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SELECTED THEMES OF HISTOLOGY, CYTOLOGY AND EMBRIOLOGY CORE

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The studying manual includes selected topics of histology, cytology and embryology core. The presented topics cover most complicate questions of typical studying program of histology. It is designed for students of first and second years of medical universities. The material of each chapter is subdivided into smaller questions. The material is based on contemporary findings in the field of histology, embryology and cytology.

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CONTENTS

Chapter 1: Introduction to the histology, history of its development, histological techniques and instruments.

Histology – is a science about development, structure and functions of cells, tissues and organs of an organism. Originally, histology was a science about tissue structure and function. But contemporary view on histology includes states that histology as a science contains following subdivisions:

1. **Histological and microscopic technique**, which studies how to make histological preparation and how to explore it with help of a microscope.

2. **Cytology**, which studies development, structure and functions of cells.

3. **Embryology**, which is a science about rules and ways of embryonic development.

4. **General histology**, which studies sources of development, structure, functions and reactive changes of tissues.

5. **Histology of various organs or microscopic anatomy**, which studies sources of development, structure and functions of various organs.
6.

An organism can be studied with help of a microscope on different levels.

1. *Subcellular level* – studying of ultramicroscopic features of cellular structure with help of the electronic microscope.

2. *Cellular level* – studying of cellular structure and reactive changes of cells with help of light microscope techniques.
3. *Tissue level* – studying of tissues structure, functions and development.
4. *Organ level* – studying of microscopic structure and functions of various organs.

History of histology

There are three periods in histology history: **premicroscopic, microscopic and synthetic**.

Premicroscopic period is characterized by very common and approximate knowledge about cell and tissue structure. It was based on macroscopic observation. This period has invested very few into understanding of tissue and organs structure and functions.

Microscopic period was started from light microscope invention. First try to invent microscope was made by Galilee in 1609-1610. Among first microscope constructors were K. Drebbel and brothers Janssen. R. Hooke was first to explore cells of plans and animals with help of the light microscope in 1677. A. Laevenhook constructed the light microscope with magnification 300 times. It allowed him to explore blood cells, spermatozoa and range of other biological objects.

In 18^{th} century in Holland and Russia the first achromatic microscopes were invented. They were possible to give fine image. This fact made a deep impact on histology development. In1801 French histologist K. Bicha on a base of macroscopic investigation made broad tissue classification. In 1819 his disciple K. Mayer introduced the term "histology".

In 1839 German scientist T, Schwan formulated cell theory. It postulated the general principles of cell structure and had a big impact on histology development. In second half of 19^{th} century it was assumed that cells form an organism no one by one but as the part of tissue. F. Leidig (1853) and A. Keliker (1855) summarized all previous material and united all know tissue types to 4 tissue kind. At the same time many important discoveries were made in histological technique. The great contribution to these discoveries was made by Check physiologist and histologist Y.Purkinje. He introduced to histological technique the main stages of section preparation which are preserved until today. He also constructed first microtome. As a result of all of this the new findings were acquired.

Thus, in 1852 R. Remark described amitosis; in 1859 P. Virchow made correction of cell theory and created elements of cell pathology. In 1861 M. Schultze gave the first definition of cell. In 1871-1879 the mitosis of plant cell (I.D. Chistiakov) and animal cell (P.I. Peremezhko, V. Fleming) were described. In 1884 O.Gertvig and E. Strassburger suggested that chromatin is material carrier of heredity. In 1875-1876 O.Gertvig and E. van Beneden discovered cell center, in 1898 R. Altmann discovered mitochondria, in 1899 K. Golgi described endoplasmic reticulum.

At the end of XIX century the microscopic description of organs and tissues were generally completed and microsopic anatomy were founded. With help of silver impregnation method the most difficult region – nervous tissue – was investigated. This investigation was performed by S. Ramon-i-Kahal, K. Golgi, A.S. Dogel, B.I. Lavrentiev. The findings of these scientists helped to formulate neuronal theory.

The great contribution to the histology development was made by Russian scientists. A.I. Babuchin studied structure and functions of nervous and muscular tissue. A.S. Doge, M.D.Lavdovskiy, A.N. Mislavskiy thoroughly studied peripheral and central nervous system. A.O.Kovalevskiy and I.I. Mechnikov studied tissue formation in evolution and created basement of evolutionary histology. Formulated by I.I. Mechnikov phagocytosis theory had a great importance. In honor to his works he was awarded by Nobel Prize.

In the beginning of XX century the descriptive pattern of histology was enriched by comparative and experimental works. The great contribution to evolutionary histology was made by A.A. Zavarzin, who was first to formulate the theory of tissue evolution. On a base of similarity in tissue structure of mammalians and arthropoda he made the conclusion that all animals have four tissue systems due to one pattern of interaction with external environment. The tissue systems perform four main functions: 1) defense or external exchange, 2) internal exchange or homeostasis maintenance, 3) locomotion, 4) reactivity. The Zavarzin's theory was named theory of parallel tissue development. According to this theory, the animals of different types have common principle of tissue organization and have four tissue systems.

N. G. Hlopin continues studying theoretical problems of tissue evolution. He formulated the theory of divergent evolution. According to this theory the evolutionary development of tissues occurs with diversification of signs, e.g. divergent. This results in multiply tissue types.

The great contribution in histology development in the beginning of XX century was made by A.A. Maximov. His works are actual and today.

He formulated unitary theory of hemopoiesis, described blastransformation reaction of lymphocytes, and made first description of hemopoietic stem cell.

Until 50s years of XX century the main histological works were concentrated in descriptive, evolutionary and experimentally directions. The impact on histology development was made by discovery of electronic microscope by E. Rusca, M. Kiolle, B. Borrie in 1928-1931. The new stage of histology development was started. In a short period of time the cell structure on ultrastructural level was studied. In 1954 A. Rodin made description of peroxisomes. In 1955 G. Pallade described ribosomes and endoplasmic reticulum and K. de Duve discovered lysosomes. In the beginning of 60s all unknown before organneles were discovered. In 60s-80s the methods of electronic histochemistry and electronic autoradiography were introduced into histology. The ultramicroscopic structure of cells from different tissues was studied. The scanning electronic microscopy gives 3-dimenitional image of structures.

At the same time the methods of light microscopy are still updated. The immunohistochemistry and immunocytochemistry, which are based on monoclone antybodies reactions, were introduced into histology. This methods help to detect different cells and point different subtypes of them. They are very specific and they became wide spread in clinical setting. Today we are in sintetic period of histology development, which is characterized by using many different approaches to achieve one aim – discover secrets of cell being.

Histological methods and techniques

All methods which are used in histology can be divided into two groups: microscopic techniques (different methods of object microscoping) and histological techniques (methods which allow making histological preparation).

Microscopic techniques

These methods are based on studying different object with microscope. According to source which sends through the object to be examined, all microscopes are divided into light and electron.

Light microscoping.

The usual light microscope uses a visible light source with a system of condenser lenses to send the light through the object to be examined. The image of this object is then magnified by two sets of lenses, the objective and the eyepiece. There are two indexes which can characterize any microscope: the total magnification and resolution power. Total magnification is then the product of these two lens systems, e.g., 40 X 10 = 400. The resolution or resolving power - how close two structures can be and still be seen as separate - is a measure of the detail that can be seen, and for the light microscope is about 0.25 μm. This limit to resolution is determined mostly by the wavelength of the light; and, however powerful the lens, 0.25 μm cannot be improved upon. The only way to improve resolving power is to reduce substantially the wavelength of the light.

Types of light microscopy

1. Standart light microscopy. Here the visible light is used for microscoping. Wavelenght is 0.4 mcm. Resolving power 0.2 mcm. Total magnification is 2500 times.
2. Ultraviolet microscopy. Here the ultraviolet light is used for microscoping. Wavelength is 0.2 mcm. Resolving power 0.1 mcm. The acquired image is recorded on photograph because it is invisible for naked eye.
3. Fluorescencent microscopy. This type of microscopy is based on fluorescent effect. It is when some molecules in tissues under short wave radiation become exited and start to shine. The generated light has larger wavelength than inducing light. There are special stains that may cause fluorescence in tissues (e.g. acridine orange).
4. Interference microscopy. Here the light is divided into two beams. One beam goes through the object, other passes it by. Then they meet together and make interference picture. By phase shift in this picture we may detect precise concentration of a substance in a cell. So we may conclude that it is quantitative method.
5. Polarization microscopy. Here the light is separated to two perpendicular beams. If they pass through structures with strict orientated molecules, they late one to another due to different

refraction. It helps to detect character of molecules localization in cells, for examples myofibrils.

6. Phase-contrast microscopy. Here the light is separated to several phases. When they come through object they change their position regarding to others. This results in object contrast increasing. With help of this microscopy we can observe even unstained preparations.

Electronic microscopy and it's types.

The only way to improve resolving power is to reduce substantially the wavelength of the light. This is achieved by the electromagnetic beam of the electron microscope. The beam is focused through the object suspended on its metal grid, and is magnified before striking a fluorescent screen to be transformed into a visible image The resolutions so far achieved in biology with transmission electron microscopy (TEM/EM) are of the order of 1 nm at a magnification of X 2 000 000. Another variant of electronic microscopy is scanning electronic microscopy. Such microscopes allow achieving 3-dimenitional image of object. The working principle oa such microscopes is concluded in following. The electrons beam moves along the object surface and knock out secondary electrons. These electrons are detected and acquired image is transmitted to monitor. One more variant of electronic microscopy is transmission electronic microscopy by electrons of high power. The electrons are accelerated before passing the object. Several years ago the type of electronic microscopy was invented. It is scanning atomic electron microscopy. This type of microscope uses a very thin needle which moves along object surface. This needle can either send electron beam to surface or touch surface by its end. By touching it evaluates the mechanical properties of surface.

Other histological techniques to study biomaterial

Histochemistry

It is based on ability of some stains selectively bound amino acids, carbohydrates, fats and other components of cells and tissues. Bounded to these substances, the stains make them visible so we can evaluate their intercellular localization. The variant of histochemistry is immunohistochemistry. This method is based on reaction "antibody-

antigen". We can get monoclone antibody to any biological molecule. Than we express this antibody to the tissue and it binds specific antigens in it. We can reveal the localization of "antibody-antigen" complex with help of secondary antibodies with attached fluorescent or enzymatic mark. These methods are widely used to determine the level of cells differentiation in immune system and during hemopoiesis.

Historadiography

This method is based on isotope using. The cell is subjected to isotope containing environment. In this environment some important biologically active molecules may contain isotopes. Chemically and physiologically substances with isotopes are same as without them. Than we take samples from tissue, make preparation, cover them by photoemulsion and study the localization of biologically active substances by isotope radiation.

Vital microscopy

It is the microscoping of living cells. For this we can use specially cultivated cells. Cells are placed on nutritive medium where they grow in one layer. Than we stain these cells and study under microscope. Here the non-toxic stains are used. The cells actively phagocytate stain particles and became good visible under microscope. Here is supravital microscopy. The main difference from vital microscopy is that the cells are observed after taking them out of organism.

Shooting of a cell movement film

Cells in a culture are shot on a film with interval 5 minutes. Acquired film is demonstrated with speed 24 cadres per second (as usual movie). Thus we can see the changes which were happen in cells in dynamics, e.g. during mitotic division.

Cytomicrosurgery

This method allows making microperation in a cell, such as nucleus transplantation and so on. The special range of instruments was invented for this purpose.

DNA hybridization methods

These methods are used to detect gene localization in chromosome, to determine nucleotide sequence in a gene and to detect presence of some nucleotides in environment. It is based on ability RNA probes bind complementary sequences of DNA or RNA.

Methods of quantitative histology (morphometry)

The simplest quantitative method is the counting of structures which are visible in microscope. The evaluating object size with help of ocular-micrometer is also type of quantitative methods. To count structures histologists use morphometric girds. Such girds have points. The most popular Avtandilov's gird contains 100 points, so if a cell on preparation is covered by 10 points of gird that means that the cell takes 10% of preparation volume.

Nowadays there is modern equipment, which allows automatically count histological structures. It is automatic systems of image analysis. It includes: scanning, light or electronic microscope, digital video camera, computer and display. Data from microscope with help of video camera are imputed to computer, where they are processed and presented on display screen.

Cytospectrophometry

It is method to study chemical compounds of a cell. It is based on selective absorption of rays with estimated wavelength by different chemical substances of a cell. The intensity of absorption points the concentration of substance.

Steps needed to make and study a histological section:

- *Fixation* to prevent post-mortem decomposition, preserve structure, and intensify subsequent staining.
- (a) Steps involved in *imbedding* the tissue in a block of wax or plastic, or (b) *freezing* of the material to a firm mass, for
- *cutting* into thin sections on a microtome; 1-150 microns (μm) thick for light microscopy (LM); 30-60 nanometres (nm) for electron microscopy (EM).

- *Units*: based on the metre (m): *micron*/micrometre (μm) = 10^{-6}m; *nanometre* (nm)/ millimicron (mμ) = 10^{-9}m; *Angstrom* (A) = 10^{-10}m; 10A=1nm.
- *Mounting* of the section on a glass slide or metal grid. *Staining* of the section with one or more reagents, e.g., solutions of metallic salts, in one or more stages.
- For light microscopy, the removal of surplus stain and water, and steps involved in holding a thin glass coverslip to the section with a *mounting medium* having a refractive index close to that of glass.
- *Observation* and *recording* by means of the microscope, and notes, photomicrography, projection drawing, labelled sketches, counting and reconstructions, digital and videorecording. A drawback to using our eyes as part of the observing instrument is that the visual system does not record accurately. Memory is unreliable.

Tinctorial properties of tissues

The tinctorial properties of tissues are ability to be stained by stains.

1. Oxyphylia – it is the ability to be stained by acidic stains. The structures which are stained have basic properties. An example is erythrocyte; it has oxyphilic staining due to having basic protein hemoglobin.
2. Eosinophilia (variant of oxyphylia) - it is the ability to be stained by eosin stain. The cytoplasm of many cells has eosinophylic staining.
3. Acidiphylia – the same as oxyphylia.
4. Basophylia - it is the ability to be stained by basic stains. The structures which are stained have acidic properties. An example is RNA and DNA. They are acids and they can bind basophilic stains. That why the nucleus of any cell has basophylic staining. The cytoplasm of actively protein producing cells is also basophilic due to abundance of rough endoplasmic reticulum and ribosome in it.
5. Polychromatophylia – it is the ability to be stained by basic and acidic stains as well. Such type of staining can be observed in granules of neutrophil leukocytes, but as a synonym the world NEUTROPYLIA is also used.
6. Metachromosia - it is the ability to change the original color of stain during staining. The metahromasia is specific for complex carbohydrates.
7. Argentophylia - it is the ability to be stained by argentums salts.
8. Chromophylia - it is the ability to be stained by chromium salts.

Chapter 2: Cytology 1

Cytology – is a science about a cell. It studies structure and functions of cell in tissues of multicellular organism, single organisms, processes of cells replication, cells growth, cells regeneration, adaptation of cells to changing environmental conditions and other processes, which allow to understand general functions and properties of cells.

Cell – is elementary structural unit of organism, containing nucleus, cytoplasm and limited by cell coat. It can perform all functions, which are applicable to living matter: metabolism of substances and energy, multiplication, growth, irritability, contractility, saving and transmitting of hereditary information.

Main statements of cellular theory and it's value

In 1839 German zoologist T. Schwan reported principles of cell theory, such as:

1. A cell is main structural unit of all animal and plant organisms.
2.The growth, development and differentiation of animal and plant tissues are due to cell formation.
3.A cell in appropriate limits is an individum, and organism is summ of them.
4.New cells are appeared from cytoblastemm.

The first tree conclusions of T. Schwann are still correct. The fourth one isn't.

Further development of cell theory is connected with a name of German scientist P. Virchow (1821-1902), who published his work "The cellular pathology" in 1858. P. Virchow was a first describing pathological process by materialistic way. He showed the connection of the pathological events with changes in cell structure. He corrected the fourth T. Schwann thesis and suggests a new one: "Omnis cellula e cellula" - each cell is from cell. And today we still know only one way of cell arising - by cell division. However, it might be considered that on early stages of life development cell appeared from non cellular structures. The P. Virchow conclusion that there is no life outside of the cell is still correct. But others his conclusions weren't proved by further science development. In particular, P. Virchow intensively developed incorrect conclusion of T. Schwann about organism as a cell summ, from which it might be interfered that pathological process of organism is a summ of pathological processes in particular cells. P. Virchow and his fellows didn't recognized the differences between part and total, observing organism without it historical development and enviroment. Assessing the P. Virchow's "The cellular

pathology" in general, it may be pointed that it was an important sign in a history of biology and medicine. And after slight correction it made a basement for contemporary views to organism cell structure.

The formation of cell theory was completed on a base of new findings acquired from modern cell researches. Main statements of cell theory are:

1.All organisms are composed of one ore more cells, within which the life processes of metabolism and heredity occur.

2.Cells are the smallest living things, the basic unit of organization of all organisms.

3.Cells arise only by division of previously existing cell.

4.Cells of multicellular organisms are spetializated in function and form tissues.

5.Cells of spetializated tissues form organs.

The cell theory is a great generalization of XIX century. The creating of cell theory had a great value for development of materialistic view on life in all branches of biology and medicine.

The value of cell theory is in following:

1. It became the basement for development of many biological disciplines, such as cytology, histology, embryology, physiology and pathology.
2. It allowed understanding mechanisms of ontogenesis - individual development.
3. It became the base for materialistic understanding of life and environment.
4. It became the base for explaining of organisms evolution.

Cell structure

A cell may be single living or as a part of tissue in multicellular organism. In tissue the cells are main tissue element.

All cells are divided into procariotic and eucariotic cells.

The procariotic cells haven't nuclear envelope, nucleus and oranelles. All genetic information is stored in circular double DNA molecule. The procariotic cells are surrounded by hard cellular wall. They have no mitotic apparatus. The representatives of procariotic cells are bacteria and some types of algae.

All other cells are eucariotic cells. They are differ from procarioticcells by having chromosomes, system of intracellular membranes, which are used in organelles structure. Cytoplasmic membranes also make nuclear envelope. There is mitotic apparatus. The

adult human organism has about 10^{13} cells, which are subdivided into 200 types with wide range in functions and structure. But all cells have common features in structure.

The eucariotic cells have the following components:

1. Cell coat (cellular surface).
2. Cytoplasm.
3. Nucleus.

Every component has it's smaller parts.

Cell coat is made of three parts: outmost layer is presented by glycocalyx, middle layer is presented by cytoplasmic membrane and innermost layer is submembranic layer of supportive and contractive structures.

Cytoplasm has hyaloplasm, organelles and inclusions.

Nucleus has four components: Nuclear envelope, nucleolus, chromatin (chromosomes), nuclear juice.

Cell coat

The main part of the cell coat is cytoplasmic membrane (cytolemm), which has a structure of elementary biological membrane. It is widest amoung other biological membranes (7.5 – 11nm).

BIOLOGICAL MEMBRANES – are lipoproteid structures, which separate cell from outside and form some organelles and nuclear envelope. They have three layars on electronic microphotography. There are two dark layers separated by white one. The main chemical components of membrane are lipids (comprise about 40%), proteins (50%) and carbohydrates (10%).

Lipids molecules have hydrophilic and hydrophobic parts. The polarity of lipids determines the permeability of biological membranes. The non-polar substances can easily pass through membrane, whereas polar substances can enter a cell only with help of transmitter or by endocytosis. The lipids form a bi-layer. The insoluble, hydrophobic ends are hidden inside bi-layer, whereas soluble hydrophilic ends look towards outside. The tails of lipids form central light layer of membrane. The lipids are of following types: phospholipids, sphingolipids and cholesterol. The membrane lipids have incorporated arachidinic acid. The derivate of arachidonic acid are biologically active substances like prostaglandins, leucotriens, tromboxans and ets. They perform many different functions.

Proteins of membranes are divided into 3 main groups: superficial (located over cytolemm or under cytolemm), integral (penetrating whole width of membrane) and semi-integral (penetrating only half of llipid bi-

layer). Functionally, the proteins can be enzymes, receptors, transport proteins and structural proteins.

The proteins are scattered in lipid bi-layer. They like the icebergs in the lipid sea. While intercellular interactions, the proteins can congregate in one pole of cytoplasm (so called *capping*). The important role in protein movement along the cytolemm play elements of cytoskeleton (microfillaments).

The described above model of membrane structure are known as liquid-mosaic quasi- crystalline (membrane has crystal like structure in which proteins freely move perhaps of liquid properties of membrane).

Carbohydrates are included in membranes as components of complex lipids and proteins.

Functions of biological membranes

1. Separation – it separates a cell from external environment, it separates nucleus from cytoplasm and ets.
2. Barrier-defense function – it protects a cell from external harmful factors.
3. Reception.
4. Transportation: transport of different substances to and from cell.
5. Participation in intercellular relationships: formation of intercellular junctions.

Second part of cell coat is GLYCOCALYX. It is presented by carbohydrate ends of complex proteins (glycoproteins) and of complex lipids (glycolipids). Glycocalyx includes superficial proteins and semi-integral proteins as well. Their functional regions are located in glycocalyx. They may work as enzymes. There are receptors of tissues compartibility, for immunoglobulines, for hormones and spots for enzymes absorption.

Functions of glycocalyx

1. Reception.
2. Intercellular contacts and relationships.
3. Orientation of proteins in membrane.
4. Particcipation in substance transport.

Third component of cell coat is - SUBMEMBRANIC LAYER OF SUPPORTIVE AND CONTRACTIVE STRUCTURES. It includes contractive structures – actine filaments, and support apparatus – keratine

filaments, microtubules. The submembranic layer is tightly connected with cytoskeleton from one hand, and with cellular receptors from another.

Functions of submembranic layer of supportive and contractive structures

1. Maintaining of cellular shape
2. Changing of cellular surface, by that cell participates in endo- and exocytosis, movement and secretion.
3. It connects cellular surface with components of cytoplasm and maintain the pattern of their orientation.

Concept about cytoreceptors

Receptors are protein molecules on a cell surface, in cytoplasm or in cell nucleus which specifically react with ligands (hormones, neurotransmitters, cytokines) or with other cells. Accordinary to their localization all receptors can be classified to superficial and internal. Internal receptors are subdivided into cytoplasmatic and nuclear.

Superficial receptors are made of superficial proteins of membranes and glycocalix. They exist for polar substances, which can not pass lipid membrane without assistance, so they act through the system of external receptors and secondary messengers. They are subdivided into catalytic receptors, receptors connected with ion channels, G-protein receptors and receptors which connect intercellular matrix with cytoskeleton.

Glycocalix forms "antennas", which are composed from several polysaccharide chains. These "antennas" have various configurations. They are able to bound different agents. Such agents are hormone molecules, neurotransmitters, growth factors, cytokines and etc. Receptive proteins and carbohydrate chains are connected with enzymes (catalytic receptors). Such receptive proteins are integral proteins and contain receptive and catalytic regions.

Membrane receptors can change membrane permeability for ions, which lead to electric impulse formation (neurotransmitter receptors). It is receptors connected with ion channels.

Receptors also control entry of different substances to a cell, connect molecules of extracellular matrix with components of cytoskeleton (receptors which connect intercellular matrix with cytoskeleton). Such receptors are integrins. They are reffered to molecules of cell adhesion. Integrins – are integral proteins percepting molecules of extracellular matrix, in particular fibronectine and laminine. It its turn fibronectine contacts with other molecules of extracellular matrix (fibrin, collagen, heparin and etc.), whereas integrine contacts with cytoskeleton

components. The irritation of this receptor type may cause changes of submembrane layer condition resulting in cell movement, exocytosis, endocytosis and etc.

The very special type of superficial receptors is G-protein receptors. It is integral proteins which can be connected with either ion channel or enzyme. They have two part: receptive, interacting with signal molecules, and subunits of G-protein, α, β, γ. G-protein is protein binding guanosinetriphosphate. After biding signal molecule, G-protein changes its configuration. Changed configuration activate associated enzyme – adenilatcyclase. The enzyme catalyzes reaction of secondary messenger synthesis – cAMP (cyclic AdenisineMonoPhosphate). Calcium ions also can be secondary messenger. G-protein receptors mediate the action of majority of hormone and neurotransmitters.

Intracellular receptors are inside of a cell – in hyaloplasm, on organelles membranes (cytoplasmatic receptors) and in nucleus (nuclear receptors). They are exist for non-polar hormones which can pass lipid membrane without assistance. The very interesting type is nuclear receptors. These receptors bind such hormones as steroids, thyroid hormones, vitamin D3 and etc. the molecules of such receptors contain two regions: one for hormone binding, second for interacting specific DNA regions in the nucleus. The nuclear receptors are transcription factors. Some of them are protooncogenes – genes of normal genome regulating cells proliferation differentiation and intercellular contacts. As result of somatic mutation of protooncogenes we can face malignant cell transformation.

Intracellular receptors are on organelles membranes, for example mitochondria have receptors for thyroid hormones.

Molecules of cell adhesion

Adhesion - is a process of specific interaction of membrane glycoprotein between two contacting cells, which recognize each other, or between cells and extracellular matrix. If glycoproteins make connections, the adhesion takes place, which results in formation tight intercellular junction or contacts of cell and extracellular matrix.

All molecules of cell adhesion are subdivided into 4 classes:

1. Cadherines. It is transmembrane proteins which use calcium ions for adhesion. They are responsible for cytoskeleton organization and intercellular connection.
2. Integrines. It is membrane receptors for extracellular matrix proteins such as fibronectine and laminine. They connect

extracellular matrix with cytoskeleton through intracellular proteins talline, vinkuline and α-activin. They act as cellular-extracellular as intercellular adhesive molecules.

3. Selectines. They provide leukocyte adhesion to endothelium of vessels and by this provide leukocyte-endothelial interaction, leukocyte migration through vessels wall to a tissue.
4. Immunoglobuline family. They are very important in immune response, during wound healing and etc.

So we can see that adhesion is a very important part of cellular regeneration, takes part in intercellular interaction and cell interaction with extracellular matrix. Adhesive processes are absolutely necessary for such biological processes as embryogenesis, immune response, growth, regeneration and etc. they take part in regulation of tissue and cellular homeostasis.

Cytolasm

HYALOPLASM. It is also knows as cellular juice or cellular matrix. It is the main part of cytoplasm, which comprise about 55% of cell volume. The main cellular metabolic processes take place in the cell matrix. The hyaloplasm is complex colloid system. It consists of homogenic small-grained substance with low electronic density. It contains water, proteins, nucleic acids, polysaccharides, lipids and inorganic substances. The hyaloplasm may change aggregative state: to be transformed from liquid condition (sol) to more viscous condition (gel) and back. While this , the shape, metabolism and motility of a cell may be significantly changed.

Functions of hyaloplasm:

1. Metabolic.
2. Internal environment
3. Participation in cell movement.

ORGANELLES. Organelles are second important component of a cell. The important sign of organelles is that they have strictly determined structure and functions. By functions, all organelles are divided into 2 groups:

1. **Organelles of general purpose**. They arte in all cells, because they are needed for cell living. They are mitochondria, EPR, Golgi complex, centrioles, ribosome, lysosomes. Peroxysomes, microtubules and microfilaments.
2. **Organelles of special purpose.** They are only in the cells which perform some particular function. The examples are myofibrils in muscular fibers, neurofibrils in neurons, flagella and cilia.

By structure all organelles are divided into: 1) organelles of membranous type and 2) organelles of no- membranous type. Furthermore, the no- membranous organelles may be made by fibrillar and granular type.

In the membranous organelles, the main component is intracellular membranes. The organelles which are made by that type are mitochondria, EPR, Golgi complex, lysisomes, peroxisomes. The no-membranous organelles of fibrillar type are microtubules, microfilaments, cilia, flagella, centrioles. The no-membranous organelles of granular type ribosomes and polysomes.

Membraneous organelles

ENDIPLASMIC RETICULUM (EPR). It was firstly described by K. Potter in 1045. it was describe with help of electronic microscope. EPR is a system of connected canals, vacuoles, sacs, which make a continious network in the cell. The elements of EPR on ultrathin cuttings may look as isolated vacuoles. The EPR is made of thiner membranes than those of cellular membrane. But they contain more proteins because of having numerous enzyme systems. There are two types of EPR: **granular (rough) and agranular (smooth).** One type may merge into another. The place of intergange is called **transitional zone**.

Granular EPR have ribosome (polysome) attached to the surface. It is the organelle of protein biosinthesis. The polysomes and ribosomes are connected with EPR with help of so called "docking protein". Furthermore in EPR membrane there are integral proteins – ribophorins, which help to attach ribosomes and to form transmembranous canals for entering of polypeptide chain into the lumen of EPR.

Function of granular EPR is protein synthesis for outside usage – for export. Moreover, here primary posttranslational changes take place like hydroxylation, sulphatation, phosphorilation and ets.

Agranular EPR is three-dimensional network of canals without ribosomes. It may be connected with rough EPR or stay alone. The vesicles with produced substance are segregated from transitional zone.

Functions of smooth EPR:

1. Cytoplasm separation on compartments, each of them has special set of biochemicalreactions.
2. Biosynthesis of lipids and carbohydrates.
3. Peroxysomes formation.
4. Biosynthesis of steroid hormones.

5. Desintoxication of exo- and enodogenic toxins, hormones, biogenic amines, drugs due to activity of special enzymes.
6. Calcium ions storage.
7. The source of membranes for nuclear envelope repair after mitosis.

GOLGI COMPLEX. This organelle was described in 1898 by Italian histologist K. Golgi. The light microscope can not give us whole view on this organelle. In light microscope, it is visible as complex network, with connected or separate cells. The morphology of Golgi complex depends on secretory cycle phase. It leaded to conclusion that Golgi complex is the organelle for product accumulation. In electrone microscope,it is clear that Golgi complex consists of membranous structures: flat membranous sacs with ampular dilatations on ends, large and small vacuoles. All these structures are united to dictiosome. One dictiosome includes 5-10 ampullar cisterns. There are several tens dictiosomes in a cell. Each dictiosome is connected with neighboring one by vacuoles. Each dictiosome has proximal, immature, CIS-zone (it looks toward the nucleus) and distal, TRANs-zone (it looks toward cell coat). CIS-zone is the place of accepting of vesicles derived from EPR. The membranes of vesicles merge with CIS-zone membrane. The secretory vesicles and lysosomes are segregated from TRANS-zone. Thus, we may conclude that there is constant flow and maturation of membranes in Golgi complex.

Functions of Golgi comlex:

1. Accumulation, maturation and condensation of protein biosynthesis products.
2. Synthesis of polysaccharides and conversion of simple proteins to glicoproteins.
3. Formation of Lipoproteins.
4. Formation of secretory inclusions and excretion them from the cell.
5. Formation of primary lysosomes.
6. Formation of cellular membranes.
7. Formation of acrosome – the structure containing enzymes. It is located on the top of sperm head. It is needed for fertilization.

MITOCHONDRIA. The organelles provide oxidation of organic substances and ATP formation. They were discovered by German scientist R. Altman in 1890. It is interesting that R. Altman assumed that mitochondria are bacteria, which invaded a cell with parasitic aim. But after a while these bacteria became symbiotic organisms.

The size of mitochondria is about 0.5-7 mcm. Their total number may vary from 50 to 5000. their well visible in light microscope, but we unable to say a lot about them. With help of electron microscope, we got more

information about mitochondrion structure. It has two membranes – internal and external, each of them has the width 7 nm. There is gap about 20 nm between external and internal membranes.

The internal membrane has cristae. The cristae are folds of internal membrane. There are fungiform structures on the crista's surface. They are known as oxysomes, ATPsomes or F_1-somes. It is APT-synthetase complex. There is mitochondrial matrix is separated by internal membrane. It contains numerous enzymes for oxidation, mitochondrial DNA, ribosomes, t-RNA, enzymes of mitochondrial genome activation. Internal membrane contains the proteins of three types: APT-synthetase complex, oxidative enzymes, transport enzymes.

External membrane has enzymes for lipid conversion to substances capable to take part in oxidative reactions.

Intermembrane gap has enzymes for oxidative phosphorylation.

Due to having own genenome, the mitochondria have autonomic system of protein sytnthesis and they can partially make membrane proteins.

Functions:

1. Providing energy for the cell in form of ATP.
2. Participation in steroid hormone biosynthesis.
3. Calcium storage.
4. Participation in nucleic acid synthesis.

It was detected some cases of mitochondrial DNA mutations. It results in mitochondrial diseases with very wide range of symptoms.

LYSOSOMES. They are invisible in light microscope. They were discovered by K. de Duve in 1955 with help of electron microscope. They are membranous vesicle containing proteolytic enzymes: acid phosphatase, lipase, proteases, nucleases and other, totally more than 50 enzymes. There are 5 types of lysosomes:

- **Primary lysosomes** – they just have been segregated from Golgi complex.
- **Secondary lysosomes** – they are lysosomes merged with phagosome – phagocytated particle surrounded by membrane.
- **Residual bodies** – they are multi-layer structures. Which appear if degradation of phagocytated particles can not be completed. The examples are lipofuscin inclusion, which are accumulated with aging.
- **Autophagosomes** – they appear when primary lysosomes merge with aged organelles and destroy them.
- **Multivesicular bodies** – they are large vacuoles containing several smaller ones. Inner vacuoles are segregated from surface of the large

one. The smaller vacuoles are gradually dissolved inside large vacuole.

Functions of lysosomes:

1. Intracellular digestion.
2. Participation in phagocytosis.
3. Participation in mitosis – degradation of nuclear envelope.
4. participation in intracellular regeneration.
5. Participation in autolysis – self-degradation of cell after it's death.

There is group of diseases, which is called diseases of accumulation. The cause of them is insufficiency of one or another lysosome enzyme. The cell accumulates undigested products, which leads to gradual cell death.

PEROXISOMES. They are organelles looking like lysosomes, but they contain enzymes for synthsis and degradation of endogenic peroxides. In electronic microscope, they look like vesicles with moderate dense core. They are made by segregation from smooth EPR. They enzymes are made separately in cytoplasm. Than, the enzymes migrate to peroxisomes.

Function of peroxisomes:

1. They are organelles which together with mitochondria utilize oxygen. The product of the utilization is H_2O_2.
2. Degradation of peroxides excess – protection of cells.
3. Degradation of toxic products with help of peroxides made in peroxisomes (detoxication. This function can be applied to liver cells, kidney cells).
4. Participation in metabolism in cell. The enzymes of peroxisomes catalyse degradation of fatty acids, facilitate amino acids exchange.

There are sso called peroxysomal diseases related with defects in peroxisomal enzymes. They are characterized by severe organs failure and are resulted in death in early childhood.

No-membranous organelles

RIBOSOMES. They are organelles of protein biosynthesis. They have two subunits: large and small. To make protein chain, these two subunits need to be united with mRNA between them. There are free ribosomes and ribosomes attached to EPR. There are single ribosomes and polysomes. Polysome is a complex of several ribosomes beaded on one mRNA.

Function of ribosome. Free ribosomes produce the proteins for cells own use. Ribosomes on rough EPR produce the proteins for out-cellular usage.

MICROTUBULES. They are organelles of fibrillar type. They have diameter 24 nm and length about several mcm. They are straight, hollow cylinders, made of 13 perypheral threads – protofilaments. Each thread consists of globular protein **tubulin,** which has two subunits – α and β. These subunits are positioned one by one in the thread. The threads are located spirally in the microtubule. There are Microtule Associated Proteins (MAP). They are branched off microtubules in various directions. They stabilize microtubules and facilitate attachment of microtubules to other components of cytoskeleton. The kinesin protein is also connected to microtubules. It has a site for ATP degradation. It uses the energy of ATP degradation for moving organelles along the microtubule. It connects with organelle by one end and slides along the microtubule by another end.

Microtubules are very dynamic structures. They have two poles: (+) and (-). The negative pole is the place of microtubule depolymerization i.e. degradation. The positive pole is the place for polymerization i.e. synthesis. In some cases, the negative pole is anchored in some structures and degradation is terminated. It results in length increasing due to growing on positive pole.

Functions of microtubules are in following:

1. They are the part of cytoskeleton.
2. They participate in organelles and substances transport in a cell.
3. They participate in the division spindle formation.
4. They are included to centrioles, flagella, cilia.

If a cell was treated by colchicines, which destroys microtubules, the cell shrinks and looses ability to division.

MICROFILLAMENTS. They are second component of cytoskeleton. There are two types of microfilaments: 1) actin filaments, 2) intermediate filaments. Beside pointed above structures, the cytoskeleton includes a lot of accessory proteins which bind filaments with each other and with other cellular structures.

Actin filaments are made from actin protein as result of polymerization of the protein. There are two forms of actin in a cell: 1) globular actin, or G-actin and, 2) polymerizated actin, in form of fibrilles or F-actin. There is dynamic balance between these two forms. Similary to microtubules, there are positive and negative poles. The process of formation and degradation of actin filaments always takes place. This process is called tread-milling. It is important for changing of aggregate state of cytoplasm, cell motility, formation of pseudopodia, cilia, exocytosis and endocytosis.

Intermediate filaments – they are filaments with larger diamenter than in actin filaments, but smaller than in microtubules. They are most stable filaments of cells. They perform supportive function. For example, they are located along processes of nervous cells, in desmosomes, in cytoplasm of smooth myocytes. The cells of different type have the different intermediate filaments. The filaments of neurons are made of three different polypeptids. The neural glial cells have filaments with acid glial protein. The cells of epithelial tissues contain keratin filaments. The muscular tissue cells (excluding smooth myocytes of vessels) have fillamentss of desmin protein. In different cells of mesenchyme origin (including smooth myocytes of vessels), there are vimetin filaments.

CENTRIOLES. They are visible in light microscope, but their definite structure was revealed only with help of electron microscope.. there are two centrioles in a cell while interphase. Two centrioles form the cell center. The centrioles are located at the right angle to each other. Each centriole is made of 9 triplets of microtubules located circularly. The neighboring segments are connected by dinein protein. It makes "bridges" between segments. There are no central microtubules. The formula of centrioles is (9x3)+0. Each triplet of microtubules is connected with spherical structures – satellites. The microtubules branch off satellites in various direction making the centrosphere.

The centrioles are dynamic structures. They are different during different periods of mitotic cycle. In the cell, which is not subject to division, the centrioles are located centrally near the nucleus. The reduplication of centrioles takes place while S-period of interphase. In the daughter centrioles there are only 9 single microtubules. The triplets are formed during maturation. The couples of centrioles move to the cell poles while mitosis, they become centers for mitotic spindle organization. Value of centrioles:

1. They are the center of mitotic spindle organization.
2. They take place in cilia and flagella formation.
3. They provide intracellular movement of organelles.

Some authors consider the second and third functions as the main functions, assuming that plant cells have no centrioles, but they are divided very actively with spindle formation.

CILIA AND FLAGELLA. They are the special organelles for movement. Only several cells have them – spermatozoa, epithelial cells of trachea, epithelial cells of ductus deferens and etc. It was revealed with help of electron microscope, that there is basal body in the basement of cilia and flagella. Basal body is congregation of granules. It is the matrix

for cilia growth. The 9 duplets of microtubules arise from basal body. Each duplet connected with neighboring one by dinein protein. There is central pair of tubules coated by muff. The duplets give of spokes to central pair. The formula of cilia and flagella is (9x2)+2.

The main protein of microtubules is tubulin. The dinein has ATPase activity. It can degrade ATP and use energy to slide microtubule duplets one along another. It is how the wave-like movement of cilia and flagella occurs.

There is the hereditary disease –Cartagener syndrome. There are no dinein proteins or central pair of microtubules in the cells of the patients. Such patients suffer from severe repeating bronchitis, sinusitis, tracheitis. The male are infertile due to sperm immobility.

MYOFIBRILLES are located in muscular tissues. Their structure is described in the topic "Muscular tissues".

NEUROFIBRILLES are located in neurons. They consist of neurotubules and neurofillaments. Their function is support and transport.

Inclusions

Inclusions – are temporary components of a cell, which haven't constant structure. They can be revealed only during some periods of life or life cycle.

CLASSIFICATION.

1. **Trophic inclusions** are nutrients, which are saved for reserve. The examples are glycogen and fat inclusions.
2. **Pigmennt inclusions.** The example of such inclusion is hemoglobin in erythrocytes. Some cells can accumulate lipofuscin. It is considered as aging pigment. It is believed that lipofuscin not carry any function. It is formed in result of wearing out of organelles. Hemoglobin participates in gases transport. Melanin, the pigment inclusion, protects form UV radiation.
3. **Secretory inclusions** are revealed in secretory cells. They encount biologically active substances, hormones and other substances, which are necessary for organism living. They look as vesicles surrounded by membrane with different electronic density.
4. **Excretory inclusions** – are inclusions, which are needed to be evacuated from cell. The example is urea inclusions in kidney cells.
5. **Special inclusions** – are phagocyteted particles.

Intercellular junctions and relationships

Intercellular relationships – are relationships between cells. They can be distant and contact, as well. The distant relationships are performed with help of soluble substances,which are secreted by cells into cell environment. The substances reach and affect target cell. Such substances are called mediators or transmitters. Hormones, biogenic amines, antibodies and may other substances can play the role of mediators or transmitters. All these substances act on the target cell through superficial receptors. Therefore, such relationships are suitable in immune reactions, hormone action, embryonic induction and in other important reactions.

Moreover, in multicellular organism the cells connected with each other with help of intercellular junctions (contact relationships). Contact relationships are complex process. They have several phases and include distant relationships as the first phase.

1. Recognizing of one cell by another one (can be distant, by mediator, or contact, by receptors).
2. Setting the vulnerable connections between cells.
3. Formation of close stable contacts.

The second and the third stages are performed with help of molecules of cell adhesion.

All intercellular junctions are divided into three classes:

1) Adhesion contacts. They mechanically bind cell to another. The main type of such junctions are desmosomes. The desmosomes can be of three types
   - ✓ Adhesion spots (macula adherens). They bind cells in some particular spots. At the site of desmosome the plasma membrane (of each cell) is thickened because of presense of a dense layer of proteins on its inner surface. The thickened areas of two membranes are held together by fibrils that appear to pass from one membrane to the other across the gap. The intermediate filaments attach to the thickened area from iside of cell. The junction gap is about 25nm.
   - ✓ Adhesive belts (Zonula adherens). They lie along the cell side as a strip or belt. This belt is made of actine filaments from cytoplasm side. There are electronic dense material (incuded molecules of cell adhesion) in the gap.
   - ✓ Hemidesmosomes. These are similar to desmosomes, but the thickening plasma membrane is seen only on one side. The contacts of such type facilitate attachment of a cell to non-cellular structures, for example to basement membrane.

2) Tight junctions. Such type of contacts bind adjoin cells so tightly, that substances can not pass between them. The cell membranes are connected with help of special proteins. The gap in junction is 5 nm.
3) Communicating junctions. Here, it is possible to transmit some molecules from one cell to another through the junction. The junction gap is 3 nm. There are canales in the membranes of adjoin cells. These canals made of connexin proteins. The molecules with low molecular weight can pass through the canals. The example of such junction is the nexuses in cardiac muscle cells. The other example is synapses between nervous cells.

There is one more type of intercellular junctions. It is interdigitatory projections. The cytoplasm of one cell bends down the cytoplasm of the other cell, forming, so called, digitatory projections. It increases the surface and strength of junctions.

Mechanism of substance transport to a cell. Exocytosis and endocytosis

The substances required for a cell may enter the cell by different ways. Small molecules are transported by active and passive transport. The passive transport occurs without energy lost. The substances are moved along the concentration gradient through special transportation canals made of integral proteins. Active transport requires energy for transportation. It is performed by integral proteins, as well. Large molecules are transported to a cell by endocytosis.

Endocytosis – it the process of macromolecules entering to a cell. It has two variants: phagocytosis (entry of big solid particles) and pinocytosis (entry of fluids).

Endocytosis may be divided into receptor-mediated and receptor-independent. The later one is concluded in following. The substance enters to cytolemm invagination. The substance affects unspecific superficial receptors of the cell. It stimulates complex of contractive proteins in sub-membranous layer. The elements of cytoskeleton cause progressing of cytolemm invagination. It results in vesicle formation. It segregates from plasmalemm and moves deep in cytoplasm. If the vesicle contains solid substance, it is called phagosoma. If the vesicle contains liquid substance, it is called pinosoma. The phagosomes can fuse with primary lysosmes and can form phagolysosomes.

The second variant of endocytosis is receptor-mediated endocytosis. The substance (ligand) binds with specific receptors on cell surface. The ligand with receptors is absorbed more quickly.

The often event while receptor-mediated endocytosis is capping. The receptors migrate laterally to forming endocytotic pits. Thus, the concentration of receptors in endocytotic pits becomes higher. Claritin protein is accumulated outside of forming vesicles. It forms reticular coat. It is the way of formation the coated vesicles. The content of the vesicles may undergo further transformations only after lost of claritin coat. Until this, the vesicle is unable to fuse with lysosomes or any other organelle. The coated vesicles are used for transportation of immunoglobulines, yolk inclusions in ovocyte, growth factors, low density lipoproteins and etc. They are so called accumulators of cellular receptors. The receptors from these vesicles may be re-incorporated to membrane structure. The coated vesicles allow capturing a lot of substances with low consumption of receptors and cellular membranes. The example of receptor mediated endocytosis is capture of bacteria coated by antibodies by a macrophage.

Exocytosis – it is a process quite the contrary to endocytosis. It is excretion of terminal metabolic products or products of secretion by a cell. In case of secretion, the secretory vesicles are segregated from Golgi complx and are moved to the cell membrane. They merge with it letting out the secretion products. Exocytosis is a basic mechanism of merocrine secretion of glands.

Excreted substances may stay on a cell surface as receptors, or may be included to intercellular ground substance, or act as biologically active substances.

Pinocytotic vesicles may be utilized in a cell or may be transported though the cell and be released from the other side of the cell. The later event is called transcytosis. The transcytosis includes both endocytosis and exocytosis. It is especially prominent in the endotheliocytes of vessels.

CYTOSKELETON. Cytoskeleton is integrity of supportive and contractive structures of a cell. It is a three-dimentional framework of actine filaments, microtubules, microtrabecules and intermediate filaments. Actine filaments are labile. They can be destroyed and reconstructed easily (tread-milling). As result of this reconstruction, the shape of the cell is changed. Microtubules have the same ability. Microtubules together with intermediate filaments work as supportive units. Intermediate filaments have larger diameter than actine microfilaments, but smaller than microtubules.

Microtrabecules are visible only with help of electronic microscopy of high voltage. They are the worst studied element of cytoskeleton. It has diameter 2-10 nm. They form gentle network. The ribosomes and organelles are located in the nodes of the network.

Cytoskeleton is connected from one side with contractive and supportive elements of cellular membrane, and from another with organelles and nucleus. The extracellular signals can be transmitted by cytoskeleton to any organelle and nucleus.

Functions of cytoskeleton:

1. Support.
2. Regulation of cellular viscousity, cellular shape and movement.
3. Participation in endo- and exocytosis.
4. Participation in cytotomia while mitosis.
5. Intracellular transport of vesicles and organelles.
6. Providing lateralmovement of membrane proteins and capping.
7. Intermediate filaments are the sign of tissue origin. The cells of one tissue type have same pattern of intermediate filaments. Like, epithelial tissues have keratin filaments, muscular tissues cantain desmin filaments, connective tissues – vimetin filaments, nervous tissue – neurofillaments.

EXTRACELLULAR MATRIX. Extracellular matrix – is substance located between cells. In connective tissues, the extracellular matrix is one of tissue elements. It is called intercellular ground substance. It contains fibers and amorphous substance. Amorphous substance contains water and different maromolecules: proteins, carbohydrates, proteoglycans, glucoseaminoglycans and others. In epithelial tissues the ground substance is absent. Epithelial tissues have special form of extracellular matrix – basement membrane.

The main macromolecules involeved into "cell-matrix" relationships are laminin, fibronectin, nidogen/endotactin. They interact with superficial receptors on cells, which transmit information through intracellular proteins tallin, vinculin and α-actinin to actin filaments of cytoskeleton. That is why mechanical, chemical and other changes in extracellular matrix influence functional activity of cells.

Functions of extracellular matrix:

1. Support.
2. Maintaining of metabolic processes.
3. Providing substances entry to a cell.
4. Regulation of cells activity.
5. Morphgenetic. That means extracellular matrix takes place in setting tissue architecture, reparation, wound healing.
6. Transportation.

Interaction of cells structures during its metabolism (on an example of synthesis of proteins and non-protein substances)

All cellular structures are connected with each other while performing cell's functions. It can be shown on example of synthesis of proteins and non-protein substances.

The chain of events while protein synthesis is the following.

1. Transcription of DNA results in mRNA formation.
2. Nucleolus produce ribosomes, which than travel to cytoplasm.
3. Ribosomes attach to EPR (in case of protein synthesis for outside usage).
4. Mitochondria produce ATP, which is needed for protein synthesis.
5. The polypeptide chain is produced on rough EPR.
6. Polypeptide chain goes to Golgi complex. Here, the last stages of processing take place and protein is packed for excretion.
7. Secretory granules are moved by cytoskeleton to cell surface. The protein is excreated by exocytosis.

The chain of events while non-protein substances synthesis is the following.

1. Transcription of DNA results in mRNA formation. Nucleolus produce ribosomes, which than travel to cytoplasm.
2. Free ribosomes in cytoplasm produce enzymes for synthesis of non-protein substances.
3. Enzymes travel to smooth EPR. Here, the non-protein substances are made.
4. Than they travel to Golgi complex. Here, they are packed to the vesicles for excretion.
5. Secretory granules are moved by cytoskeleton to cell surface. The non-protein substances are excreted by exocytosis

Chapter 3: Cytology 2

Stucture and functions of cell nucleus

Nucleus of a cell is the major cell component. Its functions are:

1. Hereditary information storage in DNA molecules.
2. Realization of hereditary information by controlling of living processes of a cell.
3. Transmitting the hereditary information while cell division to descents.

4. Control and regulation of structural-functional condition of cytoplasm, cell coat, cytoreceptors.

Number of nucleuses, shape of the nucleuses and size of the nucleuses depend on cell type and functional state of a cell. The most common are uninuclear cells but some cells, as hepatocytes are, may have several nucleuses due to active functioning state. For some cells, the having of many nucleuses is the normal feature.

Shape of nucleus may be different.

Size of nucleus depends on functional state of a cell. Functionally active cells have larger nucleus. Polyploid cells also have larger nucleus.

There are post-cellular structures in organism, like platelets, erythrocytes and etc. They have no nucleus. It has been lost during differentiation. The majority of processes, which are typical for usual cell, are absent in post-cellular structures. They perform their particular function and than die.

During interphase a nucleus has 4 components:

1. Chromatin (interphase form of chromosome being).
2. Nucleolus.
3. Nuclear coat (or envelope).
4. Nuclear juice.

CHROMATIN. It is interphase form of chromosome being. During interphase, the chromosomes are decoiled. That is why they are invisible in light microscope. The regions of DNA with decoiled DNA are called euchromatin. Condensed dense chromatin has significant basophilia and it is visible in light microscope. Such zones are inactive and they are called heterochromatin. Heterochromatin can be of two types: 1) constitutive heterochromatine – such type of chromatin which never and nowhere can be decoiled. It is usually localized near cenromeres, 2) facultative heterochromatin - such type of chromatin which can became euchromatin in particular cells or under special conditions.

The color of a nucleus depends on quantity of heterochromatin in it. If the nucleus is significantly basophilic, it means that there is a lot of heterochromatin and it is a sign of inactive cell. On the contrary, if a cell have light nucleus, the euchromatine prevails over heterochromatin. It is a sign of the active cell.

NUCLEOLUS. It is dense structural component of nucleus. The cell may contain one or several nucleoluses. The nucleolus is integrity of regions from 10 chromosomes (13.14.15.21.22 pairs). Such regions are called nucleolar organizing centers. They contain multiply copies of rRNA

genes. The transcribtion of information about rRNA takes place in nucleolus. The nucleolus disappears during mitosis.

Function of nucleolus – is to produce ribosome RNA.

NUCLEAR ENVELOPE. It is made of two biological membranes. External membrane merges with EPR. There is vimetin filaments network from the cytoplasm side. There is perynuclear space between two membranes (20-40 nm in width). It is analog of granular EPR and may contain products of protein synthesis.

Internal membrane is smooth. It is closely connected with lamina (or nuclear lamina). It is a condensing of intermediate filaments. They have a contact with network of intermediayte filaments which form the nuclear skeleton.

Nuclear envelope has pores. They are the holes in nuclear membrane. There is pore complex inside of a pore. It is a complex of fibrillar and granular structures, which regulate substances flow to/from nucleus.

Functions:

1. Border
2. Defense
3. Transport regulation

NUCLEAR JUICE – it is a fluid component of nucleus. It is colloid solution of proteins, carbohydrates, nucleotides and different salts. The most important proteins are histons, enzymes and etc.

Functions:

1. Environment for all processes in nucleus.
2. rRNA, mRNA, tRNA transport to pores.

CHROMOSOMES. They are visible only in mitosis. It is most convenient to study them in metaphase (metaphase chromosomes plates). The main chemical compounds of chromosomes are DNA and proteins. DNA and histon proteins together make fibrilar structure – elementary chromosome fibril, which is made of nucleosomes. Each nucleosome is a complex of 8 histon proteins. DNA molecule turns twice aroung the nucleosome. The DNA regions, which connect two neighboring nucleosomes, are named linker DNA. The next level of organization is nucleomere or chromatin fibril. One nucleomere contains 8 nucleosomes. It has diameter about 30 nm. During interphase, the chromosomes are made of chromatin fibrils (nucleomeres). The chromosomes are coiled before mitosis. The nucleomere subject to packing and becomes chromomere. Chromomere has loop domens. Each loop domen has diameter up to 300 nm and corresponds to one or several genes. The next

step of chromosome packing is spirilized chromosomes, which are visible in mitosis.

Morphology and classification of chromosomes

Each chromosome looks as a band in light microscope. Most of the chromosomes have primary constriction or centromere (or kinetochore). The centromere divides chromosomes to short and long arms. If the length of the arms is approximately equal, the chromosome is classified as metacentric. If the arms are only slight differently in length, the chromosome is classified as submetacentric. If the difference between arms is significant, the chromosome is classified as acrocentric. Some chromosomes have secondary constriction. The part of chromosome, which is separated by secondary constriction, is called satellite body. Secondary constriction are concerned with the formation of nucleoliand are called nucleolar organizing centers.

There is Denever's chromosome classification (1960). It accounts chromosomes size, primary and secondary constrictions. In compliance with Denver's classification there are 7 groups of chromosomes (A,B,C,D,E,F,G). There is also Paris chromosome classification. It is based on differential staining of chromosomes by different stains. Staining reveals alternative black and white regions, which are unique for each chromosome. Staining is reliable way to identify chromosomes.

All chromosomes of a cell make karyotype. The chromosomes may be somatic and sex chromosomes. Somatic chromosomes make homologous (similar) pairs. A human has 22 pairs of somatic chromosomes. Sex chromosomes are different in male and female organism. A male cell has X and Y chromosomes. A female cell has two X chromosomes.

Ways of cells reproduction

The universal mechanism of cells reproduction is mitosis. There are variants of mitosis – endomitosis and meiosis. Some investigators concern amitosis as an independent way of reproduction. But today, it seems that eukaryotic cells are not subject to amitosis.

MITOSIS. It is indirect cell division connected with changes of nucleus. There are 4 mitotic phases: prophase, metaphase, anaphase and telophase.

The PROPHASE of mitosis includes the flowing ivents:

1. The chromosomes become visible due to coiling of chromatin. Each chromosome consists of two chromatids.
2. The nucleolus disappears due to chromatin condensation. The synthesis of rRNA is temporally canceled.

3. The spindle of division is formed from cytoplasmic microtubules. The organizing centers of spindles are centrioles located on the cell poles. Microtubules are attached to centromere of chromosomes. Kinetochore is formed from proteins of special kind in the attachment region.
4. The nuclear coat falls down on small pieces. It becomes indistinguishable from EPR. The pore complex and lamina are also degraded to subunits.

METAPHASE. All chromosomes are located on cell equator. Thry are fixed in this position by microtubules of mitotic spindle. Daughter chromatids start to move apart, but they still connected in the centromere region. The chromosome make metaphase (or equatorial) plate.

ANAPHASE. Daughter chromatids move apart towards cell poles with speed up to 1 mcm per minute. The length of anaphase is about several minutes. The mechanism of chromatid movement to poles is not fully clear. It is assumed that the signal to movement is rapid increase of calcium ions concentration in cytoplasm. It is possible that the reason of movement is depolimerization of microtubules from kinetochore end. Other suppose that the reason is interaction of actin, myosin and dinein proteins located around mitotic spindle.

TELOPHASE. When the daughter chromatids reach cell poles, the kinetochore tubules disappear. The new nuclear coat is formed around each group of chromatids from agranular EPR. Pore complex subunits and lamina, which are already exist in cytoplasm, are included to new nuclear coats. Condensed chromatin starts to decoil. The nucleoli appear. The organelles are distributed between two daughter cells. Then, the contractive ring is formed in the center of a cell perhaps working of actin filaments. The ring constriction progresses. It results in cytoplasm division and formation of two new cells.

At the same time with normal mitosis, the abnormal variants of mitosis are observed. The unequal distribution of hereditary information (aneuploidy) between daughter cells may take place. The chromosome aberration may be detected. They frequently appear after X-ray radiation. Pathological mitoses are typical for tumor cells.

ENDOMITOSIS. It is a variant of mitosis, when chromosome replication not results in formation two new cells. There are several variants of endomitosis.

1. POLYTENIA – here, the chromosome replication leads to enlargement of chromosomes in several times. It takes place in invertebrates.

2. POLYPLOIDITY – it is chromosome number multiplication divisible on two. Later, polyploid cells may have genome segregation and fall down into several cells with diploid chromosome set.
3. FORMATION OF TWO NUCLEAR AND MULTINUCLEAR CELLS. They are formed in case of nuclear division without cytoplasm division. Later, those cells may fall down with formation of mononuclear cells.

Endomitosis results in cell size enlargement. Such cells are more functionally active. It is taken to have adaptation effect for a cell.

AMITOSIS. Nowadays, the majority of scientists refuse the existence of amitosis. That is why amitosis is not discussed in many textbooks as way of cell reproduction.

Amitosis – it is cell division without any changes in chromosome apparatus. It results from simple nucleus and cytoplasm division without chromosomes and spindle formation. One form of amitosis is genome segregation – multiply division of polyploid nucleus.

Those investigators, who assume amitosis, can distinguish reactive amitosis (as response on external factors), pathological amitosis (in case of pathology) and degenerative amitosis (in aging cells).

MEIOSIS. It is division of reproductive cells as variant of mitosis. It results in formation of cells with haploid chromosome set. Meiosis consists of two following mitotic divisions: MEIOSIS I AND MEIOSIS II.

Meiosis I is called reduction division. There is chromosome number reduction in two times. Meiosis I has complex prophase including 5 periods or phases:

- ➔ LEPTOTENE – chromosomes look like thin threads.
- ➔ ZYGOTENE – conjugation of homologous chromosomes takes place.
- ➔ PACHYTENE – chromosomes become thicker and shorter.
- ➔ DIPLOTENE – chromosomes are split on two chromatids. There are tetrads consisting of four chromatids.
- ➔ DIAKINESIS – chromosomes become more shorter and move apart.

The following stages of meiosis I are the same as in mitosis, but the chromsomes move to the poles in spite of chromatids in mitosis. It leads to chromosome set reduction.

Meiosis II is similar to mitosis. Details about meiosis you can find in Embryology chapter.

Nuclear-cytoplasmic ration as a parameter of functional state of a cell

The ratio between nucleus volume and cytoplasm volume is called nucleo-cytoplasmic ratio (NCR). The NCR shows the state of a cell. If the ration is more than 1, it means that the cell has big nucleus and few cytoplasm. This ratio is typical for stem cell, lymphocytes, and aging cells. These cells are functionally inactive; usually they have ability to division. Over wise, the cells with NCR less than 1 have large volume of cytoplasm and therefore many organelles. They are highly differentiated and capable to work actively.

Mitotic cycle. Life cycle of a cell

Mitotic cycle – is the time from one division to another. It is divided to mitosis and interphase. The interphase has three periods:

1. **G_1-period**. It is characterized by activization of metabolic processes needed for DNA replication. The cell growth, protein synthesis and RNA synthesis are observed. The cell returns to normal size and set the normal quantity of organelles. There is synthesis of special **S-period activation proteins**.
2. **S-period**. It is the period of DNA replication. The chromosomes become fully replicated. The centrioles also double.
3. **G_2-period.** Here, we have synthesis of m-RNA, r-RNA, tubulin. Tubulin is needed for spindle formation. The energy storage takes place. It is followed by mitosis.

Life cycle – is the time from one cell division to another or to the cell death. There are three cells types with different life cycle:

1) **Stem cells.** These cells are capable for permanent cell division. They maintain tissue homeostasis by new cells formation on a place of died or lost cells. The life cycle of these cells corresponds with mitotic cycle. Notwithstanding the not limited division ability, the stem cells divide very rare. After division they stay in elongated G_1-period. Some stem cells can become semi-stem cells after division. The semi-stem cells are the cells which divide very actively.
2) **Differentiated cells.**
   - ❖ ***Irreversible differentiated cell.*** Such cells are capable for division only during embryonic period. When the population of the cells reaches the necessary volume, there are no more divisions among the cells. The examples of such cells are neurons and cardiac myocytes. The life cycle of such cells has the following periods: mitotic cycle → determination (choosing of differentiation way) →

differentiation (forming the particular features of cell for performing the function) → specialization → period of active functioning → aging → death.

- ***Reversible differentiated cells***. Such cells (like liver cells) can leave mitotic cycle and enter G_0-period or resting state. From this point they have two ways to go. One is mitotic cycle and another is way of differentiation. The preference is given accordinary to tissue needs. If there is tissue lost, these cells enter mitotic cycle. If there is functional load on tissue, these cells become differentiated cells to perform the function of organ. That is why reversible differentiated cells are called the reserve of the tissue.

Types of cellular populations. Mechanisms of homeostasis regulation in different types of cellular populations

The size of a cellular population is strictly regulated in a multicellular organism. The mechanisms of tissue homeostasis are complicate. There are mitosis and apoptosis on the different sides of the range.

As it was pointed above, there are three cell types accordinary to life cycle. The tissues are made of such cells combinations. French scientist K.Leblon suggested classifying all cell population of an organism to three main groups

1. **Static (stationary) cell populations**. There are only irreversible differentiated cell in mature state of tissue. The stem cells are absent. The examples of such populations are nervous and cardiac muscular tissues. The total cell number can not be increased in these populations. Moreover, as times goes by some cells of the population dies by necrosis or apoptosis. While aging the process becomes more active.

2. **Growing cell populations**. There are groups with small proliferative index in normal state. But, there is small cell lost, as well. Such populations contain: 1) very few stem cells, 2) differentiated cells, 3) resting cells.

The examples of this type of populations are liver parenchyma, kidney cells, thyroid gland. During embryogenesis, hepatocytes population growths rapidly. After birth, the rate of divisions in liver falls down. In adults mitosis rate is extremely low. At the same time, the liver can successfully repair cell lost while injury. Resting cells come back to the mitotic cycle. The multiplication of resting cells recover cell lost.

3. **Renewing cell populations**. The intensive multiplication of cells in the populations of this type is balanced by intensive cells lost by apoptosis. Such populations have: 1) relatively small fraction of stem cells, which

maintains cell number in population by divisions. Most of the time they spend in elongated G_1-period. 2) irreversibly differentiated cells, which perform main functions of population.

The mechanisms of homeostasis maintaing depend on the population type.

1. In static cell populations the regulatory mechanisms are directed on apoptosis regulation

2. In growing cell populations the regulatory mechanisms may be directed on:

- ❖ Regulation of entry/quit of cells to/from resting state.
- ❖ Regulation of mitotic cycle length.
- ❖ Regulation of differentiation rate.
- ❖ Regulation of apoptosis death rate.

3. In renewing cell populations the regulatory mechanisms may be directed on:

- ❖ Regulation of entry/quit of stem cells to/from elongated G_1-period.
- ❖ Regulation of mitotic cycle length in stem cells.
- ❖ Regulation of apoptosis death rate.

In last case, the cell population number depends on ratio between mitotic activity and apoptotic cell death. If the both are equal, the population is balanced in stationary state. If cell proliferation exceeds death, there are cells incomes, tissue hypertrophy, and adaptation to harmful factors. If apoptotic death exceeds proliferation, there are cells lost, tissue atrophy. It may take place, when tissue returns to a normal state after hypertrophy.

General features of resting cells (G_0-period)

There are some mechanisms in resting cells, which can keep macromolecules in balanced state, saving cells from death in inappropriate conditions. Perhaps, this can maintain the resting state extremely long. At the same time the cells can perform some specific function, but with small rate. The reparation of DNA may take place in the resting state.

The resting cells have the following features:

1. They are smaller than proliferative cells.
2. They have more condensed chromatin.
3. They have low level of DNA synthesis.
4. The RNA concentration has been decreased with synchronous increasing of its synthesis/degradation processes.
5. Cytolemm permeability is decreased.

6. Metabolic processes and respiration rate are decreased.

Mechanisms of cell regeneration

Regeneration – is ability of a cell to repair damaged or lost parts. There are intracellular regeneration and cellular regeneration. Intracellular regeneration includes repair of old organelles and damaged cell parts. Cellular regeneration includes cells division and restoring cell number by mitosis.

Regeneration can be physiological and reparative. Physiological regeneration is renewing of old cell parts or whole cells. Reparative regeneration is the cell repair after injury. After injury, there are compensative and adaptive changes in a cell together with reparation. They are directed on smoothing injury consequences. If number of organelles increases during regeneration, it is called hyperplasia of organelles. If number of organelles stays the same, but they become larger – it is hypertrophy of organelles. These two processes cab be combined. These processes resulting in cell enlargement. The cell becomes more resistant to harmful factors by this.

Reactive properties of cells. The concept about cellular hyperplasia and hypertrophia. Cells death. Necrosis

Reactive properties of cells – are changing in structure and functions of cells in response on external factors influence. If external factor is a moderate one, the cell doesn't die, but it subject to compensative and adaptive changes. Such changes may be as following:

1. External factor may activate cells division. The cells number increases. If the factor acts on larger cells number, its influence on one particular cell is decreased. The process of cell multiplication is named cellular hyperplasia.

2. External factor may affect cell which unable to divide. In this case, it causes hypertrophy and hyperplasia of organelles. The protein synthesis is activated, as well as, DNA reparation. It results in the cell growth. The process called cellular hypertrophy.

3. External factor influence may lead to diploid and polyploid cell formation. Such cells are larger in size and they are functionally more active. By this they become more resistant.

4. External factor may cause rising of metabolism rate. The cells become functionally more active. The cells increase square of the surface, it may become more complex. The phagocytosis may be activated, especially in those cells, in which it is one of main functions. Cells may increase locomotion. The muscular cells will response on an irritation by

contraction, nervous cells – by impulse exiting, glands – by producing more secrete and so on.

5. Any strong external influences cause stress reactions in cells. They have the same mechanism. Some genes become activated. They provide synthesis of Heat Shock Proteins (HSP). It is universal proteins, which protect a cell. They are more resistant. They prevent coagulation, damage, aggregation of other proteins. They can split pathological conglomerates of proteins, which was already made.

6. If the influence of external factors is especially strong, the cell will die by necrosis. Usually, the necrosis affects the groups of closely lying cells. We can observe morphological changes in nucleus and cytoplasm. The following changes may occur in cytoplasm. The activated lysosome enzyme DNAase spite nuclear DNA on fragments of different length. It results in changing chromatin distribution. It concentrates in small congregates under nuclear envelope. Than, nucleus subject to following changes:

- KARYOPIKNOSIS – shrinking of nucleus until it fully disappear.
- KARYOLYSIS – dilution of nucleus with graduate disappearing.
- KARYOREXIX – rapture of nucleus on separate fragments, which than disappear.

The nucleus deprived cell is unviable and gradually die.

There is organelles degeneration in cytoplasm. Cysternae of EPR are militated. Rough EPR loses ribosomes. The mitochondrion matrix become lighter, the intermenbraneous gap becomes wider. Finally, the mitochondrion membranes are ruptured and mitochondria are destroyed. The lysosome membranes become vulnerable and enzymes come to the cytoplasm. It causes self-digestion of cytoplasm. The damage of cellular membrane connected with calcium accumulation in cell. It activates phospholipases. These enzymes can destroy phospholipids of membranes. The vacuoles are formed in cytoplasm (vacuole dystrophy). The atypical lipid and protein inclusions may appear in cytoplasm (lipid and protein dystrophy). The remains of the cell are phagocytated by macrophages.

Genetically programmed death (apoptosis)

Apoptosis is often called as physiological, altruistic cell death, whereas necrosis represents accident cell death. The term "apoptosis" (fall of the leaves) was suggested by G. Kerr in 1971. He insisted those

apoptotic cells are similar to falling leaves: apoptotic cell shrinks and fall out of tissue context.

Apoptosis is opposite to mitosis. It has genetic base. There are apoptotic genes, as well as, proliferative genes in genome of a cell. One of most studied mechanisms is induction of Fas/Apo-1 (CD95). Apoptosis together with mitosis regulates tissue homeostasis. It is interesting that the same factors in different situations may either stimulate mitosis or set apoptosis.

Mechanism of apoptosis

Apoptosis is induced through receptors of cell membrane. The line of events while apoptosis induction may look as following.

Signal to apoptosis (ligand) → ligand binding to receptor → transmition of signal to cell nucleus → activation of apoptotic genes → synthesis of apoptosis proteins → regulated activation of Ca^{2+}-dependent endonucleases → internucleosome fragmentation of DNA → cell death.

The differences of apoptosis from mitosis are presented in a chart below.

APOPTOSIS	NECROSIS
The cells, which are subject to death, located mosaic in a tissue	There is massive cell death located close to each other.
It is genetically programmed cell death	It is a death resulted from " emergency accident"
It is energy dependent process connected with synthetic processes (protein synthesis).	Energy independent process. All proteins, which are needed, are already made.
There is regular internucleosome splitting of DNA.	DNA degradation is irregular. The fragments, which have been made, are of different size.
There are karyopiknosis and karyorexis only.	There are karypiknosis, karyorexis and karyolysis.

Morpholgy of apoptosis.

Changings in nucleus. The regular internucleosome fragmentation results in chromatin "packing" in form of demilunes under karyolemm. The nucleus becomes dense with jags. Than, nucleus falls to pieces surrounded by membranes (karyopiknosis and karyorexis only).

Changings in cytoplasm. The active and progressive destruction of cellular organelles results in cytoplasm condensation. The oxyphilic

inclusions appear. Due to cytoplasm condensation, the cell looks as surrounded by light band.

Changings in cell surface. The many projections of cytoplasm appear on cellular surface (blabbing). These projections may contain organelles and parts of the nucleus. Later, they are segregated from cytoplasm. Cell fall to surrounded by membrane pieces – apoptotic bodies. They are phagocytated by local macrophages.

Regulation of apoptosis

As important factor of tissue homeostasis regulation, apoptosis is strictly regulated on different levels.

1. Genomic-nuclear level. One of most studied mechanisms of apoptosis is induction of expression of Fas/Apo-1 (CD95). This gene produces specific receptor of cell surface APO-1. The exiting of the receptor starts suicide programm. One of the factors which bind the receptor is Tumor Necrosis Factor (TNF). There is a family of intracellular messengers, which are involved in signal mediation in cytoplasm.

2. Tissue level. Here, the apoptosis regulation is performed by different cell populations. For example, Langherhans cells of skin may induce keratinocytes apoptosis. The lymphocytes may also induce apoptosis.

3 Organism level.

- Immune regulation. Different cells and mediators of immune system may induce apoptosis. The antibody-mediated apoptosis was proved. Antibodies may affect cellular receptors causing apoptosis.
- Hormone regulation. One of apoptosis inductor is steroid hormones. The cells deprived of steroid receptors are not subjected to cell death. In takes place in leucosis cells. The mechanism of glucocorticoid action is in stimulation DNA fragmentation. Because of this action, the glucocorticoids are used in leucosis treatment.

In other cases, the apoptosis may be induced by hormone insufficiency. If the level of testosterone in blood falls down, the increasing of apoptotic cell death takes place in prostate gland and in adrenal cortex. The effect of castration of patients with prostate cancer is in absence of androgen stimulation of cancer cells. From other side, the female hormone stimulates apoptosis in prostate gland, as well.

Nervous regulation. Nervous system also participates in apoptosis regulation. It was stated, that apoptotic death is increased after denervation of an organ.

The factors, which stimulate and inhibit apoptosis, are listed below.

INUCTORS OF APOPTOSIS	INHIBITORS OF APOPTOSIS
Tumor Necrosis factor	Growth factors
Deprivation of growth factors	Intercellular matrix
Detachment from intercellular matrix	Androgens, estrogens
Calcium	Interleukin-2,3,4,10
Glucocorticoids	Tumor inductors
Interleukin-1	Interferon α
Interferon γ	Zinc

Apoptosis may be induced by action of high and low temperatures, viral infection, bacterial toxins, X-ray radiation, UV-radiation and by other factors.

General and medial value of apoptosis

1. Apoptosis in embryogenesis. There is not only cell growth in embryogenesis. Some embryo rudiments are subjected to regression. The apoptosis is highly involved in these processes.

2. Apoptosis of aging cells in adult organism. The apoptosis is a "scavenger" of old cells. It clears the space for new cell to grow. It static cell population, the apoptosis decreases cell number.

3. Apoptosis play important role in some organs involution. For example uterus involution after delivery, mammary gland involution, gonads involution in elderly.

4. Apoptosis in immune system rule thymus involution, involution of peripheral organs after immune response.

5. Apoptosis as reaction on weak external factors and injuries.

6. Apoptosis in degenerative, atrophic, inflectional and ontological diseases. There are diseases connected with inhibition and induction of apoptosis. Some of them are listed below.

Diseases connected with inhibition of apoptosis	Diseases connected with induction of apoptosis
Bronchial asthma	AIDS
Atopic dermatitis	Anemia
Autoimmune diseases	Myocardial infarction
Glomerulonephritis	Stroke
Schizophrenia	
Oncological diseases	

7. Apoptosis of cells in renewing cell populations. Normally, the number of cell produced in such populations is more than it is necessary for homeostasis maintaining. The excess of cells is subjected to apoptosis.

It is necessary to make a basement for adaptation. If any factor affects the tissue, the some part of cells dies. In that cells, which was directed to apoptosis, the program is changed. They turn to differentiation.

8. Apoptotic death of mutated cells and cells affected by virus. It helps to keep an organism well.

The factors of apoptosis induction may be suppressed while oncological diseases. The tumor cells not subject to apoptosis by this. It results in tumor growth. Apoptosis induction may serve as a treatment in this case. The immune cells can induce apoptosis in cancer cell. Thus, they protect our organism.

9. Apoptosis and immortality problem. The mutation in apoptotic genes may provide immortality for cells. The regulated changes of these genes are possible solution of immortality problem.

Chapter 4: The human embryology

Embryology – is the science about embryonic development of a human as part of human ontogenesis. The term "embryology" comes from Greek "em brio" that means "in coats". Medical embryology studies human embryonic development, causes of its failures, influence of exogenic factors on embryogenesis and mechanisms of its regulation. Recently medical embryology studies provided the possibilities for extracorporal fertilization and development as methods of infertility treatment.

Medical embryology is not only morphological science. It also studies development of organism functions, biochemical changes during embryonic development and etc. That why it includes several directions such as:

1. Describing embryology which uses methods of visual observation and description of development processes.
2. Evolutionary embryology studies embryonic development in evolutionary aspect to determine common features in phylo- and ontogenesis and to use them to human embryonic development.
3. Experimental embryology designs different experiments to reveal hidden features of embryonic development.
4. Biochemical embryology studies biochemical aspects of embryonic development, chemical factors which regulate ontogenesis and etc.
5. Histological embryology studies morphological aspects of human embryonic development on tissue, cellular and subcellular level.
6. Pathological embryology is a biomedical scientific direction which studies etiology, pathogenesis and preventive measures of human

embryonic failures. This direction has close relations with teratology – the science about embryonic failures.

The aims of medical embryology can be easily concluded from its subject. It is studying of general mechanisms of embryonic development to provide normal treatment of pregnancy and delivery, to prevent formation of crippled children. It is very important for obstetrics.

Embryonic period, as part of ontogenesis, includes the time between fertilization and birth. Whole embryogenesis is subdivided into three periods: early period (1^{st} week), embryonic period (2^{nd}-8^{th} week), and fetal period (9^{th} week until birth). It is obstetric schedule of embryogenesis.

There is also another schedule of embryogenesis which is based on main events of embryogenesis. It is embryologic schedule.

1 Fertilization stage, which results in zygote formation.

2 Cleavage stage, which results in blastula formation.

3 Gastrulation stage, which results in formation embryonic layers.

4 Notogenesis stage which results in formation axial buds complex from embryonic layers.

5 Histogenesis, organogenesis and systemogenesis stage. During this stage the tissues, organs and organ systems are formed.

The first and the second stage are included into early embryogenesis period. The embryonic period includes the third, fourth and firth stages. The firth stage extends in fetal period. Many embryologists refer the formation of reproductive cells – progenesis – to embryogenesis. It is wise decision because optimal embryogenesis is provided by optimal progenesis.

Features of human embryogenesis

Embryonic development of vertebrates has many general features and the pattern of development is similar. But at the same time mammalians and a human have their own features which are very specific to them. We list human embryonic features in following:

1. The main feature of mammalian embryonic development is that their development occurs inside of maternal organism with very close relationships with it. The Primates has most perfect system of such relationships.
2. Long duration of embryonic period. Human has one from the longest periods among mammalians – 280 days (9 moon months, 10 obstetrics months or 40 weeks).

3. The development of female reproductive cells occurs in embryonic period. The ovicells of mammalians have few nutritive substances and they are oligoisolecital eggs: with little yolk which is equally distributed in ooplasm. The mature ovicells regulary leave ovarium with interval in one month. Male reproductive cells are constantly produced in testis.
4. Insemination is internal and polyspermal. The fertilization is interal and monospermal: only one sperm brings its chromosome set to ovicell. The fertilization occurs in uterine tubes and lasts for several hours.
5. Cleavage is full, non-equal and asynchronic.
6. Close relationships with maternal organism. The formation of such relationships begins from implantation (getting deep inside to the uterine mucosa) and placentation (placenta formation). In compare with other mammalians, the human has deep implantation (instead of superficial in other mammalians) – interstitial, the embryo enters deep in endometrium to approach nutritive substances of maternal blood. So humans have double switch of feeding pattern: from autotrofic (using nutrients of zygota) through histotrofic (using secrete of uterine tube mucosa) to hemotrofic.
7. Gastrulation has two stages and it is performed by delamination, immigration and partial invagination of cells.
8. Histogenesis and organogenesis begins from 17-20th days of embryogenesis and includes presomite, somite stages and stage of definite organogenesis.
9. Embryogenesis of mammalians and humans is characterized by early development of provisional organs, which are typical for other chordates, and by formation of new provisional organs such as placenta, chorion and umbilical chord. Human placenta is referred as discoidal, hemochorial placenta.
10. Whole embryogenesis is subdivided into early, embryonic and fetal stages with their own specific features.
11. The histo- and organogenesis period is very long and it lasts almost all embryogenesis. It is not completed even after birth.
12. Human development is characterized by intensive development of brain which leads to high cefalization index (ratio between brain mass and fetus mass).

The structure of sex cells

Spermatozoid

Spermatozoid consists of head and tail. The tail is divided into *connective, intermediate, main and distal parts.* The nucleus of spermatozoid is basophilic. It has very tight paked chromatin. The nucleus coat hasn't nucleus pores. The genetic material is haploid and contains 22 autosomes and 1 sex chromosome (X or Y).

There is *acrosome* on the top of the spermatozoid head. This is a derivate of coplex Golgi and has similar structure as lysosome. In the acrosome there are enzymes which are able to disolve proteins of ovicell's zona pellucida .

The cytoplasm is reduced to minimum.

The connective part of the tail contains proximal centriol, which is very close to nucleus. Nearby there is and distal centriol. It serves as a basement for *acsonemm,* which has cilium like structure with 9 duplets of microtubules on the side. The acsonemm passes through all parts of the tail reducing in the distal part. Outside of each duplet of microtubules there is *segmented column.*

In the intermediate part the segmented columns change to 9 *dense fibres* . In this part there are mitochondria around acsonemm, which provide energy for spermatozoid movement.

In the main part the two from nine dense fibres change to longitudinate columns, which exist oposite to each other. By this outside coat of fibres is formed. This coat gives strengt to tail

In the distal part the number of microtubules significantly decreases. With help of the tail movements the spermatozoa are able to move with the speed 1-5 mm per second.

Ovicell

This is a female sex cell with haploid genetic material.It has a round shape with diametr 130 mcm. The cell has a lot of cytoplasm in which there are complex Golgi, mitochondions, EPR and inclusions (pigment and vitelin (for food suply)). Complex of ovicell membrane and 3mm cytoplasm layer under it is called *cortical layer.* This layer contains granules with several enzymes, which can change properties of zona pellucida after fertilization.The ovicells have very good developed cytoskeleton. They are surrounded by zona pellucida and by layer of follicular cells.

Progenesis

Progenesis (gametogenesis) is a process of sex cell formation. In its turn it is divided into spermatogenesis (spermatozoa formation) and ovogenesis (ovicell formation). The development of sex cells in embryogenesis happens early in development. They appear in extraembryonic yolk entoderm at the end of 3rd week of embryogenesis. Later these cell (they are called gonoblasts) migrate to sexul glands bud on medial surface of pronefros and take part in sexual gland formation.

Spermatogenesis

Spematogenesis has 4 phases: reproduction, growth, maturation and formation.

During reproduction period the male sexual cells are presented by spermatogonia. It is small, round cells which are subject to mitotic division. They are subdivided into dark and light. Dark spermatogonia are true stem cells, which can resist harmful influences. They subject to mitotic division very rare. Light spermatogonia are subdivided into A and B spermatogonia. A-spermatogonia are semistem cell, which are capable to frequent mitotic divisions. Every division of each A-spermatogonia may results in formation of two A-speermatogonia or in formation of one A-spermatogonia and one B-spermatogonia. B-spermatogonia is subject to mitotic division, but cytotomy doesn't happen. The cells leave cytoplasmic connection between each other, which lead to cell clone (associations) formation.

After some time B-spermatogonia enters the growth phase, uring which they are transformed into spermatocyte I. This period is characterized by intensive cytoplasm and nucleus growth of developing cells. They enlarge their size up to 4 times.

Spermatocytes I enter maturation period, which consist of two following meiotic divisions (meiosis I and meiosis II).

Meiosis I is called reduction division, because it leads to chromosome number reduction and formation of haploid chromosome set. Meiosis I has a complicate prophase, having 5 stages: leptotene, zygotene, pachytene, diplotene and diakinesis.

During leptotene the chromosomes become visible as long thin treads. During zygotene homologus chromosomes conjugate. The crossing over also takes place. During pahytene chromosomes become shorter and thicker. Diplotene is characterized by chromosomes splitting on

chromatids and tetrade formation. Durind diakinesis chromosomes become shorter and start to move apart.

In metaphase chromosomes are placed on cell equator. In anaphase homologous chromosomes move apart to the cell poles, it is the moment of reduction beginning. In telophase, there is cytotomy resulting in two spermatocytes II formation. The chromosomes of sprematocyte II consist of two chromatids.

Miosis II is also called equation division. It is started right after meiosis I and ressemble ordinary mitosis. In anaphase meiosis II the chromatids move apart to the cell poles. The telophase results in spermatids formation. Spermatids, as spermatocytes II, have haploid chromosome set, each chromosome is presented by one chromatid.

All spermatogenesis cells are connected between each other by cytoplasmic connections. They form cellular associations or clones. Definite cell separation occurs only in formation phase. Preserved cytoplasmic connections have a great biological importance. It is true that for appropriate spermatozoa differentiation there is necessary in full diploid genome and its products. Firstly, the defect genes can be in initial diploid genome and the cells which acquire such genes may die in case of absence of normal allele products. Secondly it is a fact that half of male sex cells acquire X-chromosome whereas others acquire Y-chromosome. Each contains many important genes for spermatozoa formation. So thus with help of cytoplasmic connections the cells acquire the products of diploid genome.

Formation phase is longest phase of spermatogenesis. It results in spermatozoa formation from spermatids. It lasts for about 50 days. The process of sperm formation begins from formation of acrosome, which contain enzymes to dissolve coats of ovum. The centrosone moves on the opposite pole. The proximal centriole lies close to the nucleus, whereas a distal centriole divides on two parts. From one of them the flagella is formed, which later will be transformed to axial tail tread. The second plays a role of basal body. The elements of cytoskeleton are also formed. The sperm cytoplasm is subject to reduction. The nucleus elongates and become more compact. On terminal stages spermatozoa separate from each other and become free. Cytoplasm, which is left after separation, is phagocytated.

Ovogenesis

In general it has similar structure as spermatogenesis, but it has its particular features. The initial cells of ovogenesis are gonoblasts, which

are developed in early ontogenesis in female sex gland – ovarium. These cells are the part of epithelium of indifferent sex gland. Later the epithelium gives growing processes into mesenhyme of mesonephros and it is dismantled into separated islets. In this islet we can find reproductive cells and surrounding them epitheliocytes (follicular cells). The gonoblasts are transformed to oogonia. These small cells enter the reproduction phase where they are subject to intensive mitotic division. At the end of embryonic development the number of oogonia is around 7 millions. The period of reproduction is terminated right after birth. Starting from 3rd month of embryonic development some oogonia are transformed to oocyte I, whereas other continue division. After birth the division is terminated and all oogonia are transformed to oocytes I. These oocytes I are blocked on a stage of diplotene of first meiotic division.

Then oocytes I enter the long growth period. It is subdivided into period of small or idle growth (from birth to sexual maturation) and period of large or rapid growth (it happens regulary during each menstrual cycle). Thus the growth period may last 12-50 years. The third phase – maturation starts before ovulation. The first meiotic division is completed, which results in formation of oocyte II and reduction body. In it turn reduction body may split on two. Oocyte II is blocked in metaphase of meiosis II. Further maturation is induced by fertilization. Oocyte II splits on ovicell and reduction body. As result of maturation we have three reduction body and one ovicell. Ovicell loses itss centrioles. The reduction bodies are phagocyteted by other cells.

DIFFERENCIES BETWEEN SPERMATOGENESIS AND OVOGENESIS.

SPERMATOGENESIS	OVOGENESIS
The reproduction phase starts from sexual maturation and lasts during rest of the life.	The reproduction phase occurs only during embryonic development.
Short growth phase.	Long growth phase, which is subdivided into idle and rapid growth.
Maturation phase is characterized by equal spermatocytes division.	Maturation phase is characterized by non-equal oocytes division resulting in one ovicell and three reduction bodies.
The formation phase is present.	The formation phase is absent.
"Economy" of spermatogenesis: one	"Wastefulness" of ovogenesis: one

spermatogonia gives four spermatozoa.		oogonia gives one ovicell and three reduction bodies.
It last during all life of the men.		It is terminated after menopause.

Fertilization

Fertilization - it is a process of merging of female and male sex cells, which lead to zigota formation. It takes place in the ampular part of utherine tube. Before ferilization sprmatozoa are subject to *capacitation.* That means that spermatozoa become activated with help of utherine tube mucose and become more eager to *acrosome reaction.* To perform fertilization process it is nessesary to have at least 200 millions spermatozoa. If there are less than this amount ferilization can not be performed becouse of lack of proteolytic enzyme activity.

The spermatozoa reach ovicell 2 hours after insemination. Then they touch follicular cells they perform *acrosome reaction* - liberation of proteolytic enzymes from acrosome. The acrosome reaction is initiated by Ca ions influx. With help of proteolitic enzymes spermatozoa disolve follicular cells layer and zona pellucida. In the zona pellucida there are receptors ZP 2 and ZP3. This receptors help to disolve zona pellucida in the appropriate place and easier. When spermatozoid finaly touches ovicell membrane, membrane forms accepting hill. The membranes of ovicell and spermatozoid are merged. And then spermatozoid nucleus enters the ovicell.

Mechanism of polyspermia blocking

There is only one spermatozoid who can give its gene material to new embryo, inspite thousands being attached to ovicell membrane. If it is more than one, it can lead to development abnormalities. To prevent this there are several mechanisms.

1. The cortical reaction in the ovicell that lead to liberation of cortical layer enzymes, which change zona pellucida making it unpermeable to spermatozoa.
2. The enzymes also degrade ZP2 and ZP3 receptors and block acrosome reaction of spermatozoa.
3. Also after fertilization the charge of cytoplasm of ovicell is changed to negative. And negative charged spermatozoa are repulsed from it.

Formation of zigota

After fertilization nucleuses of speratozoid and ovicell move to each other then unite to one nucleus. This process is called synkaryon. As result of this a new organism is formed. Its name is zigota, which has diploid chromosome set.

The changes in ovicell after fertilization

1. In first 10 minutes after fertilization, the carbohydrate exchange is enhanced. The glycogen degradation is activated, which shows increased energy need.
2. The oxygen consumption is rapidly raised.
3. In first minutes we observe increased concentration of nuleic acids, which is a sign of dissimilation processes.
4. The phosphate and calcium exchange is raised in 100 and more times.
5. The membrane increase selective permeability for phosphate ions.
6. The proteolytic enzyme activity is raised.
7. The synthesis of DNA and RNA is started.

The cleavage

The cleavage is transformation of unicellular zygote to multicellular embryo. The cell are divided very quickly. Because of G1 period absence, cells do not grow. So the total size of embryo is the same during cleavage. The cleavage may be full (when all zigote material is subject to division) and non full (only part of material is divided); equal (if blastomers have a same size) and non equal (if they have different size); synchronic (if division of blastomer occur at the same time) and asynchronic (if they divide at the different time). The cleavage of human is full, non equal and asynchronic. As result of clevage is formation of two layer sphere shape embryo. The external layer is trofoblast (it futher serves for defence of embryo and formation of chorion and placenta). The internal layer is embryoblast (it futher serves for embryo formation).

The gastrulation

The gastrulation is a next stage of embryo formation and it has two phases. The first phase occurs at 7th day of development at the same time when implantation occurs. It is performed by delamination (spliting) of embryo on two layers: primary ectoderm (epiblast) and primary entoderm (hypoblast). Embryo and amnion are formed from primary ectoderm. Primary entoderm only takes part in formation of yolk sac. Between

gastrulation phases there is a time for provision organs formation such as yolk sac, amnion and chorion.

The second phase of gastrulation begins at 14 – 15th day of development. It is performed by cell migration and partial invagination. The cell of epiblast intensivly reproduce itself. And then they start to move form the sides of the embryo disc to its pole. Afterward they move along the central part of the disc and form primary strip. Then these cells migarate inbetween two layers and form third layer - mesoderm. Part of primary strip material migrates to entodern layer and shift the cells of primary entoderm to side position. There primary entoderm cells take part in formation of yolk sac. As result of gastrulation we have a 3 layer embryo with *ectoderm, mesoderm and entoderm.*

The embryo structure on second week of development

The second phase of gastrulation begins at 14 – 15th day of development. Before second stage of gastrulaation the embryo has following structure. There is chorion outside. It has two layers: trophoblast and extaembryonic mesenhyme. The trophoblast is divided into external siplastotrophoblast and internal cytotrophoblast. The chorion forms secondary vilia.

The embryo cavity is full filled by extraembryonic mesenhyme. Thre are two vesicles inside of it: amnion and yolk sac. They lies close to each other and are attached to chorion by *amniotic root.* The body of embryo is formed by cells of the amniotic vesicle bottom and yolk sac vesicle top. It is called embryo disc. It consist of ectoderm (epiblast) and entoderm (hypoblast).

The embryo structure on third week of development.

After formation 3 layer embryo, the differentiation of embryonic layers is started. It happens on 3rd week of embryogenesis. We will follow the differentiation of each embryo layer.

ECTODERM. In the beginning it is called *primary ectoderm* because it has material for further development of skin ectoderm, neuroectoderm, chord, intestine entoderm and mesenhyme. During second phase of gastrulation the following buds leave ectoderm: mesenhyme cells, chord cells and intestine entoderm cells. At the end of 3rd week, the *nervous plate* is formed in ectoderm. Than it is dipped into mesoderm and become *nervous tube.* At the same time, the *ganglionic plates* are formed from ectoderm which is placed between nervous tube and ectoderm. The process of nervous tube formation is called neurulation. Nervous tube is a source for formation of following organs as brain, spinal cord, pituitary gland,

motor spinal nerves, cranial nerves, retina of eye. The ganglionic plates are a source for formation of following organs as spinal, cranial and autonomic ganglions, and adrenal medulla.

As it was pointed above, some ectoderm sell travel to primary entoderm cells and settle among them. Such cells form intestine entoderm, whereas primary entoderm cells become extraembryonic mesenhyme of yolk sac.

After giving out all pointed above derivates, the primary ectoderm become secondary entoderm or skin ectoderm. It is a source for formation of striated eithelia: skin epidermis and its derivates (hairs, nails, glands), oral cavity epithelium, anus epithelium, vagina epithelium, teeth enamel, adenohypophysis, cornea, lens, olfactory epithelium and so on.

MESODERM. It is subject to differentiation from 20's day of embryogenesis. Originally it is loose irregular cell group (presomit mesoderm). Than, it is divided into dorsal and ventral mesoderm. Dorsal mesoderm is divided into segments along the embryo body. Such segments called somites. The segmentation starts on anterior end and then it spreads in caudal direction. The somit formation is very important part of embryogenesis, some investigators concern it as somit period. Each somit consist of three parts: external – dermatom, intermediate – myotom, internal – sclerotom. Dermatom gives rise for dermatom mesenhyme, which forms skin derma. Myotom gives rise for striated muscular tissue. Sclerotom gives rise for sclerotome mesenhyme, which forms bone and cartilage tissues.

Between ventral and dorsal mesoderm there is intermediate mesoderm – nephrotom. It is subject to segmentation in anterior end of the body and it is not segmented in caudal end. It gives rise for kidney and reproductive organs.

Ventral mesoderm (splanchnotom) is not subject to segmentation. It is subdivided into two layers: visceral and parietal. They enclose secondary cavity of a body – coelom. The layers of splanchotom give rise for mesothelium, striated cardiac tissue, abrenal cortex, gonad epithelium. The cells of visceral splanchnotom layer form splanchnotom mesenhyme, which forms connective tissue and smooth muscular tissue of internal organs and vessels.

ENTODERM. The very important process – separation of embryo from extraembryonic organs – is started on 20's day of development. The embryo body is lifted above provisional organs with help of *body's folds*. So the embryo body acquires the tubular shape. This leads to formation of intestinal tube, which is separated from entoderm of yolk sac. The intestine

tube is a source for formation of gastric epithelium, intestinal epithelium, liver, gall bladder, pancreas.

NOTOGENESIS. It is process of axial buds complex formation. The notogenesis includes three main processes: neurulation, differentiation of embryonic layers and formation of body's folds. Axial complex includes following buds:

1. Skin ectoderm. 2. Nervous tube and ganglionic plates. 3. Somites including dermatom, myotom and sclerotom. 4. Nephrotom. 5. Splanchnotom. 6. Chord. 7. Intestine tube. 8. Mesenhyme.

Chapter 5: The introduction to the general histology

General histology studies the development, structure and functions of tissues.

What is a tissue? It was made several trials to make full and correct definition of tissue. We will not list all previous definitions of tissue. But here, we have to point that today all theoretical basement of general histology is based on differon principle of tissue structure.

Cellular differon – is integrity of cellular forms on one or another differentiation line from stem cell to terminally differentiated cell. The components of a differon are: 1) stem cell → 2) semistem cell → 3) differentiated cell → 4) aged cell.

The modern definition of tissue that concerns differon principle is the following: **"Tissues are mosaic morphofunctional system of interacting cellular differons, which are different in origin, differentiation line and level."** [Klishov 1981]

There are monodifferon tissues (include only one differon) and polydifferon tissues (include main differon and several secondary differons).

Tissue elements

There are three types of tissue elements: cells, ground substance and symplast. Some authors include syncitium and postcellular structures into tissue elements.

The cell was discussed in cytology core. It is the main tissue element, which produce other types of tissue elements.

The ground substance is secreted by cells. It full fills space between cells making appropriate environment for them. It consists of amorphous

substance and fibers. Amorphous substance is a tissue matrix with homestatic, trofic, regulative functions. It is made of water, proteins, cardohydrates, lipids and various salts. The fibers perform supportive, regulative, elastic functions. They can be collagen, elastic and reticular fibers.

The symplast – it is a region of protoplasm with many nucleuses separated from external environment by plasmalemm. It is the result of cells merging in compare with multinuclear cells, which are the result of uncompleted cell division. The example is striated muscle fiber.

The syncitium – it is the integrity of cells, which are connected with each other by their processuses. There is "true" syncitium – where cells have no membranes between (male reproductive cells). There is "false" syncitium – where cells have membrane septa between (reticular cells, thymus epithelium).

The postcellular elements – are such cell derivates, which lost many cells functions in differentiation process such as ability to reproduce itself, large part of metabolism and ets. They have no nucleus and majority of organelles. But such structures have the properties that allow them performing very narrow, but highly specialized function. The examples are erythrocytes, platelets and ets.

General functions of multicellular organisms as base for tissue appearance in onto- and phylogenesis

Every organism has list of functions which provide its well being. The first in this list are functions of internal and external exchange. It is undoubtful that these functions are first to appear in evolution. They play major role in primitive animals. If we imagine such animals as a dense sphere of closely adjoined cells, some cells will be on the surface of the sphere, some will be inside of it. Superficial cells have direct contact with environment, whereas internal cells are separated from environment by superficial cells. So internal cells appear to be in less favorable conditions for feeding, but they are better protected form external damage. On a basement of such relationships the internal medium of organism appeared. Thus we may conclude that the general functions for any multicellular organism are:

1. Borderline function or function of external exchange.
2. Function of internal exchange.

Every function is provided by the appropriate morphological basis. So evolution of such functions resulted in appearance of two main tissue types:

1. Borderline tissues or epithelia.
2. Tissues of internal environment.

Borderline tissues or epithelia. They have compact structure as closely connected cellular layers. The cells of such layers are polar – one surface looks toward external environment, whereas another toward internal medium.

Tissues of internal environment. The cells of such tissues are non-polar. Tissues of internal environment are rich in intercellular ground substance.

But evolution continues. The necessity in active locomotion appeared due to necessity of active food searching. This gives more freedom and decrease dependence from food sources. Thus the contractive or muscular tissues appeared. The more complex structure of an animal required the good management of functions. This was an impact for nervous tissue development. The first two tissue types are tissues of general purpose, whereas muscular and nervous tissues are specializated tissues.

Thus the fundamental functions of any multicellular organism are:

1. Borderline function or function of external exchange.
2. Function of internal exchange.
3. Function of contractility and locomotion.
4. Function of irritability, reactivity and integration.

Tissue classification

The first classifications of tissues were suggested in the middle of XIX century. They were based on the microscopic structure of tissues. There are 4 tissue types accordinary to these classifications: epithelial, connective with blood, muscular, nervous.

Soviet histologist A.A. Zavarzin suggested classification which was based on evolutionary principle and on fundamental functions of organisms. He subdivided tissues on following types:

1. Tissues of general purpose:
1.1Borderline tissues.
1.2Tissues of internal environment.
2. Specializated tissues:
2.1Muscular tissues.

2.2Nervous tissues.

Another histologist N.G. Hlopin suggested classification which was based on genetic tissue origin.

The concept about stem and differentiated cells of tissues

In the tissues we can find stem and differentiated cells as well.

The stem cells are self-maintaining population of rare dividing cells, which are able to give descents differentiating in many different directions under influences of environmental factors. Stem cells have following features:

1. They are able to maintain cell number in population on constant level. It is performed by rare mitotic divisions and following cell differentiation to specialized cells. Most of the time stem cells stay in resting state (elongated G1 period) but when it is necessary they can turn back to mitotic cycle.
2. It is small cells with high nuclear-cytoplasmic ratio and with few organelles of general purpose.
3. They have autosintetic metabolism: they produce substances only for itself.
4. They are resistant to harmful factors. It is due to compact chromatin packing and deep localization in tissue.
5. They can differentiate in various directions.

In the differentiation process we observe the following stages: stem cell → semistem cell → unipotent precursor → blast cell (actively dividing) → differentiating cell → differentiated cell.

Differentiated cells are the cells which have definite, special features of their structure which are necessary to perform definite function. They have following features:

1. Unable to divide.
2. Only that part of genome is active which provide performing of special function.
3. They have low nuclear-cytoplasmic ratio.
4. They have heterosintetic metabolism: they produce substances for other cells.
5. Differentiated cells have very specific structures which enable them to perform different functions: basophily of cytoplasm, polarity, well developed organelles ets.

The concept about cambial and non-cambial tissues

There are *cambial* and *non-cambial* tissues.

Cambial tissues are such tissues which have stem cells (or cambial cells) during all postnatal ontogenesis. Simply, the histogenesis of the tissues can be presented in following. One group of cells after division is subject to determination and differentiation. Second group remain undifferentiated state serving as stem cells. In case of aging and dieing of cells from first group, cells from second group divide and replace cells from first group.

The examples of cambial tissues are connective, epithelial and muscular (cardiac muscular tissue is an exception) tissues. They can be subdivided into two groups: *cambial renewing* and *cambial growing*. In the cambial renewing tissues the pool of stem cells is maintained during whole their life (LICT, blood, some epithelia). In the cambial growing tissues (striated muscular tissue, hepatocytes of liver) the pool of stem cells is reduced to minimum during their life. When tissues reach its definite state, the stem cells may even disappear. The volume of such tissues is enlarged due to intracellular regeneration.

Non-cambial tissues are tissues without stem cells. During embryonic development cells divide reaching necessary tissue volume. Then all cells become differentiated and start to perform special functions. Due to lack of stem cells, the regeneration occurs only on intracellular level. The example is nervous tissue.

The mechanism of tissue homeostasis maintaining

Tissue homeostasis – it is the integrity of processes of maintaining steady state of a tissue. It is perfomed by following mechanisms:

1. Maintaining of cells differentiation.
2. Maintaining of cells number.
3. Maintaining of necessary volume of extracellular matrix.
4. Providing normal balance of metabolic reaction.
5. Maintaining sufficient level of physiological regeneration.

Regeneration.

Regeneration is an ability of an organism to replace and repair died and lost parts. It is directed to maintain the determined level of tissue

differentiation. The regeneration is subdivided into physiological and reparative.

Physiological regeneration occurs in normal condition. The cells of organism constantly die so to maintain cell number the new cells have to appear at the same rate as cells die. This equality is supported by physiological regeneration. There are several types of physiological regeneration accordinary to its topology:

1. **Mosaic regeneration**. In this case, regeneration takes place in many different positions in a tissue. The dieing cells are replaced on their original locations. The examples are LICT, mesothelium, endothelium.
2. **Zonal regeneration**. Here, the cells divides in one tissue zone and die in other tissue zone. So there is territorial uncoupling of repairing and destruction processes. The examples are striated epithelia, adrenal cortex and ets.
3. **Distant regeneration**. Here, the new cells formation occurs in one organ, whereas physiological death – in others. The example is blood: the leukocytes are produced in red bone marrow, but they die in variety of organism organs.

Reparative regeneration – is regeneration as response on damage. The new elements arise or undamaged elements of tissue grow to replace tissue lost. The physiological and reparative regeneration are based on the same mechanisms, which are realized on cellular and intracellular level. So, we can distinguish cellular and intracellular regeneration.

Intracellular regeneration is the regeneration of cell organelles (increasing organelles' size and number).

Cellular regeneration is cell division and increasing of their number to replace lost parts of a tissue.

Regenerative ability of tissue depends on presence of stem cells in it. The non-cambial tissues are able to regenerate only on intracellular level. The cambial tissues can apply both levels of regeneration: cellular and intracellular.

Epithelial tissue

General morphofunctional characteristics

1. The epithelia are cells layer laying o basement membrane – border position.
2. Epithelial tissues are made from only one tissue element – cells.

3. They have polarity. In simple epithelium the cells are polar – they have apical and basement pole. In stratified epithelium, the basement and superficial layers are different in structure.
4. All epithelia contain specific type of intermediate filaments – keratins. Each epithelium type has its own keratins set.
5. Epithelia have no vessels. The nutrition is performed through basement membrane.
6. Epithelium has very good innervation.
7. All epithelial tissues perform 5 main functions: border function, defense, secretion, excretion, and adsorption.
8. Epithelia have very good regenerative potential due to having stem cells in its.
9. Epithelia are derived from all embryonic layers. Ectoderm gives rise to striated epithelia, entoderm and mesoderm – to simple epithelia.

The classification of epithelia

The classification of the epithelium is based on the number of cell layers and the morphology of the surface cells. Based on these criteria, the **simple epithelium** consist of a single layer of cells, **pseudostratified epithelium** consist of single layer of cells in which all cells attached to the basement membrane but not all cells reach the surface, and the **stratified epithelium** consist of two or cell layers. The epithelium is separated from connective tissue by basement membrane.

THE SIMPLE EPITHELIUM is subdivided on several types:

1. simple squamous epithelium consist of single layer of irregular, flattened or squamous cells. In the cardiovascular system it is called *endothelium*, in the lining of the peritoneal, pleural and pericardial cavities it is called *mesothelium*.

2. simple cuboidal epithelium consist of cell that are as tall as they are wide. Its function is secretory or absorptive (proximal and distant convoluted kidney tubes).

3. simple columnar epithelium consist of cell that are taller than they are wide. In the digestive organs it exhibits a striated border and it major function is absorption of fluids or nutrients, or secretory.

4. pseudostratified columnar epithelium consist of single layer of cells in which all cells attached to the basement membrane but not all cells reach the surface. In the respiratory organs it is ciliated and its major function is to move mucus and dust particles across cell surface. In the

epididymis, this epithelium contains stereocilia whose main function is absorption of fluids that were produced in the testis.

THE STRATIFIED EPITHELIUM has the same subdivisions except pseudostratified. But it also has new subdivision which is called **transitional epithelium.**

1. **stratified squamous epithelium** contains numerous cell layers. The basal cell are cuboidal to columnar in shape; this give rise to cell that migrate toward the free surface and become squamous. The main function of the stratified squamous epithelium is protection, and its multilayer composition is well adopted to withstand wear and tear or abrasion. There are two types of stratified squamous epithelia: *nonkeratinized and keratinized.* The nonkeratinized exhibits live superficial cells with nuclei. It lines in the moist cavities of the mouth, pharynx, esophagus, vagina and anal canal. The keratinized type contains nonliving, keratinized superficial cells and it lines the skin. The major function of the keratinized epithelium is to protect the body from abrasion, desiccation, bacterial invasion and other similar factors.

2. **stratified cuboidal epithelium and stratified columnar epithelium** have limited distribution in the body. Both types are found in the ducts of lager glands, the pancreas, and the salivary and sweat glands. They usually consist of two or three layers of cells.

3. **transitional epithelium** is designed to change shape when it is stretched. This epithelium can resemble both the stratified squamous or stratified cuboidal epithelium, depending on degree of stretch. The surface cell is dome-shaped during contraction and squamous during stretching. Transitional epithelium lines the urinary passages (minor and major calyxes, pelvis urethra and bladder). Its major function is to allow stretch during urine accumulation and contraction during empting of the urinary passages without breaking cell contacts in the epithelium. In addition, the cells of transitional epithelium form an important osmotic barrier between urine and the underlying tissues.

Structure and functions of basement membranes

Basement membrane is well visible in electron microscope. We can find 3 layers in its structure.

1. **Light lamina** lies close to cytolemm of epithelial cells and is connected to it with help of semidesmosomes. It contains glycoproteins (laminin) and proteoglicans (heparin-sulphate).

2. **Dense lamina**. It is made of amorphous substance and fibrillar structures. It contains anchoring filaments, made of collagen VII type. In addition it contains collagen V type, glycosaminoglicans, and glycoproteins (laminin).

3. **Reticular lamina**. It is made of collagen fibers of I and III type of connective tissue, which are connected with anchoring filaments.

Functions of basement membrane:

- Transport of substances.
- Support.
- Border between epithelium and underlying connective tissue.
- Mechanical connection of epithelium and connective tissue.
- Regulation and morphogenesis. It maintains normal polarity of epithelium and prevents epithelium growth into connective tissue.

Glands.

Glands are organs or parts of organs which are able to secrete. They are made of secretory epithelium.

Classification of glands

There are several points of glands classification.

A. **By number of cells in a gland**: unicellular and multicellular.
B. **By localization relatively epithelial layer**: exoepithelial and endoepithelial.
C. **By organization level**: gland as independent organ and gland as part of an organ.
D. **By place of secrete liberation**: exocrine (to external environment) and endocrine (to internal environment).
E. **By chemical compounds of secrete**: protein, mucous, mixed, sebaceous ets.
F. **By mechanism of secrete liberation**: merocrine, holocrine, apocrine.
G. **By morphology** (see the table below).

Table: Morphological classification of glands.

Glands				
Endocrine	**Exocrine**			
1. Trabecular type (adrenal gland, pituitary).	Simple (one duct).		Compound (many ducts).	
2. Follicular type (thyroid gland).	Branched (terminal	Non-branched	Branched (terminal	Non-branched

part is branched)	(terminal part is non-branched)	part is branched)	(terminal part is non-branched)
Tubular Alveolar		Tubular Alveolar Mixed	

Cytology of secretion

1 Serous secretion (e.g., in pancreatic exocrine acini)1 Enzymes formed are proteins, and the path of synthesis can be revealed by following radioautographically the fate of *tritium-labelled amino acids*, e.g., leucine. Other serous products include antimicrobial proteins. 2 In the *basal* region of the cell, amino acids are chain-linked at the ribosomes attached to the GER, in sequences determined by mRNA from the *nucleus*. The energy needed is released by plentiful *mitochondria*.3 The protein passes into the cisternae of the GER and 4 travels in the cisternal space to near the *Golgi complex*. 5 The protein is shuttled to the cis/forming/proximal face of the supra-nuclear Golgi complex by *transporting vesicles*. 6 *Condensing vacuoles* concentrate the secretion before its dispatch from the concave trans/secretory/maturing/distal face of the Golgi to become 7 membrane-bound, apical, zymogen *storage granules*. 8 With appropriate stimulation, the granules pass to the cell's *luminal membrane* for release by *exocytosis*, whereby the granule's enclosing membrane fuses with the cell's, which then breaks allowing the granular content to spill out into the acinar lumen.

2 Mucous secretion (e.g., by goblet cell)1 *Oligosaccharides* are completed by the Golgi complex, sulphated, if necessary, and linked with a protein to form 2 *mucin*, stored as droplets dilating the apical cytoplasm. 3 *Granular ER* - for synthesis of the core protein of the glycoprotein and of sugar-attaching (glycosylating) enzymes - is well developed in the narrow basal stem of the cell. 4 After one cycle of activity, the gut goblet cell is normally shed to be replaced from a pool of undifferentiated cells. 5 Mucous cells of salivary glands are not shed. They have GER and, when they are immature, or in the early secretory phase with little mucin accumulated, they are basophilic and may resemble serous cells. 6 The mucin type of glycoprotein has its hundreds of chains of sugar moieties attached to the peptide core - the apomucin - by hydroxyls of serine or threonine - the *O-linkage*. In contrast, serum-type glycoproteins are *N-linked*, since their sugars attach via amido groups of asparagine. The O-

and N-linked classes differ in their affinities for lectins, what agents block sugar-chain biosynthesis, and in whether the first glycosylation is in the Golgi complex or GER. 7 The mucin molecules are further classified as neutral or acidic, based in part on the amount of sialic acid present. The molecules join end-to-end, and then tangle up for bulk and high viscosity.

3 Liberation of secretion

I. *Merocrine/epicrine/eccrine* manner involves exocytosis, or the discharge of only secretory material without any loss of cytoplasm, as in a serous gland. The cell then returns to the synthesizing phase of its secretory cycle.

II. *Holocrine secretion* requires that the cell fill itself up with secretion which is liberated by the cell's breaking open and dying, e.g., in a sebaceous gland. Precursor cells must multiply to replace those lost, for the gland to continue secreting.

III. *Apocrine* way was thought to involve a significant loss of apical cytoplasm along with the secretion, but not cell death. EM suggests that this occurs rarely, if at all, and the classic apocrine-merocrine distinction is invalid. However, apocrine is now applied to a release of secretion where the product, milk fat, departs from the mammary cell enclosed in a membrane.

4 Myoepithelial cells (basket cells). These lie between glandular and duct cells and the BL, and clasp those cells in long branching processes filled with filaments. They closely resemble smooth muscle cells, and *contract* to help squeeze the secretion out of large exocrine glands (breast and salivary) or the long, tortuous sweat gland.

5 Duct-lining cells. Ducts are not usually passive tubes for conveying secretions. Their lining cells often are cuboidal or columnar, and *acidophilic*, with many basal mitochondria serving active transport mechanisms to modify the secretion's concentration and electrolyte composition, by actions similar to those of kidney tubules. Such ducts may be called *secretory* or *striated* (from the many parallel mitochondria); they lead to less active *excretory* (drain pipe) ducts. (Secretory ducts are usually intralobular, but not all intralobular ducts are secretory.)

Chapter 6: The blood and lymph

Mesenhyme is a part of an embryo which surrounds all embryonic structures. It gives rise to all tissues of internal environment. The tissues of

mesenchymal origin are blood, lymph, connective tissue, smooth muscle tissue and etc. The general characteristics of these cells are:

1. They all originated from mesenhyme.
2. They all contain two types of tissue elements – cells and extracellular matrix.
3. They have no poles.
4. They are polydifferon tissues.
5. They have a lot of vessels.
6. They have good regenerative potential, i.d. they are cambial tissues.
7. They have similar functions: defense, food supply, support, regulation, plastic function (participating in inflammation, regeneration etc.).

The blood and lymph

Cells of blood are called *formal elements*. The intercellular substance of blood is called plasma. The ratio between formal elements and plasma is called hematocrit. It is usually around 40/60. It may serve as indicator of blood dilution.

Functions of blood may be concerned in following:

1. Transportation.
2. Defense.
3. Homeostasis maintaining.

Blood plasma

It consists of 90% of water, 95 of organic substances and 1% of inorganic substances. Among organic substances the most abundant are proteins. They can be of tree general types: albumins, globulins and fibrinogen. The blood plasma without fibrinogen is called serum. Fibrinogen is a part of blood clotting system. Albumins perform transportation function. Globulins are subdivided into α, β and γ families. γ-globulins are produced by plasma cells and take part in immune response. All other plasma proteins are produced in liver.

Blood formal elements

Formal elements are of three main classes: erythrocytes, leukocytes and platelets.

Erythrocytes.

They are the postcellular structures. They have no nucleus. Most of them have discoid shape. Such shape provides an increased surface for better permeability of gases. Also it helps erythrocyte to bend in narrow capillaries. There are erythrocyte with another shape such as sphere shaped (sphercytes), sickle shaped, plane shaped and ets. If erythrocyte expresses any other shape than discoid, it is a marked of aged or pathological erythrocyte (like in sickle cell anemia).

Noraml size of erythrocyte is 7-8 mcm. Such erythrocytes are called normocytes. There are a few macrocytes (more than 10 mcm in size) and microcytes (less than 6 mcm in size). The presence of erythrocytes which are different in size in blood at the same time is called *anizocytosis.*

The erythrocyte count is different in representatives of each sex. In males it is 4.5 – 5.3*10^12 per liter and in females it is 4.0 – 4.5*10^12 per liter. The life span of erythrocyte is around 90-120 days. Than they are destroyed in spleen or liver and they are replaced by new from red bone marrow.

In general I may say that erythrocyte is membrane sac full filled by hemoglobin. The structure of erythrocyte membrane is similar to general membrane structure. Hemoglobin is respiratory pigment. It function is to transport oxygen and carbon dioxide. The intensity of bond between hemoglobin and oxygen is concentration dependent. If oxygen concentration is high (in lungs), the hemoglobin catches it, but when oxygen concentration falls down (in tissues), the hemoglobin releases it. In mature erythrocyte there are no organelles, just a few ribosomes.

In the blood there are immature forms of erythrocytes – reticulocytes. They count is around 1-2% from total erythrocyte count. They contain rests of EPR, which are looked like a net (rete in Latin). They have sphere shape and they are less active in gases transportation. Their count increases while active blood formation.

Blood platelets

They are derivates of megakariocytes of red bone marrow. Their size is about 2-3 mcm. Their life span is about 5-10 days. Thier count is 200-300*10^6 per liter. They contain rests of organelles and several types of granules:

1. α-granules – contain factors for blood clotting.
2. dense granules – contain histamine, serotonin.

3. λ-granules – are typical lysosomes.
4. microperoxisomes – contain peroxidase.

Also they have two channels system: superficial and system of dense tubules. Membrane has highly developed contractive elements, which provide clot retraction.

Functions of platlets:

1. Participation in blood clotting.
2. Stimulation of tissue regeneration.
3. Providing normal endothelium state.

Blood leukocytes.

They are white blood cells. The total leukocyte count in blood is 4-9*10^9 per liter. They can be of two types – granular and agranular.

Granular leukocytes have segmented nucleus and granules to be stained in different ways: basophilic or/and acidophilic.

Eosinphil leukocytes have acidophilic granules.

Basophil leukocytes have basophilic granules.

Neutrophil leukocytes have basophilic and acidophilic granules as well. They are also called polymorph leukocytes because their nucleus may vary in shape having from 1 to 5 lobes in nucleus.

Agranular leukocytes. There are two types of agranularleukocytes. The more numerous and smaller are *lymphocytes* (they are found in lymph as well as in blood). The larger and less numerous are *monocytes*.

Neutrophils.

Count: they make up 60-70% of total leukocyte count. It's own count is 3 - 6*10^9 per liter. It is considered as normal range. The life span of neutrophils is about 8 days.

Origin: they develop from myeloid tissue of red bone marrow, where they pass through many development changes before liberating to a blood. Normally only mature leukocytes exist in a blood. But during some diseases, like general inflammation, the immature forms may leave red bone marrow and persist in blood stream.

Morphology: mature polymorphs have a nucleus divided into 2 to 5 lobes. The term lobe refer to part of nucleus aerial that is either completely separated from all other mass or connected to it more than very delicate strand. The heterochromatne prevails here. Cytoplasm occupies larger

volume than the nucleus does. It contains specific granules (basophilic and eosinophilic) and azurophil granules which are smaller and can be seen only with help of electronic microscope. They are found in all leukocytes. It is the more primitive and less special type of granules. The only way when they become visible is severe inflammatory state (sepsis and other). That means those leukocytes are not as mature as they always are. This condition is named "toxic granulation of leukocytes".

Immature leukocytes: In red bone marrow leukocytes pass through several development stages. The last stages in this line are juvenile leukocyte and band (or stab) leukocyte. Juvenile leukocytes have nuclei that are in form of indented ovoids. As this cell develop further, its nucleus becomes increasingly indented until it becomes frankly horseshoe-shaped, and this stage of development called band leukocyte. Under normal condition the horseshoe-shaped nucleuses of band leukocyte becomes segmented to divide the nucleus into 2 or more parts, and than leukocytes are released to a blood. But if there is a great need for leukocytes, the band or even juvenile leukocytes are released to a blood stream. It was stated that number of immature forms is written on a left side of blood analysis paper, whereas number of mature leukocytes on a right side. So, if obtained smear from patient shows an increased number of immature leukocytes, it called "left shift". But if in obtained smear will be lack of immature leukocytes and abundance of old forms, it is called "right shift". (see the leukocyte count below).

The main functions of neutrophils are participation in inflammation and immune reactions.

Eosinophils.

Count: vary from 1-3% of total leukocyte number. The life span of eosinophils is about 10 days.

Origin: they develop from myeloid tissue of red bone marrow too.

Morphology: they slightly bigger than neutrophils. