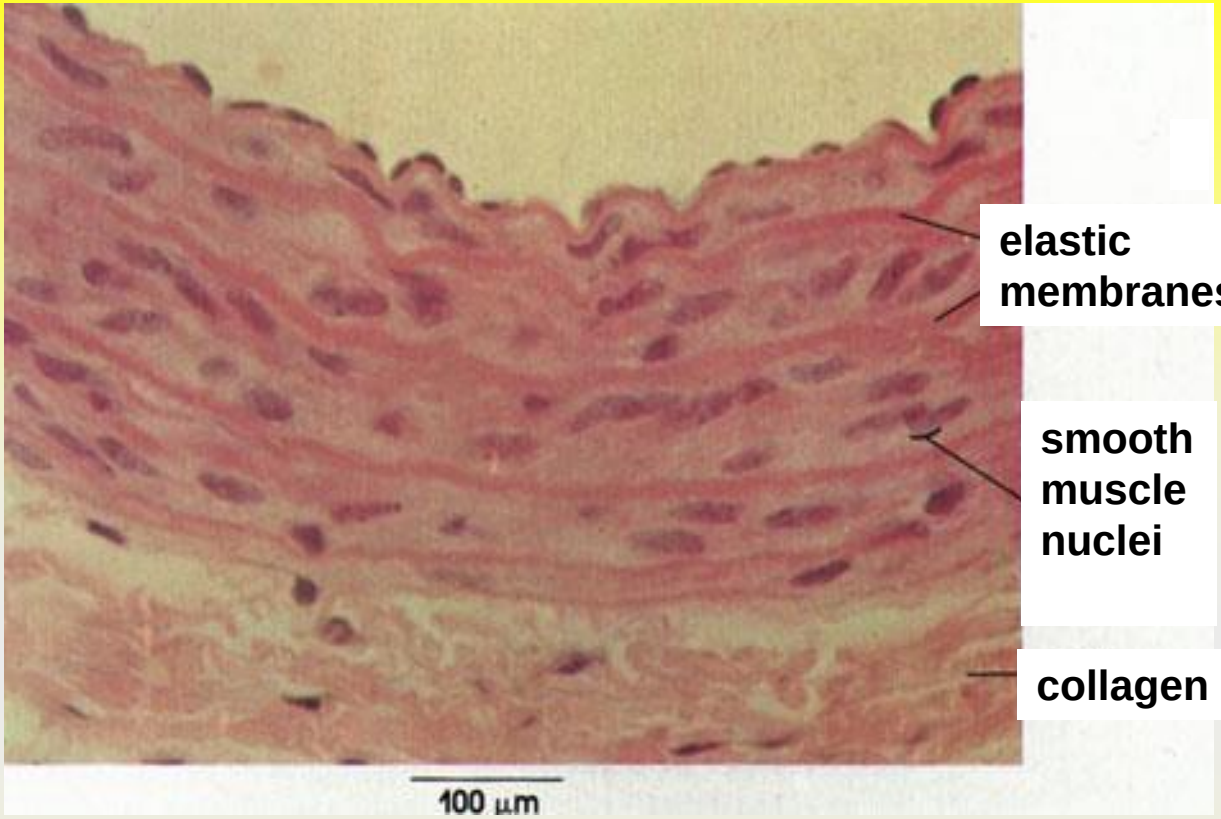




TEM

In EF glycoprotein microfilaments (fibrillin) surround and organizing a core region of crossed-linked elastin.

Ultrastructurally the elastin core appears as an electron-dense area (E) with microfilaments (M) arranged peripherally.The fibrillin microfibrils appear to organize secreted elastin so that it is deposited between the microfibrils to form distinct EF. Microfibrils are 8-12 nm in diameter.They are also found in the extracellular matrix of renal glomerului (mesangium) and the suspensory fibers of the lens. Microfibrils are believed to mediate adhesion between digfferent components of extracellular matrix.



ELASTIC MEMBRANES COLLAGENOUS FIBERS

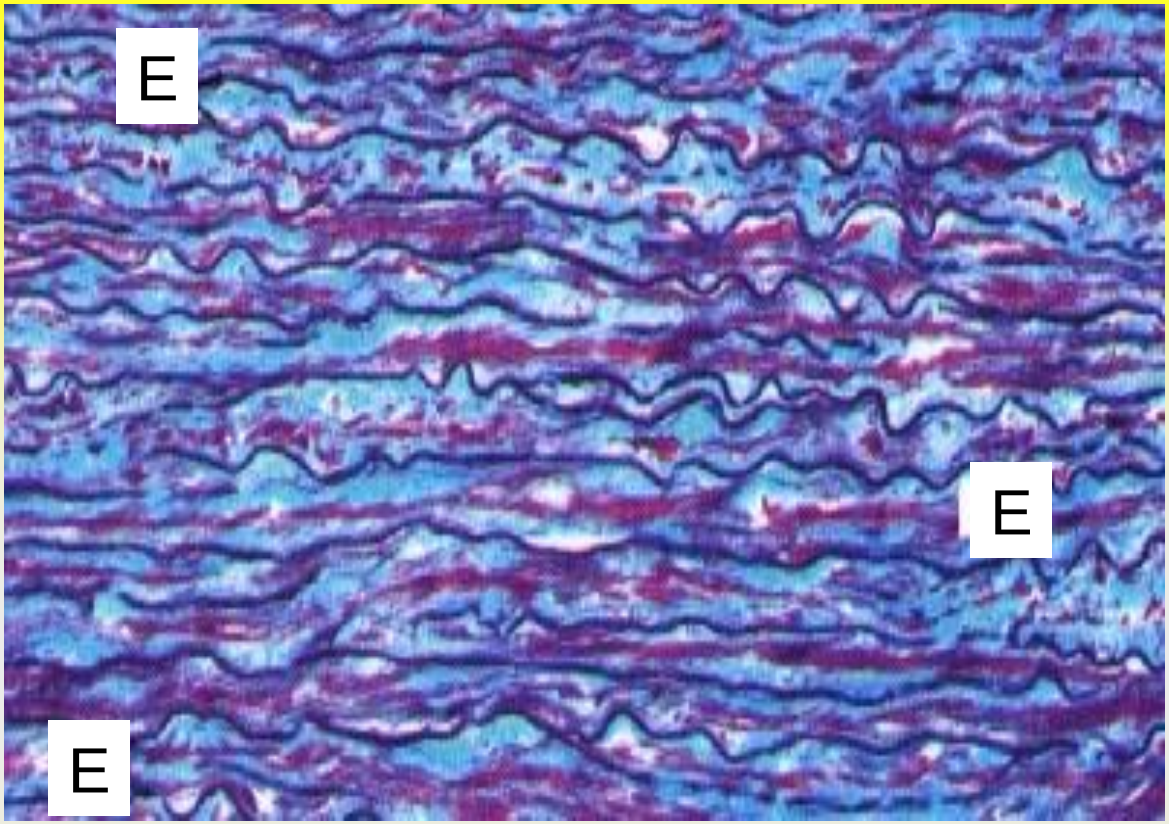
Aorta, Rat, H & E, x162.

The pronounced eosinophilia of the EF reflects their high content of basic amino acids.

Elastic membranes: Abundant in the media of elastic arteries. The EF anastomose to form a fenestrated "membrane," which is circularly arranged in layers. Smooth muscle fibers are located between the elastic fiber networks. Circularly disposed. See their nuclei

Collagen: In the adventitia, collagen forms a loose irregular CT layer surrounding the blood vessel. EF, not distinguishable by this method, are also found in this CT coat.

Aorta, Human, Weigert's elastic tissue stain and phloxine, 162 x.



Aorta, Tunica Media

At the histological section of aorta and the laminae will appear as undulating lines due to postmortem arterial collapse.

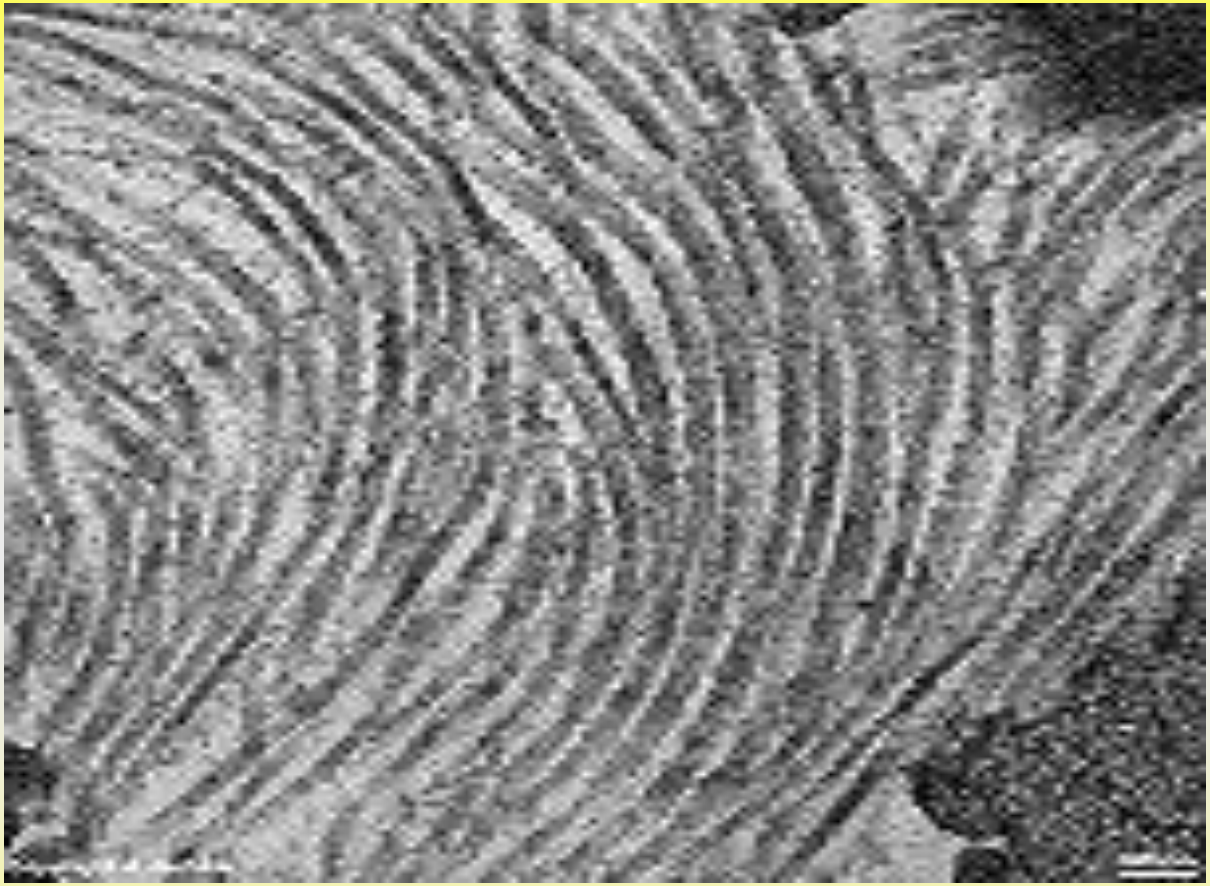
The lamellae of elastin are stained black. In between are layers of collagen and extracellular matrix, stained blue and smooth muscle cells stained red. The smooth muscle cells produce the elastin, collagen and matrix.

CLINICAL CORRELATIONS:

- The integrity of elastic fibers depends on the presence of microfibrils. Patients with Marphan syndrome have a defect in the gene on chromosome 15 that codes for fibrillin; therefore their elastic fibers do not develop normally.

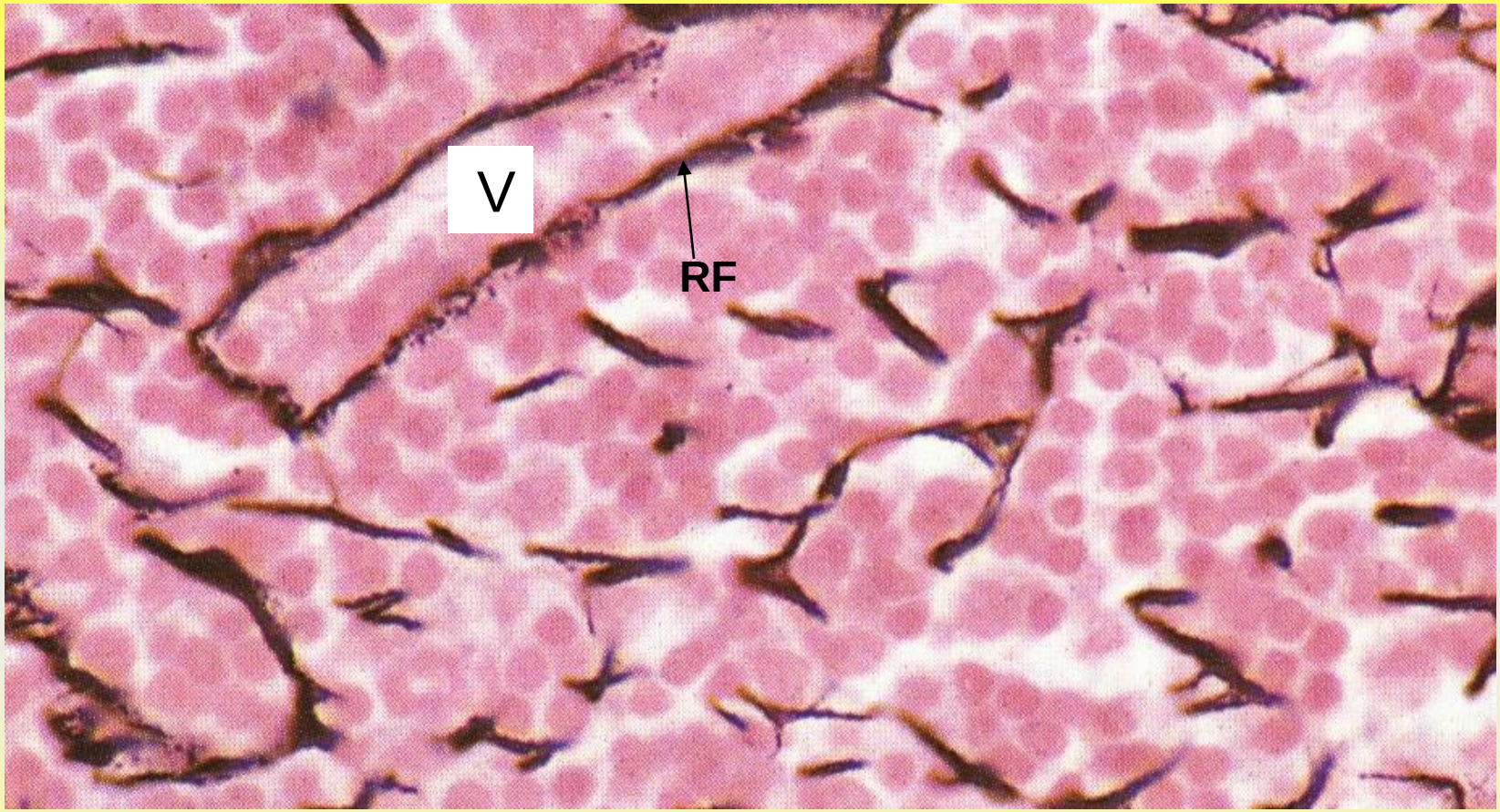
- People who have Marfan's syndrome are unusually tall, have a very wide arm span, are prone to develop subluxation of lens and are also prone to develop fatal rupture of aorta. The absence of fibrillin which interacts with elastin in tissues provokes lens dislocates, as its suspensory fibers normally contain fibrillin. A lack of elastin recoil in aorta would weaken the wall & predispose to rupture. The growth of long bones is somewhat constrained by the presence of fibrillin, and hence bones grow longer in its absence.

Reticular Fibers, TEM, 20,000x.



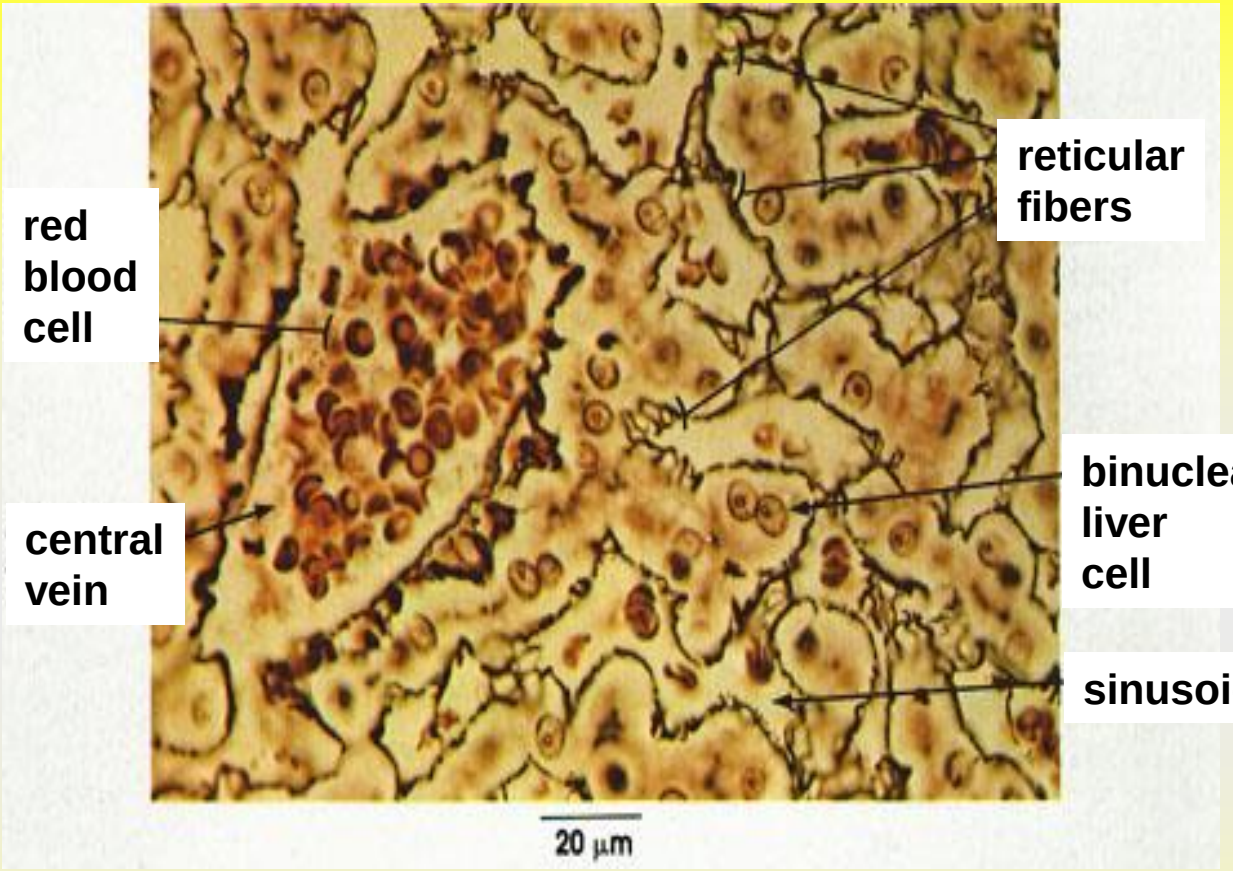
Reticular fibers do not gather into bundles as do collagenous fibers but tend to form delicate networks.

Reticular Fibers (RF)



RF cannot be seen in H & E sections, but can be stained by silver impregnation methods or by PAS reagent. In this microphotograph, RF is a lymph node are seen as fine black lines, with lymphoid cells stained red in the background. V, vessel.

RETICULAR FIBERS
Liver Rhesus monkey, Wilder's* method, 612 x.



Reticular fibers branch and anastomose in a delicate fibrous network delineating the sinusoids. They are of small diameter and are resistant to dyes, making them difficult to demonstrate except by special techniques such as the method used in this preparation.

Key Features of General Connective Tissue

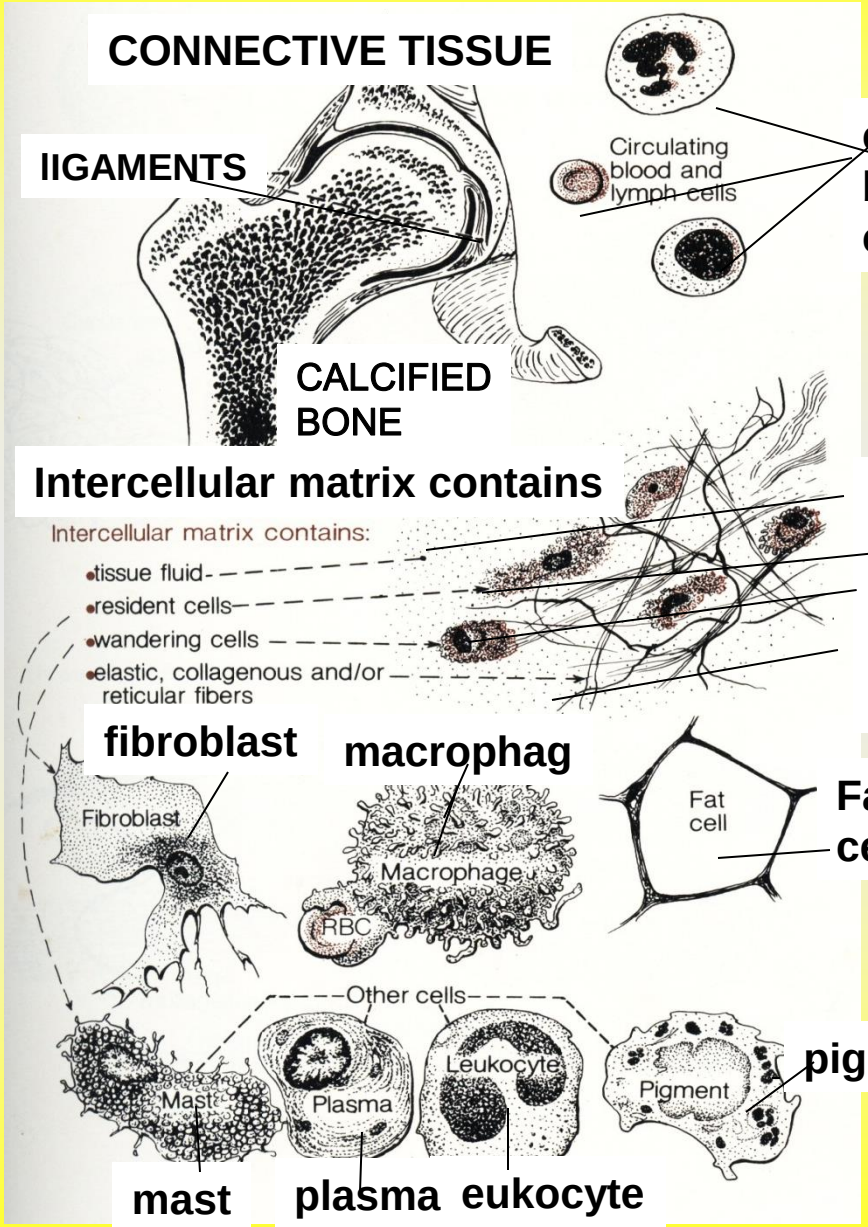
Fiber Type	*Light Microscopic Appearance*	*Electron Microscopic Appearance*	*Primary Locations*
Collagen fiber (type I collagen)	Coarse fibers 0.5-10.0 μm in diameter; indefinite length; stain with protein dyes	Unit fibrils 50-150 nm in diameter; repeating transverse bands every 64 nm; organized into large fibers	Tendon, ligament, dermis, fascia, capsules, sclera, bone, dentin
Reticular fiber (type III collagen)	Delicate network of fine fibers; must be stained specifically to demonstrate, usually by reduction of silver	Banded unit fibrils 50 nm or less in diameter, organized into tiny fibers	Stroma of lymphatic organs, bone marrow, glands
Elastic fiber	Smooth, homogeneous fibers; varying diameter; must be stained specifically to demonstrate (orcein, Verhoeff`s stain)	Amorphous core of elastin; microfibrils 11 nm in diameter at periphery of fiber	Dermis, lung, arteries, organs that expand

Comparative Characteristics of Connective Tissue Fibers

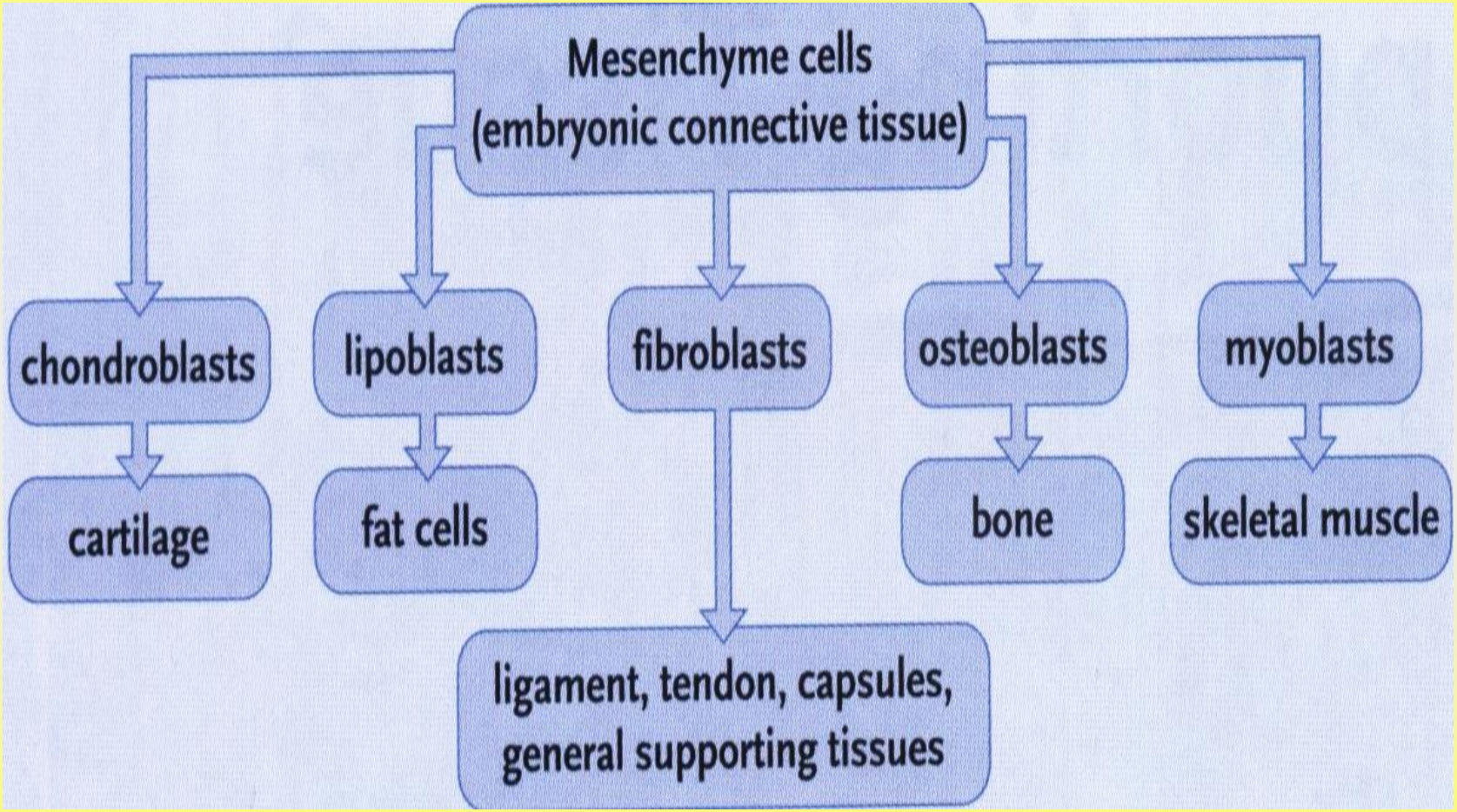
Feature	*Collagen*	*Reticular*	*Elastic*
Molecular organization	Triple-stranded helix; each strand ~1000 AA; molecule ~ 300 nm long, 1.5-nm diameter (glycine, hydroxyproline, hydroxylysine)	Type III collagen	Elastin 830 amino acid residues long; contains desmocine, isodesmocine (formed from four molecules of lysine)
Fibrillar organization	Fibers 2-10 μm in diameter (unbranched); fibrils ~50 nm in diameter; smaller microfibrils	Fibers 0.2-2 μm in diameter; fibrils 25-45 nm	Fibers 1-4 μm in diameter; fibers branch No fibrils Mocrofibrils ~12 nm in diameter
Axial periodicity	Fibrils 670 A; axial periodicity	670 A	None
Boiling water	Converts collagen to gelatin		Resistant
Weak acids and weak alkalis	Swells	Similar to collagen	Resistant to weak acids and alkalis
String acids and strong alkalis	Dissolved		
Staining	With acidophilic stains	Silver (argyrophilic) PAS+	Resorcin fuchsin, resotcin orcein
Enzyme effects	Pepsin and collagenase dissolve		Sensitive to elastase
Cells producing fibers	Fibroblast Smooth muscle cells in blood vessels Osteoblasts Chondroblasts Odontoblasts Type IV collagen produced by epithelial cells and endothelial cells	Reticular cells Fibroblasts Schwann cells (for endoneurium)	Fibroblast Smooth muscle cells in blood vessels

Connective Tissue Cells

The fibroblasts are the most abundant cell type in the CT. They are responsible for the synthesis of almost all of the extra-cellular matrix.

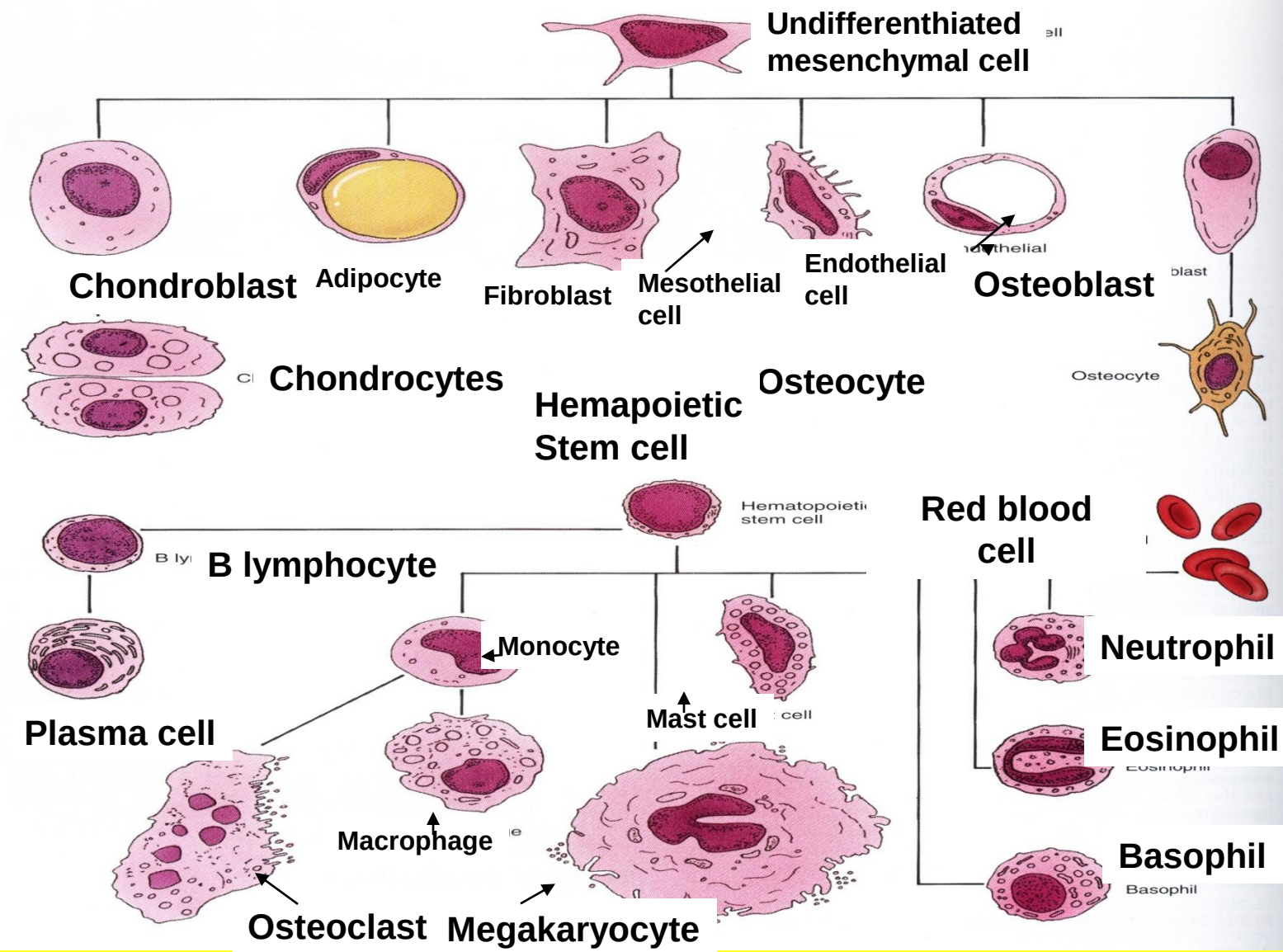


Cell Lines Derived from Mesenchyme Cells



Mesenchyme cells can potentially develop into a variety of cells which make up different tissue types.

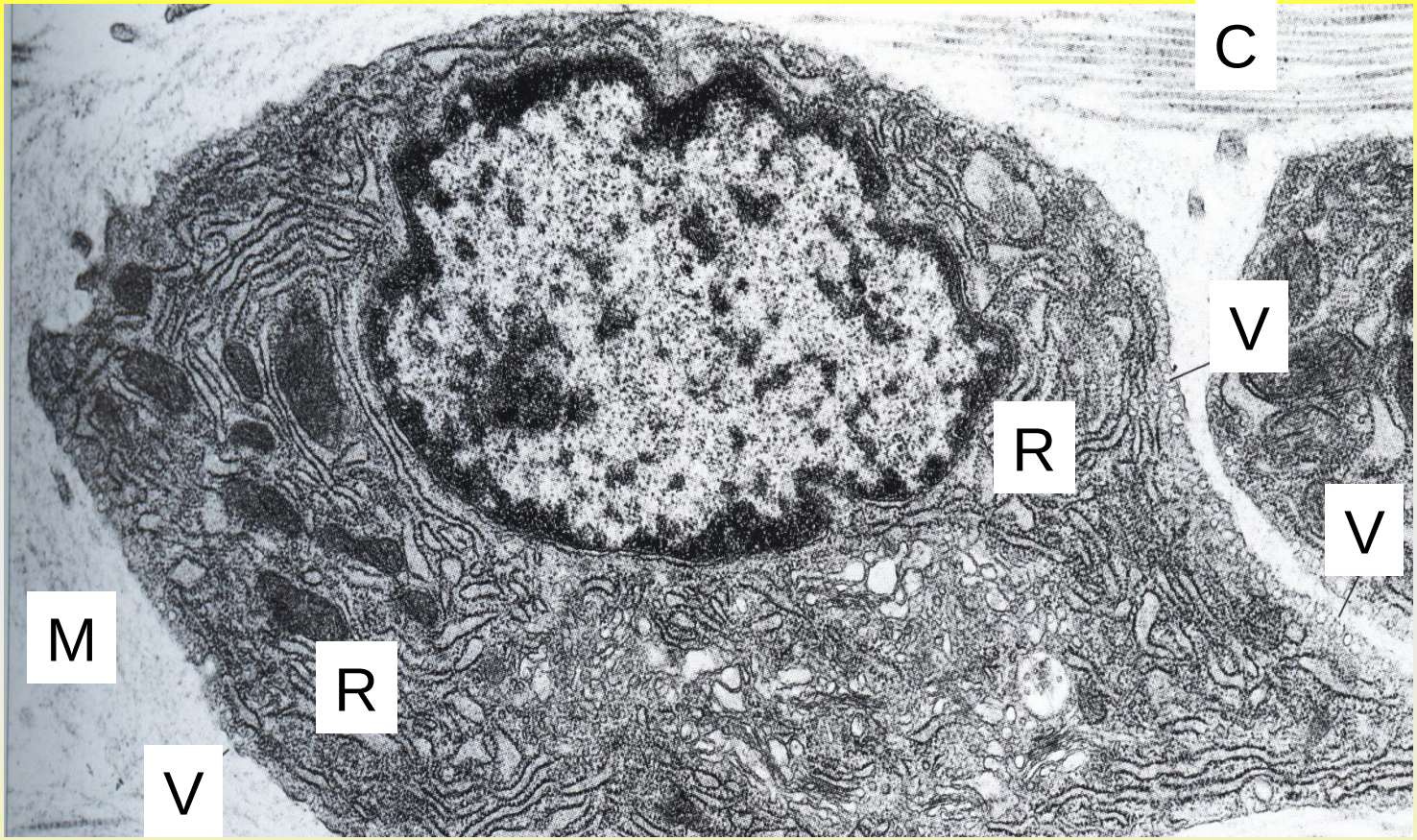
Schematic Diagram of the Origins of Cells of Connective Tissue



CELLS OF CONNECTIVE TISSUE

Cells	*General Functions*
Fibroblast	**Produces Fibers (collagen, reticular, elastin) and amorphous jellies (glycosaminoglycans, proteoglycans)**
Macrophage	**Phagocytic (e.g., bacteria) Antigen presentation Secretory (e.g., interleukin-l, interferon-γ)**
Pericyte	**Differentiate into fibroblasts, reticular cells, macrophages, smooth muscle cell in blood vessel, adipocytes**
Mast cell	**Secrete heparin, histamine, slow-reacting substance of anaphylaxis, eosinophilic chemotactic factor of anaphylaxis**
Foreign body giant cell	**Phagocytic (larger particulate material)**
Reticular cell	**Produce reticular fibers (type III collagen) for lymph nodes, spleen, bone marrow, etc.**
Adipocytes	**Fat storage, mobilization**
Chondroblast (chondrocyte)	**Secrete collagen or elastic fibers, as well as cartilage amorphous intercellular substances (glycosaminoglycan, proteoglycan), and other proteins**
Osteoblasts	**Secrete collagen, bone matrix (proteoglycans)**

Fibroblasts and Collagen

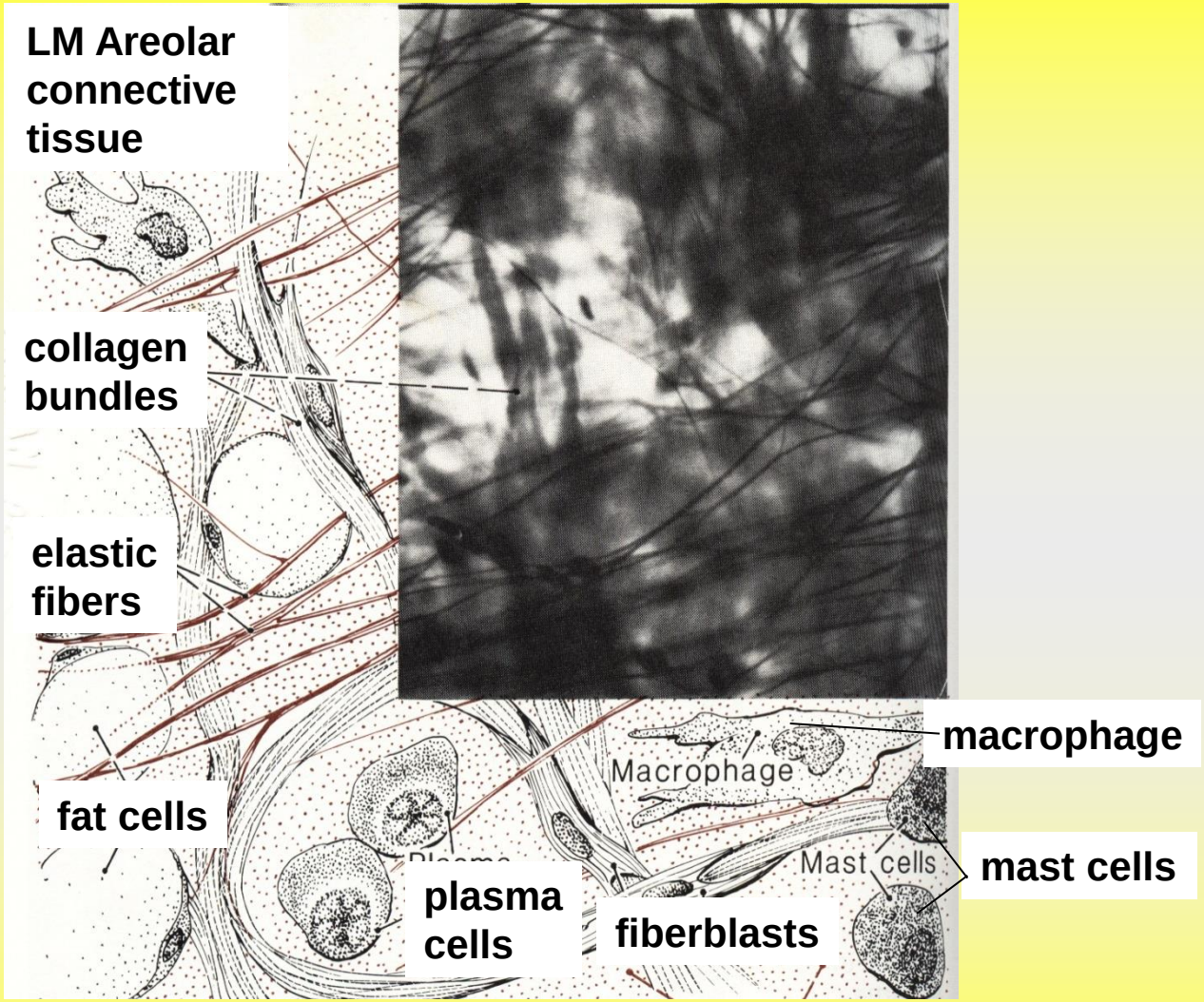


A fibroblast actively synthesizing collagen molecules. The intracellular precursor form of collagen, procollagen, is secreted into extracellular space via vesicles (V). The matrix shows regions of fibrous aggregations – probably tropocollagen molecules derived from procollagen, which self-assemble into collagen fibrils ©.

Fibroblasts and Collagen, TEM, x20,000

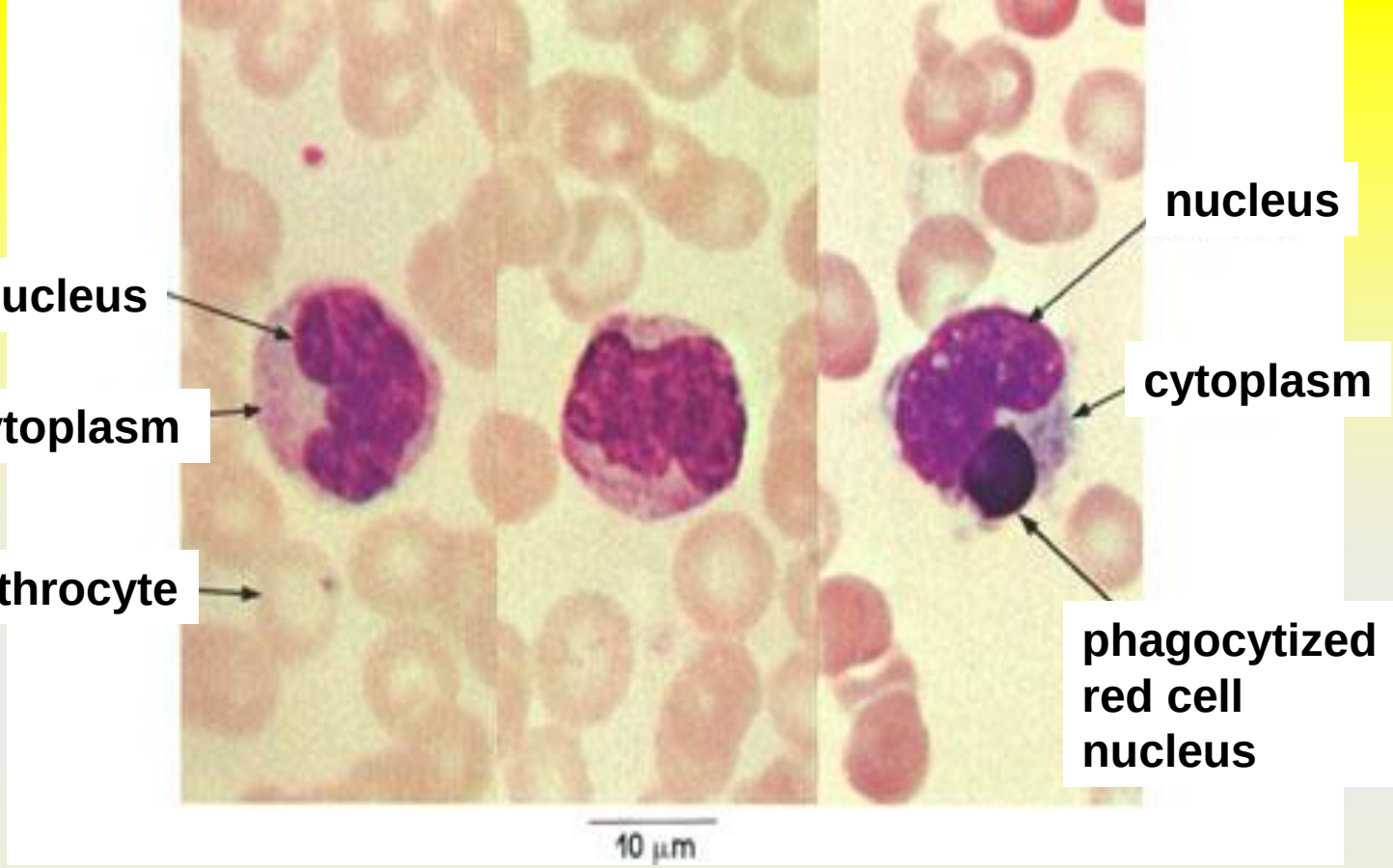
Fibroblasts may occur either in active or quiescent state (fibrocytes, F).

Loose Connective Tissue Cells



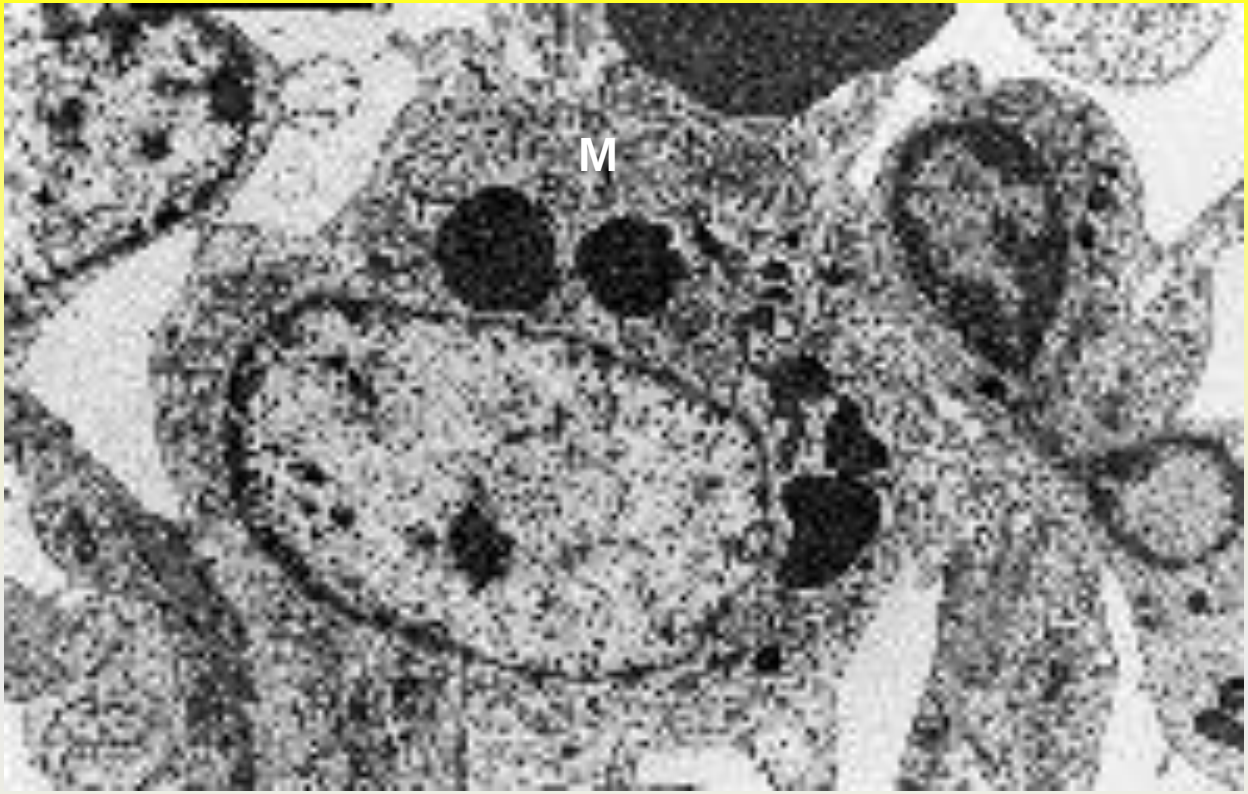
The macrophages phagocytose foreign substances and damaged and senescent cells as well as cellular debris; they also assist in the initiation of the immune response.

Monocytes, human, air-dried blood smear, Wright's stain, 4416 x.



Monocytes are the largest cells found in normal blood. The nucleus is centrally or peripherally located, indented, and ovoid or horse-shoe- shaped; the nuclear chromatin is not as dense as that of lymphocytes. Cytoplasm is abundant and contains azurophilic granules. Monocytes are voracious phagocytes. The monocyte seen on the extreme right shows pseudopodia extending from the cell body and contains a phagocytized red cell nucleus. Note the comparative size of erythrocytes and monocytes.

Macrophage, TEM, x20,000



Macrophages (M) belong to the mononuclear phagocyting system and are subdivided into two groups of cells, phagocytes and antigen-presenting cells. Because they are active phagocytes, they function in removing cellular debris and in protecting the body against foreign material. They are irregularly shaped, about 10-30 mcm in diameter. Their cell surface is uneven, varing from short blunt projections to finger-like filopodia. More active cells have pleats and folds as a consequence of cell movement and phagocytosis.

This illustration shows a cross section of a terminal bronchiole with phagocytized material (black) in macrophages within the lumen of the bronchiole (airway). The pleating of the epithelial lining denotes a constricted bronchiole. Note the low columnar epithelial lining of the wall of the bronchiole and the smooth muscle bundle adjacent to the lining epithelium

MACRO-PHAGES, Lung terminal bronchiole, Cat, H & E, 162 x.

Functional Aspects of Macrophages

Surface receptors for:	Receptors that bind C3b component of complement; Fc receptors, IgG; IL-2, IL-1, IL-6; Tumor necrosis factor (TFN); (Interferon); ATPase; 5`-Nucleotidase
Lysosome content	Acid hydrolases; Lysozyme; Myeloperoxidase
Macrophage activators	Lipopolysaccharide; Interferon-γ
Interleukin effects produced by macrophages	Activates B lymphocytes; Chemotactic factor for neutrophils; Increases circulating neutrophils; Division of fibroblasts
Products phagocytosed	Dead cells; Cellular debris; Bacteria
Antigen presentation	Presents antigen with MHC II molecules to helper T lymphocytes (T_H cells); IL-1 (a mitogenic protein for T lymphocytes); IL-6, IL-8; TNF-α; Interferon-α, -β; involved in fighting virus; Colony-stimulating factors Macrophage-colony stimulating factor (M-CSF) Granulocyte-colony stimulating factor (G-CSF) Granulocyte-macrophage colony stimulating factor (GM-CSF) Erythropoietin; Platelet-derived growth factor (PDGF)
Selected secretory products	Fibroblast growth factor (FGF); Transforming growth factor-β (TGF-β); Protease inhibitors; Elastase, collagenase; Prostaglandins; Leukotrienes; Neutral proteases; Coagulation factors (II, VII, IX, X, XII); Thrombospondin; Plasminogen activator; Factor inducing monocytopoiesis; Complement components; Pyrogens (mediate fever); Proteoglycan-degrading enzymes; Hydrogen peroxide; Lipases; Superoxide

The Macrophage System

Histologists once believed that the macrophages were derived from a precursor cells in the reticuloendothelial system which included nonphagocytic cells such as reticulocytes. More recently this classification has been replaced with the mononuclear phagocyte system.

All its members arise from a common stem cell in the bone marrow, possess lysosomes, are capable of phagocytosis, and display FcepsilonRI receptors and receptors for complement.

Stem cells
Monoblasts (in bone marrow)
Promonocytes
↓
Monocytes (in circulating blood)
↓
Macrophages (in tissue and organs; both free and fixed, unless noted otherwise)
↓
Lining lymph sinuses
- lymph nodes

↓
Lining blood sinuses or sinusoids
- liver (fixed Kupffer cells)
- spleen (splenocytes or hemophages)
- bone marrow

Lining serous cavities (pericardial, peritoneal, and pleural)
Areolar connective tissue (fixed histiocytes)
Lung (alveolar macrophages or dust cells)
Circulating blood (monocytes)
Central nervous system (fixed mocroglia or mesoglia)
Joint cavities (type A synovial cell)
Bone (osteoclasts)

Macrophage System

Name of Cell	*Function (s)*	*Location*
Macrophage	Phagocytosis, antigen presentation	Loose (areolar) connective tissue
Peritoneal or pleural macrophages	Phagocytosis	Serous cavities
Macrophage	Blood cell destruction, antigen presentation	Bone marrow, Spleen, Thymus, Lymph node
Alveolar macrophage (or dust cell)	Phagocytosis	Alveoli of lung
Langerhans cell	Antigen presentation	Epidermis
Kuppfer cell	Phagocytosis	Liver (perinsinusoidal macrophage)
Microglia	Phagocytosis, antigen presentation	Central nervous system
Osteoclast (multinucleate)	Bone resorption	Bone surfaces (form from fusion of monocyte-derived macrophages)
Fibroblast-derived macrophage	Phagocytosis	Intestine-lamina propria Uterus-endometrium
Foreign body giant cell (multinucleate)	Phagocytosis	Induced in areas of large particulate material (e.g., talc on mesentery) (fusion of monocytes, macrophages)

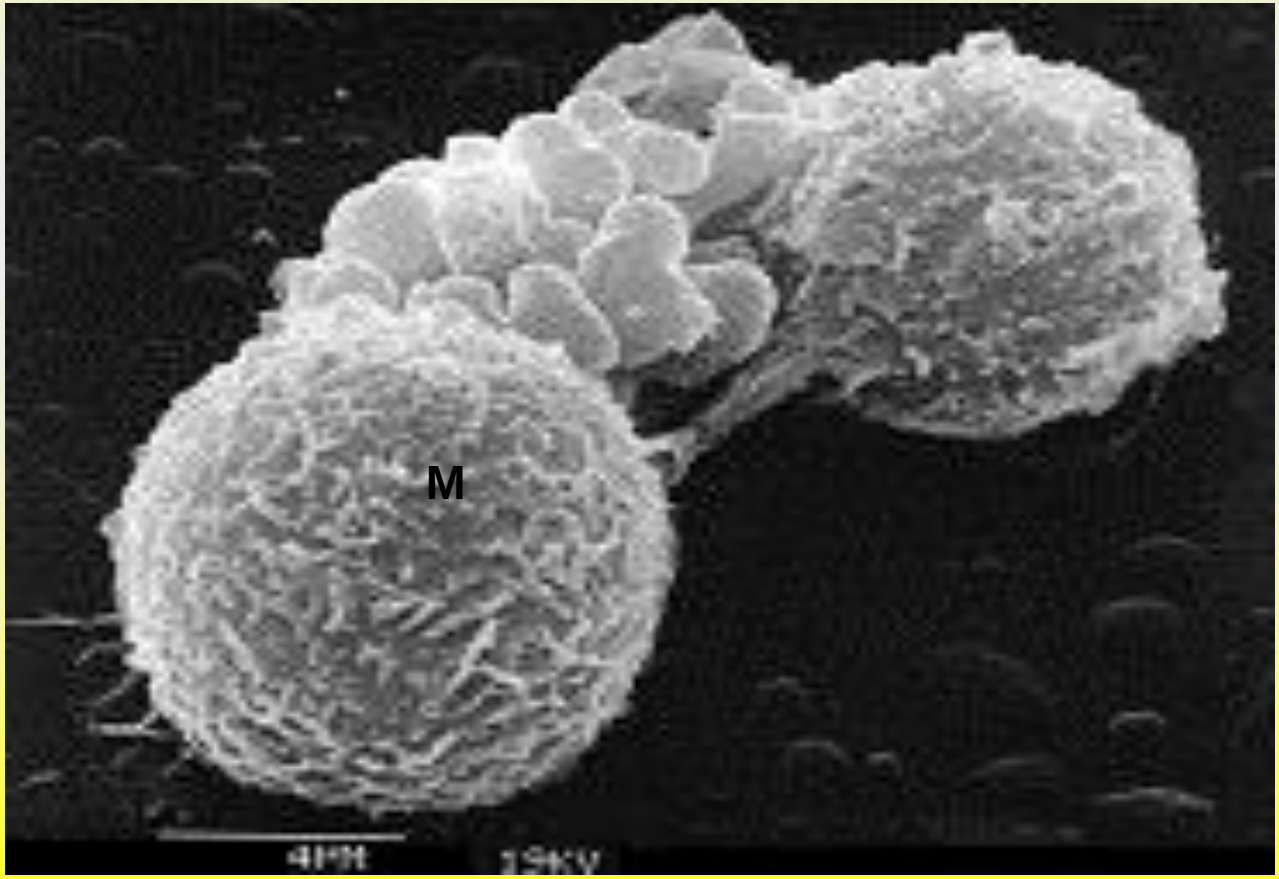
Macrophages (M) residing in the CT were previously called fixed macrophages, and those that developed as a result of an exogenous stimulus and migrated to the particular site were called free macrophages. These names have been replaced by more descriptive terms resident and elicited macrophages, respectively.

