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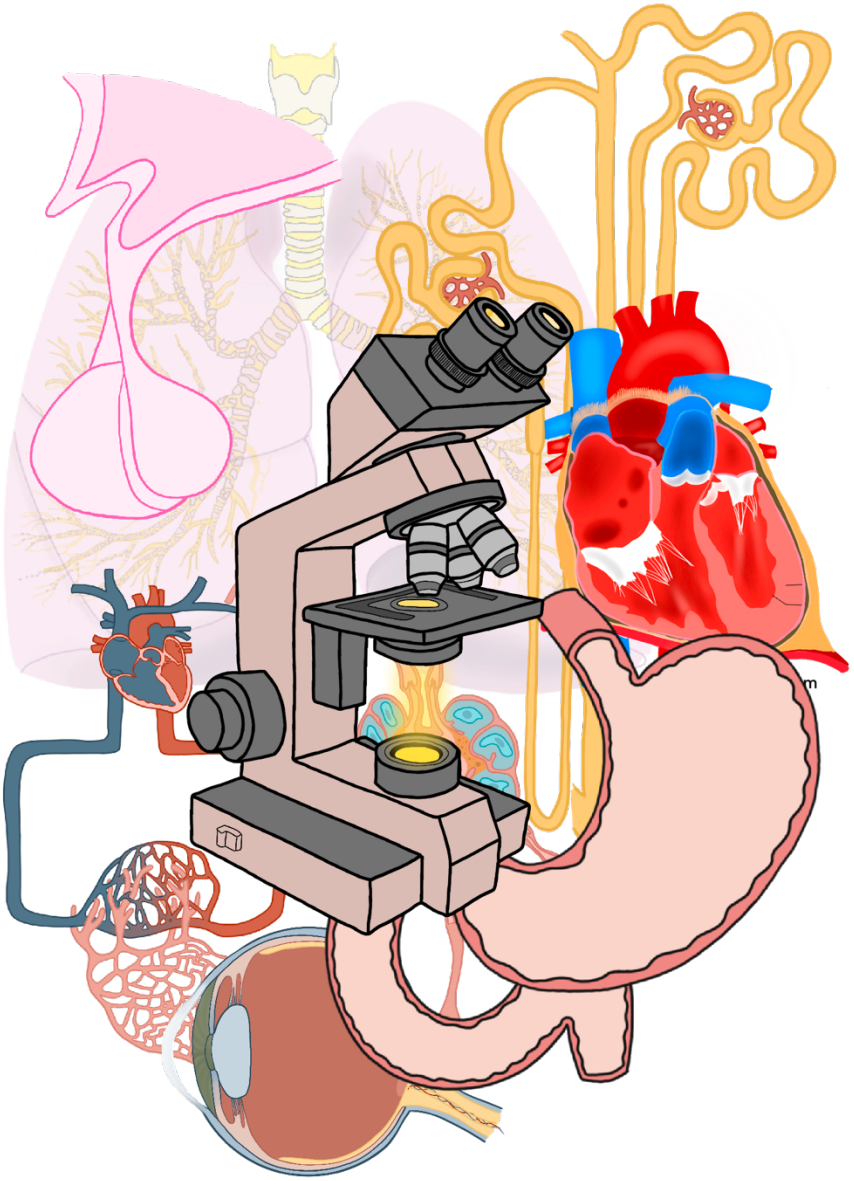

Histology

Systems

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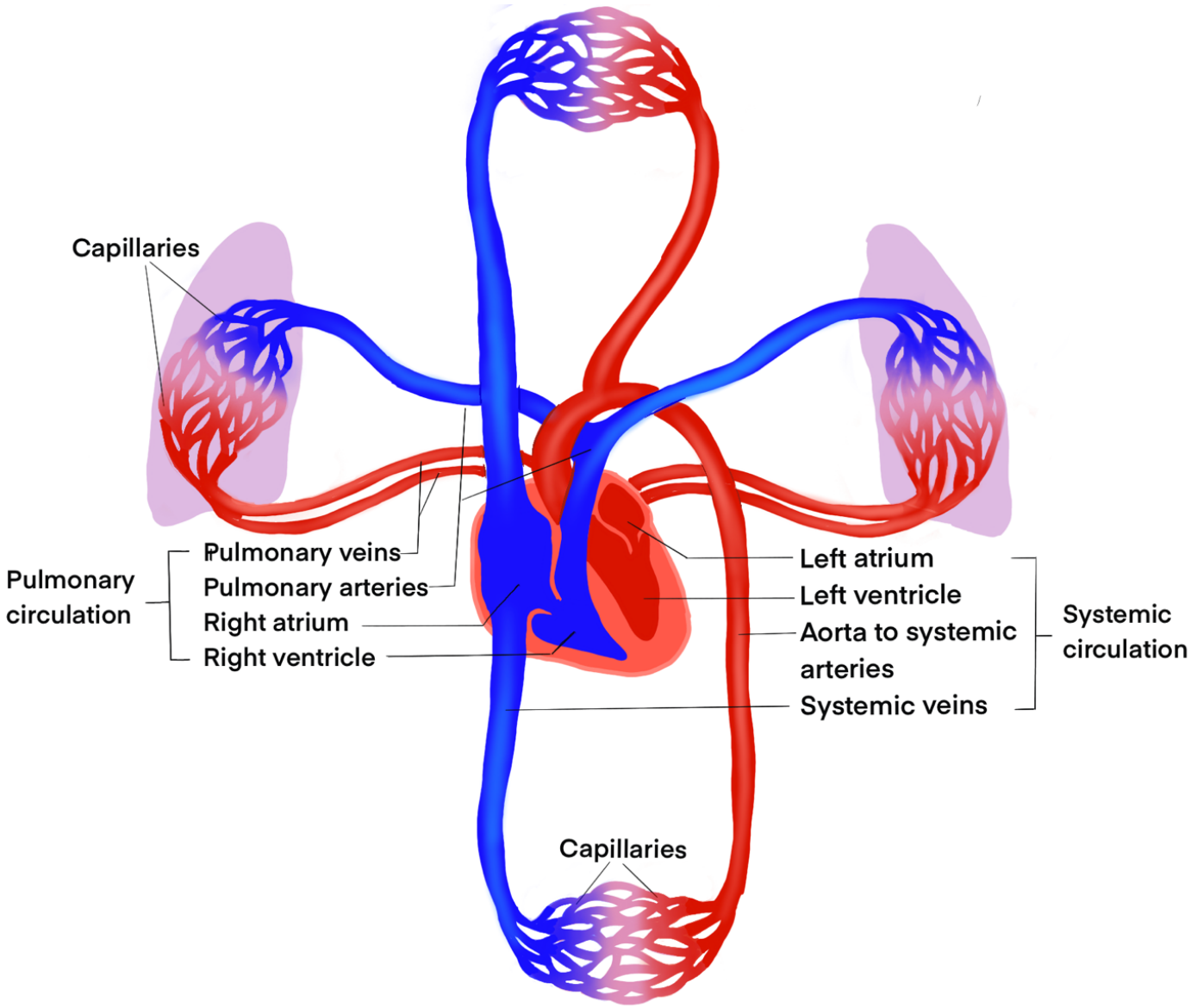
Table of Contents

Section 1 – The Vascular System

1.1 – Circulatory System



I. Pathway of circulation

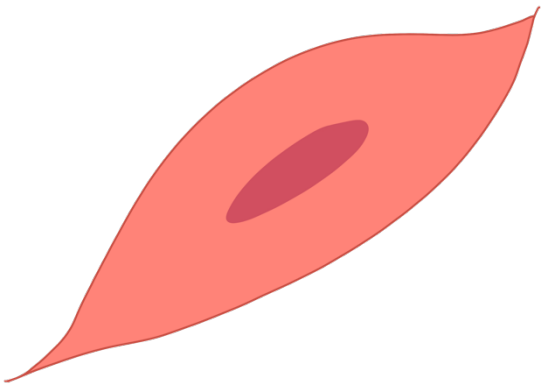
- Blood is pumped out from the left ventricle of the heart into systemic circulation via the aorta
- The arteries supply blood to the body: Arteries → arterioles → capillaries
- Veins transport blood back to the right atrium: Capillaries → venules → veins
- Blood moves from right atrium to right ventricle and is pumped into the pulmonary artery and into capillary beds in the lungs
- Blood is oxygenized in the capillary beds in the lungs, and transported via pulmonary veins to the left atrium
- Blood is then pumped back into the left ventricle

1.2 – Vascular Wall

- How these elements are distributed in the vascular wall depends on mechanical and metabolic factors that reflect the needs of the surrounding tissue

Endothelium	Specialized simple squamous epithelium
Smooth muscle	Occur in the walls of all vessels larger than capillaries In arterioles and small arteries, the smooth muscle cells permit vasoconstriction and vasodilation which is important in regulation of blood pressure.
<u>Connective tissue elements</u> **1. Collagen and reticular fibers** **2. Elastic laminae/fibers** **3. Connective tissue cells**	The smooth muscles cells produce the elastic laminae, and some collagen and reticular fibers Collagen fibers are found between the smooth muscle layers, and in the outer covering. Elastic fibers provide the ability of the vascular wall to expand under pressure. Important in large arteries.

1.2.1 – Endothelial Cells



I. Characteristic of endothelial cells

- Mesenchymal origin
- Produce basal lamina
- Squamous, flat and elongated cells
- Multiple pinocytotic vesicles
- Weibel-Palade bodies containing von Willebrand factor
- Cell junctions include: adherent, gap and tight junctions

II. Functions of endothelial cells

Provides non-thrombogenic surface	Provides a smooth lining that facilitates undisturbed blood flow as well as secreting agents controlling local clot formation
Control transport and migration	Controls transport of substances, and migration of blood cells through the vascular wall
Regulate vascular tone and blood flow	Secretes factors stimulating smooth muscle contractions (e.g. ACE) and relaxation (e.g. nitric oxide)
Participates in inflammation and local immune responses	Endothelial cells in venules stops white blood cells at sites of injury and inflammation Secretes interleukins Some specialized endothelial cells e.g. in the liver take up pathogens and cell debris circulating in blood
Angiogenesis	Play a leading role in angiogenesis, the formation of new vessels
Participates in coagulation	Produce and secrete components important for blood coagulation
Modify biologically active substances	Some biologically active substances circulating in the blood are modified

1.2.2 – Transport Across the Endothelium

For repetition of transport across cell membranes see Section 1.3 in Histology booklet part 1

I. Transport of smaller molecules

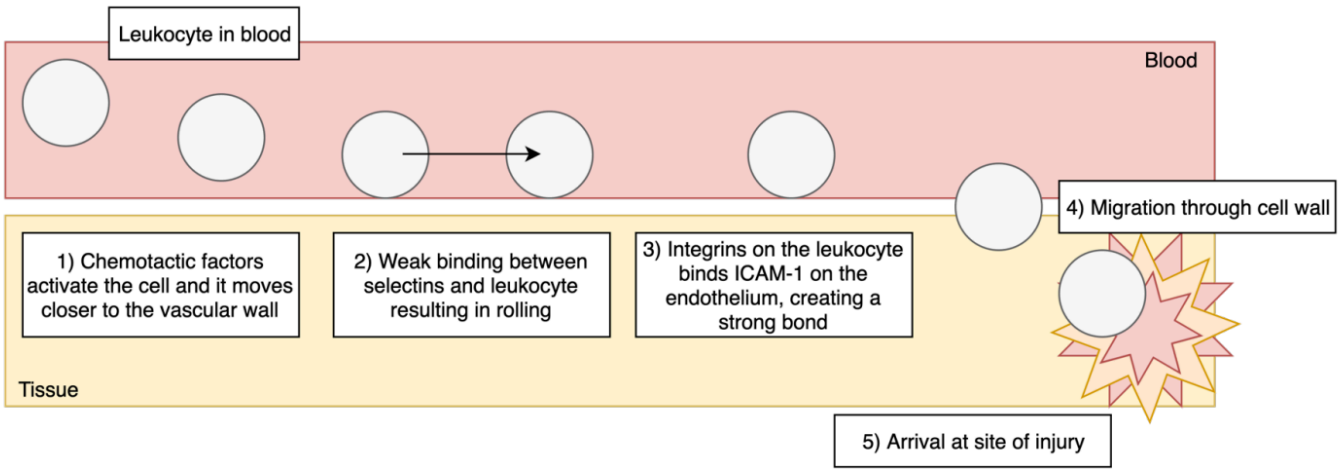
- Free diffusion
    1. Gases
    2. Hydrophobic molecules
- Transporters
    1. Ions
    2. Glucose
    3. Other simple compounds

II. Transport of larger molecules

- Transcytosis: endocytosis + exocytosis
- Through pinocytotic channels
- Through fenestrations (see Section 1.3.X Types of capillaries)
- Through intercellular clefts

III. Diapedesis

- The process of transporting leukocytes across the blood vessel wall
    1. Margination
    2. Rolling
    3. Adhesion
    4. Migration



IV. Important endothelial secretions

Components of extracellular substance	Pro- and anticoagulants	Vasoconstrictors and vasorelaxants	Growth factors
- collagens - laminin - glycoproteins - proteoglycans	- von Willebrand factor - platelet activating factor - plasminogen activator - prostacyclin (PGI_2)	- Endothelins - Nitric oxide (NO)	- VEGF (vascular endothelial growth factor)

1.2.3 – Endothelial Progenitor Cells

I. Origin and location

- Originate from mesenchymal stem cells located in bone marrow (See section 5.4 in Histology booklet part 1)
- Circulate in peripheral blood

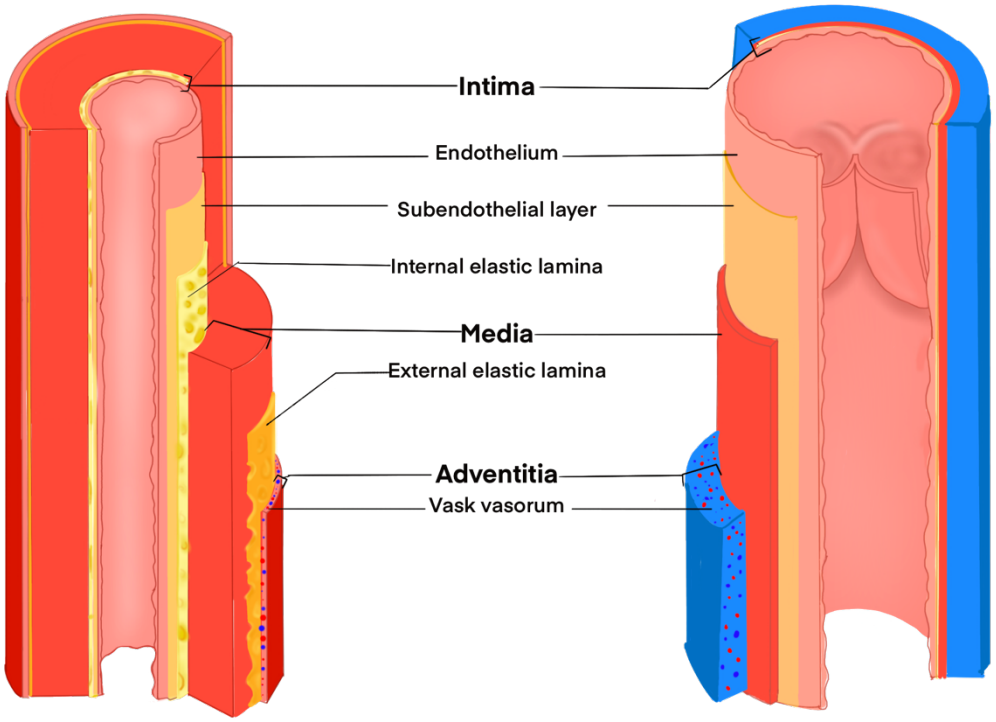
II. Function

- Repair injured epithelium
- Promote formation of new capillaries

III. Amount in peripheral blood

- Decreases with
    1. Age
    2. Cardiovascular risk factors
    3. Progressing atherosclerosis

1.3 – Larger Vessels



I. Layers of the vessel wall

- Except for capillaries, all blood vessels have the same three layers

Layers of the vessel wall	Content of the layer	Function
Tunica intima	Endothelium Layer of loose connective tissue Sometimes smooth muscle fibers Arteries and large veins also have internal elastic lamina, composed of elastin, which allow for better diffusion of substances into the vascular wall	Innermost layer towards the blood, provides smooth surface for undisturbed blood flow
Tunica media	Predominantly smooth muscle cells Between the smooth muscle cells there can be variable amounts of connective tissue Arteries may have a thin elastic lamina separating It from the tunica adventitia	More muscular layer, regulates size of lumen and blood flow rate
Tunica adventitia	Primarily collagen and elastic fibers In larger vessels, more in arteries than veins, this layer contain a network of unmyelinated autonomic nerve fibers which release the vasoconstrictor norepinephrine	Attaches the vessel to surrounding tissue

II. Vasa vasorum – «Vessels of the vessel»

- Large vessels can have their own blood supply with arterioles, capillaries and venules in the outer part of the media and in the adventitia
- Necessary due to the thickness of the wall in the larger vessels. Diffusion of nutrients from the lumen is not enough
- Large veins commonly have a greater need for vasa vasorum than arteries, as they carry deoxygenated blood

III. Vasoconstriction and vasodilation

- Contraction and relaxation of the vascular smooth muscles are controlled by
    1. Vasomotor nerve fibers (Autonomic fibers) in tunica adventitia and media
    2. Hormones and regulatory substances present I blood
    3. Secretions of endothelial cells (e.g. endothelins and nitric oxide)

IV. General distinctions between arteries and veins

	Arteries	**Veins**
Wall	Thicker	Thinner
Layers	More distinct	Less distinct
Elastic fibers/laminae	Common	Rare
Tunica media	Smooth muscle cells Elastic laminae	Smooth muscle cells Collagen fibers
Smooth muscle cells in intima and adventitia	Rare	Common
Valves	None	In some veins

1.4 – Arteries

- Arteries can be divided into two types with different composition and function: elastic and muscular

Type of artery	Composition	Function	Location
Elastic arteries	Most prominent feature is thick media with multiple layers of elastic laminae alternating with smooth muscle cells Adventitia is much thinner than media Intima has many smooth muscle cells, and inner elastic laminae	Maintain arterial pressure and reduce the difference between systole and diastole	Aorta, pulmonary artery and their largest branches
Muscular	Intima has a prominent internal elastic laminae Media consists of many circular layers of smooth muscle cells, with a variable amount of elastic laminae External elastic laminae is present only in large muscular arteries Lymphatic capillaries, vasavasorum and nerves are found in adventitia. Can also extend into outer part of media	Distribute blood to organs	Large, medium and small arteries

CLINICAL CORRELATION

Atherosclerosis

Atherosclerosis is the formation of plaque in arteries, and is the main cause of infarct and stroke.

It is characterized by changes in the intima of arteries:

- Lipid filled macrophages (Foam cells) and smooth muscle cells accumulate
- Connective tissue fibers increases
- Calcification of the vascular wall may occur

These changes leads to damage of the endothelium, local blood clotting and can lead to occlusion of the vessels.

Predisposing factors include dyslipidemia, diabetes, hypertension and smoking.

1.5 – Arterioles

I. Location

- Smallest branch of arteries
- Indicate beginning of microvasculature

II. Size and composition

- < 0,1 mm in diameter
- 1-3 layers of smooth muscle cells
- Formation o finner elastic laminae
- Formation of adventitia

III. Function

- Branch of to form anastomosing networks or capillary beds
- Smooth muscle fibers act as precapillary sphincters, regulating blood flow into capillaries (*See section 1.4.3 and 1.4.4*)
- Contribute to peripheral vascular resistance as muscle tone usually keeps arterioles partially closed

CLINICAL CORRELATION

Hypertension

Blood pressure (BP) is calculated by cardiac output (CO) multiplied with total peripheral resistance (TVP).

BP = CO x TVP

Total peripheral resistance is highly regulated by the arterioles. Elevated blood pressure, hypertension, can be secondary to renal or endorcrine conditions, but is most commonly primary. Primary hypertension is due to a wide variety of mechanism that increase arteriolar constriction.

1.6 – Capillaries

- Smallest arteries and veins in the body, ranging from 5-10 µm in diameter
- Responsible for exchange of both gases and various substances between the tissues and blood
- Capillaries have sphincters at the beginning which helps with regulating blood flow by cyclically closing and opening

1.6.1 - Components of Capillary Wall

- Endothelium
- Basal Lamina
- Pericytes

I. Structure of the capillary wall

- The wall of the capillary is composed of one single layer of endothelial cells
- The shape and structure of the endothelial cells forming the capillary wall, are held together by the basal lamina and cell-junctions.
- The endothelial cell-junctions, especially tight junctions, have an important role in capillary permeability

II. Pericytes

- Considered a type of mesenchymal stem cell, that are attached to capillaries
- Produces their own basal lamina which may fuse with that of the endothelial cells.
- Have cytoplasmic processes that surrounds the capillary
- Have contractile properties and facilitate blood flow through the capillaries.
- Have potential to differentiate into multiple different cells; fibroblasts, chondroblasts, osteoblasts, adipocytes and smooth muscle cells
    1. In the case of injury, the property to proliferate into cells in the vessels helps reestablish the microvasculature.

CLINICAL CORRELATION

Diabetic microangiopathy

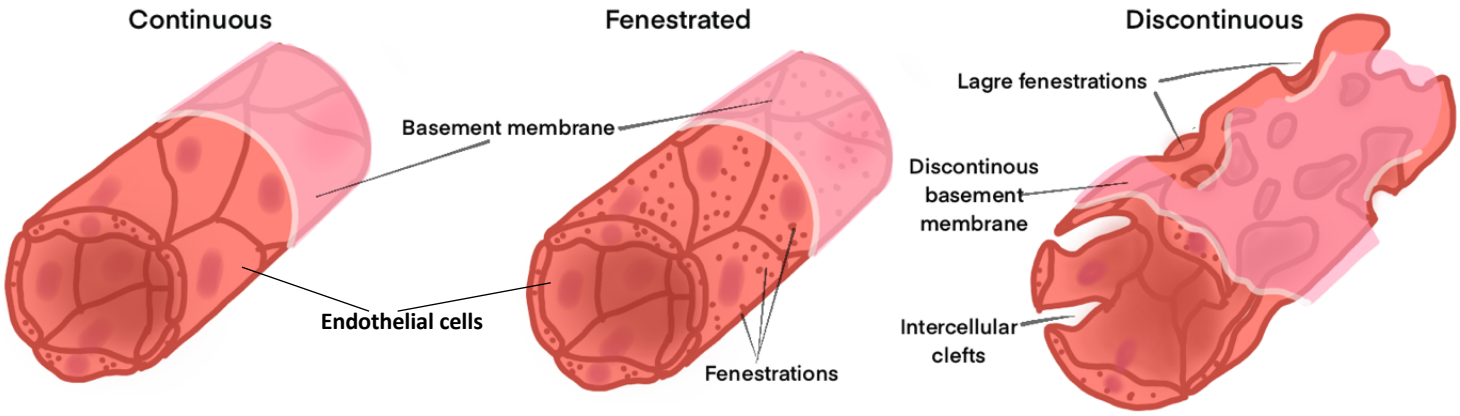
Diabetes is a more and more common disease in the developed world. One of the complications of this disease is diabetic microangiopathy. The high blood sugars lead to thickening of the capillary basal laminae, and thereby reduces the metabolic exchange in these vessels. This is particularly in the kidneys, retina, skeletal muscle and skin.

1.6.2 – Types of Capillaries

I. Three types of capillaries

- Histological division of capillaries are dependent of the continuity of endothelial cells and the basal lamina

	Continuous capillaries	Fenestrated capillaries	Discontinuous capillaries
Endothelium	Continuous	Pores/Fenestrations	Large pores and intercellular clefts
Basal lamina	Continuous	Continuous	Absent or discontinuous
Permeability	Low Highly selective transport	High Non-selective transport	Maximal No regulation of transport. Even cells pass easily
Pericytes present	Yes	Yes	No
Organs	Most common Present in most organs	Organs of rapid interchange of substances Kindey, intestines and endocrine glands	Organs with high exchange of substances and cells. Liver, spleen and bone marrow



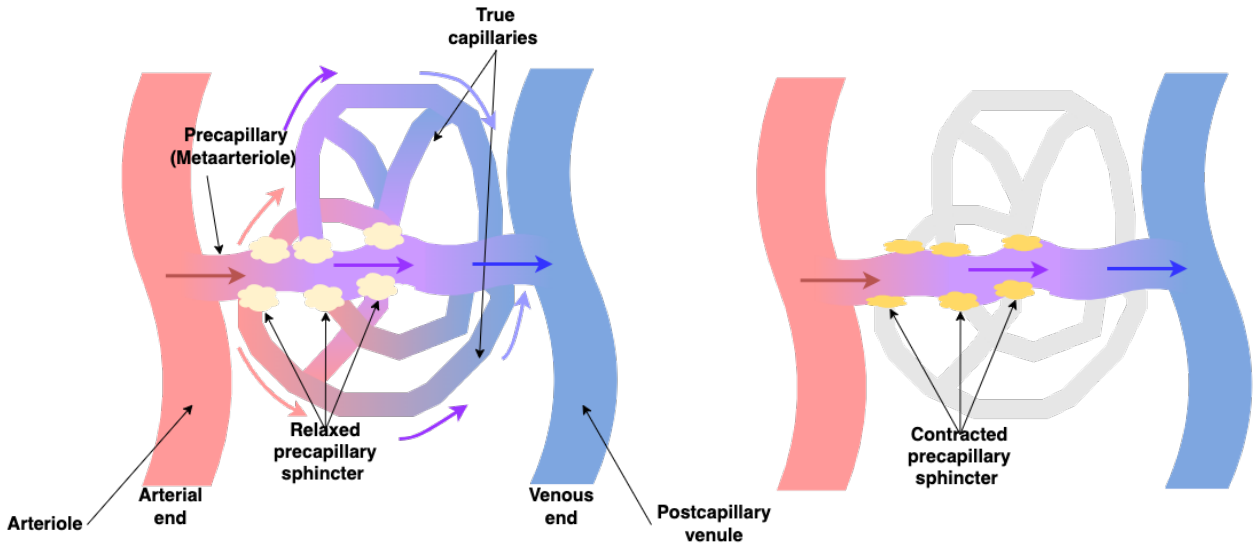
1.6.3 – Capillary Beds

I. Function of the capillary bed

- Facilitate exchange of substances from blood to tissues
- Structures with high metabolic activity have a richer capillary network than structures with low metabolic activity.

II. Structure of the capillary bed

- The capillary bed is supplied by a metarteriole (precaplliary), a terminal branch of an arteriole.
- Metarteriole connects with thoroughfare channel that is connected with the postcapillary venule.
- True capillaries branches of the metarteriole and reattaches to the thorough fare channels.
- Where the true capillaries branch of the metarteriole, they are encircled by smooth muscle cells, forming a precapillary sphincter.

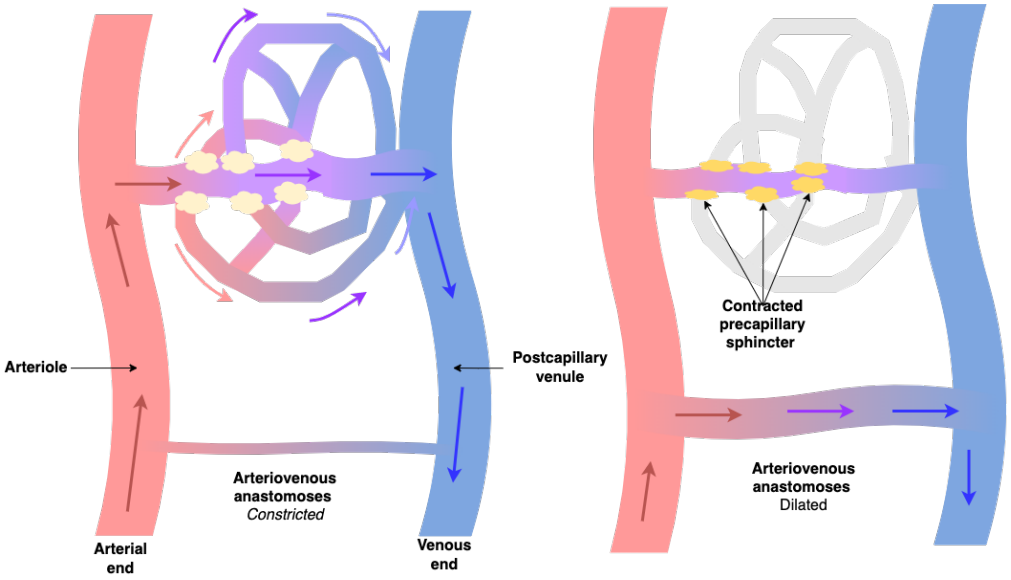


Structure of capillary bed	Anatomy and function
Precapillaries (Metaarterioles)	- Outer layer of circular smooth muscle cells - Pressure forces blood into capillaries when sphincters are open
Precapillary sphincter	- Most sphincters are completely or partially closed until the tissue has metabolic needs - By opening, the sphincter allows for blood flow in the capillary bed - Makes it possible for blood flow in certain areas to be switched on and off depending on the temporary requirements
True capillaries	- Blood flows through when sphincters are open - Optimal place for diffusion of oxygen and other metabolites
Thoroughfare channel	- Blood flow through when precapillary sphincters are closed
Postcapillary venules	- Outer layer of pericytes - Increases permeability in response to proinflammatory mediators - Preferential site of leukocyte migration from blood to tissues

1.6.4 – Arteriovenous Anastomoses

I. Anatomy and function

- Arterioles connects directly with venules and bypass capillary circulation
- Regulate blood flow in larger areas
    1. Innervated by sympathetic and parasympathetic fibers, which control vasoconstriction and regulate blood flow.
    2. With constriction of the vessels in the arteriovenous anastomoses, blood flows into the capillary bed. With dilation, less blood flows to the capillary bed.



CLINICAL CORRELATION

AV shunts

Arteriovenous anastomoses (AV shunts) play and important part in thermoregulation. If you expose yourself to cold temperatures, your vessels will work to maintain your body temperature. One mechanism behind this by reducing capillary blood flow in the skin. The autonomic nervous system stimulates vasodilation of the AV shunts, making less blood flow through the capillaries of the skin where heat is easily dissipated.

1.6.5 – Angiogenesis

- Formation of new capillaries
- Important for tissue repair and regeneration
- Angiogenic factors
    1. Vascular Endothelial Growth Factor (VEGF)
    2. Basic Fibroblast Growth Factor (bFGF)
    3. Platelet-Derived Growth Factor (PDGF)
    4. Platelet-Derived Endothelial Cell Growth Factor (PD-ECGF)
    5. Transforming Growth Factor (TGF)

CLINICAL CORREATION

Cancer treatment

Angiogenesis is an important mechanism in tumor growth as tumors need vascular supply to continue to grow. Anti VEGF drugs are used in treatment regimes in multiple types of cancers.

1.7 – Veins

I. Function

- Carry blood back to the heart
- Blood is pushed by contraction of smooth muscle cells in tunica media and by external compression from surrounding muscles and structures
- Valves, projections of tunica intima, prevent backflow of blood.

II. Composition

Venules	Thin walls with indistinct layers
Small and medium veins	Thicker wall, still indistinct layers
Large veins	Well developed intima. Thin media with small bundles of smooth muscle cells mixed with reticular and elastic fibers. Adventitia is thicker than media and frequently contains longitudinal smooth muscle bundles.

III. Specialized veins

Large veins in thorax and abdomen	Increased stiffness of the wall due to numerous longitudinal smooth muscle bundles in thick adventitia
Meningeal veins	Have no walls. They are just canals in dense connective tissue covered by endothelium.
Veins of legs	Transport blood against gravity and contain many valves that are thin folds of intima.
Superficial veins of legs	Have thick muscular wall Thick media and smooth muscle cells in all layers

1.8 – Summary of Vessels

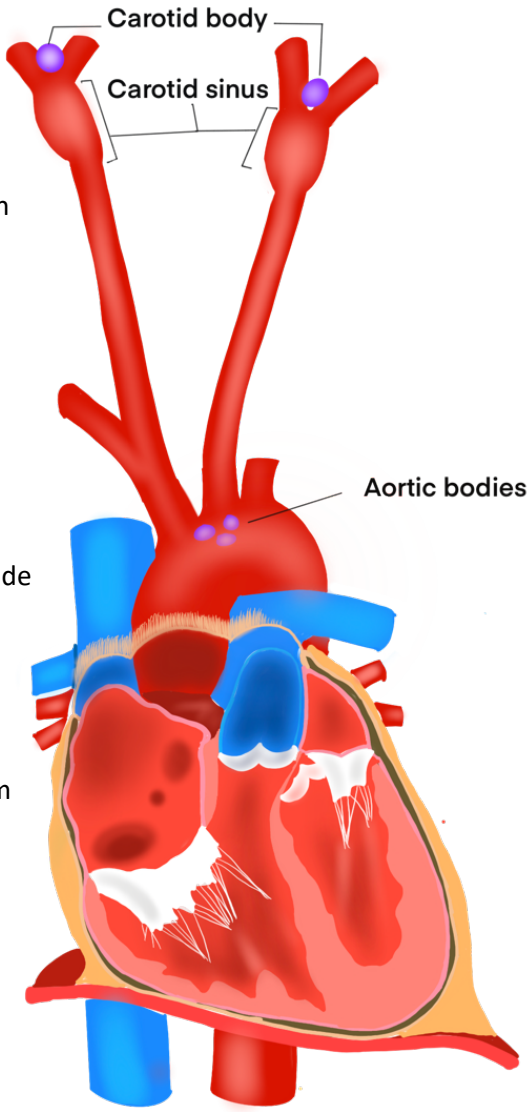
I. Capillaries

	Continuous capillaries	Fenestrated capillaries	Discontinuous capillaries
Continuous endothelium	Yes	No	No
Continuous basal lamina	Yes	Yes	No
Permeability	Low	High	Maximal
Pericytes present	Yes	Yes	No

II. Larger vessels

Type of artery	Intima	Media	Adventitia
Elastic arteries	Endothelium Connective tissue with smooth muscle	Many elastic lamellae alternating with smooth muscle	Connective tissue, thinner than media
Muscular arteries	Endothelium Connective tissue with smooth muscle, prominent internal elastic lamina	Many smooth muscle layers, with much less elastic material	Connective tissue, thinner than media Vasa vasorum may be present
Small arteries	Endothelium Connective tissue, less smooth muscle	3-10 layers of smooth muscle	Connective tissue, thinner than media No vasa vasorum
Arterioles	Endothelium	1-3 layers of smooth muscle	Very thin connective tissue layer
Capillaries	Endothelium	Pericytes	None
Venules	Endothelium: no valves	Scattered smooth muscle cells	None
Small veins	Endothelium Connective tissue with scattered smooth muscle fibers	Thin, 2-3 loose layers of smooth muscle cells	Connective tissue, thicker than media
Medium veins	Endothelium Connective tissue, with valves	3-5 more distinct layers of smooth muscle	Thicker than media: Longitudinal smooth muscle may be present
Large veins	Endothelium Connective tissue, smooth muscle cells, prominent valves	>5 layer of smooth muscle, with much collagen	Thickest layer, with bundled longitudinal smooth muscle

1.9 – Carotid and Aortic Bodies and Carotid Sinus



1.9.1 – Carotid and Aortic Bodies

I. Location
- Located in the connective tissue, close to carotid and aortic arch

II. Composition
- Rich capillary network
- Glomus cells
    1. Filled with dense-core vesicles containing dopamine, acetylcholine and other neurotransmitters
- Sheath cells – modified Schwann cells

III. Function
- Glomus cells monitors serum levels of oxygen (O_2), carbon dioxide (CO_2) and pH
- Appropriate ion channels in the glomus cells membranes respond to primarily hypoxia ($\downarrow O_2$), hypercapnia ($\uparrow CO_2$), or acidosis ($\downarrow$ pH). The glomus cells then release neurotransmitters
- Sensory fibers branching of glossopharyngeal nerve (CN IX) form synapses with the glomus cells. These fibers communicate with cardiac and respiratory center of the CNS
- The brain will then adjust cardiac and respiratory activity to compensate

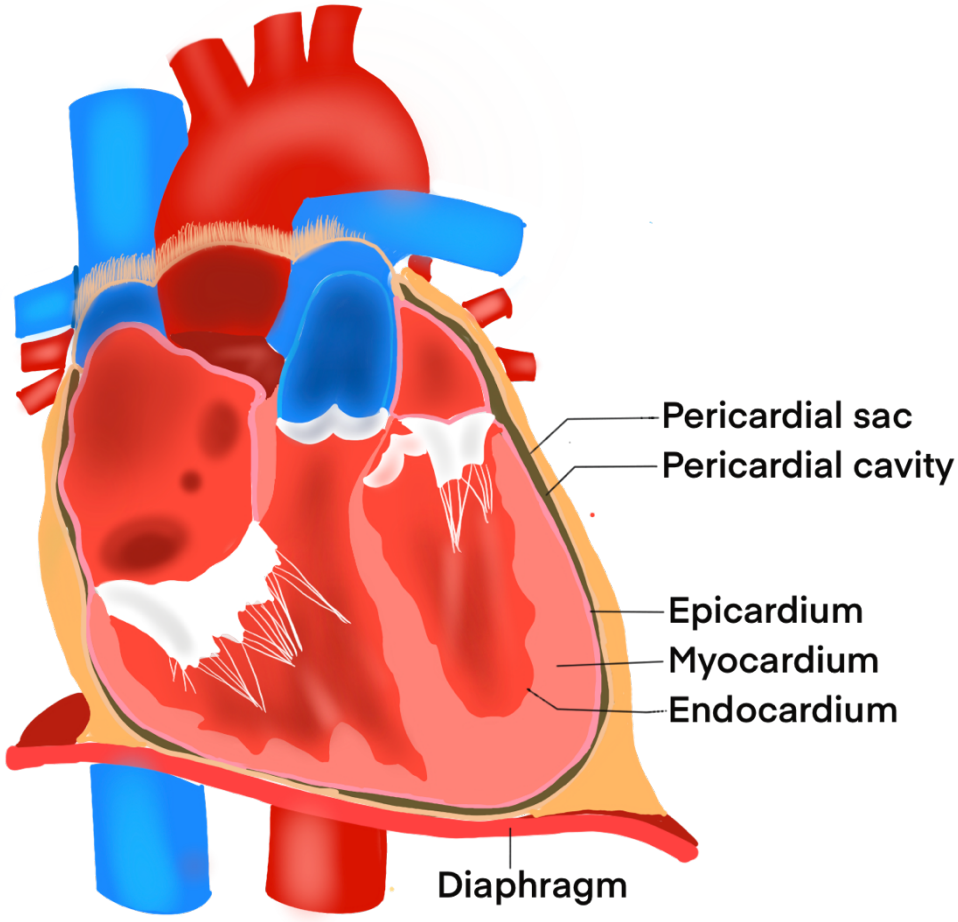
1.9.2 – Carotid Sinus

I. Location
- Dilated part of the internal carotid artery bilaterally

II. Composition
- Thick adventitia with numerous nerve endings from glossopharyngeal nerve (CN IX)
- Thin media that allow for greater distension of the wall
- Baroreceptors who respond to stretching of the walls

III. Function
- Monitor blood pressure via the baroreceptors
- Nerve signals are transmitted to vasomotor centers of medulla oblongata
- The brain adjust vasoconstriction to maintain normal blood pressure

1.10 – The Heart



I. Layers of the heart wall

- Similar to the main layers of the vascular wall
    1. Endocardium – lining the inside of the heart
    2. Myocardium – the muscle
    3. Epicardium – the outside layer of the heart. Lined with special simple squamous epithelium → mesothelium

II. Mesothelium

- Mesenchymal origin
- Similar to endothelium
- Reduces friction by producing phospholipids
- Controls transport of substances to pericardial fluid
- Can secrete cytokines if activated
- Lines the whole pericardial cavity

III. Cardiac valves

- Part of the endocardium
- Connective tissue lined with endothelium

Section 2 – The Lymphatic System

2.1 – Defense Mechanisms of the Human Body

2.2 – Types of Immune Reactions

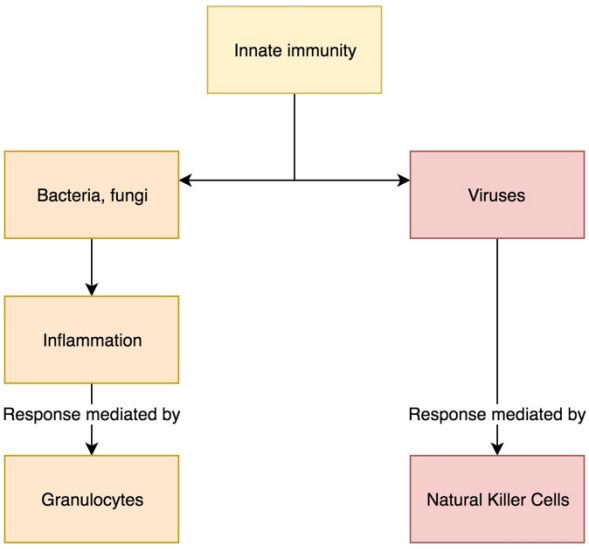
2.3 – Lymphoid Tissue

Word list

Term	Definition
Antigen	A molecule or protein that trigger immune reactions
Epitope	= antigenic determinant. The specific site on the antigen that binds with the antibody
Antibody	A protein produced by plasma cells (a type of B-cell) that binds to antigens
Effector cell	A cell responsible for a certain action
Humoral	"in fluid"

2.1 – Defense Mechanisms of the Human Body

2.1.1 – The Innate Immune System



- *Non-specific*: initial defense against foreign material that occurs regardless of the type
- Consists of:
    1. Epithelial cells: barriers that physically keep foreign material out
    2. Phagocytic cells: eats the foreign material
    3. Pattern recognition receptors: recognize compounds specific to non-human cells
    4. Natural Killer (NK) cells: kills cells presenting abnormal antigens on their surface
    5. Complement system: enhances the inflammatory process (i.e. complements the response)
    6. Acute inflammation: Neutrophils, macrophages, other granulocytes, mast cells

I. Pattern recognition receptors

- Found on cells participating in non-specific defense reactions
- Recognize molecular patterns present on, or released by, non-human cells, such as:
    1. Bacteria: lipopolysaccharide, peptidoglycan, flagellin, pilin, bacterial DNA
    2. Fungi: glycolipids, zymosan
    3. Viral nucleic acids: DNA and RNA
- Receptors recognizing over 100 molecular patterns have been identified so far
- Types:
    1. Endocytic PRRs: trigger selective endocytosis of microorganisms
    2. Signaling PRRs: signals the cytoplasm and nucleus of the immune cells to induce expression of genes and produce cytokines. This class of receptors includes toll-like receptors (TLRs), CD 14 receptor and NOD receptors (cytoplasmic)

II. NK cells

- Similar to B- and T-cells, but are always "ready to kill". Mechanism of killing is similar to $T_{cytotoxic}$ lymphocytes
- Large: 12 µm
- Contain large azurophilic granules, a special form of hydrolase vesicles
- Have receptors recognizing immunoglobulins ***stimulating*** cytotoxic activity and receptors recognizing MHC antigens: ***inhibiting*** cytotoxic activity
    1. Kill cells with non-self-antigens, especially coated with antibodies and cells not presenting their own MHC antigens. The classic examples are virus-infected cells and tumor cells, which have low expression of MHC

2.1.2 – The Adaptive Immune System

- Takes a little longer to respond, but is in turn more specific to the pathogen and remembers for next time
- Consist of:
    1. B-cells
    2. T-cells
    3. Antigen-presenting cells (APCs)
    4. Macrophages

I. Antigen-presenting cells

- Responsible for endocytosis of non-self-antigen, processing antigens, and presenting MHC II molecules with the foreign antigen on their cell membrane for T-cells to notice. Can be professional and non-professional

<table>
<tr><th colspan="2">Professional: act spontaneously and have PRRs</th></tr>
<tr><td colspan="2">Macrophages</td></tr>
<tr><td colspan="2">B-lymphocytes</td></tr>
<tr><td colspan="2">Dendritic cells</td></tr>
<tr><td>Dendritic cells</td><td rowspan="2">Lymphoid organs</td></tr>
<tr><td>Interdigitating cells</td></tr>
<tr><td>Langerhans cells</td><td>epidermis, epithelia of oral cavity and respiratory tract</td></tr>
<tr><th colspan="2">Non-professional: needs stimulation by cytokines to function</th></tr>
<tr><td colspan="2">Thymic epithelial reticular cells</td></tr>
<tr><td colspan="2">Endothelial cells</td></tr>
<tr><td colspan="2">Fibroblasts</td></tr>
</table>

II. Antigens

- Self-antigens: of the individual, tolerated by immune system: MHC antigens class I and II
- Non-self-antigens: Foreign to the individual, attacked by the immune system. E.g bacterial, viral, parasitic, transplanted tissue

2.1.3 – Lymphocyte Subpopulations

I. B-lymphocytes (B-cells)

- Effector cells in humoral immune response, have B cell receptors called immunoglobulins (= antibodies)
- Most important surface proteins: CD 19, CD20, CD40

II. T-lymphocytes (T-cells)

- Effector cells in cell-mediated immune response, have T cell receptors (TCR)
- T helper (T_H, CD4) – participate in initial phases of both immune response types
- T cytotoxic (T_C, CD8) – kill cells in cell-mediated immune response
- T regulatory (T_{reg},CD4, CD25) – suppress cell-mediated immune response

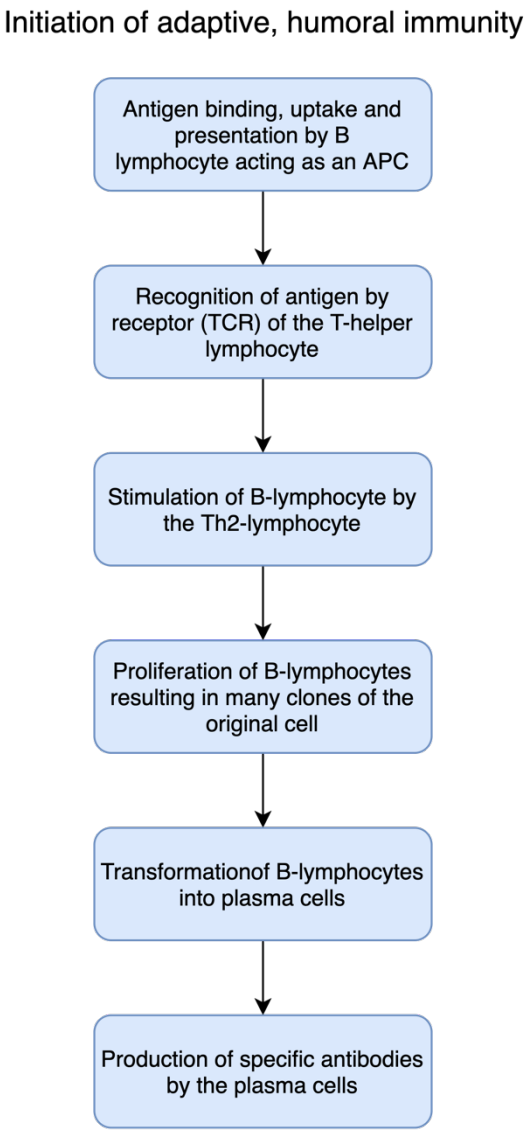
III. NK (natural killer) lymphocytes

- Most important surface proteins: CD16, CD56

2.2 – Types of Immune Reactions

2.2.1 – Humoral Immunity

- Humoral immunity involves components of both the innate and adaptive immune system.
    1. Example of innate, humoral immunity: the xcomplement system
    2. Example of adaptive, humoral immunity: antibodies
- Initiation of *adaptive*, humoral immunity occurs with the following steps:
- Some B-cells do not transform into plasma cells but instead remains as B memory cells allowing for a quicker response next time the same pathogen is encountered
- During the immune responses, lymphocytes, antigen-presenting cells and macrophages „cross-talk" to each other via chemical signal molecules, cytokines: interleukins (IL), interferon (IFN), tumor necrosis factor (TNF)



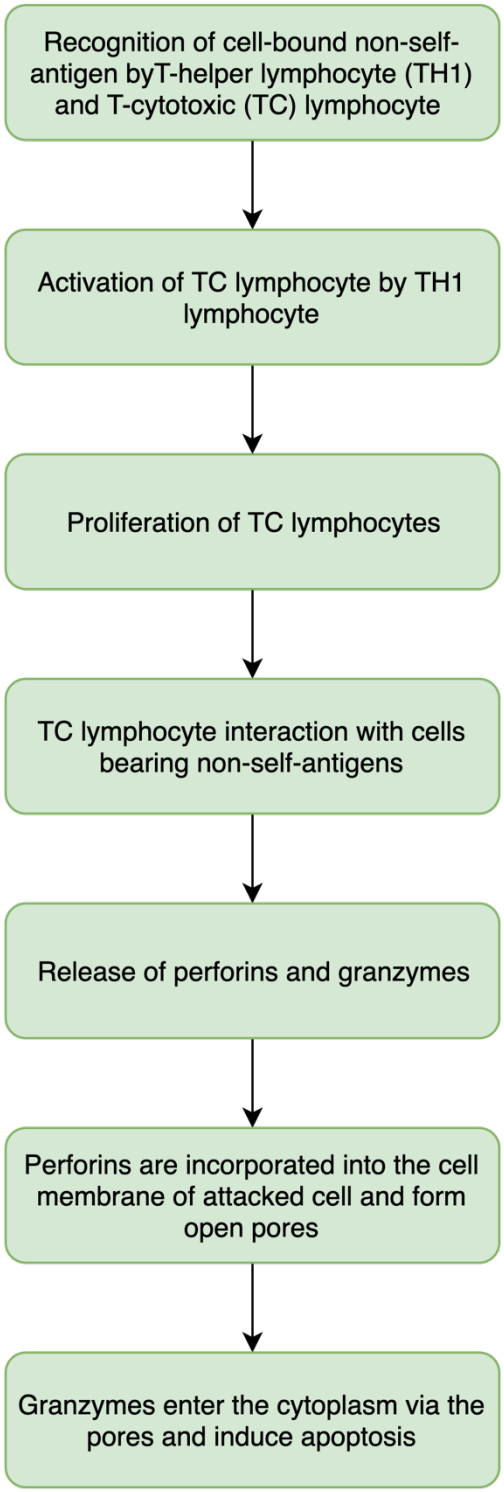
FUN FACT

Humoral immunity

Humor = fluid. Humoral immunity involves any molecule floating in the serum (complement, antibodies)

2.2.2 – Cell-Mediated Immunity

- Initiation of adaptive, cell-mediates immune response occurs with the following steps:
- Some TC-lymphocytes remain as T memory cells similar to memory B-cells



2.3 – Lymphoid Tissue

- The site of immune reactions
- Consists of reticular connective tissue and lymphocytes

I. Locations of lymphoid tissue:

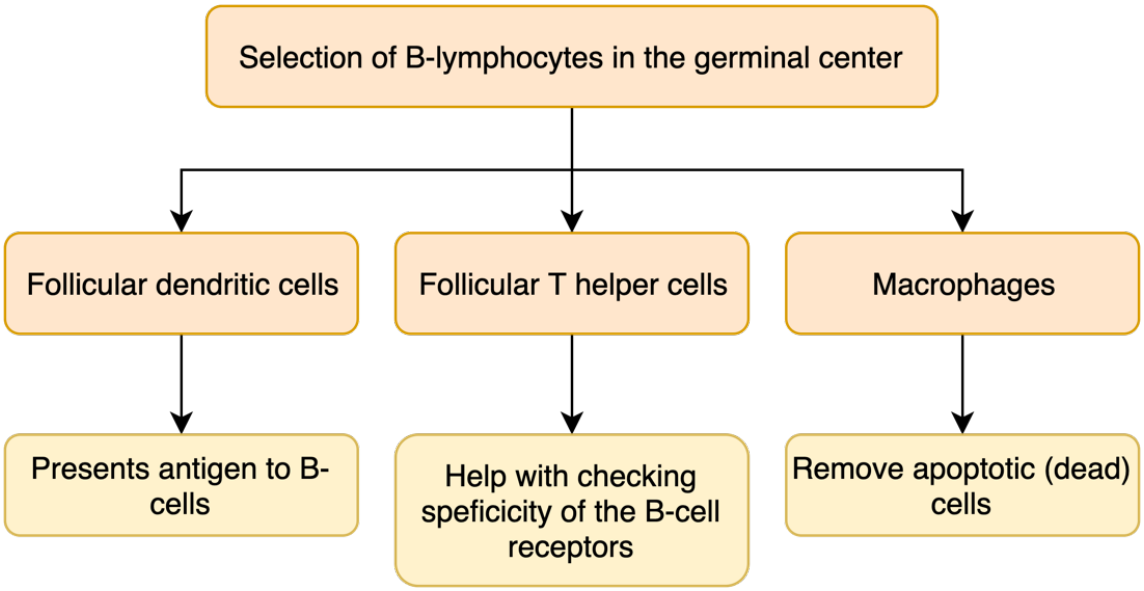
- Lymph nodes
- Spleen
- Thymus
- Mucosa-associated lymphoid tissue (MALT):
    1. Tonsils
    2. Digestive tract: gut-associated lymph tissue (GALT) and appendix
    3. Respiratory tract: bronchi associated lymph tissue (BALT)

II. Types of lymphoid tissue

- Nodular: mainly B lymphocytes
- Diffuse: T and B lymphocytes
- The lymphoid nodule is a spherical aggregate of lymphoid tissue
    1. Primary (dormant): appears uniform
    2. Secondary (after antigenic stimulation): Mantle and germinal center. B lymphocytes proliferate and start transformation into plasma cells

III. Selection of B lymphocytes in the germinal center

- Happens in the germinal center of lymphoid nodules
- Cells with receptors showing the highest specificity for the antigen survive , the others die by apoptosis.



2.3.1 – The Lymph Node

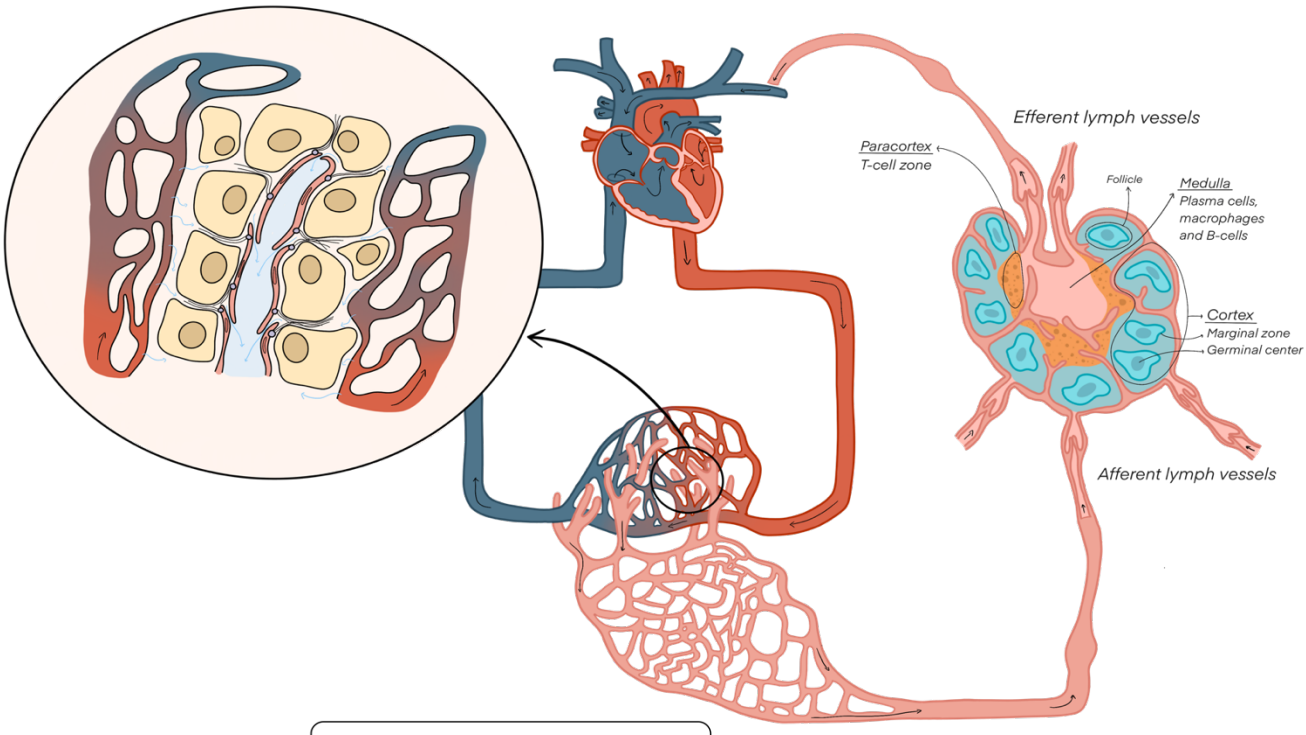
- Lymph = extracellular tissue fluid
- Fluid is drained from tissues by lymphatic vessels and returned to the blood
- Lymph nodes act as filters along the pathways of lymphatic flow, monitoring the antigens present in the lymph, facilitating the immune response
- Lymphatic capillaries:
    1. Endothelial cells: continuous but highly permeable
    2. Basal lamina
    3. Larger lymphatic vessels: structure of the wall similar to that of thin-walled veins including presence of valves

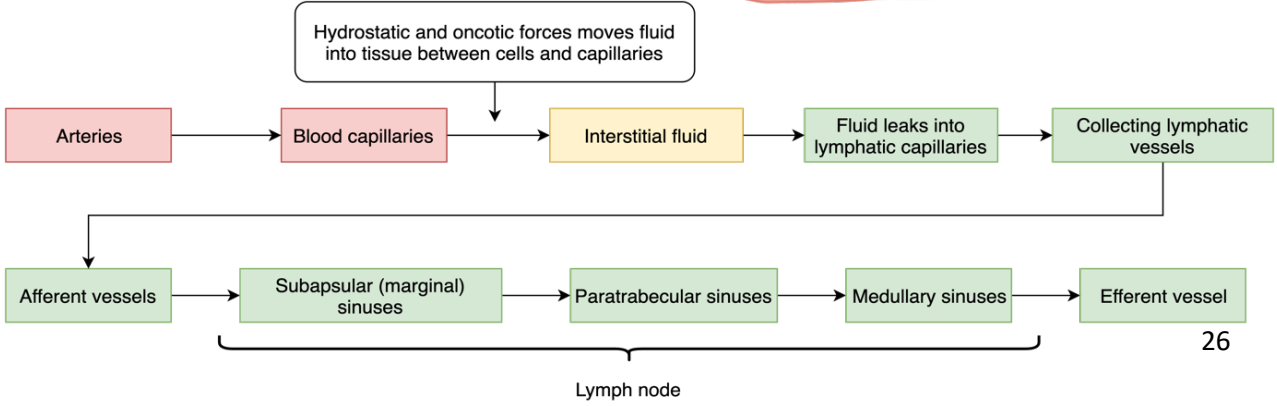
I. Lymphocyte recirculation

- lymphoid tissue of the node –> sinuses –> efferent lymphatic vessel –> blood –> high endothelial venules –> lymphoid tissue of the node
- High endothelial venules (HEV) are postcapillary venules lined with tall, cuboidal or columnar endothelial cells. Their cell membrane contains adhesion molecules (addressins) utilized by lymphocytes to find the lymph nodes. The lymphocytes have „homing receptors" on their cell surface that allows them to bind to the adhesion molecules

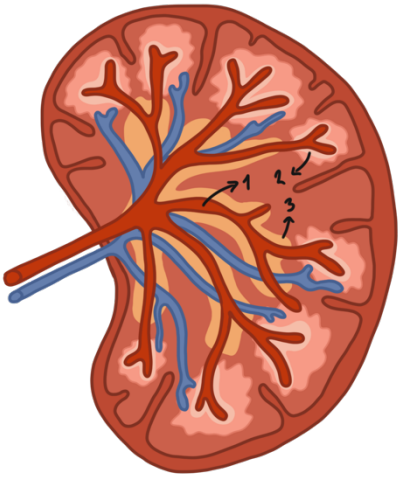
II. Pathways of lymph flow in the lymph node

- Lymph node sinuses: irregular spaces lined with flat, endothelium-like fibroblastic reticular cells, loosely filled with other reticular cells and their processes





2.3.2 – The Spleen



1 - Central arteries
2 - B-cell zone (germinal center + marginal zone)
3 - T-cell zone (PALS)

I. Connective tissue scaffolding

- Capsule
- Trabeculae
- Areas:
    1. White pulp: lymphoid tissue
    2. Red pulp: reticular connective tissue with numerous thin-walled blood vessels

II. White pulp

- The lymphoid tissue distributed around small arteries (central arteries) where immune response to non-self-antigens occurs
- The marginal zone: site of first contact between antigens and lymphoid tissue, rich in antigen-presenting cells and small sinusoidal blood vessels
- Periarterial lymphatic sheath (PALS): T lymphocytes
    1. Splenic (lymphoid) nodules (B lymphocytes): local thickenings of the PALS

III. Red pulp

- Splenic cords: reticular connective tissue rich in macrophages
- Splenic sinusoids: discontinuous capillaries
    1. Fusiform endothelial cells with wide intercellular spaces
    2. Circular reticular fibers
    3. Discontinuous basal lamina (only between endothelial cells and fibers)
- Pulpal veins
- Macrophages of the red pulp phagocytize and digest old erythrocytes that are less flexible and have altered composition of glycocalyx

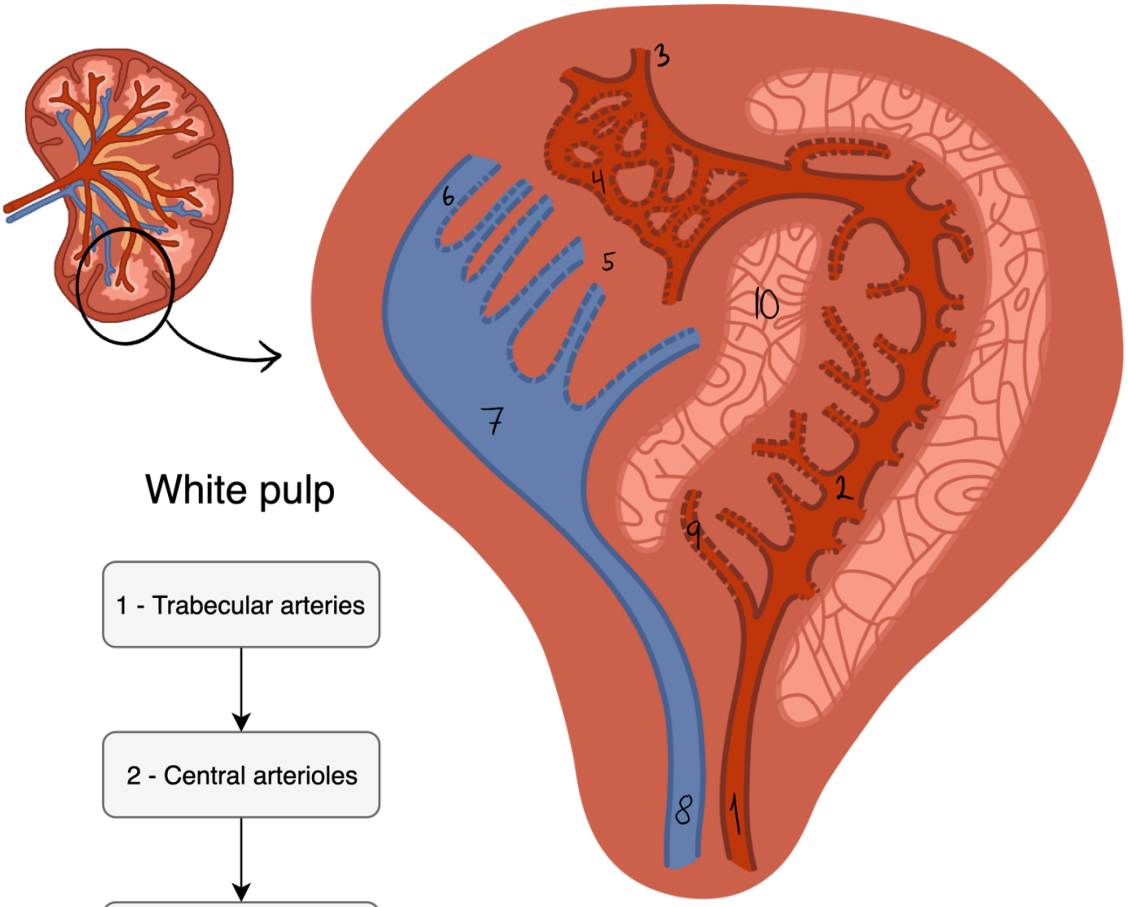
CLINICAL CORRELATION

Hereditary spherocytosis

Caused by defects in RBC membrane proteins preventing the red blood cells from maintaining their usual shape. Leads to hemolysis and anemia, and sometimes the anemia can become so severe that the only option is to remove the spleen

IV. Splenic circulation

- The spleen has an open system of blood circulation



Red pulp	White pulp
1 - Trabecular arteries	1 - Trabecular arteries
2 - Central arterioles	2 - Central arterioles
3- Penicillar arteries	9 - Open branches of central arterioles
4 - Open sheathed capillaries	Intercellular spaces of marginal zone
5 - Intercellular spaces of splenic cords	10 - Open sinusoids of marginal zone
6 - Open splenic sinusoids	
7 - Pulpal veins	
8 - Trabecular veins	

2.3.3 – Thymus

- "School" for T lymphocytes: immature T lymphocytes get their specialization and learn to *tolerate* self-antigens: they acquire the immunocompetence.
- Loose connective tissue forms capsule and incomplete septa dividing the organ into smaller parts (lobules)
- Differs from other lymphoid organs:
    1. Epithelial origin
    2. No reticular connective tissue or lymphoid nodules
    3. Only T lymphocytes
    4. No immune reactions against non-self-antigens

I. Areas of the thymic lobule

- Cortex: numerous lymphocytes
- Medulla: less lymphocytes
- The inner scaffolding of the thymic lobule is formed by different types of epithelial reticular cells (ERC)
- The meshes of network formed by ERC are occupied by:
    1. T lymphocytes
    2. Macrophages
    3. Dendritic cells

Type of ERC	Function	Type of ERC
Antigen presenting cells	*Teachers* Express self-antigens on their surface and present them to immature T lymphocytes	Cortex: Type II ERC Medulla: Type V ERC
Barrier cells	*Blood-thymus-barrier* Processes interconnected by tight junctions and form a barrier separating the cortex from connective tissue, blood vessels and medulla. Prevents access of non-self-antigens to the cortex. Premature activation of T lymphocytes leads to apoptosis.	Type I, III, and IV
Hassall's corpuscle cells	*Maturation of T_{reg} cells* Hassall's corpuscles with concentrically arranged epithelial cells are located only in the medulla. In central region of the corpuscle, cells show signs of keratinization. Hassall's corpuscles are unique to the thymus. They produce cytokines controlling maturation of T_{reg} lymphocytes.	Type VI

II. Principles of the “thymic school” In the cortex:

- Immature T cells express TCR and CD4 + CD8 molecules –> differentiation into TH, TC or Treg
    1. First selection: ERC type II present MHC antigens to maturating T cells In the medulla
    2. Second selection: ERC type V and dendritic cells present self-antigens specific for various tissues together with MHC antigens to maturating T cells.
- T cells which either *do not* recognize self-antigens at all, or *attac*k self-antigens die by apoptosis and are eliminated by macrophages.
- Around 2% of lymphocytes graduate
- Epithelial cells of thymus secrete peptides regulating proliferation and specialization of the surviving T lymphocytes: thymosins, thymopentin, thymulin, thymic stromal lymphopoietin
- B lymphocytes undergo maturation and acquire immune competence in the *bone marrow*. They are selected in a similar manner as T lymphocytes in thymus
    1. Self-antigens are presented by bone marrow stromal cells

III. Involution of thymus

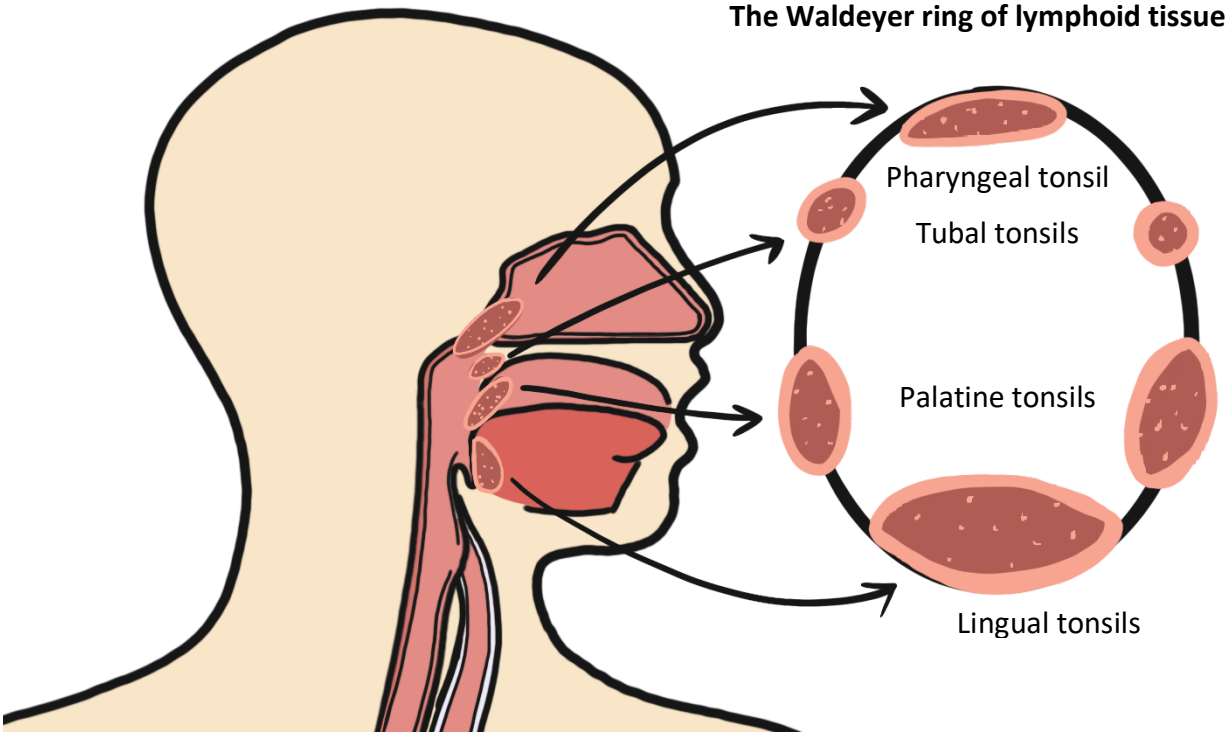
- During puberty, the lymphoid structures in thymus disappear and are replaced by adipose tissue considerably reducing the proliferation and differentiation of new T-cells
- Only scarce, small islets of the lymphoid tissue remain in the thymus of adults.

2.3.4 – The Tonsils

- Belong to MALT
- Have epithelial surface and invaginations surrounded by lymphoid tissue
    1. Tubular invaginations = crypts or infoldings
- B lymphocytes predominate
- No afferent lymphatic vessels, but efferent lymphatic vessels are present
- crypts
- The tonsils react to non-self-antigens in air or food if they cross the epithelial barrier of the oropharynx
- The antigens are transferred by special cells (M cells) present in the epithelium

Location	Structure	Epithelium type
Palatine	The largest tonsils, surrounded by a connective tissue capsule with numerous deep crypts	Stratified squamous epithelium
Lingual	Single branched crypt	
Pharyngeal (= adenoids)	Epithelial furrows	Airway epithelium: pseudostratified ciliated with goblet cells
Tubal (near auditory tubes)	No epithelial invaginations	

The Waldeyer ring of lymphoid tissue



Section 3 – The Integument

3.1 – Epidermis
3.2 – Dermis
3.3 – Hypodermis
3.4 – Defense Mechanisms of the Skin
3.5 – Hair
3.6 – Glands of the Skin
3.7 – Types of Skin
3.8 – Innervation of the Skin

- The integument = skin + hypodermis + appendages (glands, hair, nails)

I. Functions

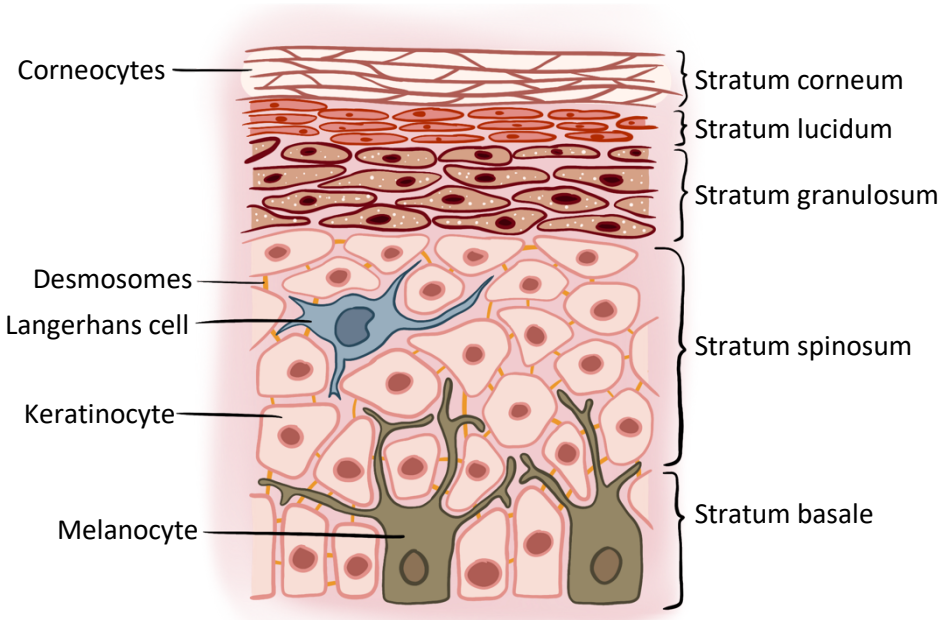
- Protection
- Thermoregulation
- Water/electrolyte regulation
- Sensation
- Synthesis of Vit D

II. Layers of the skin

- Epidermis: epithelium
- Dermis: loose & dense connective tissue
- Hypodermis: subcutaneous tissue = adipose tissue + loose connective tissue

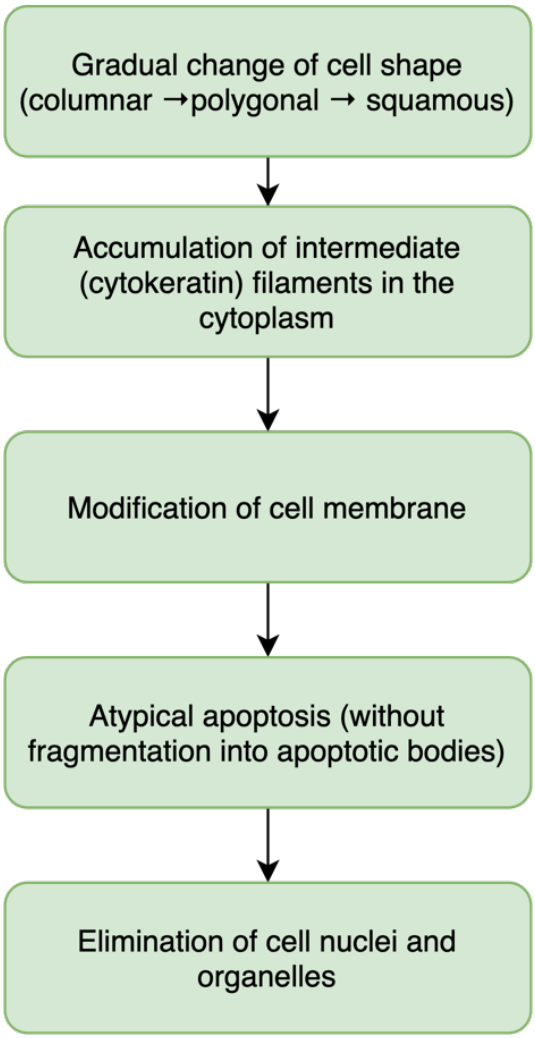
3.1 – Epidermis

- Keratinized stratified squamous epithelium containing four cell types:
    1. Keratinocytes (90%)
    2. Melanocytes
    3. Langerhans cells
    4. Merkel cells



3.1.1 – Keratinization

- The main cell population, keratinocytes, migrate from the basal layer towards the surface of the epidermis, undergoing a coordinated transformation into dead keratin plates.
- The result is distinct layers in the epidermis reflecting the successive stages of the keratinization process



3.1.2 – Layers

Inner <— Outer "come let's get sun burned"	Stratum..	Components	Function
	Corneum	- Keratinocytes become dead, stiff plates (corneocytes) with a dense network of keratin filaments - Surrounded by cell envelope	Form protective barrier
	Lucidum	Keratinocytes die by atypical apoptosis: - Elimination of nuclei and organelles - The cytoplasm contains thick bundles of cytokeratin filaments - Thickening of the cell membrane by additional layer of proteins	
	Granulosum	Flattened keratinocytes with basophilic granules: - Keratohyalin granules (no membrane) containing filaggrin (cytokeratin filament-aggregating protein) - L granules (no membrane): aggregates of protein loricrin - Lamellar bodies (keratinosomes) rich in lipids which are released to the extracellular space and form a *hydrophobic barrier* preventing penetration of water	
	Spinosum	- Polygonal keratinocytes interconnected by cytoplasmic processes with desmosomes and cytokeratin (intermediate) filaments - Langerhans cells	- Intense synthesis of cytokeratins - Production of involucrin, cytokines, EGF and vitamin D3
	Basale	- Stem cells and dividing cells - Hemidesmosomes connecting the s. basale with the basement membrane - Melanocytes - Merkel cells	- Renewal of the epidermis - Production of cytokines, growth factors and vitamin D3

3.1.3 – Cells in the Epidermis

I. Corneocytes

- Stiff and mechanically resistant due to dense network of keratin filaments linked by filaggrin
- Impermeable to water due to the presence of
    1. Outer lipid envelope: lipids released from lamellar bodies
    2. Cell envelope composed of cell membrane and inner layer of insoluble proteins (involucrin, loricrin)

II. Melanocytes

- Have neuroectodermal origin
- Synthesize melanin in melanosomes converting them into melanin granules
- Transfer melanin granules to the neighboring keratinocytes, protecting the living cells in epidermis from the harmful effects of UV

III. Langerhans cells

- Originate from bone marrow
- Function as antigen-presenting cells: "young" forms of dendritic cells
    1. After taking up non-self-antigen, they migrate to dermis and then with the lymph to lymph nodes, where they present the antigen to T lymphocytes. During this migration they become mature dendritic cells. T lymphocytes migrate from lymph nodes to skin and trigger cell-mediated immune response
- Contain Birkbeck granules
    1. Birbeck granules contain glycoprotein (langerin) which after secretion is mounted on the cell membrane and serves as receptor for mannose

IV. Merkel cells

- Serve as mechanoreceptors
- Have granules with dense cores containing neuropeptides
- Make contacts with afferent nerve terminals

V. Epidermal stem cells

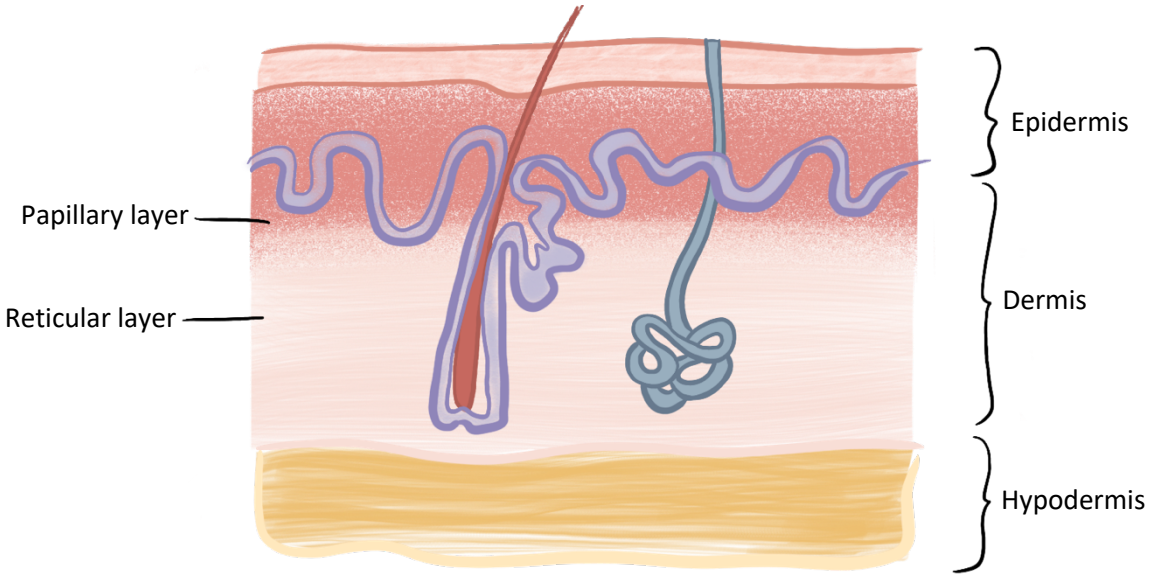
- The primary niche of epidermal stem cells is located in the outer root sheath of the hair follicle, close to arrector pili muscle attachment
- From this site stem cells migrate to the basal layer of the epidermis and to the hair matrix
- Differentiate into
    1. Epidermal keratinocytes
    2. Cells of all epithelial structures of the hair follicle
    3. Cells of all skin glands
- location of primary niche is optimal for hair cycle

CLINICAL CORRELATION

Langerhans cell histiocytosis
A group of proliferative disorders involving the Langerhans cells presenting with lytic bone lesions +/- skin rash. The Langerhans cells are functionally immature and can't adequately present antigens to T-cells. In the microscope the characteristic Birbeck granules can be observed looking like tennis rackets.

