

## **CYTOLOGY, HISTOLOGY AND EMBRIOLOGY** **EXAM QUESTIONS**

First Year Medical Students, English Language Course  
Medical University “Prof. Dr. Paraskev Stoyanov” – Varna

### **I. CYTOLOGY**

- 1. Living matter – characteristics. Cell – definition and general concepts. Main principles of the cell theory.
- 2. Cytological and histological methods of study.
- 3. Chemical composition and cell organization hierarchy.
- 4. External morphology of the cell.
- 5. Classification and general characteristics of the cellular structures.
- 6. Biological membranes – characteristic, relationships, importance and functions.
- 7. Plasmalemma. Glycocalyx.
- 8. Cell matrix (cytosol).
- 9. Endoplasmic reticulum.
- 10. Golgi apparatus (Golgi complex).
- 11. Lysosomes.
- 12. Peroxisomes.
- 13. Mitochondria.
- 14. Interphase nucleus – general data, chemical composition and optic-microscopic characteristics.
- 15. Interphase nucleus – electron microscope characteristics.
- 16. Chromosomes. Human karyotype.
- 17. Ribosomes. Polysomes.
- 18. Cytoskeleton – microfilaments, intermediate filaments.
- 19. Cytoskeleton – microtubules.

- 20. Microtubule derivatives – centrioles
- 21. Microtubule derivatives – basal bodies, cilia and flagella.
- 22. Cell surface specializations of the apical, lateral, and basal surface of plasma membrane.
- 23. Nonobligatory cell organelles.
- 24. Cell inclusions.
- 25. Transmembrane, intracellular and transcellular transport.
- 26. Endocytosis and exocytosis.
- 27. Cell metabolism. Assimilation and dissimilation. Biosynthesis and secretion.
- 28. Cell signaling.
- 29. Cell cycle.
- 30. Cell growth and differentiation .
- 31. Cell replication. Mitosis (incl. endomitosis) and amitosis. ?
- 32. Cellular and intracellular movements.
- 33. Excitability and cell reactivity .
- 34. Cell aging and death. Apoptosis.

## II. GENERAL HISTOLOGY

- 35. Tissues – definition, classification, origin and general properties.
- 36. Epithelial tissue - definition, classification, origin, characteristics and functions.
- 37. Covering epithelia - definition, classification, distribution, and histophysiology.
- 38. Exocrine glandular epithelium - definition, classification, distribution, and histophysiology.
- 39. Endocrine glandular epithelium - definition, organization forms, distribution and histophysiology.
- 40. Connective tissue - definition, classification, origin, characteristics and functions.
- 41. Connective tissue cells.

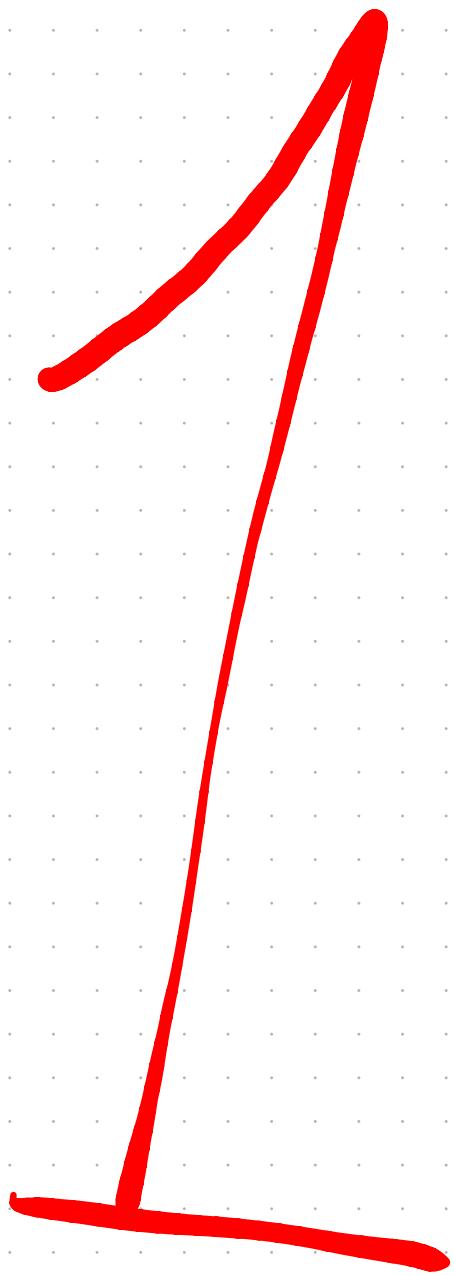
- 42. Connective tissue extracellular matrix.
- 43. Connective tissue with nondifferentiated extracellular matrix - mesenchyme, mucous connective tissue.
- 44. Connective tissue with differentiated fibrous extracellular matrix - loose connective tissue.
- 45. Connective tissue with differentiated dense fibrous extracellular matrix - collagenous, elastic, reticular and adipose tissue.
- 46. Connective tissue with rigid extracellular matrix-cartilaginous tissue.  
Chondrogenesis.
- 47. Connective tissue with rigid extracellular matrix - osseous tissue. Osteogenesis.
- 48. Blood. Lymph.
- 49. Hemopoiesis - embryonic, fetal and postnatal.
- 50. Erythrocytes.
- 51. Erythropoiesis.
- 52. Granulocytes.
- 53. Granulopoiesis.
- 54. Monocytes. Monocytopoiesis.
- 55. Lymphocytes.
- 56. Lymphocytopoiesis.
- 57. Platelets (formation).
- 58. Muscle tissue - definition, classification, origin, characteristic and functions.
- 59. Skeletal muscle tissue.
- 60. Cardiac muscle tissue.
- 61. Smooth muscle tissue.
- 62. Nerve tissue - definition, classification, origin, characteristic and functions. Nerve tissue cells.
- 63. Neurons - classification, structure, distribution and functions.

- 64.Synapse. Interneuronal synapses.
- 65.Neurosecretory cells. Paraneurons.
- 66.Neuroglia – types, structure, distribution and functions
- 67.Nerve fibers.
- 68.Receptor nerve endings.
- 69.Effector nerve endings. *functions?*

### III. GENERAL EMBRYOLOGY

- 70.Subject, aim, tasks, methods and relations of the general embryology to other medical sciences. *more*
- 71.Meiosis and gametogenesis. Deviations of normal course of meiosis.
- 72.Differences between male and female meiosis.
- 73.Spermatogenesis.
- 74.Spermatozoa - structure and function. *more*
- 75.Ovogenesis.
- 76.Ovulation - structure and function of the mature oocyte.
- 77.Cyclic changes of the endometrium during the menstrual cycle.
- 78.Semen – formation, ingredients and characterization.
- 79.Insemination. Sperm migration in the femal reproductive tract. Transport of the secondary oocyte after ovulation.
- 80.Fertilization.
- 81.I<sup>st</sup> week of human development – cleavage.
- 82.I<sup>st</sup> week of human development – blastocyst formation.
- 83.Implantation.
- 84.II<sup>nd</sup> week of human development – differentiation of the trophoblast.
- 85.II<sup>nd</sup> week of human development - differentiation of the embryoblast.
- 86.II<sup>nd</sup> week of human development – development of the extraembryonic mesoderm.

- 87. Abnormal blastocysts. Abnormal implantation sites.
- 88. Assisted reproductive technology.
- 89. III<sup>rd</sup> week of human development – gastrulation (formation of embryonic mesoderm and endoderm).
- 90. III<sup>rd</sup> week of human development – formation of the notochord.
- 91. Growth of the embryonic disc.
- 92. III<sup>rd</sup> week of human development – further development of the trophoblast.
- 93. III<sup>rd</sup> – VIII<sup>th</sup> week of human development – derivatives of the ectodermal germ layer.
- 94. III<sup>rd</sup> – VIII<sup>th</sup> week of human development – development of the mesodermal germ layer.
- 95. III<sup>rd</sup> – VIII<sup>th</sup> week of human development – differentiation of the paraxial mesoderm.
- 96. III<sup>rd</sup> – VIII<sup>th</sup> week of human development – differentiation of the intermediate mesoderm and lateral plate mesoderm.
- 97. Embryonic blood circulation. not done
- 98. III<sup>rd</sup> – VIII<sup>th</sup> week of human development - derivates of the endodermal germ layer.
- 99. External appearance of the human embryo during the second month.
- 100. Embryonic and fetal membranes: yolk sac, amnion, allantois. Amniocentesis.
- 101. Placentation and placenta.
- 102. Umbilical cord.
- 103. Twins and multiple births.
- 104. Congenital malformations. Prenatal diagnosis.



## 1. Cytology

### ✓ 1. Living matter – characteristics. Cell – definition and general concepts. Main principles of the cell theory.

Cell theory – 1665 Robert Hook discovered that all living things are comprised of cells. He also discovered that Cells are the smallest “living” part of an organism and that one cell comes from a previously existing cell.

The human body contains  $10^{13}$  cells but all come from one single cell! All cells store their hereditary information in the same linear chemical code (DNA).

All cells are prokaryotic (the distinctive nucleus) eukaryotic (keeps DNA in a separate membrane → nucleus)

### 2. Cytology and histology methods of study.

Methods of study reflect the level of structural organization (Atom – Organ Systems). To study the different cells and tissues Light Microscope or Electron Microscope are used.

Chemical way: To prepare the histological tissue it needs to get fixed and then embedded. To do that the small piece has to undergo dehydration by being transferred through a series of increasingly more concentrated alcohol solutions, ending in 100%, which effectively removes all water from the tissue. The alcohol is then removed in a clearing solution miscible in both alcohol and melted paraffin. When the tissue is then placed in melted paraffin at 58°C it becomes completely infiltrated with this substance. Then the paraffin is allowed to harden. The resulting paraffin block is trimmed to expose the tissue for sectioning (slicing). The hard block gets cut with a microtome and is sliced by the microtome's steel or glass into sections 1-10 µm.

Physical way: The tissues are fixed by freezing and at the same time become hard and thus ready to be sectioned. This method is commonly used during surgery.

Staining: Most tissues are colourless. To see the tissue in the microscope it needs to be stained. Tissue component with net-negative charge (anionic) stain more readily with basic dyes and are termed basophilic. Cationic components, such as protein with many ionized amino groups, have affinity for acidic dyes and termed acidophilic. The most common dyes are Haematoxylin, to dye the DNA and RNA-rich in blue, and Eosin, to stain other cytoplasm and collagen pink.

Light Microscope: Is based on the interaction of light and the tissue components and can be used to reveal and study tissues.

Bright-field microscopy: examination by means of ordinary light that passes through the specimen. The resolving power is approximately 0,2 µm by a magnification of 1000-1500 times.

Fluorescence microscopy: when certain tissue sections are irradiated with a certain light of a proper wavelength, they emit light with a longer wavelength. → Fluorescence. The tissues are irritated usually by ultraviolet light (UV). The fluorescence substance appears brilliant on a dark background.

Electron Microscope: It is based on the interaction of electrons and tissue components.

Problem in the study of tissues sections: Because the slide that is studied went through a series of processes the end product might be damaged → Artifacts. The structure might differ from the living structure. Also is to remember that a tissue is 3D but the section observed is 2D.

### / 3. Chemical composition and cell organization hierarchy

#### Level of cell organisation:

- Bio molecules (building blocks)
- Macromolecules (nucleic acids, proteins, polysaccharides)
- Supramolecular complexes (DNA/protein; RNA/protein)
- Organelles
- Cell

### / 4. External morphology of the cell

All cells are surrounded with the cell membrane (Plasma membrane, plasma lemma). It separates the cytoplasm from the extra cellular matrix. The Plasma membrane contains Proteins called integrins, which connects the cytoplasm with the extra cellular matrix. Through the linkage is a constant exchange of influences in both directions.

### 5. Classification and general characteristics of the cellular structures

Cells come in different size:

- Small 5-10 µm → small lymphatic
- Medium-size 11-30 µm → granulocytes
- Large cells 31-100 µm → Purkinje cell
- Giant cell 101-200 µm → some pyramid – shaped neurons, oocytes (ovary)

Cells are also various in shapes:

- Squamous → Endothelial cells
- Columnar → Enterocytes
- Cuboidal → Kidney tubule cells
- Spherical → Oocytes
- Pyramidal → Neurons
- Stellate → Osteocytes
- Spindle-shaped → Fibroblasts
- Polyhefral → Hepatocytes

Most cells are colourless but some cells have pigments!

All cells are surrounded with the cell membrane (Plasma membrane, plasma lemma). It separates the cytoplasm from the extra cellular matrix. The cytoplasm contains cytosol, organelles, cytoskeleton and other minor cytoplasm structure.

- Cytosol - fluid component, in which are contained
- Organelles - metabolically active structures
  - Membranous (e.g. mitochondria)
  - Non-membranous (e.g. ribosomes and proteasomes)

- Cytoskeleton - determines the shape and motility of eukaryotic cells
- Other minor cytoplasmic structures are - inclusions - deposits of carbohydrates, lipids, or pigments

## ✓ 6. Biological membranes – characteristic, relationships, importance and function

All cells are surrounded with the cell membrane (Plasma membrane, plasma lemma). It separates the cytoplasm from the extra cellular matrix. The Plasma membrane contains Proteins called integrins, which connects the cytoplasm with the extra cellular matrix. Through the linkage is a constant exchange of influences in both directions.

The membrane consists phospholipids, cholesterol and chains of oligosaccharides covalently linked to phospholipids and protein molecules. One important rule of the membrane is to keep the ion constant inside the cell, which is different to the extra cellular fluid.

The cell membrane is 7.5-10nm thin and is only visible under the electron microscope. Plasma lemma and all other organelle membrane have a tri-laminar structure and are called unit membrane.

## ✓ 7. Plasma lemma Glycocalyx

The cell boundary is defined by the cell membrane or plasmalemma. Glycocalyx is a polysaccharide that can be found on the outer surface of the cell membranes. Collectively, the cytoplasm and nucleus form the protoplasm of a cell. The folds on the inner mitochondrial membrane are called cristae. The cytoplasm that surrounds organelles is the cytoplasmic ground substance or cytosol.

- The glycocalyx is a type of identifier that the body uses to distinguish between its own healthy cells and transplanted tissues, diseased cells, or invading organisms. Included in the glycocalyx are cell-adhesion molecules that enable cells to adhere to each other and guide the movement of cells during embryonic development. The glycocalyx plays a major role in endothelial vascular tissue, including the modulation of red blood cell volume in capillaries, as well as many other functions of the vascular system

## ✓ 8. Cell matrix (cytosol)

The cell matrix is composed of a fluid, cytosol, which contains metabolically active structures, organelles, which can be membranous (mitochondria) or non-membranous (ribosome and proteasomes). Other minor cytoplasmic structures are inclusion, which are general deposits of carbohydrates, lipids or pigments.