During the immune response, factors released by lymphocytes activate macrophages increasing their phagocytic activity.

Alveolar Macrophages, SEM, 6,000x.

Criteria for designating macrophages:

1)avidly phagocytic
2)strong affinity for dyes and particulates
3)store particulates
4)adhere to glass surfaces in culture
5)have antibody receptor sites on cell membranes



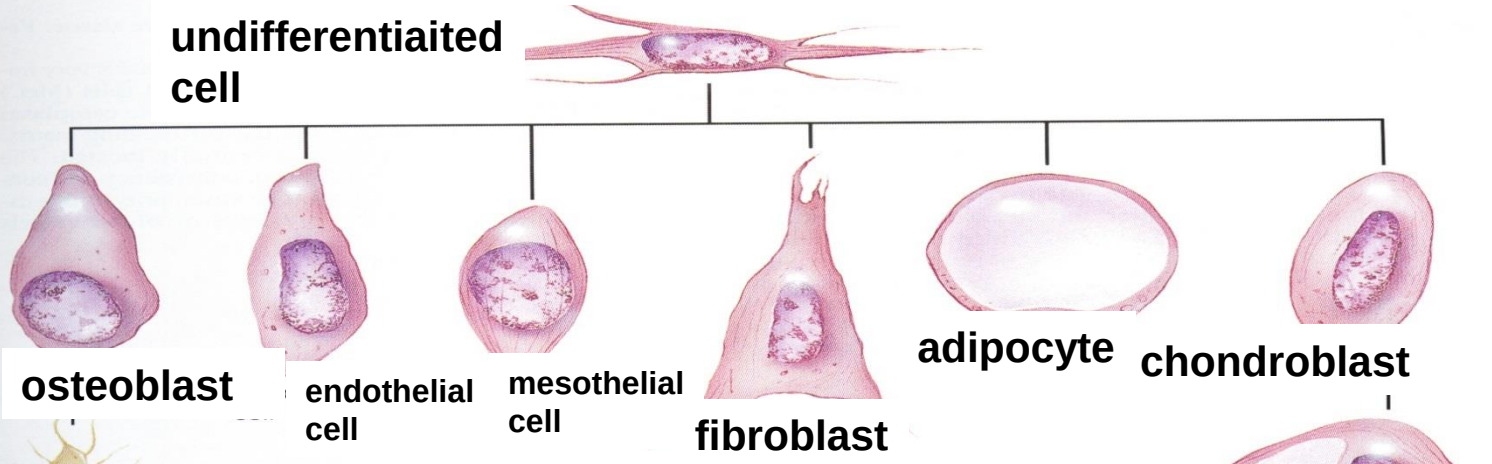
Peritoneal Macrophages (M), SEM, 10,000x.

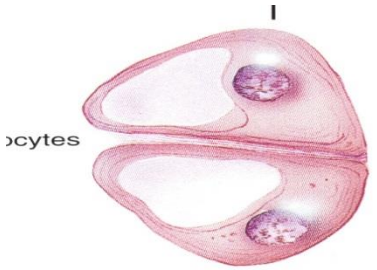
Comparison of Fibroblasts & Macrophages

	FIBROBLASTS	MACROPHAGES
Synonyms	Fibrocyte	Histiocyte, clasmatocyte, polyblast, wandering cell
Origin	Ordinarily from mesenchyme; also from macrophages, especially in wound healing	Mostly from monocytes, some from mesenchyme and fibroblasts
Functions	Synthsis of collagenous and reticular fibers, assist smooth muscle in synthesis of elastic fibers; produce mucopolysaccharides in ground substance	Important in defense against infections; are scavengers that rid the body of senile blood cells, cellular debris, bacteria and foreign bodies; contribute to the immune response of the body by engulfing, processing, and storing antigens; furnish receptor sites for antibodies; salvage and store iron from ingested RBCs for reuse in blood formation
Shape and size	Large, flattened, spindle-shaped cells with long branching processes	More rounded, often kidney-shaped; usually short, blunt processes
Nucleus	Large, pale, usually oval or indented, with finely granular chromatin and one or two prominent nucleoli	Smaller, oval or bean-shaped, coarser chromatin which stains darker; nucleoli absent or inconspicuous
Phagocytosis	Slight ability to engulf foreign particulate matter, e.g., trypan blue and carbon dust; do not ingest cellular fragments or bacteria	Highly active in ingesting foreign particulate material, cellular debris, and some bacteria
Motility	Move in a definite direction by slow streaming of protoplasm into processes	May be a rapid ameboid movement of entire surface involved; blunt pseudopodia or undulating (ruffled) membranes envelop foreign particles
Metaphasia	Into fat cell, some endothelial cells, macrophages, osteoblasts, and chondroblasts	Perhaps only into fibroblasts and monocytes

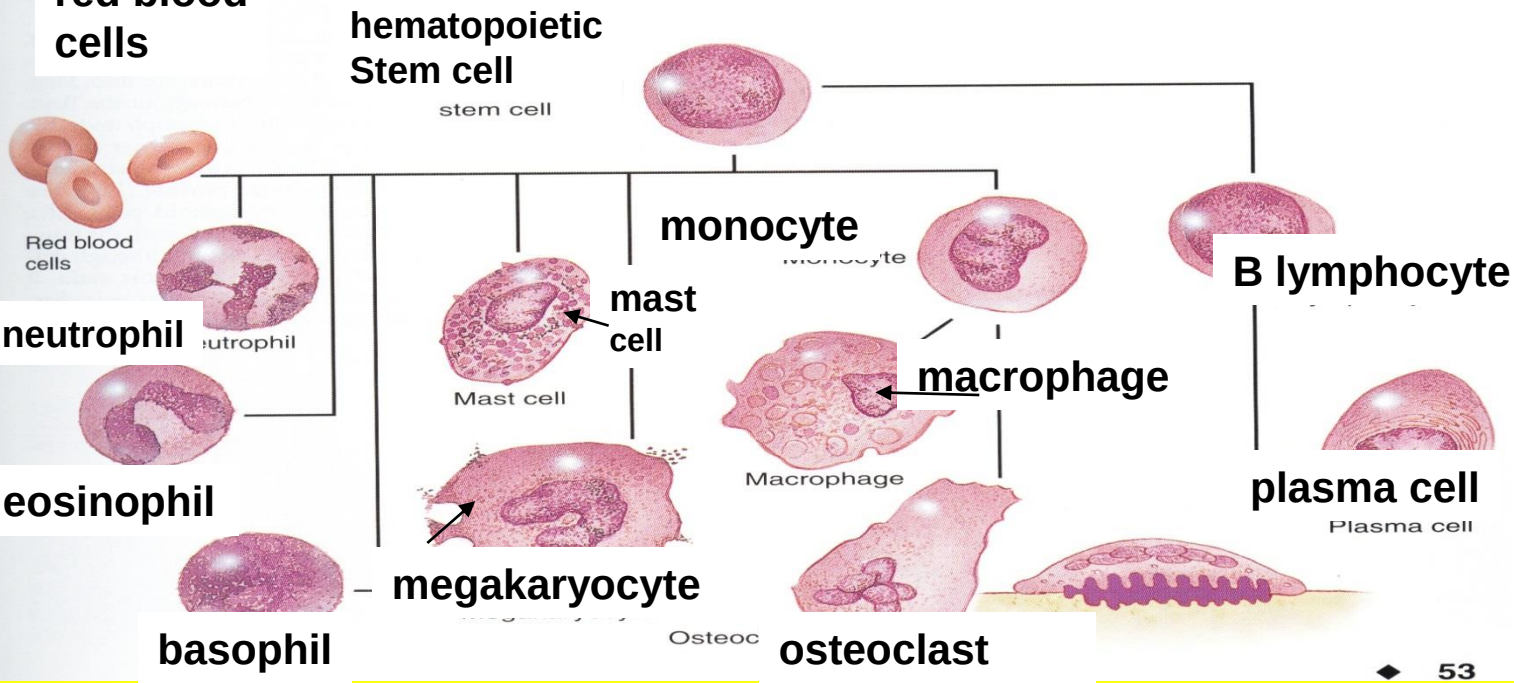
GRAPHIC 3-2.

Connective tissue cells

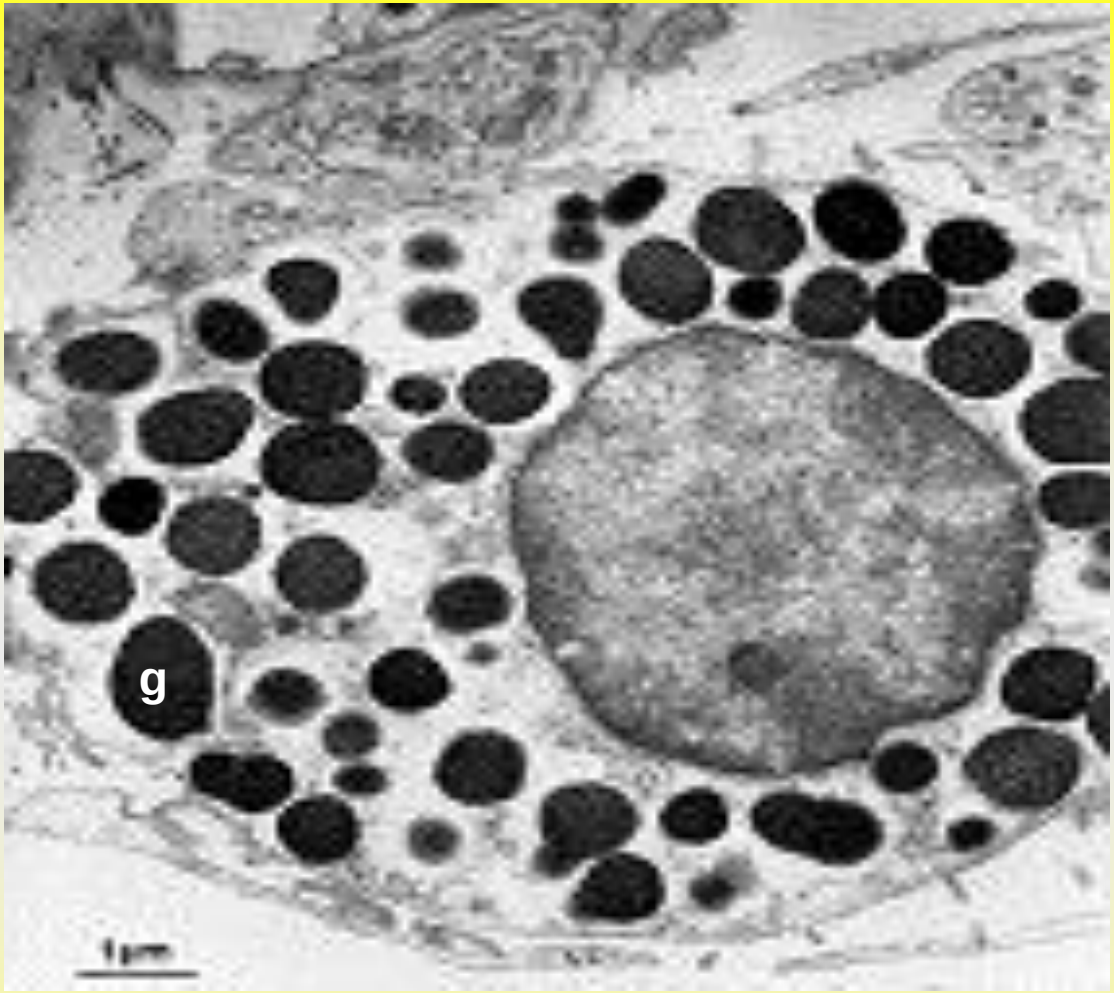




Mast cells

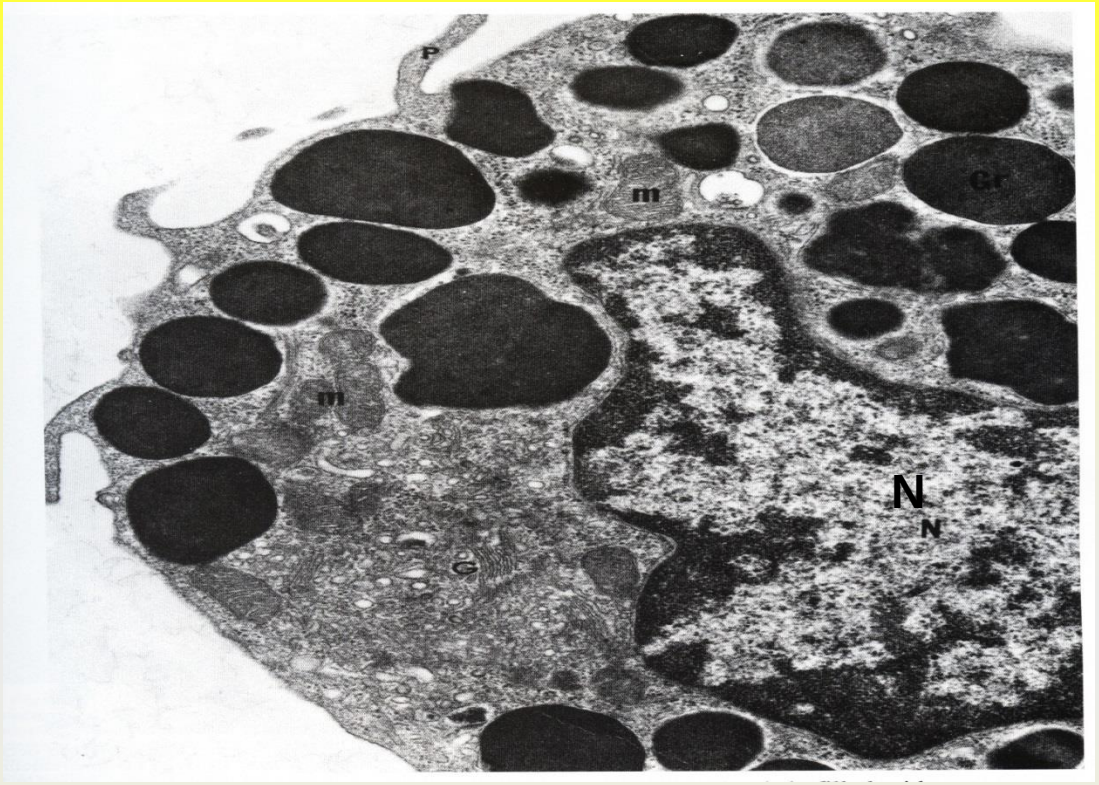


Mast Cell Human, TEM, 10,000x.

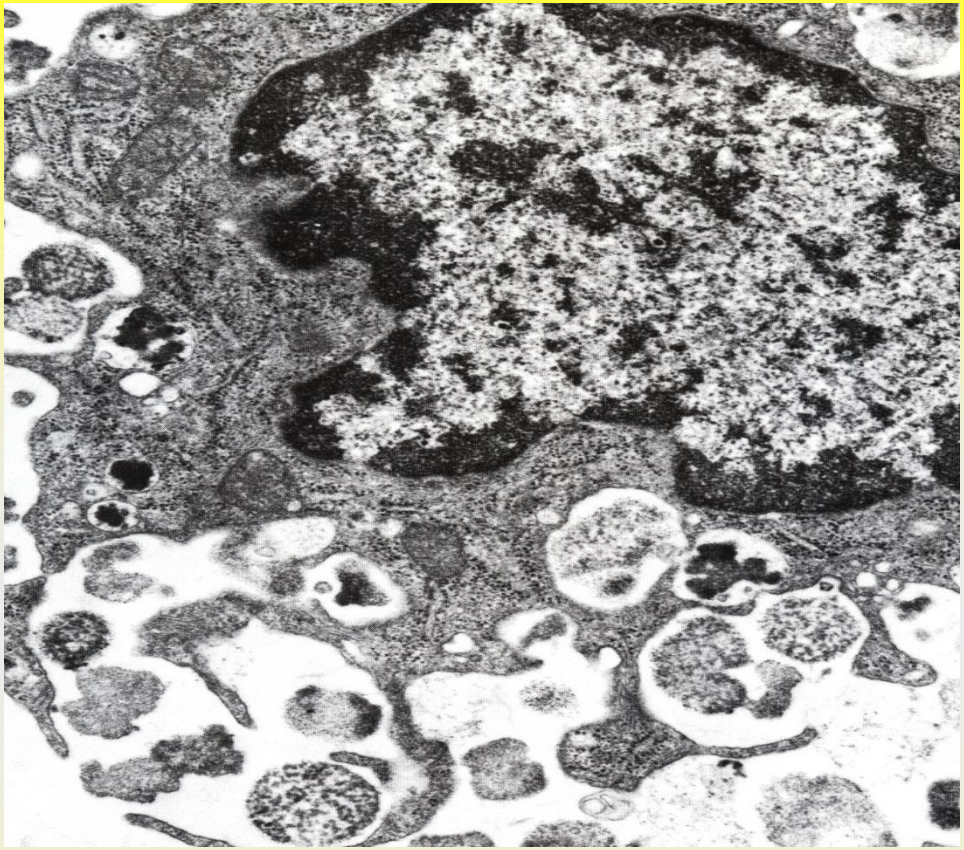


Mast cells promote immediate hypersensitivity reactions (hay fever, asthma, anaphylaxis) following their release of secretory granules with heparin and histamine which act as chemical mediators. G- granules of the mast cell.

Mast Cell Human, TEM, 10,000x.



Mast cells are among the largest of fixed cells of the CT, they are 20-30 mcm in diameter. The presence of numerous granules in the cytoplasm is the identifying characteristic of mast cells. These membrane-bound granules range in size from 0.3 to 0.8 mcm. In addition to heparin, a sulfated GAG they contain histamine, neutral proteases, chemotaxic factors etc. N – nucleus of the mast cell.



Mast Cell Human, TEM, 10,000x.

Mast cells possess high-affinity cell-surface Fc receptors (Fc-epsilonRI) for IgE. Cross-linking of their surface IgE molecules by antigen causes their clumping and this triggeres mast cell degranulation, with release of several mediators of allergic reaction. -

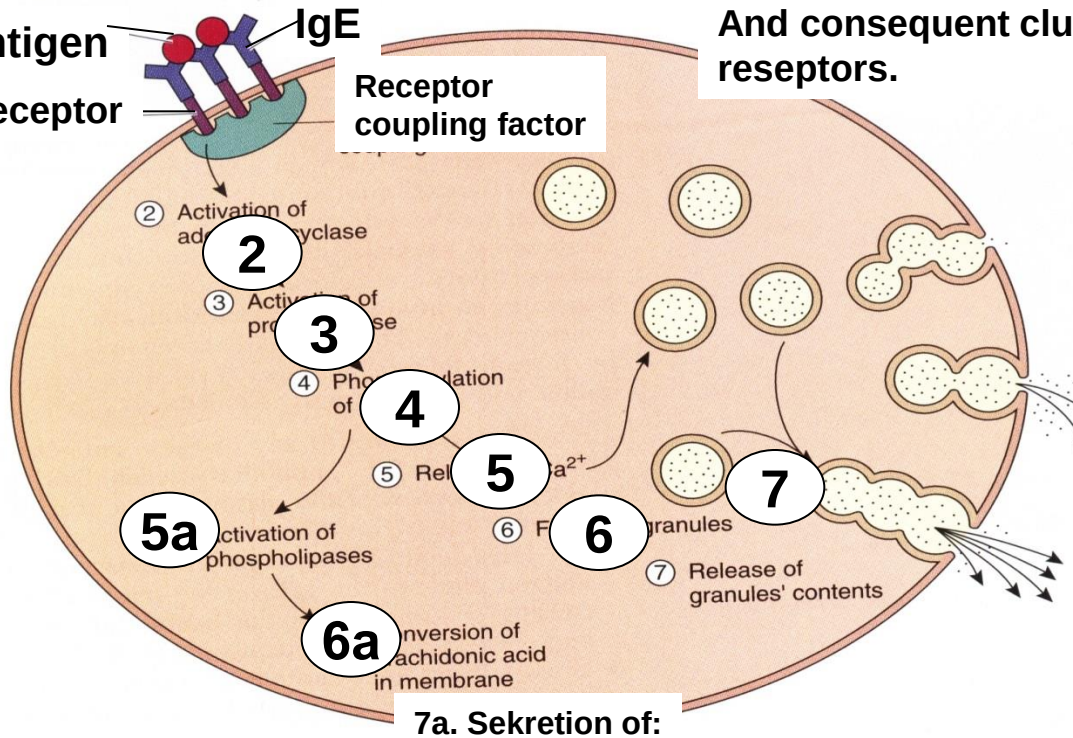
Principal Primary and Secondary Mediators Released by the Mast Cells.

Substance	*Type of mediator*	*Source*	*Action*
Histamine	Primary	Granule	Increases vascular permeability; vasodilation; smooth muscle contraction of bronchi; increases mucus production
Heparin	Primary	Granule	Anticoagulant binds and inactivates histamine
Chondroitin sulfate	Primary	Granule	Binds to and inactivates histamine
Aryl sulfatase	Primary	Granule	Inactivates leukotriene C_4, thus limiting the inflammatory response
Neutral proteases	Primary	Granule	Protein cleavage to activate complement (especially C3a); increases inflammatory response
Eosinophil chemotactic factor	Primary	Granule	Attracts eosinophils to site of inflammation
Neutrophil chemotactic factor	Primary	Granule	Attracts neutrophils to site of inflammation
Leukotrienes C_4, D_4 and E_4	Secondary	Membrane lipid	Vasodilator; increases vascular permeability; bronchial smooth muscle contractant
Prostaglandin D_2	Secondary	Membrane lipid	Causes contraction of bronchial smooth muscle; increases mucus secretion; vasoconstriction
Thromboxane A_2	Secondary	Membrane lipid	Causes platelet aggregation; vasoconstriction
Bradykinins	Secondary	Formed by activity of enzymes located in granules	Causes vascular permeability and is responsible for pain sensation
Platelet-activating factor	Secondary	Activated by phospholipase A_2	Attracts neutrophils and eosinophils; causes vascular permeability and contraction of bronchial smooth muscle

Substances Produced by Mast Cells

***Heparin* (acidic GAG)**	Anticoagulant: binds to fibronectin, growth factors, coagulation proteins, complement compounds; has anticancer activity, causes tumor regression, inhibits tumor metastasis
Chondroitin sulfate	Sometimes present in mast cell granules rather than heparin: thus, different types of mast cells exist
Histamine	Causes contraction of smooth muscle of bronchioles: causes increased capillary permeability (leakiness)
***Leukotrienes* (slow-reacting substance of anaphylaxis-SRS-A)**	Causes contraction of smooth muscle (not stored in cell- synthesized from membrane phospholipids)
Eosinophil chemotactic factor of anaphylaxis (ECF-A)	Attracts eosinophils to regions of antigen-antibody interaction; eosinophils phagocytize antigen-antibody complexes: eosinophils produce histaminase, which depresses histamine effects, and aryl sulfatase, which counteracts leukotrienes
***Lysosomal enzymes* including β-glucuronidase, hexosaminidase, aryl sulfatase**	Functional role unclear: may degrade GAGs in extracellular matrix
Neutrophil chemotactic factor (NCF)	Chemoattractant for neutrophils

Schematic Diagram Illustraing the Binding of Antigens & Cross-Linking of IgE-receptor complexes on the Mast Cell Membrane



1.Binding of antigen to IgE-receptor Complex causes cross-lincing of IgE And consequent clustering of reseptors.

2.activation of adenylate cyclas

3.activation of protein kinase

4.phosphorylation of protein

5.release of Ca2+

6.fusion of granules

5a.activation of phospholipases

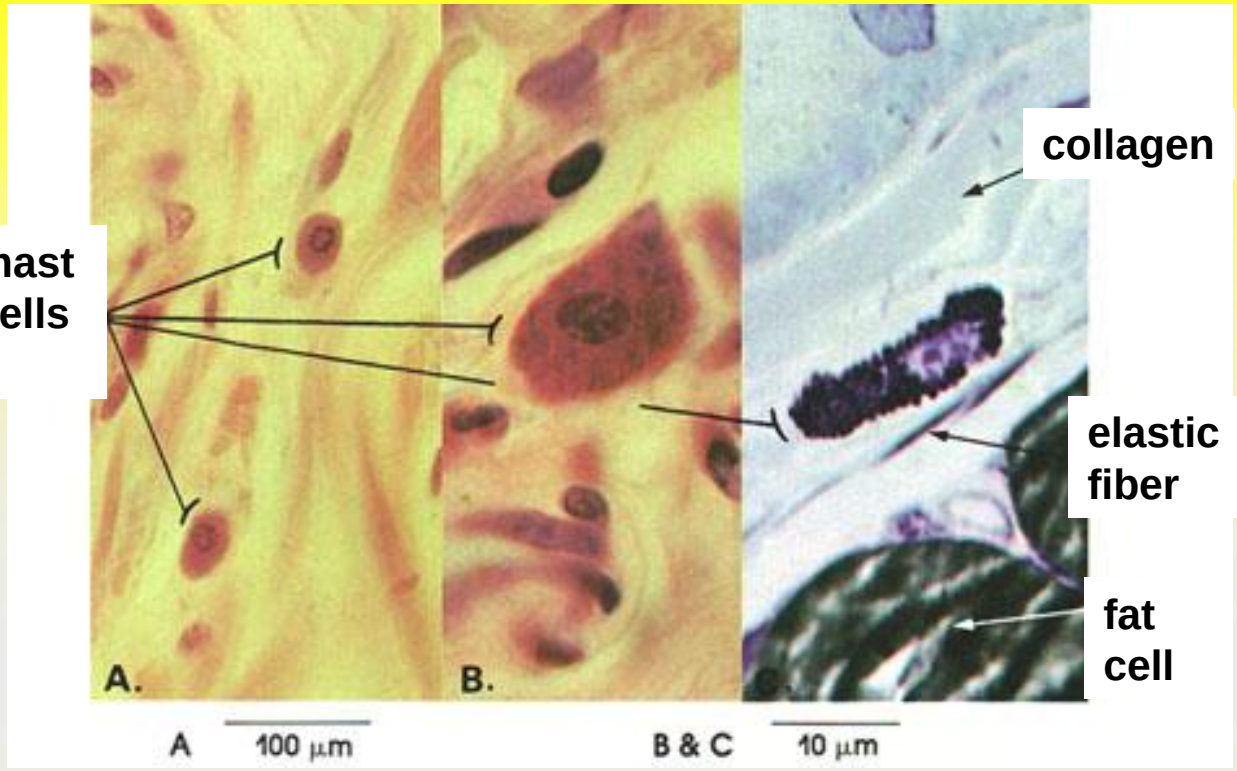
6a.conversion of arachidonic acid in membrane

7.release of granules' contents

Chondroitin sulfate
Histamine
Heparin
ESF
NSF
Aryl sulfatase

7a. Sekretion of: leucotrienes, thromboxanes, prostoglandins

This event triggers a cascade that ultimately results in the synthesis and release of leucotriens & prostaglandins as well as in degranulation, thus releasing histamine, heparin, eosinophil chemotactic factor (ECF), and neutrophil chemotactic factor.



Mast Cells.

a) human, H & E, x162

b) rat,tolui-dine blue, x1416

Mast cells are found in areolar CT and along the course of small blood vessels.

They have a spheroid nucleus and abundant cytoplasm. The cytoplasm is filled with coarse granules that stain red in H. & E. preparations (A), but stain metachromatically with toluidine blue and other basic aniline dyes (B and C). Granules may be so abundant as to obscure the nucleus.

Mast cells produce heparin, an anticoagulant substance that prevents blood clots. They also produce histamine, which increases the permeability of capillaries and influences the blood pressure.

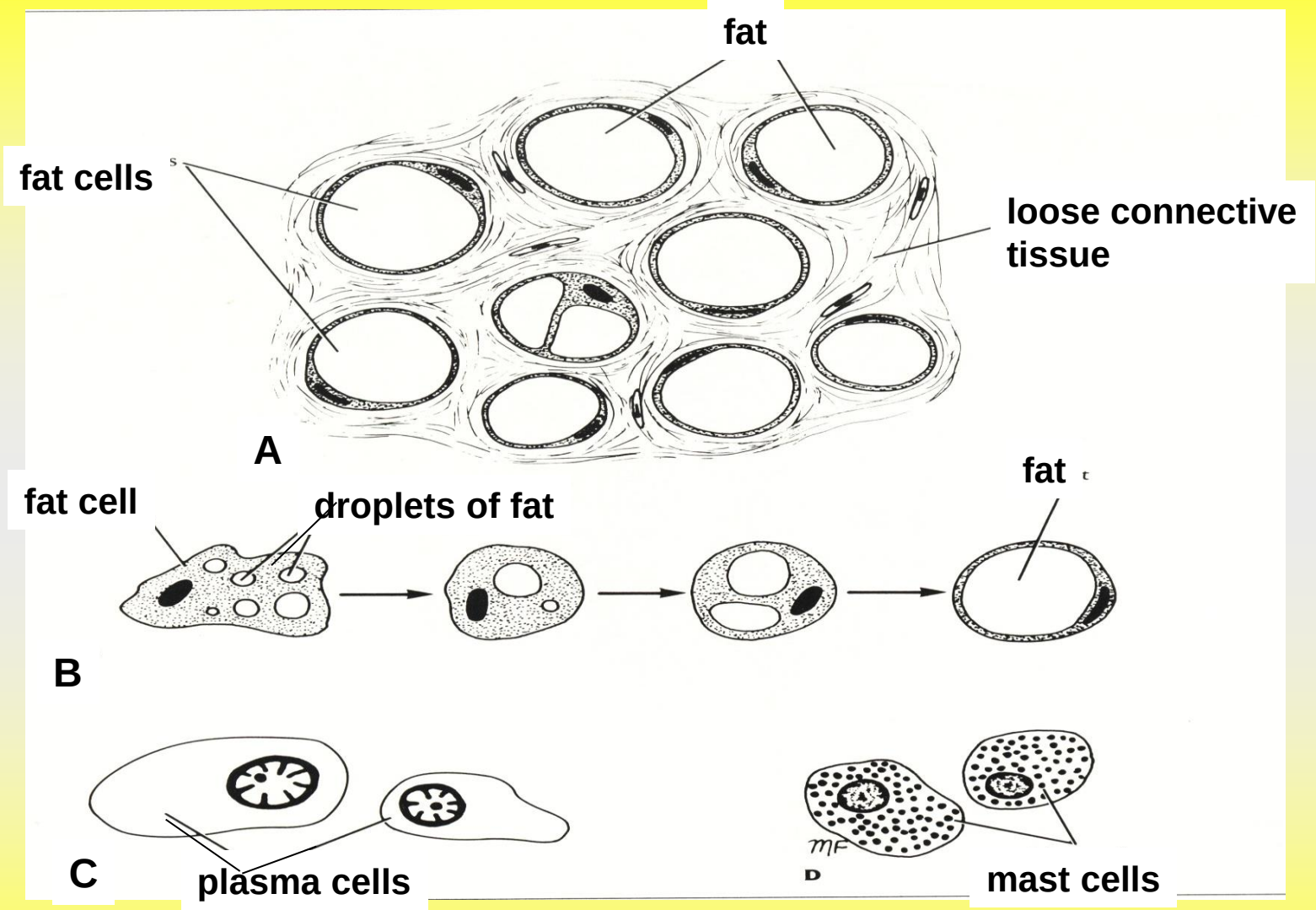
CF & EF are scattered in the interstices between mast cells.

CLINICAL CORRELATIONS:

- Victims of hay fever attacks suffer from the effects of histamine being released by the mast cells of the nasal mucosa, which causes localized edema from increased permeability of the small blood vessels. The swelling of the mucosa results in feeling “stuffed up” and hinders breathing .

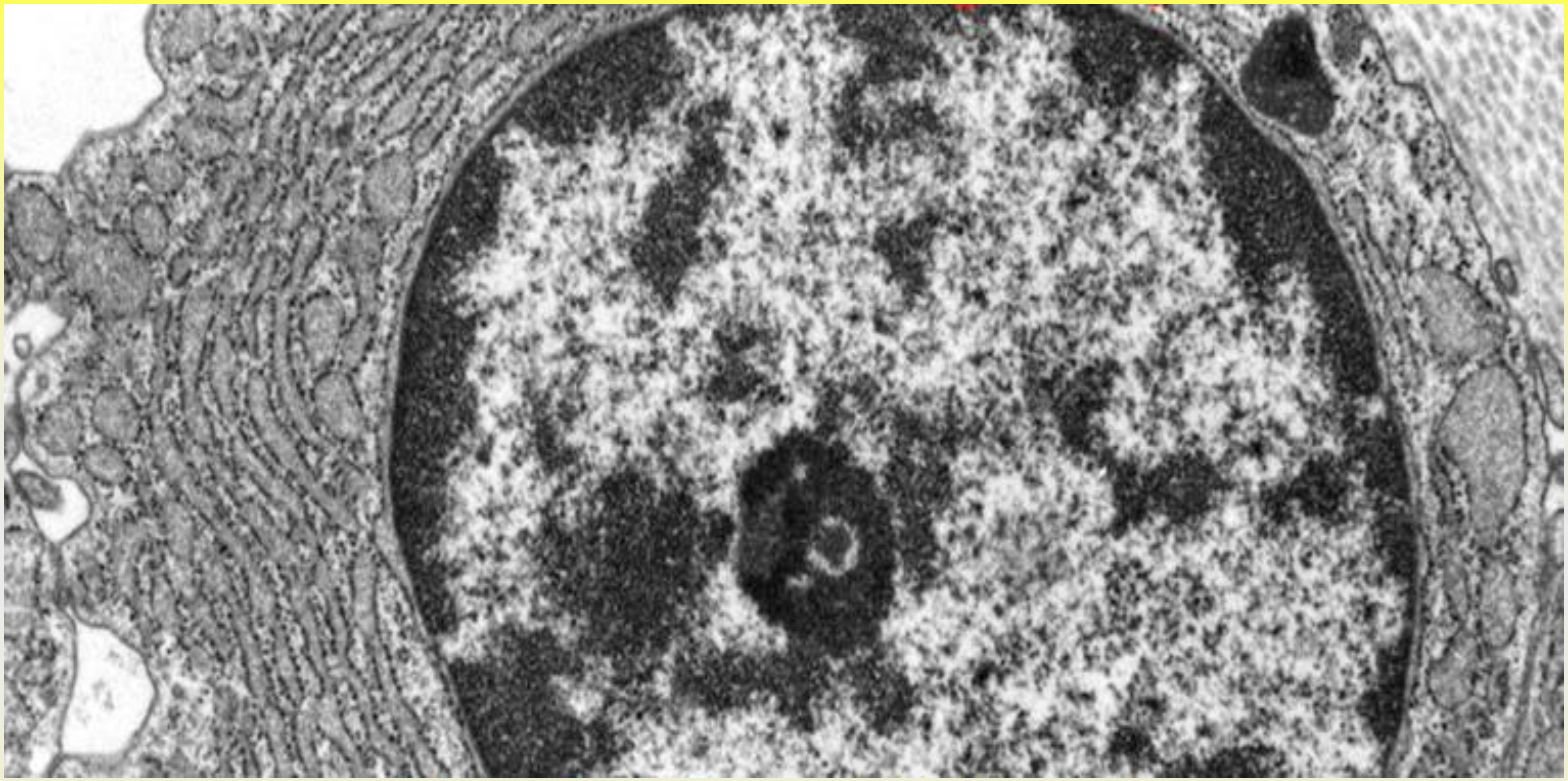
- Victims of asthma attacks suffer from difficulty in breathing as a result of bronchospasm caused by leukotriens released in the lungs.

Cells of the Loose Connective Tissue



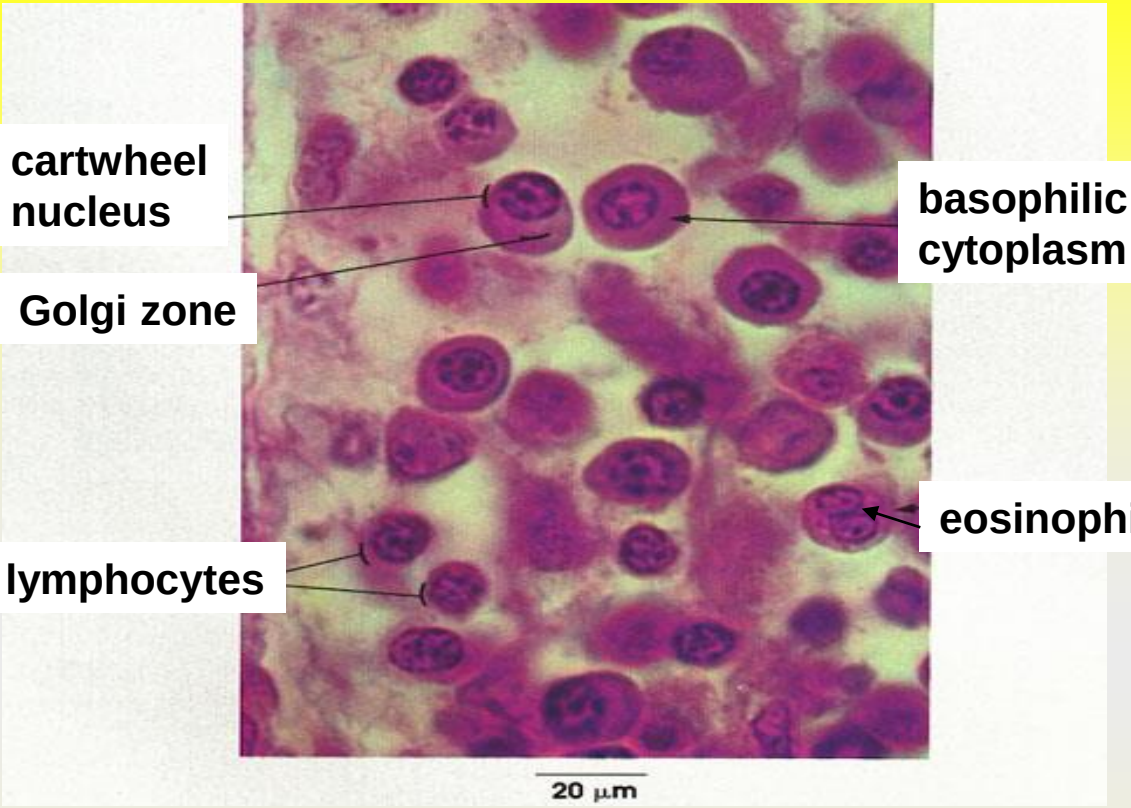
The plasma cells have eccentric nucleus with spoke-like distribution of heterochromatin in the nucleus.

Plasma cell, TEM, x15,000



Although plasma cells are scattered throughout the CT, they are present in greatest numbers in areas of chronic inflammation and where foreign substances and microorganisms have entered the tissues. They are derived from B-lymphocytes that have interacted with antigen. The nucleus of plasma cell possesses heterochromatin radiating out from the center giving it a characteristic “clock-face” or “spoked” appearance.

Plasma Cells, Lamina Propria, Jejunum, x612

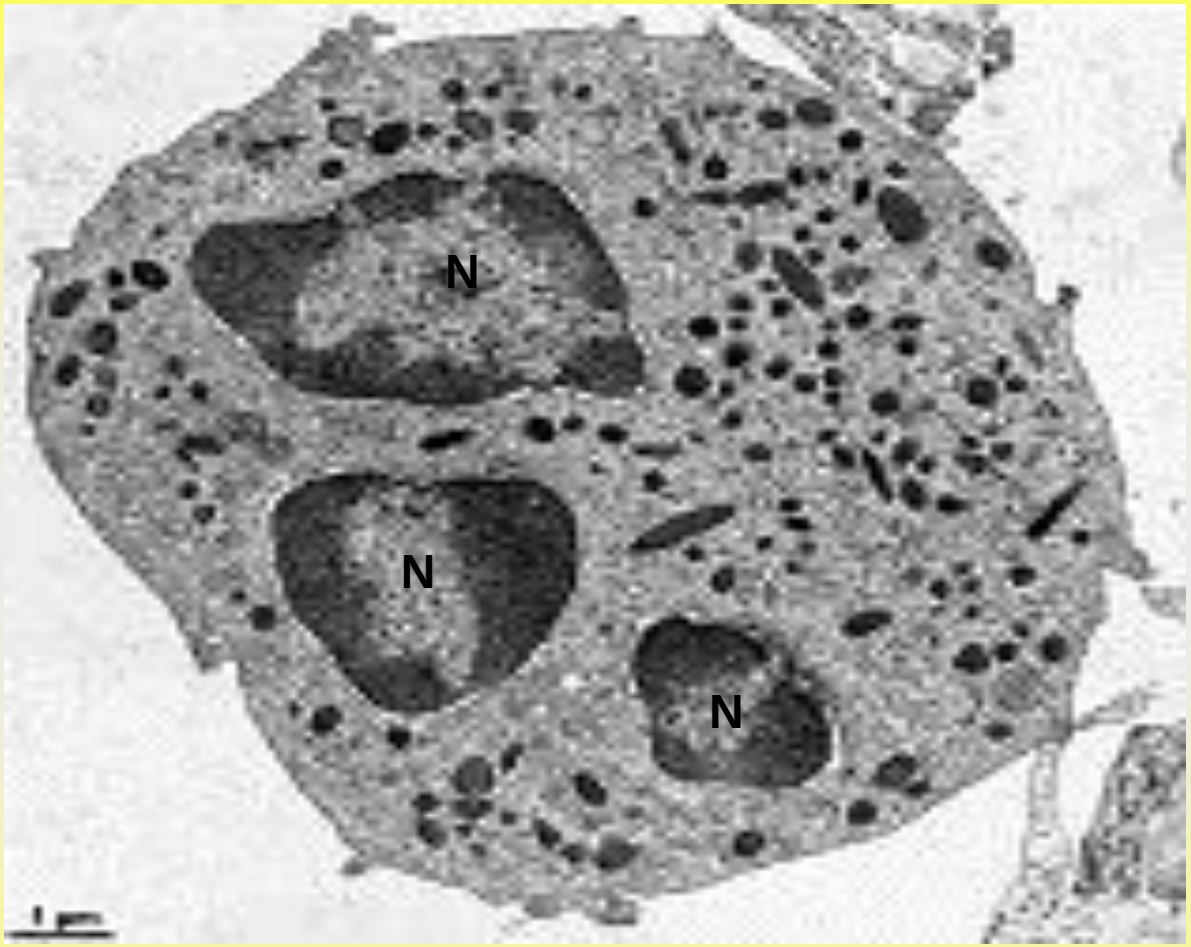


Plasma cells, although uncommon in loose CT, are plentiful in the lamina propria of the digestive tract. Note the ovoid shape of the cell, the eccentric round or oval nucleus.

Cytoplasm is intensely basophilic. The less densely stained area of the cytoplasm in juxtaposition to the nucleus contains the Golgi complex and centrioles. Nuclear chromatin is characteristically clumped around the periphery of the nucleus and produces, in negative image, a radial pattern resembling the spokes of a wheel.

The basophilia of the cytoplasm is shown by electron microscopy to be due to an extensive system of membrane-bound ribonucleoprotein. These cells produce and secrete antibodies.

Neutrophil, TEM, x10,000

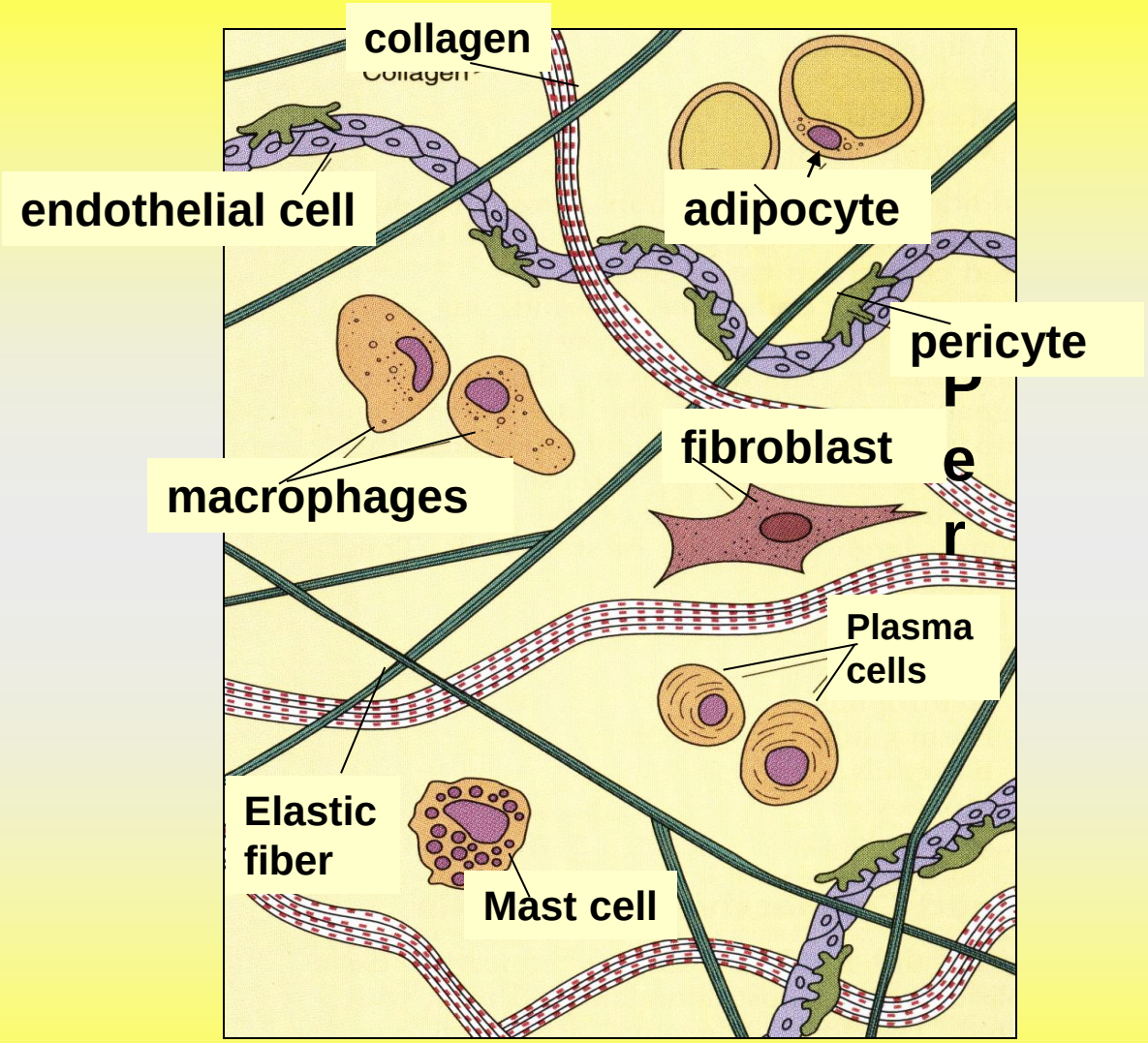


Neutrophils phagocytose and digest bacteria in areas of acute inflammation resulting in formation of pus, an accumulation of dead neutrophils and debris. N- fragments of the nucleus of the neutrophil.

Lymphocyte, TEM, x10,000

Lymphocytes are present in small numbers in most CT, except at sites of chronic inflammation where they are abundant. N – nucleus of the lymphocyte.

CONNECTIVE TISSUE CELLS. ADIPOCYTES.

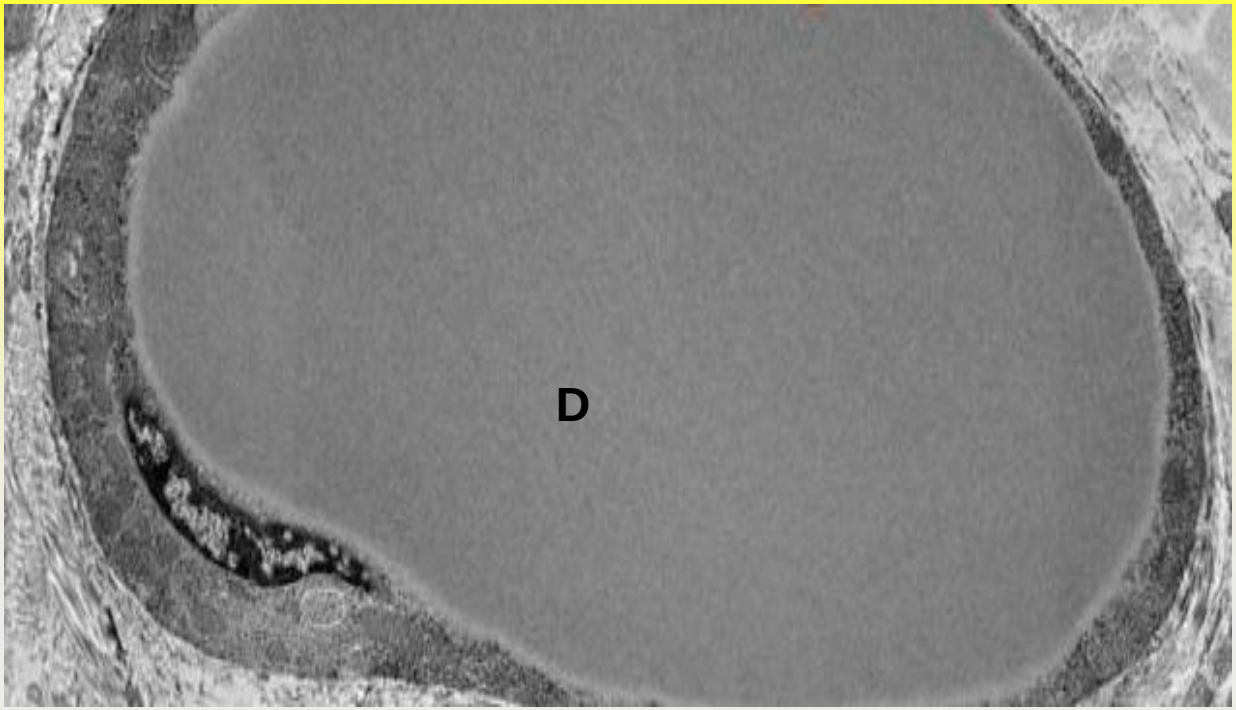


Adipocytes may be unilocular (white CT) or multilocular (brown CT).

Developing rat hypodermis in a region of developiung hair follicle (hf). The peripheral aspect of the hair follicle presents a small adipocyte (sa) whose nucleus contains prominent nucleolus. Although white adipose cells are unilocular, in that the cytoplasm of the cell contains a single, large droplet of lipid, during development lipid begins to accumulate as small droplets (l) in the cytoplasm of the small adipocyte. As the fat cell matures to become a large adipocyte (la), its nucleus is displaced peripherally, and the lipid droplets (l) fuse to form several large droplets which will eventually coalesce to form a single central fat deposit.

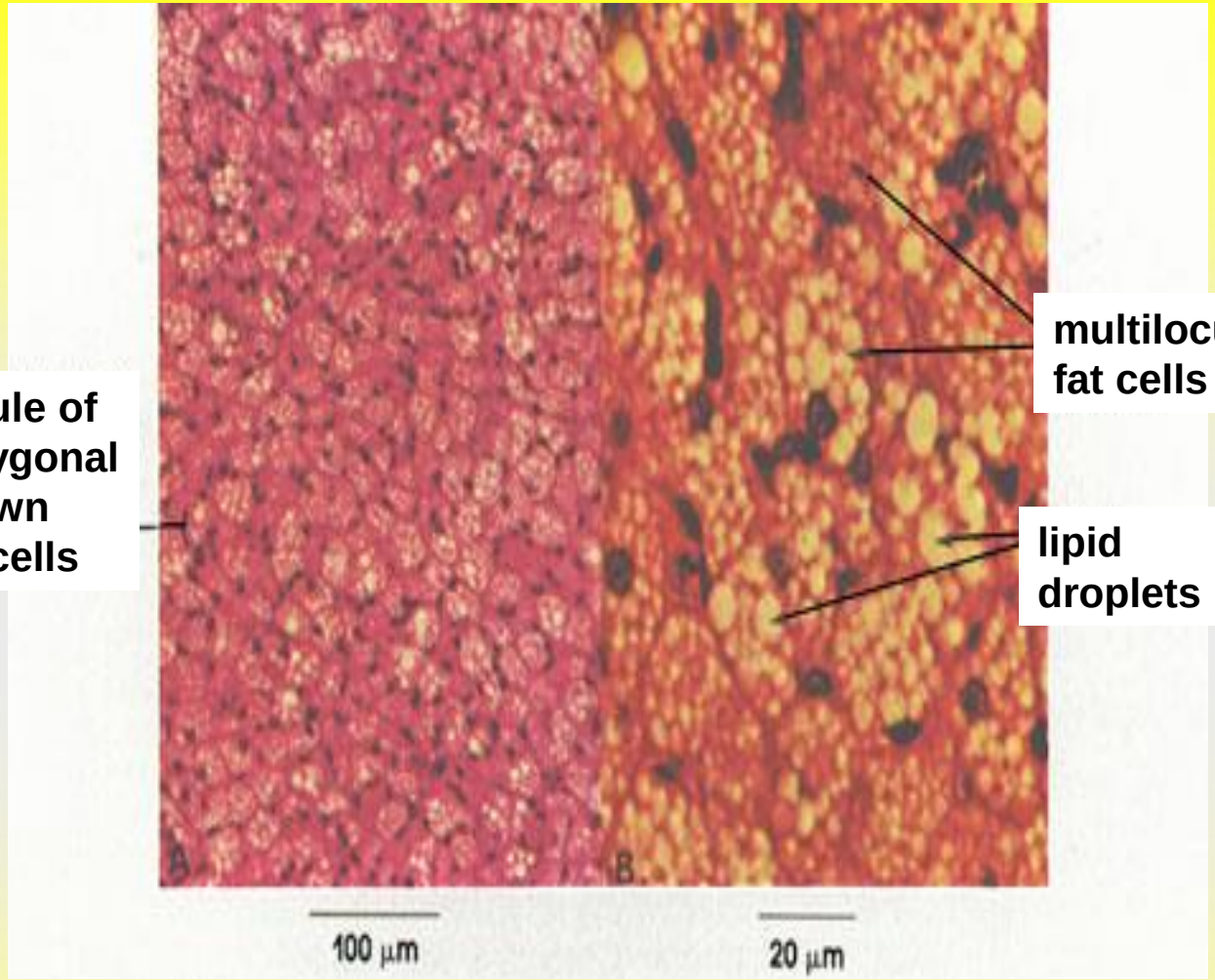
Developing Fat Cell, TEM, x3000

FAT CELL, Unilo-cular, TEM, 15,000



The fat cell lipid is in the form of a single droplet (D), and these cells are described as unilocular. Cytoplasm of fat cells appears as a thin rim at the periphery of the cell. Stored fat is the predominant component of cytoplasm. The nuclei are flattened in the cytoplasm, permitting maximum storage of fat globules. Fat globules appear as empty spaces because the fat has been dissolved out by solvents used in the preparation of tissues.

BROWN FAT

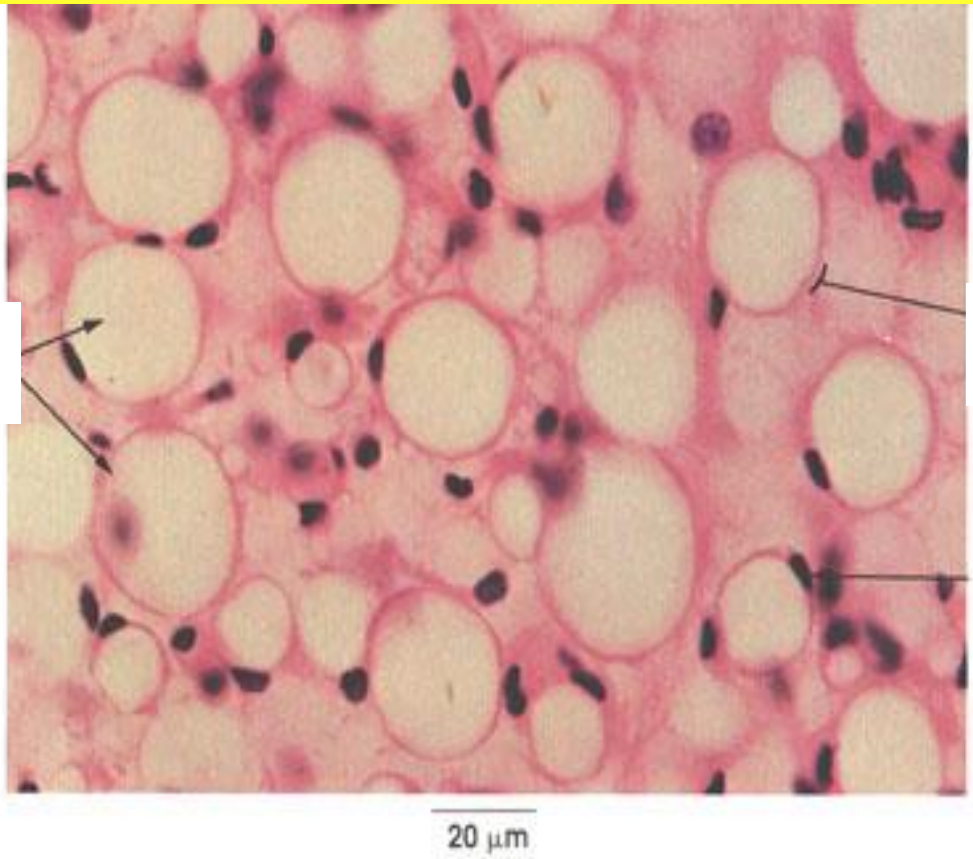


Mediasti-num, Rhesus monkey, H. & E.,

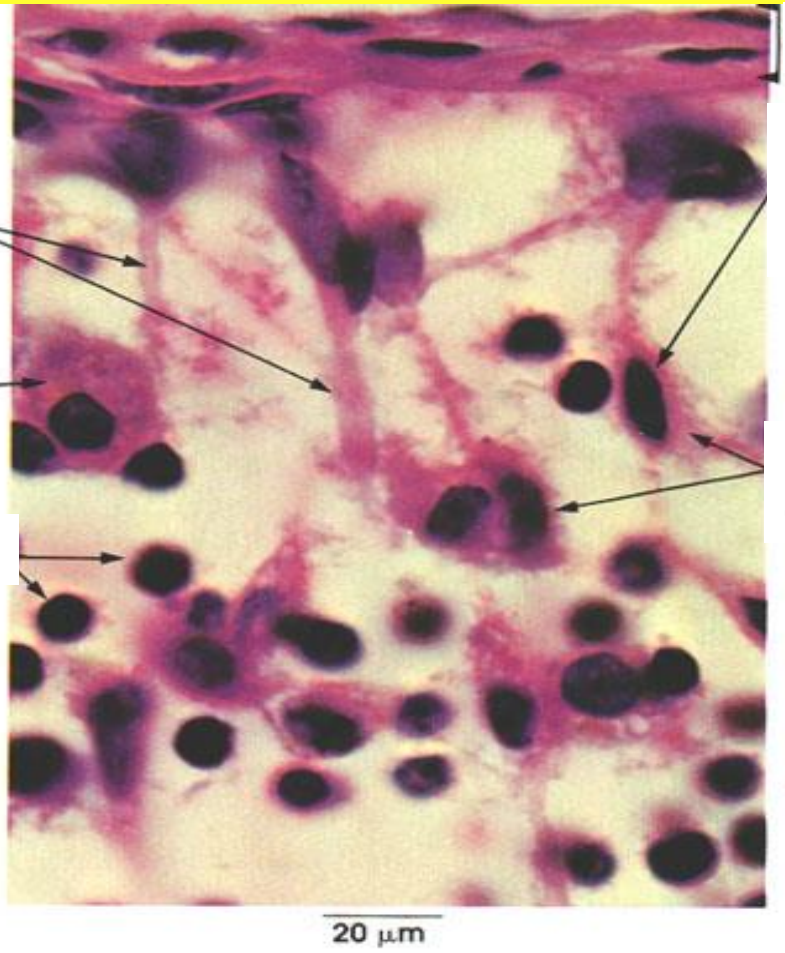
A. 162 x;
B. B. 612 x.

Brown fat is an uncommon variety of human fat found in the upper back (interscapular region) of the body. Unlike the more common white fat, brown fat cells contain a number of small lipid droplets, hence the name multilocular fat. White fat cells, in contrast, contain a single lipid droplet.

FAT CELLS
Panniculus adiposus
Human, 612x.



The fat cell lipid is in the form of a single droplet, and these cells are described as unilocular. Cytoplasm of fat cells appears as a thin rim at the periphery of the cell. Stored fat is the predominant component of cytoplasm. The nuclei are flattened in the cytoplasm, permitting maximum storage of fat globules. Fat globules appear as empty spaces because the fat has been dissolved out by solvents used in the preparation of tissues.



RETICULAR CELLS

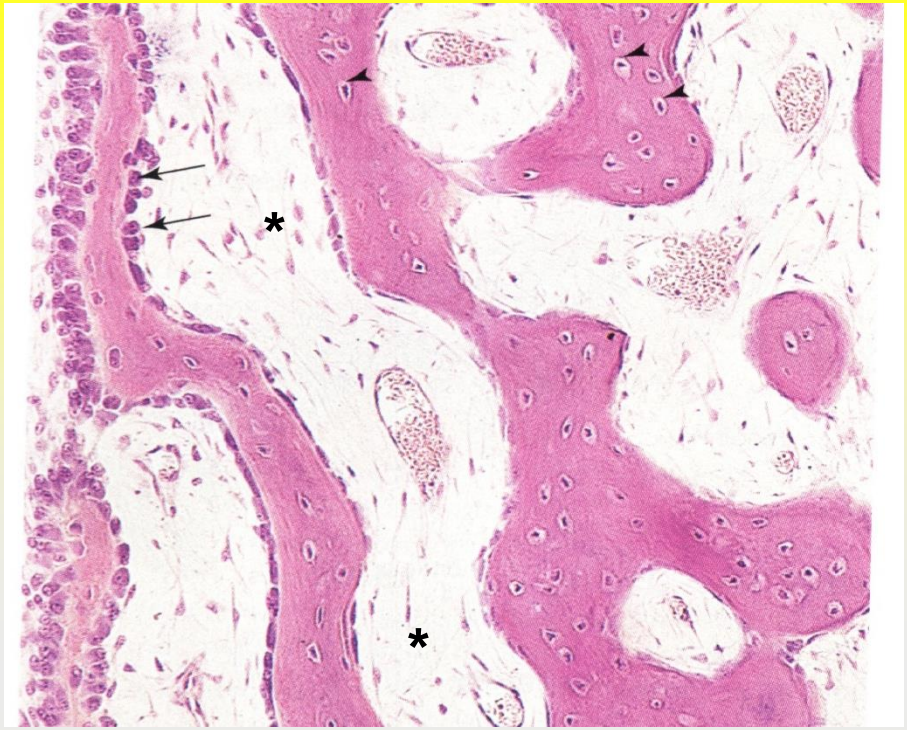
Lymph node subcapsular sinus. Rhesus monkey, H. & E., 612 x.

The subcapsular sinus of a lymph node is a lymph channel beneath the capsule of the node.

The component elements of sinus: reticular cells with processes. Cells are "star-shaped," with lightly staining cytoplasm and processes that are in contact but not continuous with processes of adjacent cells. These stellate reticular cells and their processes form the reticular tissue meshwork of the node in which lymphocytes and free macrophages are found.

Key Features of General Connective Tissue

Cell Types	*Nuclear Characteristics*	*Cytoplasmic Characteristics*	*Primary Activity*
Resident **Fibroblasts**	Oval, centrally placed, staining variable depending on activity	Elongate, spindle-or stellate-shaped cell; usually not visible in sectioned material	Produce fibers and proteoglycans
Myofibroblasts	Same as above	Same as above; bundles of actin filaments at electron microscopic level	Produce collagen fibers, contact
Adipose cells **Unilocular fat cells**	Usually compressed at edge of cell (signet ring-like), staining variable	Forms a thin rim around single central lipid droplet	Store lipid
Multilocular fat cells	Central, spheroid, light staining	Numerous lipid droplets, abundant mitochondria	Store lipid
Mast cells	Central, spheroid to ovoid, may show abundant heterochromatin	Filled with granules	Store and release histamine, heparin, eosinophil chemotactic factor
Macrophages	Large, ovoid, most frequently indented	Light staining; contains phagocytosed material	Phagocytic for a variety of materials
Plasma cell	Usually eccentric, spheroid; heterochromatin clumps	Basophilic, slate gray in color; may show negative Golgi image	Antibody production
Migratory **Neutrophils**	Polymorphonuclear, 3-5 lobes common, chromatin dense	Lilac staining	Phagocytic for small particles
Eosinophils	Polymorphonuclear, 2-4 lobes common, chromatin dense	Red-orange granules fill cytoplasm	Phagocytic for antigen-antibody complexes, degrade histamine
Lymphocytes	Single, spheroid, abundant heterochromatin	Thin rim, light blue staining	Antibody production, cytotoxic agents



MESENCHYME
Fetal pig
H. & E., A. 88 x

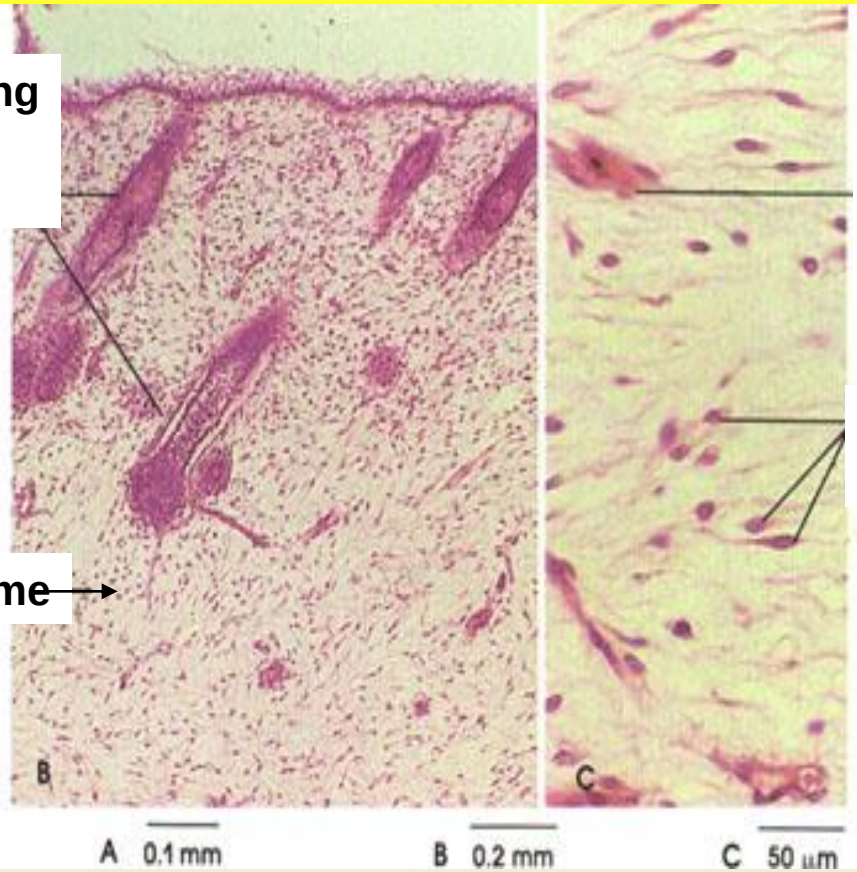
Mesenchymal CT has a delicate spongy consisten-cy and is compos-ed of cells and a viscous matrix or ground substance containing few fibers.

Mesenchymal cells (asterisks) are characterized by oval elongate nuclei with prominent nucleoli and a mix of hetero- and euchromatin. These cells have little cytoplasm but many thin processes that appear to extend from the nucleus. The matrix is composed of two classes of compounds: glycosaminoglycans and structural glycoproteins.

In this plate, note several of the mature cell types that have differentiated from mesenchymal cells. Examine the developing tooth in A.

Perichondrium

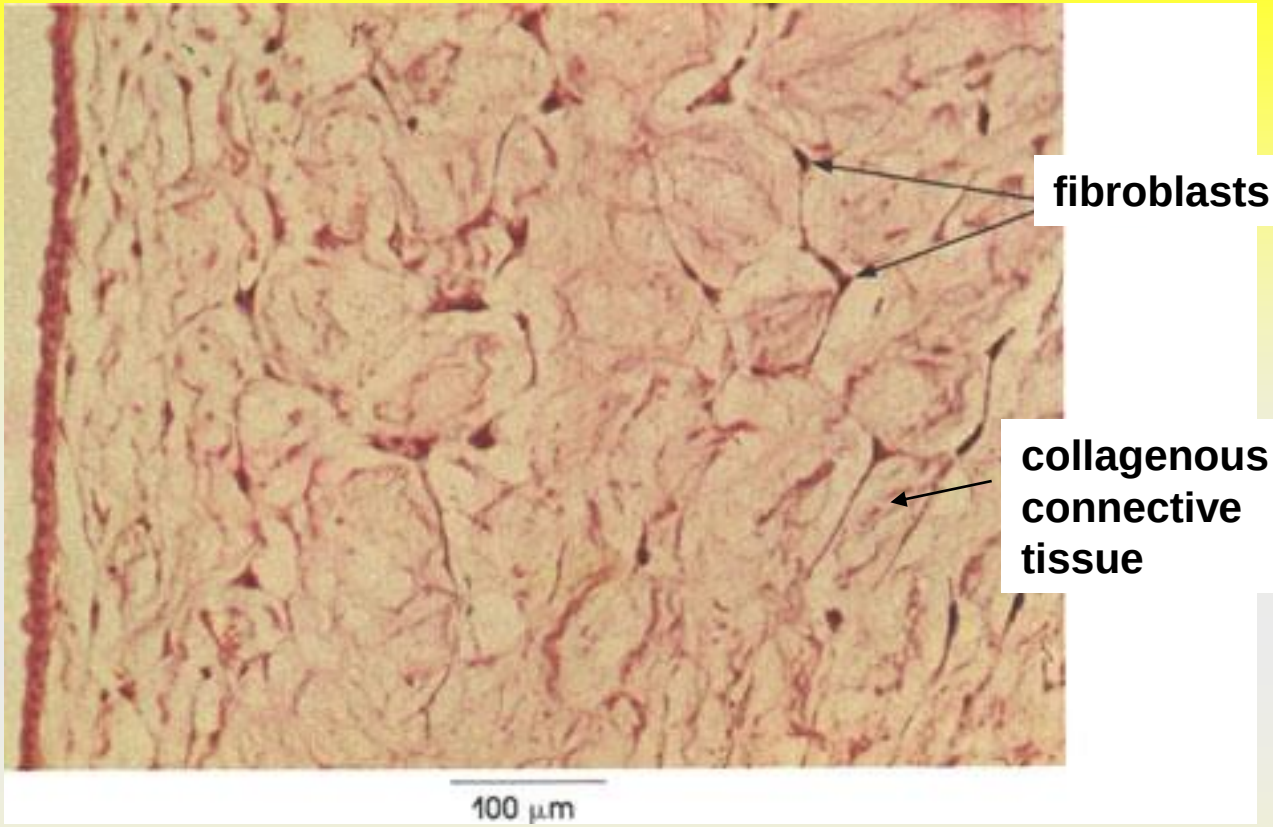
MESEN-CHYME
Fetal pig
H. & E.,
B. 55 x;
C. 220 x.



Mesenchyme

Mesenchymal cells can differentiate into most of the adult connective tissue cell types, including: (1) fibroblasts, (2) chondroblasts, (3) osteoblasts, (4) odontoblasts, (5) reticular cells, and (6) adipocytes.

In this plate, note several of the mature cell types that have differentiated from mesenchymal cells. Examine the developing hair follicles in B.

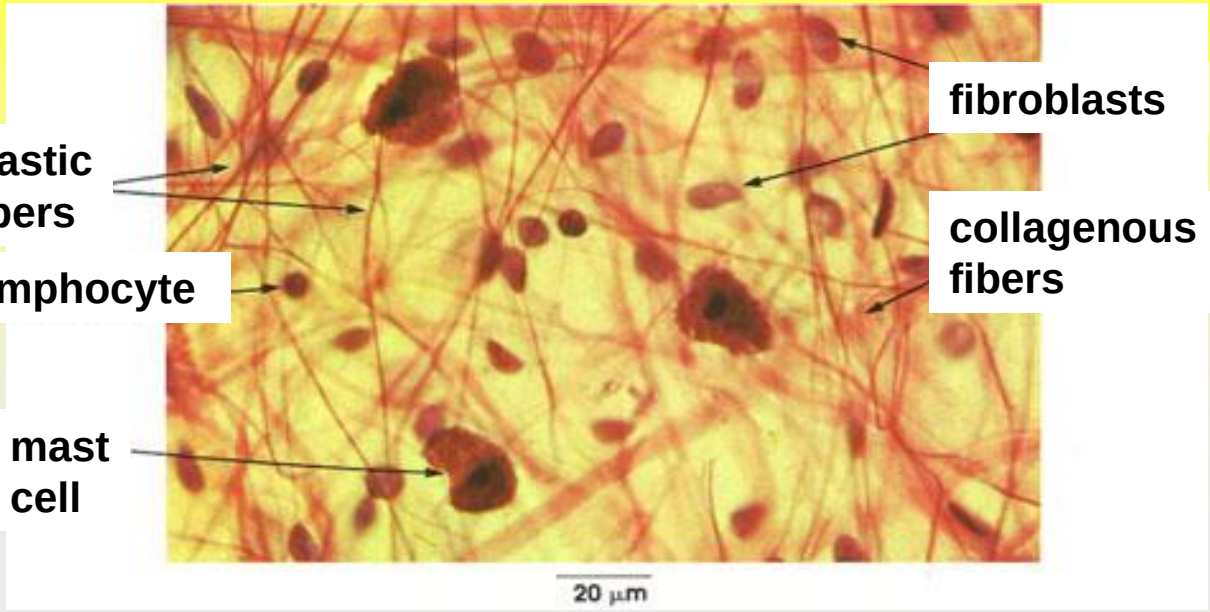


MUCOUS CONNEC-TIVE TISSUE Umbilical cord, Monkey, H & E, X612.

Mucous CT is characteristically found in the umbilical cord. It also is transiently encountered as a stage in the differentiation of mesenchyme into CT.

The distinctive cell of mucous CT is a primitive fibroblast, which may be spindle-shaped or stellate. In H. & E. preparations, only nuclei of fibroblasts are evident. Fine CF aggregate in the ground substance, which is characteristically abundant and gelatinous.

AREOLAR CONNECTIVE TISSUE, Subcutaneous, Rat, H& E, x 612.



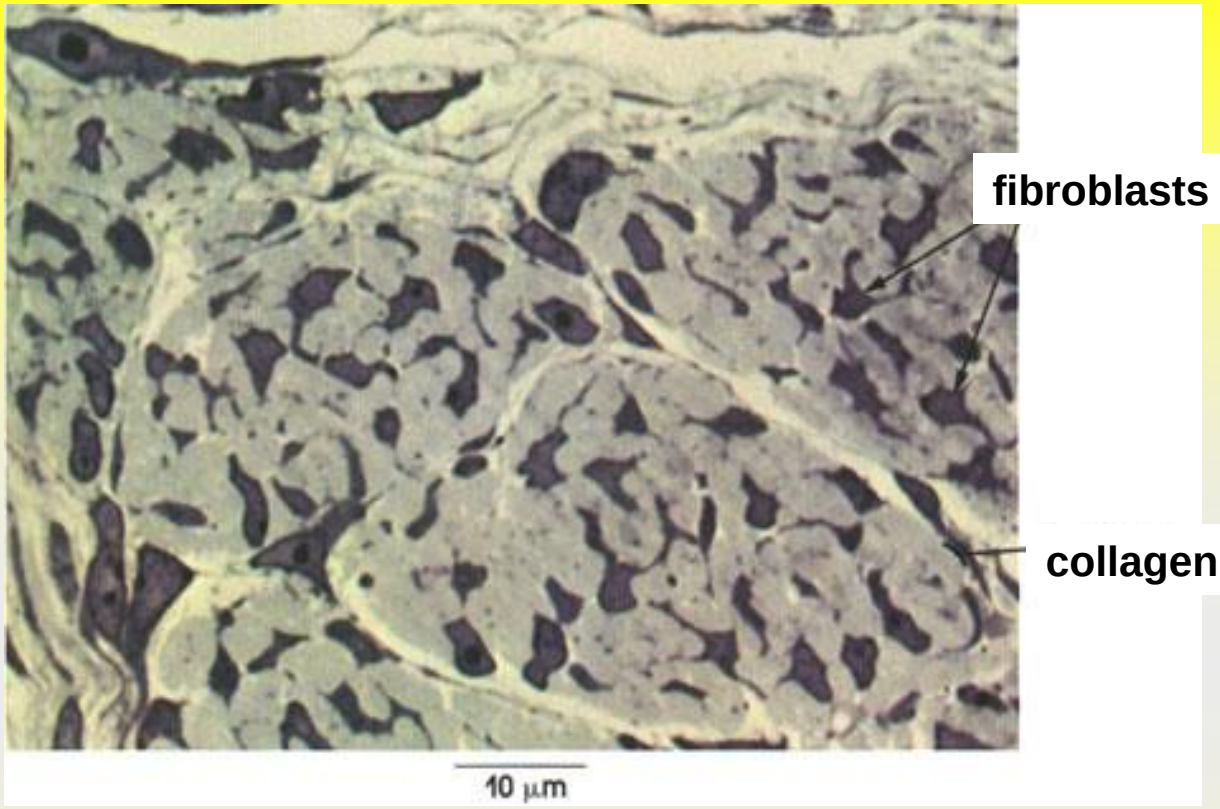
Areolar CT is so-named because of the many small areas or potential spaces that are seen within this tissue. It is the most widely encountered type of CT and contains most of the CT components.

CF: Coarse interlacing bundles of fibers that run in all directions in the CT. EF: Slender network of branching fibers irregularly dispersed in the CT. Smaller than the CF bundles.

Mast cell: A large cell with a small spherical nucleus and abundant cytoplasm containing coarse granules. Produces heparin and histamine.

Fibroblasts: Only nuclei are seen in this preparation. Nuclei are ovoid and larger than other CT nuclei. Fibroblasts are the most common cell type found in areolar CT. They synthesize and deposit collagen.

Lymphocyte: Only nuclei are seen in this preparation. Smaller than fibroblast nuclei, rounder and more deeply stained. Not abundant.



TENDON
Embryonic triceps muscle tendon, Toluidine blue, x1416

In dense CT fibers are either randomly distributed (irregular arrangement) or show orderly arrangement (regular arrangement).

Fibroblasts: Also known in mature tendons as tendon cells, or fibrocytes, they are the only cell type present. They are stellate in shape with cytoplasmic processes extending between and around the collagen bundles.

Collagen: In thick bundles or fascicles, separated by tendon cells and loose CT.

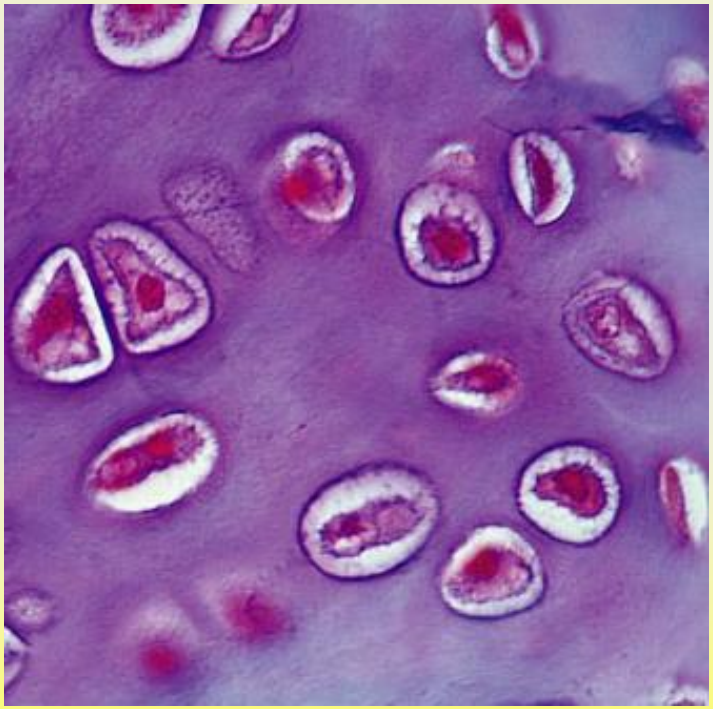
Diseases due to disorders of collagen

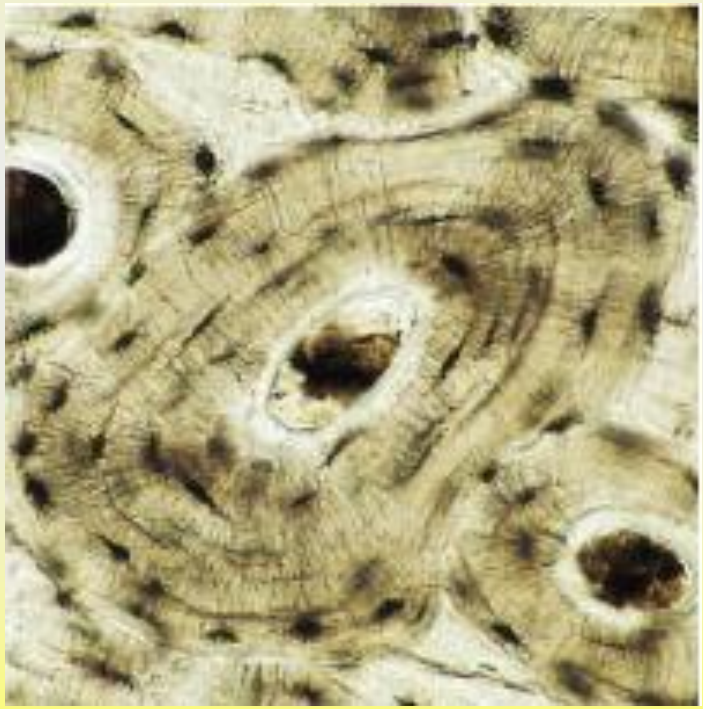
There are many inherited diseases caused by mutations in genes coding for collagen. The main effect is reduced tensile strength in support tissues, leading to abnormal tissue laxity or susceptibility to injury.

Important types of disease:

- **Osteogenesis Imperfecta is a syndrome in which defective collagen formation is caused by genetic abnormalities and leads to abnormality fragile bones. Individuals affected by this disease suffer repeated fractures after relatively minor trauma. There are several genetic subtypes of disease, although most cases are due to point mutations in genes coding for type 1 collagen.**
- **Ehlers-Danlos syndromes are characterized by abnormally extensible skin and joint laxity leading to recurrent dislocations. There are several genetic subtypes of disease. However, in some individuals this phenotype is due mutations in genes for type 1 collagen.**

“Cartilage and Bone”

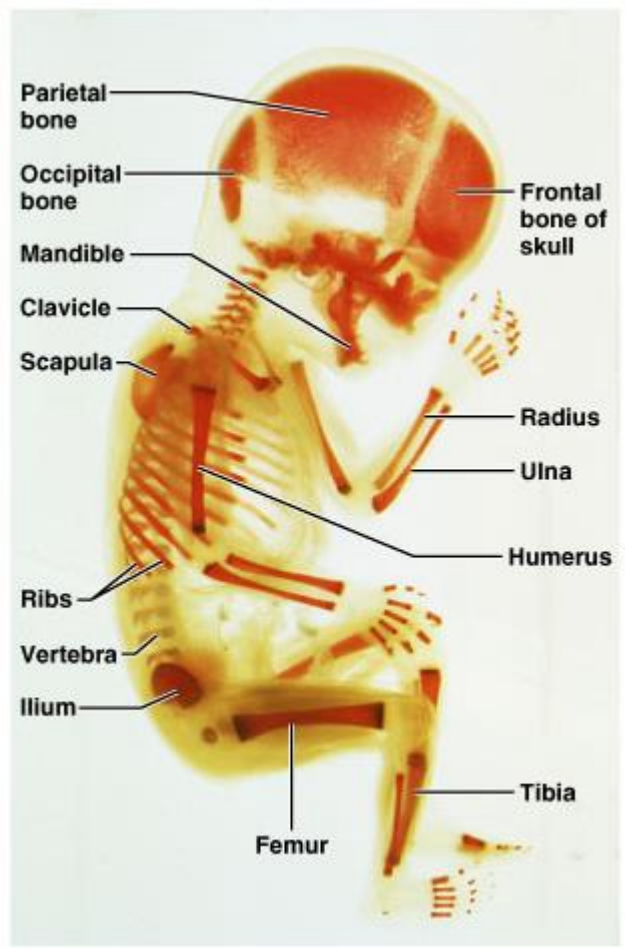




Common embryonic origin:	**Mesenchyme**			
Cellular descendants:	**Fibroblast**	**Chondroblast**	**Osteoblast**	**Hematopoietic stem cell**
	Fibrocyte	**Chondrocyte**	**Osteocyte**	**Blood cells* (and macrophages)**
				
Class of connective tissue resulting:	**Connective tissue proper**	**Cartilage**	**Osseous (bone)**	**Blood**
Subclasses:	**1.** Loose connective tissue Types: Areolar, Adipose, Reticular **2.** Dense connective tissue Types: Regular, Irregular, Elastic	**1.** Hyaline cartilage **2.** Fibrocartilage **3.** Elastic cartilage	**1.** Compact bone **2.** Spongy (cancellous) bone	* *Blood cell formation and differentiation are quite complex. Details are provided in Chapter 17.*

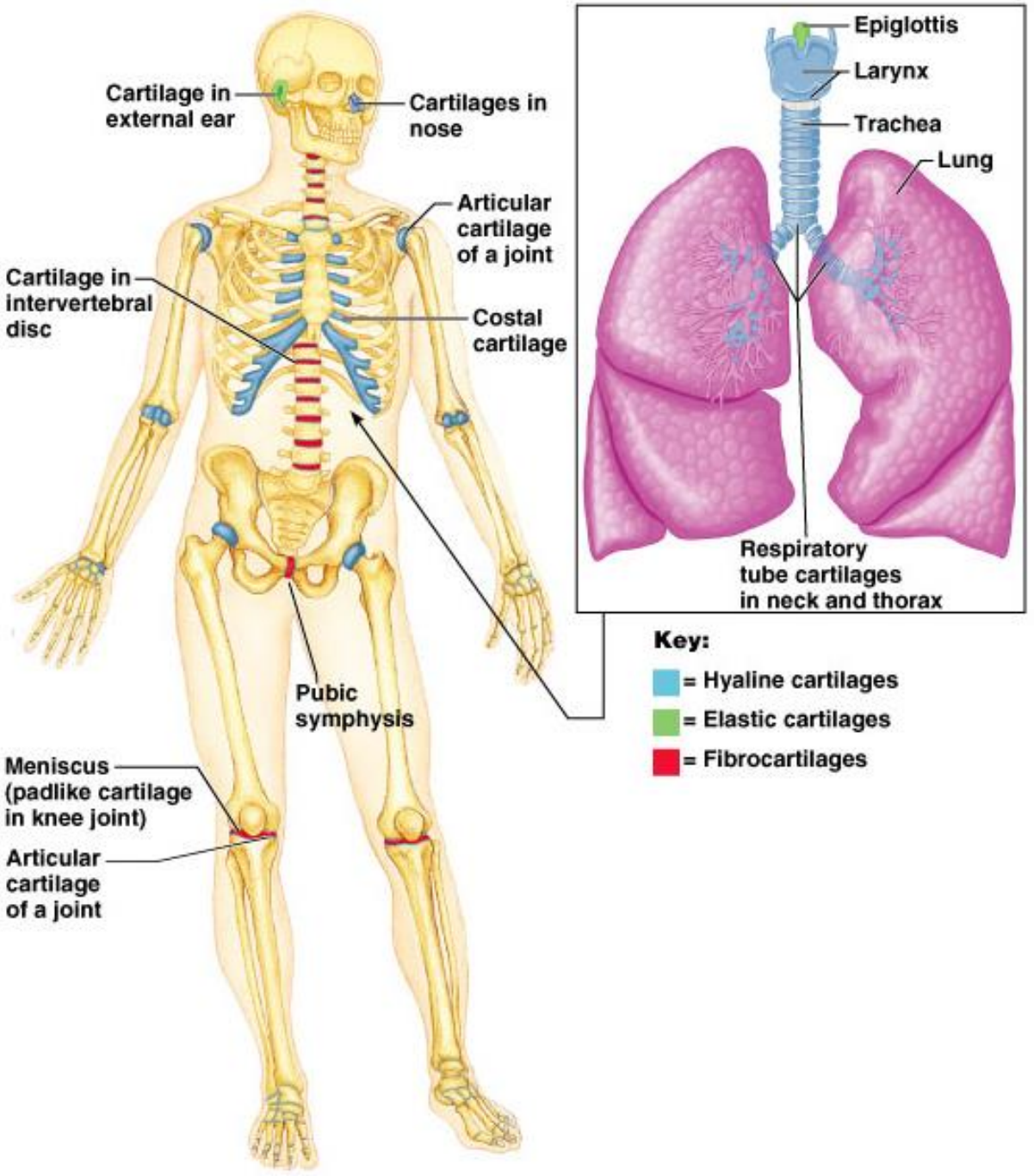
Cartilage

- Embryo
  - More prevalent than in adult
  - Skeleton initially mostly cartilage
  - Bone replaces cartilage in fetal and childhood periods

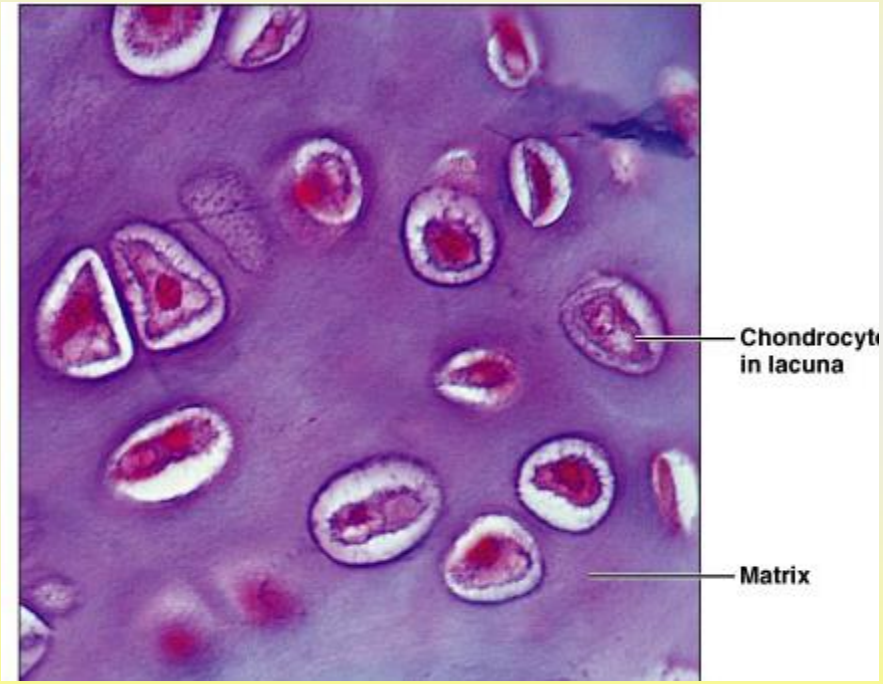


Location of cartilage in adults

- External ear
- Nose
- “Articular” – covering the ends of most bones and movable joints
- “Costal” – connecting ribs to sternum
- Larynx - voice box
- Epiglottis – flap keeping food out of lungs
- Cartilaginous rings holding open the air tubes of the respiratory system (trachea and bronchi)
- Intervertebral discs
- Pubic symphysis
- Articular discs such as meniscus in knee joint



Cartilage is connective tissue

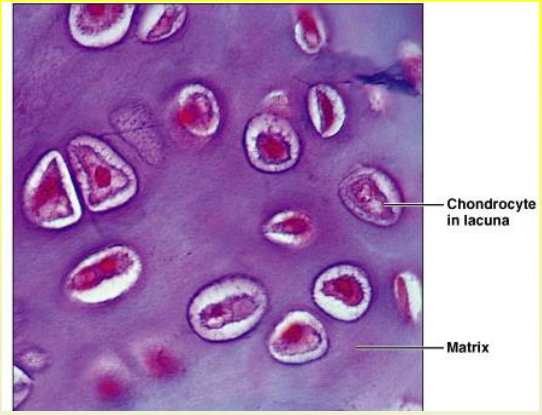


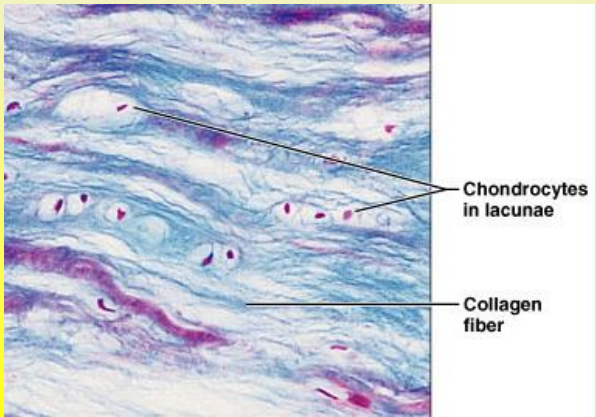
(hyaline cartilage)

- Cells called **chondrocytes**
- Abundant **extracellular matrix**
  - Fibers: collagen & elastin
  - Jellylike ground substance of complex sugar molecules
  - 60-80% water (responsible for the resilience)
  - No nerves or vessels

Types of cartilage: 3

1. Hyaline cartilage: flexible and resilient
   - Chondrocytes appear spherical
   - *Lacuna* – cavity in matrix holding chondrocyte
   - Collagen the only fiber
2. Elastic cartilage: highly bendable
   - Matrix with elastic as well as collagen fibers
   - Epiglottis, larynx and outer ear
3. Fibrocartilage: resists compression and tension
   - Rows of thick collagen fibers alternating with rows of chondrocytes (in matrix)
   - Knee menisci and annunulus fibrosis of intervertebral discs





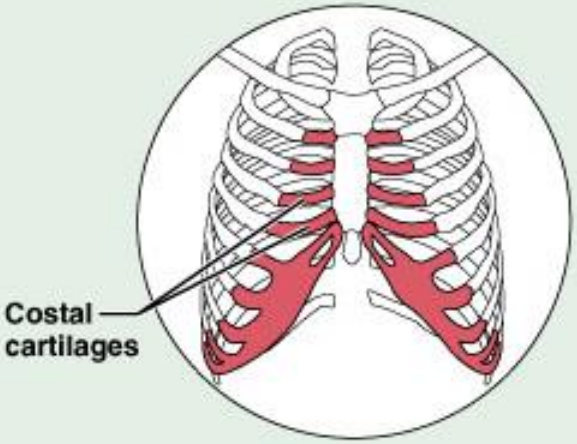
Hyaline Cartilage

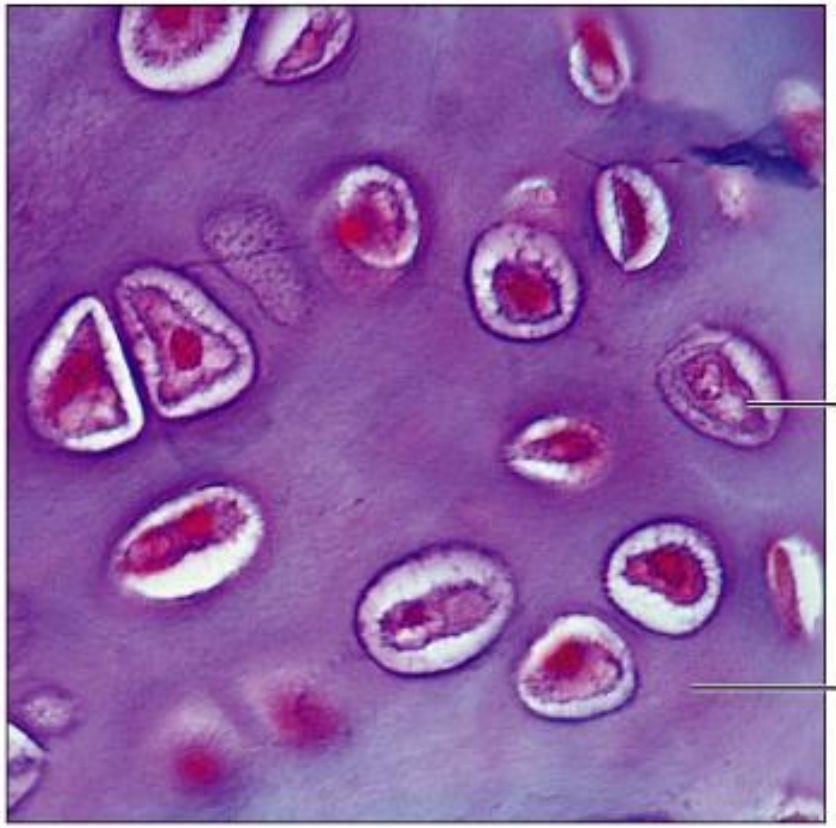
(g) Cartilage: hyaline

Description: Amorphous but firm matrix; collagen fibers form an imperceptible network; chondroblasts produce the matrix and when mature (chondrocytes) lie in lacunae.

Function: Supports and reinforces; has resilient cushioning properties; resists compressive stress.

Location: Forms most of the embryonic skeleton; covers the ends of long bones in joint cavities; forms costal cartilages of the ribs; cartilages of the nose, trachea, and larynx.





Photomicrograph: Hyaline cartilage from the trachea (300×).

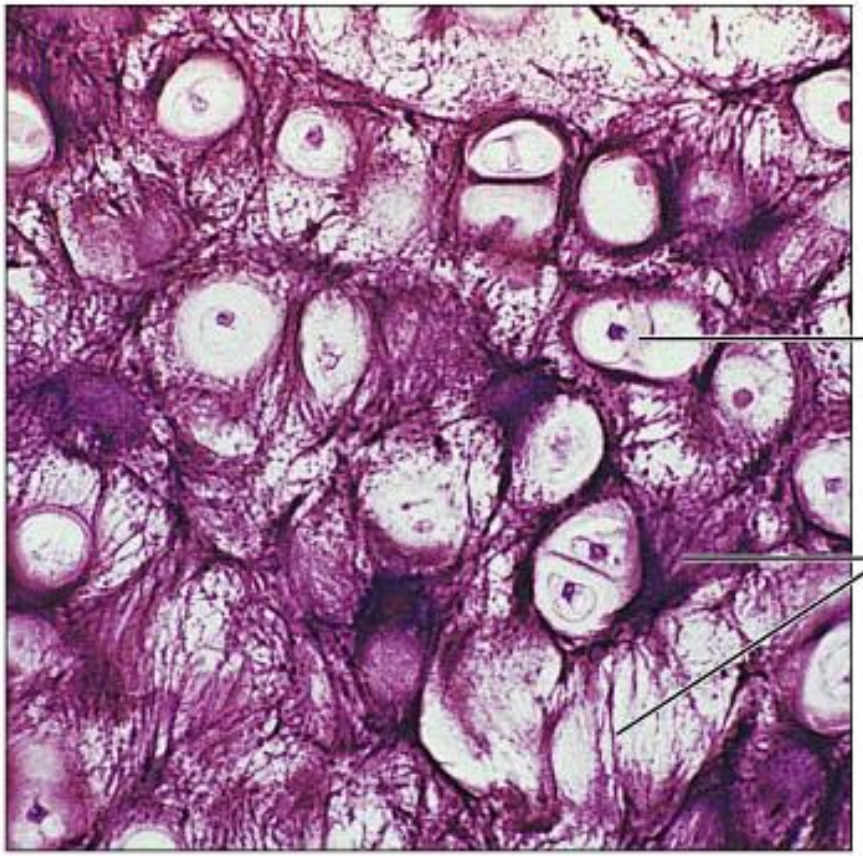
Elastic Cartilage

(h) Cartilage: elastic

Description: Similar to hyaline cartilage, but more elastic fibers in matrix.

Function: Maintains the shape of a structure while allowing great flexibility.

Location: Supports the external ear (pinna); epiglottis.



Photomicrograph: Elastic cartilage from the human ear pinna; forms the flexible skeleton of the ear (400×).

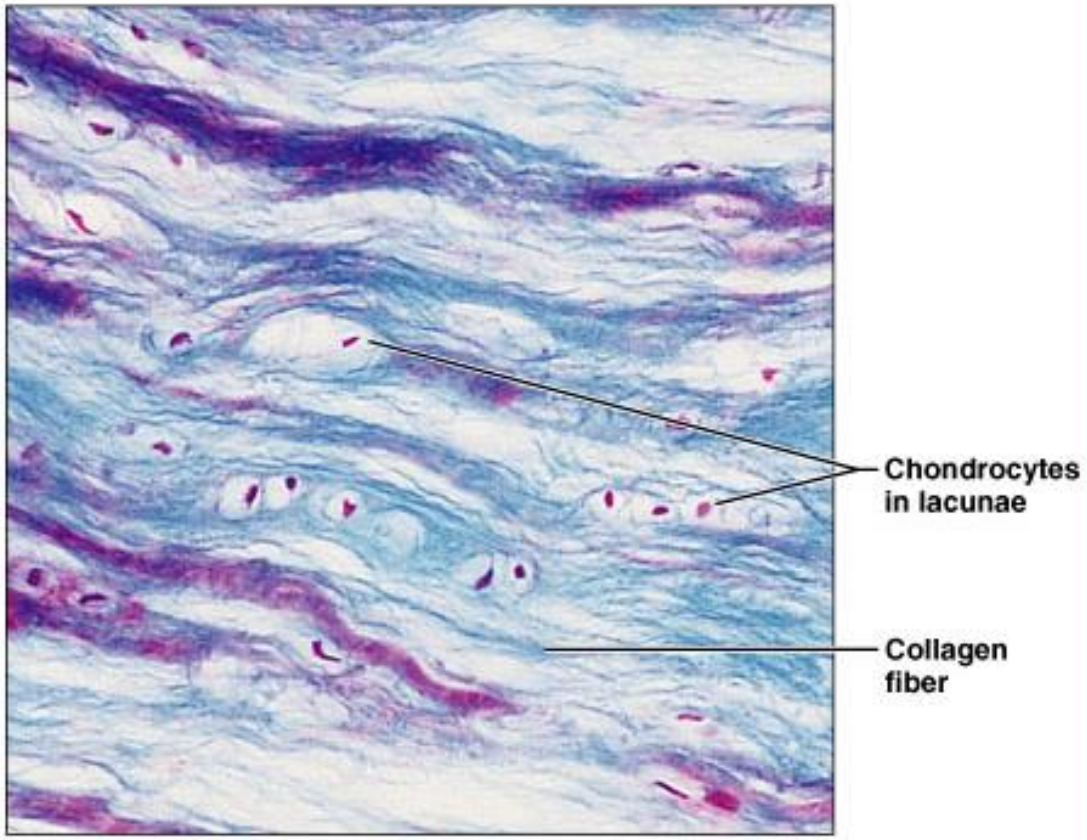
Fibrocartilage

(i) Cartilage: fibrocartilage

Description: Matrix similar to but less firm than that in hyaline cartilage; thick collagen fibers predominate.

Function: Tensile strength with the ability to absorb compressive shock.

Location: Intervertebral discs; pubic symphysis; discs of knee joint.

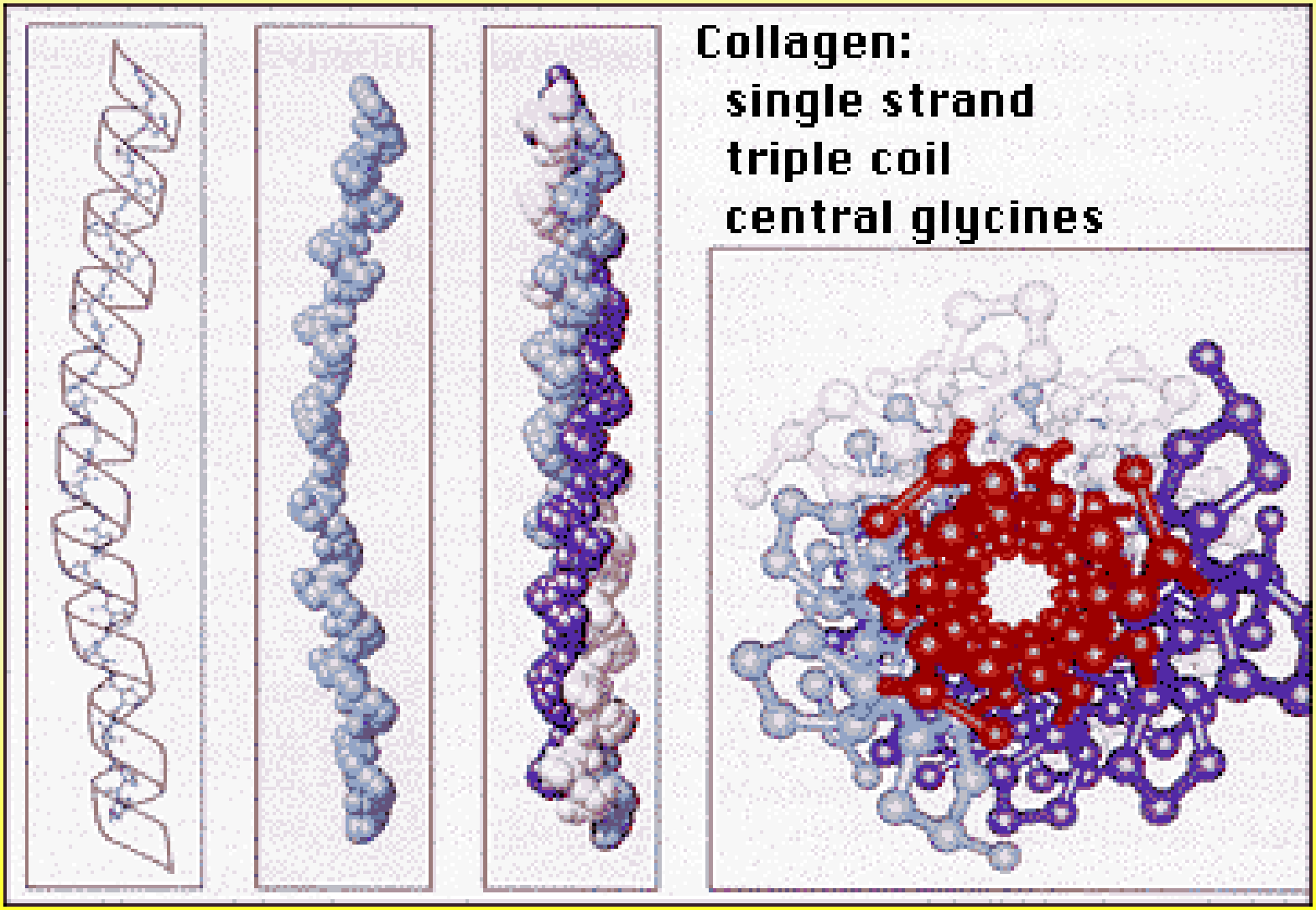


Photomicrograph: Fibrocartilage of an intervertebral disc (200×).

- Hyaline cartilage: flexible and resilient
  - Chondrocytes appear spherical
  - *Lacuna* – cavity in matrix holding chondrocyte
  - Collagen the only fiber
- Elastic cartilage: highly bendable
  - Matrix with elastic as well as collagen fibers
  - Epiglottis and larynx
- Fibrocartilage: resists compression and tension
  - Rows of thick collagen fibers alternating with rows of chondrocytes (in matrix)
  - Knee menisci and annulus fibrosis of intervertebral discs

Triple helix of collagen molecules form fibril

Fibrils aggregate into collagen fibers



Growth of cartilage

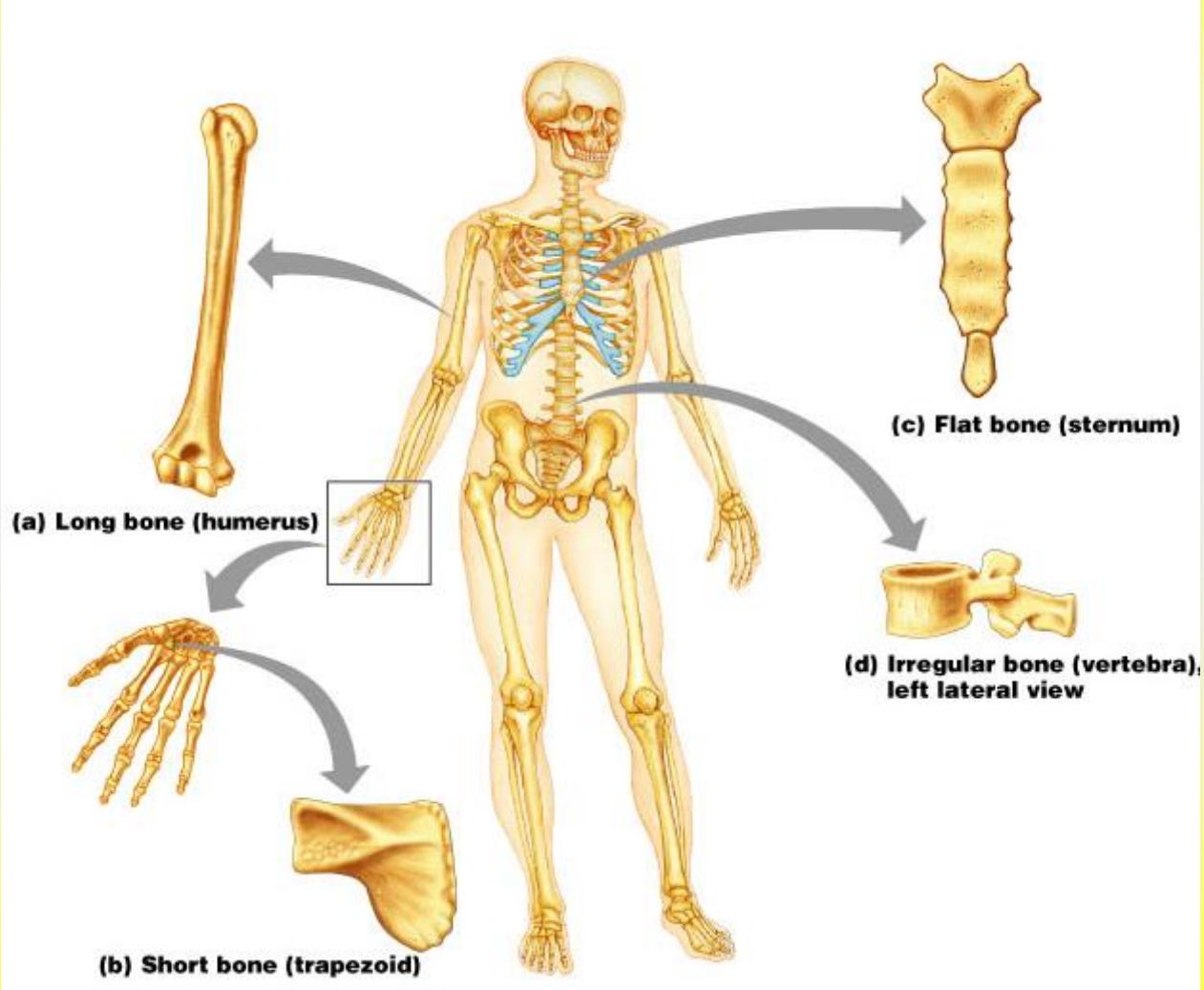
- Appositional
  - “Growth from outside”
  - Chrondroblasts in perichondrium (external covering of cartilage) secrete matrix
- Interstitial
  - “Growth from within”
  - Chondrocytes within divide and secrete new matrix
- Cartilage stops growing in late teens (chrondrocytes stop dividing)
- Regenerates poorly in adults

Bones

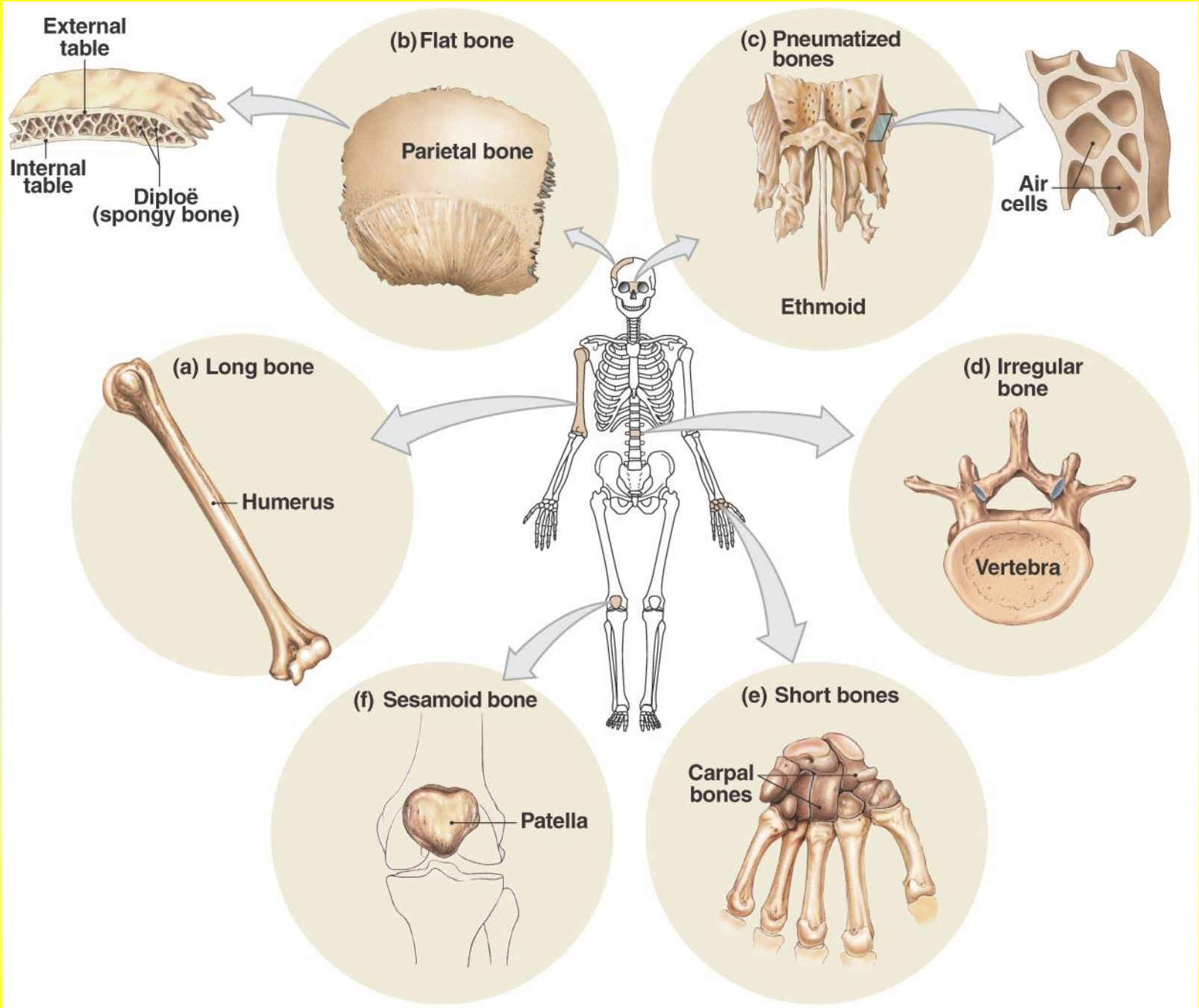
- Functions
  - Support
  - Movement: muscles attach by tendons and use bones as levers to move body
  - Protection
    - Skull – brain
    - Vertebrae – spinal cord
    - Rib cage – thoracic organs
  - Mineral storage
    - Calcium and phosphorus
    - Released as ions into blood as needed
  - Blood cell formation and energy storage
    - Bone marrow: red makes blood, yellow stores fat

Classification of bones by shape

- Long bones
- Short bones
- Flat bones
- Irregular bones
- Pneumatized bones
- Sesamoid bones

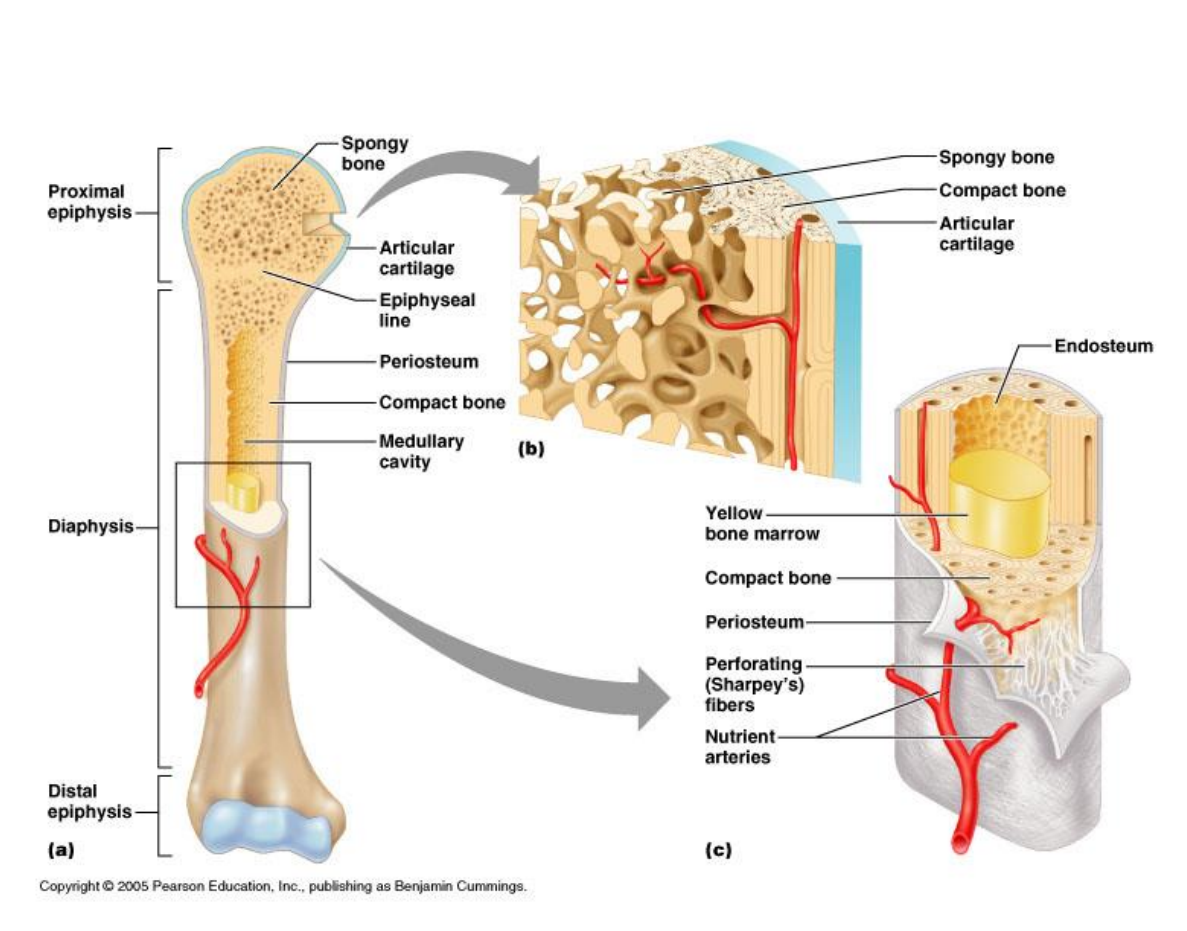


(Short bones include sesmoid bones)



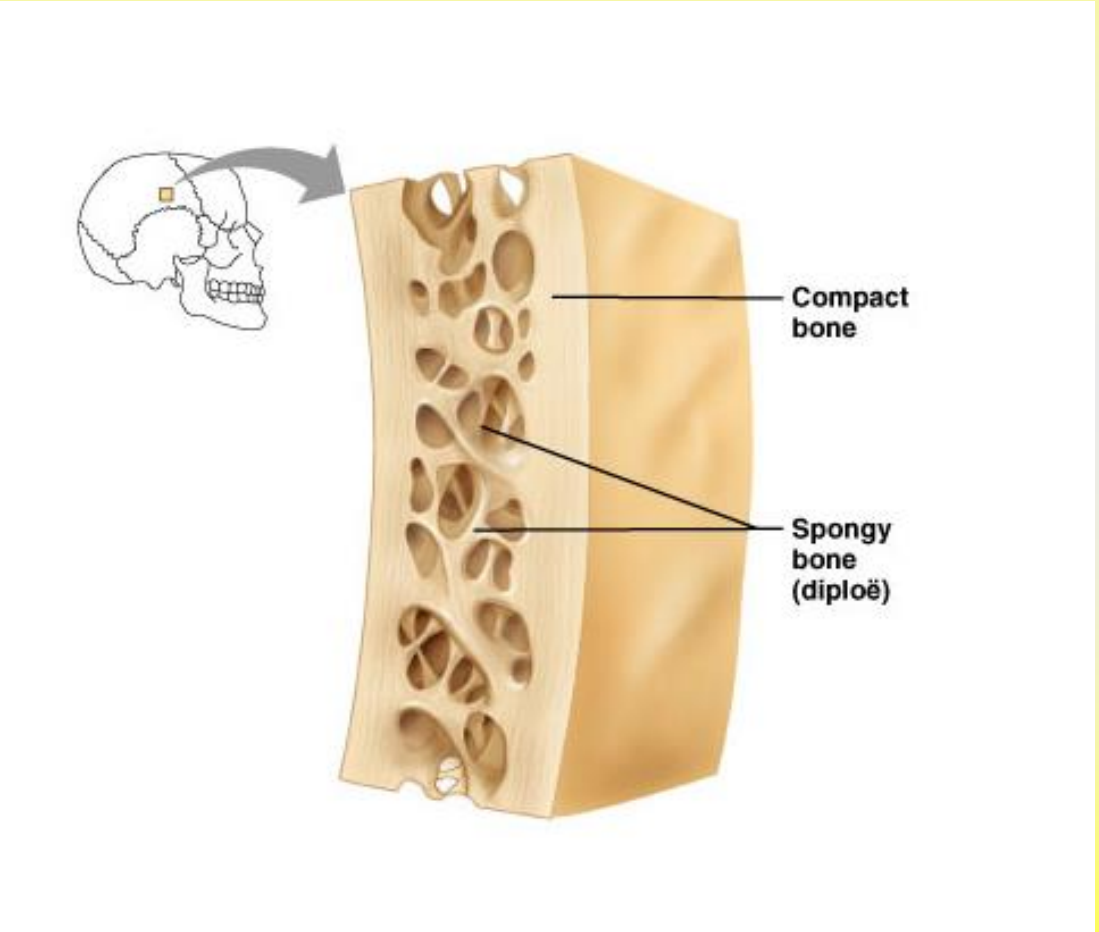
anatomy of bones

- Compact bone
- Spongy (trabecular) bone
- Blood vessels
- Medullary cavity
- Membranes
  - Periosteum
  - Endosteum

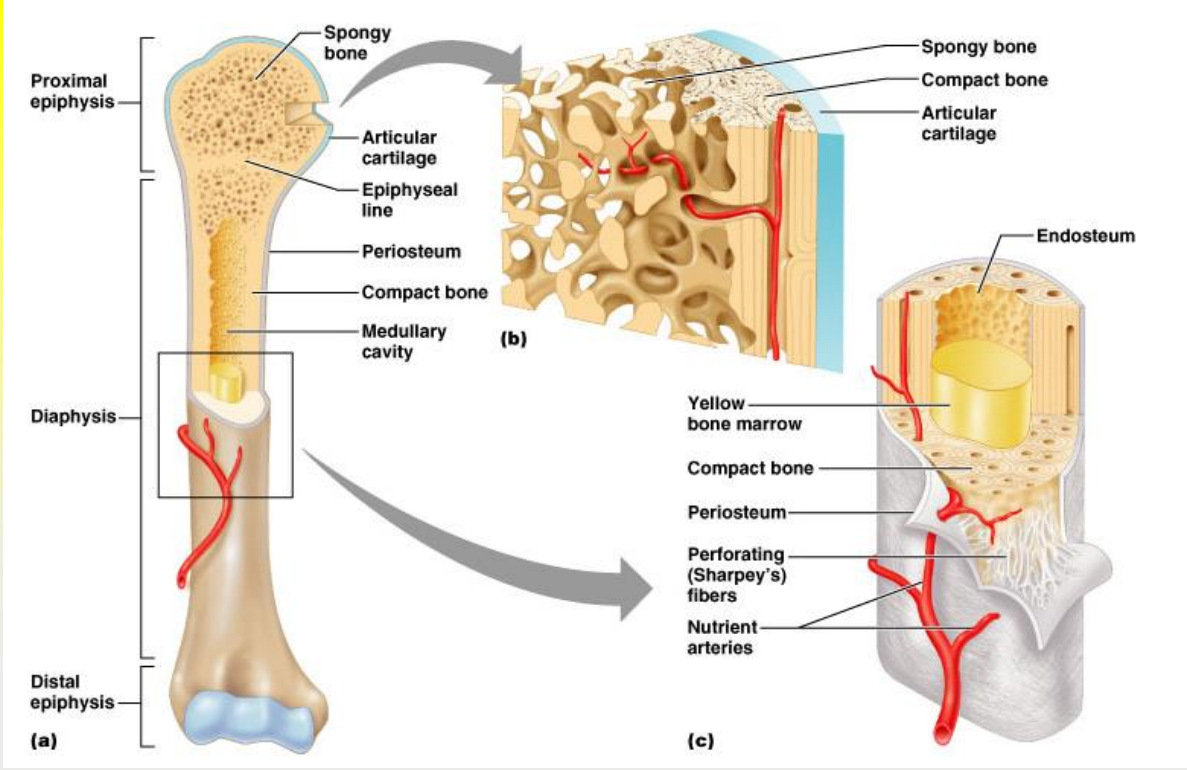


Flat bones

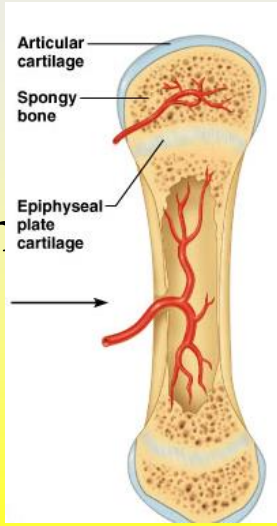
- Spongy bone is called diploe when its in flat bones
  - Have bone marrow but no marrow cavity



Long bones



- Tubular ***diaphysis*** or shaft
- ***Epiphyses*** at the ends: covered with "articular" (=joint) cartilage
- Epiphyseal line in adults
  - Kids: epiphyseal growth *plate* (disc of hyaline cartilage th grows to lengthen the bone)
- Blood vessels
  - Nutrient arteries and veins through nutrient foramen

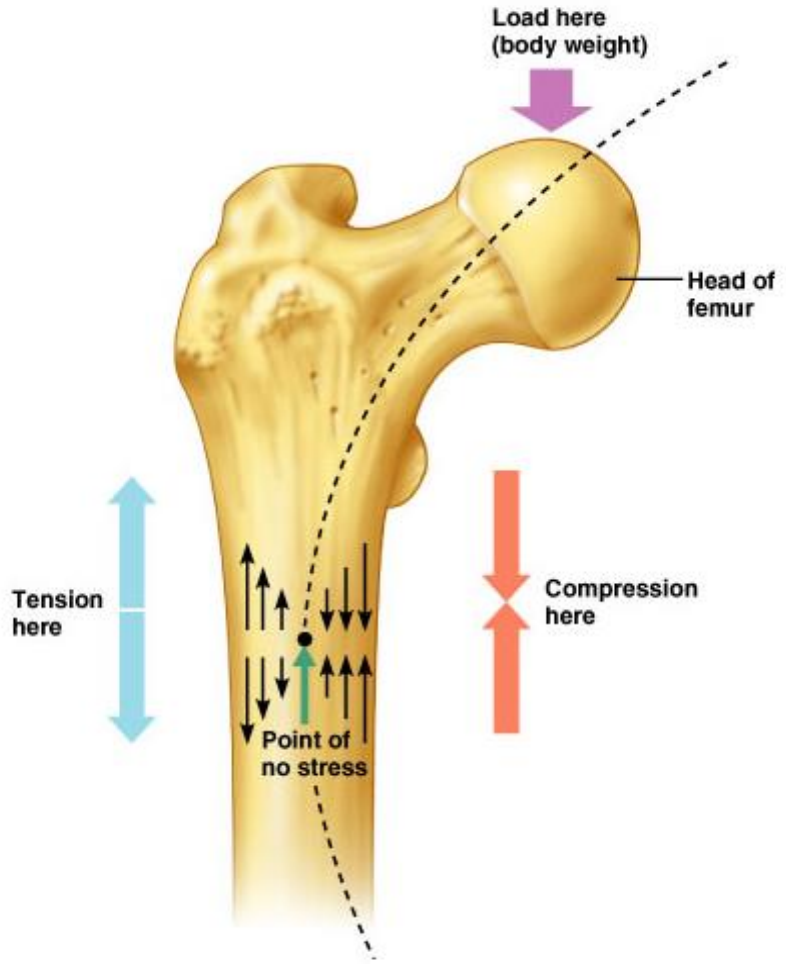


Periosteum

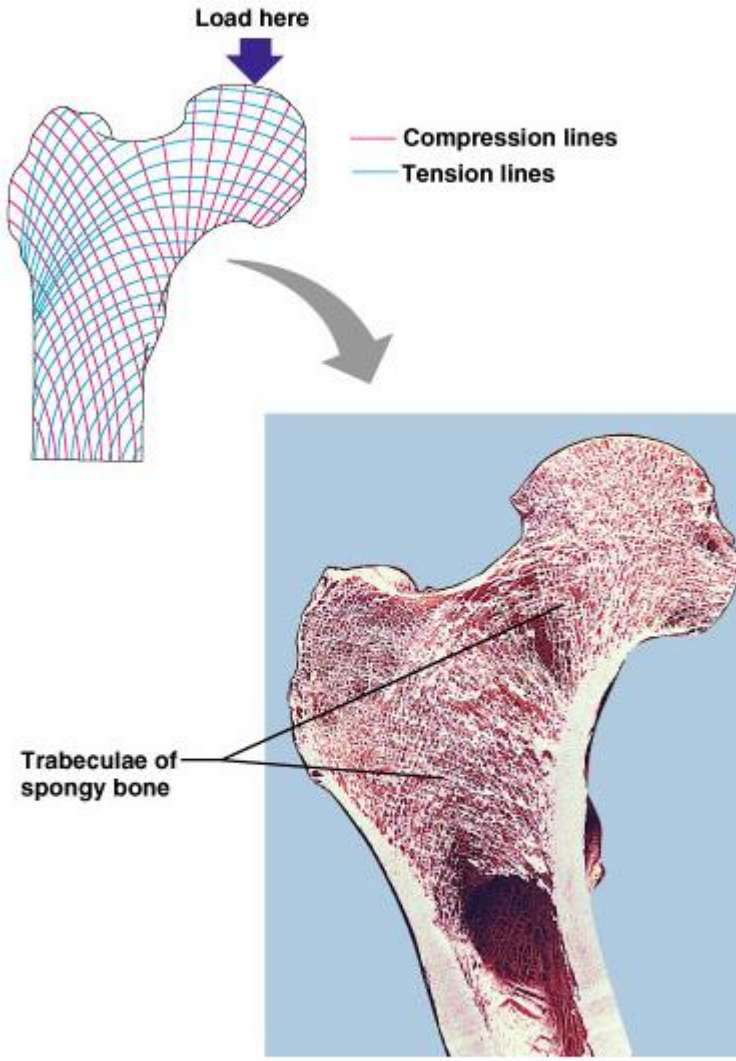
- Connective tissue membrane
- Covers entire outer surface of bone except at epiphyses
- Two sublayers
  - 1. Outer fibrous layer of dense irregular connective tissue
  - 2. Inner (deep) cellular ***osteogenic*** layer on the compact bone containing osteoprogenitor cells (stem cells that give rise to osteoblasts)
    - ***Osteoblasts***: bone depositing cells
    - Also ***osteoclasts***: bone destroying cells (from the white blood cell line)
- Secured to bone by perforating fibers (Sharpey's fibers)

Endosteum

- Covers the internal bone surfaces
- Is also ***osteogenic***


Load here
(body weight)
Head of
femur
Tension
here
Compression
here
Point of
no stress

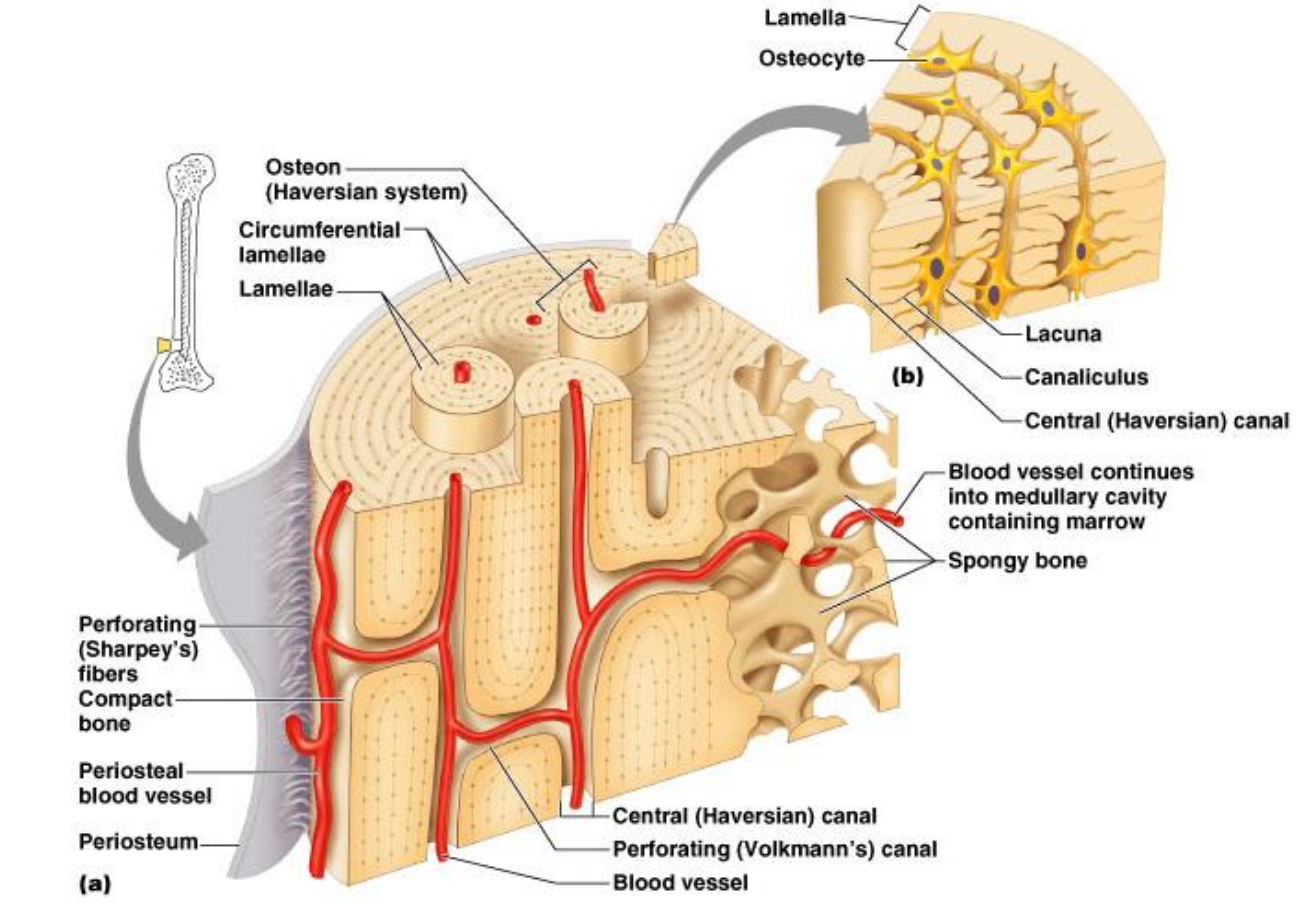
(a)


