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LIGHT AND ELECTRON MICROSCOPIC APPEARANCES OF THE CELL

Preparation of Tissues for Study

- Chemical fixatives such as formalin are used to preserve tissue structure by cross-linking and denaturing proteins, inactivating enzymes, and preventing cell autolysis or self-digestion.
- Dehydration of the fixed tissue in alcohol and clearing in organic solvents prepare it for embedding and sectioning.
- Embedding in paraffin wax or epoxy resin allows the tissue to be cut into very thin sections (slices) with a microtome.
- Sections are mounted on glass slides for staining, which is required to reveal specific cellular and tissue components with the microscope.
- The most commonly used staining method is a combination of the stains hematoxylin and eosin (H&E), which act as basic and acidic dyes, respectively.
- Cell substances with a net negative (anionic) charge, such as DNA and RNA, react strongly with hematoxylin and basic stains; such material is said to be “basophilic.”
- Cationic substances, such as collagen and many cytoplasmic proteins react with eosin and other acidic stains and are said to be “acidophilic.”

Light Microscopy

- Bright-field microscopy, the method most commonly used by both students and pathologists, uses ordinary light and the colors are imparted by tissue staining.
- Fluorescence microscopy uses ultraviolet light, under which only fluorescent molecules are visible, allowing localization of fluorescent probes which can be much more specific than routine stains.
- Phase-contrast microscopy uses the differences in refractive index of various natural cell and tissue components to produce an image without staining, allowing observation of living cells.
- Confocal microscopy involves scanning the specimen at successive focal planes with a focused light beam, often from a laser, and produces a 3D reconstruction from the images.

Autoradiography

- This process localizes cell components synthesized using radioactive precursors by detecting silver grains produced by weakly emitted radiation in a photographic emulsion coating the tissue section or cells.
- With either light microscopy or TEM, autoradiography permits unique studies of processes such as tissue growth (using radioactive DNA precursors) or cellular pathways of macromolecular synthesis.

Cell & Tissue Culture

- Cells can be grown in vitro from newly explanted tissues (primary cultures) or as long-established cell lines and can be examined in the living state by phase-contrast light microscopy.
- ### Enzyme Histochemistry
- Histochemical (or cytochemical) techniques use specific enzymatic activities in lightly fixed or unfixed tissue sections to produce visible products in the specific enzyme locations.
 - Fixation and paraffin embedding denatures most enzymes, so histochemistry usually uses frozen tissue sectioned with a cryostat.
 - Enzyme classes for which histochemical study is useful include phosphatases, dehydrogenases, and peroxidases, with peroxidase often conjugated to antibodies used in immunohistochemistry.

Visualizing Specific Molecules

- Some substances specifically bind certain targets in cells.
- Immunohistochemistry is based on specific reactions between an antigen and antibodies labeled with visible markers, often fluorescent compounds or peroxidase for light microscopy and gold particles for TEM.
- If the cell or tissue antigen of interest is detected by directly binding a labeled primary antibody specific for that antigen, the process is considered direct immunohistochemistry.
- Indirect immunohistochemistry uses an unlabeled primary antibody that is detected bound to its antigen with labeled secondary antibodies.
- The indirect immunohistochemical method is more commonly used because the added level of antibody binding amplifies the signal detected and provides greater technical flexibility.
- Specific gene sequences or mRNAs of cells can be detected microscopically using labeled complementary DNA (cDNA) probes in a technique called in situ hybridization (ISH).

Interpretation of Structures in Tissue Sections

- Many steps in tissue processing, slide preparation, and staining can introduce minor artifacts such as spaces and precipitates that are not normally present in the living tissue and must be recognized.
- Sections of cells or tissues are essentially 2D planes through 3D structures, and understanding this fact is important for their correct interpretation and study.

QUESTIONS

1. In preparing tissue for routine light microscopic study, which procedure immediately precedes clearing the specimen with an organic solvent?
a. Dehydration b. Fixation c. Staining d. Clearing e. Embedding
2. Which of the following staining procedures relies on the cationic and anionic properties of the material to be stained?
a. Enzyme histochemistry
b. Periodic acid-Schiff reaction
c. Hematoxylin & eosin staining
d. Immunohistochemistry
e. Metal impregnation techniques
3. In a light microscope used for histology, resolution and magnification of cells are largely dependent on which component?
a. Condenser
b. Objective lens
c. Eyepieces or ocular lenses
d. Specimen slide
e. The control for illumination intensity
4. Cellular storage deposits of glycogen, a free polysaccharide, could best be detected histologically using what procedure?
a. Autoradiography
b. Electron microscopy
c. Enzyme histochemistry
d. Hematoxylin & eosin staining
e. Periodic acid-Schiff reaction

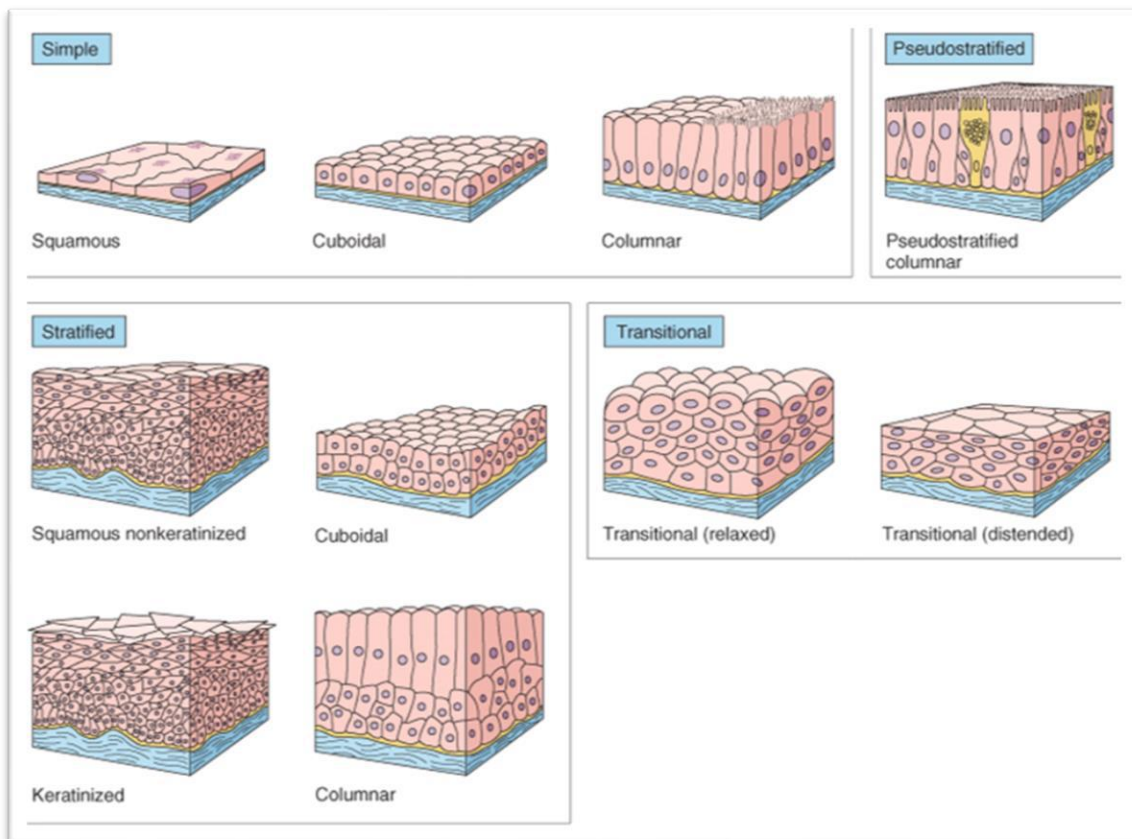
5. Adding heavy metal compounds to the fixative and ultrathin sectioning of the embedded tissue with a glass knife are techniques used for which histological procedure?
- Scanning electron microscopy
 - Fluorescent microscopy
 - Enzyme histochemistry
 - Confocal microscopy
 - Transmission electron microscopy
6. Resolution in electron microscopy greatly exceeds that of light microscopy due to which of the following?
- The wavelength of the electrons in the microscope beam is shorter than that of a beam of light.
 - The lenses of an electron microscope are of greatly improved quality.
 - For electron microscopy the tissue specimen does not require staining.
 - The electron microscope allows much greater magnification of a projected image than a light microscope provides.
 - An electron microscope can be much more finely controlled than a light microscope.
7. Microscopic autoradiography uses radioactivity and can be employed to study what features in a tissue section?
- The types of enzymes found in various cell locations
 - Cellular sites where various macromolecules are synthesized
 - The sequences of mRNA made in the cells
 - The dimensions of structures within the cells
 - The locations of genes transcribed for specific mRNA
8. To identify and localize a specific protein within cells or the extracellular matrix one would best use what approach?
- Autoradiography
 - Enzyme histochemistry
 - Immunohistochemistry
 - Transmission electron microscopy
 - Polarizing microscopy
9. In situ hybridization is a histological technique used to visualize what type of macromolecule?
- Proteins
 - Carbohydrates
 - Certain enzymes
 - Nucleic acids
 - Lipids
10. Hospital laboratories frequently use unfixed, frozen tissue specimens sectioned with a cryostat for rapid staining, microscopic examination, and diagnosis of pathological conditions. Besides saving much time by avoiding fixation and procedures required for paraffin embedding, frozen sections retain and allow study of what macromolecules normally lost in the paraffin procedure?
- Carbohydrates
 - Small mRNA
 - Basic proteins
 - Acidic proteins
 - Lipids

Answers: 1a, 2c, 3b, 4e, 5e, 6a, 7b, 8c, 9d, 10e

EPITHELIAL TISSUE

- × Derived from all three embryonic germ layers;
 - Ectoderm: oral and nasal mucosae, cornea, epidermis of the skin, and glands of the skin and the mammary glands
 - Endoderm: liver, the pancreas, and the lining of the respiratory and gastrointestinal tract
 - Mesoderm: uriniferous tubules of the kidney, the lining of the male and female reproductive systems, the endothelial lining of the circulatory system, and the mesothelium of the body cavities
- × Functions
 - Protection
 - Transcellular transport
 - Secretion
 - Absorption
 - Selective permeability
 - Detection and sensation¹
- × Basal lamina
 - separated from the underlying connective tissue by an extracellular matrix
 - synthesized by the epithelial cells
- × Cell arrangement and morphology are the bases of classification of epithelium.
- × Epithelium is avascular (lack of blood vessels)
- × Bitişigindeki destekleyici bağ dokusu bazal lamina boyunca difüzyonla beslenme ve oksijen sağlar.
- × Importance of layering
 - Multilayered:
 - Protect against friction and injury
 - Barrier to water, disease some toxins etc.
 - Lower layers regenerate upper layers
 - Single layered:
 - Communication / Gateway
 - Important in regulated transport of cells/molecules
- × Classified number of cells
 - Simple Epithelium: single layer
 - Stratified Epithelium: more than one layer
- × Classified morphology of cells
 - squamous (flat)
 - cuboidal
 - columnar
- × 2 distinct types
 - pseudostratified
 - transitional