3.2 – Dermis

- Papillary layer: finger-like protrusions of loose connective tissue (papillae)
    1. Contain capillary loops, nerve fibers and mechanoreceptors
    2. Rows of papillae form dermal ridges (e.g. fingerprints)
- Reticular layer
    1. Dense connective tissue rich in elastic fibers
    2. Contains glands and/or their ducts, hair follicles, blood vessels (two plexuses, glomus type anastomoses), mechanoreceptors. subpapillary plexus and dermal plexus
- Dermis contains numerous cells participating in defense processes: lymphocytes, macrophages, dendritic cells, mast cells



3.3 – Hypodermis

- Yellow adipose tissue and loose connective tissue
- Contains glands, hair follicles, blood vessels, mechanoreceptors

3.4 – Defense mechanisms of the skin

- Barrier preventing invasion of microorganisms
- Stratum corneum with its hydrophobic barrier
- Tight junctions interconnecting keratinocytes of stratum granulosum
- Cells participating in defense:
    1. Keratinocytes: Keratinocytes of stratum spinosum have pattern recognition receptors. after contact with a pathogen they secrete antimicrobial substances and lymphocyte-attracting cytokines
    2. Langerhans cells, T and NK lymphocytes, macrophages, dendritic cells, mast cells, neutrophils
- Some T memory lymphocytes remain in stratum spinosum of the epidermis as „resident Tc lymphocytes" and in dermis as „resident Th lymphocytes". The next encounter with the same pathogen will trigger a faster immune reaction.
- Skin does not contain B lymphocytes

3.5 – Hair

- All skin appendages, including hair follicles and glands, develop from infoldings of the epidermis into dermis and hypodermis: they are epithelial structures
- During growth, the hair undergoes keratinization

I. Hair follicle

- Hair bulb
- Hair papilla (connective tissue) with capillary vessels, surrounded by hair matrix (proliferating epithelial cells and melanocytes)

II. Hair

- Undergoes keratinization
- Medulla, cortex and cuticle
- Inner root sheath (undergoes keratinization)
    1. Cuticle
    2. Huxley's layer
    3. Henle's layer
- Outer root sheath
    1. Continuous with invagination of epidermis, does not undergo keratinization
    2. Hair capsule (connective tissue)
    3. Hair matrix

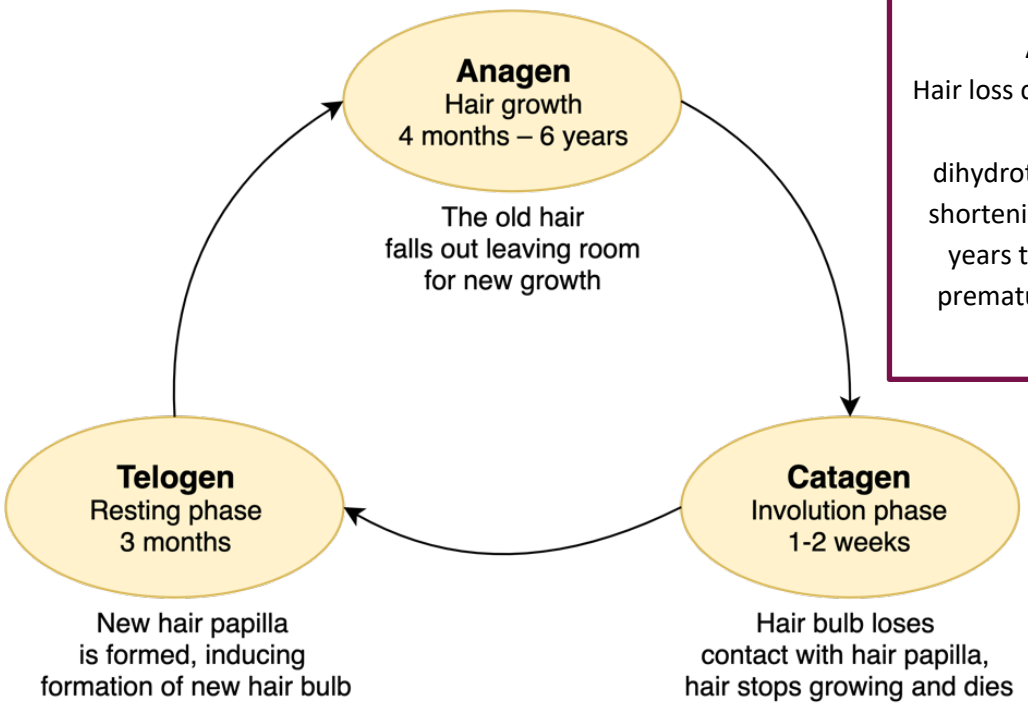
III. Arrector pili muscle

- Bundle of smooth muscle cells
- Attached to hair capsule and upper layer of dermis
- Autonomic innervation
- Contraction straightens the hair (goose bumps)

IV. Vellus hair

- Thin, short, colorless hair with identical structure of hair follicles as visible hair
- Even macroscopically hairless areas of the skin show the presence of vellus hair

3.5.1 – Hair Cycle



CLINICAL CORRELATION

Androgenic alopecia
Hair loss caused by increased sensitivity of the hair follicle to dihydrotestosterone (DHT). Leads to shortening of the anagen phase from years to just a few weeks, causing premature balding in both men and women

3.6 – Glands of the Skin

I. Eccrine sweat glands

- Simple tubular coiled glands
- Secretory portion: columnar secretory cells with eccrine (merocrine) secretion (exocytosis)
    1. Dark = protein-producing, clear = ion-transporting
    2. Consist of myoepithelial cells and basal lamina
    3. Product: water, ions (Na, K, Cl), some proteins, trace amounts of urea and ammonia
- Duct: double cuboidal epithelium, reabsorbs ions and secretes urea and ammonia
- Sweat pore: spiral canal in the epidermis

II. Apocrine sweat gland

- Simple tubular coiled gland, larger that eccrine sweat gland
- Secretory portion: cuboidal/columnar secretory cells with apocrine secretion (pinching off apical cytoplasm with secretory material) and eccrine secretion
    1. Consist of myoepithelial cells and basal lamina
- Duct: double (occasionally triple) cuboidal epithelium, opens to the hair follicle
- Product: water, fatty acids, alkanols, steroids, proteins
- Lipid droplet not surrounded by membrane

III. Sebaceous gland

- Branched acinar gland
- Secretory portion: stratified epithelium with cells producing secretory material (lipids) and then undergoing degeneration and dying (holocrine secretion)
- Short duct (stratified squamous epithelium) opening to hair follicle
- Product: lipids mixed with cell debris

3.7 – Types of Skin

	Thick (glabrous) skin	Thin (hairy) skin
Location	Palms of hands and soles of feet	Rest of body surface
Epidermis	Thick with distinct layers and very thick stratum corneum	Thin with indistinct layers and thin stratum corneum
Dermal papillae	Tall, regular with distinct dermal ridges	Smaller and irregular dermal papillae
Associated structures	Only eccrine sweat glands	All associated structures present

3.8 – Innervation of the skin

- Cutaneous sensory receptors:
    1. Nonencapsulated
    2. Encapsulated

Type of nerve endings	Constituents	Location	Sensation
Free (petricial)	Nerve ending only	Living layers of the epidermis, dermis, around hair roots	touch, pressure, pain, temperature
Merkel disk	Merkel cell and nerve terminal	Epidermis (especially numerous in fingertips and lips)	Delicate touch (e.g. Braille script)
Meissner corpuscle	Nerve endings surrounded by lemnocytes (modified Schwann cells)	Dermal papillae	Touch, esp. shearing movements of epidermis against dermis
Pacinian corpuscle	Nerve ending surrounded by multiple concentric layers of lemnocytes and flat fibroblasts, with fluid inbetween	Hypodermis, also joint capsules, mesentery, some organs	Pressure, high frequency vibration

I. Nerve endings

- Krause end bulbs
    1. Location: dermis (especially genital organs) and some mucous membranes
    2. Sensitive to: touch
- Ruffini corpuscles
    1. Location: dermis, also joint capsules, periodontal ligament Sensitive to: stretching

Section 4 – The Oral Cavity and Salivary Glands

- The inner lining of tracts (alimentary, urinary, respiratory, etc.) is the mucosa consisting of:
    1. Epithelium
    2. Lamina propria: dense/loose connective tissue, connective tissue cells, migratory cells, blood vessels, nerve fibers, small glands, aggregates of lymphoid tissue
    3. Submucosa: loose/dense connective tissue. Contents as in lamina propria, provides stability of lamina propria against the underlying tissues

4.1 – The Oral Mucosa

- Stratified squamous epithelium: nonkeratinized or keratinized
- Lamina propria and submucosa with small salivary glands
    1. Labial, buccal, palatine and lingual glands

I. Vermilion

- Modified skin: the red part of the lips
- Thin epidermis with subepidermal blood vessels and without skin glands hair follicles

II. Types of oral mucosa

- *Masticatory mucosa* with keratinized epithelium: areas exposed to mechanical loads such as the gingivae, hard palate and the dorsal surface of the tongue
    1. No submucosa, mucosa is firmly attached to the underlying tissues
- *Lining mucosa* with non-keratinized epithelium: other areas of oral cavity
    1. Submucosa present

III. Epithelium lining the oral cavity

- Keratinized:
    1. Similar to epidermis but without stratum lucidum and only thin stratum corneum
    2. In some places parakeratinization occurs: nuclei present in stratum corneum cells, no stratum granulosum
- Non-keratinized:
    1. All cells are living
    2. Cells contain less cytokeratin filaments, no keratinization-associated proteins or lipids
    3. Higher permeability,
    4. Layers: basal, spinous, superficial
- Both types of epithelium contain melanocytes, Langerhans cells and Merkel cells, and are capable of rapid renewal (5-8 days)

4.2 – Teeth

- Mineralized components: enamel, dentin and cementum (acellular & cellular)
- Non-mineralized components: dental pulp and periodontal ligament
- Enamel: 96% minerals (hydroxyapatite [HA] crystals), glycoproteins (enamelins)
    1. Structural subunits: enamel rods
    2. Enamel is the hardest substance in the organism

I. Dentin

- 70% minerals (HA crystals) with small amounts of ground substance
- Collagen I fibers
- Dentinal tubules: thin canaliculi containing
    1. Processes of odontoblasts (cells located in dental pulp)
    2. Unmyelinated (sheathless) nerve fibers

II. Cementum

- 60% minerals (HA) with small amount of ground substance
- Collagen I fibers
- Acellular cementum (upper part of tooth root): only extracellular substance
- Cellular cementum (lower part of tooth root): contains lacunae and canaliculi housing cell bodies and processes of cementocytes (modified osteocytes).
    1. Cellular cementum is most similar to bone

III. Dental pulp

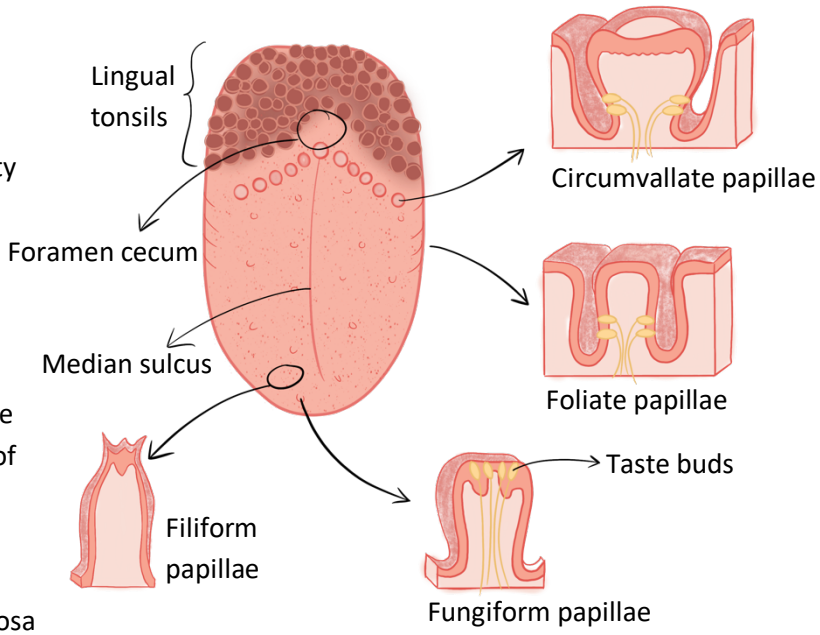
- Gelatinous connective tissue with numerous cells
- Layer of odontoblasts
- Blood vessels and nerve fibers

IV. Periodontal ligament

- Thick bundles of collagen I fibers connecting cementum of the root with alveolar bone, between loose connective tissue with blood vessels cementum alveolar bone

4.3 – The Tongue

- Core: skeletal muscle
- Ventral mucosa: thin epithelium, vascular plexuses, high permeability (sublingual pills)
- Dorsal mucosa: lingual papillae, no submucosa
- Mechanical papillae: filiform
- Sensory papillae (with taste buds): fungiform, foliate and circumvallate
- Lingual papillae: local protrusions of the mucosa



I. Tongue papillae

- Primary papilla: protrusion of mucosa
- Secondary papillae: invaginations of lamina propria into epithelium

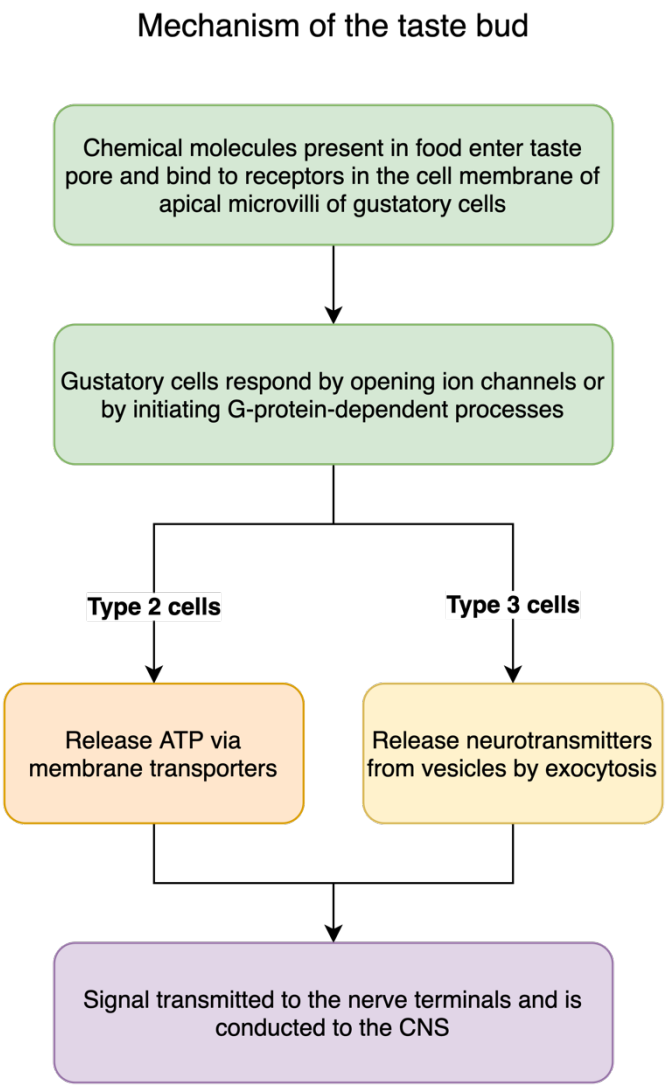
Type	Location	Structure	Keratinized?	Function
Filiform	Most abundant (90%)	Pointed and keratinized	Yes	Facilitates mechanical manipulation of food by creating a rough surface NO taste buds
Fungiform	Between the filiform papillae	Mushroom shaped	No or mildly	Few taste buds in upper regions
Foliate	Lateral margins of the tongue	Form folds from three regular secondary papillae Contain small serous glands	No	Numerous taste buds lateral in the epithelium Well developed in childhood and becomes rudimentary in adulthood
Circumvallate	Along terminal sulcus	Very large, surrounded by a deep groove. Numerous secondary papillae. Von Ebner glands	No or mildly	Numerous taste buds lateral in the epithelium

II. Von Ebner glands

- Large compound serous glands located under the *circumvallate papillae*
- Located deeply, between muscles
- Ducts open to groove
- Produce lipase digesting lipids which block taste receptors
- Secretory fluid washes the grooves

4.3.1 – Taste Buds

- Barrel-shaped group of fusiform epithelial cells mounted in the surrounding stratified squamous epithelium
- Some taste buds are also found in the epithelium of soft palate and pharynx
- Content
    1. Basal (undifferentiated) cells
    2. Fusiform type 1/2/3 differentiated gustatory cells
    3. Afferent nerve terminals
- Type 1 cells (supporting cells): dark cytoplasm, microvilli, a few secretory granules
- Type 2 cells (gustatory cells): pale cytoplasm, microvilli, SER
- Type 3 cells (gustatory cells): dark cytoplasm, microvilli, synaptic-like vesicles with neurotransmitters: serotonin, GABA
- Nerve terminals make contacts with the basal regions of gustatory cells
- Tastes: salty, sour, bitter, sweet, umami (glutamate)
    1. Salty taste: sodium channels
    2. Sour taste: H^+ activated cationic channels
    3. Sweet, bitter and umami tastes: G protein-associated receptors (slower reaction)
- One *gustatory cell* can sense one taste
- One *taste bud* senses all tastes



4.4 – Minor Salivary Glands

- Located in the submucosa of the oral cavity
- Compound
- No capsule, usually no lobular structure
- Serous acini and/or mucous tubules
- Von Ebner's glands – serous
- Other lingual and palatine glands – mucous
- Labial and buccal glands – mixed (seromucous)

4.5 – Major Salivary Glands

- Compound glands with lobular structure composed of secretory portions (serous acini, mucous tubules) and ducts
- Narrow spaces between secretory portions are occupied by capillary vessels and nerve fibers (mostly autonomic)
- Composition of saliva:
    1. Water
    2. Ions: K+
    3. Enzymes: amylase, lipase, peroxidase
    4. Antibacterial and defense proteins: lysozyme, lactoferrin, proline-rich proteins, histatins, cystatins, IgA
    5. Epidermal growth factor (EGF)
    6. Mucins: glycoproteins with numerous (80%) short sugar chains

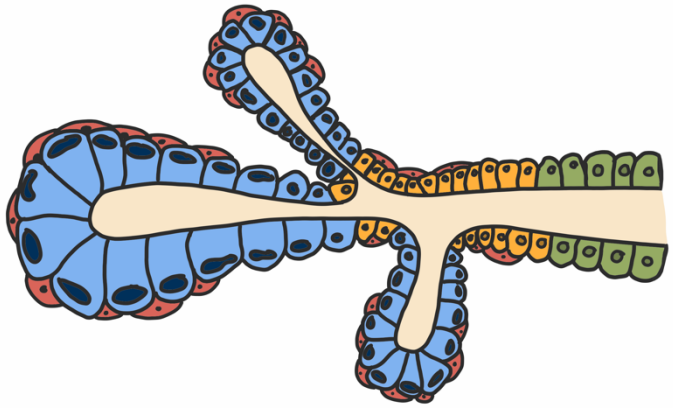
4.5.1 – Serous Acinus

- Serous = protein-producing & secreting
- Acinus = small, sac-like cavity
- Serous secretion: thin fluid composed of water, ions and proteins
- Content of the serous acinus
    1. Serous secretory cells: pyramidal with round basal nuclei, RER, Golgi, dark secretory granules and intercellular canaliculi. Produce almost all proteins present in saliva and also secrete IgA
    2. Myoepithelial cells
    3. Basal lamina

4.5.2 – Mucous Tubule

- Mucous secretion: thick, viscous lubricating fluid rich in glycoproteins (mucins)
- Content of mucous tubules:
    1. Mucous secretory cells: flattened/irregular basal nuclei with very pale cytoplasm in H-E staining, golgi, RER and pale secretory granules
    2. Serous secretory cells (serous demilune)
    3. Myoepithelial cells
    4. Basal lamina
- Serous demilune
    1. a „cap" composed of serous cells on the top of mucous tubule
    2. Produces lysozyme, EGF and other salivary proteins
    3. Origin is not completely clear. Could be from primordial serous acinus (developmental) or the blind end of mucous tubule with mucous and serous cells so swelling mucous cells „push out" serous cells during fixation (fixation artifact)

4.5.3 – Ducts



Acinar cells	Produce the saliva
Myoepithelial cells	Move saliva into ducts
Intercalated ducts	Modify the saliva
Striated ducts	

- Responsible for final composition of saliva
- Intralobular ducts: intercalated and striated duct
- Interlobular duct and principal (main, terminal) duct: in connective tissue between the lobules

I. Intercalated duct

- Low cuboidal epithelium
- Alkalization of saliva: exchange Cl for HCO3
- Production of lysozyme and EGF

II. Striated duct

- Columnar epithelium
- Basal infoldings of the cell membrane with numerous vertical mitochondria
- Exchange Na+ for K+
- Secretion of heavy metal ions and IgA
- Production of lactoferrin, EGF and kallikreins

III. Interlobular duct

- simple columnar → pseudostratified epithelium

IV. Principal duct

- pseudostratified → stratified columnar → stratified squamous epithelium

4.5.4 – The Glands

I. Parotid gland

- Only serous acini, no mucous tubules
- Long intercalated ducts
- Clusters of adipocytes

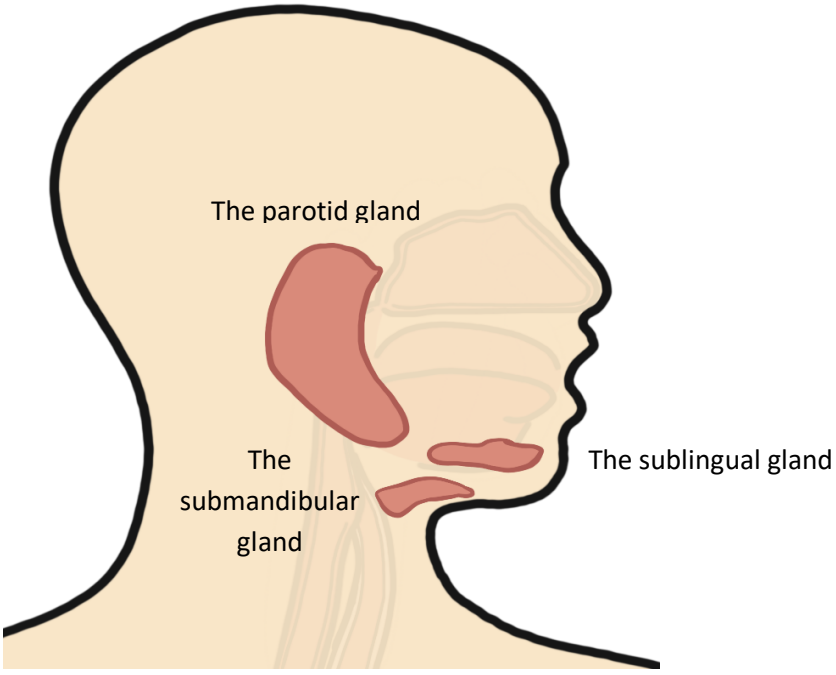
II. Sublingual Gland

- Predominantly mucous: mucous tubules with poorly developed serous demilunes, no serous acini
- Striated ducts with indistinct striations: shallower infoldings of the basal cell membrane

III. Submandibular Gland

- Mixed
    1. 80-90% serous acini
    2. 10-20% mucous tubules with well-developed serous demilunes
- The longest striated ducts
- Clusters of adipocytes (increase with age)

The major salivary glands



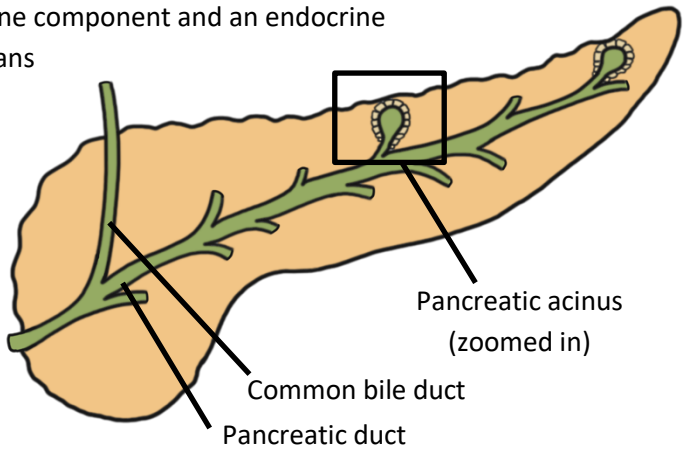
Section 5 – The Pancreas and Liver

5.1 – The Pancreas

5.2 – The Liver

5.1 – The Pancreas

- A compound lobular gland with a dominant exocrine component and an endocrine component called the pancreatic islets of Langerhans



5.1.1 – The Exocrine Pancreas

- A serous gland consisting of many densely packed serous secretory portions and a tree-like system of ducts
- Secretory unit of the exocrine pancreas: the pancreatic acinus
    1. Surrounded by capillaries
    2. Pancreatic exocrine (acinar) cells
    3. Centroacinar cells: squamous centroacinar cells are found in the initial portion of the duct and partially enters the lumen of the acinus
    4. Basal lamina
- Appearance of the acini
    1. The centroacinar cells are flat, poorly equipped with organelles and produce alkaline, bicarbonate-rich fluid
    2. The pancreatic exocrine cells are highly polarized protein producing secretory cells resulting in double-color appearance of pancreatic acini
- Secretory products are mainly potent digestive enzymes released into the small intestine
    1. Proenzymes activated in the lumen of duodenum: trypsinogen, chymotrypsinogen, procarboxypeptidase, proelastase (proteases) and prophospholipase A2
    2. Active enzymes: alpha-amylase, triglyceride lipase, DNAse and RNAse
- Other secretory products: lipase, cofactor, trypsin inhibitor, acid proteoglycan

I. The duct system

- Intercalated ducts (simple squamous to low cuboidal epithelium)
- Intralobular ducts (simple cuboidal epithelium)
- Cells of intercalated, intra- and interlobular ducts secrete alkaline, bicarbonate-rich fluid, which neutralizes the acidic chyme passing from the stomach to the duodenum
- During regeneration, these cells can differentiate into pancreatic exocrine and endocrine cells

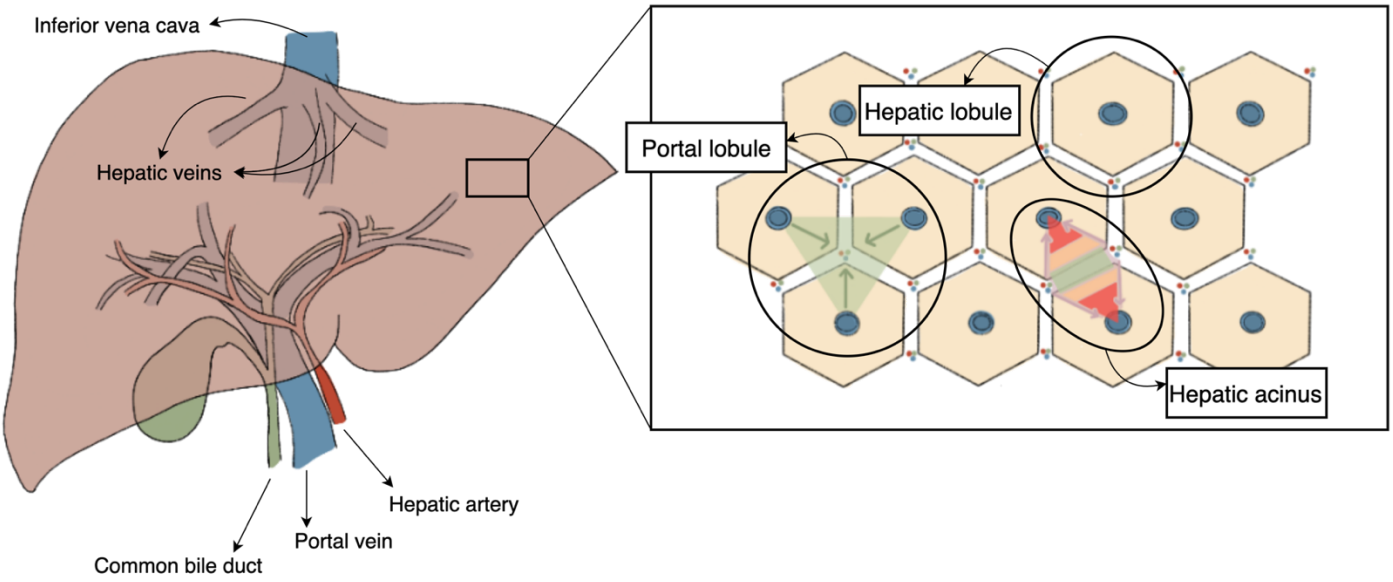
	Interlobular ducts Located in the connective tissue of septa	**Principle ducts** Two: main and accessory
Type of epithelium	Simple columnar epithelium	
Components	Principal, basal stem cells, endocrine and brush cells	Connective tissue Smooth muscle

5.2 – The Liver

- A large compound gland and the metabolic center of the organism
- Functions:
    1. Production of bile, plasma proteins and lipids
    2. Metabolism of exo- and endogenous substances
    3. Storage of vitamins and iron
    4. Elimination of pathogens and old red blood cells

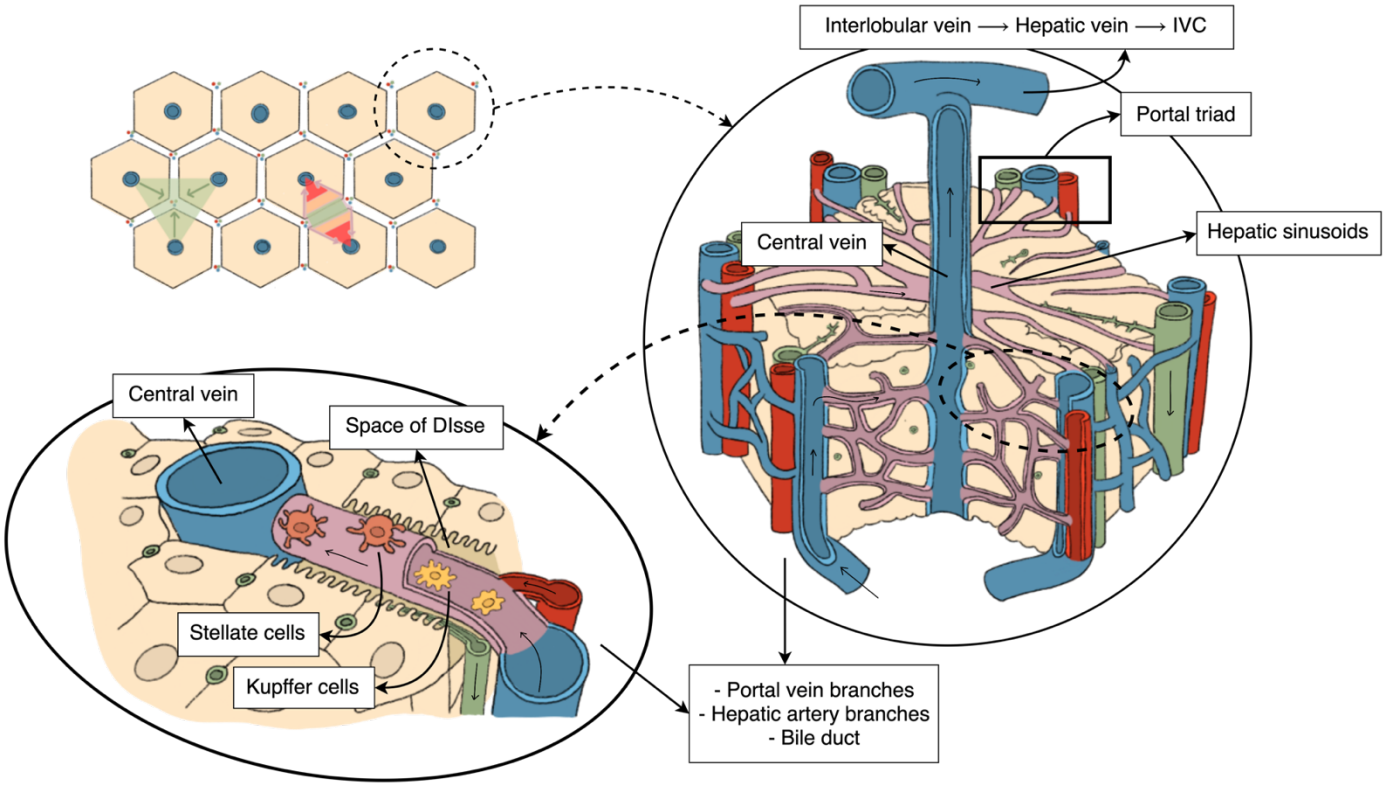
5.2.1 – Structure of the Liver

- Composed of structural and functional subunits
- Some animal livers have lobules separated by connective tissue septa. In the human liver on the other hand, the lobules are not separated by septa but are distinguished by the architecture of the liver tissue.
- There are three ways of organizing the liver parenchyma
    1. Anatomical organization: hepatic lobule
    2. Bile flow: portal lobule
    3. Metabolic activity: hepatic acinus



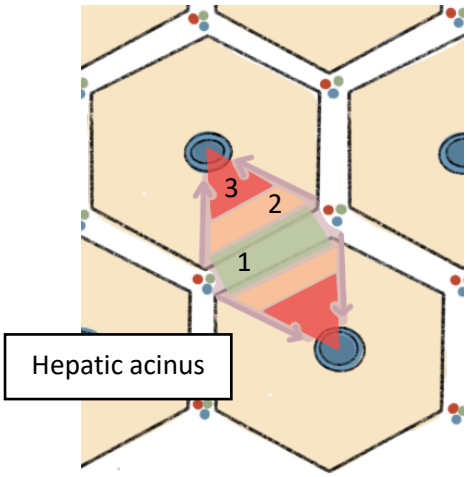
I. The classic hepatic lobule

- Plates of hepatocytes
- Hepatic sinusoids: capillary vessels
- Central vein
- Portal areas (conn. tissue) with triads: interlobular artery (branch of hepatic artery), interlobular vein (branch of portal vein), interlobular bile duct
- Plates of hepatocytes and sinusoids are surrounded by networks of reticular fibers
- Blood, lymph and bile flow in hepatic lobule:
    1. Blood: centri*petal*
    2. Lymph and bile: centri*fugal*



II. The hepatic acinus

- Perilobular vessels are the axis of hepatic acinus
- Zones of the hepatic acinus:
    1. High level of metabolism: the zone closest to the periportal area with the hepatic artery and is therefore rich in oxygen. large mitochondria with numerous cristae, abundant RER and SER, more glycogen
    2. Intermediate
    3. Low level of metabolism: located in the pericentral area, furthest away from the artery and therefore have less oxygen available. Small mitochondria with sparse cristae, abundant SER, less glycogen, early degenerative changes blood flow



5.2.2 – The Hepatocyte

- The best equipped cell in the body: all organelles are well developed

Function	Relevant organelle
Production of bile	Golgi apparatus
Synthesis of plasma proteins (except immunoglobulins)	Rough endoplasmic reticulum
Lipid metabolism: Degradation of chylomicrons, synthesis of cholesterol, phospholipids, production of VLDL	Smooth endoplasmic reticulum Golgi apparatus Lipid droplets (storage)
Detoxification	Smooth endoplasmic reticulum Peroxisomes
Glucose metabolism and storage	Glycogen granules (storage) Mitochondria
Endocrine function	–
Secretion of IgA	–

- Hepatocytes can have different appearances
    1. Binucleated (25%)
    2. Polyploid (30-50%) and have considerable regenerative capability
    3. Sinusoid
- Each hepatocyte has two poles (domains):
    1. Sinusoidal domain: absorption & secretion
    2. Canalicular (lateral) domain: secretion
- Perisinusoidal space of Disse: space between sinusoidal domains of hepatocytes and sinusoid wall (endothelium)

Domain	Main organelles	Function	Membrane structure
Sinusoidal (basolateral)	RER	Secretion of proteins, lipoproteins, glucose Absorption of digestion products from blood	Microvilli
Canalicular	Golgi Lysosomes	Secretion of bile and IgA	Bile canaliculus with microvilli (symmetrical invaginations of the cell membranes) Cell junctions

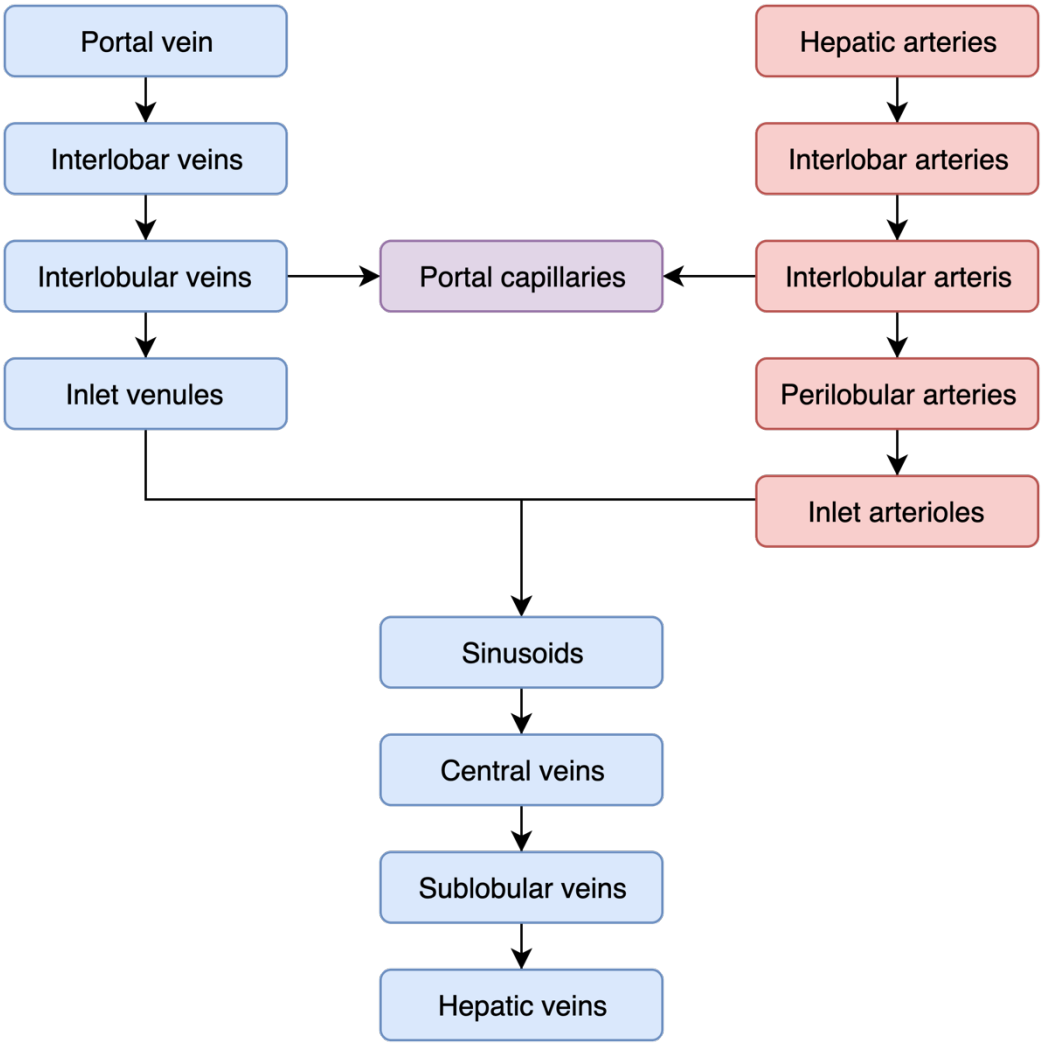
I. The hepatic sinusoids

- Wide and irregular, discontinuous capillaries
- No basal lamina
- Freely permeable
- Three types of cells are associated with the walls of hepatic sinusoids:
    1. Kupffer cells: macrophages resident in the liver: phagocytose bacteria, cell debris, old erythrocytes; produce cytokines influencing hepatocytes, endothelial cells and pit cells. Located at the inner surface of the sinusoid.
    2. Stellate (fat-storing, Ito) cells: special myofibroblasts, store lipids and Vit. A, influence blood flow in sinusoids, under pathological conditions produce collagen (liver fibrosis). Located in the perisinusoidal space.
    3. Pit cells: liver-specific natural killer (NK) cells that kill virus-infected cells and tumor cells. Located mostly at the inner surface of the sinusoid.

II. Scavenger endothelial cells

- Endothelial cells of hepatic sinusoids have a potent endocytic capcity
- Together with Kupffer cells they create an efficient blood-cleaning system in the liver and participate in innate immunity.

Hepatic circulation



5.2.3 – Production of Lymph

- Liver is the largest producer of lymph in the organism
- Direction of flow:
    1. Perisinusoidal space
    2. Lymphatic space of Mall (between hepatocytes and connective tissue of portal area)
    3. Interlobular lymphatic vessel (in portal area)
- The intrahepatic bile ducts
    1. Bile canaliculi
    2. Bile ductules (cholangioles, canals of Hering): cuboidal cells (cholangiocytes), ovoid cells
    3. Interlobular bile ducts: simple cuboidal to low columnar epithelium (cholangiocytes)
- Cholangiocytes secrete alkaline, bicarbonate-rich fluid
- Ovoid (oval) cells are able to proliferate and differentiate into duct cells and hepatocytes

5.2.4 – The Gallbladder

- Epithelium and wall layers (mucosa, muscularis, serosa) as in extrahepatic ducts
- Mucosal folds
- Occasional small mucous glands
- Tubular infoldings of mucosa into muscularis

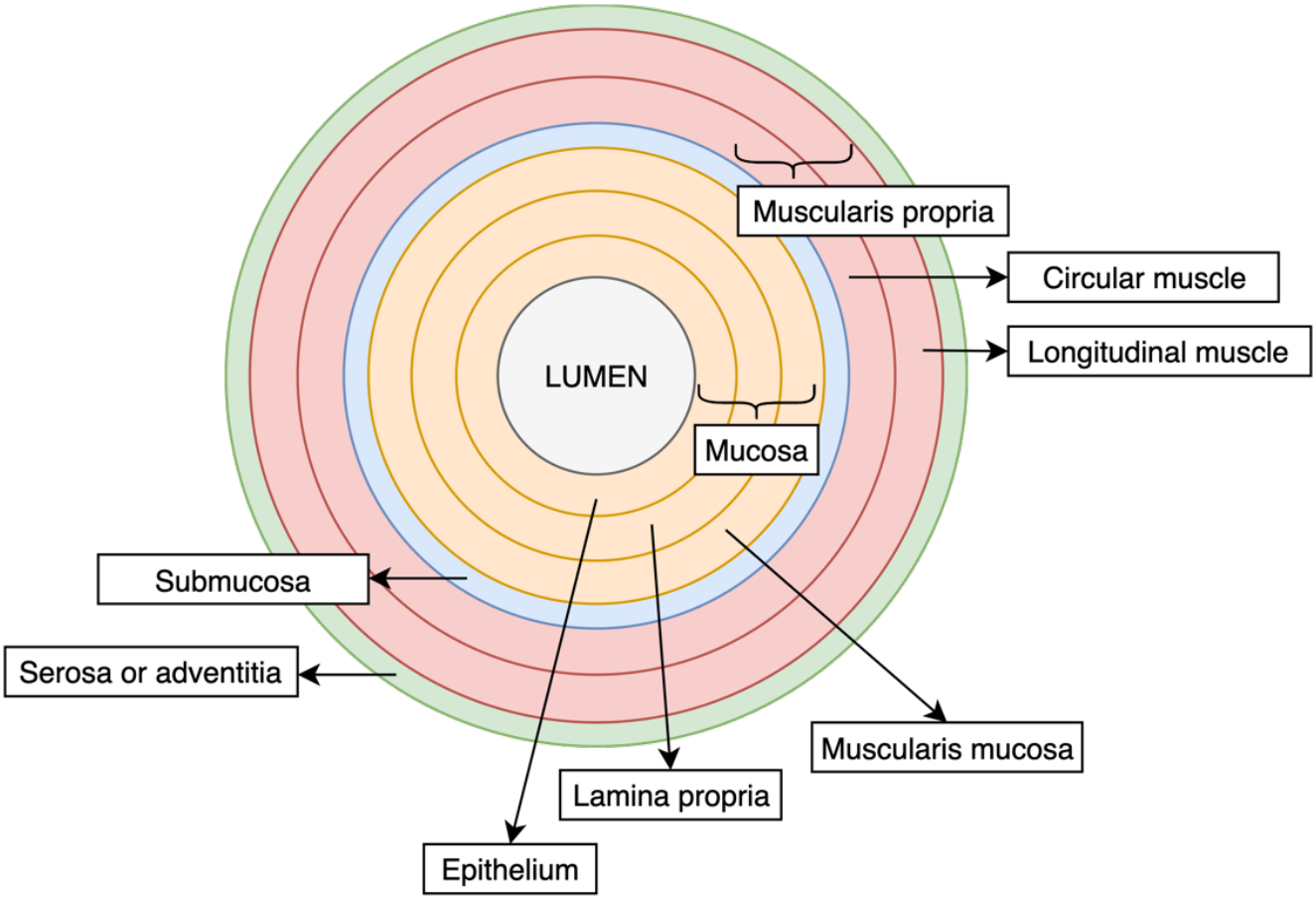
I. The extrahepatic bile ducts and gallbladder

- Mucosa covered by simple columnar epithelium (clear cells and a few brush cells), layer(s) of smooth muscle and fibrous adventitia/serosa
- Clear cells:
    1. Apical microvilli
    2. Complexes of cell junctions
    3. Mitochondria near cell apex and base
    4. Lateral folds of the cell membrane
    5. Function: absorption of water and ions

Section 6 – The Alimentary Canal

6.1 – The Esophagus
6.2 – The Stomach
6.3 – The Small Intestine
6.4 – The Large Intestine
6.5 – Gut-Associated Lymphoid Tissue
6.6 – The Enteric Nervous System

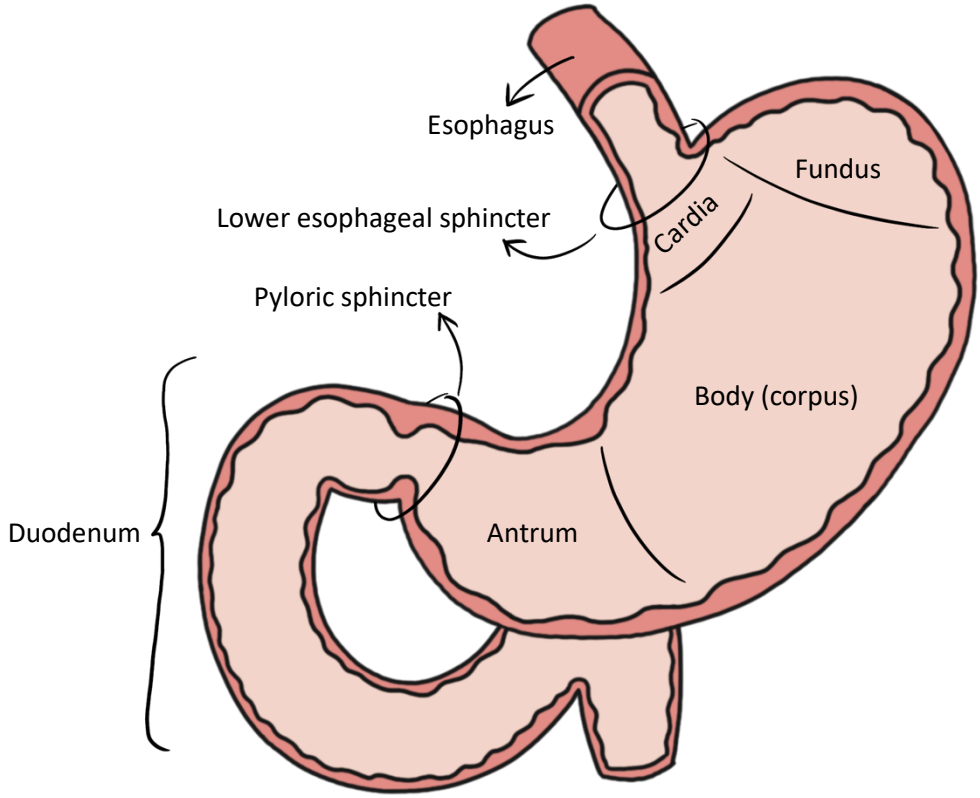
Layers of the intestinal canal



6.1 – The Esophagus

- Stratified squamous nonkeratinized epithelium
- Esophageal cardiac glands (mucous) in lamina propria
- Irregular, longitudinal muscularis mucosa
- Esophageal glands proper (mucous) in submucosa (secrete mucus, bicarbonate ions, lysozyme)
- Skeletal and smooth muscles in muscularis externa
- Outermost fibrous adventitia

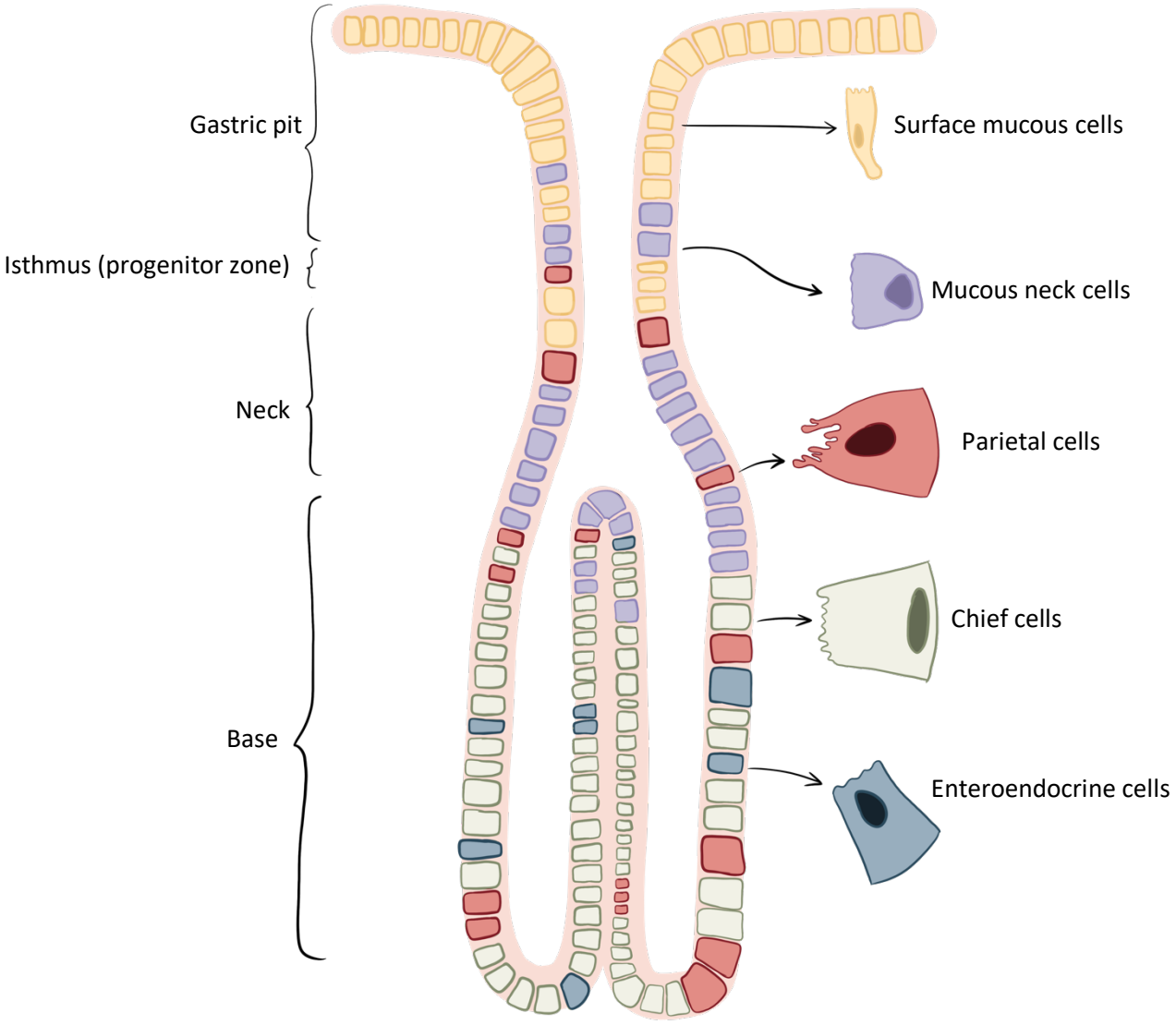
6.2 – The Stomach



- Simple columnar surface lining epithelium forming invaginations (gastric pits)
    1. Tall columnar mucous cells that produce an insoluble, alkaline mucus that protects the stomach lining from aggressive acidic fluid secreted by gastric glands.
    2. The fluid is alkalinized by bicarbonate from the blood
- Lamina propria is occupied by tightly packed glands that differ slightly depending on their location
- Additional innermost oblique layer of muscularis externa in body/fundus
- The cardia consist of shallow, irregular pits and cardiac glands
- Cardiac glands: convoluted tubular glands containing
    1. Mucous secretory cells (similar to mucous neck cells)
    2. Some enteroendocrine cells
    3. Parietal cells

6.2.1 – Body and Fundus

- Structure of fundic glands
    1. Simple tubular glands tightly packed in the lamina propria, each surrounded by some loose connective tissue
- Each fundic gland has three segments: isthmus, neck and base



Types of cells in the gastric gland

Cells	Location	Characteristics	Function
Stem cells	Isthmus	The stem cell niche: Subepithelial fibroblasts, capillaries, telocytes and parietal cells	Undifferentiated cells able to divide and differentiate towards surface lining cells and all cell types of the fundic glands
Mucous neck cells	Neck	Produce soluble, lubricating mucus	
Parietal cells	All segments	- Large, oval/pyramidal cells with acidophilic cytoplasm and numerous mitochondria - Sometimes binucleated - Tubulovesicular system/intracellular canaliculi with microvilli	Produce HCl and intrinsic factor
Enteroendocrine cells		Produce peptide hormones, mostly exerting local effects, e.g. gastrin, stimulating HCl secretion by parietal cells and ghrelin, stimulating the appetite	
Chief cells	Base	- Basophilic cytoplasm - RER, Golgi and secretory granules	- Produce gastric enzymes: pepsinogen, gastric lipase and renin (in infants) - ECL (enterochromaffin-like) cells located in the lower half of fundic gland secrete histamine

I. Production of stomach acid

- HCl provides the acidic environment in the stomach
- Intrinsic factor enables absorption of vitamin B12
- In the parietal cells, HCl synthesis involves transport of H^+ and Cl^- ions to the lumen of intracellular canaliculi from where they pass to the lumen of the gland.
- Depending on the activity state of the parietal cell, membrane containing active transporters is either placed in:
    1. The cytoplasm as vesicles and tubules: storage
    2. Membrane lining the canaliculi: active secretion of HCL
- Important membrane transporters of parietal cell involved in HCl synthesis:
    1. Proton pump: H+, K+ ATPase
    2. Chloride bicarbonate antiporter
    3. Potassium uniporter
    4. Na+, K+ ATPase

6.2.4 – Pylorus

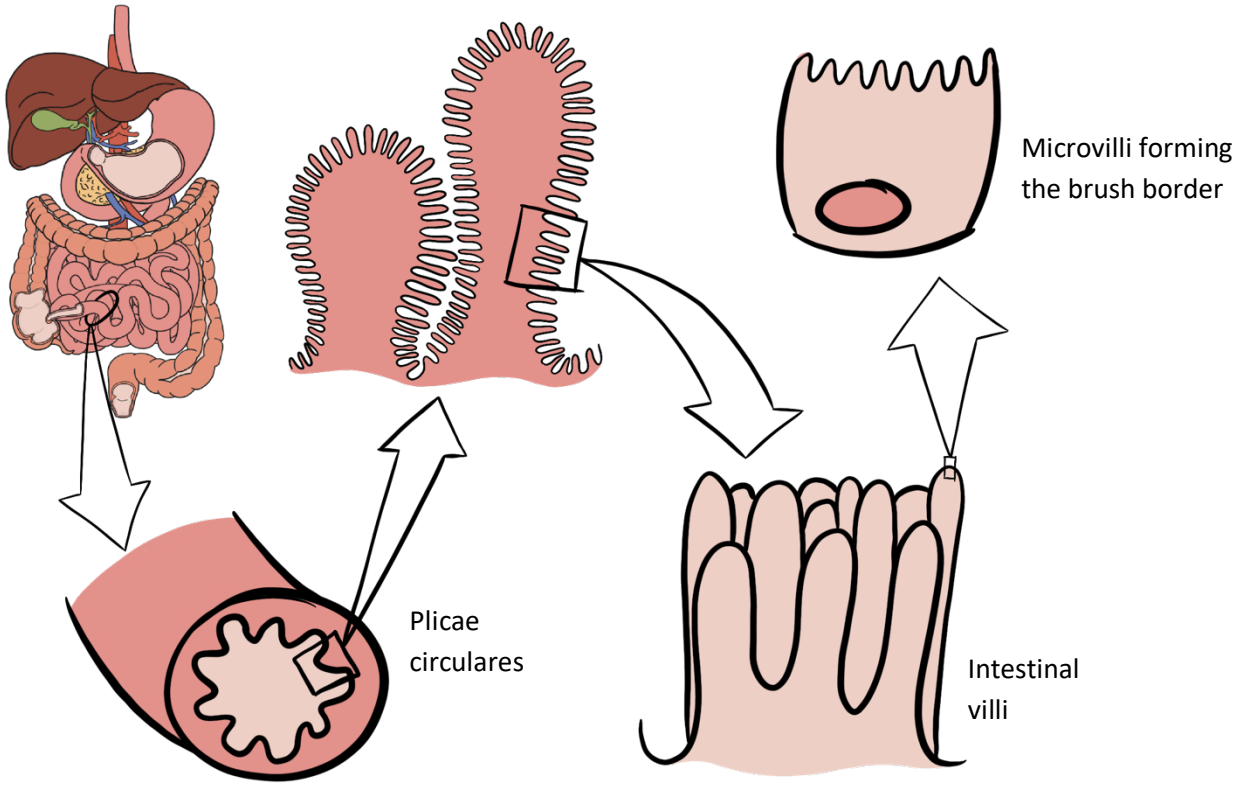
- Deep pits
- Tubular branched pyloric glands
- Thick circular layer of muscularis externa (sphincter)

I. Pyloric glands

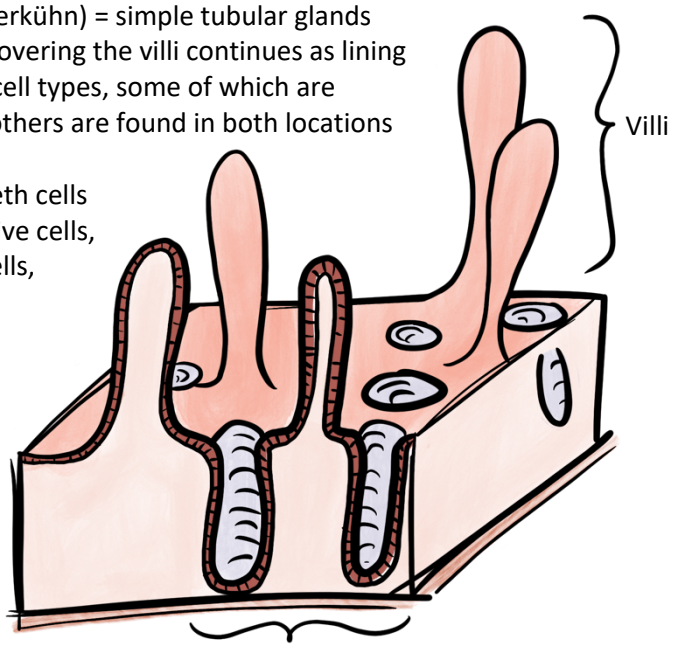
- Numerous mucous cells (similar to mucous neck cells) producing mucus and lysozyme
- Numerous entero-endocrine cells (G cells) producing gastrin
- Some parietal cells

6.3 – The Small Intestine

- The absorptive surface is stepwise increased:
    1. Circular folds of mucosa and submucosa (plicae circulares): x 2-3
    2. Intestinal villi - finger-like projections of mucosa: x 10
    3. Brush border (microvilli) on the surface of epithelial cells covering the villi: x 20



- The mucosa of small intestine can be divided into two levels:
    1. Upper: intestinal villi
    2. Lower: intestinal crypts (of Lieberkühn) = simple tubular glands
- Simple columnar intestinal epithelium covering the villi continues as lining of the crypts. It is composed of several cell types, some of which are located exclusively in the crypts, while others are found in both locations (villi and crypts):
    1. Crypts only: stem cells and Paneth cells
    2. Villi and crypts: surface absorptive cells, goblet cells, enteroendocrine cells, brush cells and M cells
- Intestinal crypt
    1. Bottom: Paneth cells and stem cells
    2. Middle: proliferating progenitor cells
    3. Upper half: differentiating absorptive cells, goblet cells, etc., migrating upwards, towards the tip of the villus



Crypts of Lieberkühn

Cell	Location	Characteristics	Function
Surface absorptive cells	Villi and crypts	- Tall columnar cells with brush border with thick glycocalyx and ectoenzymes - Numerous organelles - Junctional complexes	Absorb digested food particles from the intestinal lumen and release them to blood and lymphatic vessels, resynthesize triglycerides and bind them to proteins to form chylomicrons which are released to lymphatic vessels
Goblet cells		- Narrow base, wide apical part filled with numerous mucous secretory granules - Some ER and prominent Golgi	Produce lubricating mucus
Brush cells		- Have a tuft of long microvilli on their apex - Make contacts with nerve terminals	Probably act as chemoreceptors
Intestinal stem cells	Bottom of crypts	Niche: basal lamina, subepithelial fibroblasts, capillaries, nerve terminals of Meissner's plexus	Differentiate into all types of intestinal epithelial cells, are responsible for regeneration of intestinal epithelium. stem cells proliferating cells differentiating cells differentiated cells
Paneth cells		- Typical protein-secreting cells - Have acidophilic apical secretory granules	- Produce antibacterial proteins: lysozyme and defensins - Secrete IgA - Can take up bacteria and unicellular parasites by phagocytosis

I. Intestinal villus

- Finger-like protrusion of mucosa (0.2 x 1 mm) covered by intestinal epithelium
- Continuous layer of myofibroblasts under the epithelium: participate in the regulation of epithelium renewal and defense processes
- Inside has a core (protrusion of lamina propria): loose connective tissue very rich in cells (connective tissue cells + leukocytes). The core contains:
    1. Fenestrated capillaries
    2. Single blind lymphatic vessel: lacteal
    3. 1-3 bundles of smooth muscle cells: contraction pumps the lymph out of the lacteal

6.3.1 – Location Dependent Differences

I. Duodenum

- Large, broad villi
- Duodenal glands in submucosa: Brunner glands
    1. Branched tubular glands
    2. Produce a bicarbonate-rich alkaline fluid that neutralize the acidic chyme passing from the stomach
    3. Also secrete urogastrone (inhibits HCl secretion in stomach), EGF and lysozyme

II. Jejunum

- Narrower and shorter villi with more goblet cells

III. Ileum

- Shorter and sparser villi with more goblet cells
- Aggregates of lymphoid tissue called Peyer's patches in submucosa and lamina propria

6.4 – The Large Intestine

- Large intestine reabsorbs water, ions and produces mucus to form feces
- No villi or Paneth cells, only deep, regular crypts with numerous goblet cells
- The wall has circular folds
- Three separate bands of smooth muscle (taeniae coli) instead of continuous longitudinal layer of muscularis externa

I. The appendix

- The appendix belongs anatomically and histologically to large intestine
- Aggregates of lymphoid tissue in mucosa and submucosa with Paneth cells present in crypts
- Continuous outer layer of muscularis externa

II. The anal canal

- Anal columns: longitudinal mucosal folds
- Simple columnar → stratified cuboidal → stratified squamous epithelium
- Mucous anal glands can be found in lamina propria extending to the submucosa
- Rich venous plexuses in submucosa
- Sphincters
    1. External: skeletal muscle (under voluntary control)
    2. Internal: smooth muscle (not under voluntary control)

6.5 – Gut-Associated Lymphoid Tissue (GALT)

- Solitary lymphoid nodules in all segments of the alimentary canal
- Aggregations of lymphoid nodules and diffuse lymphoid tissue
- Peyer's patches in ileum

I. Microfold cells (M cells)

- Located in intestinal epithelium covering the lymphoid tissue
- Have microfolds on apical surface
- Take up antigens, for example bacteria, from the lumen and transfer them by transcytosis to the underlying lymphoid tissue
- In this way they monitor the antigenic composition of the alimentary canal content

6.6 – The Enteric Nervous System

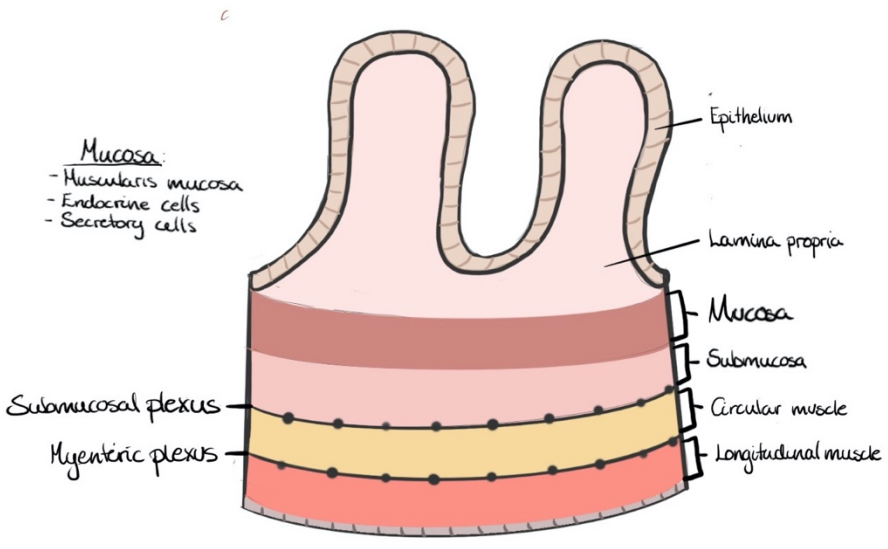
- The nervous system of the gastrointestinal tract
- The submucosal plexuses control contractility of the muscularis mucosae and the secretory activity of glands:
    1. Meissner plexus: inner submucosal
    2. Schabadasch plexus: outer submucosal
- The muscularis propria plexus controls peristalsis
    1. Auerbach plexus = Myenteric plexus
- Plexuses contain ganglionic nerve cells and glial cells similar to astrocytes

I. Interstitial cells of Cajal

- Located in the muscularis externa and cooperate with enteric nervous system
- Connected with nerve terminals and smooth muscle cells via gap junctions
- Initiate slow peristaltic waves by spontaneously generating stimuli that induces contraction of smooth muscle cells

II. Enteroendocrine cells

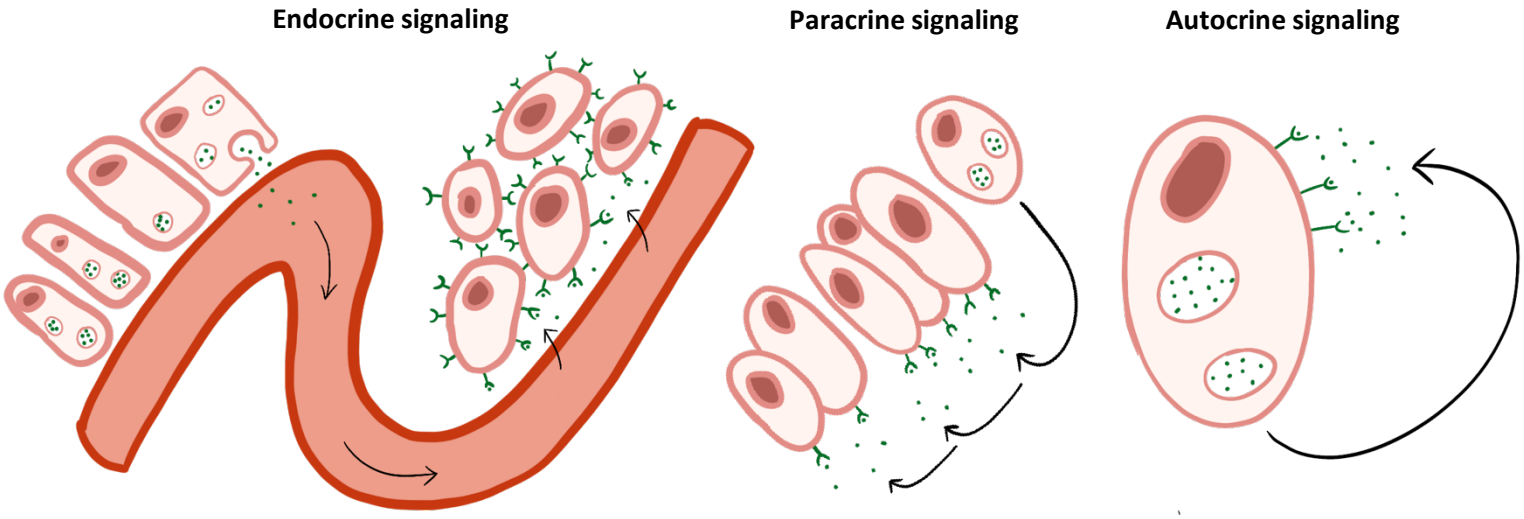
- Belong to diffuse neuroendocrine cell system (DNES)
- Produce peptide hormones that influence peristalsis, blood flow and secretory activity of
    1. Usually show local action, but can sometimes also regulate activity of remote organs
- Located in glands and sometimes in the lining epithelium
- Can be of open or closed type
- Have secretory granules in the basal region



Section 7 – The Endocrine System

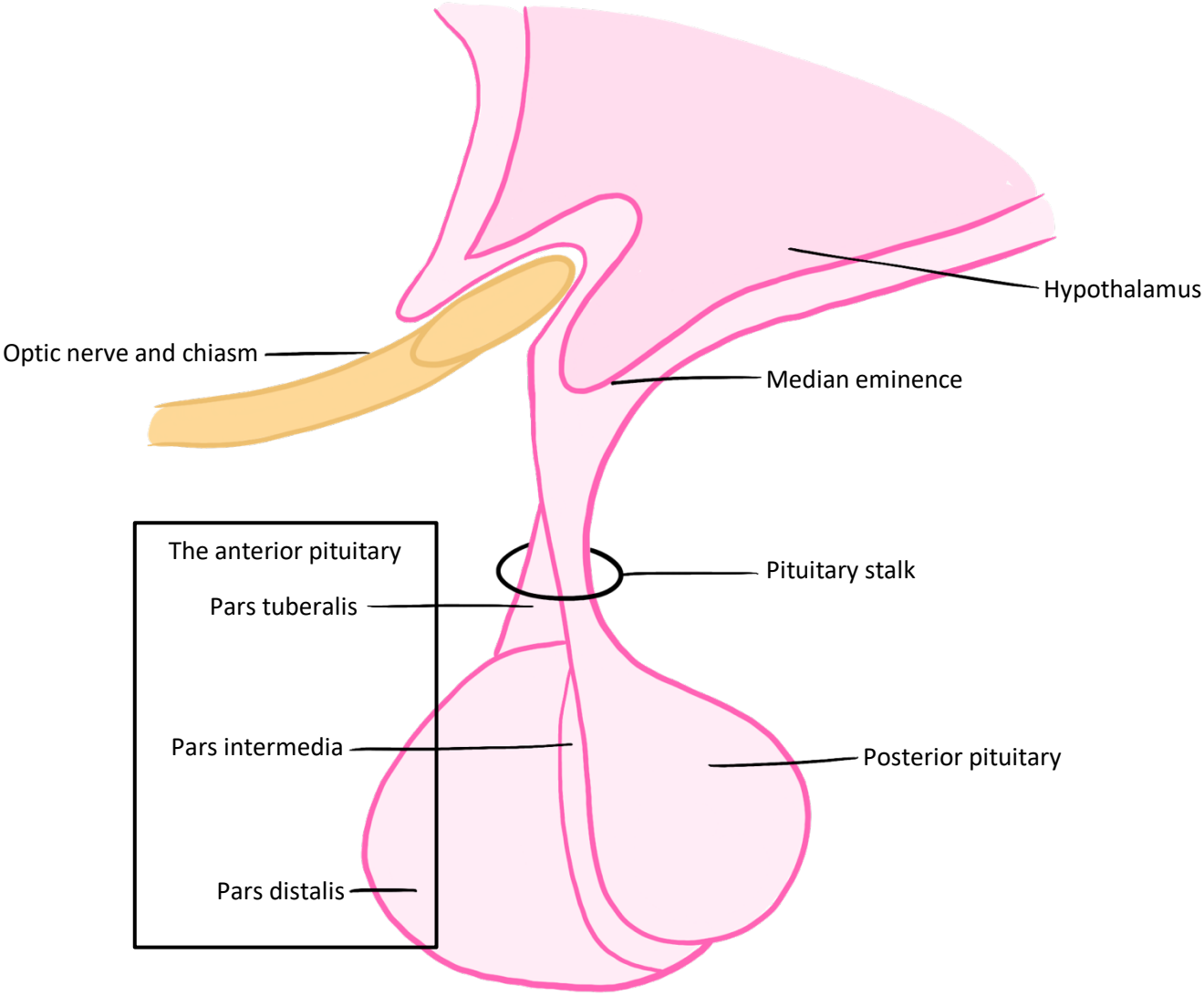
7.1 – The Pituitary Gland and the Hypothalamus
7.2 – The Thyroid Gland
7.3 – The Parathyroid Glands
7.4 – The Adrenal Gland
7.5 – The Pancreatic Islet Cells
7.6 – The Pineal Gland
7.7 – The Diffuse Neuroendocrine System

- Hormones can be made from:
    1. Proteins and peptides
    2. Amino acid derivatives
    3. Cholesterol derivatives (steroids)
- General characteristics of endocrine glands:
    1. No ducts
    2. No secretory units (exception: thyroid)
    3. Endocrine cells
    4. Accessory cells (not always)
    5. Numerous fenestrated capillaries
- Types of signaling:
    1. Endocrine: remote signaling via the blood stream
    2. Paracrine: local signaling by direct action of released hormones on nearby cells
    3. Autocrine: hormones released act on the cell that releases them



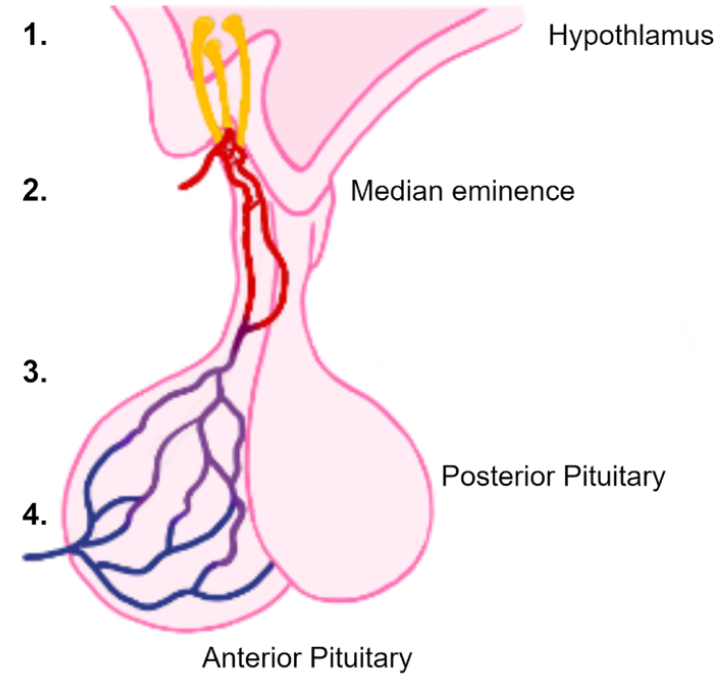
7.1 – The Pituitary Gland and the Hypothalamus

- The pituitary gland consists of two parts due to its origin from two different embryological tissues: oral and neural ectoderm
    1. The anterior pituitary originates from oral ectoderm and is termed adenohypophysis
    2. The posterior pituitary originates from neuroectoderm and is termed neurohypophysis or pars nervosa
- The hypothalamo-pituitary axis (HPA): the hypothalamus produce hormones and send them via axonal transport to the hypophysis, where they control the release of some hypophyseal hormones or are liberated to influence remote organs
    1. Neurohemal organ: association of neurosecretory nerve terminals with capillary vessels
    2. The HPA controls a wide variety of organs and functions



- There are two pathways from the hypothalamus to the pituitary gland: via the portal system to the anterior pituitary or via long axons reaching from the hypothalamus to the posterior pituitary

I. The anterior pituitary (adenohypophysis)



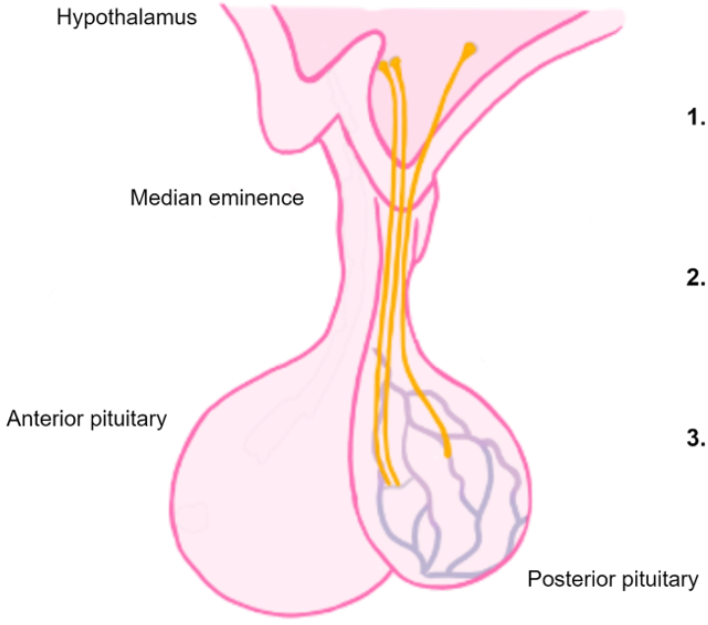
1. Small neurosecretory cells in the hypothalamus near the medial eminence synthetizes releasing or inhibiting hormones

2. The hormones travel down the axons to the median eminence of the hypothalamus, where they are secreted into the nearby capillary plexus

3. The venous blood from those capillaries drains into hypophyseal portal vessels and delivers the hypothalamic hormones to the anterior pituitary

4. The hypothalamic hormones stimulate or inhibit secretion of the anterior pituitary hormones

II. The posterior pituitary (neurohypophysis)



1. Large neurosecretory cells in two hypothalamic nuclei, supraoptic and paraventricular, produce ADH and oxytocin

2. The two hormones are transported down the axons in neurosecretory vesicles to be stored in nerve terminals of the posterior pituitary

3. Once the cell body is stimulated, the vesicles are released by exocytosis into systemic circulation to their target tissues

III. Hypothalamic hormones

Releasing hormones	Inhibitory hormones
- Thyrotropin-releasing hormone (TRH) - Corticotropin-releasing hormone (CRH) - Growth hormone-releasing hormone (GHRH, SRH – somatotropin-releasing hormone) - Gonadotropin-releasing hormone (GnRH) - Prolactin-releasing hormone (PRH)	- Dopamine (prolactin inhibitory factor, PIF) - Somatostatin (GH and TRH inhibitory factor) - Gonadotropin-inhibitory hormon (GnIH)

7.1.1 – The Adenohypophysis

- Components of the adenohypophysis:
  1. Irregular clusters and cords of cells
  2. Numerous wide fenestrated capillaries
- Classification of adenohypophyseal cells is based on the presence and staining properties of the secretory granules in the cells
  1. Chromophobes: absent or very few granules
  2. Chromophils: abundant granules

I. Chromophobes

- Chromophobe cells include
  1. Stem cells
  2. Folliculostellate cells
  3. Exhausted secretory cells
- Folliculostellate cells
  1. Have cytoplasmic processes
  2. Communicate with each other and with adenohypophyseal endocrine cells via gap junctions
  3. Respond to regulatory substances by sending signals to adenohypophyseal cells and controlling their secretory activity

II. Chromophils

- Chromophil cells can be divided into the following groups

Staining characteristic	Cell type	Hormone released
Acidophils	Somatotrophs	Growth hormone (GH, somatotropin)
	Mammotrophs	Prolactin (PRL)
Basophils	Corticotrophs	Adrenocorticotropin (ACTH)
	Gonadotrophs	Follicle-simulating hormone (FSH) Luteinizing hormone (LH)
	Thyrotrophs	Thyroid stimulating hormone (TSH)

- Characteristics of chromophil cells
    1. RER, Golgi, secretory granules
    2. Produce protein/glycoprotein hormones
- Basophils produce hormones stimulating secretory activity of other endocrine glands
- Location of different cell types in the adenohypophysis

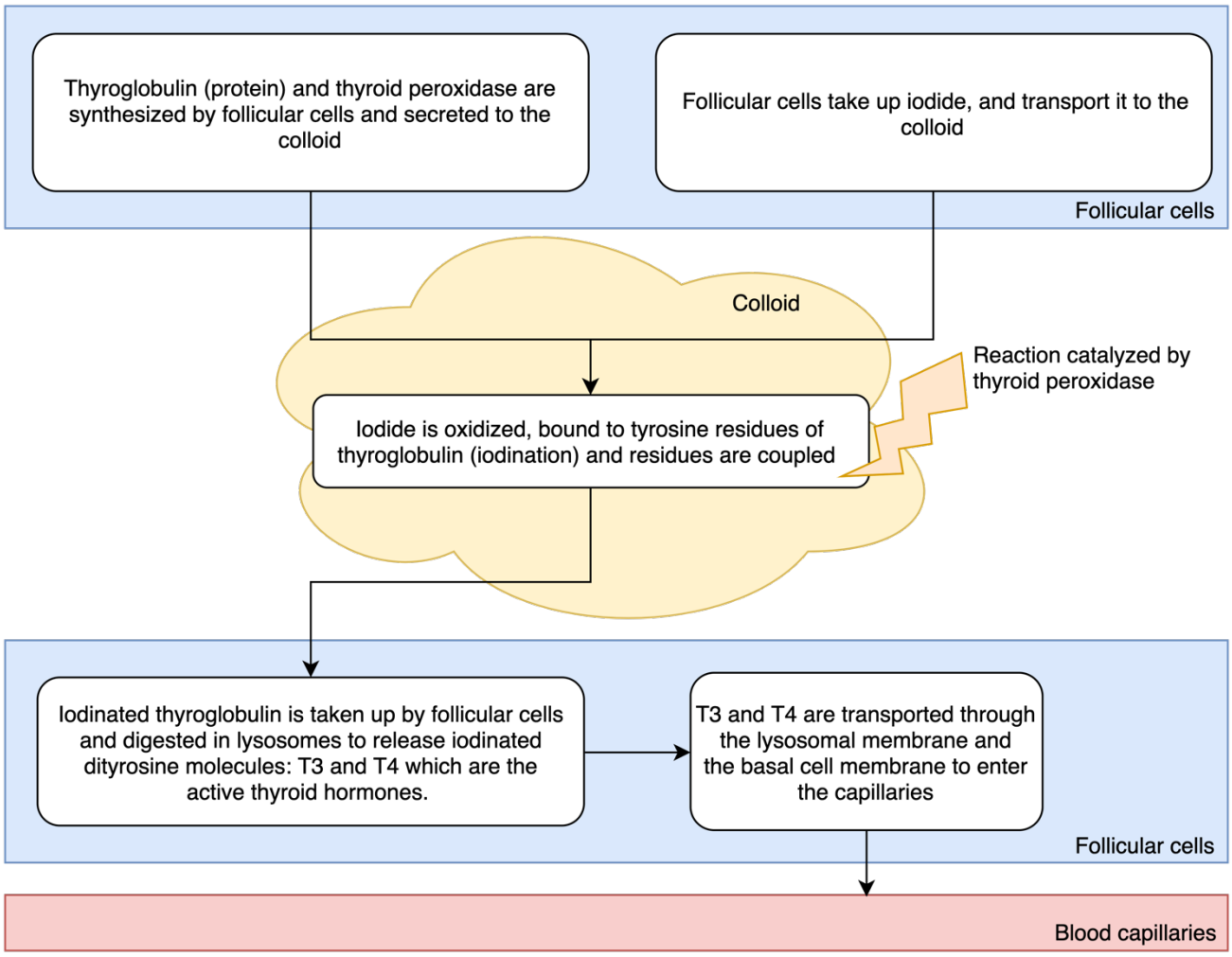
Part of the adenohypophysis	Content
Pars distalis	All adenohypophyseal cell types
Pars intermedia	- Basophils producing mainly MSH and is rudimentary in humans - Characteristic feature are Rathke's cysts filled with a gelatinous material (colloid)
Pars tuberalis	rich vascular network (mainly portal venules) and some gonadotroph-like cells

7.1.2 – Neurohypophysis

- Pars nervosa does not produce hormones, but releases ADH and oxytocin from the hypothalamus to the blood
- Components
    1. Axons of hypothalamic neurosecretory cells
    2. Pituicytes: variant of astrocytes
    3. Capillaries
- The neurohemal organ: pituicyte processes control the access of axon terminals to the capillary wall

7.2 – The Thyroid Gland

- The thyroid gland has a lobular structure
- Unlike other endocrine glands, it is composed of secretory units: thyroid follicles filled with a protein-rich colloid
- Thyroid follicle:
    1. Colloid
    2. Single layer of cuboidal follicular cells
    3. C cells
    4. Basal lamina
- Delicate connective tissue and capillaries surround the follicles
- C cells (parafollicular cells) are located between the follicular cells and the basal lamina
    1. Contain numerous secretory granules and produce *calcitonin*
- Production of thyroid hormones



7.3 – The Parathyroid Glands

- Four small parathyroid glands located in the capsule surrounding the thyroid gland
- Components:
    1. Chief cells
    2. Oxyphil cells
    3. Clusters of adipocytes
    4. Fenestrated capillaries

I. Chief cells (endocrine):

- Dark (active): produce parathyroid hormone (PTH)
    1. Very small (6-8 um)
    2. RER, Golgi, secretory granules
    3. Lipofuscin granules
- Pale (inactive)
    1. Less RER, Golgi
    2. Glycogen aggregates

II. Oxyphil cells

- Probably degenerating chief cells
- Larger (10-15 um)
- Strongly acidophilic cytoplasm
- Extremely numerous mitochondria
- Similar cells occur also in other organs and are termed „oncocytes”

CLINICAL CORRELATION

Iatrogenic hypoparathyroidism

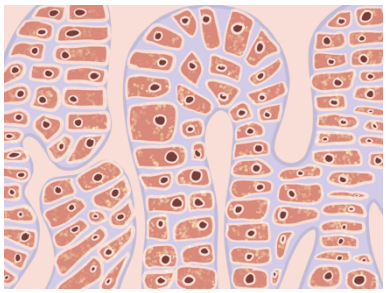
The most common cause of hypoparathyroidism is surgical removal or injury. We should keep this in mind if a patient with recent head and neck surgery or trauma presents with signs of hypocalcemia such as face twitching or tingling in hands or feet.