Load here
Compression lines
Tension lines
Trabeculae of
spongy bone

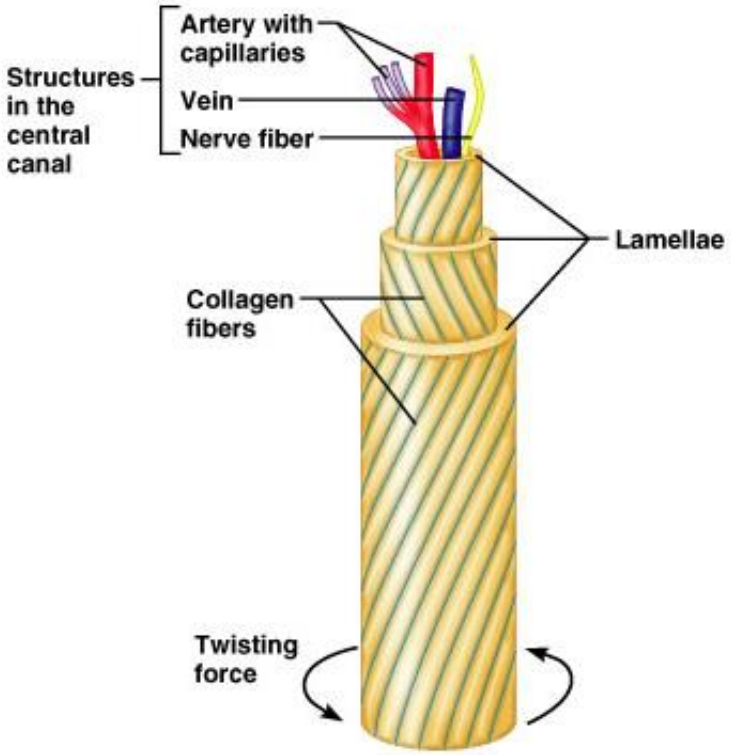
(b)

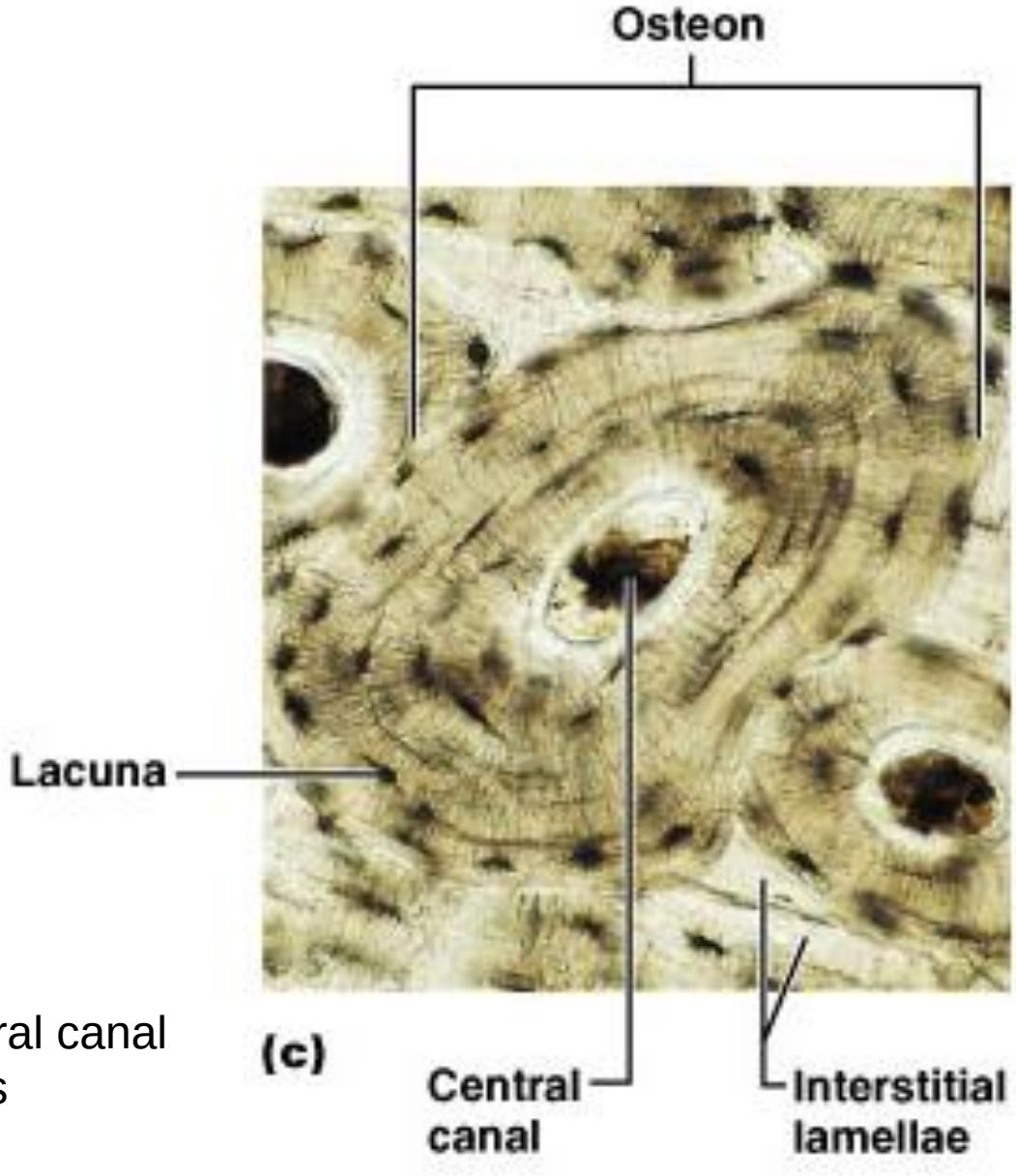
Compact bone

- Osteons: pilla
- Lamellae: concentric tubes
- Haversian canals
- Osteocytes



Isolated osteon:

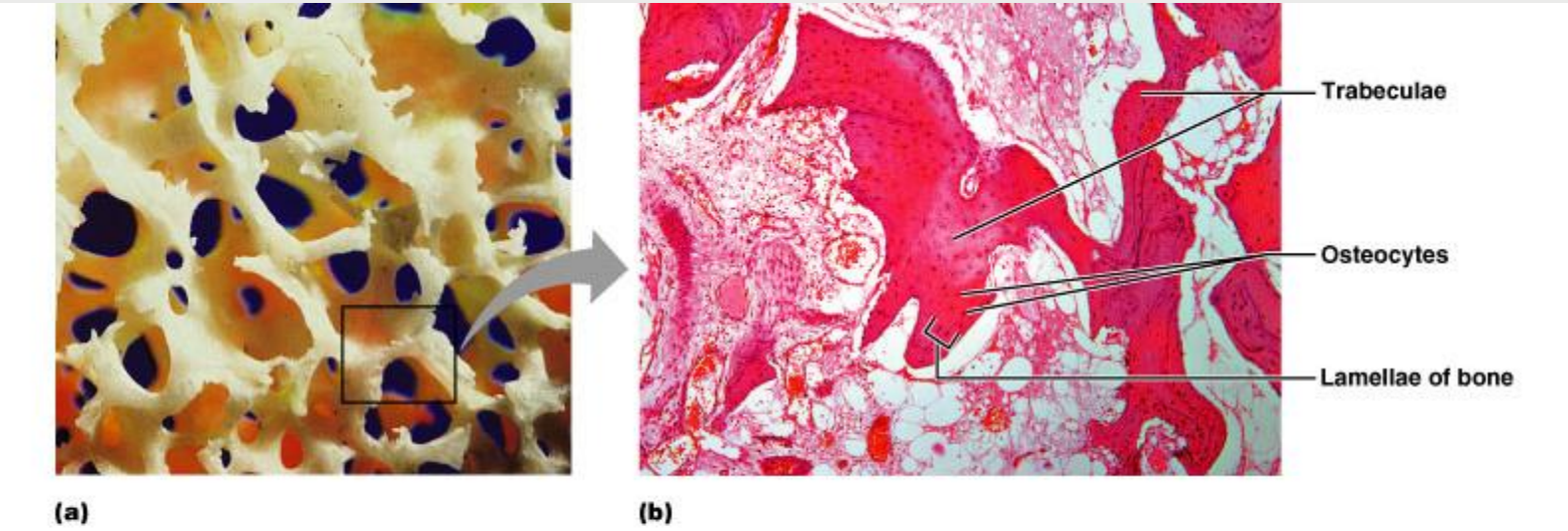




- Nutrients diffuse from vessels in central canal
- Alternating direction of collagen fibers increases resistance to twisting forces

Spongy bone

- Layers of lamellae and osteocytes
- Seem to align along stress lines



Chemical composition of bones

- Cells, matrix of collagen fibers and ground substance (organic: 35%)
  - Contribute to the flexibility and tensile strength
- Mineral crystals (inorganic: 65%)
  - Primarily calcium phosphate
  - Lie in and around the collagen fibrils in extracellular matrix
  - Contribute to bone hardness
- Small amount of water

Bone development

- Osteogenesis: “formation of bone”
  - From osteoblasts
  - Bone tissue first appears in week 8 (embryo)
- Ossification: “to turn into bone”
  - ***Intramembranous*** ossification (also called “dermal” since occurs deep in dermis): forms directly from mesenchyme (not modeled first in cartilage)
    - Most skull bones except a few at base
    - Clavicles (collar bones)
    - Sesamoid bones (like the patella)
  - ***Endochondral*** ossification: modeled in hyaline cartilage then replaced by bone tissue
    - All the rest of the bones

Three germ tissues

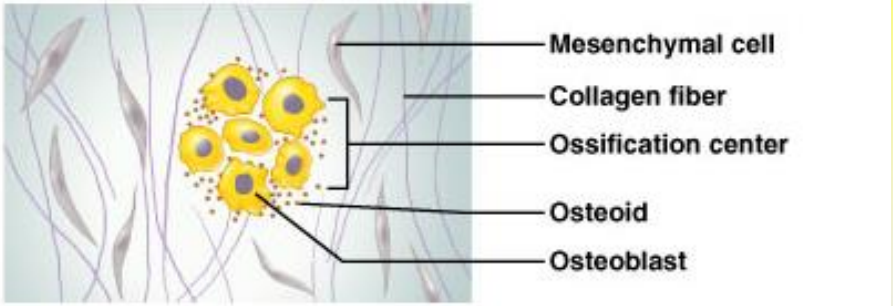
1. Ectoderm - epithelial
2. Endoderm - epithelial
3. Mesoderm is a mesenchyme tissue
   - Mesenchyme cells are star shaped and do not attach to one another, therefore migrate freely

   - From the last slide:

Intramembranous ossification: forms directly from mesenchyme (not modeled first in cartilage)

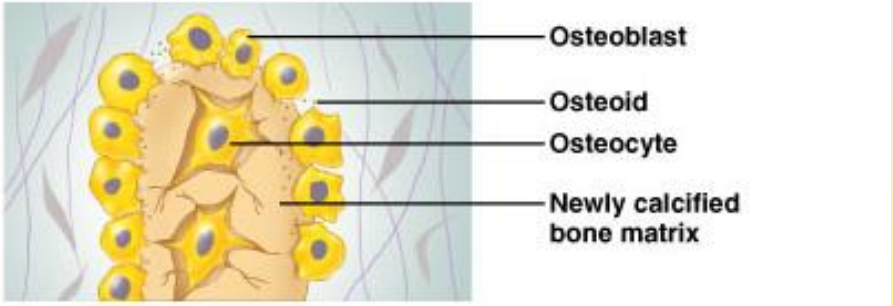
- Most skull bones except a few at base
- Clavicles (collar bones)
- Sesmoid bones (like the patella)

Intramembranous ossification



① An ossification center appears in the fibrous connective tissue membrane.

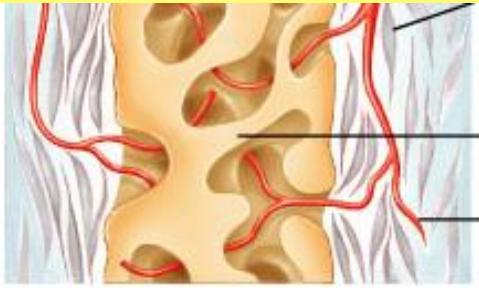
- Selected centrally located mesenchymal cells cluster and differentiate into osteoblasts, forming an ossification center.



② Bone matrix (osteoid) is secreted within the fibrous membrane.

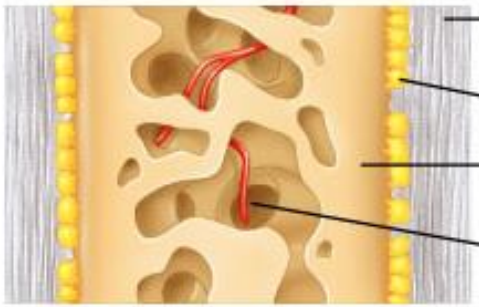
- Osteoblasts begin to secrete osteoid, which is mineralized within a few days.
- Trapped osteoblasts become osteocytes.

(osteoid is the organic part)



③ Woven bone and periosteum form.

- Accumulating osteoid is laid down between embryonic blood vessels, which form a random network. The result is a network (instead of lamellae) of trabeculae.
- Vascularized mesenchyme condenses on the external face of the woven bone and becomes the periosteum.



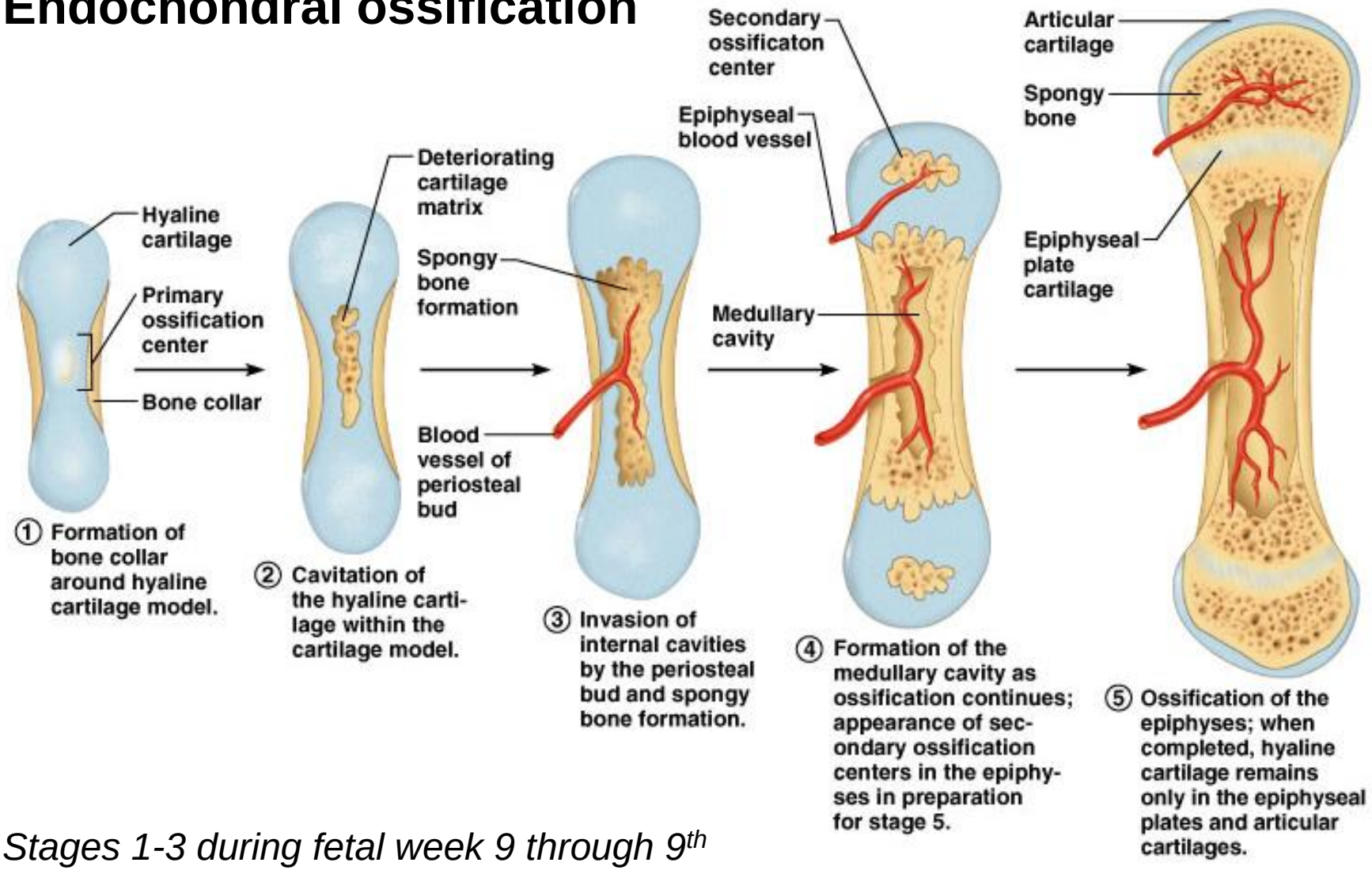
④ Bone collar of compact bone forms and red marrow appears.

- Trabeculae just deep to the periosteum thicken, forming a woven bone collar that is later replaced with mature lamellar bone.
- Spongy bone (diploë), consisting of distinct trabeculae, persists internally and its vascular tissue becomes red marrow.

Endochondral ossification

- Modeled in hyaline cartilage, called ***cartilage model***
- Gradually replaced by bone: begins late in second month of development
- ***Perichondrium*** is invaded by vessels and becomes ***periosteum***
- ***Osteoblasts*** in periosteum lay down collar of bone around diaphysis
- Calcification in center of diaphysis
- Primary ossification centers
- Secondary ossification in epiphyses
- Epiphyseal growth plates close at end of adolescence
  - Diaphysis and epiphysis fuse
  - No more bone lengthening

Endochondral ossification

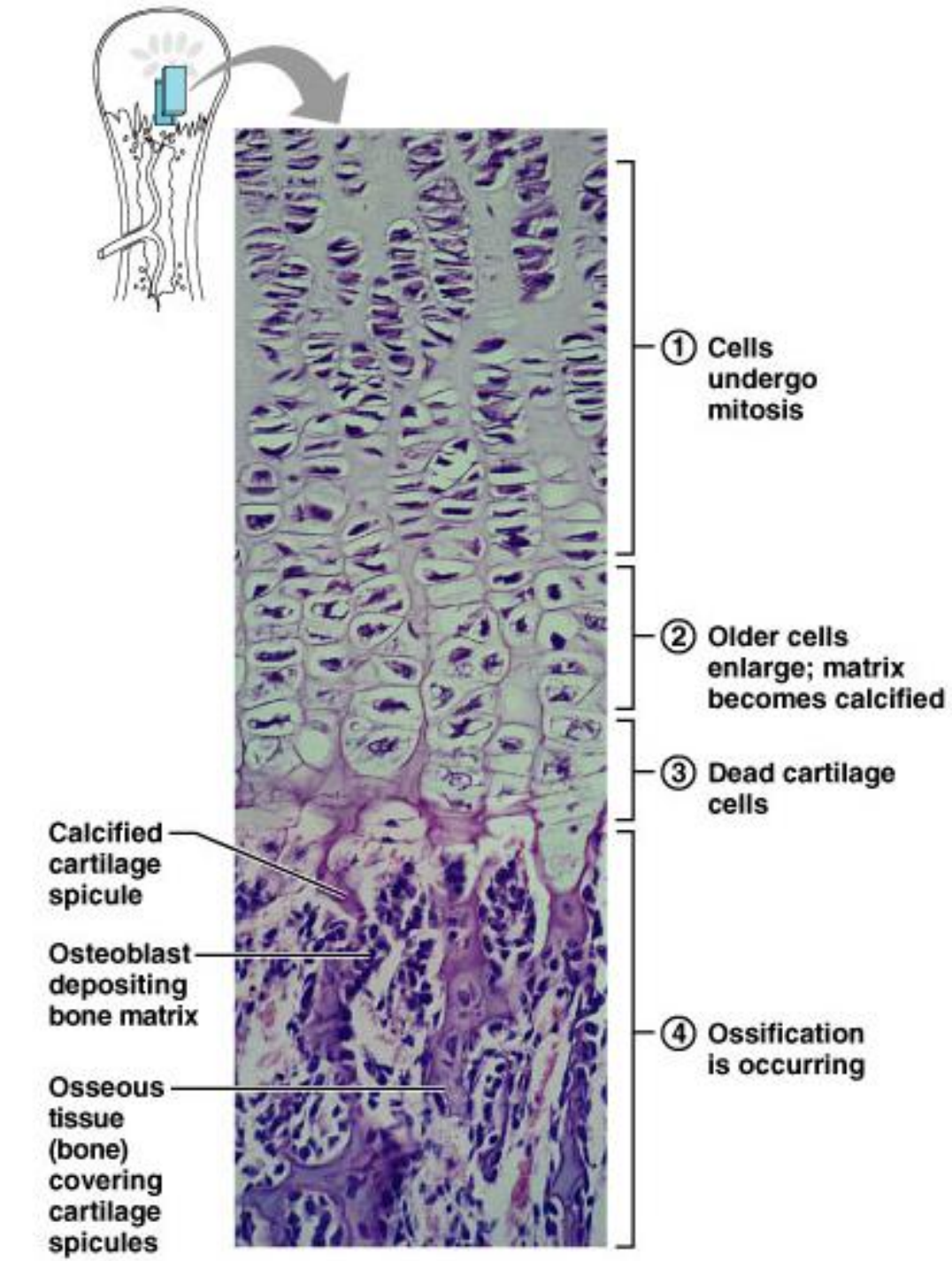


Stages 1-3 during fetal week 9 through 9th month

Stage 4 is just before birth

Stage 5 is process of long bone growth during childhood & adolescence

Organization of cartilage within the epiphyseal plate of a growing long bone



Epiphyseal growth *plates* in child, left, and *lines* in adult, right (see arrows)

(a)

(b)

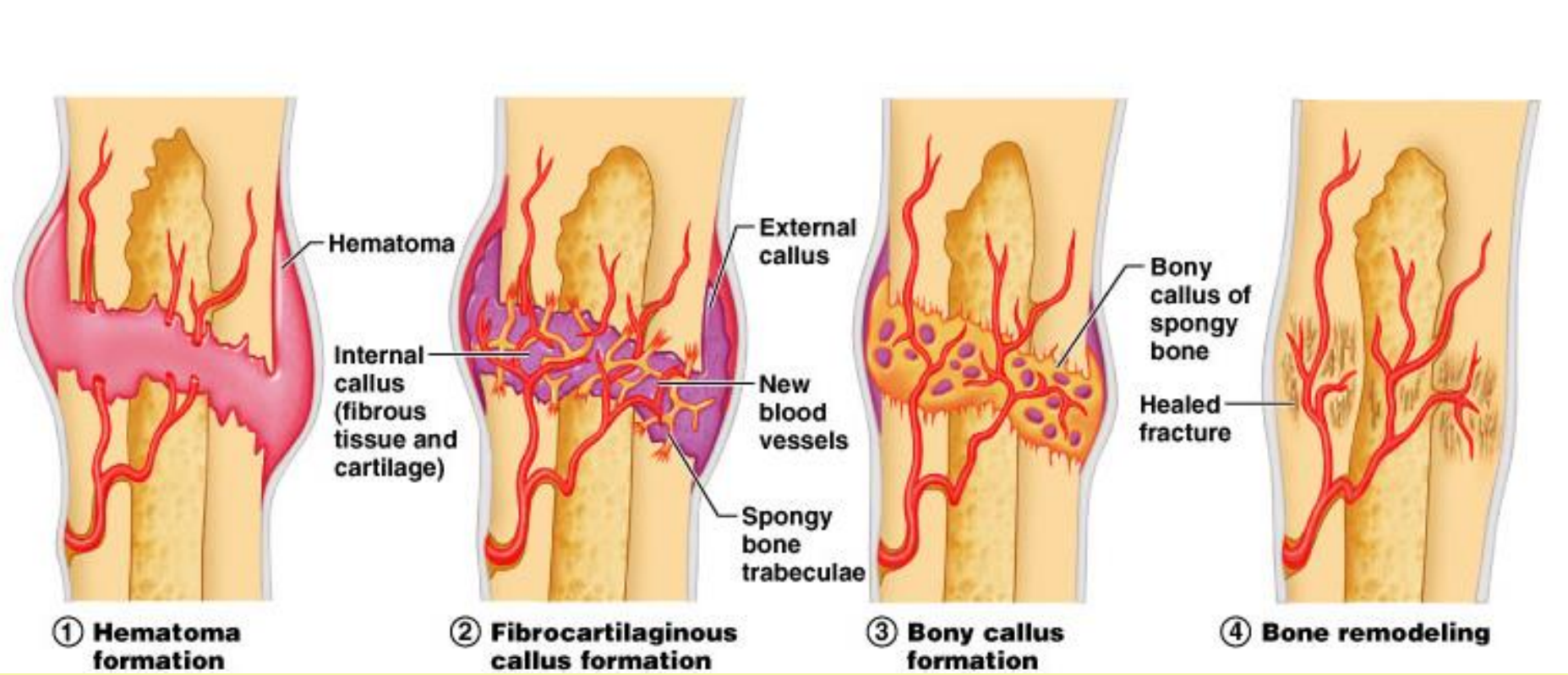
Factors regulating bone growth

- Vitamin D: increases calcium from gut
- Parathyroid hormone (PTH): increases blood calcium (some of this comes out of bone)
- Calcitonin: decreases blood calcium (opposes PTH)
- Growth hormone & thyroid hormone: modulate bone growth
- Sex hormones: growth spurt at adolescense and closure of epiphyses

Bone remodeling

- Osteoclasts
  - Bone resorption
- Osteoblasts
  - Bone deposition
- Triggers
  - Hormonal: parathyroid hormone
  - Mechanical stress
- Osteocytes are transformed osteoblasts

Repair of bone fractures (breaks)



- Simple and compound fractures
- Closed and open reduction

Disorders of cartilage and bone

- Defective collagen
  - Numerous genetic disorders
  - eg. Osteogenesis imperfecta (brittle bones) – AD (autosomal dominant)
  - eg. Ehlers-Danlos (rubber man)
- Defective endochondral ossification
  - eg. Achondroplasia (short –limb dwarfism) - AD
- Inadequate calcification (requires calcium and vitamin D)
  - Osteomalacia (soft bones) in adults
  - Rickets in children
- Pagets disease – excessive turnover, abnormal bone
- Osteosarcoma – bone cancer, affecting children primarily
- Osteoporosis – usually age related, esp. females
  - Low bone mass and increased fractures
  - Resorption outpaces bone deposition

Normal bone

(a)

Osteoporotic bone

(b)

Terms (examples)

- **chondro** refers to cartilage
  - chondrocyte
  - endochondral
  - perichondrium
- **osteo** refers to bone
  - osteogenesis
  - osteocyte
  - periostium
- **blast** refers to precursor cell or one that produces something
  - osteoblast
- **cyte** refers to cell
  - osteocyte