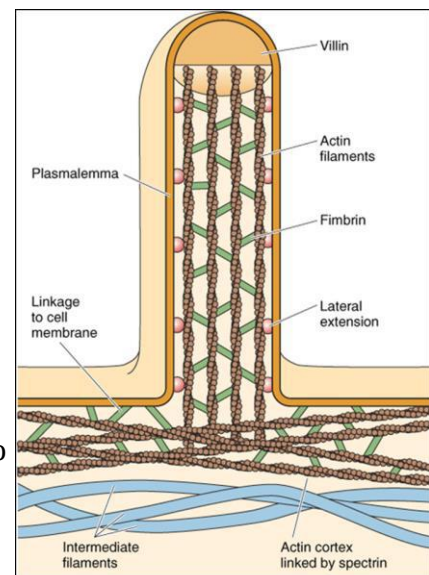
1 Detection: Keşif



- × Simple Squamous Epithelium
 - single layer of tightly packed
 - pulmonary alveoli, Bowman's capsule, endothelial lining of blood and lymph vessels
- × Simple Cuboidal Epithelium
 - single layer (polygon-shaped cells)
 - perpendicular section → square
 - ducts of many glands of the body, covering of the ovary, some kidney tubules.
- × Simple Columnar Epithelium
 - single layer (tall)
 - longitudinal section → rectangular¹
 - ovoid nuclei
 - digestive tract, gallbladder and large ducts of glands
 - microvilli
 - Ciliated in → uterus, oviducts, ductuli efferentes, and small bronchi
- × Stratified Squamous Epithelium (Nonkeratinized)
 - thick, multilayered
 - deepest layer is in contact with the basal lamina
 - usually wet
 - mouth, oral pharynx, esophagus, true vocal folds, and vagina

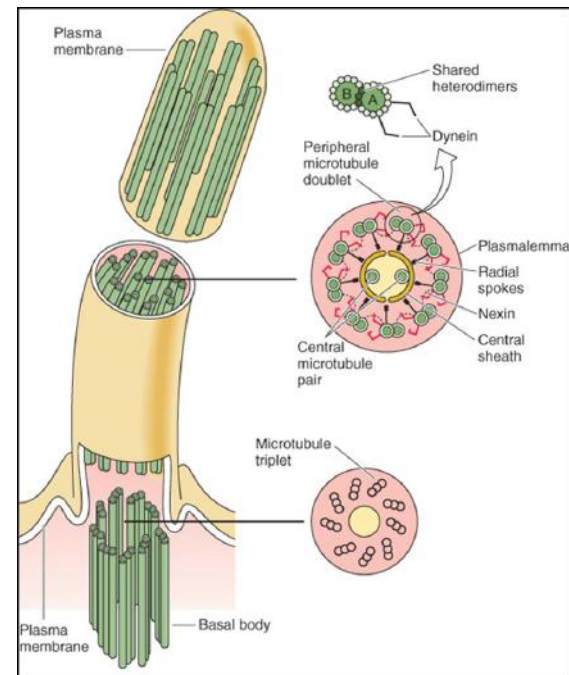
¹ Dikdörtgen biçiminde

- × Stratified Squamous Epithelium (Keratinized)
 - similar to stratified squamous epithelium nonkeratinized epithelium
 - tek farkı epitelin yüzeysel tabakasıdır, nuclei ve sitoplazması keratinleşmiş ölü hücrelerden oluşur
 - constitutes the epidermis of skin, a tough layer that resists friction and is impermeable to water
- × Stratified Columnar Epithelium
 - superficial layer → columnar
 - conjunctiva of the eye, certain large excretory ducts, and regions of the male urethra.
- × Transitional Epithelium
 - surface layer → large & dome-shaped
 - transition between stratified columnar and stratified squamous epithelia
 - when the bladder is distended, dome-shaped cells become flattened and the epithelium becomes thinner
- × Pseudostratified Columnar Epithelium
 - all cells contact with basal lamina but some cells reach the surface of epithelium
 - yüzeye ulaşamayan hücrelerin tabanı genişken apikal uca doğru darlaşır
 - single layer olmasına rağmen stratified epithelium izlenimi verir
 - male urethra, epididymis, and larger excretory ducts of gland
 - ciliated (most widespread type) → trachea and primary bronchi, the auditory tube, part of the tympanic cavity, the nasal cavity, and the lacrimal sac
- × Polarity and Cell-Surface Specializations
 - polarized cells possess;
 - apical domain
 - basolateral domain
 - apical and basolateral domains are separated from each other by tight junctions
- × **Apical Domain**
 - free surface of epithelial cells
 - rich in aquaporins, ion channels, carrier proteins, H⁺-ATPase etc.
 - secretory products are delivered for release
 - Types;
 - microvilli (associated glycocalyx)
 - stereocilia
 - cilia
 - flagella (insanda sadece spermatozoa’da var)
- × Microvilli
 - striated border of the intestinal absorptive cells
 - brush border of the kidney proximal tubule cells
 - contain actin filament
 - crosslinked by villin
 - embedded in terminal web
 - myosin-I and calmodulin → connect the actin filaments to the plasma membrane of microvillus
 - epithelia not functioning in absorption or transport may exhibit microvilli without cores of actin filaments



- × Stereocilia
 - long microvilli
 - only in the epididymis and on the sensory hair cells of the cochlea (inner ear)

- × Cilia
 - long, motile, hair-like
 - respiratory system (e.g., trachea and bronchi) and in the oviduct; single cilium in the hair cells of the vestibular apparatus in the inner ear (functions in a sensory mechanism)
 - in the respiratory tree move mucus and debris toward the oropharynx
 - in the oviduct move the fertilized ovum toward the uterus
 - axoneme: core of the cilium contains a complex of uniformly arranged microtubules
 - axoneme → 9 + 2 (2 singlet central microtubules surrounded by 9 doublets microtubules)
 - radial → spoke subunit A ile central sheat'i bağlar
 - nexin → connected the doublets
 - dynein → microtubule-associated protein
 - basal body → 9 triplets and no singlets
 - Basal bodies develop from procentriole organizers

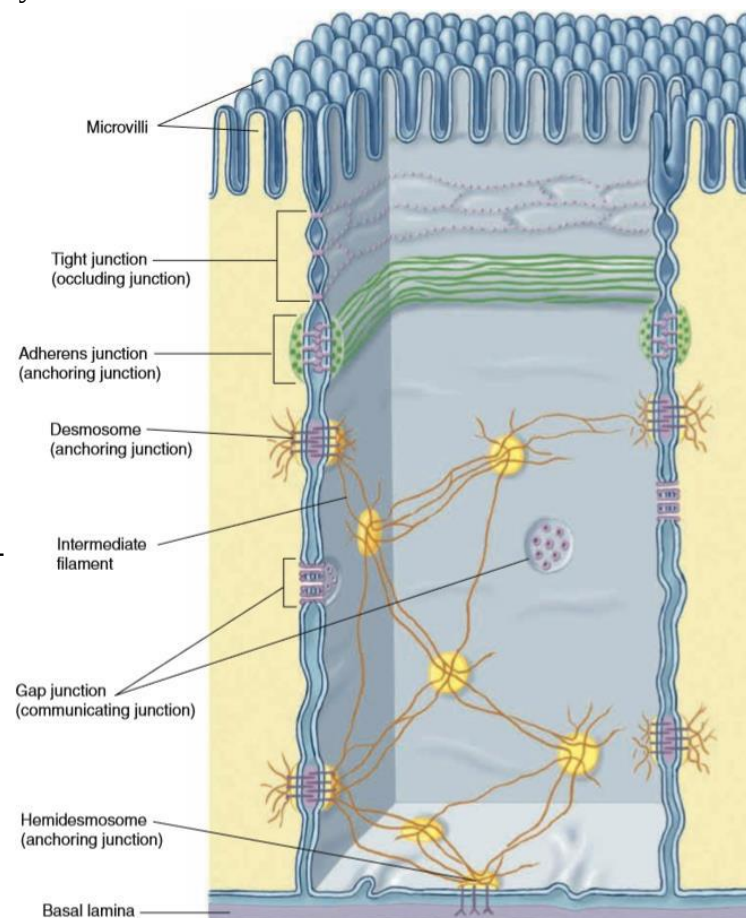


- × Kartagener's syndrome
 - Results from hereditary defects in the ciliary dynein
 - Lung infections
 - Immotile sperm

- × **Basolateral Domain**
 - two regions;
 - the lateral plasma membrane
 - the basal plasma membrane
 - receptors for hormones and neurotransmitters.

- × Lateral Membrane Specializations
 - Occluding junctions → impermeable barrier, preventing material from taking an intercellular
 - Anchoring junctions → cell-to-cell or cell-to-basal lamina adherence.
 - Communicating junctions → permitting movement of ions or signaling molecules between cells

- × Zonulae Occludentes¹ (Tight junctions)
 - *prevent movement of membrane proteins*
 - *prevent intercellular movement of water-soluble molecules*



¹ Occluding: Tıkayıcı

- circumference of the cell
- "belt-like" junction
- füzyon bölgelerinde, claudins ve occludins proteinleri birbirine bağlanır
- kontaktları cadherin ve zonula accludens proteins ile güçlendirilir
- Functions:
 - they prevent the movement of membrane proteins from the apical domain to the basolateral domain
 - they fuse plasma membranes of adjacent cells to prohibit water-soluble molecules from passing between cells
- some tight junctions are “tight”, whereas others are “leaky”¹

× Zonulae Adherentes

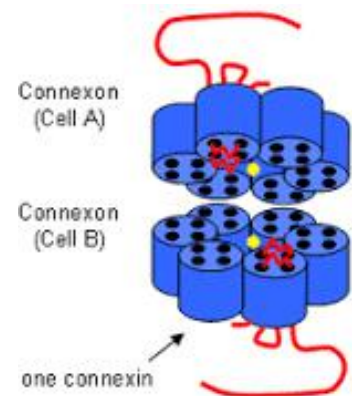
- Basal to zonulae occludentes
- Cadherins bind to each other in the intercellular space and bind to actin filaments
- Cadherins → Intercellular boşluğu doldurur ve transmembrane linker proteindir
- Fascia adherens is similar to zonula adherens but does not go around the entire circumference of the cell.
 - Cardiac muscle cells are attached to each other at their longitudinal terminals via the fascia adherens.