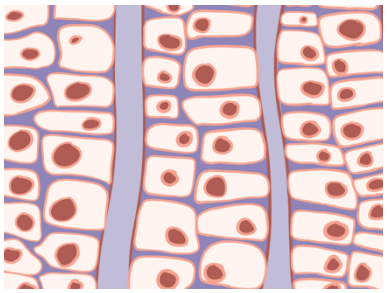
7.4 – The Adrenal Gland

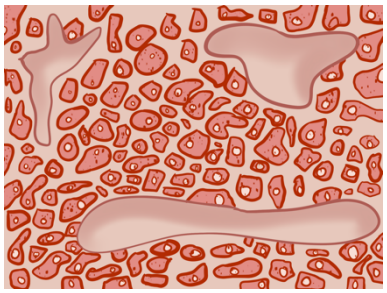
- The adrenal gland develops from two separate primordia, differentiating into the cortex and medulla of the gland
- The fetal adrenal gland consist of 3 layers
    1. “Adult” (inactive) layer
    2. Fetal layer: produce dehydroepiandrosterone (DHEA), which is transported with blood to placenta, where it serves as substrate for estrogen synthesis
    3. Immature medulla

7.4.1 – The Adrenal Cortex

- The adrenal cortex is divided into three zones with different architecture of cells and capillaries
    1. Capsule
    2. zona glomerulosa: nests
    3. zona fasciculata: strands
    4. zona reticularis: irregular
- Cells of the adrenal cortex produce steroid hormones.
- Features shared by steroid-producing cells
    1. Abundant SER: steroid synthesis
    2. Mitochondria with tubular cristae: final stages of steroid modification
    3. Lipid droplets







Layer	Cell structure	Hormones produced
Glomerulosa	Small cells with sparse lipid droplets	Mineralocorticoids (aldosterone)
Fasciculata	Large pale cells with numerous lipid droplets	Glucocorticoids (cortisol)
Reticularis	Small acidophilic cells with lipofuscin granules	Adrenal androgens (mainly DHEA)

MNEMONIC

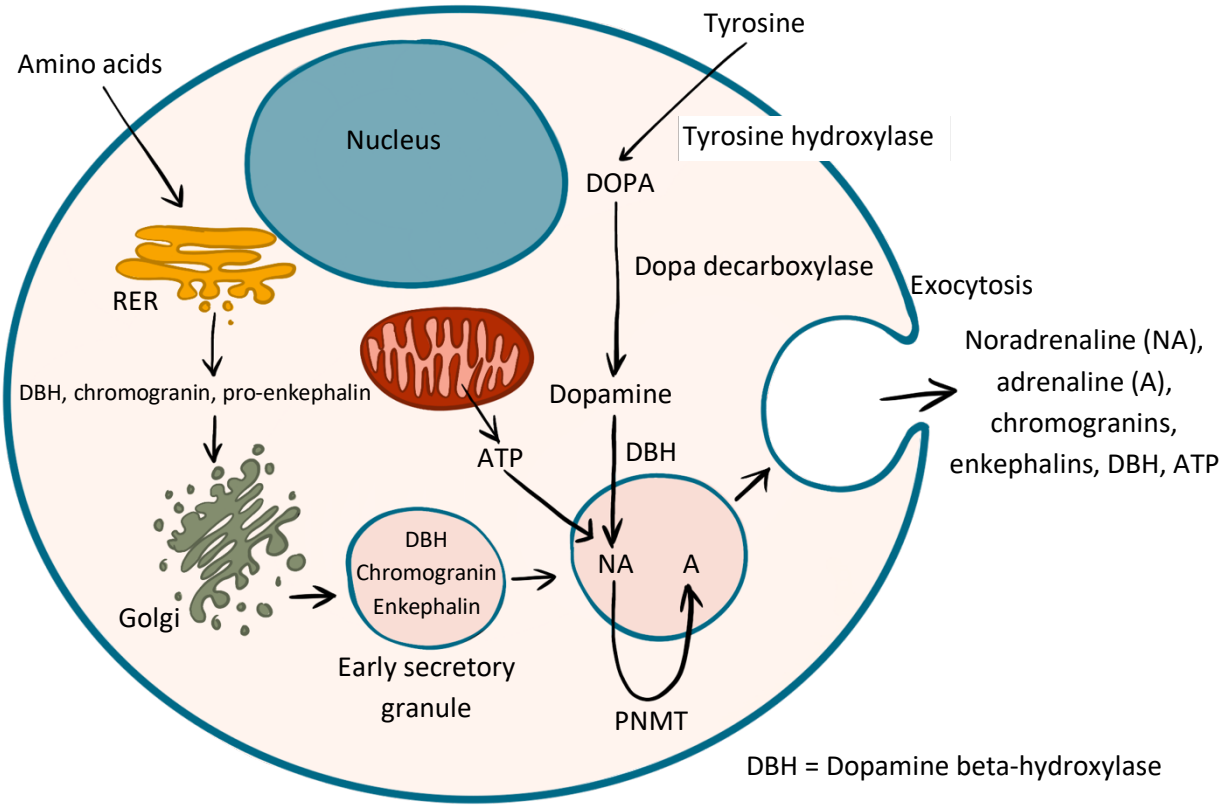
Go **F**ind **R**ex – **M**ake **G**ood **S**ex
G – glomerulosa –> **M** – mineralocorticoids
F – fasciculata –> **G** – glucocorticoids
R – reticularis –> **S** – sex hormones

7.4.2 – The Adrenal Medulla

- Chromaffin cells: produce adrenaline (epinephrine) and noradrenaline (norepinephrine)
- Ganglionic nerve cells: sympathetic
- Blood vessels: capillaries and numerous thin-walled veins

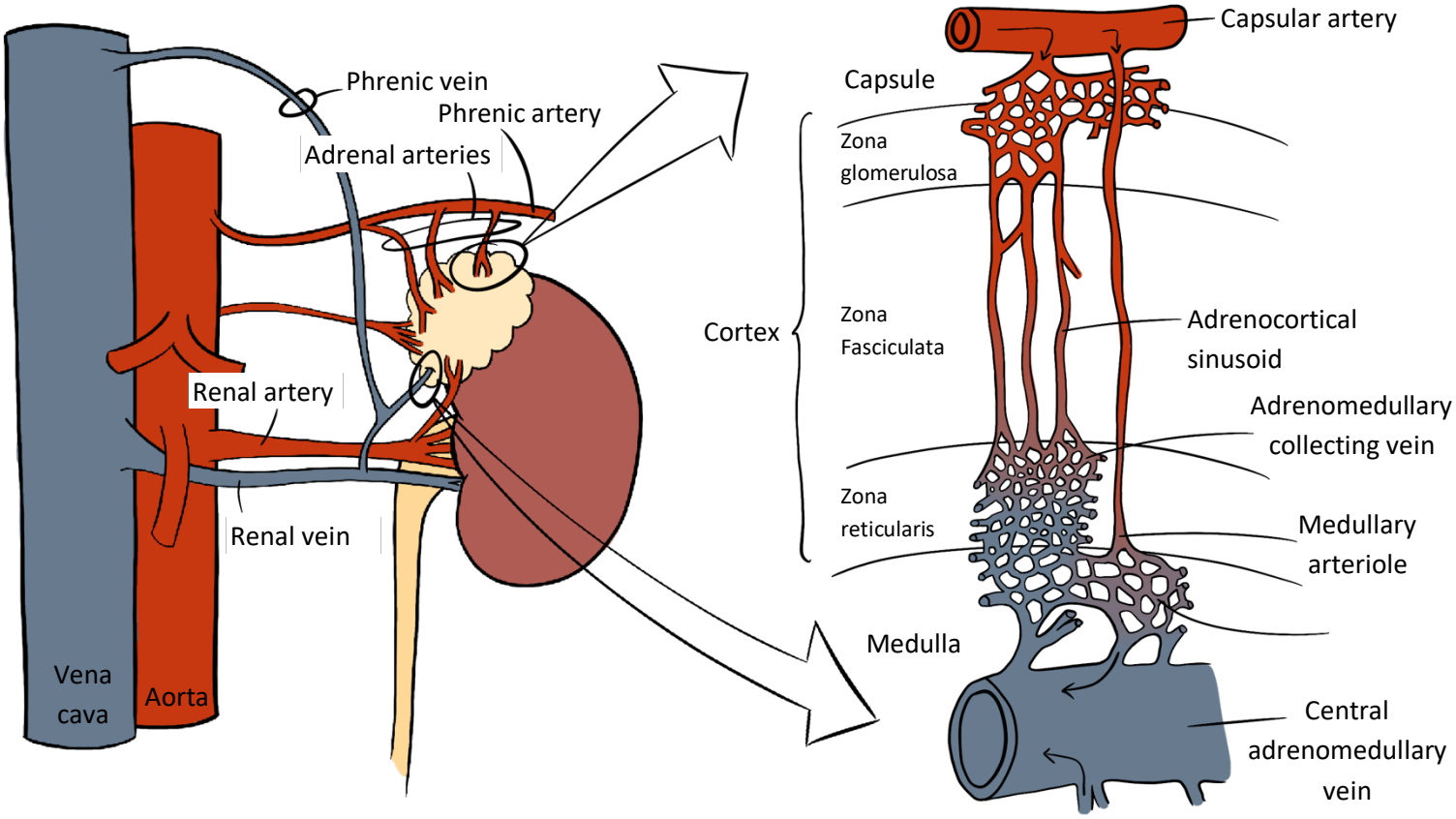
I. Chromaffin cells

- Arranged in irregular nests and cords
- Stain brown with chromium salts
- Organelles: RER, Golgi, numerous small secretory granules with dense cores (DCV, dense-core vesicles)
- Noradrenaline is a derivative of tyrosine and can be converted into adrenaline by the enzyme phenylethanolamine N-methyltransferase (PNMT)
- Both catecholamines are delivered to the secretory granules, where they are bound to the carrier protein chromogranin



7.4.3 – Communication Between the Cortex and Medulla

- Adrenal cortex and medulla communicate via blood vessels: glucocorticoids produced in the cortex activate PNMT and stimulate conversion of noradrenaline into adrenaline in the medulla



7.5 – The Pancreatic Islet Cells

- Endocrine cells with RER, Golgi and numerous secretory granules
- Fenestrated capillaries
- Nerve terminals

Cell type	Percentage	Location in islet	Product	Appearance of granules in electron microscope
α-cells	10-35%	Peripheral	Glucagon	250 nm, round dense core, narrow „halo"
β-cells	55-80%	Central	Insulin	300 nm, irregular dense core, wide „halo"
δ-cells	5-7%	Scattered	Somatostatin	350 nm, less dense content
PP-cells	0.5-2%		Pancreatic polypeptide	180 nm, dense content

CLINICAL CORRELATION

Diabetes mellitus (DM) type 1

In DM type 1 you have autoimmune destruction of the β-cells and therefore decreased production of insulin. The symptoms will not develop before 90% of the β-cells are damaged!

7.6 – The Pineal Gland

- Pineal gland develops from the central nervous system pineal gland and is a projection of diencephalon specialized to perform secretory (endocrine) function,
    1. Cells are either modified nerve cells or modified neuroglial cells
- Components of lobule:
    1. Pinealocytes: modified nerve cells acting as endocrine cells
    2. Interstitial cells: modified astrocytes
    3. Capillaries, nerve fibers
    4. Brain sand: mineral concretions
- Brain sand (Corpora arenacea) are small concretions built of calcium phosphates and carbonates, located in the pineal parenchyma between cells and in connective tissue. They increase in size and number with age.

I. **Pinealocytes**

- Have processes reaching capillaries
- Organelles: ER, Golgi, secretory vesicles, cytoskeleton, „synaptic ribbons”
- Membrane proteins typical of photoreceptors
- Contact with sympathetic nerve terminals
- Main secretory products:
    1. Melatonin
    2. Serotonin (substrate for melatonin production)
    3. Peptides (somatostatin)
- Secretory products are transported along the pinealocyte process and released at the terminal connected to blood vessel.

II. Melatonin

- Produced at night and controls both the circadian (day/night) and annual (seasonal) rhythms
    1. Synthesis is controlled by noradrenaline
- Nerve signals evoked by light reach the pineal gland via sympathetic nerve fibers
- Inhibits the release of gonadotropins by acting on hypothalamus

7.7 – The Diffuse Neuroendocrine System (DNES)

- DNES includes endocrine cells of common origin, structure, metabolism and chemical character of produced hormones.
- DNES cells can be either components of endocrine structures/glands, or can be dispersed in epithelia lining various systems.
- Origin: neurally programmed ectoderm
- Hormones produced: peptides and biogenic amines
- Metabolism: produce biogenic amines (adrenaline, noradrenaline, dopamine, serotonin, melatonin)
    1. Take up their precursors
    2. Decarboxylate precursors (to convert them into biogenic amines)
    3. Contain enzymes characteristic for nerve cells (AChE, NSE)
    4. Synthesize peptide hormones

I. Relationship between DNES and the nervous system

- Similar origin
- Various common products (some amines and peptides are also released in synapses as neurotransmitters), e.g. noradrenaline, dopamine, CGRP, VIP, substance P
- Content of enzymes typical for nerve cells (neuron-specific enolase, cholinesterase)
- The same cells may belong to both systems (neurosecretory cells of hypothalamic nuclei, pinealocytes)

II. DNES cells morphology and ultrastructure

- Numerous secretory granules
- Free ribosomes, RER, Golgi, well developed cytoskeleton
- In epithelia: inversed polarity, open and closed type

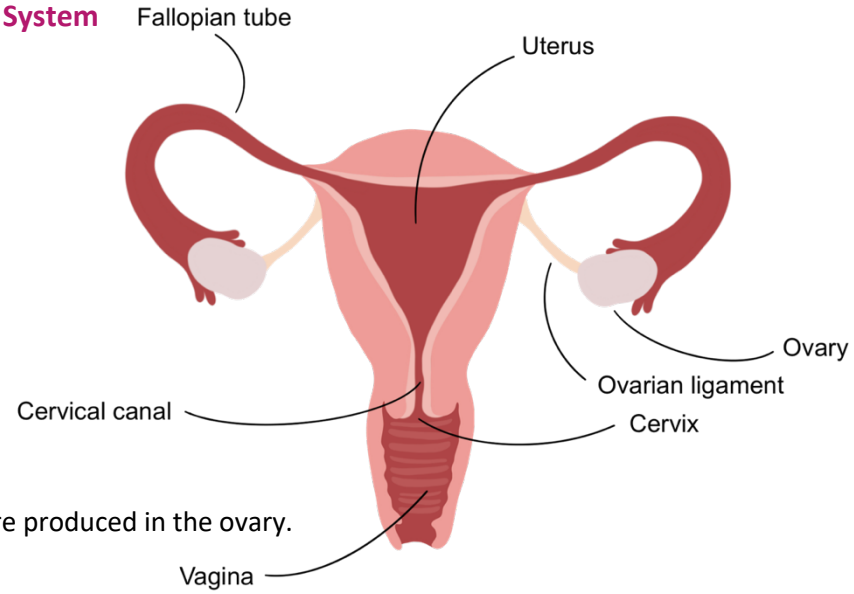
III. Central DNES cells:

- Neurosecretory hypothalamic cells
- Pinealocytes
- Adenohypophyseal endocrine cells

IV. Peripheral DNES cells:

- In endocrine glands:
    1. Thyroid: C cells
    2. Parathyroid:. Chief cells
    3. Islets of Langerhans: Alpha, beta, delta and cells
    4. Adrenal medulla: Chromaffin cells
- In epithelia:
    1. Alimentary canal: enteroendocrine cells
    2. Endocrine cells in airway epithelium
    3. Endocrine cells in other epithelia such as the urinary and reproductive tracts
    4. Epidermis: Merkel cells

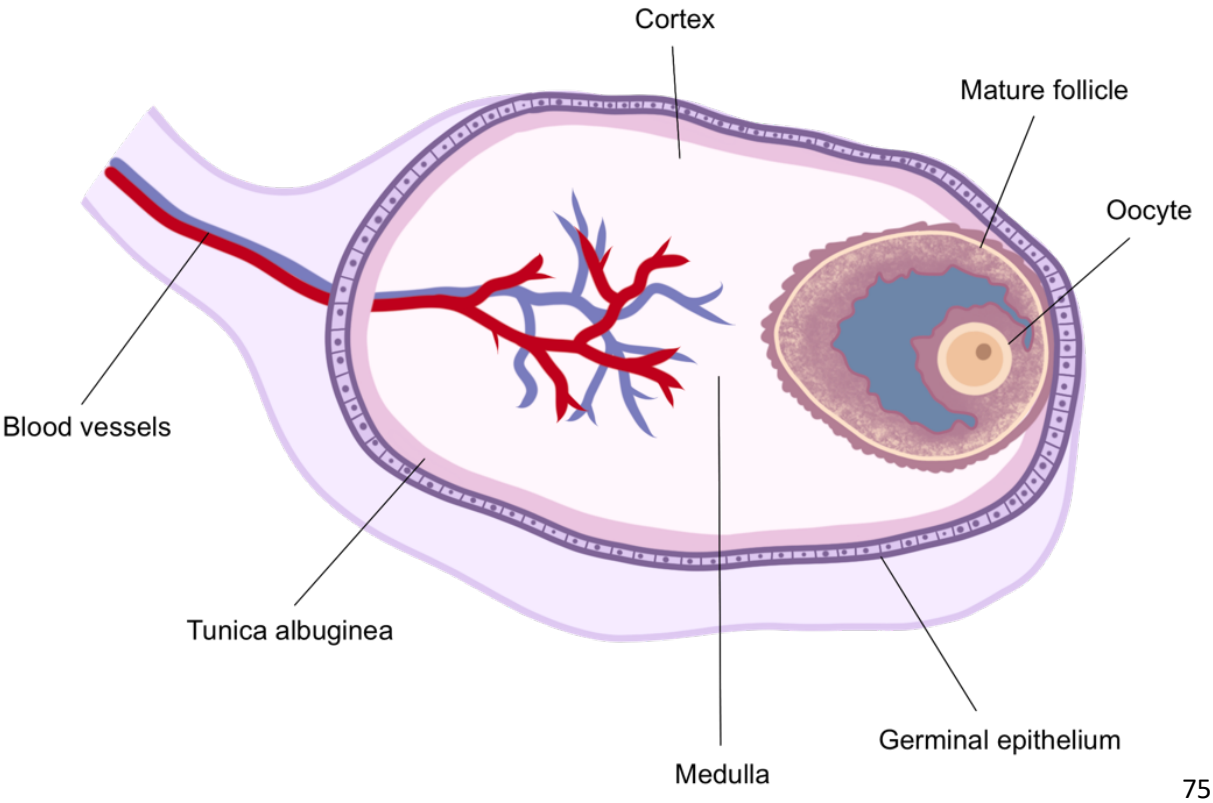
Section 8 – The Female Reproductive System



8.1 – Anatomy of The Ovary

- Both oocyte and sex hormones are produced in the ovary.

Location	Content
On the surface	Germinal epithelium: simple cuboidal epithelium
Under the surface	Dense connective tissue: tunica albuginea
The most abundant part	Cellular connective tissue called cortex. Here we can find ovarian follicles. The cortex also consist of fibroblast, macrophages and smooth muscle cells.
Most internal part	Consist of blood vessels and loose connective tissue.



8.2 – Development of Follicles

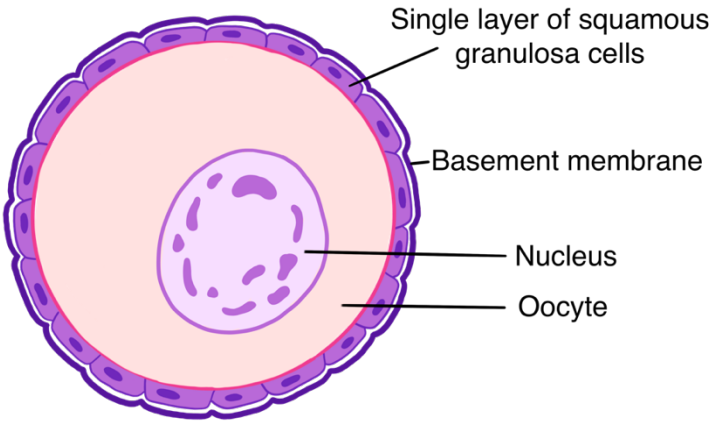
- Ovarian follicles mainly consist of oocytes surrounded by epithelial cells
- The role of the follicular cells is to help the oocyte grow and mature
- The follicular cells and oocyte are connected by gap-junctions.

PRACTICAL EXAM TIP

Differentiating follicle stages in the microscope
Count how many layers the cells are surrounded by. Are they squamous or columnar. This can help you differentiate the different stages of the follicle

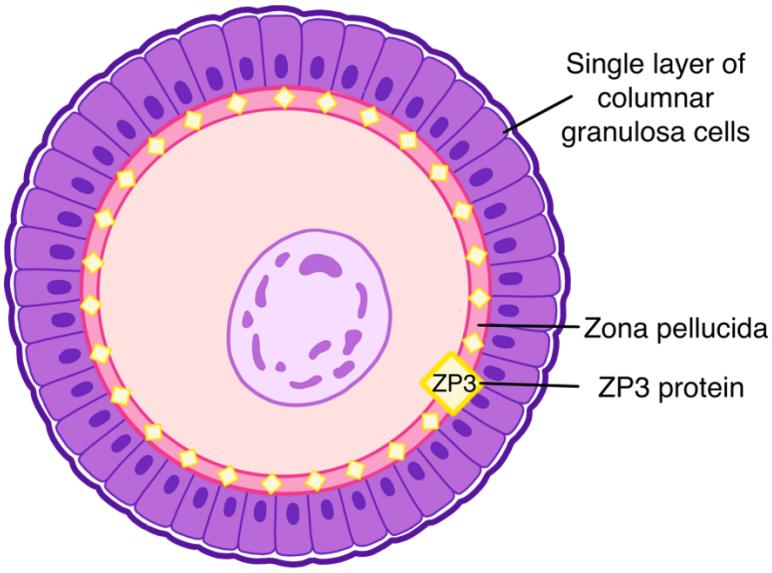
I. Primordial follicle

- Primary oocyte: in first prophase of meiosis.
- The oocyte is surrounded by one layer of follicular cells (squamous).
- In the oocyte we can find: Balbiani body, Annulate lamellae and, abundant mRNAs.



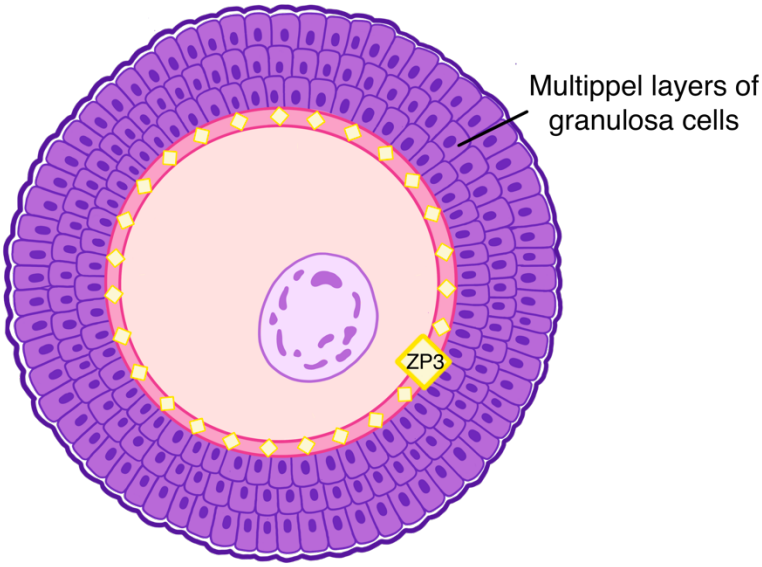
II. Primordial Unilaminar Follicle

- Beginning of formation of zona pellucida. It contains glycoproteins ZP3 and ZP4 which are important receptors for sperm.
- The oocyte is surrounded by one layer of follicular cells (columnar).



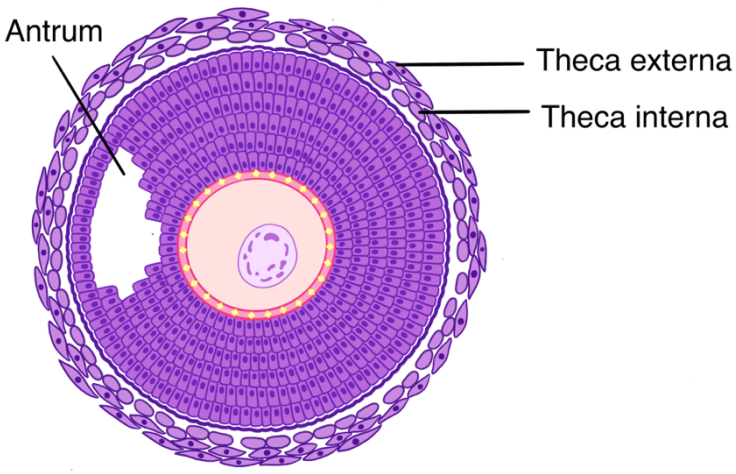
III. Primordial Multilaminar Follicle

- The oocyte is surrounded by layers of follicular/granulosa cells (columnar).
- The oocyte contains free ribosomes and granules.



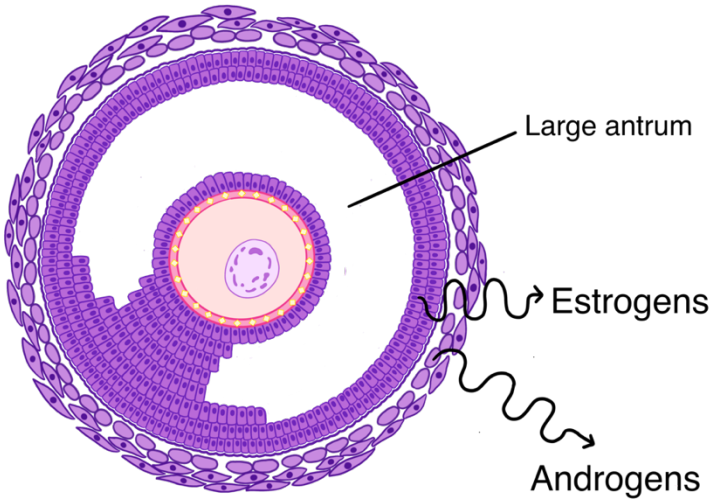
IV. Secondary follicle

- Antrum with follicular fluid is produced.
- Granulosa cells excrete follicular fluid (liquor folliculi)
- Theca folliculi is formed: theca externa (collagen fibers) and interna (capillaries). it´s role is to produce androgens. They are then transported to the follicular cells which convert it to estrogens



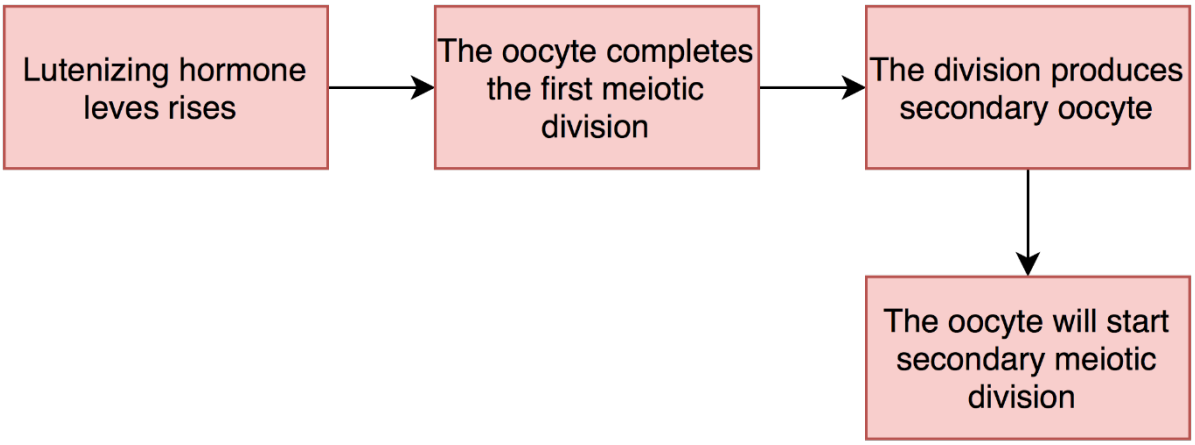
V. Graafan Follicle

- Oocyte surrounded by corona radiata.
- Granulosa cells which shows the highest activity of secretion.
- Larger antrum is developed.
- Graafian follicle consist of granulosa cells which produce estrogens and theca cells which produce androgens and protects from premature ovulation.

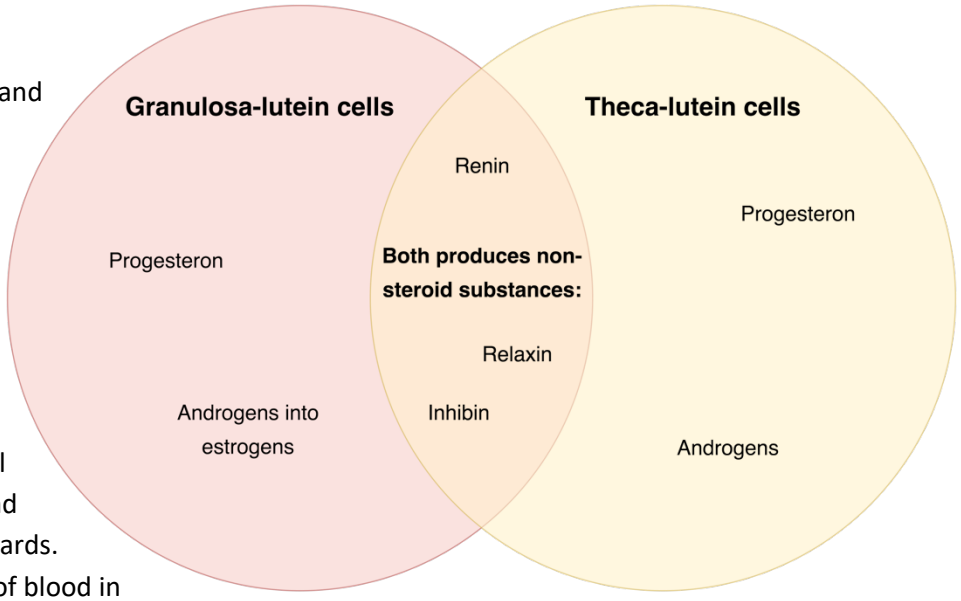


8.3 – Ovulation

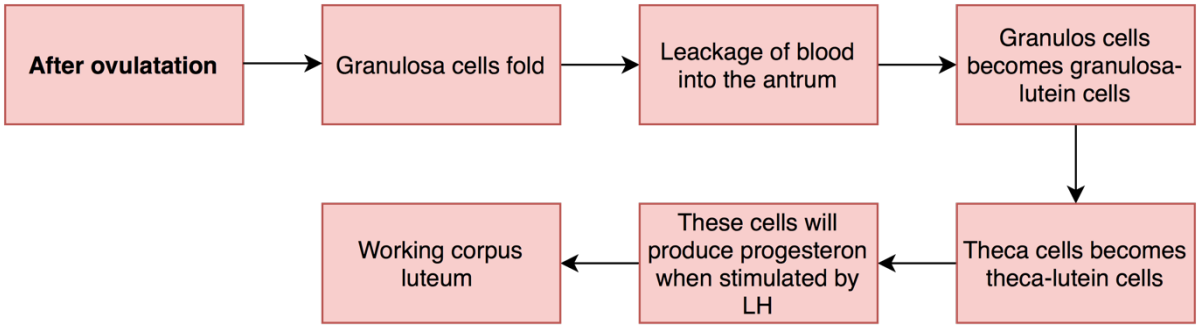
- The process in which the ovary release the oocyte.
- Occurs during menstruation, usually day 14th of the cycle that last 28-days.
- Usually only one oocyte is released each menstrual cycle.
- During childhood the ovary is not active, but from puberty and until menopause some of the primordial follicles will developed and become primary follicles.
- The remains after the ovulations gives rise to corpus luteum.



8.4 – Corpus Luteum

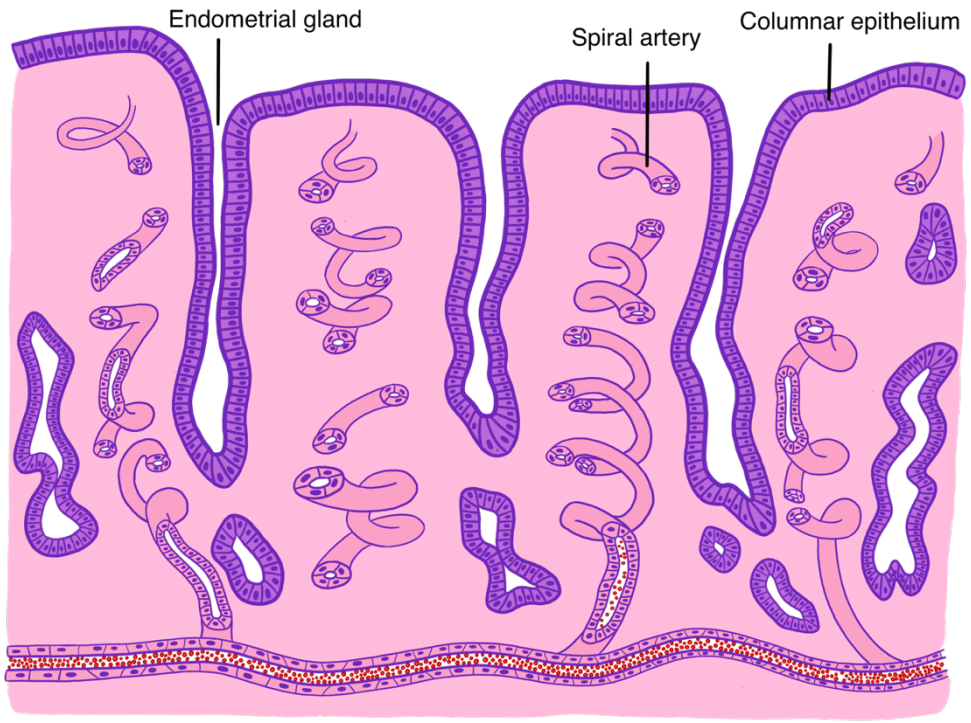


- Corpus luteum is a large gland that is made from theca and granulosa cells of a follicle that has ovulated.
- The cells of corpus luteum becomes specialized and produce steroids.
- When the follicle ruptures during ovulation, there will be a minor hemorrhage and the walls wild collapse inwards. This results accumulation of blood in the collapsed antrum.
- If a pregnancy doesn't occur than the fate of the corpus luteum is degeneration (apoptosis).
- If pregnancy occurs the corpus luteum will produce a large corpus albicans.



Cell type	Product
Follicular cells	Estrogens
Theca interna cells	Androgens
Granulosa-lutein cells	Progesterone, estrogen
Theca-lutein cells	Progesterone
Interstitial cells	Androgens
Hilus cells	Testosterone - rare

8.5 – Fallopian Tube, Uterus and Cervix

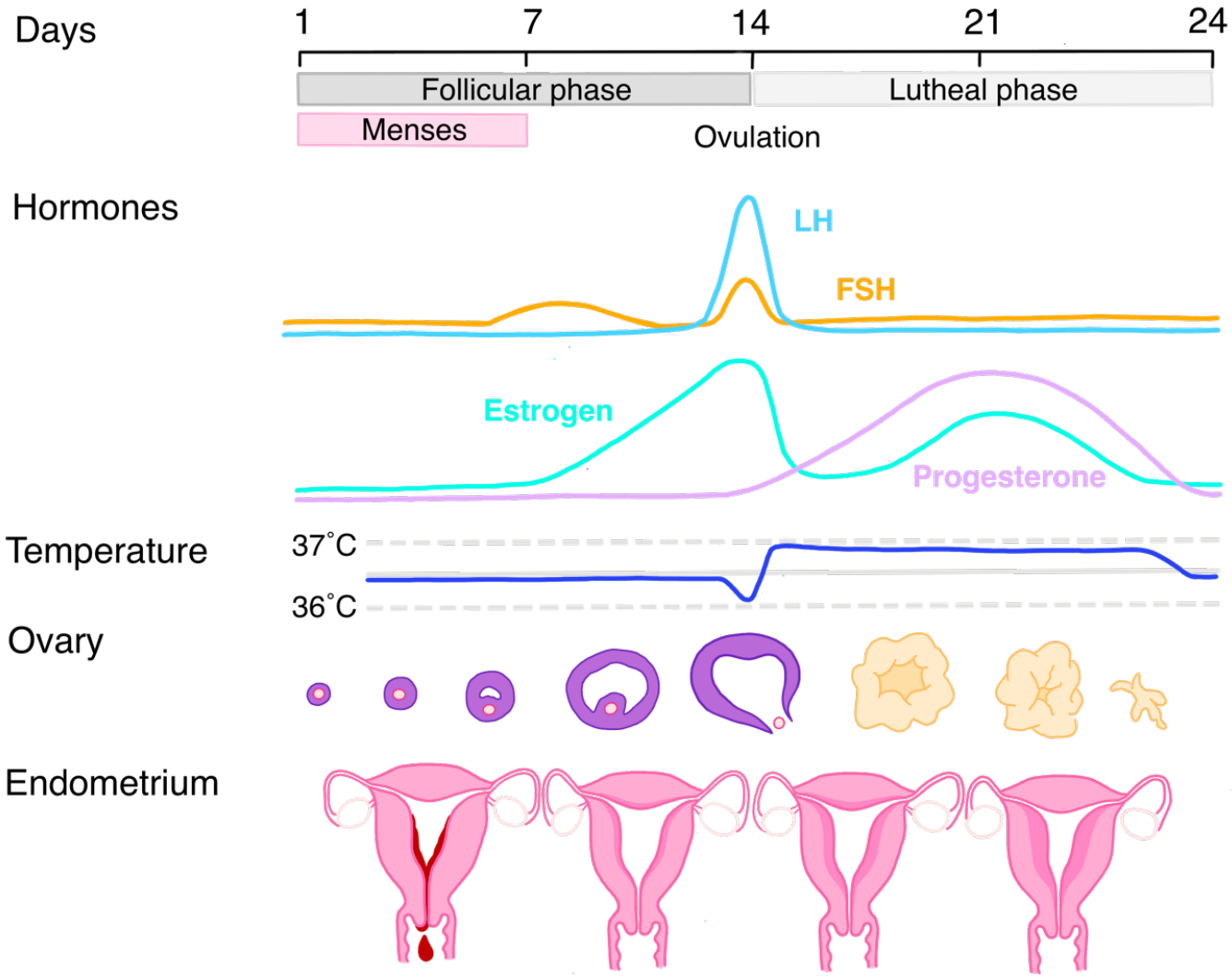


Oviduct	Uterus	Uterine cervix
The oviduct epithelium consist of ciliated cells which are responsible for the transport of the oocyte Secretory cells also known as peg cell. Stem cells (basal) which have the role to regenerate the epithelium	Endometrium and myometrium The endometrium consist of mucosa, and the myometrium consist of smooth muscle. Endometrium consist of stem cells which can be divided into epithelial and mesenchymal. Have simple columnar epithelium on the surface. Migratory cells can be found in dense connective tissue. Consist also of serous glands. Blood vessels are present.	Many cervical glands (branched). Consist of simple columnar epithelium. Mucosa in the uterine cervix is <u>not</u> involved in menstruation. The site where simple columnar epithelium transits into stratified squamous epithelium, is the main cite for cervical cancer.

8.6 – Menstrual Cycle

Physiological Phases of The Menstrual Cycle

Menstrual cycle	**Menstrual phase**	Arteries will dilate, the vascular wall will rupture due to blood pressure and fragmentation of the functional layer because of hemorrhage.
	Follicular phase (Proliferative phase)	The functional layer becomes straight and narrowed
	Luteal phase (Secretory phase)	Glands will increase their secretory activity. The functional layer will thicken. Here is where ovulation begins.
	Ischemic phase	Necrosis and ischemia of functional layer (partial), helical arteries will constrict.

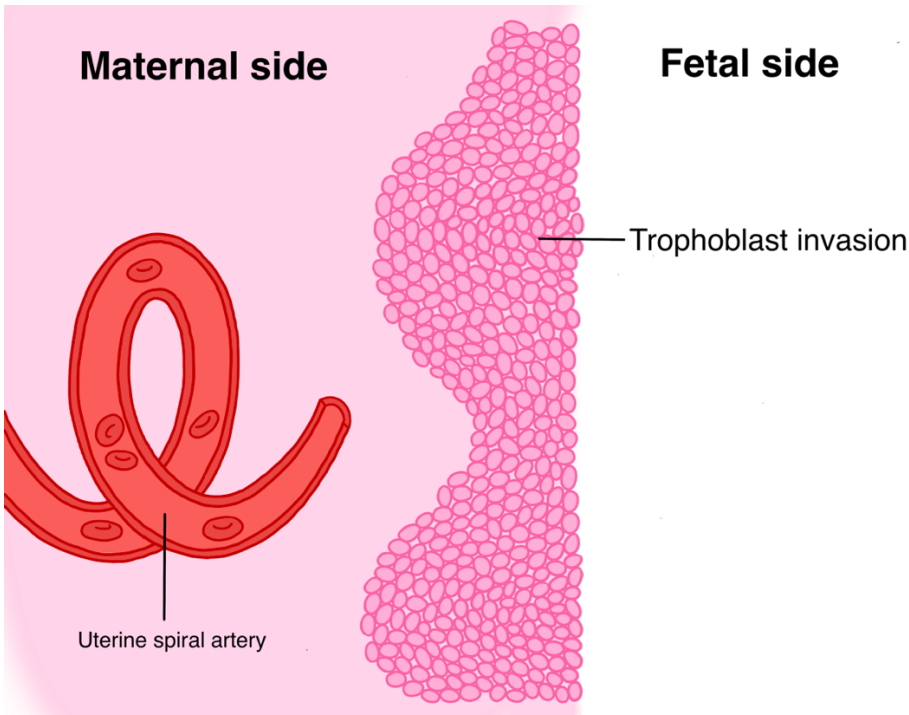


8.7 – Placenta Development

- Placenta is the place where mother and fetus exchange different nutrients.
- Chorion: part of the placenta which is from the fetus.
- Decidua: the maternal part of placenta
- The role of the chorionic villi is the to exchange important nutrient and gases. It important for the metabolic relationship between the mother and the fetus.
- The umbilical cord consist of two arteries and one vein. It has a connective tissue that is gelatinous.
- The fetal membrane contains three membranes:
    1. Amniotic membrane
    2. Chorionic membrane
    3. Decidual membrane
- Trophoblast: outer layer of the blastocyst. The embryo is in the blastocyst stage about 5 days after fertilization. The blastomeres sort themselves into and peripheral layer called trophoblast and is called embryoblast.
  trophoblast transform into:
  1. Syncytiotrophoblast: surrounds the cytotrophoblast during the placenta development. Have all organelles, microvilli and vesicles.
  2. Cytotrophoblast: surrounds the yolk sac which is a new space produce by the embryoblast. Desmosomes connect syncytiotrophoblast with cytotrophoblast.

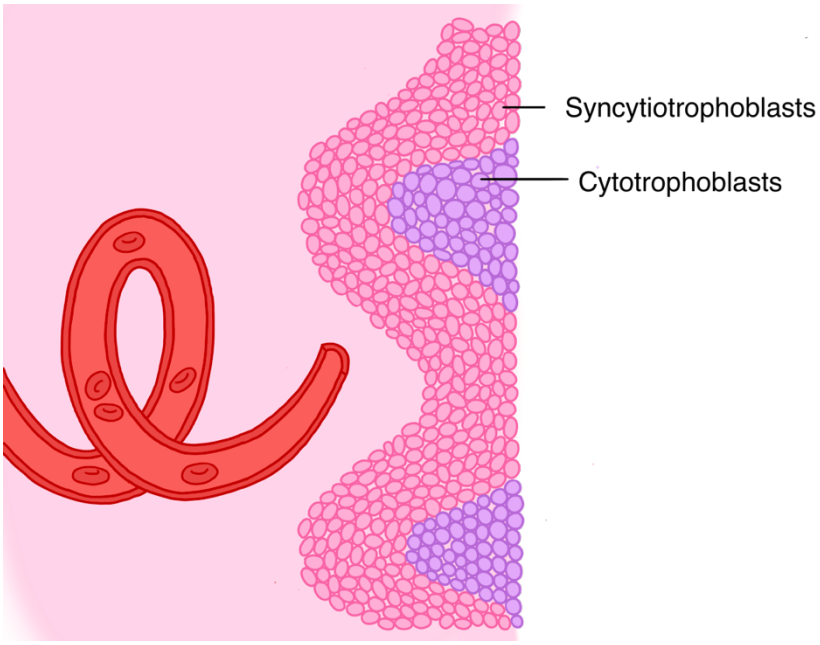
I. Invasion

- Starts on day 10 of gestation
- Open circulation is started by trophoblasts which attacks the endometrium. Blood filled spaces are made.



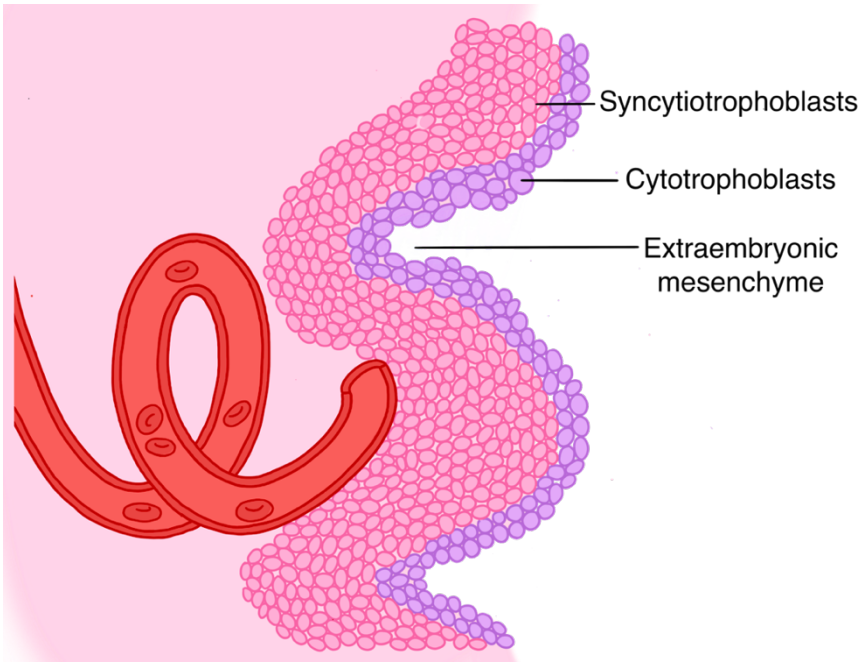
II. Primary Villi Production

- Cytotrophoblast and syncytiotrophoblast layers are present.
- The role of the syncytiotrophoblast is immunoglolbulin transport and gas exchange. Also the production of hCG, hCT, estrogen and progesterone hormones is very important.



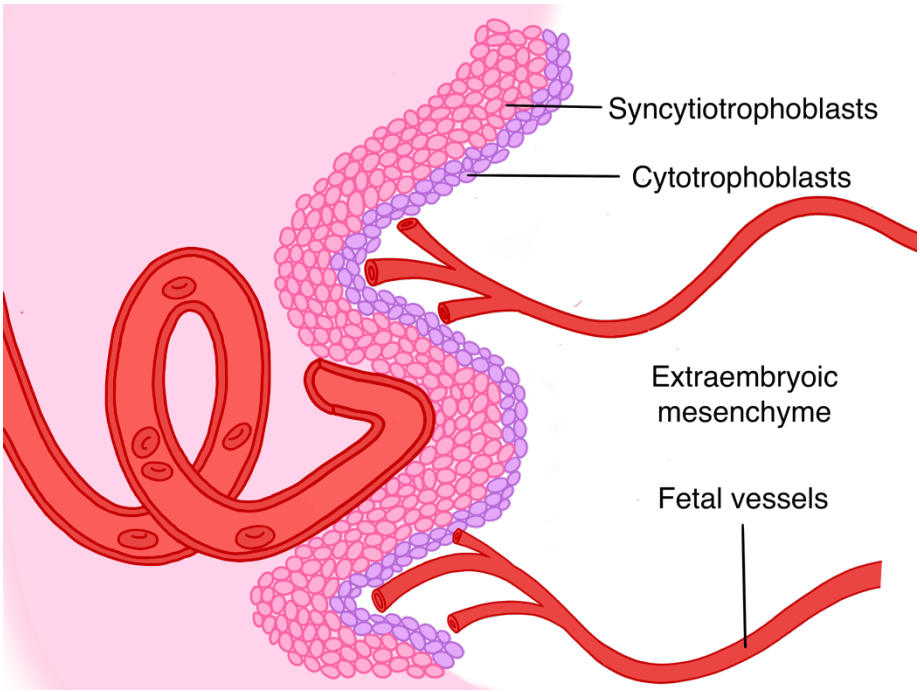
III. Secondary Villi

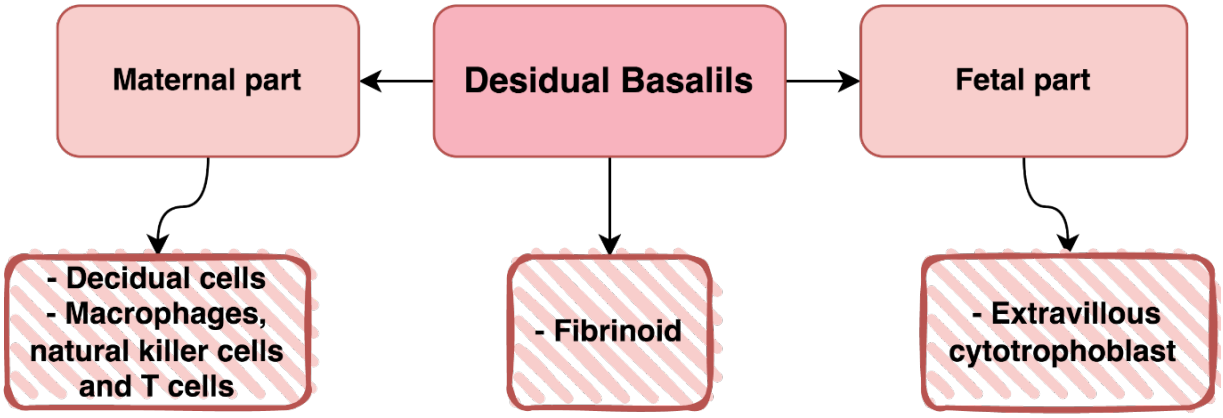
- The extraembryonic mesenchyme migrate to the primary villi. This tissue will not be present in the late/mature barrier of placenta.



IV. Tertiary Villi

- The mesenchyme which invaded the primary villi which developed into secondary will produce blood vessels.
- As the villi mature the cytotrophoblast will invade and engulf into syncytiotrophoblast.
- The tertiary villi will go through maturation which will include removal of nuclei in the cell of the syncytiotrophoblast.





CLINICAL CORRELATION

Placenta previa

When the placenta lies between the fetus and the cervical opening, blocking the birth canal. A scheduled cesarian section is required for safe delivery because attempting vaginal birth results in massive hemorrhage and most likely death of both the fetus and mother.

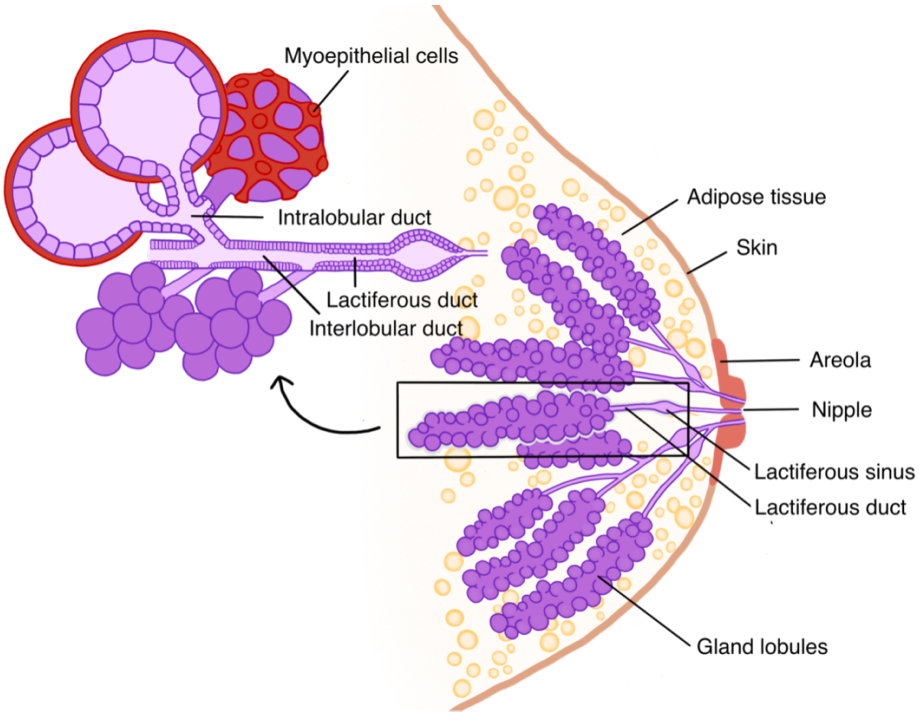
8.8 – Mammary Gland

- The mammary gland contain secretory cells which have two different secretions: eccrine and apocrine.
    1. Eccrine: proteins
    2. Apocrine: lipids

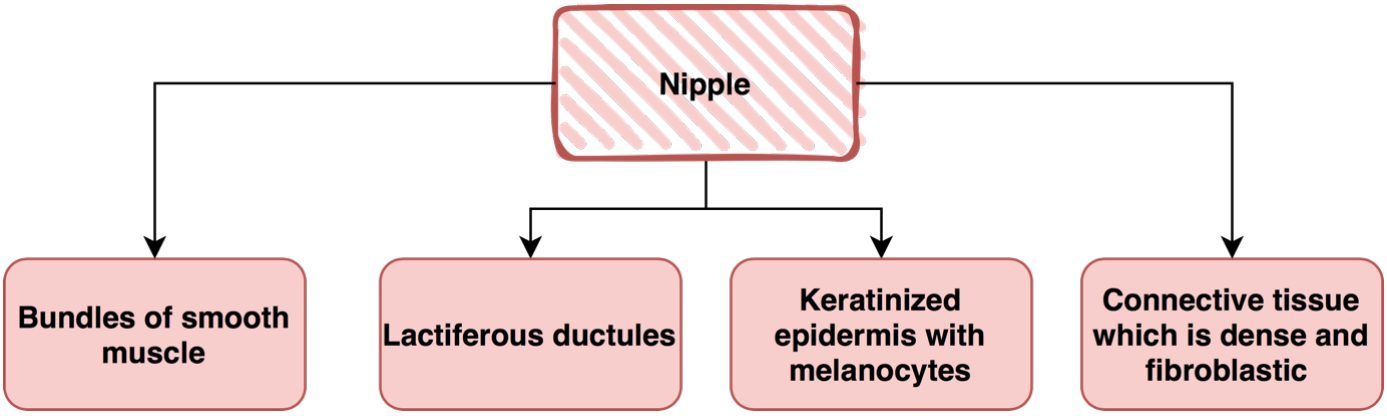
Stage	Characteristics
Prepubertal	Connective tissue (abundant). Poorly developed ducts
Postpubertal	Adipose tissue (abundant). Fully developed duct system. Undifferentiated secretory cells.
Pregnancy	Development of secretory units. Reduced adipose tissue and increased amount of glandular tissue.
Lactation	Dilated alveoli In stroma we can find connective tissue that is dense and plasma cells.
After lactation	Apoptosis and autophagy of the secretory portion. Adipose tissue increase. Mammary gland return to how it looked before pregnancy.

8.8.1 – System of Mammary Gland

Intralobular duct	Simple cuboidal epithelium
Interlobular duct	Simple columnar epithelium
Lactiferous sinus	Double cuboidal epithelium
Lactiferous duct	Double cuboidal epithelium, stratified squamous



8.8.2 – The Nipple



Section 9 – The Male Reproductive System

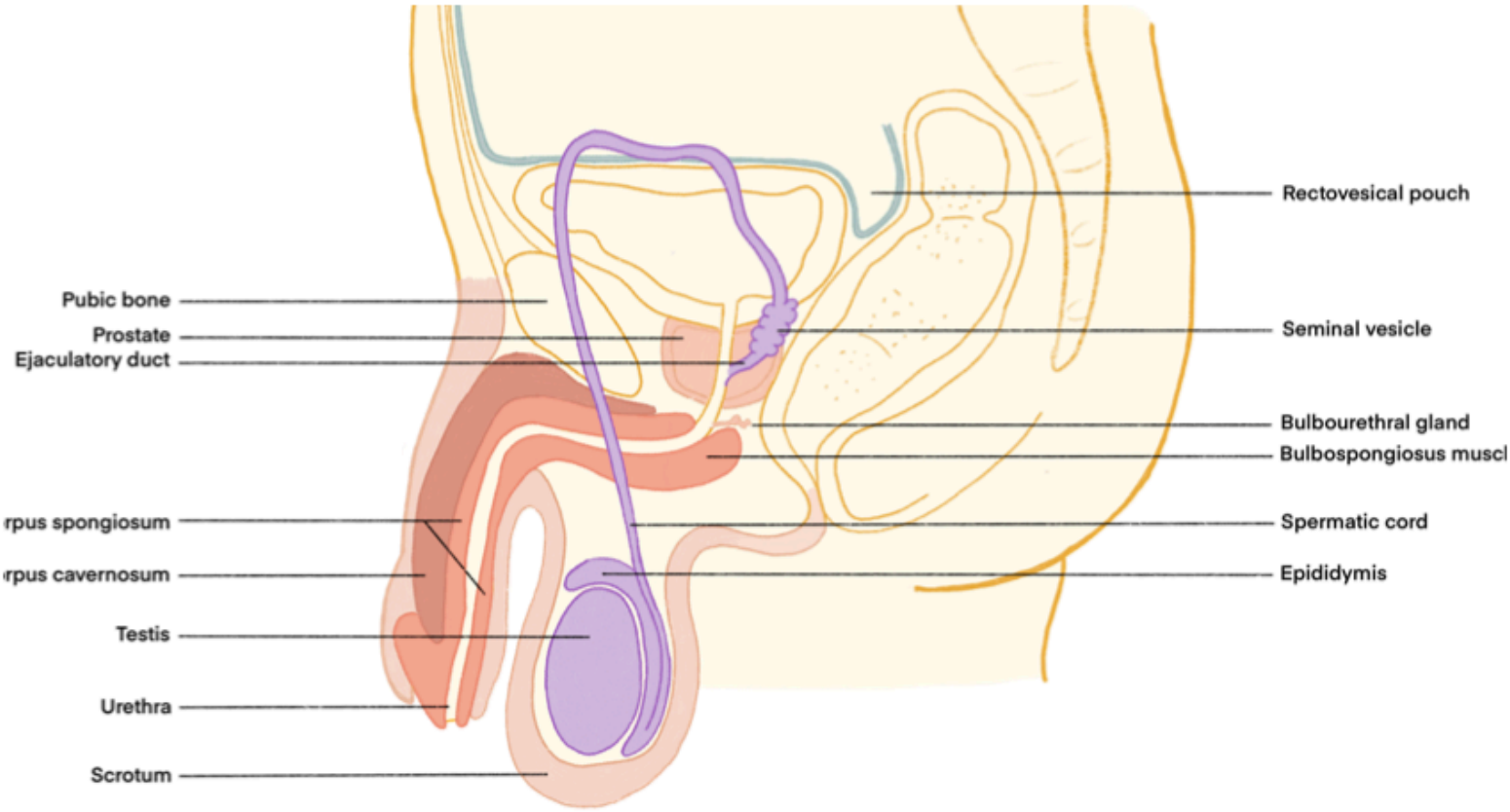
9.1 – The Testis

9.2 – Spermatogenesis and Spermiogenesis

9.3 – Ducts

9.4 – Glands

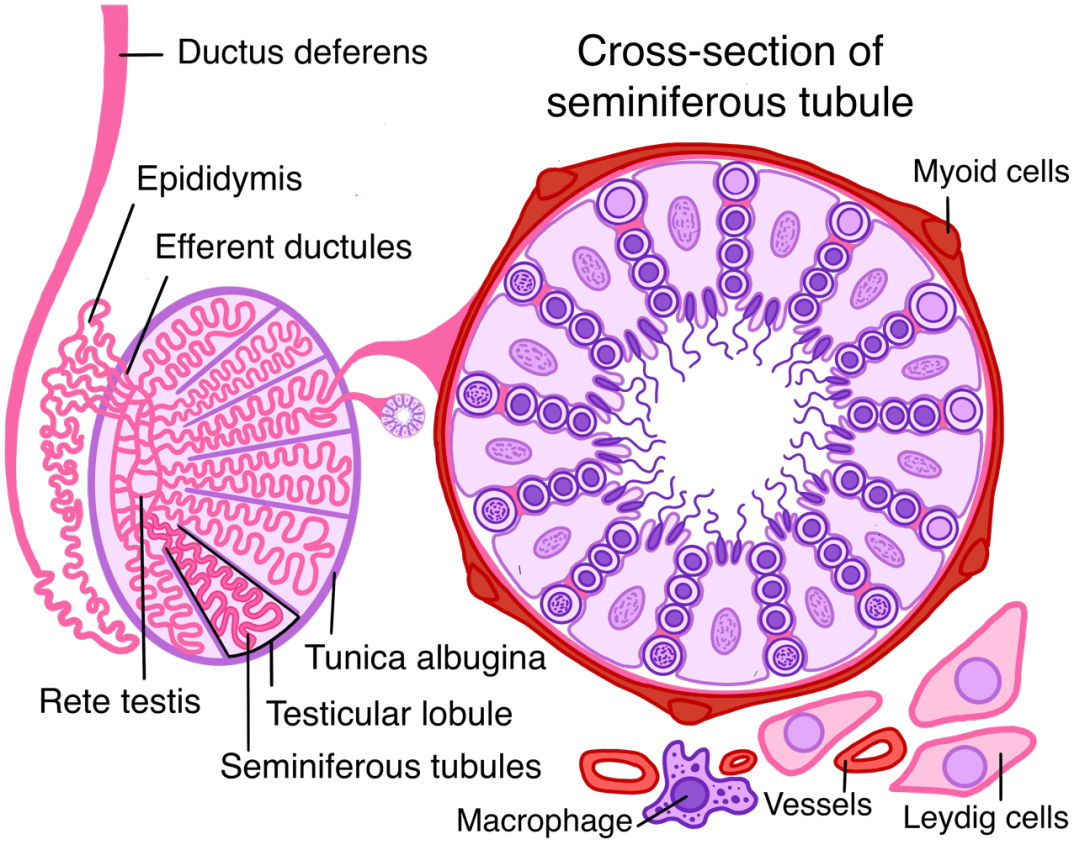
9.5 – Erectile Tissue



9.1 – The Testis

Testis	- Surrounded by Tunica albuginea (connective tissue)
Testicular lobule	- Seminiferous tubules - Surrounded by connective tissue containing: 1. Nerve fibers 2. Leydig cells 3. Blood vessels 4. Macrophages - No Lobules Behind Men - Leydig cells produce testosterone and contains crystal of Reinke[1]
Seminiferous tubule	- Site of sperm production - Tunica propria 1. Basal lamina 2. Collagen 3. Myoid (peritubular) cells 4. Lymphatic capillaries - Spermatogenic "epithelium" 1. Cells involved in spermatogenesis: spermatocytes, spermatids and spermatogonia 2. Sertoli cells: assist in the development of sperm cells

[1]More about this topic in the reproductive booklet

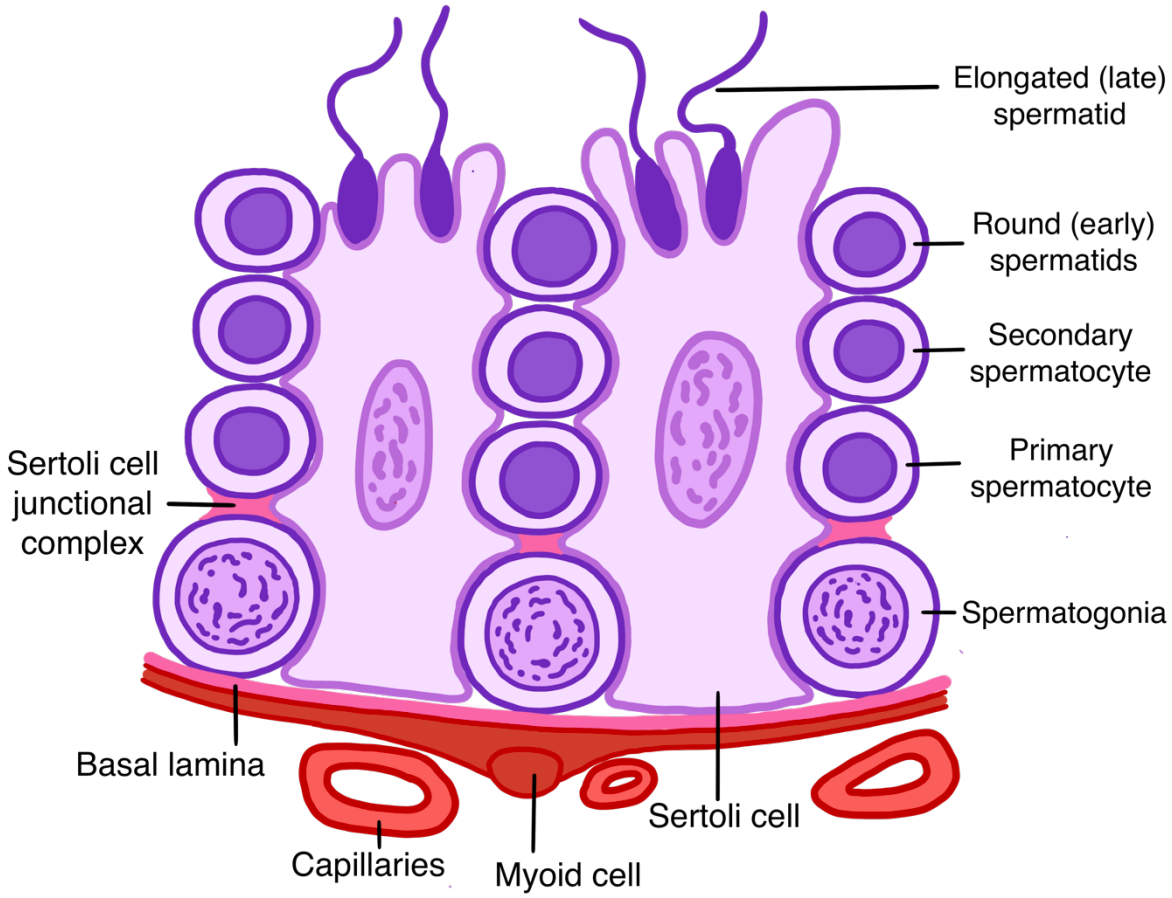


9.1.1 – Sertoli Cells

- Columnar epithelial cells
- Acts as a metabolic and structural support for the spermatogenic cells as they are becoming spermatozoa.
- Contain:
  1. Smooth endoplasmic reticulum (SER)
  2. Rough endoplasmic reticulum
  3. Golgi apparatus
  4. Mitochondria
  5. Lysosomes
- Between the Sertoli cells there is a *tight* blood testis barrier.

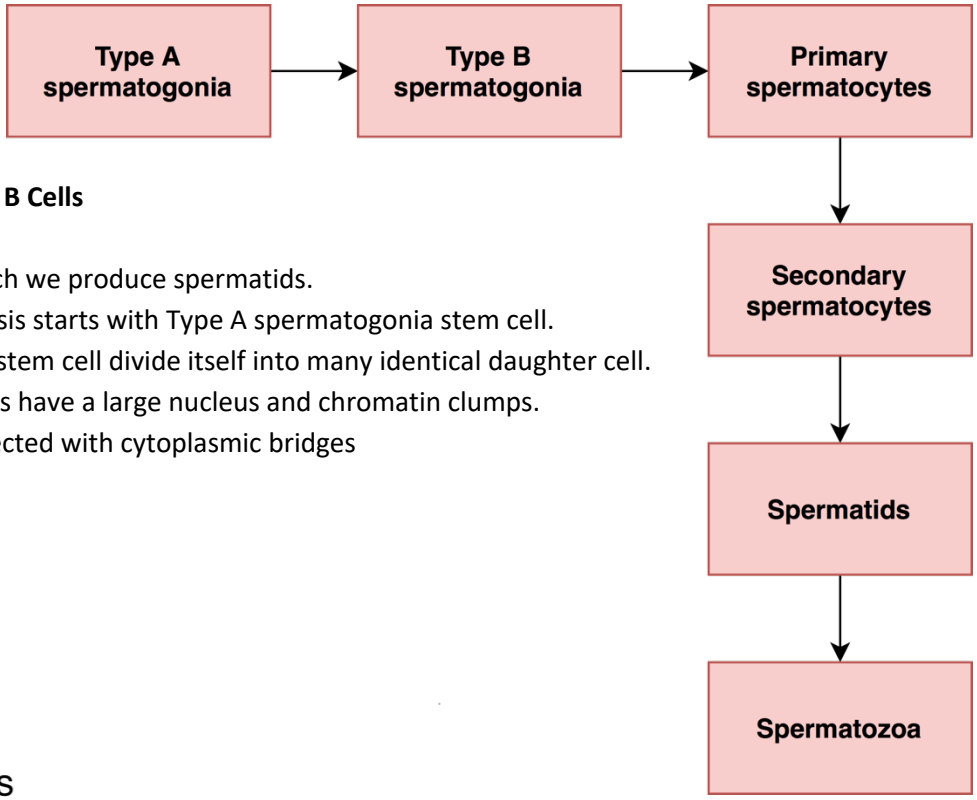
9.1.2 – Blood-Testis-Barrier

- Protect the spermatogenic cells from immune system attack.
- Separate the spermatogenic cells (cells that develop into spermatozoa) from nutrients, and thus make them dependent on the Sertoli cells to support them metabolically.



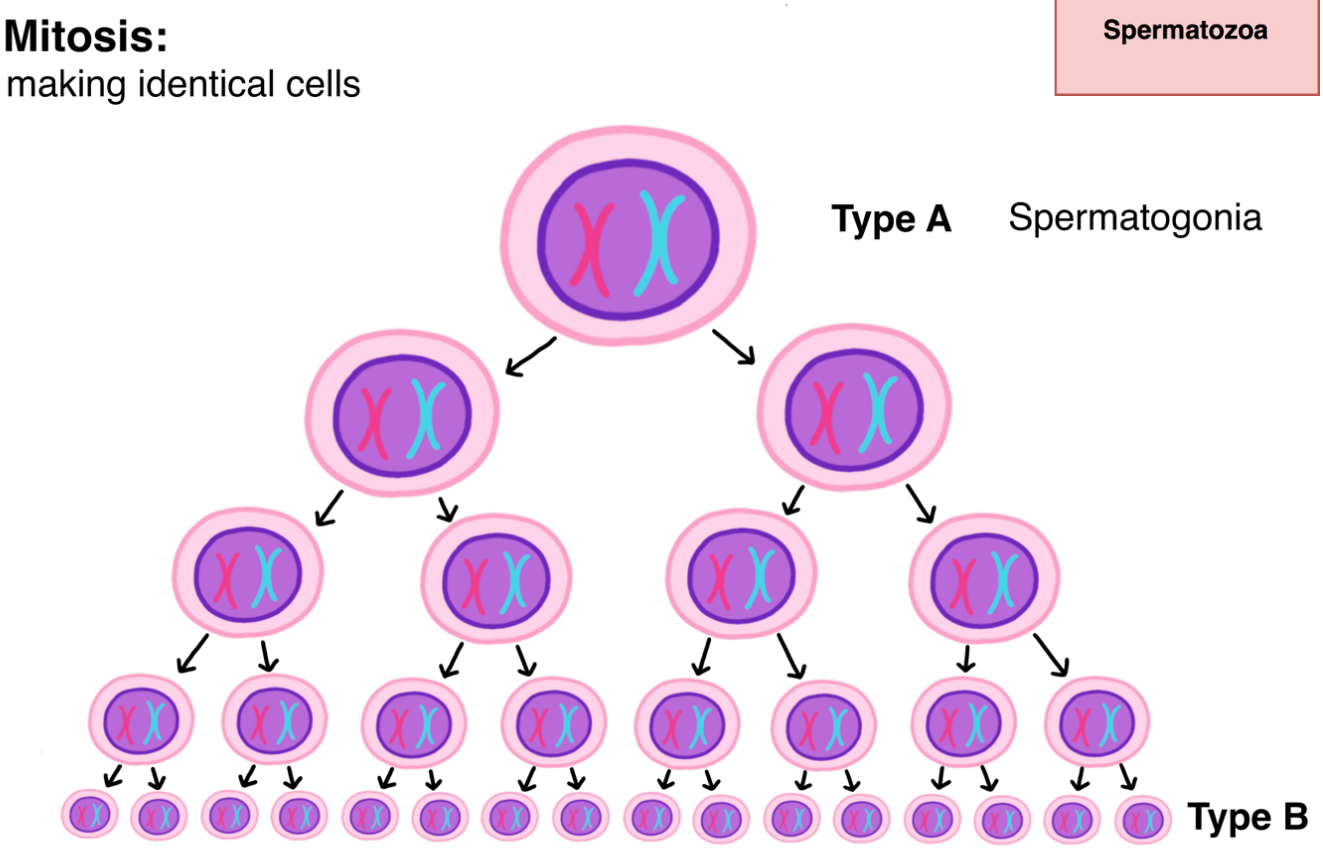
9.2 – Spermatogenesis and Spermiogenesis

- Spermatogenesis: start at puberty and involves the proliferation of stem cells and progenitor cells with the final stage being the spermatid.
- Spermiogenesis: spermatids becomes mature sperm. Considered to be final stage of spermatogenesis.



9.2.1 – Production of Type B Cells

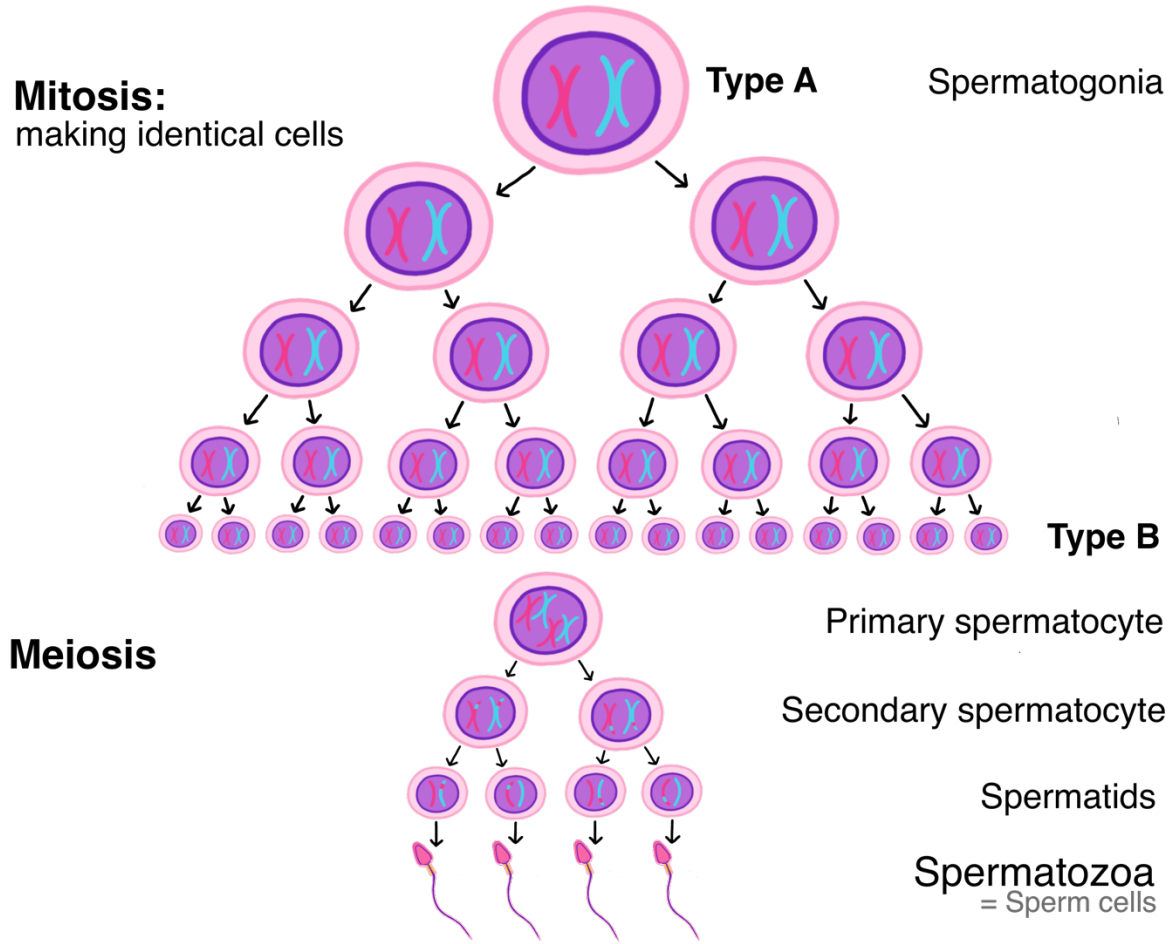
- Process in which we produce spermatids.
- Spermatogenesis starts with Type A spermatogonia stem cell.
- By mitosis the stem cell divide itself into many identical daughter cell.
- The Type B cells have a large nucleus and chromatin clumps.
- Cells are connected with cytoplasmic bridges



9.2.2 – First Meiosis of Spermatogenesis

- The first meiosis in spermatogenesis starts with primary spermatocytes
- In this stage we have the formation of acrosome and flagellum

Spermatogonia	Dark spermatogonia: chromatin (dark and dispersed), stem cells Pale spermatogonia: chromatin (pale and dispersed) Spermatogonia B: big nucleolus, chromatin (dense clumps)
Spermatocyte	Primary spermatocyte: visible chromosome, largest cells Secondary spermatocyte: short lifespan
Spermatid	Smallest cell, nucleus (dense), organelles



9.2.3 – Spermiogenesis

- Part of the development of spermatogenic cells where the cells become mature spermatozoa.

1. Golgi Phase

Production of acrosome start with pro-acrosomal vesicles that become an acrosome cap at the end of the nucleus of spermatid.

2. Cap Phase

In this phase the acrosomal cap that was produced in the previous phase extend and covers the half of the nucleus.

3. Acrosomal Phase

- Head of the spermatid that is becoming a spermatozoa is in development.

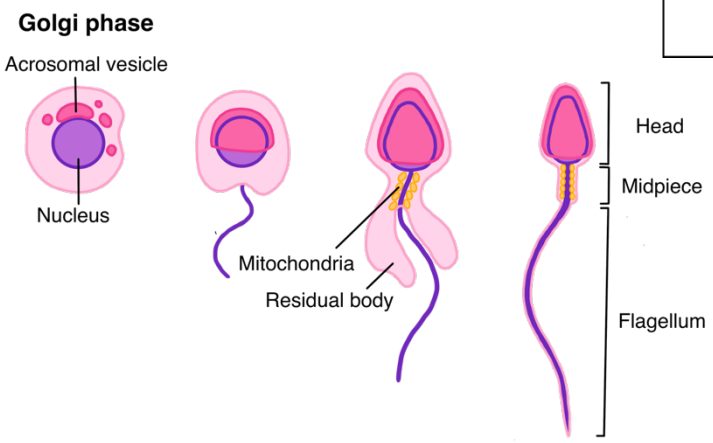
- The head of the spermatid that is developing is still protected and surrounded by the Sertoli cells.

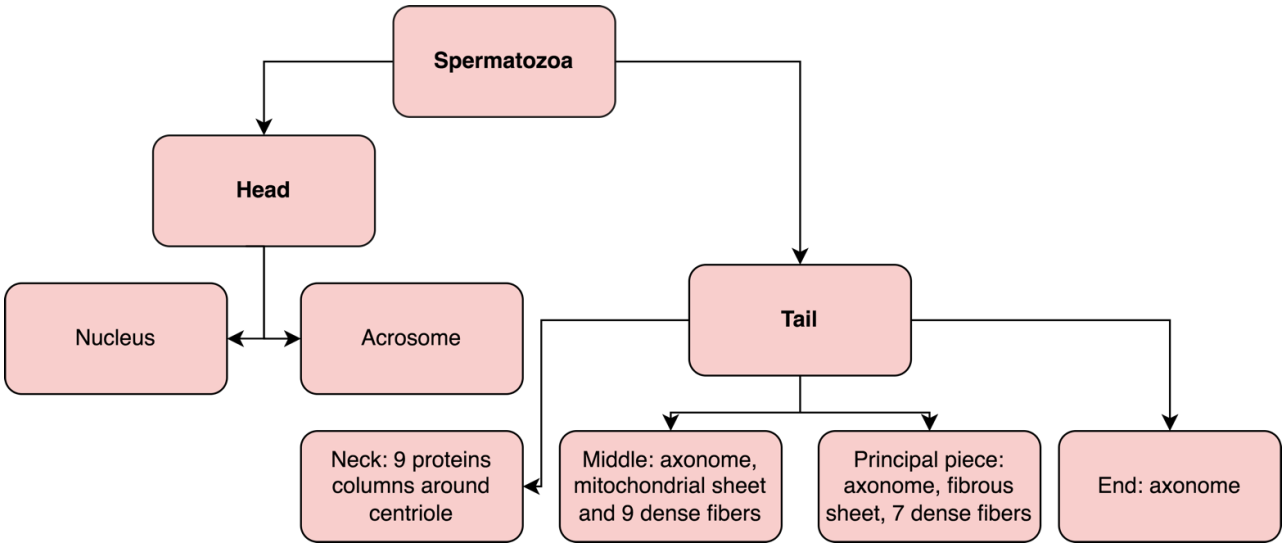
- The nucleus becomes condensed and contains protamines which are nuclear peptides.

- The axonome extends and the flagellum continues to grow.

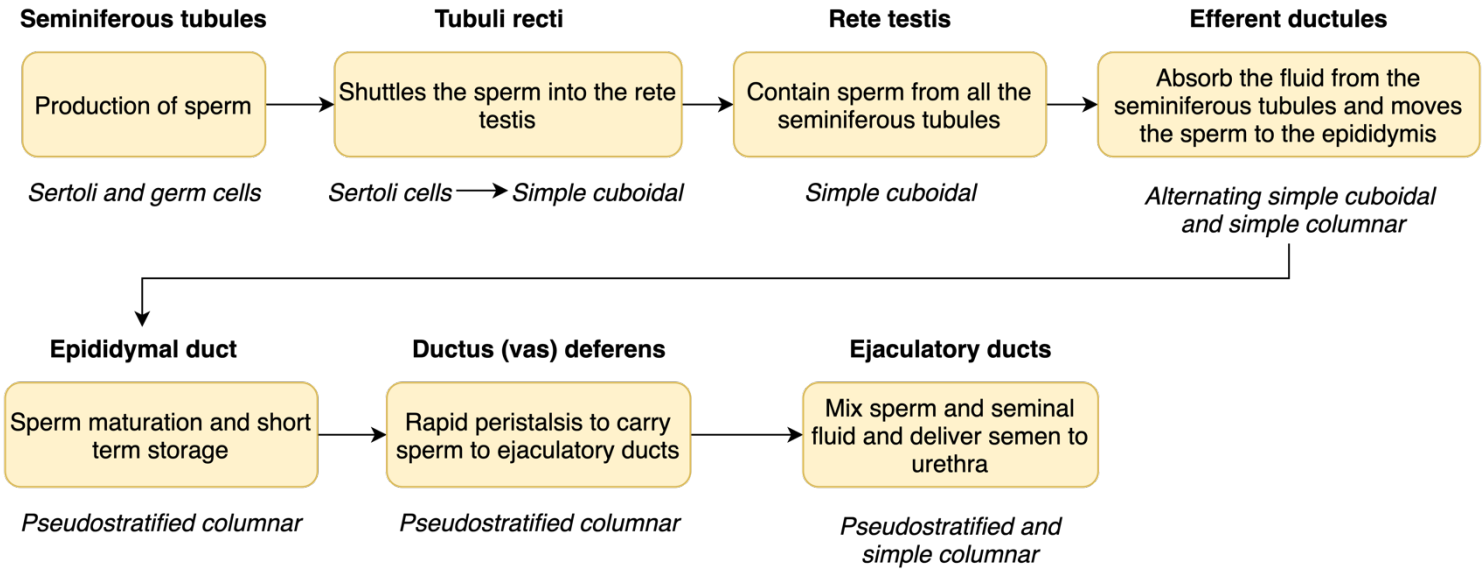
4. Maturation Phase

All extra residual body removed.





9.3 – Ducts



I. Tubuli Recti

- Connect rete testis with seminiferous Tubules.
- Consist of simple cuboidal epithelium.
- Basal lamina and myoid cells.

II. Rete Testis

- Found in mediastinum testis.
- Collect sperm from all seminiferous tubules.
- Simple cuboidal epithelium.

III. Epididymis

- Located both posterior and superior of each testis
- Divided into *head*, *body* and *tail*
- The efferent ductules connect the epididymis to rete testis at the head.
- The sperm matures in the epididymis which usually takes between 2 to 4 weeks.
- Principal cells which can be in the epididymis contains RER, SER, stereocilia, lysosomes and tight junctions.

	Wall	Epithelium
Head	Simple columnar/cuboidal epithelium, basal lamina, smooth muscle layer	Ciliated columnar cells, cuboidal cells and basal stem cells
Tail and body	Pseudostratified epithelium + stereocilia, basal lamina, smooth muscle layer	Principal cells and basal cells.

IV. Ductus (vas) Deferens

- Tube which transport the sperm from the epididymis to the ureter.
- Contains a thick muscular layer which produces contractions and moved sperm during contractions in the tube.
- The muscular layer are divided into longitudinal layer and circular layer.
- Ductus vas deferens contains also epithelium that is pseudostratified, basal lamina, and lamina propria.

V. Seminal Vesicles

- Produce 70% of the seminal fluid/sperm.
- The seminal fluid includes: fructose, prostaglandin and proteins.
- Lines with pseudostratified columnar epithelium, basal lamina, connective tissue that is fibroelastic and contains a coat of smooth muscle.

9.4 – Glands

Prostate gland	The ureter is surrounded by the prostate gland 20% of seminal fluid is produced in the prostate gland Simple columnar epithelium Basal lamina and smooth muscle cells that can be found in connective tissue Material that is mineralized
Bulbourethral gland	Release mucus during erection Mucous tubules: columnar secretory cells and basal lamina Simple cuboidal epithelium ducts Interlobular septa: skeletal muscle fibers Capsule: connective tissue

9.5 – Erectile Tissue

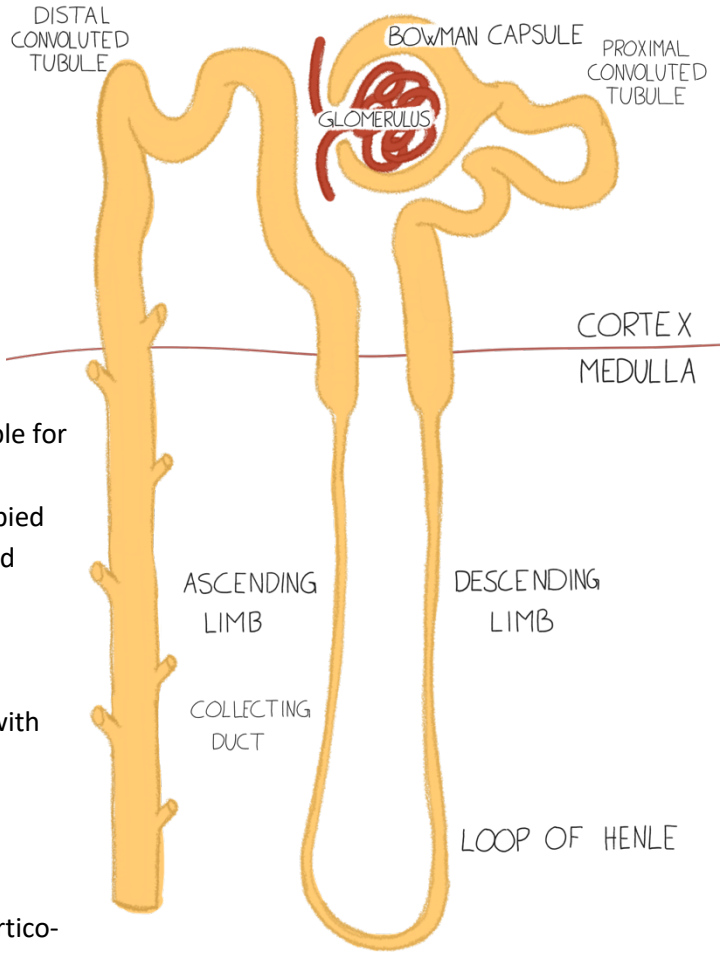
- Corpora cavernosa
- Corpora spongiosum
- Contains vascular spaces with endothelium
- Connective tissue containing smooth muscle cells

Section 10 – The Urinary System

10.1 – Nephron Segments
10.2 – Urine Concentration
10.3 – Distribution of Tubular Segments
10.4 – Direction of Blood Flow
10.5 – The Juxtaglomerular Apparatus
10.6 – The Renin-Angiotensiogen-Aldosterone System
10.7 – Interstitial Tissue
10.8 – The Excretory Passages

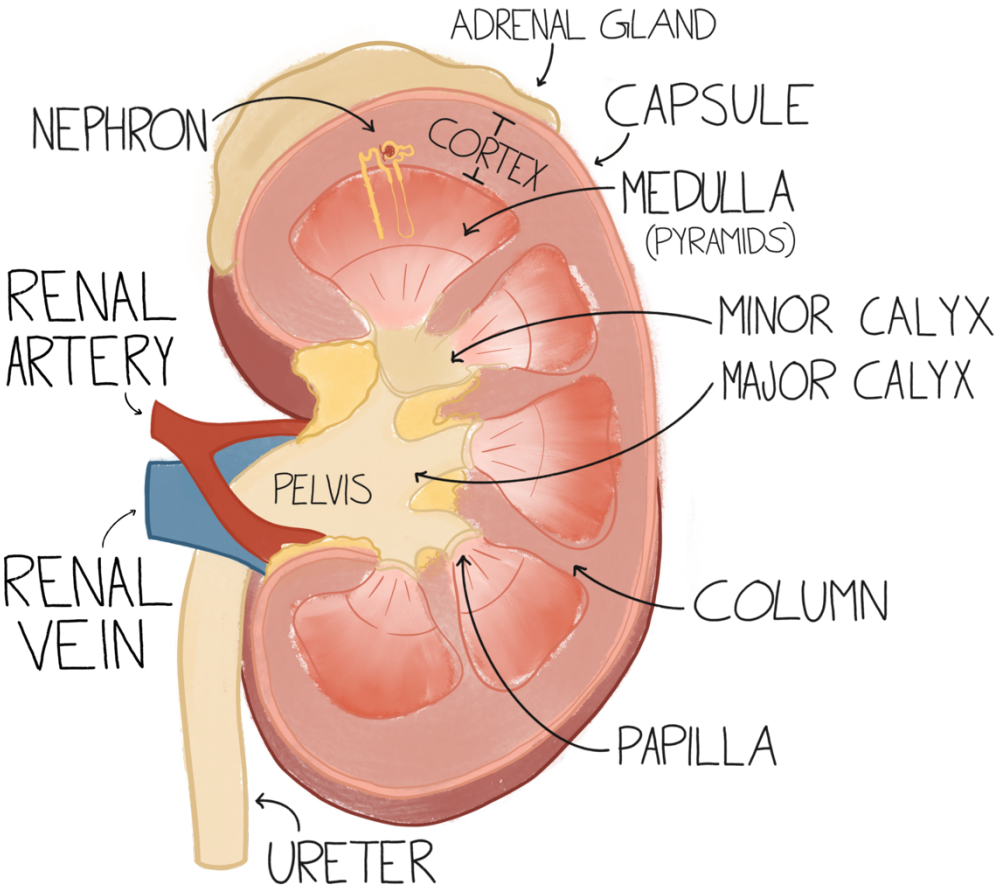
- The kidney consists of tightly packed epithelial tubules: uriniferous tubules. Their regular arrangement in the kidney is responsible for differentiation of the kidney into cortical and medullary areas. Intertubular spaces are occupied by scant interstitial tissue with numerous blood vessels

Juxtamedullary nephron



I. Uriniferous tubule

- Nephron: unbranched, has several segments with different histological appearance
- Collecting tubule: branched, several nephrons empty into single collecting tubule
- Cortical nephrons: short loops of Henle
- Juxtamedullary nephrons: located near the cortico-medullary border, with long loops of Henle

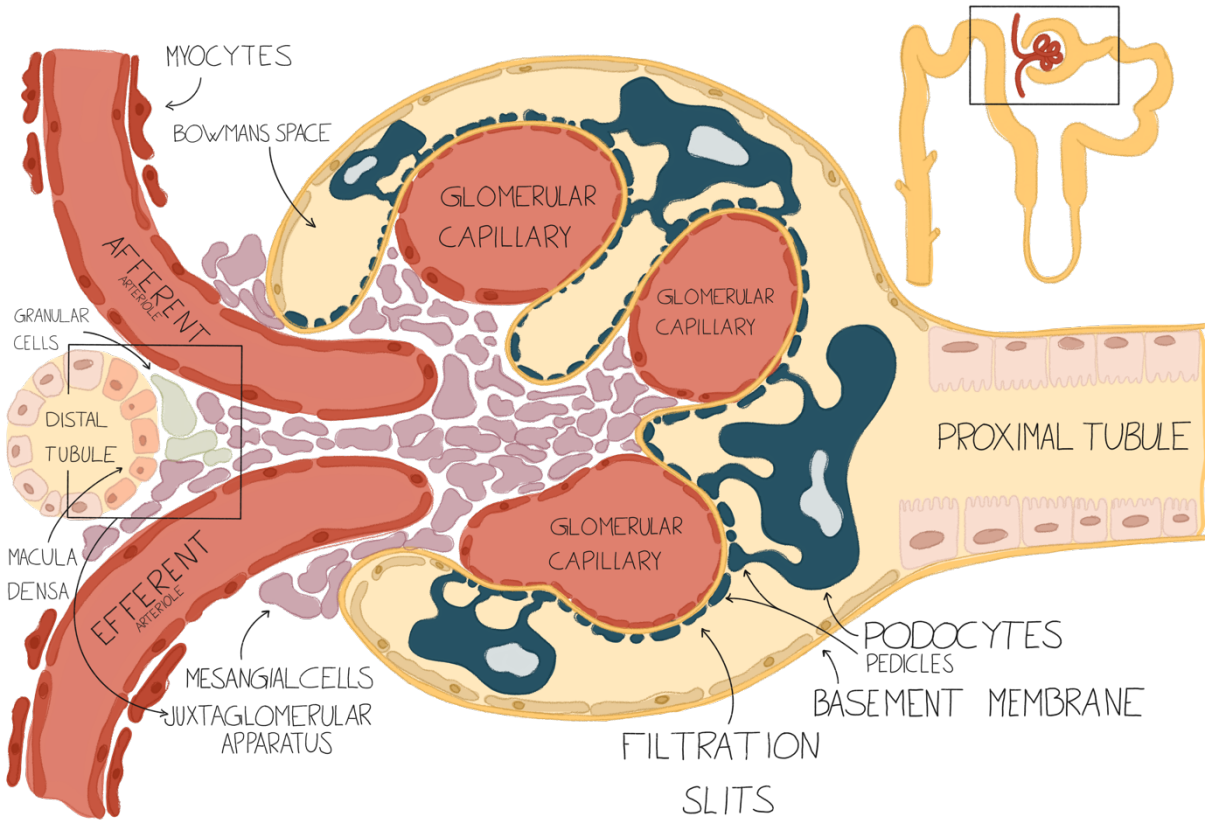


I. Renal corpuscle

- Function: filtration of blood plasma to Bowman's space (ultrafiltration)
- Glomerulus: capillary loops between mesangial cells
    1. Capillaries in the glomerulus are fenestrated and covered by podocytes
- Bowman's capsule:
    1. Outer parietal layer
    2. Inner visceral layer formed by podocytes
    3. Space between these layers are called the Bowman space
- Vascular pole: afferent and efferent arteriole
- Urinary pole: transition to proximal tubule

II. Podocytes

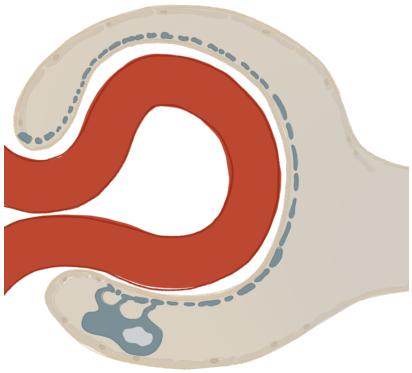
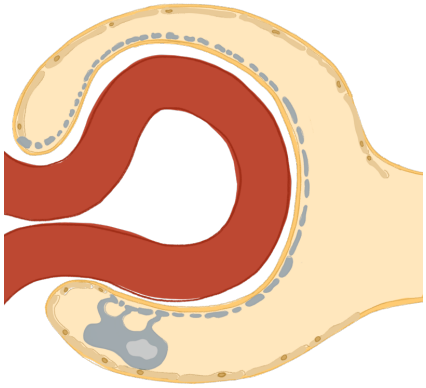
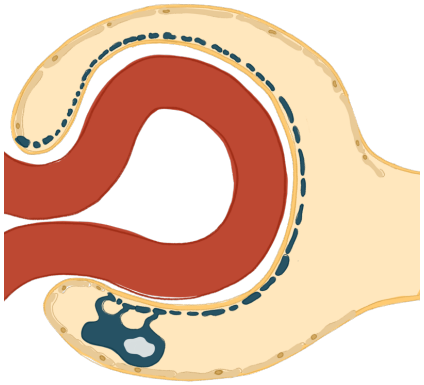
- Cell body, thick primary and thin secondary processes form basal lamina



Vascular pole **Urinary pole**

II. Filtration barrier

- Capillary walls and podocyte processes constitute filtration barrier of the renal corpuscle
- Blood plasma is filtered to the Bowman space: the glomerular ultrafiltrate (primary urine) contains all plasma components except large proteins

Blood vessel endothelium	Two fused basal laminae	Foot processes arranged around the capillaries to form small filtration slits
Fenestrated capillaries 	**Basement membrane** 	**Podocytes** 
Prevents filtration of blood cells	The meshwork structure and negatively charged groups in proteoglycans slows down large and electrically charged molecules	Prevents filtration of all molecules > 70 kDa

III. Mesangial cells

- Phagocytose basement membrane
    1. Basement membrane with trapped molecules is continuously renewed (phagocytosis by mesangial cells, renewal by endothelium and podocytes)
- Produce factors facilitating regeneration of renal corpuscles
- Have contractile properties

10.1 – Nephron Segments

I. The proximal tubule

- Simple columnar epithelium
- Proximal tubule cell
    1. Brush border
    2. Basolateral cytoplasmic folds with vertically oriented mitochondria
    3. Abundant organelles: ER, Golgi, lysosomes, peroxisomes, endocytotic vesicles/canaliculi
- Functions:
    1. Resorption of water (70-80%): diffusion
    2. Resorption ions (Na+, Cl-), glucose, aminoacids: membrane transporters

3. Resorption of proteins: endocytosis followed by lysosomal digestion
4. Rsorption of some metabolites and drugs
5. Secretion of ammonia, uric acid and some exogenous substances (drugs) - from capillaries to tubule lumen

- Resorbed compounds are transferred from urine tubules to capillaries
- Secreted substances are transferred from capillaries to the tubules

II. The thin limb (of the loop of Henle)

- Simple squamous epithelium
- Flat cells with scarce organelles and interdigitating basolateral processes
- Function: participation in urine concentration

III. Distal tubule

- Low cuboidal epithelium
- Distal tubule cell
    1. Scarce microvilli, tight junctions
    2. Apically located nucleus
    3. Deep basal cytoplasmic folds with vertically oriented mitochondria
- Functions: transport of Na+ and Cl- to the interstitial space - participation in urine concentration

IV. Connecting tubule

- Short tubule connecting distal tubule with collecting tubule
- Cuboidal epithelium
- Principal and intercalated cells

V. Collecting tubule

- Segments: cortical, medullary and papillary
- Epithelium: gradually rising from cuboidal to columnar, tight junctions
- Principal and intercalated cells

CLINICAL CORRELATION

Diabetes insipidus

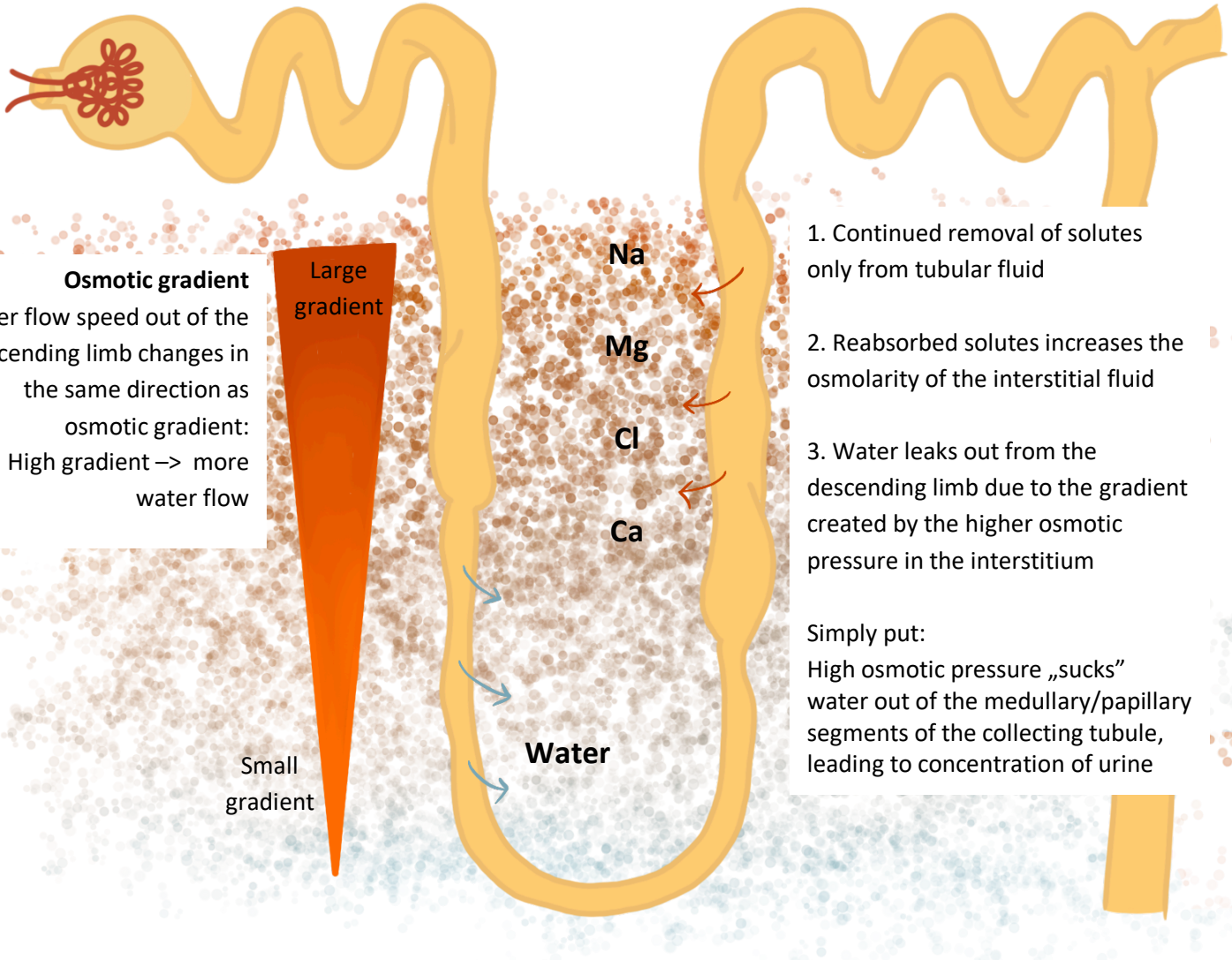
Deficient ADH causing major water loss and hypernatremia due to lack of reabsorption of water in the distal tubule and collecting duct. The lack of water reabsorption causes large volumes of dilute urine to be excreted. Diabetes insipidus can be due pituitary/hypothalamic (central) problems, or problems in the kidney.

Cells of connecting and collecting tubule

	Characteristics	Function
Principal (clear) cells	Infoldings of basal cell membrane	Final concentration of urine (resorption of water via membrane channels - aquaporins - controlled by ADH) resorption of Na+ (controlled by aldosterone) and Cl-
Alpha-intercalated (dark) cells	Connecting tubule and *cortical segment* of the collecting tubule Numerous mitochondria	Monitor extra- and intracellular pH Transport H+ and HCO3- ions Play a decisive role in the regulation of acid-base balance

10.2 – Urine Concentration

- Urine concentration results from cooperation of:
    1. Loops of Henle
    2. Collecting tubules
    3. Adjacent capillary vessels (vasa recta)
- An osmotic gradient is established in the interstitium, rising towards the papillae. This is made possible by different qualities of the segments of Henle's loop
    1. Ion-transporting ability: membrane transporters
    2. Permeability to water: tight junctions



Osmotic gradient
Water flow speed out of the descending limb changes in the same direction as osmotic gradient:
High gradient –> more water flow

1. Continued removal of solutes only from tubular fluid

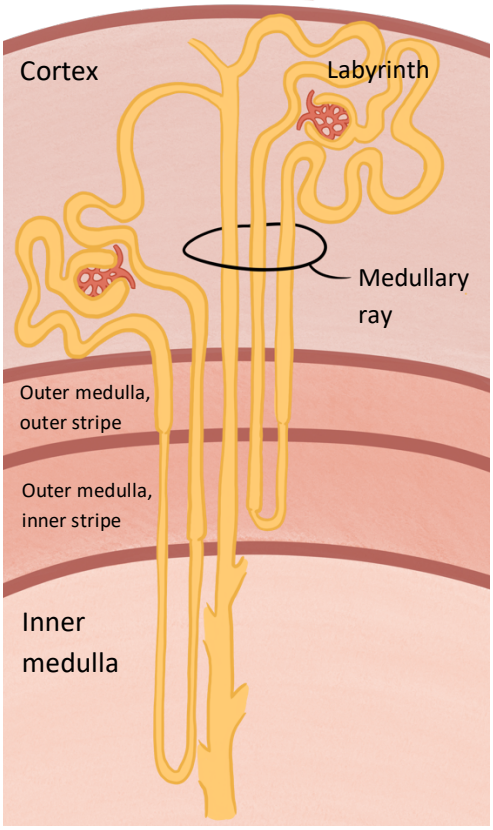
2. Reabsorbed solutes increases the osmolarity of the interstitial fluid

3. Water leaks out from the descending limb due to the gradient created by the higher osmotic pressure in the interstitium

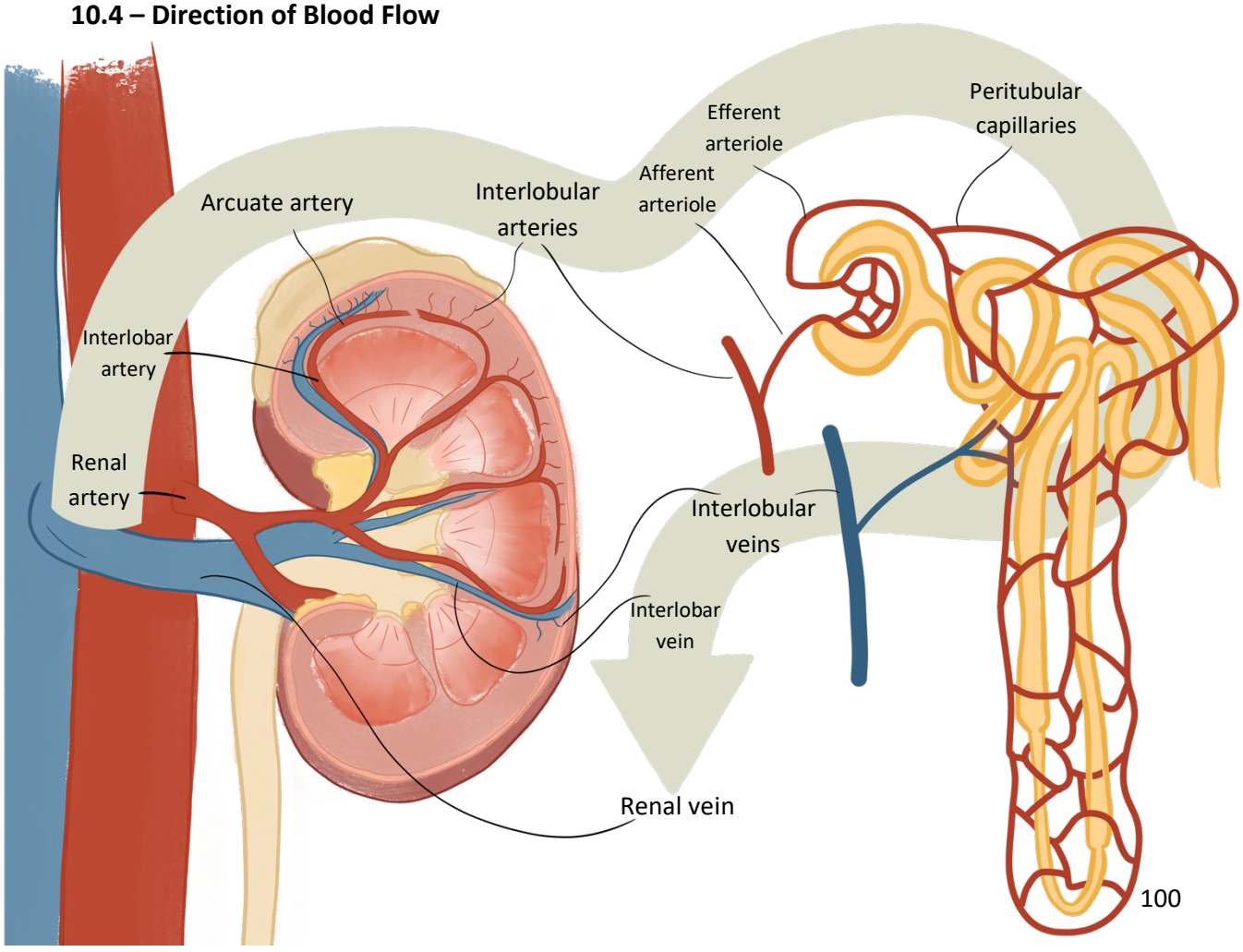
Simply put:
High osmotic pressure „sucks" water out of the medullary/papillary segments of the collecting tubule, leading to concentration of urine

10.3 – Distribution of Tubular Segments

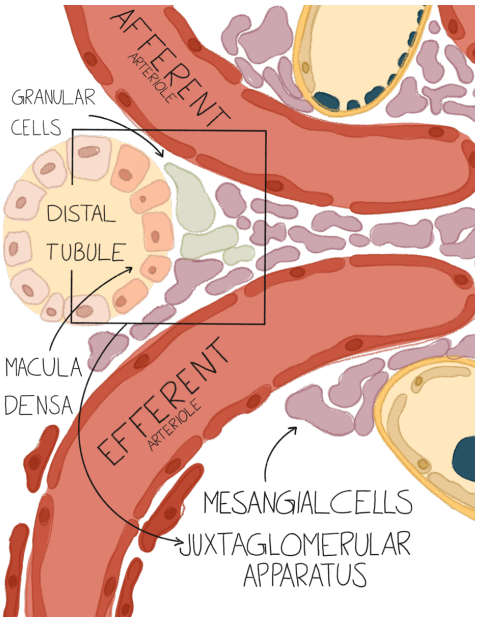
Cortex	
Labyrinth	- Renal corpuscles - Convoluted parts of proximal and distal tubules
Medullary ray	- Straight parts of proximal and distal tubules - Collecting tubules
Outer medulla	
Outer stripe	- Proximal tubules - Distal tubules - Collecting tubules
Inner stripe	- Thin limbs - Distal tubules - Collecting tubules
Inner medulla	
- Thin limbs of long Henle's loops - Collecting tubules	



10.4 – Direction of Blood Flow



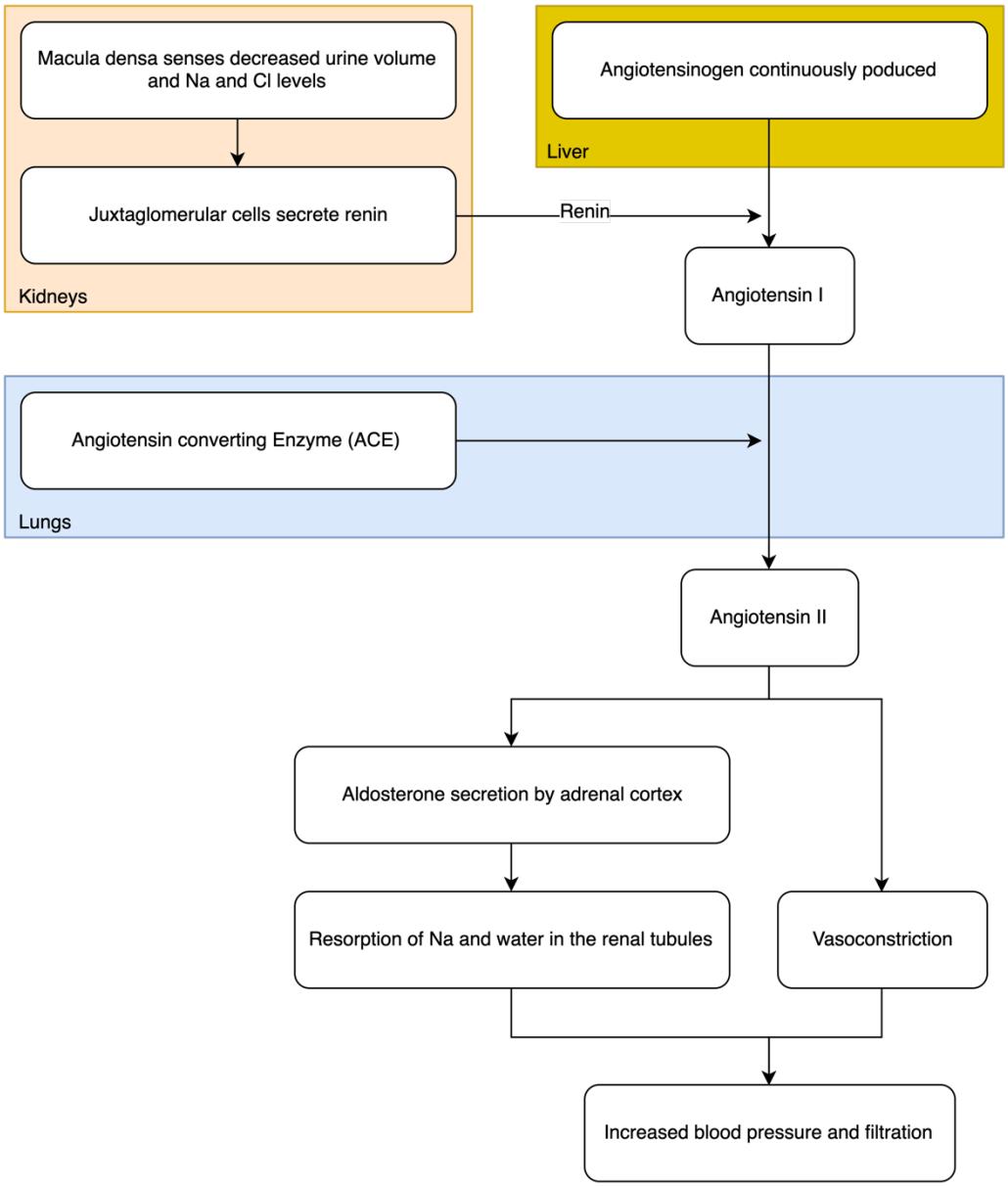
10.5 – The Juxtaglomerular Apparatus



- Function: increase blood pressure when blood supply to the kidneys decrease. In case of impaired ultrafiltration, renin released by juxtaglomerular cells increases blood pressure to improve ultrafiltration and resorption of Na
- *Juxtaglomerular (granular) cells*: modified smooth muscle cells of afferent arteriole that produce and secrete renin
- *Macula densa*: modified part of distal tubule adjacent to arterioles that monitors urine flow (volume) and Na+ and Cl- concentration
- *Extraglomerular mesangial cells*: interconnected by gap junctions and mediate signaling between macula densa cells and juxtaglomerular cells

10.6 – The Renin-Angiotensin-Aldosterone System (RAAS)

- Increases blood pressure and renal filtration



10.7 – Interstitial Tissue

- Delicate connective tissue with:
    1. Fibroblasts
    2. Macrophages
    3. Intestitial cells (only in medulla)
- Blood vessels, mostly capillaries
- Fibroblasts in cortical peritubular connective tissue produce erythropoietin
- Interstitial cells (special myofibroblasts):
    1. Elongated cells containing lipid droplets
    2. Often form „ladder"-type arrays
    3. By contraction regulate blood flow in medullary capillaries
    4. Produce medullipin (vasodilator) and prostaglandins
    5. Under pathological conditions produce collagen fibers

10.8 – The Excretory Passages

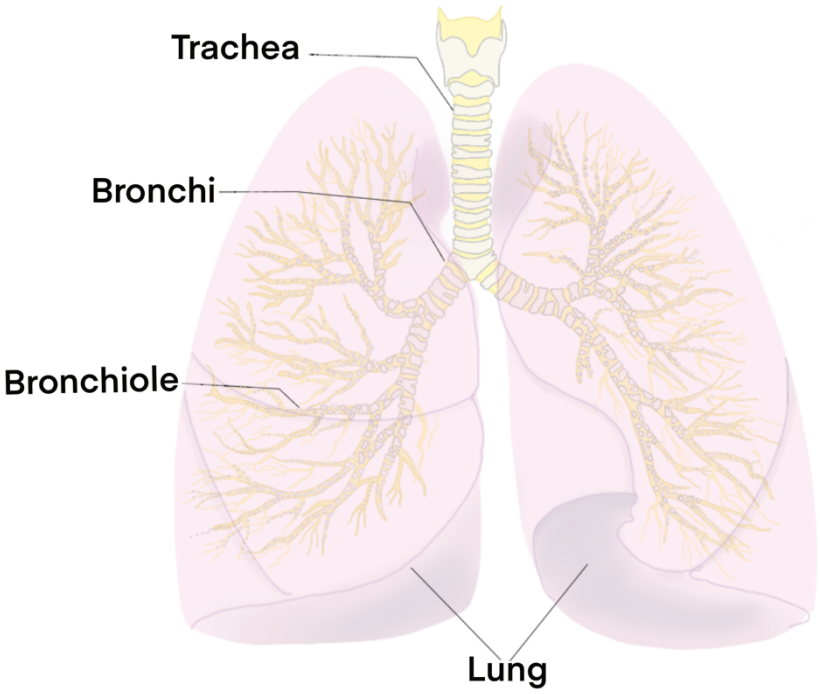
- Renal calyces and pelvis → ureter → urinary bladder → urethra
- Urothelium: stratified epithelium with dome- shaped cells on the surface, abundant tight junctions
    1. Functions: protection of underlying tissues, osmotic barrier, adaptation to changing surface area (full/empty bladder)
    2. The apical cell membrane is composed of thick, rigid plaques connected by areas of normal membrane. The plaques are built of regularly arranged complexes of a protein called *uroplakin*. They are impermeable to water and salts, creating an osmotic barrier together with tight junctions

<table>
<tr><th rowspan="2">Part of tract</th><th colspan="2">Mucosa</th><th rowspan="2">Muscularis</th><th rowspan="2">Other</th></tr>
<tr><th>Epithelium</th><th>Lamina propria</th></tr>
<tr><td>Calyces & pelvis</td><td rowspan="3">Urothelium</td><td>Thin</td><td colspan="2">Thin layer of smooth muscle</td></tr>
<tr><td>Ureter</td><td>No glands</td><td>3 layers:
- Inner and outer layers: longitudinal
- Middle layer: circular</td><td rowspan="2">Have fibrous adventitia</td></tr>
<tr><td>Urinary bladder</td><td>With small mucous glands only around urethral orifice</td><td>three poorly separated spiral layers</td></tr>
<tr><td>Female urethra</td><td>Urothelium –> pseudostratified –> stratified squamous epithelium</td><td rowspan="2">With glands of Littre (small mucous glands)</td><td rowspan="2">- Smooth muscle
- Skeletal muscle sphincter</td><td>Vascular layer with erectile tissue
Periurethral glands of Skene (similar to the prostate)</td></tr>
<tr><td>Male urethra[1]</td><td>Urothelium –> stratified columnar –> stratified squamous epithelium</td><td>Surrounded by erectile tissue, corpus cavernosum, in the penile segment</td></tr>
</table>

[1] The male urethra is composed of three segments: prostatic, membranous and penile

Section 11 – The Respiratory System

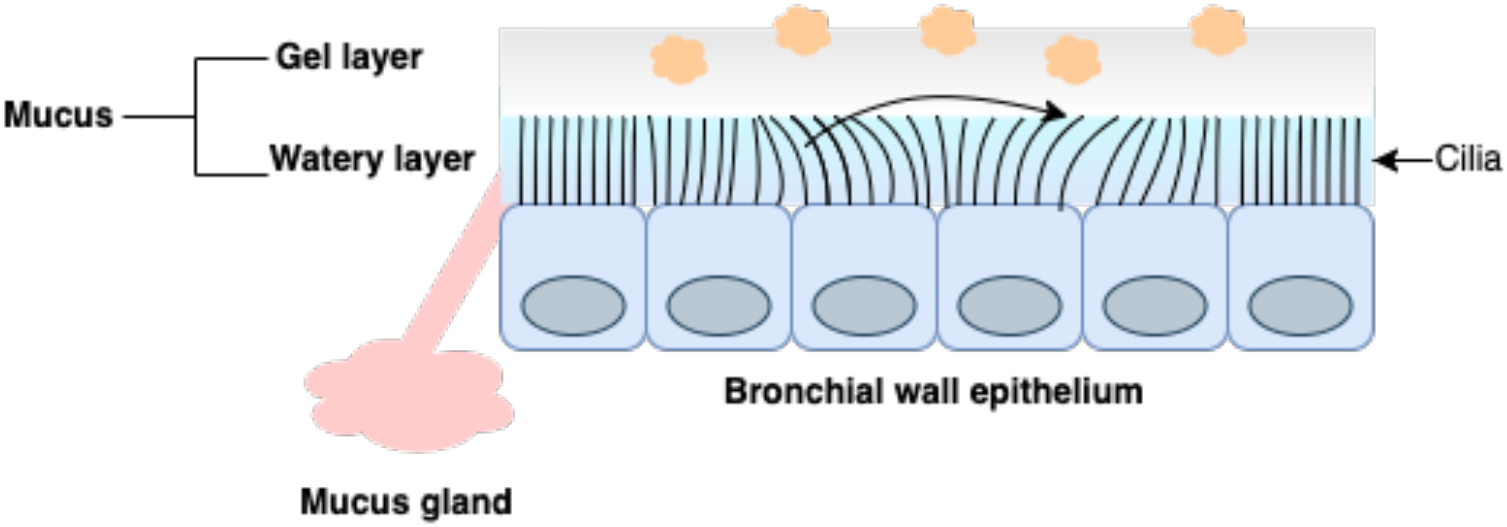
11.1 – Conducting Airways
11.2 – The Bronchial Tree
11.3 – Pulmonary Alveoli



- In the conducting airways, there is no gas exchange, forming the anatomical dead space: nasal cavity, pharynx, larynx, trachea and bronchial tree
- Respiratory airways is where gas exchange occurs and consist of respiratory bronchioles and alveoli
- Respiratory epithelium consisting of pseudostratified ciliated epithelium is present in all airways except the olfactory region and the smallest bronchioles. Composed of several cell types: Ciliated cells, goblet cells, basal stem cells, brush cells, endocrine (DNES) cells and Langerhans cells

I. Mucociliary cleaning mechanism

- Dust particles and bacteria are transported in mucus towards the pharynx, where it is swallowed
- Small glands in the wall of airways contribute to formation of two layers of fluid: an upper mucous layer and a lower watery layer just above the epithelial cells. This allows for easy sliding of the sticky mucus on the epithelial surface



II. Neuroepithelial bodies

- Small groups of DNES cells accompanied by afferent nerve terminals in the airway epithelium
- Influence the brainstem respiratory center: react to levels of O_2 and CO_2 in the inhaled air and respond by releasing neurotransmitters
- Most numerous neuroepithelial bodies are found in neonates, where they functionally replace still immature carotid bodies

11.1 – Conducting Airways

11.1.1 – The Nasal Cavity

- Mucosa: respiratory or olfactory epithelium and lamina propria
- Function: air-conditioning by warming (blood vessels) and moistening (glands) the air
- Paranasal sinuses are characterized by very thin mucosa with numerous goblet cells in the epithelium

Respiratory mucosa	Olfactory mucosa
- Rich vascularization - Numerous seromucous glands in lamina propria - Solitary lymphoid nodules - Swell bodies	- Very tall pseudostratified olfactory epithelium - Basal stem cells, sustentacular cells and olfactory cells - Olfactory (Bowman's) glands in lamina propria - Numerous nerve bundles

I. Bowman's glands

- Serous glands
- Produce protein which binds hydrophobic odorants
- Produce lysozyme
- Secrete IgA
- Their liquid secretory material covers olfactory mucosa and serves as solvent for odorants

II. Basal cells of the olfactory epithelium

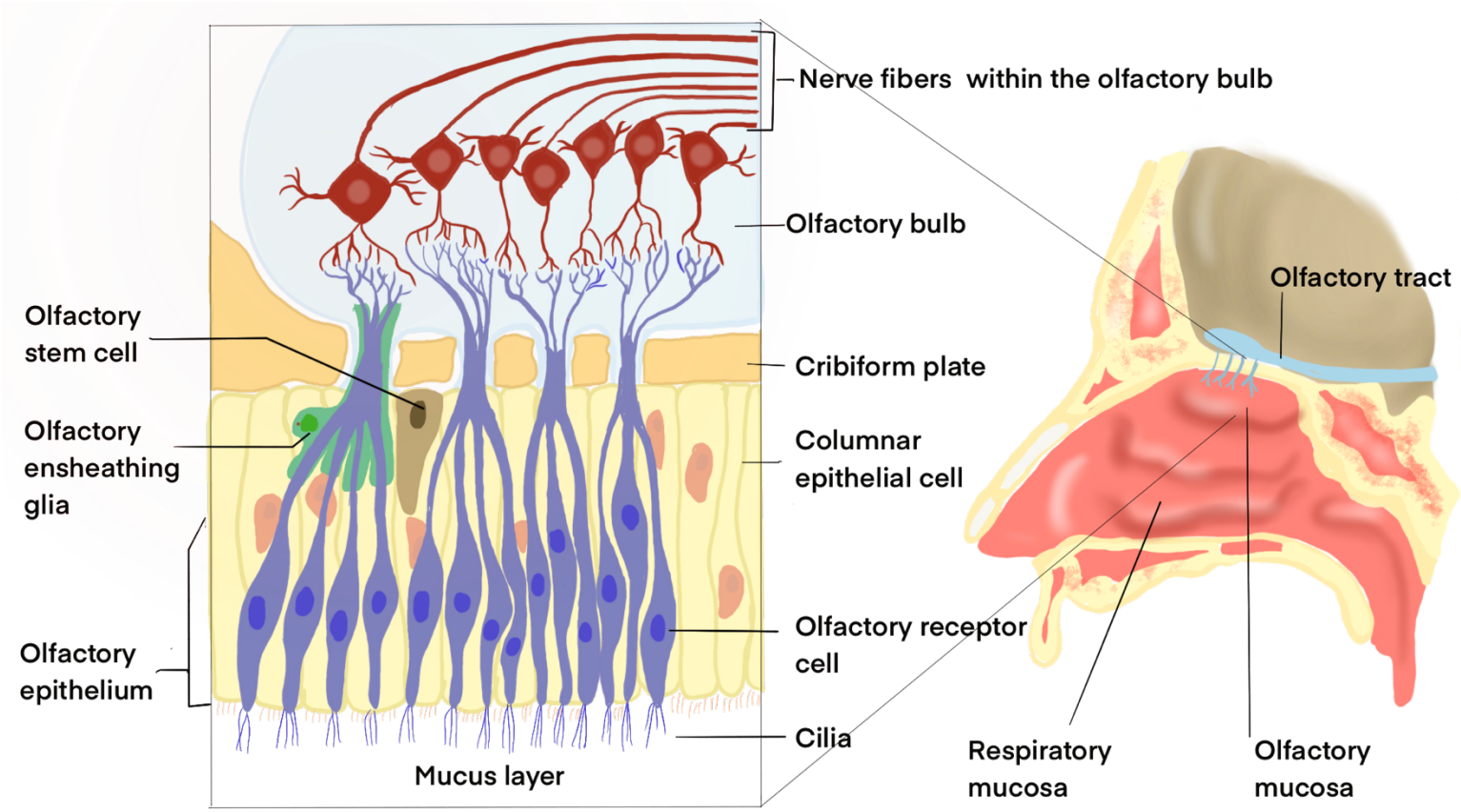
- Epithelial stem cells: renewal of sustentacular cells
- Neural stem cells: renewal of olfactory cells

III. Sustentacular cells

- Support olfactory cells
- Nucleus in apical part
- Microvilli, cytoskeleton, lipofuscin granules, cell junctions

11.1.2 – Olfaction

- Humans can sense around 10 000 different scents



I. The olfactory cell

- Bipolar nerve cell with Nissl bodies, neurofilaments, neurotubules
- Short dendrite ending with „olfactory vesicle" (knob)
- 10-20 nonmotile, modified cilia laying on the epithelial surface
- Odor receptors in the cell membrane of cilia

II. Olfaction

- Chemical substances present in inhaled air are dissolved in serous fluid covering the olfactory epithelium
- Chemical molecules bind to odor receptors on cilia of olfactory cell
- Via activation of G proteins, sodium channels open in the cell membrane of olfactory cell (depolarization)
- Action potential is sent via axon of olfactory cell to the glomerulus of the olfactory bulb (CNS, synapses between olfactory cells and mitral cells)
- Combination of signals sent by approx. 1000 glomeruli evokes impression of scent/odor

III. Olfactory ensheathing cells

- Specific glial cell forming sheaths around axons of olfactory cells. They are unique glial cells occurring in both peripheral and central nervous system
- Promote directional growth of new axons

IV. Vomeronasal organ of Jacobson

- Responsible for detection of pheromones in animals
- Only rudimentary in humans present
- Tubular invagination of mucosa in the nasal septum
- Epithelium: sustentacular cells and sensory cells
- Connected via nerve fibers with hypothalamus
- Reacts to some substances related to steroid hormones
- It is uncertain if pheromone signaling occurs in humans

11.1.3 – Nasopharynx

- Airway epithelium
- Pharyngeal glands in lamina propria
- Lymphoid tissue: pharyngeal tonsil, tubal tonsils

11.1.4 – Larynx

- Airway epithelium / stratified squamous epithelium
- Laryngeal glands in lamina propria
- Intrinsic skeletal muscles
- Hyaline/elastic cartilage skeleton
- The cartilage skeleton keep airways open: present in the wall of larynx, trachea and bronchi

11.1.5 – Trachea

- Mucosa: airway epithelium, lamina propria
- Elastic lamina
- Submucosa with tracheal glands
- Hyaline cartilage c-rings interconnected by collagen fibers
- Fibrous adventitia
- Posterior, membranous part: smooth muscle, no cartilage

11.2 – The Bronchial Tree

- Primary, mainstem bronchi
- Intrapulmonary bronchi
- Bronchioles
- Terminal bronchioles
- Respiratory bronchioles
- The primary bronchi have the same structure of the wall as trachea

I. Intrapulmonary bronchi

- Mucosa: airway epithelium, lamina propria
- Smooth muscle layer
- Submucosa with bronchial glands
- Hyaline cartilage plates interconnected by collagen fibers
- Fibrous adventitia

II. Bronchioles

- No cartilage, no submucosa, no glands
- Pseudostratified → simple columnar epithelium
- Goblet cells gradually replaced by bronchiolar club cells
- Layers of the wall:
    1. Mucosa
    2. Smooth muscle layer
    3. Fibrous adventitia

III. Bronchiolar club cells

- Previously called Clara cells
- Protrude above epithelium surface
- Organelles: RER, SER, apical secretory granules, numerous large mitochondria
- Functions:
    1. Neutralization of inhaled toxins and carcinogens
    2. Production of protective protein (CC16): anti-inflammatory and antitumor activity, protection from emphysema (COPD)
    3. Production of surfactant proteins and mucins
    4. Differentiate into other cell types of the bronchiolar epithelium

IV. Terminal bronchioles

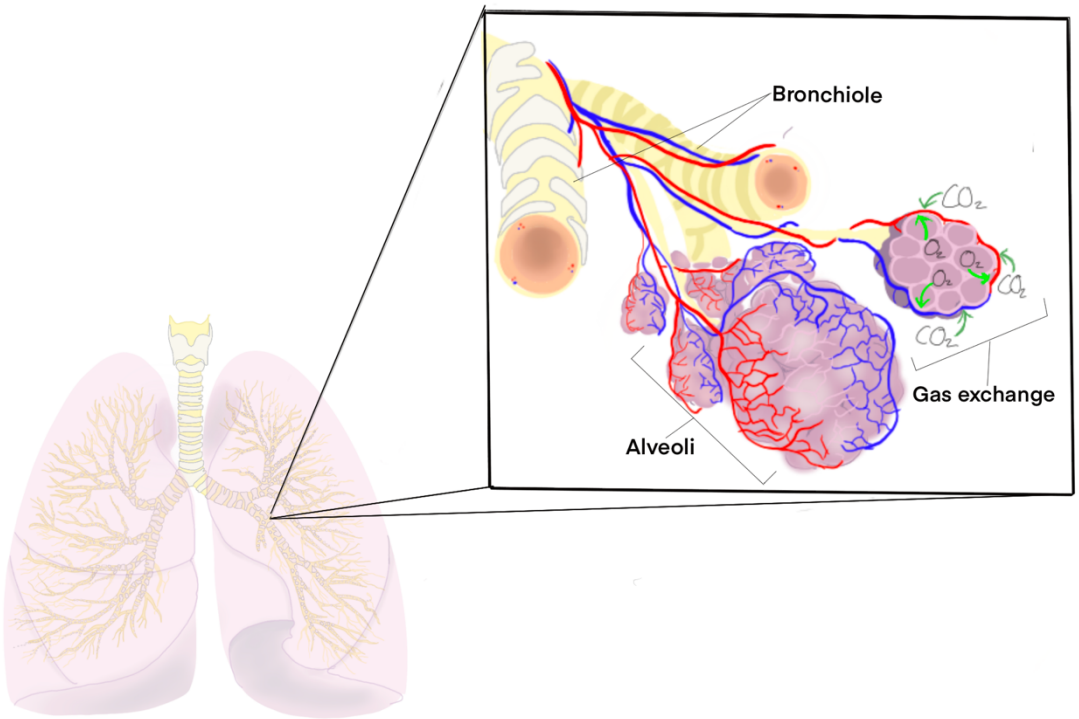
- Thin wall, simple cuboidal epithelium with ciliated cells and club cells

V. Respiratory bronchioles

- Discontinuous wall, partly consisting of alveoli
- Respiratory bronchioles, alveolar ducts and alveoli constitute the gas exchange territory (respiratory portion) of the respiratory system

11.3 – Pulmonary Alveoli

- Alveoli supplied by a single respiratory bronchiole form pulmonary acinus
- 0.2 mm in diameter, a total of 300 million alveoli make up an area of 140 m^2
- The alveoli communicate via small pores



I. Alveolar walls (interalveolar septa)

- Elastic and reticular fibers
- Myofibroblasts, macrophages
- Numerous continuous capillary vessels
- Air space-lining epithelial cells: pneumocytes (alveolar cells) type 1 and 2

11.3.1 – Type I Pneumocyte

- Alveolar macrophage
- Erythrocyte Air-blood barrier alveolar capillaries interalveolar septum (elastic and reticular fibers)
- Type 1 pneumocytes are extremely flat and participate in the air-blood barrier responsible for gas exchange. They are interconnected by tight junctions (water cannot pass to the air spaces of alveoli).
- Layers of the air-blood barrier:
    1. Cytoplasm of type 1 pneumocyte
    2. Fused basal laminae of pneumocyte and capillary
    3. Cytoplasm of endothelial cell

11.3.2 – Type 2 Pneumocyte

- Secretory cell
- Abundant RER and SER with well-developed Golgi apparatus
- Characteristic secretory granules (lamellar bodies), their content (lipids and proteins) is released by exocytosis
- Irregular microvilli
- Type 2 pneumocytes produce and secrete surfactant composed of proteins and lipids which forms a continuous layer covering the inner surface of the alveolus After exocytosis, surfactant proteins and lipids form transient „tubular myelin" and later are reorganized into separate layers

I. Surfactant

- Two layers: the inner aqueous hypophase containing surfactant proteins (A, B, C, D and the outer monomolecular layer of lipid (dipalmitoyl- phosphatidylcholine, DPPD)
- The lipid monolayer acts as a detergent: it decreases surface tension preventing the collapse of the alveolus during exhalation
- Surfactant proteins:
    1. Regulate synthesis and secretion of surfactant (SP-A)
    2. Control reorganization of surfactant after exocytosis (SP-B, SP-C)
    3. Participate in defense processes: bind to microorganisms and lymphocytes, are involved in local inflammation (SP-D), modulate immune responses (SP-A, SP-D)

CLINICAL CORRELATION

Respiratory distress syndrome

Surfactant is essential for the lungs to function, but it is not produced until around week 24 in pregnancy. Ehen a baby is born prematurely, their lungs often lack sufficient amounts of surfactant to maintain open alveoli. This may result in severe respiratory distress and dependence on supplemental oxygen. Corticosteroids stimulate surfactant production and is often given to mothers who start labor too early to increase the maturity of the lungs.

11.3.3 – Bronchioalveolar Stem Cells

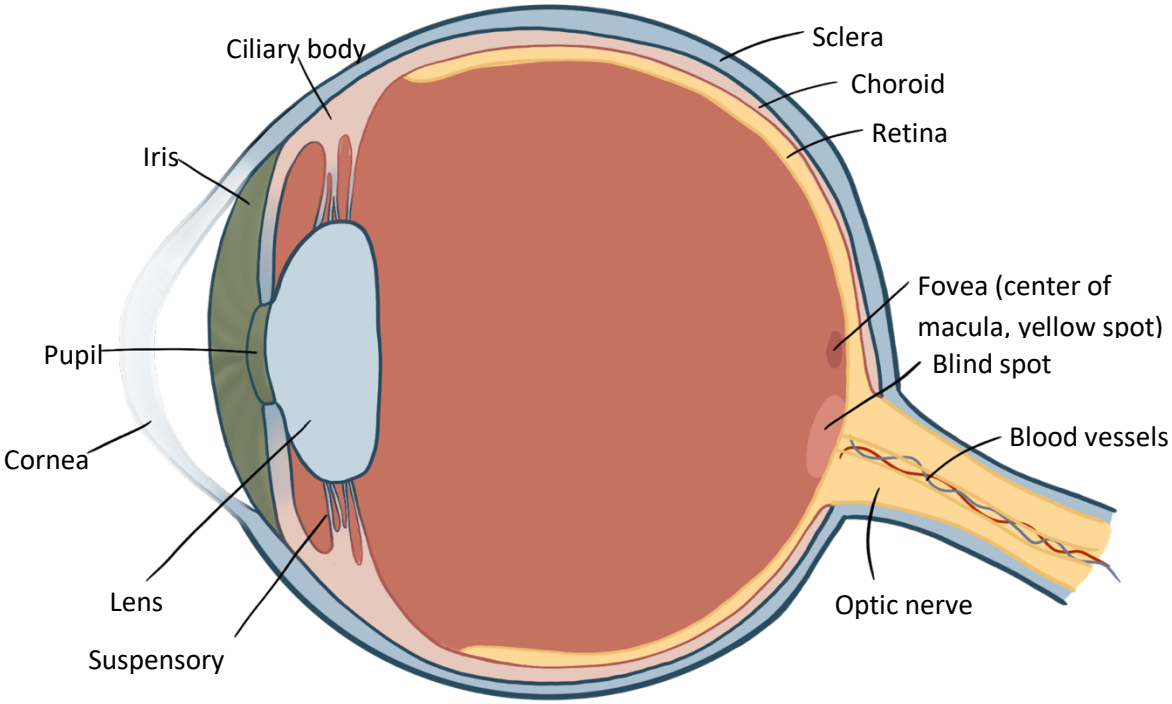
- Located in the bronchiole/alveoli transition zone
- Differentiate into both types of pneumocytes and all types of bronchiolar epithelial cells

11.3.4 – Alveolar Macrophages

- Alveolar macrophages (dust cells) reside on the inner surface of alveoli and take up dust particles and microorganisms that evaded the mucociliary cleaning mechanism of the airways; they also eliminate excess surfactant
- Renewal of alveolar macrophages: „Old" macrophages detach from alveolar walls, enter bronchioles and:
    1. Either are transported towards the pharynx by mucociliary cleaning
    2. Or migrate through walls of small bronchioles to lymphatic vessels and further to pulmonary lymph nodes
- They are replaced by „young" macrophages migrating as monocytes from blood vessels

Section 12 – The Eye

12.1 – The Retina



Three tunics of the eye	
Fibrous	Sclera and cornea
Vascular (uvea)	Choroid, ciliary body and iris
Neural (retina)	Optic retina and non-nervous anterior portion

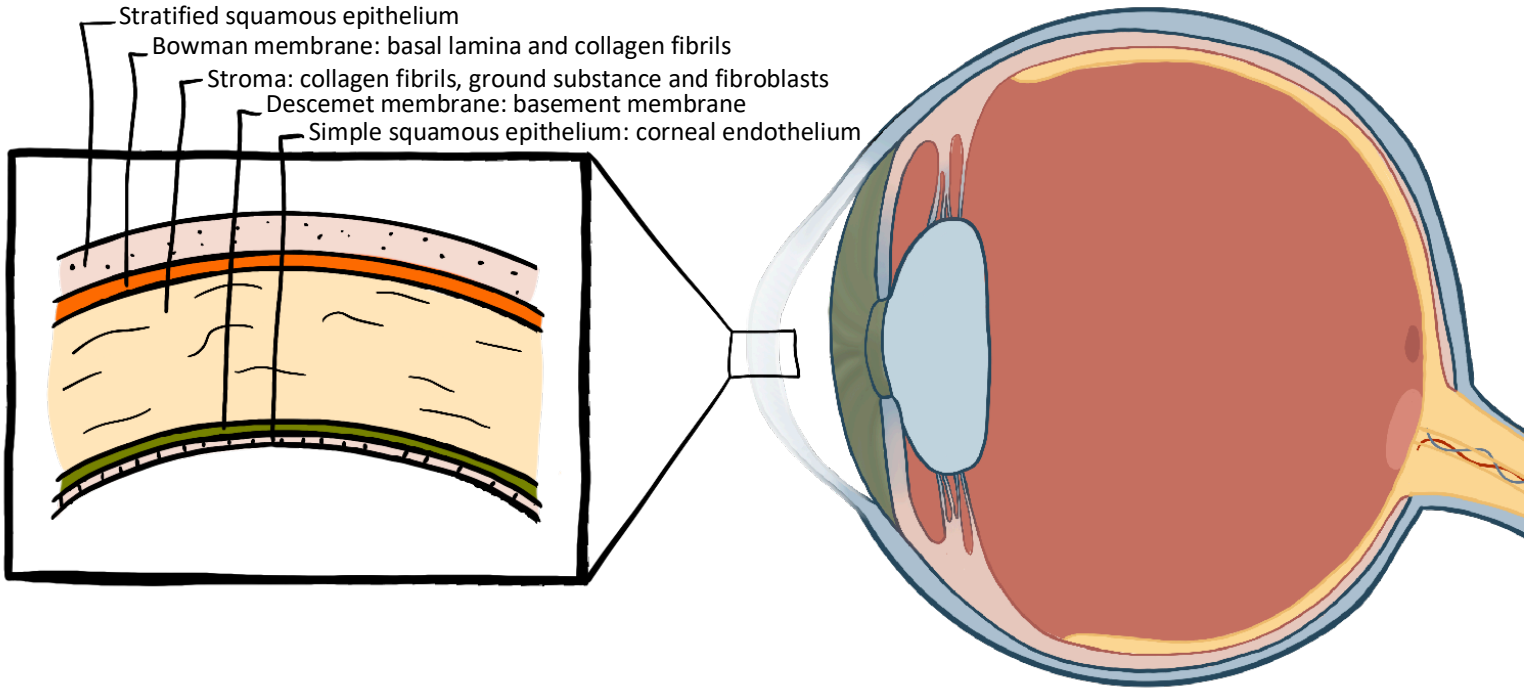
Functions of each part of the eye

Sclera	Provide mechanical strength and elasticity Attaches extraocular muscles
Cornea	Component of the optical system, refractive power 42D
Choroid	Provides oxygen and nutrients to photoreceptors
Ciliary body	Accommodation and production of aqueous humor
Trabecular meshwork	Drains the aqueous humor into the scleral veins
Iris	Adaptation to light intensity
Lens	Transmit and focus light to the retina
Vitreous body	Maintain shape of the eye, provide nutrients, part of the optical system
Retina	Convert light into electrical signals
Pigmented epithelium	Absorption of light Phagocytosis of membraneous disks released from the tips of photoreceptors

I. Sclera

- Dense connective tissue: collagen fibers, elastic fibers, quiescent fibroblasts, melanocytes and very few blood vessels

II. Cornea



- The outer corneal epithelium
    1. Non-keratinized stratified squamous epithelium, cells connected via desmosomes and tight junctions
    2. Cells have microfolds/microvilli on the apical surface which helps retain a thin layer of tear film so the cornea is always moistened
    3. Protection from UV: ferritin in cell nuclei eliminates free oxygen radicals induced by UV
    4. Numerous sensory nerve terminals
    5. Rapid renewal and regeneration
- Arrangement of parallel collagen fibrils forming layers with different orientation of fibrils in each layer allows for transparency of corneal stroma. Absence of blood vessels also contributes to this
- In the optic system, the cornea has the highest refractive power, not the lens
- Refractive power = the ability of a substance to converge or diverge light.

III. Choroid

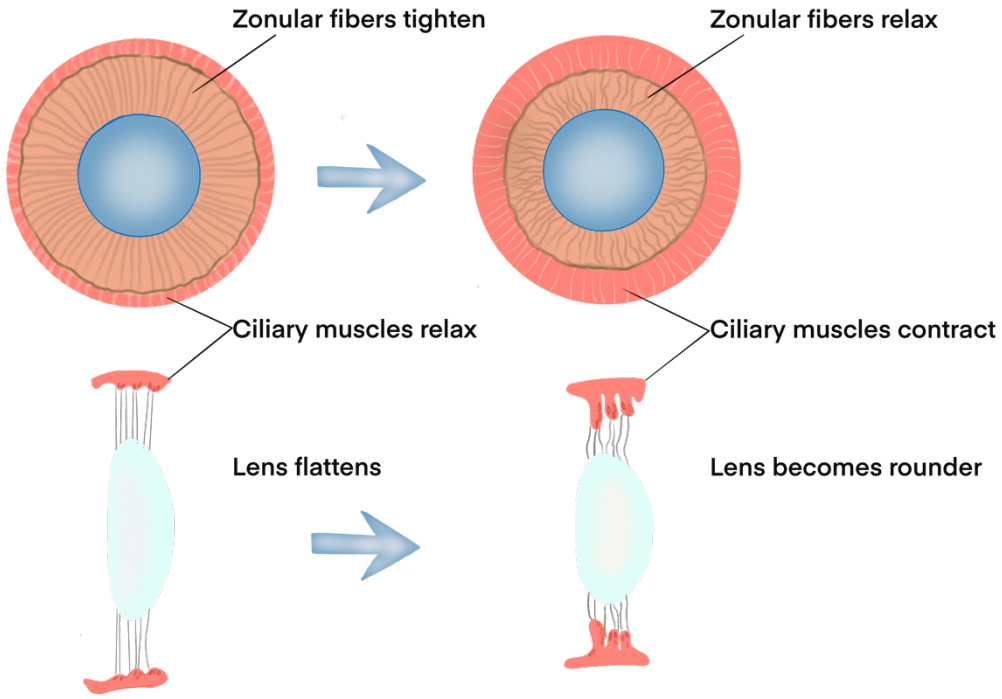
- Loose connective tissue with numerous melanocytes and blood vessels
- Layers:
    1. Vascular: larger vessels
    2. Choriocapillaris: fenestrated capillaries
    3. Bruch's membrane

IV. Ciliary epithelium

- Double cuboidal epithelium covering the free surface of the ciliary body
    1. A continuation of the retina: the non-nervous part
- Superficial layer: produces aqueous humor. Non-pigmented cells with cell membrane infoldings and numerous mitochondria
- Deep layer: continuation of the retinal pigment epithelium. Cells with numerous melanin granules

V. Ciliary body

- Stroma: loose connective tissue with blood vessels and smooth muscle
- Covered by epithelium and connected to the lens via suspensory ligaments
    1. Suspensory ligaments: zonule fibers made of fibrillin
- Accommodation
    1. Far vision: Relaxation of ciliary muscles → tension of zonular fibers → thinner lens
    2. Near vision: Constriction of ciliary muscles → relaxation of zonular fibers → thicker lens



VI. Trabecular meshwork

- A spongy network of connective tissue trabeculae lined with endothelial cells between the ciliary body and the sclerocorneal junction.
- Communicates with the canal of Schlemm.

VII. Iris

- Loose connective tissue with blood vessels and numerous melanocytes, which is what produves eye color
- Anterior (outer) surface: discontinuous layer of fibroblasts and melanocytes
- Posterior (inner) surface: pigmented epithelium (two cell layers)
    1. Contractile, myoepithelial, radial processes form the pupillary dilator muscles
- Circular smooth muscle forming the pupillary sphincter

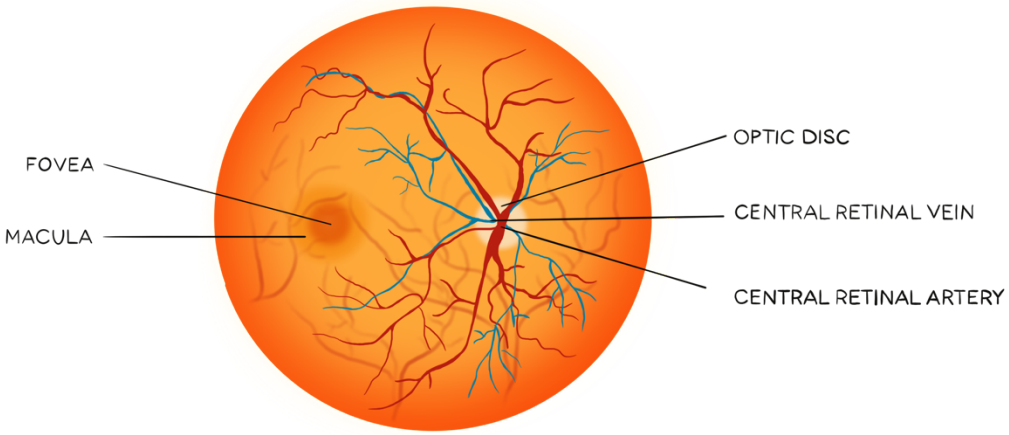
VIII. Lens

- An epithelial structure with simple cuboidal epithelium on the anterior surface and a capsule (thick basal lamina)
- In the equatorial region (the widest point)
    1. Cells of cuboidal epithelium divide, enter deeper areas of the lens and convert into lens fibers
    2. Zonule fibers are anchored to the capsule
- Lens fibers are elongated, highly modified epithelial cells with very few organelles and without a nucleus. The fibers are connected with a “ball and socket” mechanism and gap junctions
    1. The cytoplasm is filled with crystallins (proteins) providing transparency and increased refractive power of the lens

IX. Vitreous body

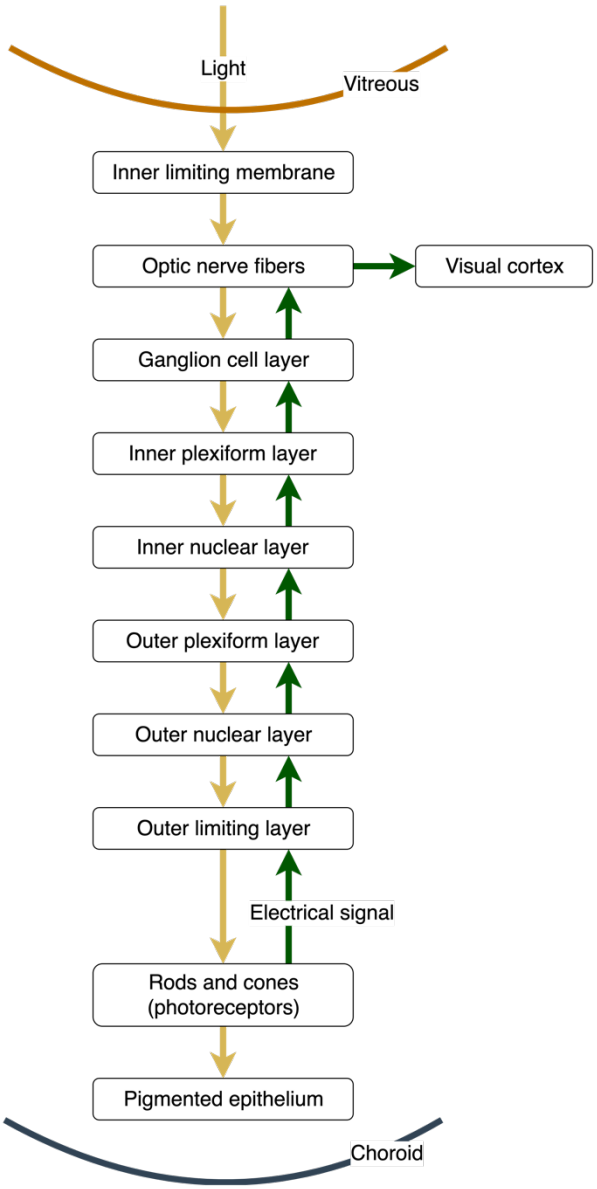
- Water, ions, hyaluronic acid and collagen fibrils (very few)
- Very few cells: hyalocytes (fibroblasts) and macrophages

12.1 – The Retina



- Signals generated by photoreceptors are processed by other retinal nerve cells, then transmitted via the optic nerve to the visual cortex of the brain

- The retina is the photosensitive part of the neural tunic, containing the first three neurons of the visual pathway, arranged in three distinct layers:
    1. Photoreceptor cells
    2. Bipolar cells
    3. Ganglionic cells



I. Layers of the retina

- Before the light reaches the photoreceptors, it must pass through most of the retinal layers. There are in total 10 layers
- The outer limiting membrane: adherent junctions between glial Müller cells and photoreceptors
    1. Müller glial cells with processes across the entire thickness of retina act as „optic cables", transferring photons to rods and cones
- Outer plexiform layer contains axodendritic „ribbon" synapses between photoreceptor cells and bipolar & horizontal cells
- Inner granular layer contains perikaryons of bipolar cells (2nd neuron), horizontal cells (neurons modulating synaptic activity), amacrine cells and interplexiform cells (neurons providing feedback signaling)
- Inner plexiform layer contains axodendritic synapses between bipolar cells and ganglion cells (3rd neuron, electrical synapses!), and amacrine cells
- Optic nerve fiber layer contains unmyelinated axons of ganglion cells

II. Photoreceptor cells

- Photoreceptor cells (rod and cone cells) are specialized bipolar nerve cells with dendrites transformed into photoreceptors (rods and cones)
    1. Outer segment: membranous discs with the photopigments rhodopsin and iodopsins
    2. Rudimentary cilium (rudimentary)
    3. Inner segment: ellipsoid part with mitochondria and myoid part with RER and Golgi producing proteins for the membranous discs
    4. Perikaryon (cell body) with cell nucleus
    5. Axon
    6. Inhibitory synapse

	Rod	Cone
Shape	Narrower	Broader
Membranous disk	Separated from cell membrane	Continuous with cell membrane
Connecting stalk between inner segment and perikaryon	Yes	No
Photopigment	Rhodopsin	Iodopsins
Type of light sensitivity	Dim light	Bright light
Color sensitivity	No	Yes

- How photoreceptors work
    1. Photons activate rhodopsin/iodopsin which results in hyperpolarization of the cell and inhibition of inhibitory neurotransmitter release. This allows the second neuron to fire signals.
    2. Phosphodiesterase lowers the cytoplasmic level of cGMP Sodium channels close, the cell becomes hyperpolarized
    3. The cell stops releasing inhibitory neurotransmitter (glutamate), allowing the second neuron (bipolar cell) to fire signals. Light therefore stops inhibition and allows us to see, meanwhile darkness will inhibit the signals from the second neuron.

III. Pigment epithelium

- Columnar/cuboidal cells with abundant melanin granules, interconnected by tight junctions
- Apical cytoplasmic folds surround and separate the tips of photoreceptors

IV. Ganglion cell layer: photosensitive ganglion cells

- Responsible for providing information to brain areas that perform light-dependent, non-visual tasks like the circadian rhythm and mood
- Respond to slow changes in the light that surrounds us
- 4% of ganglion cells are intrinsically photosensitive
- They contain melanopsin, a photopigment activated by light

V. Special areas of retina yellow spot (macula lutea)

	Yellow spot: the macula	Blind spot
Photoreceptors	Photoreceptor layer exposed with other layers pushed aside No signal summation Only cones	None Optic nerve fibers gather, become myelinated and exit the eye as the optic nerve large vessels enter/exit the eye
Visual acuity	Highest visual acuity	None

VI. Vascularization of retina

- Outer 1/3 of retina: choriocapillaris
- Inner 2/3 of retina: capillaries originating from vessels located on the inner surface of retina (fundus of the eye)

VII. Blood-retina barrier:

- Tight junctions between
    1. Pigmented epithelium cells
    2. Endothelial cells of retinal capillaries

12.2 – The Eyelid

- Conjunctiva
    1. Stratified columnar epithelium with goblet cells
    2. Lamina propria
- Tarsal plate: dense connective tissue with large, branched sebaceous glands called Meibomian glands
    1. Produces a lipid film that covers the cornea

I. Other glands of the eyelid

- Apocrine glands of Moll
- Glands of Zeiss: small sebaceous glands associated with hair (eyelash) follicles

II. The lacrimal gland

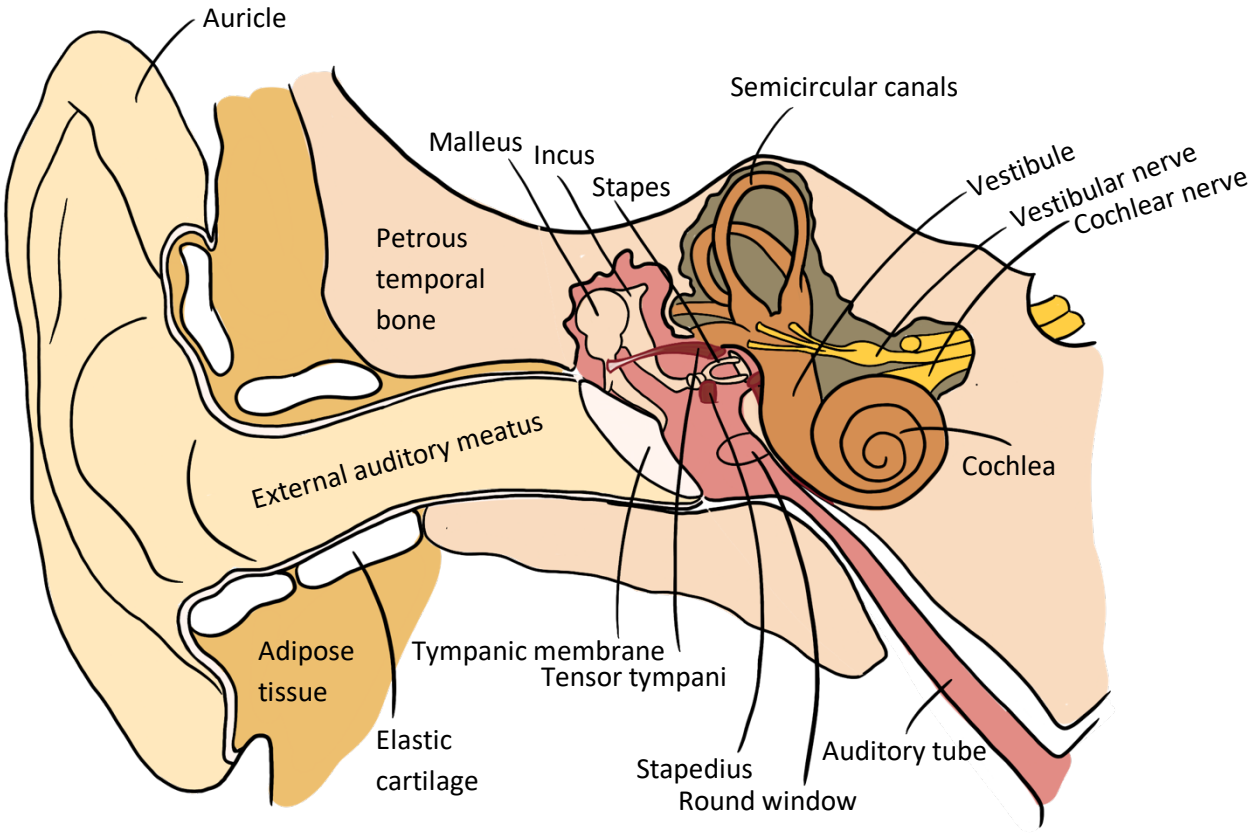
- Typical lobular serous gland composed of serous acini surrounded by myoepithelial cells and basal lamina
- Branched system of ducts with simple cuboidal/columnar epithelium
- Products: water, ions, lysozyme, lactoferrin, IgA
- The tear-draining passages consist of lacrimal canaliculi (stratified squamous epithelium), the lacrimal sac and the nasolacrimal duct (both lined with pseudostratified ciliated epithelium)

Section 13 – The Ear

13.1 – The External Ear

13.2 – The Middle Ear

13.3 – The Inner Ear



13.1 – The External Ear

- Transmission of sound waves and conversion into mechanical energy
- The auricle (pinna): elastic cartilage, adipose tissue and skin
- External auditory meatus: skin, elastic cartilage and bone
- Tympanic membrane: middle fibrous layer, outer epithelium (epidermis) and inner epithelium (simple cuboidal)

13.2 – The Middle Ear

- Transmission of vibrations created by the tympanic membrane to the fluid of the inner ear
- Auditory tube: stabilization of pressure
- Tympanic cavity lined with thin mucosa: simple cuboidal epithelium.
    1. In the lower part: simple columnar with cilia.
- Auditory ossicles: malleus, incus and stapes.
    1. Woven bone with mucosa, connected by joints into a chain
- Skeletal muscles: tensor tympani and stapedius
- Auditory (eustachian) tube
    1. Ciliated columnar –> ciliated pseudostratified with goblet cells –> airway epithelium
    2. Connected to the airways
    3. Bone –> elastic cartilage –> hyaline cartilage
    4. Contain the tubal tonsil

13.3 – The Inner Ear

- Responsible for hearing and balance
- The labyrinths consist of:
- Bony labyrinth: occupies the petrous portion of temporal bone and houses the membranous labyrinth
- Membranous labyrinth: soft tissues that line the bony labyrinth
    1. Parts: the utricle and saccule, semicircular canals and the cochlear duct
    2. Location of sensory areas with sensory cells and supporting cells
    3. Sensory cells have hair cells called stereocilia, which make contact with afferent and efferent nerve terminals. They depolarize when the hair cells bend, releasing neurotransmitters

13.3.1 – The Cochlear Duct

- One of three parallel ducts located in the spiral cochlea:
    1. Cochlear duct (middle): filled with endolymph
    2. Scala vestibuli: contains perilymph. Separated from the cochlear duct by the Reissner (vestibular) membrane.
    3. Scala tympani: contains perilymph and is separated from the cochlear duct by the basilar membrane
- The Reissner membrane is covered by simple squamous epithelium on both surfaces, with a basement membrane, collagen and elastic fibers between.
- Stria vascularis is the membrane located on the lateral wall of the cochlear duct. It has 3 cell layers and produces endolymph
    1. Basal cells: clear, connected by tight junctions
    2. Intermediate cells: melanocytes
    3. Marginal cells with basal infoldings of the membrane, with many mitochondria
- The cochlear duct also contains the organ of Corti, or the spiral organ, which is where vibrations are detected.

I. The organ of Corti

- Basilar membrane
    1. Collagen fibers
    2. Upper surface: organ of Corti cells
    3. Lower surface: simple squamous epithelium
- Tectorial membrane: produced by fibroblasts in the spiral limbus and covers the tips of hair cell stereocilia
    1. Mainly composed of the glycoproteins tectorin and otogelin, scattered collagen fibrils (collagen II, V and IX)
- Supporting cells
    1. Flanking the tunnel of Corti are the Pillar cells. Narrow, connected by apical parts, stiff and reinforced by numerous microtubules
    2. Outer and inner Phalangeal cells: surround hair cells partially (outer) or completely (inner), interconnected bu gap junctions. Outer phalangeal cells have long processes connected to apical regions of hair cells
- The reticular lamina made up by the apical regions of supporting and hair cells interconnected by tight and adhering junctions.
    1. Stabilizes apexes of hair cells and makes a barrier for ions
- Potassium ions are circulated to supporting cells after being released by hair cells. The ions are then collected by fibroblasts, transferred to cells of the stria vascularis and released back into the endolymph. This allows for the environment in the endolymph to be optimal for depolarization of the hair cells.
    1. Gap junctions make this circulation possible.

II. Hair cells

- Stereocilia, rough and smooth ER, synaptic vesicles and mitochondria in the basal region
- There are 2 types of hair cells:
    1. Type I (called inner hair cells in the cochlea): bottle shaped, embedded in afferent nerve terminals and have synaptic ribbon in the cytoplasm. Not in contact with efferent nerves.
    2. Type II (called outer hair cells in the cochlea): columnar, in contact with both afferent and efferent nerve terminals
- Inner (type I) hair cells: a single row
    1. Linearly arranged stereocilia
    2. Hair cells almost completely surrounded by inner phalangeal cells
- Outer (type II) hair cells: more numerous, arranged in three rows
    1. Stereocilia are arranged stepwise, each cilium increases in height
    2. Cell bases are surrounded by outer phalangeal cells and cell apexes by the phalangeal cell processes
- The stereocilia
    1. Very still cilia that can only bend at the base
    2. Made from actin filaments connected by fimbrin and espin, the root is made of actin binding proteins
    3. Connected by protein filaments on the sides, tip links and cadherin 23, that are anchored to a stress-activated potassium channel called a mechanoelectric transductor
    4. Influx of potassium ions and depolarization of the cell occurs when the stereocilia bends
- Depolarization of hair cell causes influx of calcium ions and increase in their cytoplasmic concentration. This triggers exocytosis of neurotransmitter (glutamate) from the hair cell
- Excess potassium and calcium is constantly removed from the cell by cell membrane transporters

III. Converting vibrations to neurological impulses

- Vibrations of the endolymph causes the tectorial membrane to movie relative to the basilar membrane, resulting in bending of hair cell stereocilia
- The inner hair cells make contact with afferent nerve fibers and are responsible for the basic perception of sound
- The outer hair cells make contacts with both afferent *and* efferent nerve fibers and are responsible for signal amplification and tuning: discrimination of pitch.
    1. They modulate tension of the basilar membrane by rapid oscillatory changes in height. These movements are driven by a unique, potential-dependent motor enzyme – prestin: the fastest motor enzyme known (presto = fast)
- The relation between sound frequency and the basilar membrane: the elasticity of the membrane changes from the base to the apex of the cochlear duct.
    1. High pitch sounds: perceived by hair cells close to the base
    2. Low-pitch sounds: perceived by hair cells close to the apex

13.3.2 – The Vestibule, Utricle, Saccule and Semicircular Canals

- The sense of equilibrium is produced by the displacement of endolymph and stereocilia in the utricle, saccule and the semicircular ducts when we move our head
- The hair cells in the vestibule have a kinocilium, a longer cilium, in addition to the stereocilia. The stereocilia increases in height toward the kinocilium, and the direction the stereocilia bends in relation to the kinocilium decides what happens:
    1. Bending stereocilia toward kinocilium: depolarization
    2. Bending stereocilia away from the kinocilium: hyperpolarization
- The hair cells involved in balance are not manipulated by vibration like in hearing, but by the movement of calcium carbonate crystals, otoliths, in the otolithic membrane across the stereocilia.
    1. The otolithic membrane helps provide information about the position of the head, sense of gravity and linear movement
- In the cristae ampullares of the semicircular canals the hair cells are located on protrusions of connective tissue stroma and is covered by the cupula. The cupula is similar to the tectorial membrane in the cochlea. When the endolyph around the cupula moves, the cupula move and subsequentially the stereocilia are bent
- The location of the semicircular canals in three planes provide complete information about rotational direction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