The cytosol contains hundreds of enzymes, such as those of the glycolytic pathway, that produce building blocks for large molecules and breaks down small molecules to liberate energy. The protein synthesis by ribosomes (mRNA, transfer RNA, enzymes and other factors) takes place within the cytosol. Oxygen, CO<sub>2</sub>, electrolytic ions, etc. are all diffuse through the cytosol, either freely or bounded to proteins, passing or leaving the organelles where they are used or produced.

## ✓ 9. Endoplasmic reticulum

In all eukaryotic cells the cytoplasm contains a connected network of intercommunicating channels and sacs formed by a continuous membrane, which enclose a space called cisterna. This membrane system is called Endoplasmic Reticulum (ER). There are two different kinds of ER: rough and smooth.

Rough Endoplasmic Reticulum (RER): RER is prominent in cells specialized for protein secretion (pancreas acinar cells, fibroblasts and plasma cells). It is formed of saclike and parallel stacks of flattened cisternae. The membrane of the RER is connected to the outer layer of the nucleus. The name ROUGH Endoplasmic Reticulum refers to the presence of polyribosomes on the membrane. Polyribosomes are formed because many ribosomes can bind to a single mRNA molecule. Ribosomes can be free unattached to the ER and attached.

Smooth Endoplasmic Reticulum (SER): Is continuous with the RER but in most cells less abundant. There are no polyribosomes on the SER and the cisternae, is more tubular and appears more like a profusion of interconnected channels.

The major function of the SER:

- Synthesis of the various phospholipids molecules (which constitute all cellular membranes).
- Synthesis of extra cellular Lipids (Hepatocytes)
  - Synthesis of cholesterol for lipoproteins
  - Detoxification – cytochrome P450 complex
- Sequestering  $\text{Ca}^{2+}$  from the cytosol – myocyte
  - $\text{Ca}^{2+}$  is stored in the smooth ER
  - Release and reuptake of  $\text{Ca}^{2+}$  are strictly regulated

## ✓ 10. Golgi Apparatus (Golgi complex)

The Golgi apparatus is named after its discoverer Camillo Golgi in 1898. It is composed of smooth membranous saccules and the cells post office. It is positioned between the nucleus and the cell membrane.

It consists of an ordered series of compartments:

- Cis Golgi network (CGN) – a network of interconnected tubular and cisternal structures – protein sorting (secretory vs. retrieval proteins)
- Collection of 4-6 membrane-enclosed flattened cisternae linked by tubules (dictyosomes) – cis-Golgi, medial-Golgi, and trans-Golgi compartment – oligosaccharide processing, proteoglycan assembly
- Trans Golgi network (TGN) – a network of interconnected tubular and cisternal structures – protein sorting II (proteins for secretion granules, lysosomes, and plasma lemma)
- Golgi matrix proteins – help Golgi complex integrity

The Golgi apparatus is important for glycosylation, sulfation, phosphorylation and limited proteolysis. The apparatus also initiates packing, concentration, and storage of secretory products.

## 11. Lysosomes

Lysosomes are intra cellular vesicles. They are sites of digesting and turnover of the cellular

## Lysosomes

components. They are membrane-enclosed structures with 40 different hydrolytic enzymes. In cells with great phagocytic activity they are particularly abundant (etc. macrophages, neutrophils). Lysosomal enzymes like phosphatase, phospholipase nucleases or sulfatase, are capable of breaking down most macromolecules.

Lysosomes hydrolases (enzymes) are synthesized and segregated in side the RER and transferred to the Golgi, where the enzymes are further modified and packaged in vacuoles → Lysosomes. Material taken from the cellular environment by endocytosis is digested when lysosomes fuse with the membrane of the phagosome or pinocytotic vesicles. Inside the hydrolytic enzyme and endocytosed material mix and proton pump activates the membrane to lower the pH → digestion. The new composition is called heterolysosome.

During digestion of macromolecules, released nutrients diffuse into the cytosol through the lysosomal membrane. Indigestible material remains inside and is called residual body or telolysosomes.

Lysosomes also remove non-functional or excess cytoplasmic structure → Autophagy. A membrane is formed around this structures (autophagosomes) and fuses with the Lysosomes. The fusion initiates lysis of the enclosed cytoplasm. Digested products from autophagosomes are reutilized in the cytoplasm.

## 12. Peroxisomes

Peroxisomes are spherical membrane-limited organelles and contain more than 40 oxidative enzymes (urate oxidase, catalase, and D-amino acid oxidase).

Peroxisomes utilize oxygen and do not produce ATP and don't participate in cellular metabolism. Peroxisomes oxidize specific organic substances by removing hydrogen atoms that are transferred to molecular oxygen ( $O_2$ ). This produces  $H_2O_2$  hydrogen peroxide which potentially damage the cell.  $H_2O_2$  is broken down by catalase, an enzyme in all peroxisomes. The transfer by catalase from  $H_2O_2$  to other components has clinical implications: It oxidizes various toxic molecules (alcohol) and prescribed drugs. This happens particularly in liver and kidney cells where the peroxisomes are large and abundant and contain additional enzymes like D- and L-amino acid oxidase.

Peroxisomes also contain enzymes involved in lipid metabolism. → The  $\beta$ -oxidation of long-chain fatty acids is preferentially accomplished peroxisomal enzymes that differ from the mitochondrial counterparts.

The formation of Peroxisomes are not well understood but involves precursor vesicles that appear at the bud of the ER. Many peroxisomal enzymes are synthesized on free cytosolic polyribosomes, with a small sequence of amino acids near the carboxyl terminus that functions as a specific import signal. Proteins with this signal are recognized by receptors located in the membrane of the peroxisomes and internalized by the organelle.

## 13. Mitochondria

Mitochondria are membrane-enclosed organelles with enzymes specialized to produce ATP (adenosine triphosphate). This stores energy in high-energy phosphate bonds and is used in most energy requiring cellular activities. Glycolysis converts glucose anaerobically to pyruvate in the cytoplasm, releasing some energy. When the pyruvate enters the mitochondria the rest energy is captured and oxidized to  $CO_2$  and  $H_2O$ . Some of the energy released in the Mitochondria is not stored by the ATP but dissipated as heat, which maintains body temperature.

Mitochondria change their shape rapidly and fusing with one another. They move through the cytoplasm along microtubules. The number of mitochondria in a cell depends on the energy needs of the cell. Cardiac muscle and some kidney tubules need a lot of energy.

Mitochondria are often big enough to be seen under the light microscope. Under the electron microscope it is seen to have 2 separate and very different membranes which create 2 compartments: the inner most matrix and narrowed inter membrane space. Both membranes contain a larger number of protein molecules and have reduced fluidity. The outer membrane is smooth, it contains transmembrane proteins called porins that form channels through which molecules pass; the inner membrane has many sharp folds called cristae, which increases the surface area greatly. The lipid bilayer (Doppelschicht) contains unusual phospholipids and is impermeable to ions. Built in proteins including transport proteins make the inner membrane selectively permeable to small molecules, which are required by the mitochondrial enzymes in the matrix. Matrix enzymes include those that oxidize pyruvate and fatty acids to form acetyl coenzyme A (CoA) and those of the citric acid cycle that oxidize acetyl CoA, while releasing CO<sub>2</sub> as waste and small energy rich molecules which provide electrons for transport along respiratory chain and electron transport chain. Enzymes and other components of this chain are embedded in the inner membrane and allow oxidative phosphorylation, which produce ATP in animal cells.

Chemiosmotic process → Formation of ATP by oxidative phosphorylation enzymes of respiratory chain.

Other membrane proteins make up the ATP synthase system, forming globular or stalk-like structures on the matrix side of the inner membrane. Through the enzyme complex runs a hydrophilic pathway that allows protons to flow down the electronchemical gradient in to the matrix. Proton passing through the narrowed channel and causes spinning of specific polypeptides, in the globular ATP synthase complex, converting the energy of proton flow into the mechanical energy of proton movement. This energy is stored in the new phosphate bond of ATP by other subunit polypeptides that bind ADP and inorganic phosphate.

Mitochondrial matrix contains a small circular chromosome of DNA, ribosomes, messenger RNA and transfer RNA. Protein synthesis occurs in the mitochondria but because of the small amount of mitochondrial DNA just a few proteins are produced there.

During cell mitosis each daughter cell receives the half amount of mitochondria of the parent cell.

#### **14. Interphase nucleus-general data, chemical composition and optical-microscopic characteristics**

The nucleus frequently appears round or oval and in the center of the cell. Its main components are the nuclear envelope and the chromatin consisting of DNA and associate proteins and a special region of chromatin called nucleolus.

##### **Nuclear envelope:**

The nuclear envelope is built of 2 parallel unit membranes. Between the membranes is the perinuclear space. On the outer membrane are polyribosomes which show the connection between nucleus and ER. The inner membrane is connected with a meshwork of fibrous proteins called nuclear lamina, which help to stabilize the envelope. The lamina is composed of intermediate lamina filaments called lamins, which bind 2 membrane proteins and associate with chromatin in nondividing cells.

Where the outer and inner membrane fuse, the resulting lipid-free space contains nuclear pores complex or NPC, which regulates the transport in and out of the nucleus.

### Chromatin:

There are 2 different kinds of chromatin and both are visible under the light microscope.

16 Heterochromatin (HC), which is electron dense, appears in the light microscope as basophilic clumps.

Euchromatin (EC) is the less coiled protein of the chromosomes and is visible as light stained basophilic areas in the light microscope.

The difference of both is seen as light and dark section of the nucleus.

### Nucleolus:

The nucleolus is a generally spherical, highly basophilic structure in the nuclei active in the protein synthesis. Nucleoli are always associated with the nuclei of the cells that are intensely synthesizing proteins for growth or secretion.

## **14=15. Interphase nucleus – electron microscope characteristics**

The nucleus frequently appears round or oval and in the center of the cell. Its main components are the nuclear envelope and the chromatin consisting of DNA and associate proteins and a special region of chromatin called nucleolus.

### Nuclear envelope:

The electron microscope shows that 2 parallel unit membranes, separated by a perinuclear space, surround the nucleus. Polyribosomes are attached to the outer membrane. The inner membrane is connected with a meshwork of fibrous proteins called nuclear lamina, which help to stabilize the envelope. The lamina is composed of intermediate lamina filaments called lamins, which bind 2 membrane proteins and associate with chromatin in nondividing cells.

Where the outer and inner membrane fuse, the resulting lipid-free space contains nuclear pores complex or NPC, which regulates the transport in and out of the nucleus. It is possible to see the pores and the electron microscope.

### Chromatin:

Heterochromatin (HC), which is electron dense, appears under the electron microscope as coarse granules.

Euchromatin (EC) is the less coiled protein of the chromosomes and is visible as finely dispersed granular material in the electron microscope.

The difference of both is seen as light and dark section of the nucleus.

## **16. Chromosomes, Human karyotype**

In nondividing cells chromatin is the chromosomal material in a largely uncoiled state. There are 2 types of chromatin, Heterochromatin HC and Euchromatin EC. Both are visible in light and

14 electron microscope. HC is electron dense and EC is less coiled protein of chromosomes. The difference of both is seen as light and dark section of the nucleus is seen in both electron and light microscope.

Chromatin is composed mainly of coiled DNA bound to basic proteins called histones and various nonhistone proteins. The basic structure of chromatin and histones is the nucleosome, which has a core of 8 small histones, which are wrapped in DNA made of 150 base pairs. The series of nucleosomes in chromatin is also associated with many diverse nonhistone proteins. DNA bound of nucleosomes is folded further to 30-nm fiber, and then into visible chromosomes.

Cells with light stained nuclei are more active in protein synthesis than with dark nuclei. Light

nuclei contain more euchromatin and then heterochromatin → more DNA surface is available for transcribing RNA.

The human cell has 46 chromosomes, presented in 23 homologous pairs of chromosomes.

- 23 maternal pairs (22 autosomes + 1 sex chromosome: X)
- 23 fraternal pairs (22 autosomes + 1 sex chromosome: Y)

Females: XX; males: XY → one of the two X chromosomes in females is compacted (inactive) as heterochromatin → Barr body

#### Karyotype:

Chromosome staining performs the number and characteristics of chromosomes encountered in an individual Karyotype. Cells are grown in vitro and mitosis is arrested during metaphase using colchicine (binds tubulin and disrupts microtubules). Arrested cells are then immersed in a hypotonic solution, which causes swelling, stained in various ways, and then flattened between a glass slide and a cover slip. The mitotic chromosomes from one nucleus are photographed under the light microscope, cut individually from the photograph, and arranged so that the stained chromosomal bands can be analyzed.

## 17. Ribosomes, Polysomes

Ribosomes are small electron-dense particle; they are in the cytosol, composed of 4 segments of rRNA (ribosome RNA) and about 80 different proteins. All ribosomes are composed of 2 different-sized subunits.

In all eukaryotic cell the RNA molecules of both subunits are synthesised inside the nucleus. The numerous proteins are synthesised in the cytoplasm and enter the nucleus and associate with rRNA. The large and small subunits are built and leave the nucleus to participate in protein synthesis.

The small and large subunits come together by binding a mRNA strand. Polysomes or polyribosomes are present on the mRNA. The compact of each ribosome contain rRNA molecules, which provide structural support and position of tRNA in the correct "reading frame". To the ER attached polyribosomes translate the mRNA that code for proteins that are sequestered across the membrane of this organelle.

## 18. Cytoskeleton – microfilaments, intermediate filaments.

The cytoskeleton is an intricate cytoplasmic 3D meshwork of ~~an intricate cytoplasmic 3D~~ ~~protein filaments~~ that are responsible for the maintenance of:

- Cellular morphology
- Cellular motion (organelles within the cell; or motion of the entire cell)

It is a complex network of microtubules, microfilaments and intermediate filaments. This protein structure determines the shape, movements and movements of organelles and cytoplasmic vesicles

#### ① Microfilaments (Actin Filaments):

Contraction in cells is the result from an interaction between actin and myosin. Actin is present as thin polarized microfilaments composed of globular subunits organized into a double-stranded helix. Actin is usually found in cells as polymerized filaments of F-actin mixed with free globular as G-actin subunit.

Microfilament can be organized in different ways:

In skeletal muscle, they assume a stable array integrated with thick myosin filaments.

In most cells microfilaments are located under the plasma lemma. They are involved in shape changing and cell locomotion

Microfilaments play a role in moving and shifting cytoplasmic components.

Microfilaments are associated with myosin and form a "pure-String" ring of filaments, whose construction results in the cleavage of mitotic cells.

In crawling cells actin filaments are organized in parallel contractile bundles called stress fibers.

#### Intermediate Filaments:

Intermediate filaments are stable and vary in their protein subunit structure in different cell types. They are essentially rod-like rather than globular proteins that form coiled tetramers which self-assemble into large cable-like arrays stabilized by further interaction laterally.

Intermediate filaments have been organized into 4 groups:

- **Keratins:** family of more than 20 proteins found in the epithelial cells and the hard structure produced by the epidermal cells (nails). In epidermal cells keratins strength the tissue and provide against abrasion and water loss.
- **Vimentin:** Is a single protein and is the most common intermediate filament protein in mesenchymal cells. Important Vimentin-like protein: desmin (in muscle cells), glial fibrillar acidic protein (In astrocytes, supporting cells of CNS)
- **Neurofilaments:** consist of at least three high-molecular-weight polypeptides with different chemical structures and roles. All are restricted to neurons
- **Lamins:** consist of three proteins present in the nucleus of animal cells. They form a structural framework just inside the nuclear envelope.

## ✓ 19. Cytoskeleton- microtubules

The cytoskeleton is an intricate cytoplasmic 3D meshwork of an intricate cytoplasmic 3D meshwork of protein filaments that are responsible for the maintenance of:

- Cellular morphology
- Cellular motion (organelles within the cell; or motion of the entire cell)

It is a complex network of microtubules, microfilaments and intermediate filaments. This protein structure determines the shape, movements and movements of organelles and cytoplasmic vesicles.

#### Microtubules:

Microtubules are within the cytoplasmic matrix. Act as intracellular "railway"! They are also found as cilia or flagella. Microtubules are variable in length and are hollow cylinders made of protein tubulin. They have typically one end attached to a single microtubule-organizing center MTOC called a centrosome.

Microtubules are assembled of heterodimers of  $\alpha$  and  $\beta$  tubulin. Tubulin are arranged to form 13 protofilaments. The specific orientation of the tubulin dimers results in structural polarity of the microtubule. The microtubules grow rapidly on one end of the existing microtubules. This end is the + end. The length and location of microtubules differ from cell activity.

- Cytoplasmic microtubules play a role in the formation and maintenance of cell shape.
- Complex microtubule network participate in the intracellular transport of organelles and vesicles.
- Microtubules provide the base for several complex cytoplasmic components: centrioles, basal bodies, cilia and flagella.

Centrosome = 2 centrioles



## ✓ 20. Microtubule derivatives- centrioles

Under normal circumstances these organelles are found in pairs and orientate at right angle to another. The pair is called centrosome. The centrosome is the microtubule organization center for the mitotic spindle. Each centriole consists of nine reality short microtubular triplets linked together in a pinweehl-like arrangement. The centrosome duplicates and is divided equally during a cell interphase. At the onset of mitosis the tow daughter centrosome move to opposite sides of the nucleus and become the two poles of the mitotic spindle of microtubules attached to chromosomes.

Function:

- Microtubule support: Organizes microtubules and support their growth in non-dividing cells
- Cell division: directs formation of mitotic spindle in dividing cells.

## ✓ 21. Microtubule derivatives – basal bodies, cilia, flagella

Cilia and flagella are motile process, covered by cell membrane with a highly organized microtubule core. The main function of cilia is to sweep fluid along the surface of a cell sheets. In human the spermatozoa are the only cell type with flagellum.

Cilia and flagella posses the same core structure, consisted of nine peripheral microtubules surrounding tow central microtubules. This is called axoneme. At the base of each cilium and flagellum is a basal body, similar to a centriole, which controls the axoneme.

## 22. Cell surface specializations of apical, lateral and basal surface of plasms membrane.

Cell polarity is a fundamental feature of many types of cells. Epithelial cells are one example of a polarized cell type, featuring distinct 'apical', 'lateral' and 'basal' plasma membrane domains. Epithelial cells connect to one another via their lateral membranes to form epithelial sheets that line cavities and surfaces throughout the animal body. Each plasma membrane domain has a distinct protein composition, giving them distinct properties and allowing directional transport of molecules across the epithelial sheet. How epithelial cells generate and maintain polarity remains unclear, but certain molecules have been found to play a key role

Since basal and lateral membranes share the same determinants, another mechanism must make the difference between the two domains. Cell shape and contacts provide the likely mechanism. Lateral membranes are the site of contact between epithelial cells, whereas basal membranes connect epithelial cells to the basement membrane, an extracellular matrix layer that lies along the basal surface of the epithelium. Certain molecules, such as Integrins, localise specifically to the basal membrane and form connections with the extracellular matrix.

apical membrane

the layer of plasma membrane on the apical side (the side toward the lumen) of the epithelial cells in a body tube or cavity, separated from the basolateral membrane by the zonula occludens

**basal membrane,**

a sheet of tissue that forms the outer layer of the choroid and lies just under the pigmented layer of the retina. It is composed of elastic fibers in an otherwise thin homogenous layer.

(adj 1. describing the minimal functions necessary for life.

adj 2. located at or forming the base of a structure.

n 3. the fundamental structures from which an organism is derived)

lateral- sideways

## 23. Non obligatory cell organelles

Secretory vesicles or granules

Myofibrils

Melanin granules

Synaptic vesicles

## 24. Cell inclusion

Material in cytoplasm, which may or may not be surrounded by membrane. Is not present in all cells and take little or no part in metabolic activity. Filled with stored macromolecules:

Fat drops: Accumulation of lipid molecules and prominent in adipocytes, adrenal cortex cells and lever cells.

Glycogen granules: Glycogen is the most common storage form of glucose. They are especially abundant in cells of muscle and liver.

Pigments: Occur in many cell types and may contain various complex substances

- Lipofuscin - accumulating by-product of lysosomal digestion in long-lived cells
- Melanin - protects cell nuclei from damage to DNA caused by light
- Hemosiderin granules - containing the protein ferritin, which forms a storage complex for iron; very electron-dense, but with the light microscope appear brownish and resemble lipofuscin.

Crystals: Found in few cells, probably crystalline forms of certain proteins. Examples

- Sertoli cells of the testis - Crystals of Charcot-Böttcher
- Leydig cells of the testis - Crystals of Reinke
- Macrophages (sometimes)

## 25. Transmembrane, intercellular and transcellular transport

Transmembrane: single pass / multi pass

Transmembrane: Glycophorins / Band 3

Glycophorin A - entry of Influenza & Hepatitis virus, P. falciparum / Band; Ankyrin; Spectrin:

Hereditary spherocytosis(HS), Hereditary elliptocytosis(HE)  
Band 3: Southeast Asian ovalocytosis(SAO)/ Distal renal tubular acidosis(dRTA)  
Intracellular: Spectrin / Actin  
Some Integral Proteins have hydrophobic Transmembrane Anchors

## ✓ 26. Endocytosis and exocytosis

### Endocytosis:

The process whereby a cell ingests macromolecules, particulate matter, and other substances from the extracellular space is referred to as endocytosis.

There are 3 types of endocytosis:

- Phagocytosis literally means cell eating. Certain white blood cells, such as macrophages and neutrophils, are specialized for eating and removing bacteria, protozoa and dead cells.
- Fluid-phase Endocytosis, cell drinking, where the cell takes liquid from the extracellular matrix and build a vesicle to transport liquid from one side to the other thru the cell membrane.
- Receptor-mediated Endocytosis This type of pinocytosis provides an efficient pathway for internalization of specific macromolecules that are recognized by cell surface receptors.

### Exocytosis:

In exocytosis a membrane-limited cytoplasmic vesicle fuses with the plasma membrane, resulting in the release of its contents into the extracellular space without compromising the integrity of the plasma membrane.

## ✓ 27. Cell metabolism; Assimilation and dissimilation; biosynthesis and secretion

Metabolism is the set of life-sustaining chemical transformations within the cells of living organisms. These enzyme-catalyzed reactions allow organisms to grow and reproduce, maintain their structures, and respond to their environments. The word metabolism can also refer to all chemical reactions that occur in living organisms, including digestion and the transport of substances into and between different cells, in which case the set of reactions within the cells is called ~~intermediary metabolism~~ or intermediate metabolism.

Metabolism is usually divided into two categories. Catabolism breaks down organic matter, for example to harvest energy in cellular respiration. Anabolism uses energy to construct components of cells such as proteins and nucleic acids.

In biology dissimilation is the opposite of assimilation in the process of metabolism, consisting in the decomposition of organic compounds and conversion of protein, nucleic acids, fats, and carbohydrates (including those ingested) into simple substances. A number of dissimilation processes—respiration, fermentation, and glycolysis—play the central role in metabolism. As a result of these processes, energy contained in the molecules of complex organic compounds is released, partially to be transformed into adenosinephosphoric acids (chiefly ATP). The fundamental end products of dissimilation in all organisms are water, carbon dioxide, and ammonia. In animals these products are eliminated as they accumulate. In plant organisms CO<sub>2</sub>,

partially, and  $\text{NH}_3$ , totally, are used in the biosynthesis of organic matter, thus serving as the primary materials for assimilation.

The inseparable link between dissimilation and assimilation assures constant tissue renewal in organisms. Thus, in human blood one-half of the existing albumin is exchanged for new albumin molecules in ten days; the life span of erythrocytes is about four months. The relationship of the intensity of assimilation and dissimilation changes in relation to the stage of development, age, and physiological condition of the organism. The growth and development of the organism are characterized by the predominance of assimilation, which is manifested in the formation of new cells, tissues, and organs; their growth and differentiation; and in a general increase in body weight. In some pathological conditions and in starvation dissimilation usually predominates over assimilation, leading to a decrease in body weight.

### ✓ Biosynthesis

The synthesis of more complex molecules from simpler ones in cells by a series of reactions mediated by enzymes. The overall economy and survival of the cell is governed by the interplay between the energy gained from the breakdown of compounds and that supplied to biosynthetic reaction pathways for the synthesis of compounds having a functional role, such as deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and enzymes. Biosynthetic pathways give rise to two distinct classes of metabolite, primary and secondary. Primary metabolites (DNA, RNA, fatty acids,  $\alpha$ -amino acids, chlorophyll in green plants, and so forth) are essential to the metabolic functioning of the cells. Secondary metabolites (antibiotics, alkaloids, pheromones, and so forth) aid the functioning and survival of the whole organism more generally. Unlike primary metabolites, secondary metabolites are often unique to individual organisms or classes of organisms.

### ✓ Secretion

The export of proteins by cells. With few exceptions, in eukaryotic cells proteins are exported via the secretory pathway, which includes the endoplasmic reticulum and the Golgi apparatus. Secreted proteins are important in many physiological processes, from the transport of lipids and nutrients in the blood, to the digestion of food in the intestine, to the regulation of metabolic processes by hormones. See Cell (biology), Cell organization

Proteins destined for export are synthesized on ribosomes attached to the outside of the rough endoplasmic reticulum, a portion of the endoplasmic reticulum that is specialized for the synthesis of secretory proteins and most of the cell's membrane proteins. After they are folded, the proteins enter small vesicles in which they are transported to the Golgi apparatus. When the proteins reach the last cisterna of the Golgi, a highly tubulated region known as the trans-Golgi network, they are sorted and packaged again into transport vesicles, some of which are in the form of elongated tubules. From here, there are two pathways that proteins can take to the cell surface, depending on the cell type. Proteins can be transported directly to the plasma membrane (constitutive secretion) or to secretory granules (regulated secretion). See Endoplasmic reticulum, Golgi apparatus

In all cells, there exists a constitutive secretion pathway whereby vesicles and tubules emerging from the trans-Golgi network fuse rapidly with the plasma membrane. The emerging vesicles and tubules attach to microtubules, cytoskeletal elements emanating from the Golgi region, that accelerate their transport to the plasma membrane. See Absorption (biology), Cell membranes

In cells that secrete large amounts of hormones or digestive enzymes, most secretory and membrane proteins emerging from the trans-Golgi network are not immediately secreted, but are

stored in membrane-bounded secretory granules. Secretory granules release their contents into the extracellular space in a process known as exocytosis, when their membranes fuse with the plasma membrane. Exocytosis occurs only after the cell receives a signal, usually initiated by the binding of a hormone or neurotransmitter to a receptor on the cell surface. The receptor triggers a signal transduction cascade that results in increased concentrations of second messengers such as cyclic adenosine 3', 5'-monophosphate and phosphatidylinositol triphosphate. In most secretory cells, the second messengers or the hormone receptors themselves trigger the opening of calcium channels through which calcium ions stream into the cytoplasm. Calcium initiates the docking of the secretory granules with the plasma membrane and the activation of the fusion apparatus. See Enzyme, Hormone, Signal transduction

In exceptional cases, proteins can be exported directly from the cytoplasm without using the secretory pathway. One such protein is fibroblast growth factor, a hormone involved in the growth and development of tissues such as bone and endothelium. Several interleukins, proteins that regulate the immune response, are also released via an unconventional route that may involve transport across the plasma membrane through channel proteins. These channels have adenosine 5'-triphosphatase (ATPase) enzyme activity and use the energy derived from the hydrolysis of ATP to catalyze transport. See Cellular immunology

## 28. Cell signalling

Cells in a multicellular organism need to communicate with one another to regulate their development into tissues to control their growth and division, and to cooperate their functions. Many cells form gap junctions to couple close-by cells and allow the exchange of ions and small molecules. Signals pass through the channels from cell to cell without reaching the extracellular matrix.

Receptor proteins only found on target cells are bind by soluble extracellular molecules. Each cell type in the body contains a different set of receptor proteins. There are different routes for the signalling:

Endocrine signaling: signal molecules (hormones) are carried in the blood to target cells.

Paracrine signaling: chemical mediators are rapidly metabolized so that the act only on local cells very close.

Synaptic signaling: neurotransmitters act only on close-by cells through special contacts areas called synapses

Autocrine signaling: signal bind receptor in the same cell type that produced the messenger molecule

Juxtacrine signaling: important in the early embryonic tissue interaction, signal molecules remain part of the cell's surface and bind surface receptors of the target cell when the two cells make directly physical contact.

## ✓29. Cell cycle

The cycle alternation between mitosis and interphase is known as cell cycle and occurs in all tissues with cell turnovers. The cycle has 4 distinct phases: Mitosis, and three interphase periods termed G<sub>1</sub> (the time gap between mitosis and DNA replication), S (the period of DNA synthesis and beginning of centrosome duplicating)) and G<sub>2</sub> (the gap between DNA duplication and the

next mitosis).

During the G<sub>1</sub> phases there is active synthesis of RNA and protein, and the cell grows back to its normal size.

During the S phases there is synthesis of DNA and histones, and the centrosome begin to duplicate.

G<sub>2</sub> phases is relative short, the proteins required for mitosis accumulate.

## ✓30. Cell growth and differentiation

The term cell growth is used in the contexts of cell development and cell division (reproduction)

When used in the context of cell division, it refers to growth of cell populations, where one cell (the "mother cell") grows and divides to produce two "daughter cells".

Cell growth is part of the Cell cycle, which is a regulated sequence of events that control cell growth and cell division

Most cells periodically divide into two daughter cells, so a cell has a life cycle extending from

one division to the next. This cell cycle is divided into two main phases, interphase and mitosis

According to their mitotic activity, somatic cell in the adult organism population may be classified as Static (postmitotic cells)/Stable (divide episodically)/Rennewing (divide regularly)

## ✓31. Cell replication; Mitosis (incl. endomitosis) and amitosis

Mitosis is the division of the cell. During this process the parent cell divides and each daughter cell receives a chromosomal set identically to that of the parent cell. Mitosis is divided into four phases:

Prophase: chromosomes are condense and the nuclear envelope is intact

Metaphase: the chromosomes are at a spindle equator and the envelope is absent

Anaphase: chromosomes separate, the envelope is still absent

Telophase chromosomes are at spindle poles and the cell envelope reassembles.

During endomitosis chromosome duplication without cytokinesis – cell with 2 or more nuclei (e.g. some hepatocytes, megakaryocytes)

## 32. Cellular and intercellular movements

A schematic of the three stages of cell movement,  
based on:

1. After determining its direction of motion, the cell extends a protusion in this direction by actin polymerization at the leading edge.
2. It then adheres its leading edge to the surface on

which it is moving and deadheres at the cell body and rear.

3. Finally, it pulls the whole cell body forward by contractile forces generated at the cell body and rear of the cell.

To migrate, the cell body must modify its shape and stiffness to interact with the surrounding tissue structures.

The extracellular matrix (ECM) provides the substrate, as well as a barrier towards the advancing cell body.

Cell migration through tissues results from a continuous cycle of interdependent steps.

### **33. Excitability and cell reactivity**

Excitable cells are those that can be stimulated to create a tiny electric current.

Muscle fibers and nerve cells (neurons) are excitable

The electric current

in neurons is used to rapidly transmit signals through the animal  
in muscles is used to initiate contraction

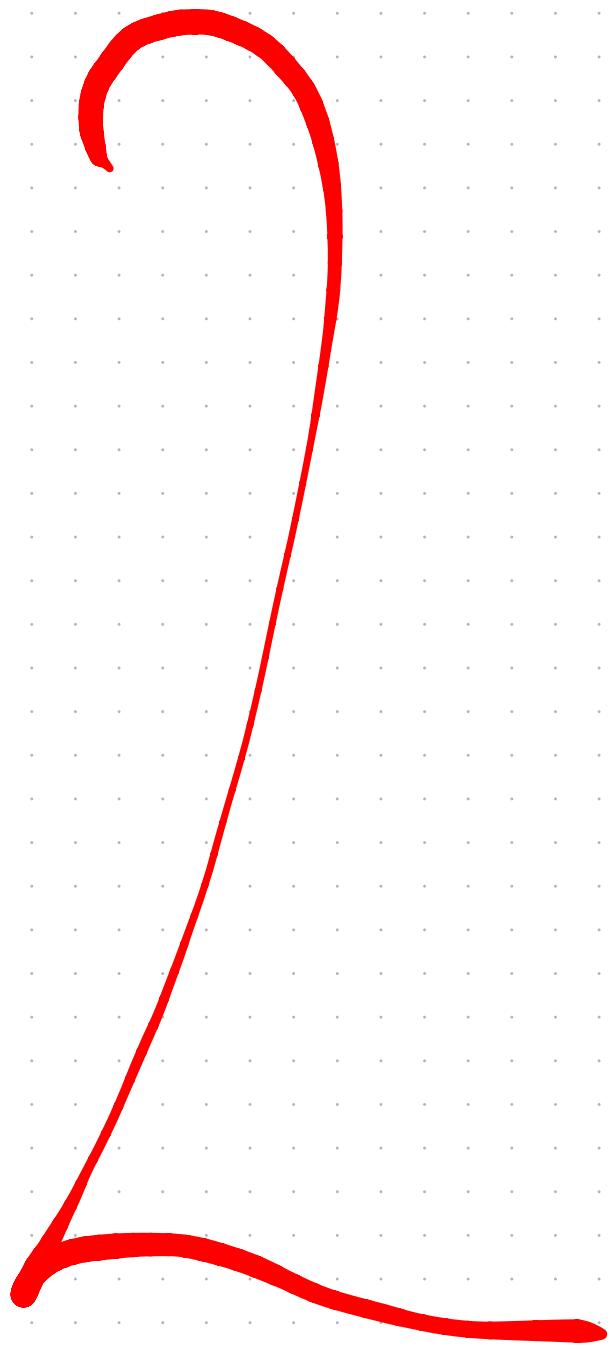
All cells (not just excitable cells) have a resting potential: an electrical charge across the plasma membrane, with the interior of the cell negative with respect to the exterior. The size of the resting potential varies, but in excitable cells runs about - 70 millivolts (mv)

### **✓34. Cell aging and death; apoptosis**

There are 3 major types of cell death:

- Necrosis - a series of changes that accompany cell death, largely resulting from the degradative action of enzymes on lethally injured cells. Necrotic cells are unable to maintain membrane integrity, and their contents often leak out.
- Apoptosis - a pathway of cell death that is induced by a tightly regulated suicide program in which cells destined to die activate enzymes capable of degrading the cells' own nuclear DNA and nuclear and cytoplasmic proteins
- Autophagy - lysosomal digestion of the cell's components as a survival mechanism in times of nutrient deprivation, such that the starved cell lives by eating its own contents.

## **II. General Histology**



# General Histology

## ✓ 35. Tissues – definition, classification, origin and general properties

One tissue consists of similar cells, which perform common or related functions. Cells and molecules of the extracellular matrix form a tissue. The human body is composed of 4 basic types of tissue:

- Epithelial (is composed of closely aggregated polyhedral cells with very little extracellular substance),
- Connective (is characterized by the abundance of extracellular material produced in its cells),
- Muscular (is composed of elongated cells specialized for contraction and movements)
- Nervous (is composed of cells with elongated processes extending from the cell body that have specialized of receiving, generating and transmitting nerve impulses).

Organs can be divided into:

- Parenchyma: is composed of the cells responsible for the main functions typical of the organ
- Stroma: supports the tissue. Except the brain and the spinal cord the stroma is made of connective tissue.

## ✓ 36. Epithelial tissue – definition, classification, origin, characteristics and function

Epithelial tissue is composed of closely aggregated polyhedral cells with very little extracellular substance. These cells have strong adhesion and form cellular sheets that cover the body and line its cavities. The main functions of epithelia tissue are:

- Covering, lining, and protecting
- Absorption
- Secretion
- Contractility
- Sensory

Epithelial tissue is present in 2 forms:

- Covering epithelium - as sheets of contiguous cells that cover the body on its external surface and line the body on its internal surface
- Glandular epithelium - glands, which originate from invaginated epithelial cells

Origin of epithelium - from all three embryonic germ layers

- Ectoderm gives rise to the oral and nasal mucosae, cornea, epidermis of the skin, and glands of the skin and the mammary glands.
- Endoderm gives rise to the liver, the pancreas, and the lining of the respiratory and gastrointestinal tract
- Mesoderm gives rise to the uriniferous tubules of the kidney, the lining of the male and female reproductive systems, the endothelial lining of the circulatory system, and the mesothelium of the body cavities

Common characteristic features of epithelial cells

- Epithelial cells have polyhedral form
- Epithelial cells show polarity

- Most epithelia rest on connective tissue – it provides support and nutrition to the epithelium (epithelium is avascular!) as well as binds it to underlying structures
- Epithelial cells have basal lamina at the interface with connective tissue

### ✓37. Covering epithelia – definition, classification, distribution and histophysiology

Covering epithelia - the cells are organized in Covering (lining), they are organized in layers that cover the external surface or line the cavities of the body.

The number of cell layers and the morphologic features of the cells in the surface layer classify them.

- Simple epithelia – one layer. Based on the shape they are:
  - Squamous – thin cells
  - Cuboidal – roughly as thin as they are wide
  - Columnar – taller than they are wide
- Stratified epithelia – more than one layer. Classified according to the Superficial layer:
  - Squamous
  - Cuboidal
  - Columnar
  - Transitional

Stratified squamous cells can be keratinized or nonkeratinized. The most keratinized cells are found in the epidermis of the skin. It protects against water loss across the epithelium. Nonkeratinized cells line wet cavities.

### 38. Exocrine glandular epithelium – definition, classification, distribution and histophysiology *and*

Glandular are formed by cells specialized to secrete. The molecules to be secreted are generally stored in the cells in small membrane-bound vesicles called secretory granules.

The epithelia that form glands can be classified according to various criteria. Unicellular glands consist of large isolated secretory cells and multicellular glands have clusters of cells. Glands develop during fetal life from covering epithelia by means of cell proliferation and invasion of the connective tissue under it.

Exocrine glands retain their connection with the surface epithelium, the connection taking the form of tubular ducts lined with epithelial cells through which the secretion pass to the surface. The ducts of the exocrine glands have different morphology and that allows the gland to be classified.

- Simple (unbranched) or compound (two or more branches)
- Tubular (either short or long coiled) or acinar (round or globular)
- Either type of secretory portion may be branched
- Compound glands can have tubular, acinar, or tubuloacinar secretory portion

Exocrine glands are also classified by their function:

Merocrine secretion: involves typical exocytosis of proteins or glycoproteins.

Holocrine secretion: involves the cell filling with secretory product and then the whole cell being disrupted and shed.

## Myoepithelial cells

Aporine secretion: the secretory product is typically a large lipid droplet and is discharged together with some of the apical cytoplasm and plasmalemma.

### 39. Endocrine glandular epithelium – definition, organization forms, distribution and histophysiology *no answer*

Glandular are formed by cells specialized to secrete. The molecules to be secreted are generally stored in the cells in small membrane-bound vesicles called secretory granules.

The epithelia that form glands can be classified according to various criteria. Unicellular glands consist of large isolated secretory cells and multicellular glands have clusters of cells. Glands develop during fetal life from covering epithelia by means of cell proliferation and invasion of the connective tissue under it.

Endocrine glands lost their connections to the surface from which they originated during development. These glands are therefore ductless and their secretions are picked up and transported to their sites of action by bloodstream.

Endocrine glands are the producer of hormones. Hormones are released into the blood for circulation and bind specific receptors on target cells. Hormones can be secreted by one single cell that is sparsely distributed. Some endocrine cells release more than one hormone.

### ✓40. Connective tissue – definition, organization form, distribution and histophysiology *Support function*

The different types of connective tissue help to maintain the shape of the organs. They connect and bind other tissues and cells together and give metabolic support. Structurally 3 classes of components form connective tissue: cells, fibers and ground substance. The major constituent of connective tissue is extracellular matrix, which consists of protein fibers and ground substance.

In addition to its major structural role, molecules of connective tissue serve an important biological function, such as forming a reservoir of factors controlling cell growth and differentiation. The hydrated nature of much connective tissue provides the medium through which nutrients and metabolic waste are exchanged between the cells and their blood supply.

The connective tissue originates from the mesenchyme, an embryonic tissue formed by elongated undifferentiated cells, the mesenchymal cells. Mesenchymes develop mainly from the mesoderm.

### ✓41. Connective tissue cells *Mesenchyme < mostly mesoderm some ectoderm*

A variety of cells with different origin and function are present in connective tissue.

✓Fibroblast – are originated in the mesenchymal cells and spend all their life in connective tissue. They are the most common cells in the connective tissue and are responsible for the synthesis of extracellular matrix components. They have two stages active and quiescent (inactive). Active fibroblast has an abundant (rich) and irregularly branched cytoplasm. The quiescent fibroblast is smaller than the active and is usually spindle shaped.

✓Mast cell – originate from the hematopoietic stem cells in bone marrow, circulate in the blood and move into the connective tissue where they remain and execute their functions. Mast cells are large and round connective cells, whose cytoplasm is filled with basophilic secretory granules. The small spherical nucleus is centrally situated.

✓ Macrophages - originate from the hematopoietic stem cells in bone marrow, circulate in the blood and move into the connective tissue where they remain and execute their functions.

✓ Plasma cells - originate from the hematopoietic stem cells in bone marrow, circulate in the blood and move into the connective tissue where they remain and execute their functions. Plasma cells are large and ovoid cells that have a basophilic cytoplasm due to their richness in RER. The average lifespan is short, 10-20 days.

✓ Leucocytes - White blood cells are transient cells of most connective tissue. They also originate in bone marrow and move to the connective tissue where they reside for a few days, then usually die by apoptosis. Leukocytes migrate from blood vessels to the connective tissue by diapedesis. They are the wandering cells of the connective tissue. The migration increase during inflammations. Leukocytes do not return to the blood after arriving in connective tissues.

✓ Adipocytes  
@ specialized form of CT: adipose tissue

## 42. Connective tissue extracellular matrix

The extracellular matrix is composed of protein fibers and ground substance.

There are three types of protein fibers:

- Collagen - Collagen is the most abundant protein in the human body, representing 30% of its dry weight. The collagens are produced by several cell types and are distinguished by their molecular compositions, morphologic characters, distribution, functions and pathologies. More than 20 types of collagen are distinguished and classified in 4 categories: collagens that form long fibrils (forming structures such as tendons, organs, capsules and dermis), fibril-associated collagens, collagens that form anchoring fibrils and collagens that form networks.

Reticular - Reticular fibers consist mainly of collagen type III. They constitute a network around the parenchymal cells of various organs.

Elastic - Are thinner than the average collagen fibers and form a network with collagen bundles in many organs subject to much bending and stretching. Elastin fibers are composed of elastin and fibrillin and other glycoproteins.

Ground Substance:

The ground substance is highly hydrated, transparent, complex mixture of macromolecules, principally in three classes:

Glycosaminoglycans (GAGs) = polysaccharides! Unbranched, highly extended conformations of polysaccharide chains composed of repeating disaccharide units. GAGs are highly negatively charged, the most anionic molecules (sulfate and carboxyl groups) produced by animal cells.

Proteoglycans - It consists of a protein core molecule bound with many different types of GAGs. For example, a PG from cartilage matrix can have 30 keratan sulfate and 100 chondroitin sulfate GAG chains.

Multiadhesive glycoproteins -

## ✓ 43. Connective tissue with nondifferentiated extracellular matrix -

## *Connective tissue with mesenchyme, mucous connective tissue.*

Mucous connective tissue is found mainly in the umbilical cord, fetal tissue and pulp cavity of young teeth. It is composed of hyaluronic acid what makes it jellylike and contains very though collagen fibers.

Mesenchyme is the embryonic tissue, form be undifferentiated, elongated cells. It consists largely of a simple ground substance, hyaluronic acid. There is almost no collagen in mesenchyme.

### ✓ 44. Connective tissue with differentiated fibrous extracellular matrix – loose connective tissue

Loos connective tissue supports many structures which are under pressure (epithelial tissue) it forms a layer around small blood and lymphatic vessels, it ~~feels~~ the spaces between muscles and nerve fibers, it is found in the papillary layer of the dermis, in the hypodermis and in the linings of the peritoneal and pleural cavity.

It has all components of connective tissue in equal parts. Cells are mostly fibroblast and macrophages but other types of cells are also present. Fibers are collagen, elastic and reticular. It is flexible and well vascularized and not very resistant to stress.

### 45. Connective tissue with differentiated dense fibrous extracellular matrix – collagenous, elastic, reticular and adipose tissue

Dense connective tissue is composed of fibroblast and macrophages but other types of cells are also present. There are few cells and a lot of collagen fibers. It is stress resistant and not very flexible. There are two types of dense connective tissue irregular and regular.

The collagen fibers in the irregular tissue form a 3D- network, providing stress resistance from all direction. It is located at the near loose connective tissue and they grade into one another.

The collagen fibers in the regular tissue are arranged in a definite pattern, that offers great resistance of traction forces. Tendons and Ligaments are examples. Long parallel bundles of collagen fibers fill the spaces between fibrocytes, containing elongating nuclei. There is very small quantity of ground substance.

Some ligaments contain parallel elastic fibers like the yellow ligament of the vertebral column.

Reticular tissues form a 3D network and are type III collagen fibers, produced by reticular cells. They form a framework for bone marrow, lymph node and spleen. Along this the reticular cells are dispersed. It is s sponge like structure though which cells and fluid are moving.

A specialized type of connective tissue in which adipocytes ~~are specialized type of CT in which~~ ~~adipocytes~~ predominate. Adipocytes are combined with loose or irregular ~~Adipocytes are combined with loose or irregular~~ connective tissue, often in large aggregates. There are white (most common type) and brown (in adults only around the kidney and adrenal glands, aorta and mediastinum) adipose tissue. The white adipose tissue is composed of cells that contain one large droplet of fat in their cytoplasm. The brown adipose tissue cells have multiple lipid droplets between many mitochondria.

### 46. Connective tissue with rigid extracellular matrix – cartilaginous tissue; Chondrogenesis

## Cartilaginous tissue

An extracellular matrix enriched with glycosaminoglycans and proteoglycans, macromolecules that interact with collagen and elastic fibers, characterizes cartilage. Cartilage consists of cells called chondrocytes and an extensive extracellular matrix composed of fibers and ground substance. There are three forms of cartilage, each exhibiting variation in matrix components:

- In hyaline cartilage type II collagen is the principal collagen type. It is the most common cartilage and forms the skeleton in the embryo. In the adult the hyaline cartilage is located in the articular surface of the movable joints, in the walls of the large respiratory passage, in the ventral ends of the ribs and epiphyseal plate.
- Elastic cartilage possesses, in addition to type II collagen, elastic fibers within the matrix. Elastic cartilage is frequently found to be gradually continuous with hyaline cartilage. It is found in the auricle of the ear, the walls of the external auditory canals, the auditory tubes the epiglottis and the cuneiform cartilage in the larynx.
- Fibrocartilage is characterised by a matrix containing a dense network of coarse type I collagen fibers. It is found in the intervertebral disk, in attachments of the certain ligaments and in the pubic symphysis.

## ✓ 47. Connective tissue with rigid extracellular matrix – osseous tissue; Osteogenesis

✓ There are two types of bone tissue:

Primary bone tissue is the first bone tissue to appear in embryonic development and in fracture repair. It is characterized by random disposition of fine collagen fibers. Primary bone tissue is normally temporally replaced in adults with secondary bone tissue. Just in very few places in the body, for example near the suture of the calvaria, in tooth sockets. In addition to the irregular array of collagen fibers, other characteristics of primary bone tissue are low mineral content and a high proportion of osteocytes.

Secondary bone tissue is found in adults. It characteristically shows multiple layers of calcified matrix and is often referred to as lamellar bone. Composed of osteon, a complex of concentric lamellae of bone surrounding a canal containing blood vessels, nerves and loose connective tissue

✓ Osteogenesis is the formation of bones. There are 2 types of osteogenesis, intramembranous ossification and endochondral ossification.

Intramembranous ossification, in which osteoblasts differentiate directly from the mesenchyme and begin secreting osteoid.

Endochondral ossification, in which the matrix of preexisting hyaline cartilage is eroded and replaced by osteoblasts producing osteoid.

## ✓ 48. Blood; Lymph

✓ Blood is specialized connective tissue in which cells are suspended in fluid extracellular matrix called plasma. A human adult has about 5 liters of blood, which gets pumped though the body by closed circulation system. The cells in the blood are called erythrocytes, leucocytes and platelets. If blood is removed from the circulatory system, it will clot. This clot contains formed elements and a clear yellow liquid called serum, which separates from the coagulum. It can be separated by centrifugation that reflects the heterogeneity of blood. Erythrocytes make up 45% of the blood

volume; it is looked at the bottom and is called hematocrit. Blood transports oxygen and other substances to the cells and  $\text{CO}_2$  to the lungs.

Blood flows in arteries and veins. Arteries have muscles, which pumped the blood through the body away from the heart. Veins have valves to stop the blood to run back. They lead to the heart. Capillaries are very thin vessels with permeable membranes, which let small molecules through.

Lymph fluid is collected from tissue spaces and returns to the heart. It flows only in one direction. Lymphatic capillaries are thin vessels consisting of a single layer of endothelium and an incomplete basal lamina. They converge in larger vessel, which have a similar structure like veins. They also have internal valves. Lymphatic vessels end in thoracic duct and right lymphatic duct.

## ✓ 49. Hemopoiesis – embryonic, fetal and postnatal

### ✓ Prenatal hemopoiesis

- Mesoblastic phase (2 wk after conception) – blood islands in the mesoderm of the yolk sac; only RBC
- Hepatic phase ( $6^{\text{th}}$  week of gestation) – leukocytes appear by the  $8^{\text{th}}$  week
- Splenic phase ( $2^{\text{nd}}$  trimester)
- Myeloid phase (end of  $2^{\text{nd}}$  trimester) – bone marrow

It is believed that a pluripotent stem cell can produce all blood cells. It is inside the bone marrow.

### ✓ Postnatal hemopoiesis

It occurs almost exclusively in bone marrow, but the liver and the spleen can revert to forming new blood cells if the need arises. From the pluripotent stem cells arise the progenitor cells, which produce precursor cells or blasts.

## ✓ 50. Erythrocytes

Erythrocytes or red blood cells don't have a nucleus and transport the oxygen through the body. They are biconcave disks and the normal concentration is  $4 - 6 \text{ mil/l}$  in an adult body. They are very flexible to move through the capillaries. They survive 120 days in the circulation.

## ✓ 51. Erythropoiesis

Erythropoiesis is the development of the erythrocytes. It starts with a Proerythroblast, a large cell with nucleus, nucleoli and basophilic cytoplasm. The next stage is the basophilic erythroblast, a slightly smaller cell with very basophilic cytoplasm. After that comes the polychromatophilic erythroblast. They are smaller and have basophilic and acidophilic areas. The next stage is the orthochromatophilic erythroblast; it is smaller and has a cytoplasm almost like an erythrocyte. Then the cell ejects its nucleus and forms reticulocyte and the erythrocyte.

## ✓ 52. Granulocytes

Belong to the white blood cells, which are  $6000 - 10\,000/\text{l}$  in the blood, have specific granules and polymorphic nuclei. There are three kinds of granulocytes: neutrophils, eosinophils and basophils.

Neutrophils granulocytes are 60-70% of leucocytes. They kill ingested bacteria with their azurophilic granules. They are usually the first leucocytes to arrive at a infection. They live only 1-4 days before dying by apoptosis.

Eosinophils are 1-4% of leucocytes. They have a bilobed nucleus and eosinophilic granules, which have cytotoxic effect on parasites and they also phagocytose antigen-antibody complexes, which is important in allergies and asthma.

Basophils are 1% in the leucocytes. Their nucleus has tow or more loops but it is not visible because of the many azurophilic granules.

### ✓ 53. Granulopoiesis

Granulopoiesis is the development of the granulocytes. The first stage is the myeloblast. The next stage is the promyelocyte, with a basophilic cytoplasm and azurophilic granules. Then specific granules are built to form neutrophilic, eosinophilic and basophilic myelocyte. The granules grow in metamyelocyte stage. In the last stage the nucleus is polymorphic.

### ✓ 54. Monocytes; Monocytopoiesis

The nuclei of monocytes have a large oval, kidney or U-shaped nucleus. The chromatin stains lighter than the Lymphocytes. The cytoplasm is basophilic. They are precursor cells of the mononuclear phagocyte system. Monocytes go through the walls of veins and differentiate to macrophages in connective tissue, microglia in the CNS and osteoclasts in the bone.

Monocytopoiesis is the development of the monocytes. It starts with the monoblast turns to the promonocyte and then monocytes.

### ✓ 55. Lymphocytes

Lymphocytes have a spherical nucleus. They can be divided into three function groups according to the surface molecules: T lymphocytes, B lymphocytes and natural killer cells. They defend against microorganism, antigens and cancer cells. Some antigens activate some lymphocytes, what makes them big. Their cytoplasm is slightly basophilic. They can life for few days or many years depending on the functions and the can return from the tissue back to the blood.

### 56. Lymphocytogenesis

Lymphocytogenesis is the development of the lymphocytes. The lymphocytes originate in the thymus and the lymphoid organs (spleen, lymph nodes, tonsils). The progenitor cells start in the bone marrow. Some of this lymphocytes migrate to the thymus, there they become T lymphocytes. Other lymphocytes differentiate into B lymphocytes in the bone marrow and then migrate to peripheral lymph organs. The development starts with the lymphoblast, the prolymphocytes, which turns to lymphocytes in bone marrow or thymus.

### 57. Platelets (formation)

Platelets or thrombocytes are nonnucleated cell fragments. They promote blood clotting and help

repair leaks in the wall of blood vessels. Platelets are 200 000 – 400 000/ l and they live about 10 days.

The origin of platelets starts with the megakaryoblast → promegakaryocytes → megakaryocytes → they are giant cells, which form several long processes called proplatelets → they pinched off from platelets.

## 58. Muscle tissue – definition, classification, origin, characteristics and function

Muscle tissue is formed of special type of cells, which are specialized for contraction that permits animals to move. Organisms use the contraction of muscle cells and the arrangement of the extracellular components of muscle to permit locomotion, constriction, pumping, and other propulsive movements. There are smooth muscles and cross-striated muscle, named skeleton muscle and cardiac muscle. Smooth and cardiac muscle are involuntary and skeleton muscles are voluntary.

The functions of the muscle tissue are:

- Movements
- Maintenance of posture
- Joint stabilization
- Heat generation

Special functions:

- Excitability
- Conductivity
- Contraction
- Elasticity
- Extensibility

The cytoplasm is called sarcoplasm, the ER is called sarcoplasmic and the plasmalemma is called sarcolemma.

Muscle fibers are long cylindrical multi nucleated cells, they result of fusion of myoblasts. In skeleton muscle are under the cell membrane, cardiac and smooth muscle have central located nuclei.

## 59. Skeletal muscle tissue

Skeletal muscle tissue is attached to the skeleton and moves the body. The whole muscle is surrounded by epimysium, a dense connective tissue. The fascicles are surrounded by perimysium and the muscle fiber is surrounded by endomysium.

Muscle fibers are separated in longitudinal section, dark and light. The dark bands are called A (anisotropic) bands and the light bands are called I (isotropic) bands. The I band is bisected by a dark transverse line, the Z line. Between two Z lines is one sarcomere, the functional subunit of the contractile apparatus. The sarcoplasm is filled primarily with cylindrically filamentous bundles, called myofibrils. This exhibits the characteristic pattern of transverse striations.

The A and I banding pattern in sarcomeres is due to the regular arrangement of 3 types of filaments – thick (myosin) and thin (actin) and elastic (titin).

The thick filament occupy the A band in the center of the sarcomere. The thin filaments run between and parallel to the thick filament and are attached to the Z line. The elastin is also

attached to the Z line and resists overstraining. The I band consists of thin filaments that do not overlap the thick filaments. In the center of the A band is the H zone, a zone consisting only of rod-like portions of the myosin molecules.

In the middle of the H zone is the M line where the connections are made between the thick filaments. Major proteins in the M line region are myomesin, a myosin-binding protein which holds the thick filaments together and in place, and creatine kinase, which catalyzes the transfer of phosphate groups from phosphocreatine to adenosine diphosphate ADP, thus helping to supply adenosine triphosphate ATP for muscle contraction.

The SER is specialized to excrete  $\text{Ca}^{2+}$  ion. The depolarization of the sarcoplasmic reticulum membrane, which results in the release of  $\text{Ca}^{2+}$  ions, is initiated at a specialized myoneural junction on the surface of the muscle cell. A release of  $\text{Ca}^{2+}$  ions through the cell would result in wave contractions with the peripheral myofibrils contracting before those more centrally positioned. To provide for a uniform contraction, skeletal muscle possesses a system of transverse (T) tubules → finger like invaginations of the sarcolemma forming a complex anastomosing network of tubules that encircles the boundaries of each sarcomere in every myofibril near the A and I band boundaries of each sarcomere.

## 60. Cardiac muscle tissue

Cardiac muscle is involuntary striated muscle limited to the heart and the proximal portions of the pulmonary veins.

During embryonic development, the mesoderm cells of the primitive heart tube turns into chainlike arrays. Cardiac muscle cells form complex junctions between extended processes. Cells within the fiber often branch and bind to cells in closed-by fibers.

Mature cardiac cells exhibit a crossstraited banding pattern like the skeleton muscle. They have 1-2 nuclei centrally located. Surrounding the muscle cells is a delicate sheath of endomysium containing a rich capillary network. A unique characteristic of cardiac muscle is the presence of dark-staining transverse lines that cross the chains of cardiac cells at irregular intervals → intercalated discs. They are the connection between the cells. They are connected with desmosomes and fascia adherents. On the more longitudinal parts of the intercalated discs are multiple gap junctions to provide ionic continuity. These act as electrical synapses and allow cells of cardiac muscle to act as in a multinucleated syncytium, with contraction signals passing in a wave from cell to cell.

The wall of the heart consists of 3 layers. The very outer layer is called the mesothelium, in the middle comes the epicardium (dense connective tissue) and in the center the endocardium. Between the mesothelium and the epicardium is the potential space and between the epicardium and the endocardium the myocardium.

## 61. Smooth muscle tissue

Smooth muscle is composed of myocytes (fibers) with a fusiform shape, which lack visible striations (i.e. smooth). Smooth muscles are involuntary and are placed in the walls of vessels, respiratory tubes, digestive tubes, urinary organs, reproductive organs, larger ducts of compound glands, inside the eye and dermis of skin (small bundles).

Smooth muscle cells contain one centrally located nucleus. Near the nucleus are mitochondria,

polyribosomes, cisternae of rough ER and the Golgi apparatus. Cells in the uterus grow in size and number during pregnancy. A sheath of endomysium surrounds smooth muscle cells. The characteristic contractile activity is related to the structure and organization of its actin and myosin filament. In smooth muscle cells, bundles of thin and thick myofilaments crisscross obliquely through the cell, forming a latticelike network. The contractions are slow and don't always use a nervous signal. They can be stimulated by hormones or stretching.

## 62. Nerve tissue – definition, classification, origin, characteristics and functions; nerve tissue cells.

The human nervous system is the most complex system in the human body histologically and physiologically and is formed by many billions nerve cells (neurones) and glial cells (glue cells). One neuron has hundreds of interconnections with other neurons, forming a very complex system. There are 2 types of nerve systems:

- Central nerve system (CNS) → brain and spinal cord
- Peripheral nervous system (PNS) → cranial nerves, spinal nerves and peripheral nerves.

The nervous tissue develops from the ectoderm, in the third week in the human embryo. The notochord gives signals, to form the neural plate out of the ectoderm. The neural plate folds to the neural groove and then to the neural tube. Neural crest gets formed out of the neural crest cells above the neural tube. They migrate laterally and form the peripheral nerves.

Nerve tissue is irritable and reacts promptly to stimuli. Nerve impulses travel long distances and transmit signals to other neurons muscles and glands.

There are neurones and glial cells.

Neurones consists of three parts the cell body, dendrites and the axons.

Glial cells originate from the neural tube in the CNS and neural crest in the PNS. Their functions myelin production and electric insulation, structural support, repair processes, blood-brain barrier and metabolic exchanges and lining cavities of CNS. Microglia arise from the bone marrow and have immune-related activity.

## 63. Neurons – classification, structure, distribution and function

Neurones are the structural and functional unit of the nervous system functional unit of the nervous system and are in the CNS and PNS. There are 3 kinds of neurones classified according to the number of process extending from the cell body:

- Multipolar
- Bipolar
- Unipolar or pseudounipolar

There are 3 kinds of neurones classified according to their function.

- Motor neurons are efferent and control muscles and glands
- Sensory neurons are afferent and carry the message to the brain
- Interneurons forming complex functional networks or circuits.

They have three parts: cell body, dendrites and axons:

- The cell body or perikaryon contains the spherical, large nucleus and surrounding cytoplasm that is abundant in rough ER, which is seen as Nissl bodies under light microscopy. Nissl bodies (stacks of RER), free ribosomes, and Golgi complex extend into

the dendrites but not into the axon, the organelle-free area at the junction between perikaryon & axon is the axon hillock.

- Dendrites are receptor processes that receive stimuli from other neurons or from the external environment. Dendrites are often multibranched (Gr. dendron, tree) → up to 200,000 axonal terminations establish functional contact with the dendrites of a Purkinje cell of the cerebellum. They are arborized so that they can receive multiple stimuli from many other neurons simultaneously. The nerve impulses received by the dendrites are then transmitted toward the soma
- Axon is a single process specialized in generating or conducting nerve impulses to other cells. Most neurons have only one axon (Gk. axis); a very few have no axon at all. Axons are usually very long processes → up to 100 cm in length (e.g. motoneuron axons). Has no RER but preserves some SER → the absence of ribosomes & RER emphasizes the dependence of the axon on the perikaryon for its maintenance. Mitochondria are especially abundant in the axon terminals. Abundant in axons (also in soma) are neurofilaments → intermediate filaments. Axonal transport is possible in both directions → anterograde and retrograde transport.

## ✓ 64. Synapse; interneuronal synapse

Synapses are specialized junction between neurons, which facilitate transmission of information. Synapses also occur between neurons and target organs (muscles, glands, etc.). A synapse has the following structure:

- Presynaptic axon terminal (terminal bouton) from which neurotransmitter is released
- Postsynaptic cell membrane with the receptors of the transmitter and the ion channels.
- Synaptic cleft (intercellular space)

There are two types of synapses:

- Chemical are more common and use chemical neuron transmitters.
- Electrical send an ionic signal through the gap junctions between the pre- and postsynaptic membranes.

Morphologically various types of synapses:

- Axosomatic
- Axodendritic
- Axonaxonic

## ✓ 65. Neurosecretory cells; paraneurones

Neurosecretory cells or paraneurones develop from the neural crest they produce neurotransmitter like substances. They have synaptic vesicle like granules and produce hormones.

## 66. Neuroglia – types, structures, distribution and functions

Numerous cells which surround both cell bodies and processes of neurons and occupy the interneuronal spaces; function in the physical and metabolic support of neurons. There are six

kinds of glial cells:

- Oligodendrocytes produce myelin sheath for the electrical insulation of neurons in the CNS. They have condensed rounded nuclei and unstained cytoplasm. Are mostly in the gray and white matter.
- Astrocytes have many radiating processes and are only in the CNS. They have supportive role for neurones. And are mostly in the gray matter.
- Ependymal cells line the ventricle of the brain and the central canal of the spinal cord. They have cilia to move the cerebrospinal fluid.
- Microglia are developed in the bone marrow. They are important for immune defense.
- Schwann cells or neurolemmocytes are only in the PNS and form myelin around a segment of one axon.
- Satellite cells of ganglia form a layer over the cell bodies of the PNS ganglia.

### ✓ 67. Nerve fibers

Nerves are bundles of nerve fibers surrounded by connective tissue sheaths. → epineurium, perineurium and endoneurium. Nerve fibers = axons + myelin sheaths! There are unmyelinated nerve fibers and myelinated nerve fibers.

- In the CNS there are many unmyelinated fibers but in the PNS all unmyelinated fibers are enveloped within simple folded Schwann cells.
- The Schwann cells wrap the myelinated fibers many times. The multiple layers of Schwann cells are called myelin. Between closed-by Schwann cells the myelin sheaths shows small gaps called nodes of Ranvier.

### ✓ 68. Receptor nerve ending

The skin is the most extensive sensory receptor. Types of receptors:

- Free nerve endings - epidermis, hair follicles, and cutaneous glands encapsulated and expanded receptors - dermis and subcutaneous tissue. They are mainly thermo and nociceptors.
- Encapsulated corpuscles are not necessary for cutaneous sensation - they act as mechanoreceptors.

### ✓ 69. Effector nerve ending

function?

Effector nerve endings are between neurons and other effector cells, for example motor end plate or neuromuscular junction.

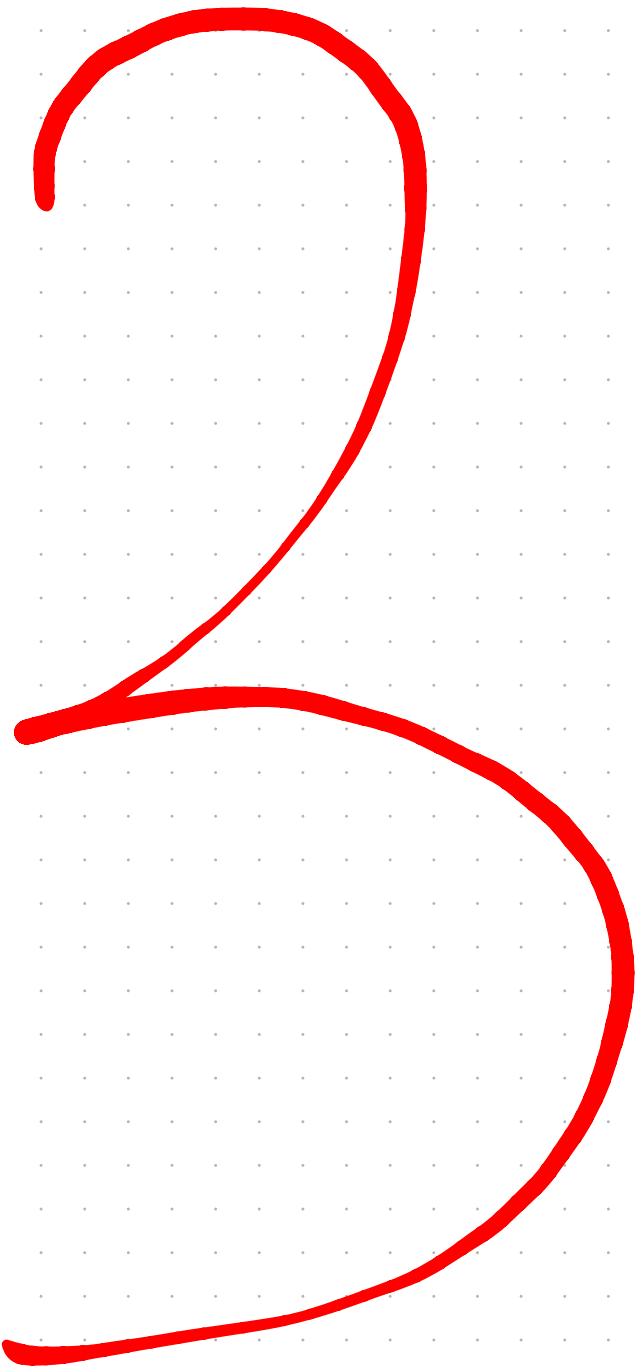
## III. General Embryology

### 70. Subject, aim, tasks, methods and relations of embryology to other medical sciences

General Embryology

2 divisions

Special Embryology



# Embryology

## 70. Subject, aim, tasks, methods + relations ..

Embryology is the sequence of events the organism from fertilization to in the birth. It can be divided into general and special embryology.

more

### **71. Meiosis and gametogenesis; deviation of normal course of meiosis**

Meiosis is a special form of nuclear division involved in sexual reproduction. The genome of 2 parents mix to generate offspring that is genetically distinct from either parent. Sexual reproduction occurs in diploid organisms (each cell contains 2 sets of chromosomes, one inherited from each parent). The specialized cells that carry out sexual reproduction, however, are haploid (1 set of chromosomes). In the final step of sexual reproduction, a haploid cell of one individual fuses with a haploid cell of another, mixing the two genomes and restoring the diploid state.

Each individual gamete contains either the maternal or paternal version of each chromosome → the choice of maternal or paternal occurs independently and randomly for each pair of homologous chromosomes.

### **72. Differences between male and female meiosis**

#### Male:

- Begins at puberty
- Goes on continuously, without stop and start mechanisms
- It takes about 24 days for a human spermatocyte to complete meiosis
- Very low error rates – 3-4% → if meiosis goes wrong, a quality control system is activated, which arrests meiosis and leads to apoptosis
- By the end of meiosis, a sperm has only just begun its differentiation

#### Female:

- Begins during embryonic life (1<sup>st</sup> month)
- Stop and start mechanisms - arrested after diplotene of meiosis I → meiosis I is complete after puberty
  - Meiosis I is completed at the time of ovulation
  - Meiosis II is completed only if the released oocyte is fertilized
- It takes nearly 40 years for some human oocytes to complete meiosis
- High error rates – 20% of aneuploidy → most of these result from nondisjunction in oocytes at meiosis I
- If homologous chromosome segregation fails to occur normally, the cells continue through meiosis and produce aneuploid eggs
- By the end of meiosis, a mammalian oocyte is fully mature

### **73. Spermatogenesis**

Spermatogenesis is the process by which spermatozooids (male germ cells) are formed. They are formed in the seminiferous tubules testis. No cell division occurs during this process.

Spermatids can be distinguished by their small size and haploid nucleus with highly condensed chromatin. They are near the lumen of the seminiferous tubules.

Spermatogenesis can be divided into three phases:

- Early Golgi phase: The cytoplasm contains a very prominent Golgi apparatus near the

nucleus, mitochondria, a pair of centrioles, free ribosomes and a tubules of smooth ER. Proacrosomal vesicles are built in the Golgi and form a single membrane-limited acrosomal near one side of the nucleus. Centrioles move to the other end of the cell to the membrane and act as a basal body, to organize an axoneme for the flagellum.

- ✓ Acrosome phase: The acrosome or acrosomal cap spread over the half of the nucleus. The axonemes project towards the lumen of the tube. The nucleus becomes elongated and the chromatin very highly condensed, with small basic peptides called protamines. The flagellum grows and the mitochondria aggregate around the proximal part of the flagellum. This is the region where the ATP is generated for the movements of the flagellum.
- ✓ Maturation phase: The unneeded cytoplasm is shed as a residual body and the mature sperm is released into the lumen.

#### ✓ 4. Spermatozoa – structure and function

Head

- Nucleus – haploid
- Acrosome – enzymes

more

Tail (= flagellum)

- Neck - axoneme + 9 dense fibers
- Middle piece - axoneme + 9 dense fibers
- Principal piece - axoneme + 7 dense fibers + fibrous sheath
- End piece - axoneme + plasmalemma

#### 75. Oogenesis

Oogenesis is the process by which the oocytes are formed.

- 1<sup>st</sup> month of development – oogonia begin to appear
- Active mitotic division
  - 2<sup>nd</sup> month - 600,000 oogonia
  - 5<sup>th</sup> month – 5 million oogonia
- 3<sup>rd</sup> month – oogonia → primary oocytes (enter meiosis I and remain arrested in diplotene)
- Puberty - 300,000 oocytes
- During reproductive life - 450 oocytes are liberated – all others die by atresia (a specific degenerative process)
- It is still a puzzle why so many oocytes are formed only to die in the ovaries

Ovarian follicles:

1 follicle = 1 oocyte + 1 or more layers of follicular cells, or granulosa cells

- Primordial follicles
  - During embryonic life (after 3<sup>rd</sup> month) → until puberty
  - 1 primary oocyte + 1 layer of follicular cells
  - The oocyte is spherical ~25 μm in diameter; large nucleus with a single nucleolus – prophase I

#### 76. Ovulation – structure and function of mature oocyte

## Ovulation

Ovulation normally occurs midway through the menstrual cycle, around the 14<sup>th</sup> day. In the hour before ovulation the mature follicle pushes against the tunica albuginea and develops a whitish, translucent ischemic (lack of blood) area, the stigma.

FSH stimulates follicle growth & estrogen production by granulosa cells. Estrogen stimulates LH (luteinizing hormone) pulse via GnRH from hypothalamus. LH pulse leads to rapid increase in blood flow through the ovary → local edema. Area of the follicle wall becomes weak (collagen degradation of the tunica albuginea, ischemia, and death of some cells).

The development of the corpus luteum results from the LH released before ovulation. Under stimulus by LH, the cells of the corpus luteum begin secreting progesterone and estrogens. Corpus luteum is programmed to exist for 10-12 days. If a pregnancy does not occur, no further hormonal stimulation takes place and the cells of the corpus luteum degenerate by apoptosis.

If pregnancy does not occur, the absence of LH leads to degeneration of the corpus luteum → corpus luteum of menstruation. The cellular remnants of the corpus luteum of menstruation are phagocytosed by macrophages. Fibroblasts invade the area and produce a scar of dense connective tissue – corpus albicans.

In case pregnancy occurs:

Human chorionic gonadotropin (hCG), secreted by the placenta, maintains the corpus luteum for 3 months → corpus luteum of pregnancy. Grows to a diameter of 5 cm and continues to secrete hormones necessary for the maintenance of pregnancy. Placenta becomes the main site of production of the various hormones involved in maintaining pregnancy, but corpus luteum continues to form these hormones for several months.

## 77. Cycle changes of the endometrium during the menstrual cycle.

The menstruation cycle is separated into 3 phases:

- Menstrual phase 1-4 day:
  - Desquamation of the functionalis layer of the endometrium
  - Coiled (helical) arteries are intermittently constricted → reduced oxygen → necrosis ~~venous decrease in oxygen cells die~~
- Proliferative (follicular) phase 4-14 day:
  - Called follicular phase because it occurs at the same time as the development of the ovarian follicles ~~remake epithelial layer~~
  - Reepithelialization of the lining of the endometrium
  - Reconstruction of the glands, connective tissue, and the coiled arteries of the lamina propria ~~regenerates~~
  - Endometrium is 2-3 mm thick
  - Under influence by estrogens
- Secondary (luteal) phase 15-28 day: prepares endometrium if fertilization occurs  
(for implantation)
  - Commences after ovulation
  - Endometrial glands become highly convoluted and branched
  - Endometrial epithelial cells accumulate glycogen
  - Endometrium thickens – up to 5 mm
  - Under influence by progesterone

## Helical arteries @ endometrium

3

- can increase their bending
- more nutrients delivered

## ✓ 8. Semen – formation, ingredients, and characters

- The fluid that is ejaculated at the time of orgasm.
- It contains: spermatozoa + secretions of the seminal vesicles, prostate, and various glands
- Below 40 million/mL – abnormally low; below 20 million/mL – sterile
- Speed - 3 mm/min → sperm cells reach the uterine tubes 30-60 minutes after copulation

Composition:

- Colour is white
- PH 7.35-7.50
- Sperm count: Average about 100 million/mL, with fewer than 20% abnormal forms
- The two testes of the human adult form up to 120 million sperm each day
- Fructose (1.5-6.5 mg/mL)
  - Phosphorylcholine
  - Ergothioneine
  - Ascorbic acid
  - Flavins
  - Prostaglandins
- Spermine
  - Citric acid
  - Cholesterol, phospholipids
  - Fibrinolysin, fibrinogenase
  - Zinc
  - Acid phosphatase

Maturation of sperm in the epididymis:

Sperm require several days to pass through the 6-meter-long tubule of the epididymis. Sperm removed from the seminiferous tubules and from the early portions of the epididymis are nonmotile. However, after the sperm have been in the epididymis for some 18 to 24 hours, they develop the capability ~~of capacity~~ of motility. Some inhibitory proteins in the epididymal fluid still prevent final motility until after ejaculation

## 79. Insemination; sperm migrate in the female reproductive tract; Transport of the secondary oocytes ovulation

Insemination is the deposition of sperm into the vagina. Sperm migrate to the uterus and uterine tubes. The sperm has to overcome some obstacles:

- Vaginal acid
- Mucus in the cervical canal
- Leucocytes in the uterus
- Can go the wrong uterine tube

Sperm mature during the passage through the female genital tract. 300 million human sperm are ejaculated during coitus but only 200 arrive at the oocyte. Capacitation - sperm modify to acquire the capacity to fertilize an egg. That takes place only in the female and takes 5-6h!!!!

Oocytes will degenerate if not fertilized within 24 h. They reach the uterus for 72 h → fertilization in ampulla. Sperm reach the ampulla by their own movements. Oocyte + some granulosa cells are carried into the tube by sweeping movements of the fimbriae and by motion of

cilia on the epithelial lining. Once in the tube, cumulus cells withdraw their cytoplasmic processes from the zona pellucida and lose contact with the oocyte.

## ✓ 80. Fertilization

Fertilization is the process by which male and female gametes fuse. Sperm adheres to the zona pellucida and penetrate the zona pellucida and the acrosome reacts. Adherence of the sperm head to the oolemma → fusion of membranes → release of the sperm nucleus into the cytoplasm of the ovum.

## ✓ 81. I<sup>st</sup> week of human development – cleavage

- Mitotic divisions that occur in the first 3 days
- 1st cleavage - ~30 hours after fertilization
- 4th cleavage - 72 hours after fertilization → morula (Lat., mulberry); at day 4-5 morula is ~ 100 cells

Morula:

- Initially uncompacted (gap junctions) the eight-cell embryos become compacted (tight junctions) → size of individual cells is reduced, while the size of the morula is preserved
- In the uncompacted state, outlines of each blastomere are distinct, whereas after compaction cell-cell contacts are maximized and cellular outlines are indistinct

## ✓ 82. I<sup>st</sup> week of human development – blastocyst

- Blastocyst – a fluid-filled hollow sphere composed of:
  - 1 outer layer (= trophoblast) → will make the placenta
  - Inner cell mass (= embryoblast) → will make the embryo
- Zona pellucida breaks → fluid enters the center of the morula

## ✓ 83. Implantation

- Process in which the conceptus becomes integrated into the endometrium of uterus
- Starts 6-7 days after fertilization (at the stage of blastocyst) → end at 14 days

Steps in implantation:

- Dissolution of the zona pellucida
- Orientation and adhesion of the blastocyst onto the endometrium
- Trophoblastic penetration into the endometrium
- Migration of the blastocyst into the endometrium
- Spread and proliferation of the trophoblast → disruption and invasion of maternal tissues

## 84. II<sup>nd</sup> week of human development – differentiation of the trophoblast

The earliest developmental processes in mammalian embryos involve the production of the extraembryonic structures, which will support and nourish the embryo during development. Production of these layers begins before implantation is complete.

### 2 Trophoblast layers:

- Cytotrophoblast – cells of the inner layer that retain their cell boundaries (plasma membranes)
- Syncytiotrophoblast – cells in the outer layer that lose their plasma membranes and invade the endometrium; merge into a syncytium
- Endometrium reacts to this injury by growing over the trophoblast and eventually enclosing it

### Trophoblastic lacunae:

- Cells of the syncytiotrophoblast penetrate deeper into the stroma and erode the endothelial lining of the maternal capillaries → sinusoids.
- The syncytial lacunae become continuous with the sinusoids and maternal blood enters the lacunar system.

## ✓ 85. II<sup>nd</sup> week of human development – differentiation of the embryoblast

The earliest developmental processes in mammalian embryos involve the production of the extraembryonic structures, which will support and nourish the embryo during development. Production of these layers begins before implantation is complete.

## ✓ 86. II<sup>nd</sup> week of human development – development of the extraembryonic mesoderm

The earliest developmental processes in mammalian embryos involve the production of the extraembryonic structures, which will support and nourish the embryo during development. Production of these layers begins before implantation is complete.

A new population of cells, derived from epiblast, appears between the cytotrophoblast and parietal hypoblast. Large cavities develop in the extraembryonic mesoderm and become confluent with extraembryonic coelom (= chorionic cavity).

- The extraembryonic mesoderm lining the cytotrophoblast and amnion is called extraembryonic somatopleuric mesoderm.
- The extraembryonic mesoderm lining the yolk sac is called extraembryonic splanchnopleuric mesoderm

## ✓ 87. Abnormal blastocysts; Abnormal implantation sites

### Abnormal blastocysts:

- Common – 20-30% of normal pregnancies
- Major types
  - Trophoblast hypo/a-plasia
  - Embryoblast hypo/a-plasia
- Hydatidiform mole – trophoblast develops (secretes hCG), embryoblast does not develop
  - May produce benign or malignant (invasive mole, choriocarcinoma) tumors

- Arise from fertilization of an oocyte lacking a nucleus followed by duplication of the male chromosomes to restore the diploid number → trophoblast is regulated mainly by paternal genes

Abnormal implantation:

- Tubal pregnancy - 95% of ectopic pregnancies occur in the uterine tube, and most of these are in the ampulla

## 88. Assisted reproductive technology

Assisted reproduction technology is a process by which eggs are fertilized by sperm outside the female reproductive tract. 10% of human couples have reduced fertility → the female partner fails to become pregnant after 12–18 months of unprotected sex. Over 1 million babies have been born via IVF. Today, every day 1 IVF baby is born

Steps in IVF:

- Evaluation and preparation of the infertile couple
- Ovarian stimulation - GnRH agonist and FSH
- Oocyte retrieval → in vitro maturation
- Assisted fertilization – ICSI
- Embryo development and assessment of viability
- Embryo transfer (ET) – the final step in IVF → transcervical route
- Monitoring IVF outcome

Disadvantages:

- IVF costs up to \$10,000 per attempt and succeeds only 14% of the time
- Multiple preembryos are usually introduced to the uterus (insurance against the low probability of implantation) → multiple births - occur in over 30% of cases, compared with about 2% in unassisted pregnancies

## ✓ 89. III<sup>rd</sup> week of human development – gastrulation (formation of embryonic mesoderm and endoderm)

This process of epiblast ingress through the primitive streak forms the primary germ layers; namely the definitive endoderm and mesoderm. Following gastrulation the epiblast is called the ectoderm.

## ✓ 90. III<sup>rd</sup> week of human development – formation of the notochord

The nervous tissue develops from the ectoderm, in the third week in the human embryo. The notochord gives signals, to form the neural plate out of the ectoderm. The neural plate folds to the neural groove and then to the neural tube. Neural crest gets formed out of the neural crest cells above the neural tube. They migrate laterally and form the peripheral nerves

## ✓ 91. Growth of the embryonic disc

- Initially flat and almost round, embryonic disk gradually becomes elongated with a broad

- cephalic and a narrow caudal end
- Expansion of the embryonic disc occurs mainly in the cephalic region; the region of the primitive streak remains more or less the same size
- In the cephalic part, germ layers begin their specific differentiation by the middle of the 3rd week, whereas in the caudal part, differentiation begins by the end of the 4th week

## 92. III<sup>rd</sup> week of human development – further development of the trophoblast

In the 3<sup>rd</sup> week:

- Mesodermal cells penetrate the core of primary villi and grow toward the decidua → secondary villi
- By the end of 3rd week, mesodermal cells in the core of the villus begin to differentiate into blood cells and vessels, forming the villous capillary system → tertiary (definitive, placental) villi

End of the 3<sup>rd</sup> week:

- Cytotrophoblastic cells surround the trophoblast entirely (form outer shell) and are in direct contact with the endometrium
- The outer shell gradually surrounds the trophoblast entirely and attaches the chorionic sac firmly to the maternal endometrial tissue
- Embryo is suspended in the chorionic cavity by means of the connecting stalk
- Maternal vessels penetrate the cytotrophoblastic shell to enter intervillous spaces, which surround the villi.
- Capillaries in the villi are in contact with vessels in the chorionic plate and in the connecting stalk, which in turn are connected to intraembryonic vessels

## 93. III<sup>rd</sup> -VII<sup>th</sup> week of human development – derivations of the ectodermal germ layer

Surface ectoderm

- skin (epidermis, hair, nails, glands) □□
- anterior pituitary □□ ear (receptor apparatus of inner ear) □□
- nose (olfactory epithelium)

Neuroectoderm

- neural tube – central nervous system, eye (iris, ciliary) □□
- neural crest – cells outside CNS

## 94. III<sup>rd</sup> -VII<sup>th</sup> week of human development – development of the mesodermal germ layer

Epiblast cells ingress through the primitive streak between ectoderm & endoderm- become elongated- detached from the epiblast

Mesoderm cells coming from primitive node and rostral primitive streak from the paraxial mesoderm (day 17)

Intermediate mesoderm- lateral to the paraxial, for a short stretch of the embryo's length

Mesoderm cells coming from the middle to caudal streak form the lateral plate mesoderm- divided into two layers: somatic (parietal) mesoderm- continuous with mesoderm covering the amnion / splanchnic (visceral) mesoderm- continuous with mesoderm covering the yolk sac

day22: the intraembryonic mesoderm differentiates into paraxial, intermediate, and lateral plate portions

The intraembryonic mesoblast is the third germinal layer.

It arises in the 3rd week via the immigration of cells at the primitive streak.

In the beginning, the cells of the mesoblast (mesodermal cells) build a thin, widely meshed layer on both sides of the median line, between the ectoderm and the endoderm.

- muscle
- outer covering of
- organs
- excretory system
- gonads
- circulatory system
- bones and cartilage
- circulatory system
- dermis

### ✓95. III<sup>rd</sup> -VII<sup>th</sup> week of human development – differentiation of the paraxial mesoderm

Paraxial mesoderm

is the area that forms just lateral to the neural tube on both sides.

Paraxial mesoderm accumulates under the neural plate .

This forms thickened streaks running the length of the embryonic disc.

During the 3rd week the paraxial mesoderm begins to segment and forms into "balls" of mesoderm paired either side of the neural groove, called somites.

Somites appear bilaterally as pairs and form earliest at the cranial end of the neural groove and add sequentially at the caudal end. Somites appear cranially to caudally, beginning at the occipital end. They can be counted and are used to roughly estimate the age of the embryo.

Segmentation of the paraxial mesoderm into somites is dependent upon a segmentation clock established by "cyclic genes

### ✓96. IIIrd – VIIIth week of human development – differentiation of the

IIIrd - VIIIth week

### **intermediate mesoderm and lateral plate mesoderm.**

The intermediate mesoderm temporarily connects paraxial mesoderm with the lateral plate.

The intermediate mesoderm gives rise to paired, segmentally organized nephrotomes from cervical to sacral region.

Cervical nephrotomes are formed early during the 4th week and are collectively referred to as the pronephros.

More caudally it forms unsegmented mass, the nephrogenic cord.

It differentiates into urogenital structures gives rise to the kidneys and associated ducts, as well as the epididymis and vas deferens in the male, and the vagina, oviducts, uterus of the female.

### **97. Embryonic blood circulation.**

#### Lateral plate mesoderm

Laterally, the mesoderm is thin and is called the lateral plate mesoderm.

A cavity develops in the lateral plate mesoderm called the intraembryonic coelomic cavity.

This cavity is continuous with the extraembryonic coelom.

The mesoderm that lies dorsal to the intraembryonic cavity is called the parietal or somatic mesoderm.

That mesoderm found ventral to the intraembryonic coelomic cavity is called the visceral or splanchnic mesoderm.

### **98. IIIrd – VIIIth week of human development - derivate of the endodermal germ layer.**

#### DERIVATIVES OF THE ENDODERMAL GERM LAYER

The gastrointestinal tract is the main organ system derived from the endodermal germ layer. This germ layer covers the ventral surface of the embryo and forms the roof of the yolk sac. With growth of the brain vesicles, the embryonic disc begins to bulge into the amniotic cavity and to fold cephalocaudally.

During cephalocaudal folding of the embryo, there is a rapid growth of the neural tube such that it becomes longer than the rest of the body. This results in the movement of the head structures cephalically, and tail structures caudally, to rotate in a ventral direction. This folding is most pronounced in region of the head and tail, where the head and tail fold are formed.

As a result of cephalocaudal folding, a larger portion of the endoderm-lined cavity is incorporated into the body of the embryo proper. In the anterior part, the endoderm forms the foregut; in the tail region, it forms the hindgut. The part between foregut and hindgut is the midgut. The midgut temporarily communicates with the yolk sac by way of a broad stalk, the vitelline duct. This duct is wide initially, but with further growth of the embryo, it becomes narrow and much longer also.

At its cephalic end, the foregut is temporarily bounded by an ectodermal-endodermal membrane called the buccopharyngeal membrane.

In the fourth week, the buccopharyngeal membrane ruptures, establishing an open

connection between the amniotic cavity and the primitive gut. The hindgut also terminates temporarily at an ectodermal-endodermal membrane, the cloacal membrane, which breaks down in the seventh week to create the opening for the anus.

### ✓99. External appearance of the human embryo during the second month.

Another important result of cephalocaudal and lateral folding is partial incorporation of the allantois into the body of the embryo, where it forms the cloaca.

The distal portion of the allantois remains in the connecting stalk.

By the fifth week, the yolk sac duct, allantois, and umbilical vessels are restricted to the region of the umbilical ring.

In humans, the yolk sac is vestigial and in all probability has a nutritive role only in early stages of development. In the second month of development, it lies in the chorionic cavity.

### ✓100. Embryonic and fetal membranes: yolk sac, amnion, allantois.

#### Amniocentesis.

Amnion – formed by epiblast; filled with amniotic fluid

provides a protective environment for the embryo

helps maintain a constant homeostatic temperature

amniotic fluid comes from maternal blood, and later, fetal urine

Yolk sac – hypoblast cells that form a sac on the ventral surface off the embryo

Forms part of the digestive tube

Produces earliest blood cells and vessels

#### Allantois

When the cloacal membrane

appears ((day 16)), the

posterior wall of the yolk sac

forms a small diverticulum

that extends into the

connecting stalk ,allantois

A little out--pocketing of the

caudal end of yolk sac

trapped in the connecting

stalk

This blind pouch is called the

allantois ((Gr..., sausage--shaped))

Importance

structural base for the

umbilical cord

becomes part of the urinary *bladder*

bladder

## 101. Placentation and placenta

### Functions of Placenta:

- Exchange of Gases
- Exchange of Nutrients and Electrolytes
- Transmission of Maternal Antibodies
- Hormone Production

By the end of the fourth month of the pregnancy, the placenta has attained its definitive form and undergoes no further anatomical modifications. It has two components: the maternal portion, formed by the decidua plate, and a fetal portion, made by the chorion frondosum. Growth continues by further ramification of the stem villi into the surrounding intervillous spaces. On the maternal side decidua septa extend into the intervillous spaces, dividing placenta into 10-38 cotyledons. The villous surface area continues to increase until term, although the rate of the increase slows from approximately 34 to 36 weeks of gestation.

Placenta consists of structures called cotyledons.

Each of these units consists of two or more placental villi, their branches and the fibrovascular meshwork that supports these structures.

During placental circulation, the maternal blood passes through the intervillous spaces that originate from the spiral arteries of endometrium. The blood ultimately enters the villi where active transport of nutrients and waste products occurs. The umbilical arteries carry poorly oxygenated blood (blue) to the placenta. Once oxygenated in the placenta, the blood is transferred by the umbilical veins (red) to the fetus. This is in sharp contrast to the oxygenation of blood after birth with arteries containing the oxygenated blood and the veins containing the poorly oxygenated blood.

### Permeability of Placenta:

Many viruses – rubella, cytomegalovirus, Coxsackie, variola, measles, polyomyelitis; Most drugs and drug metabolites including heroin and cocaine.

The placenta has a circular shape and measures about 15 to 20 cm in diameter, weighing 500 to 600 g at full term.

The maternal side of the mature placenta exhibits about 15-20 cotyledons. The deep grooves separate cotyledons from each other. Some of the decidua basalis may remain associated with the maternal side of the placenta. The umbilical cord is a vascular cable (~ 55 cm) that connects the embryo to placenta. The umbilical cord of the fetus is covered by

the amniotic epithelium and contains two umbilical arteries and one umbilical vein embedded into the Wharton's jelly.

The umbilical cord is attached to the placenta on the fetal surface. Usually, the cord attaches to the placenta eccentrically. Each umbilical cord consists of 2 arteries and a vein and are covered with a gelatinous substance which in its outer layer is covered by the amnion. In some placenta the umbilical cord is attached close to the margin of the placenta (battledore placenta).

## ✓102. Umbilical cord.

Continued development and expansion of the extraembryonic coelom restricts the attachment of the embryonic disk to a connecting stalk, which is a permanent connection between the future caudal end of the embryonic disc and the chorion. The connecting stalk forms a pathway along which vascular anastomoses of embryonic disk establish communication with those of the chorion, future umbilical cord

## 103. Twins and multiple births

Dizygotic (fraternal)

70% of twins ; 7-11 per 1000 births  
ovulation of 2 oocytes and fertilization by 2 different spermatozoa, may or may not be of different sex ; no more resemblance than any other brothers or sisters

Monozygotic (identical)

30% of twins ; 3-4 per 1000 births  
1 oocyte & 1 sperma to zoom , splitting of the zygote at various stages of development (2 -cell stage or blastocyst stage or bilaminar disk stage)

Triplets are rare (about 1/7600 pregnancies), birth of quadruplets, quintuplets, and so forth is rarer  
Dizygotic (fraternal)

A multiple birth occurs when more than one fetus is carried to term in a single pregnancy. Different names for multiple births are used, depending on the number of offspring. Common multiples are two and three, known as twins and triplets. There are two common types of multiple births, fraternal (dizygotic) and identical (monozygotic).

Identical siblings arise where one egg is fertilized and the resulting zygote splits into more than one embryo. Identical siblings therefore have the same genetic material.

Fraternal siblings result from the fertilization and implantation of more than one egg, so fraternal siblings are not genetically identical but instead have the coequal genetic similarity any other full siblings have.

In some multiple births, it is possible for a combination of these (for example, a set of triplets may have one fraternal baby from one egg, plus two identical twins from a second egg). This is called a polyzygotic birth.

Monozygotic – multiple (typically two) fetuses produced by the splitting of a single zygote.

Dizygotic – multiple (typically two) fetuses produced by two zygotes.

Polyzygotic – multiple fetuses produced by two or more zygotes.

Litter – the offspring produced by a multiple birth in non-human placentals.

There have been cases of human pregnancies that started out with ten, eleven, twelve or fifteen fetuses, but there are no known instances of live births of such high multiples in a single pregnancy.

Most of these pregnancies are the result of fertility medications and assisted reproductive technology (ART), though a set of duodecaplets (twelve) was conceived spontaneously (without the aid of fertility treatments) in Argentina in 1992.

High orders of multiple births (three or more offspring in one birth) may result in a combination of fraternal and identical siblings. The latter are also called super twins.

Identical triplets or quadruplets are very rare and result when the original fertilized egg splits and then one of the resultant cells splits again (for triplets) or, even more rarely, a further split occurs (for quadruplets).

Human multiple births can occur either naturally (the woman ovulates multiple eggs or the fertilized egg splits into two) or as the result of infertility treatments such as IVF (several embryos are often transferred to compensate for lower quality) or fertility drugs (which can cause multiple eggs to mature in one ovulatory cycle).

The number of multiple births has increased over the last decades.

Before the advent of ovulation-stimulating drugs, triplets were quite rare (approximately 1 in 8000 births) and higher order births much rarer still. Younger patients who undergo treatment with fertility medication containing artificial FSH, followed by intrauterine insemination, are particularly at risk for multiple births of higher order. Certain factors appear to increase the likelihood that a woman will naturally conceive multiples. These include: mother's age - women over 35 are more likely to have multiples than younger women. Mother's use of fertility drugs - approximately 35% of pregnancies arising through the use of fertility treatments such as IVF involve more than one child.

Twin-twin transfusion syndrome (TTTS) occurs only in those identical twins that are monochorionic, diamniotic (1/3 of all identical or monozygotic twins). In almost all of these pregnancies, the single placenta contains blood vessel connections between the twins

Multiples are also known to have a higher mortality rate, premature birth, low birth weight, and cerebral palsy. It is more common for multiple births to be stillborn, while for singletons the risk is not as high.

A study done on one set each of septuplets and octuplets, two sets of sextuplets, 8 sets of quintuplets, 17 sets of quadruplets, and 228 sets of triplets showed that the mean gestational age at birth was 33.4 weeks for triplets and 31 weeks for quadruplets. The prenatal death rate for multiple births of more than six (sextuplets) was 100%. This shows that stillbirth happens usually 3-5 weeks before the woman reaches full term and also that for sextuplets or higher it almost always ends in death of the fetuses. Though multiples are at a greater risk of being stillborn.

## **104. Congenital malformations. Prenatal diagnosis.**

Congenital disorder involves defects or damage to a developing fetus. The outcome of the disorder will further depend on complex interactions between the pre-natal deficit and the postnatal environment. Congenital disorders vary widely in causation and abnormalities.

Genetic disorder or diseases are all congenital, though they may not be expressed or recognized until later in life. Genetic diseases may be divided into single-gene defects, multiple-gene disorders, or chromosomal defects. Single-gene defects may arise from abnormalities of both copies of an autosomal gene (a recessive disorder) or of only one of the two copies (a dominant disorder). Chromosomal disorders involve the loss or duplication of larger portions of a chromosome (or an entire chromosome) containing hundreds of genes (Down syndrome – trisomy 21, Turner syndrome – 45, X karyotype). Large chromosomal abnormalities always produce effects on many different body parts and organ systems. A congenital metabolic disease is also referred to as an inborn error of metabolism. Most of these are single gene defects, usually heritable. Many affect the structure of body parts but some simply affect the function.

It may be the result of: Genetic abnormalities; Chromosomal abnormality; Intrauterine environment; Errors of morphogenesis

A congenital physical anomaly is an abnormality of the structure of a body part that may or may not be perceived as a problem condition. Many, if not most, people have one or more minor physical anomalies if examined carefully. Examples of minor anomalies can include curvature of the 5th finger (clinodactyly), a third nipple, shortness of the 4th metacarpal or metatarsal bones etc. Some minor anomalies may be clues to more significant internal abnormalities.

A congenital malformation is a congenital physical anomaly that is deleterious, i.e. a structural defect perceived as a problem. A typical combination of malformations affecting more than one body part is referred to as a malformation syndrome

Anencephaly is a cephalic disorder that results from a neural tube defect that occurs when the cephalic (head) end of the neural tube fails to close, usually between the 23rd and 26th day, resulting in the absence of a major portion of the brain, skull, and scalp

Thalidomide is a sedativehypnotic drug. It is a potent teratogen causing severe birth defects if the drug is taken during pregnancy. From 1956 to 1962, approximately 10,000 children in Africa and Europe were born with severe malformities, including phocomelia, because their mothers had taken thalidomide during pregnancy. Anencephaly is a lethal anomaly occurring in 1/1000 births.

Spina bifida is a congenital disorder (birth defect) in which the backbone and spinal canal do not close before birth.

Amelia is the birth defect of lacking one or more limbs. It can also result in a shrunken or deformed limb. For example, a child might be born without an elbow or forearm

Birth defect is a widely-used term for a congenital malformation, i.e. a congenital, physical anomaly which is recognizable at birth, and which is significant enough to be considered a problem. Birth defects are believed to be caused by a complex mix of factors including genetics, environment, and behaviors, though many birth defects have no known cause.

Birth defect, congenital malformation, and congenital anomaly are synonymous terms used to describe structural, behavioral, functional, and metabolic disorders present at birth, Teratogens (Gr. teratos, monster + gen, producing)

Major structural anomalies occur in 2 to 3% of liveborn infants, and an additional 2 to 3% are recognized in children by age 5 years – totally 4-6%.

Prenatal diagnosis is offered to women with pregnancies at increased risk of chromosome abnormality. Indications for prenatal diagnosis include increased maternal age, an increased risk from serum screening, an abnormal finding at ultrasound scan or a family history of chromosome abnormality.

Prenatal diagnosis include: Ultrasonography; Maternal Serum Screening; Amniotic Fluid Sampling; Chorionic Villus Sampling; Fetal Blood Sampling