× Desmosomes (Maculae Adherentes)

- Lateral membrane
- Help the resist² force
- Cadherins associated with plaque
- Disk şeklindeki bağlantı plakları ile bitişik epiteldeki mambranın yönleri karşılıklıdır
- Intermediate filaments → insert into the plaque
- filamentous material → desmoglein and desmocollin
- transmembrane linker proteins bind to desmoplakins and pakoglobins
- Pemphigus vulgaris:
 - Binding of the autoantibodies to desmosomal proteins disrupts cell adhesion

× Gap Junctions (Nexus)

- Intercellular communication junctions
- widespread cardiac muscle cells, smooth muscle cells, and neurons
- *but NOT in skeletal muscle cells*
- occluding and anchoring junction’dan farkı → küçük moleküllerin geçmesine izin verir
- connexins → transmembrane channel-forming proteins
- connexon → 6 connexins
- opened and closed rapidly
- pH azalması ve Ca²⁺ artışın boşluk bağlantılarını kapatır
- pH artması ve Ca²⁺ azalması boşluk bağlantılarını açar
- Functions:
 - Cellular sharing of molecules
 - Electrical coupling of cells
 - Coupling the cells of the developing embryo



¹ Leaky: Sızdıran

² Resist: karşı koymak

- × Basal Surface Specialization
 - Three important features mark:
 - the basal lamina
 - plasma membrane enfolding
 - hemidesmosomes (anchor the basal plasma membrane to the basal lamina)
- × Basement membrane: separate underlying connective tissue by extracellular supporting layer
 - Basal lamina → consists of fine protein filaments (about 100 nm thick)
 - basal lamina acts as a selectively permeable filter between epithelium and connective tissue
 - Interwoven networks of laminin & collagen IV attached by Nidogen/Entactin
 - Reticular lamina → consists of reticular fibres
 - reticular lamina are synthesised by cells of the connective tissue underlying the epithelium
- × Plasma Membrane Enfoldings
 - *Increase the surface area available for transport.*
 - **striated ducts** → certain ducts of the pancreas and salivary glands
- × Hemidesmosomes
 - *basal cell membrane to basal lamina*
 - **Attachment plaques** → cytoplasmic aspect of the plasma membrane
 - **Keratin tonofilaments** insert into these plaques (unlike desmosome)
 - **transmembrane linker proteins** are attached to the plaque
 - extracellular moieties bind to **laminin** and **type IV collagen** of the basal lamina.
 - hemidesmosomes are **integrins**
 - desmosomes are cadherin
- × Renewal of Epithelial Cells
 - high turnover rate
 - renewed at the basal layer by cell division
 - bölünmeden ölüme kadar yaklaşık 28 gün
 - cells of small intestine are replaced every 4 to 6 days

GLANDULAR TISSUE

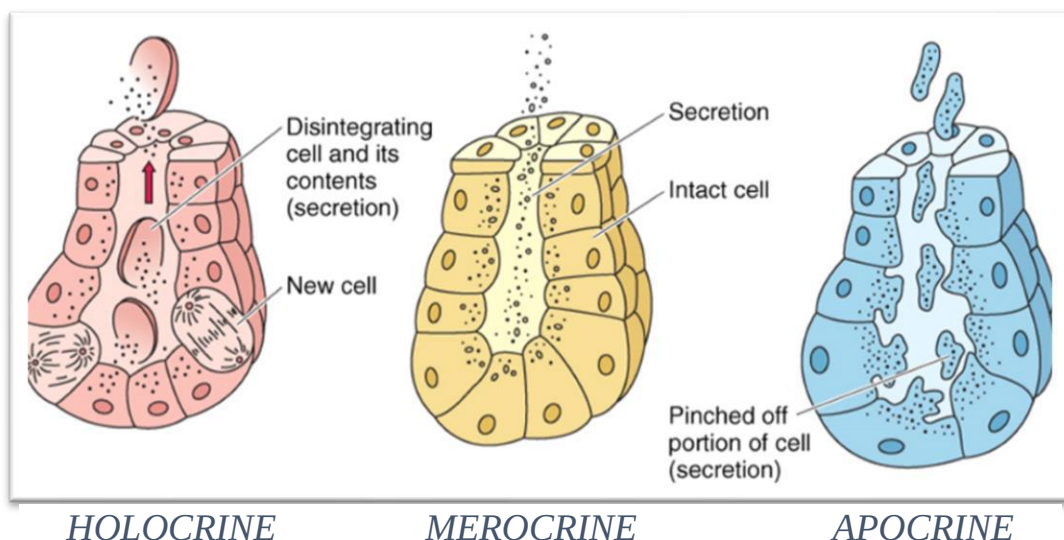
- × Originate from epithelial cells
- × Developed and penetrate into the underlying connective tissue
- × Manufacturing a basal lamina
- × **Parenchyma** → The secretory units, along with their ducts
- × **Stroma** → Elements of the connective tissue that invade¹ and support the parenchyma
- × **Secretory Granules** → Intracellular synthesis of macromolecules packaged
- × Salgı ürünleri 2 şekilde dağıtılır:
 - **Exocrine Glands**
 - Secrete via ducts.
 - Secrete to external/internal epithelial surface.
 - **Endocrine Glands**
 - Lost connection to epithelium
 - Ductless
 - Secrete to blood/lymphatic vessels
- × Secretory product:
 - A polypeptide hormone (e.g., from the pituitary gland)
 - A waxy substance (e.g., from the ceruminous glands of the ear canal)
 - A mucinogen (e.g., from the goblet cells)
 - Milk (e.g., from the mammary glands)
 - Other glands (such as sweat glands)
 - Striated ducts (e.g., of the major salivary glands)
- × Cytokines (signalling molecules)
 - cell-to-cell communication
 - Released by signaling cells and act on target cells
- × Types of signal (depending on distance)
 - **Autocrine**
 - Target: Cell itself
 - cell stimulates itself
 - **Paracrine**
 - Target: Close to signalling cell
 - cytokine does not have to enter the vascular system
 - **Endocrine**
 - Target: Far from signalling cell
 - cytokine is transported by the blood/the lymph vascular system
- × Constitutive² secretory pathway
 - Secrete continuously
 - Release immediately (without storage)
 - Release without requiring signalling molecules
- × Regulated secretory pathway
 - Concentrate and store products
 - Release with signalling molecule

¹ Invade: Saldırmak

² Constitutive: Temel, esas

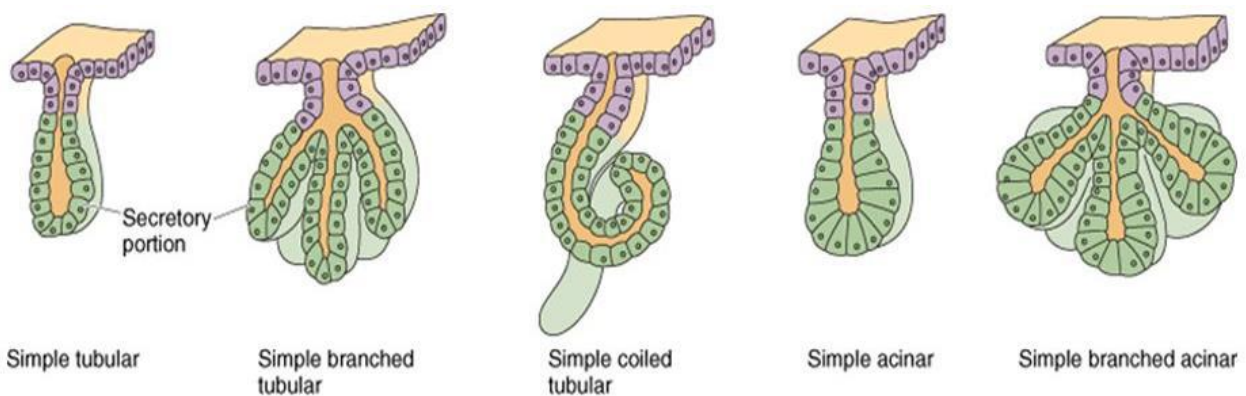
× *Exocrine Glands*

- Secrete their products via duct.
 - Classified according to;
 - Nature of their secretion (mucous, serous, or mixed)
 - Mode of secretion,
 - Number of cells (unicellular or multicellular)
- × **Mucous Glands**
- Secrete mucinogens
 - Mucins are glycoproteins which are major components of mucus
 - E.g. goblet cells and the minor salivary glands of the tongue and palate.
- × **Serous Glands**
- Secrete an enzyme-rich watery fluid
 - E.g. pancreas
- × **Mixed Glands**
- Contain acini (secretory units)
 - some of the mucous acini possess serous demilunes (group of cells that secrete a serous fluid)
 - E.g. sublingual and submandibular glands.
- × **Types of exocrine secretion (depending on mechanism)**
- **Merocrine Glands**
 - neither cell membrane nor cytoplasm becomes a part of the secretion
 - e.g. parotid gland
 - **Apocrine Glands**
 - A small portion of the apical cytoplasm is released along with the secretory product
 - e.g., lactating mammary gland
 - **Holocrine Glands**
 - As a secretory cell matures, it dies and becomes the secretory product
 - e.g. sebaceous gland

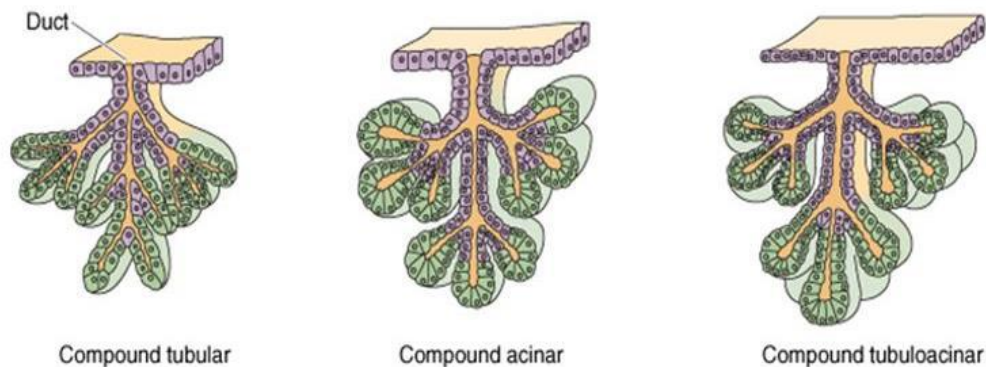


- × Unicellular Exocrine Glands
 - *The simplest form of exocrine gland*
 - isolated secretory cells
 - **Goblet cells**
 - digestive tract
 - portions of the respiratory tract
 - basal region → basal lamina
 - apical region (theca) → lumen of the digestive tube or respiratory tract
 - theca is filled secretory droplets
 - mucinogen release is regulated and stimulated by chemical irritation and parasympathetic innervation
- × Multicellular Exocrine Glands
 - *organized clusters of secretory units*
 - do not act alone
 - function as secretory organs
 - simple structure → glandular epithelium of the uterus and gastric mucosa
 - complex structure → organized in a compound branching fashion
 - Subclassified (depend on organization)
 - **Simple** → Their ducts do not branch.
 - **Compound** → Their ducts branch.
 - Subclassified (depend on morphology)
 - **Tubular**
 - **Acinar** (also referred to as **alveolar**, resembling a grape)
 - **Tubuloalveolar**

SIMPLE TYPES



COMPOUND TYPES



¹ Coiled: sarmal

² Puberty: Ergenlik

- lactating mammary gland
 - modified from skin
 - protein-rich
 - secretion stimulated by prolaktin
 - proteins → merocrine
 - lipids → apocrine
- } Secretion
- Combinations exist
 - pancreas → tubulo-acinar gland
 - Larger multicellular glands are surrounded by collagenous CT **capsule**
 - **septa** → strands of CT
 - Reticular CT → surrounds and supports secretory units of the glands
 - **myoepithelial cells**
 - origin epithelial
 - characteristics of smooth muscle cells (contractility)
 - contractions of myoepithelial → help secretion from acini (secretory unit)

× *Endocrine Glands*

- × Ductless
- × *released directly into the bloodstream/the lymphatic system*
- × Organization:
 - Discrete¹ endocrine glands
 - Hypophysis
 - Thyroid
 - Parathyroid
 - Adrenals
 - Pineal
 - Endocrine component of endocrine/exocrine glands
 - Pancreas - Islets of Langerhans
 - Ovary - Follicle, corpus luteum
 - Testis - Leydig cells
 - Kidney - Juxtaglomerular cells
 - Placenta - Syncytiotrophoblast
 - Diffuse Neuroendocrine System
- × Organized either in cords of cells or in a follicular arrangement:
 - Cord type
 - Most common
 - Hücreler kılcal damarlar veya kan sinüzoidleri çevresinde anastomoz kordonları oluşturur.
 - Hormone → stored intracellularly & released upon the signaling molecule.
 - suprarenal gland, anterior lobe of the pituitary gland, and parathyroid gland
 - Follicle type
 - Follicular cells surround a cavity and stores the secreted hormone
 - released into the blood capillaries.
 - thyroid gland

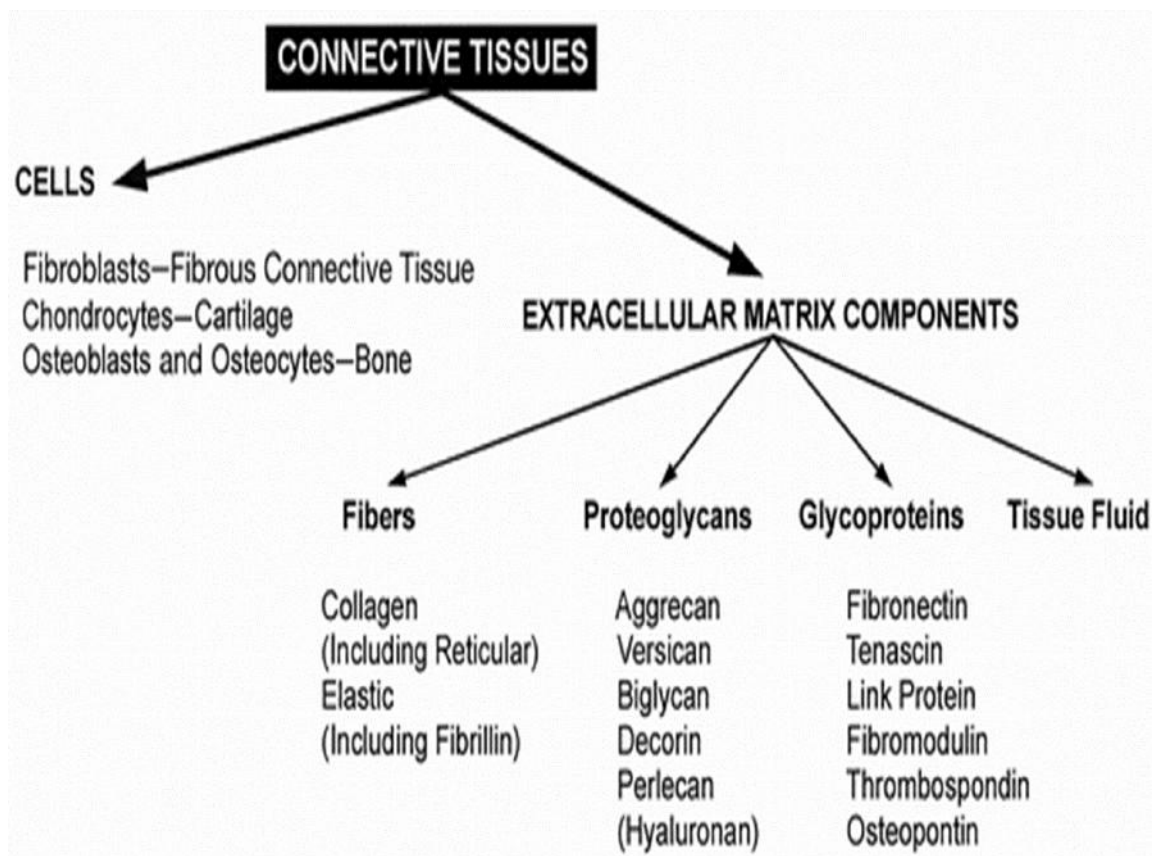
¹ Discrete: Ayrık

- Mixed type
 - The parenchyma¹ contains both exocrine and endocrine secretory units.
 - exocrine portion → secretes into a duct
 - endocrine portion → secretes into the bloodstream.
 - pancreas, ovary, and testes
- × Classification
 - Steroid Hormones (Enzymes for hormone synthesis localized in SER)
 - Ovary
 - Testis
 - Adrenal cortex
 - Placenta
 - Polypeptide Hormones
 - hypophysis (pituitary)
 - thyroid (parafoallicular cells)
 - parathyroid
 - pancreatic islets
 - diffuse neuroendocrine system - APUD cells
 - placenta
 - Amino Acid Derivatives
 - Thyroid (follicular cells)
 - Adrenal medulla
 - Pineal
 - Diffuse neuroendocrine system - APUD cells
- × Diffuse Neuroendocrine System (DNES)
 - *Produces paracrine and endocrine hormones*
 - digestive tract and in the respiratory system
 - These cells are **APUD cells** (amine precursor uptake and decarboxylation)
 - called **argentaflin & argyophil cells** (stained with silver salts)

¹ Parankim: Bir organ yada bezin görev gören dokusudur.

CONNECTIVE TISSUE

- × connect muscles to bones in the form of → tendons
- × connect bones to bones in the form of → ligaments
- × supporting tissues in vertebrates → cartilage and bone are specialized forms of connective tissue
- × Functions:
 - Supportive → structural framework for cells
 - Nutritive → matrix for blood vessels and tissue fluid
 - Lubricative → agent for the relatively friction-free movement
 - Reparative → wound healing and scar formation
 - Storage of fat
- × Types of connective tissue
 - Connective tissue proper
 - Cartilage
 - Bone
- × Origin: Mesoderm (mostly)
- × From mesoderm → mesenchyme
- × Develops and migrate → Connective tissue proper.
- × including those of bone, cartilage, tendons, capsules, blood etc. → specialized connective tissue
- × Connective tissue is formed by
 - Cells
 - Extracellular matrix
 - Fibers



- × Fibres in connective tissue
 - collagen fibres
 - reticular fibres
 - elastic fibres

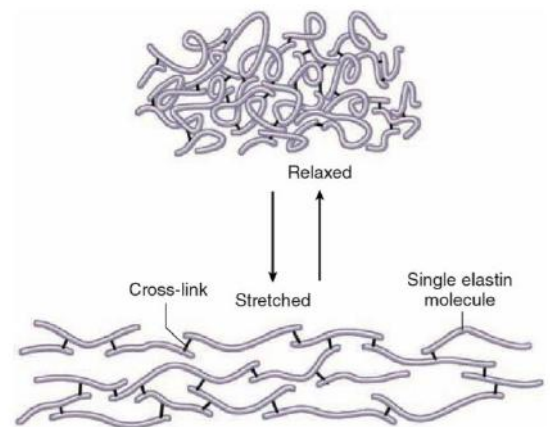
- × Collagen fibres
 - dominant fibers in CT
 - add strength to CT
 - Longitudinal striations may be visible in thicker fibres
 - Fibres → composed of thinner collagen fibrils
 - Fibrils → composed of micro fibrils
 - Microfibrils → composed of tropocollagen
 - Tropocollagen → three polypeptide strands forming triple helix
 - tensile force of several hundred kg/cm² is necessary to break human collagen fibres

 - There are about 14 types collagen (The type I, II, III comprise the bulk.)
 - Type I → bone, skin, tendon, muscles and walls of blood vessels (80 to 160nm)
 - Type II → intervertebral discs and hyaline cartilage (<80nm)
 - Type III → spleen, muscle, and aorta
 - Type IV → basement membranes and muscles.
 - Type V → embryonic cell cultures and the basement membranes
 - Type VI → muscle and skin

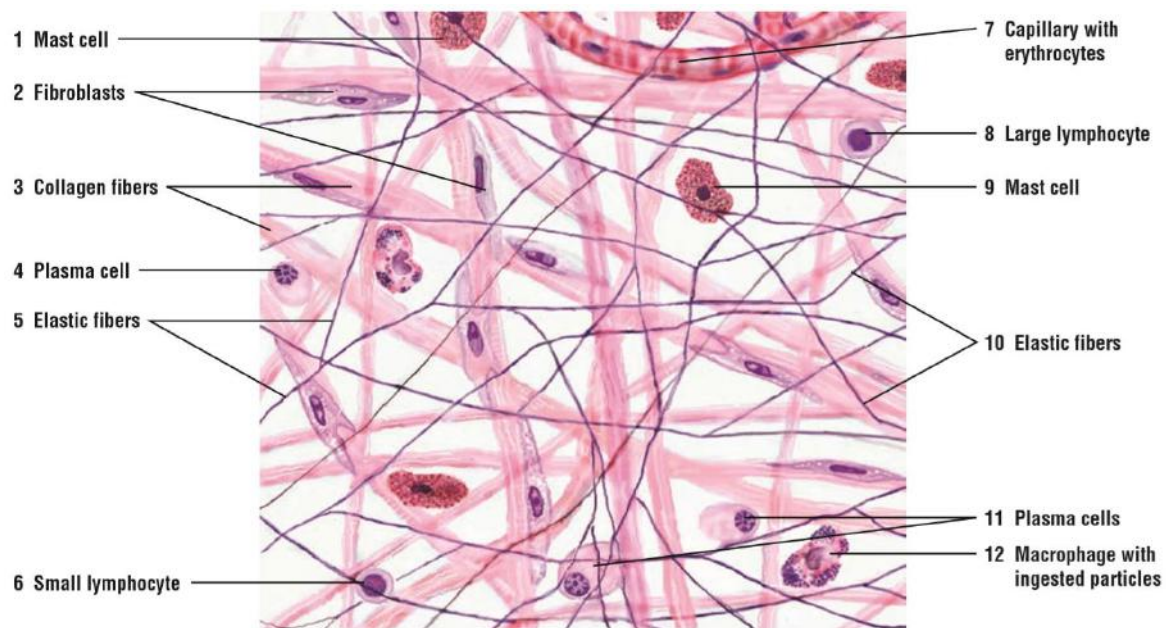
- × Elastic fibers
 - appear singly, but form branching networks
 - fibres return to original form after force is removed
 - skin, ligaments, arterial walls → pliability¹ to stretch & contract back into shape
 - elastin core → surrounded by microfibrils
 - Marfan Syndrome
 - mutation in the gene that determines the structure of fibrillin, a protein of connective tissue

 - Clinical Significance of Collagen Disorders
 - Larsen Syndrome, Osteogenesis Imperfecta & Ehlers-Danlos Syndrome
 - Ehlers-Danlos Syndrome
 - defects in fibrillar-collagen metabolism
 - %50 → Mutations in type V collagen genes
 - %50 → unexplained
 - Osteogenesis imperfecta
 - characterized by multiple fractures and resultant bone deformities
 - Recent evidence has shown that Marfan's results from integral constituent of the non-collagenous microfibrils of the extracellular matrix (mutations in extracellular protein, fibrillin)

- × Reticular fiber (type III collagen) → found in lymphatic organs mostly



¹ esneklik



Loose Connective Tissue

× Matrix (ECM)

- *Proteoglycans* (glycosaminoglycans + core proteins), water and collagen proteins

- Functions;

- Structural support
- Cellular communication
- Nutrient, hormone, pharmaceutical, nutraceutical,
- Neurotransmitter and waste transport
- Cellular protection
- Lubrication

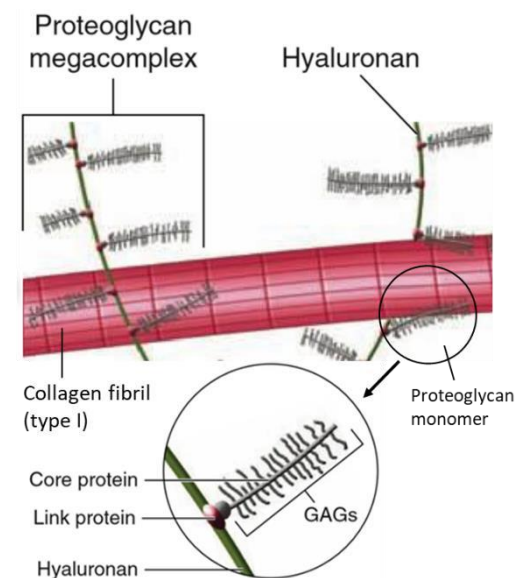
- Basal lamina → thin layer of ECM

- Proteoglycan

- consist of a core protein to which are covalently attached various numbers and combinations of the sulfated GAGs
- in the cartilage matrix, individual proteoglycans are linked to a non-sulfated GAG (Hyaluronic acid)

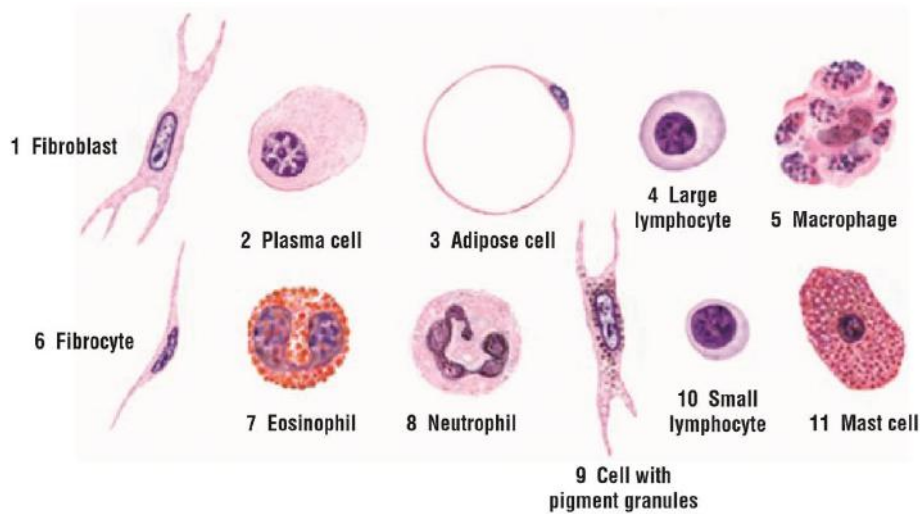
- Glycosaminoglycans (GAGs)

- Most abundant heteropolysaccharides
- Long unbranched polysaccharide → repeating disaccharide unit
- Negatively charged
- Imparts high viscosity to the solution
- Location: surface of cells & ECM
- Ideal for a lubricating fluid in the joints → because of high viscosity
- Allowing for cell migration
- Specific GAGs
 - hyaluronic acid
 - dermatan sulfate
 - chondroitin sulfate → most abundant GAG
 - heparin
 - heparan sulfate
 - keratan sulfate



Cells of Connective Tissue

- Fixed Cells → Permanent residents in the CT
- Wandering Cells → Transient migrants who have entered the CT from the blood



× Wandering Cells

- Lymphocytes
- Monocytes
- Basophils
- Neutrophils
- Eosinophils
- Macrophages
- Plasma Cells

× Fixed Cells

- Fibroblasts
- Chondroblasts & chondrocyte
- Osteoblasts & osteocytes
- Macrophages
- Adipose cells
- Mast cells

× Fixed Cells

- Fibroblasts
 - secretion of all types of fibres
 - complex carbohydrates of ground substance
 - incelendiğinde sadece çekirdeği görünür
 - fibroblast nuclei stain blue with H&E
- Chondroblasts & chondrocyte
 - matrix-secreting cells of cartilage
- Osteoblasts & osteocytes
 - matrix-secreting cells of bone
- Macrophages
 - phagocytic cells derived from monocytes
- Adipose cells
 - store neutral fat
- Mast cells
 - granules containing histamine, heparin and anaphylactic factors
 - cause hypersensitivity reactions

× Wandering Cells

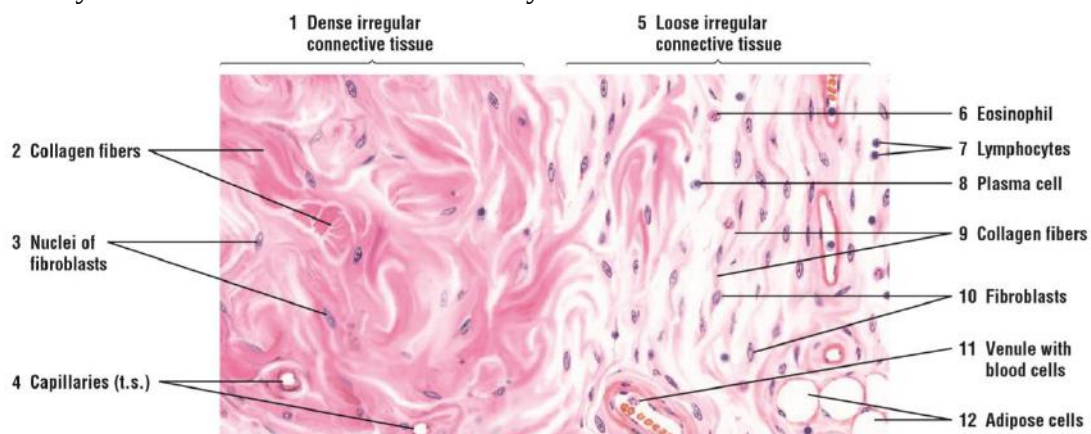
- Lymphocytes
 - immune responses that circulate in the blood
 - number increases when occurs tissue inflammation
 - numerous in the lamina propria of the respiratory and gastrointestinal tracts
 - Three groups (size) → small, medium and large

- Monocytes
 - increase phagocytes of the mononuclear phagocytic system
 - IN CT → MACROPHAGE
 - Largest WBC in blood
 - precursor of all the cells of the mononuclear phagocytic system
 - Basophils
 - WBC
 - Similar to mast cells
 - Having vasoactive agents released in response to an allergen
 - Neutrophils
 - WBC
 - Act as phagocytes in the early stages of acute inflammation
 - Eosinophils
 - Wbc that are found in the lamina propria of the gi tract
 - Allergic reaction and parasitic infection
 - Macrophages
 - Scavenger cells in phagocytosis
 - Origin: monocytes
 - Immune system in response to microorganisms and foreign proteins
 - Plasma Cells
 - Origin: Lymphocyte B
 - Immune response → secretes antibody
- } Granulocytes
 Least abundant in WBC
 Most abundant in WBC

× Which intra-cellular organelle should be abundant in the macrophage cytoplasm?
 → *Lysosome*

× Types of connective tissue

- Loose Connective Tissue
 - Many cells are present (most dominant cell → fibroblast)
 - All three fibre types are also present
 - Areolar CT is the most widely distributed connective tissue type
- Dense Connective Tissue
 - Dense Regular
 - Fibres are compact and regularly arranged in parallel sheets or bundles
 - High tensile strength to tissues (when the main fibre component is elastin)
 - Dense Irregular
 - Fibres are arranged many different directions, providing strength or elasticity in all directions
- Embryonic Connective Tissue -Mesenchymal Tissue



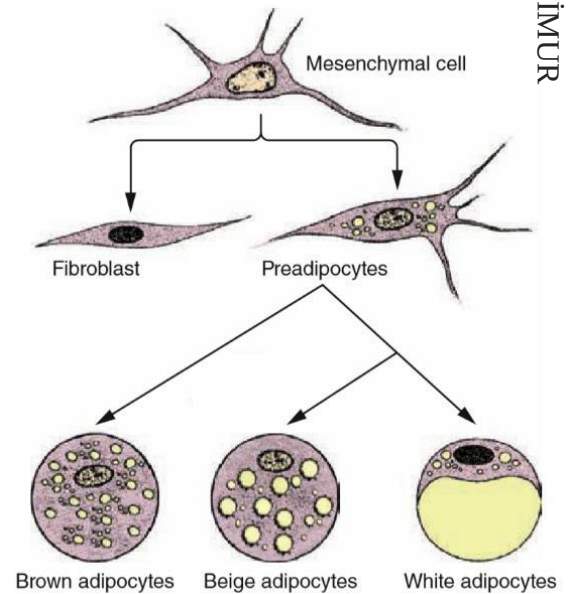
ADIPOSE TISSUE

Origin: Mesenchyme

- × Unilocular Adipose Tissue → White Adipose Tissue (WAT)
- × Multilocular Adipose Tissue → Brown Adipose Tissue (BAT)

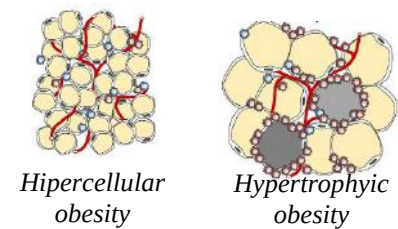
× Unilocular (WAT)

- Presents in the subcutaneous layers
 - Contains receptors for;
 - Insulin
 - Growth hormone
 - Norepinephrine
 - Glucocorticoids
- } facilitate the uptake and release of free acids and glycerol
- Obesity
 - Number of cells / volume of adipose tissue ↑
 - Hypertrophic obesity → Accumulation and storage of fat
 - Hypercellular obesity → Overabundance of adipocyte



× Multilocular (BAT)

- Found in many mammals (esp. hibernate¹)
- In newborn → neck and interscapular region
- Thermogenin
 - Trans membrane protein
 - Location: inner membrane of mitochondria
 - Role for producing heat



WAT

BAT

- | | |
|---|--|
| ✓ Location: In humans ubiquitous at all ages | 7 deposit sites in newborn only |
| ✓ Composition: 82% fat; 15% water; 3% protein | 30% fat; 55% water; 15% protein |
| ✓ Blood Supply: Rich capillary supply | Much denser than WAT |
| ✓ Innervation: Sympathetic | Sympathetic |
| ✓ Function: Food storage, padding | Thermogenesis |
| ✓ Derivation: WAT-specific mesenchymal cell | BAT-specific mesenchymal cell |
| ✓ Morphology: Usually unilocular, 80-150 μm diameter | Usually multilocular, 8-60 μm diameter, prominent mitochondria |

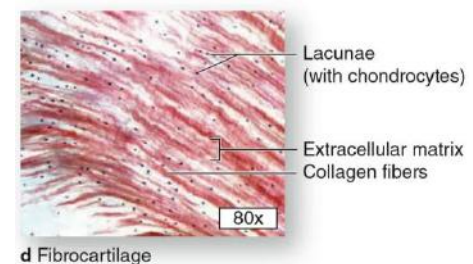
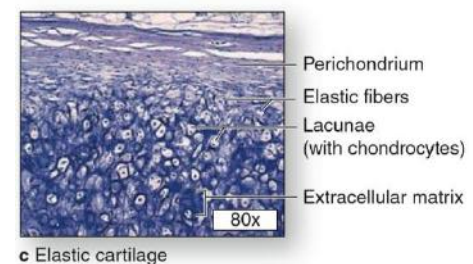
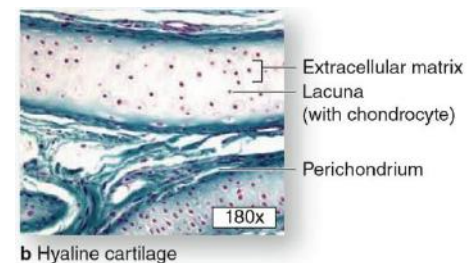
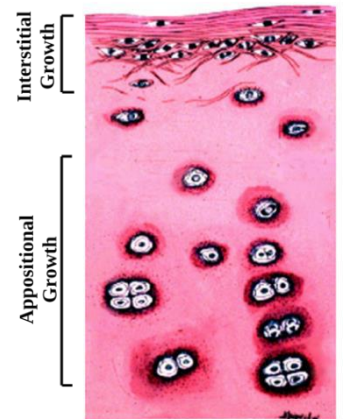
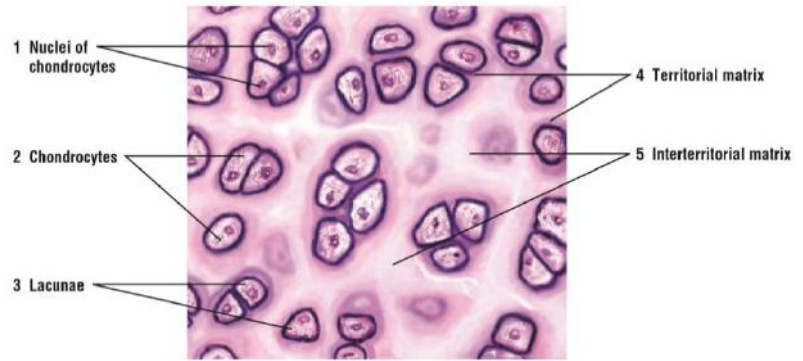
¹ Kış uykusuna yatmak

CARTILAGE

Origin: Mesenchyme

- × **NO** blood vessels (Avascular)
- × **NO** nerves
- × ECM surrounded by perichondrium
- × Matrix → Collagen + Elastic Fibers (embedded in chondroitin sulfate)
- × Strength → collagen fibers
- × Resilience¹ → chondroitin sulfate
- × Proteoglycans → %15
- × Growth of Cartilage
 - Interstitial Growth
 - from chondrocytes within cartilage
 - involving mitotic division of preexisting chondrocytes
 - Appositional Growth
 - from undifferentiated cells at the surface of the cartilage / perichondrium
 - involves chondroblast differentiation from progenitor cells in the perichondrium
- × Types of Cartilage

• Hyaline Cartilage → TYPE II • Elastic Cartilage → TYPE II • Fibrous Cartilage → TYPE I	}	Collagen
--	---	----------
- × Hyaline Cartilage
 - Avascular
 - Surrounded by perichondrium (**EXCEPT** articular cartilage or epiphyses of growing long bones)
 - It consists of chondrocytes surrounded by territorial and interterritorial matrices containing type II collagen interacting with proteoglycans
- × Elastic Cartilage
 - Avascular
 - Surrounded by perichondrium
 - It consists of chondrocytes surrounded by territorial and interterritorial matrices containing type II collagen interacting with proteoglycans and elastic fibers
- × Fibrocartilage
 - generally avascular
 - **Lacks of perichondrium**
 - It consists of chondrocytes and fibroblasts surrounded by type I collagen and a less rigid ECM



¹ Esneklik

Important features of the major cartilage types

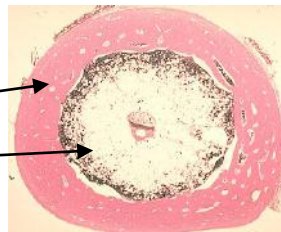
	Hyaline Cartilage	Elastic Cartilage	Fibrocartilage
Main features of the extracellular matrix	Homogeneous, with type II collagen and aggrecan	Type II collagen, aggrecan and darker elastic fibers	Type II collagen and large areas of dense connective tissue with type I collagen
Major cells	Chondrocytes Chondroblasts	Chondrocytes Chondroblasts	Chondrocytes Fibroblasts
Typical arrangement of chondrocytes	Isolated or in small isogenous groups	Usually in small isogenous groups	Isolated or in isogenous groups arranged axially
Presence of perichondrium	Yes (except at epiphyses and articular cartilage)	Yes	No
Main locations or examples	• Many components of upper respiratory tract • Articular ends and epiphysial plates of long bones • Fetal skeleton	• External ear • External acoustic meatus • Auditory tube • Epiglottis and • Certain other laryngeal cartilages	• Intervertebral discs • Pubic symphysis • Meniscus and certain other joints • Insertions of tendons
Main functions	○ Provides smooth, low-friction surfaces in joints ○ Structural support for respiratory tract	○ Provides flexible shape ○ Support of soft tissues	○ Provides cushioning ○ Tensile strength ○ Resistance to tearing and compression

BONE & JOINTS

- × Functions
 - *Support and protection* for the body and its organ
 - *Reservoir* for calcium and phosphate ions
- × Bone is composed of;
 - Support cells → **Osteoblast & Osteocytes**
 - A non-mineral matrix of collagen and GAG's → **Osteoid**
 - Remodeling cells → **Osteoclast**
 - Inorganic mineral salts deposited within the matrix
- × Osteoid and Bone Matrix
 - Organic Bone Matrix → *Type I collagen (90%)*
 - Inorganic Bone Matrix → *calcium phosphate*
- × Cells of Bone
 - **Osteoprogenitor cells** → Stem cells of bone
 - **Osteoblasts** → Synthesize the organic component of bone matrix (osteoid), mineralize it by depositing calcium and phosphate hydroxides (hydroxyapatites)
 - **Osteocytes** → *Inactive osteoblasts* trapped in mineralized bone
 - **Osteoclasts** → Origin: *Monocytes* & Location: *Howship's lacuna*
→ Multinucleate cells. Bone remodelling

× Classification of bones

- Compact bone
- Spongy or cancellous bone



Bone
Marrow

× Types of Bone (basis on organisation)

- **Lameller bone:** Typical of the **mature** or **compact bone**.
- **Woven bone:** Observed in the **developing bone**.

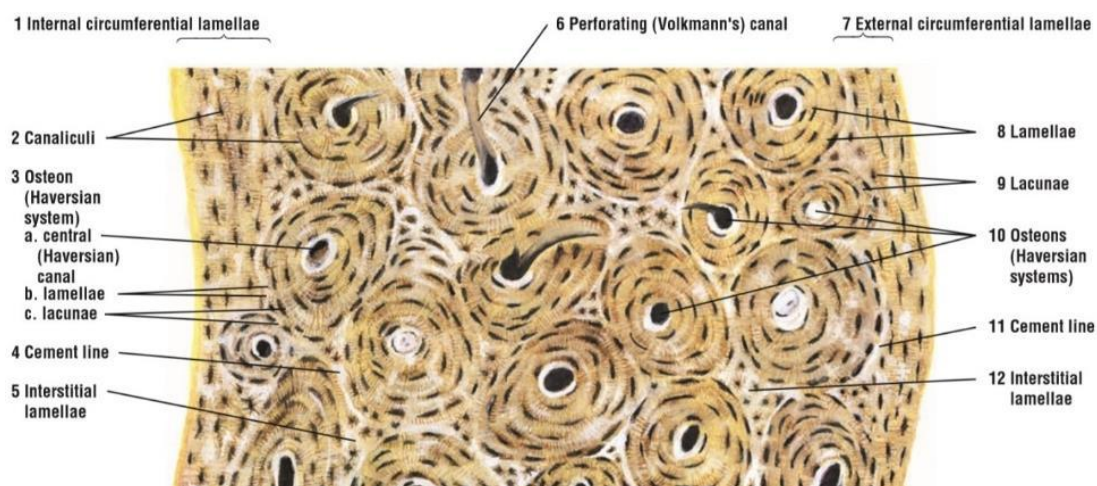
× Lameller bone → lamellae + bone matrix + osteocytes

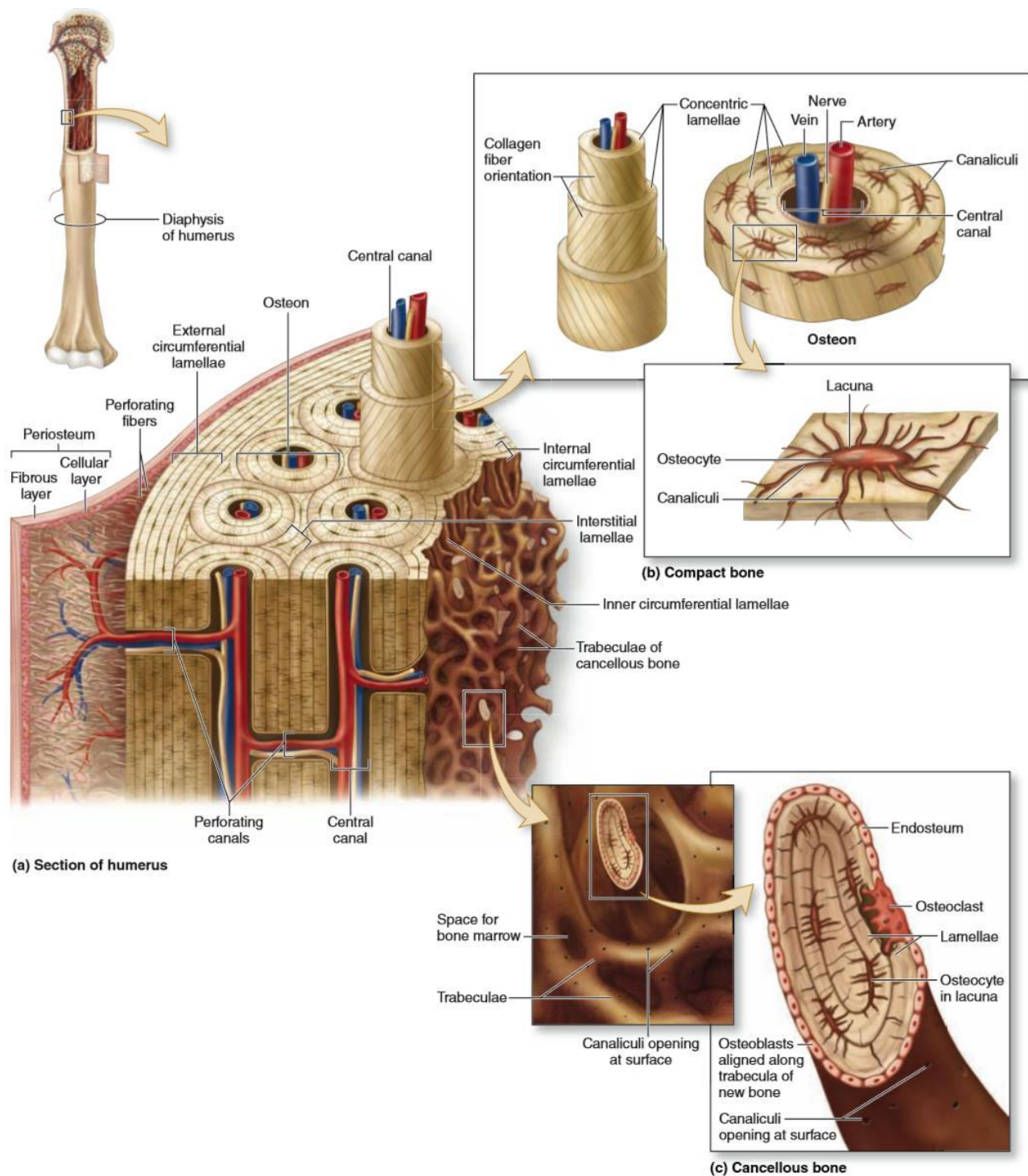
× Lameller bone (four distinct patterns)

- Osteons or Haversian system
- Interstitial lamellae
- Outer circumferential lamellae
- Inner circumferential lamellae

× Vascular channels in compact bone

- Haversian canal
- Volkman's canal





Periosteum

- Inner layer:
 - Consists of bone-forming cells (osteoblasts) – during embryonic period
 - Contains inactive *connective tissue* cells (bone injury) - in adult
- Outer layer:
 - Rich in blood vessels
 - thick anchoring collagen fibers (Sharpey's fibers) → that penetrate the outer circumferential lamellae in the bone

Endosteum

- squamous cells
- connective tissue fibers covering the spongy walls housing the bone marrow
- extending into all the cavities of the bone, including the Haversian canals.

× Mineralization of Osteoid

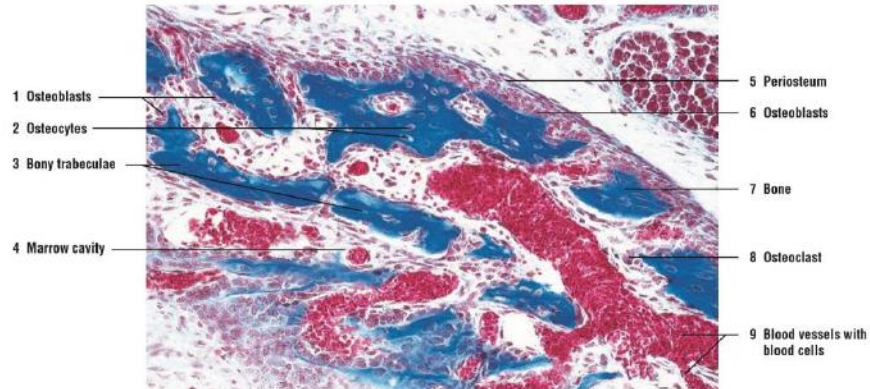
- Osteoid'deki glycoprotein extracellular Ca^{++} iyonlarını bağlar
- Alkaline Phosphatase → increases local Ca^{++} and PO_4^- concentrations
- Osteoblastın ürettiği matrix vesicle'lar Ca^{++} and PO_4^- birikimini sağlar

× Selective Bone Resorption

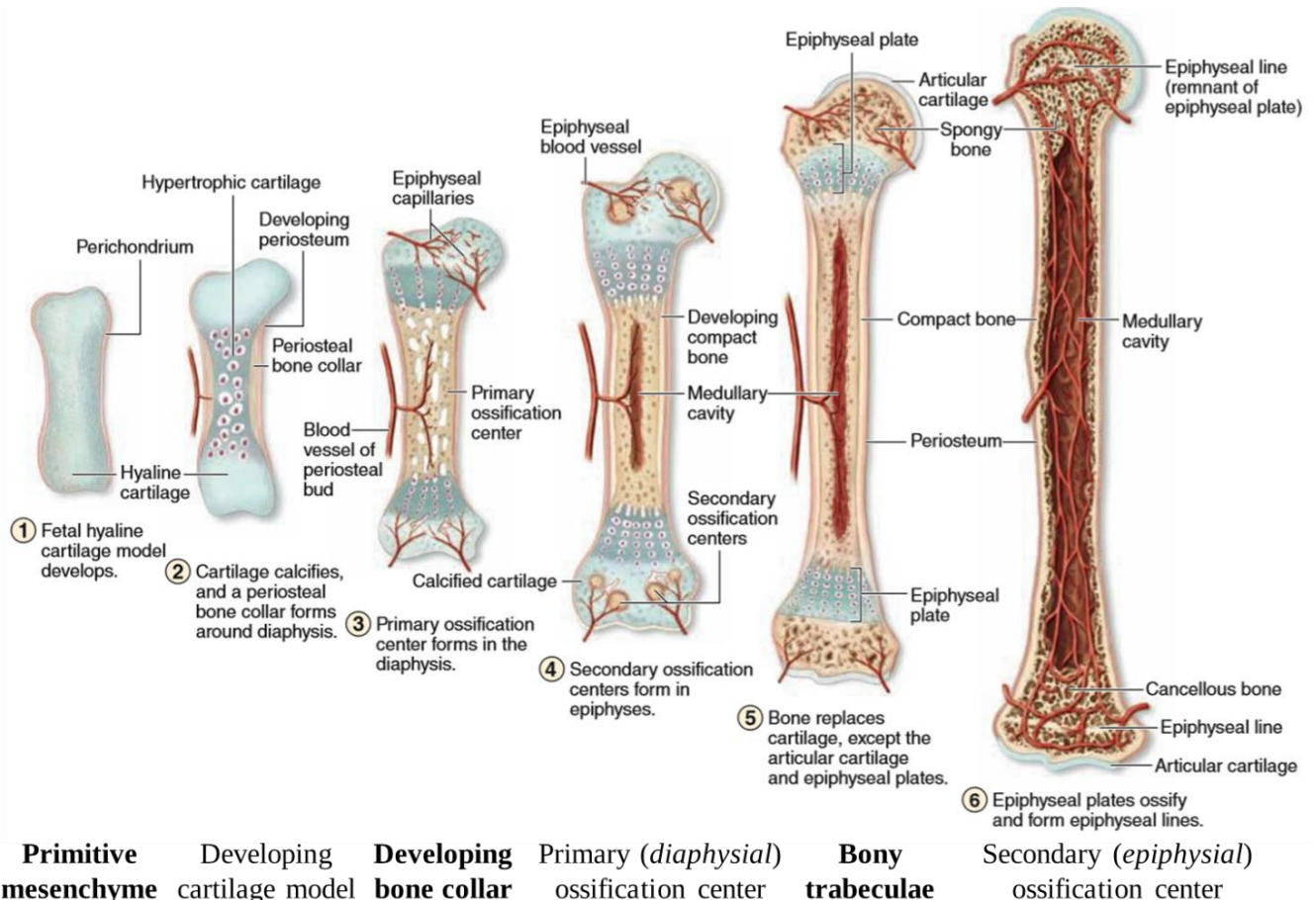
- Lysosomal enzymes → released by osteoclasts
- Local acidic conditions → break up the hydroxiapatite → releasing soluble Ca^{++} and PO_4^-
- Soluble break down products → demineralization
- Osteoclast resorption of bone
 - ▶ Stimulated by PARATHORMONE
 - ▶ Inhibited by CALCITONIN

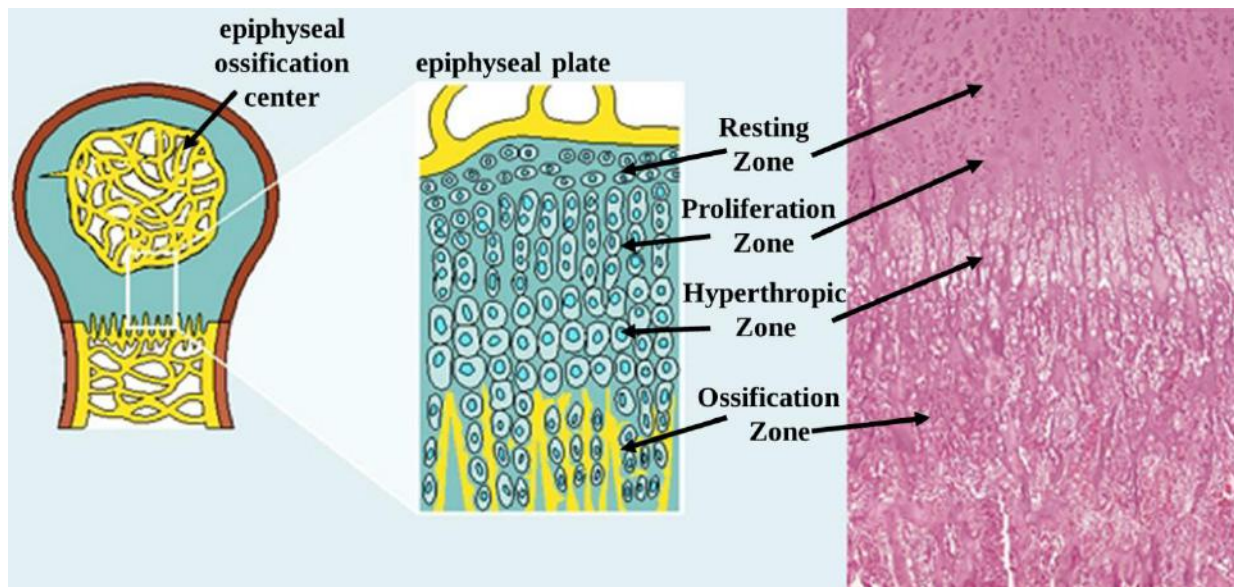
× Osteogenesis

- Intramembranous bone formation
 - **Flat bones**
 - Ossification is formed on the *mesenchymal* connective tissue
- Endochondral bone formation
 - **Long and short bones**
 1. A miniature *hyaline cartilage* is formed.
 2. The cartilage model continues to grow and serves as a structural scaffold for bone development



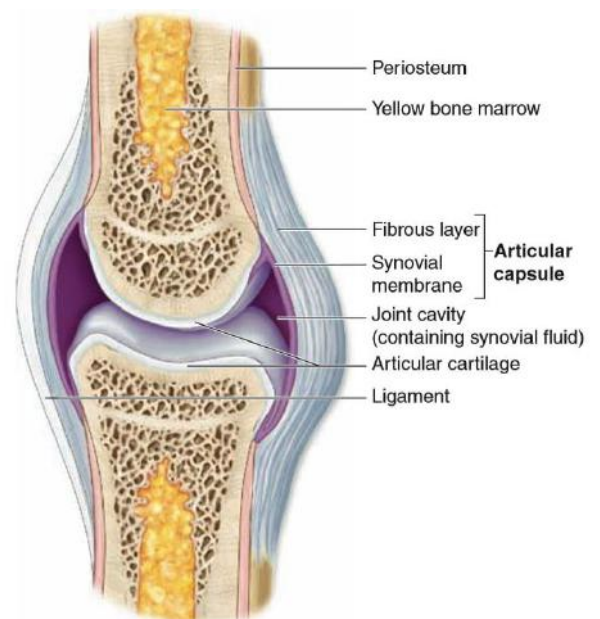
× Endochondral Ossification





JOINTS

- × Permit limited movement
- × Permit free movement
- × Semi-mobile joints (*Synarthroses*)
 - Syndesmoses → Joints between the flat bones of skull
 - Synchondroses → Joints between ribs and sternum
 - Synostosis → Fusion of two bones (in old ages)
- × Mobile joint (*Diarthroses*)
 - Joints that allow free movement between adjacent bones are termed synovial joints
- × Intervertebral disk
 - Sciatica: Wear and tear on the intervertebral disks may lead to degeneration of the annulus fibrosus, with extention of the nucleus pulposus. This results in:
 - Impaired efficiency of the disk as a shock absorber.
 - Expansion of the annulus fibrosus, causing it to bulge.
- × The internal lining of the joint capsule is a specialized secretory epithelium, the synovium, which produces synovial fluid.
- × Synovial membrane have two types of cells:
 - Type A cells: Phagocytosis
 - Type B cells: Protein synthesis
- × Arthritis
 - Osteoarthritis
 - Rheumatoid arthritis



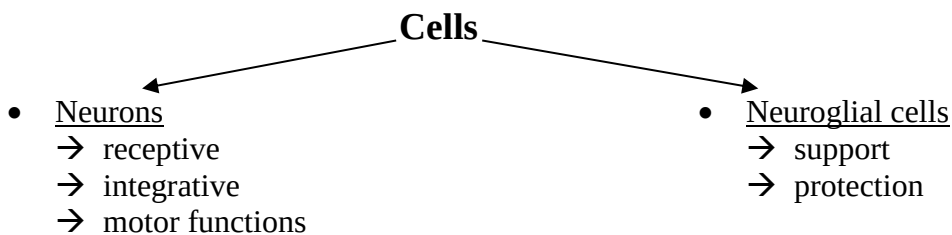
NERVOUS TISSUE

× Anatomically:

- Central nervous system (CNS)
 - Brain
 - Spinal cord
- Peripheral nervous system (PNS)
 - Cranial nerves
 - Spinal nerves
 - Ganglions

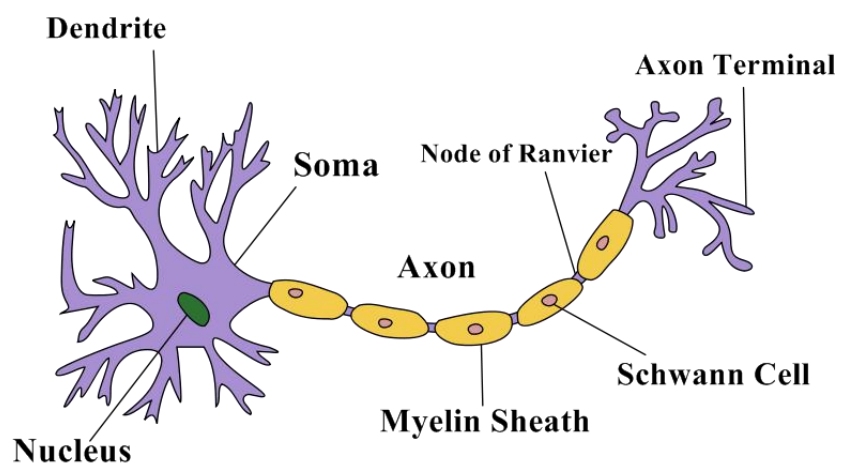
× Functionally:

- PNS
 - Sensory (afferent) component
 - Motor (efferent) component
 - Somatic system: from CNS → to skeletal muscle *via a single neuron*
 - Autonomic system: from CNS → to autonomic ganglia → then to smooth muscle, cardiac muscle and glands *via a second neuron* located in the ganglion
- Neuron
- Neuroglial cell
 - Does **NOT** receive impulse & **NOT** transmit impulse
 - Supports neurons



Neurons

- **Structure and Functions**
 - Cell body (perikaryon, soma)
 - Dendrite
 - Receive impulse from neuron and axons
 - Axon
- Most neurons:
 - *One cell body*
 - *Multiple dendrites*
 - *One axon*



- × Dorsal root ganglion neurons:
 - Round cell body, only one projection
- × CNS neurons:
 - Generally polygonal, concave surface between its projections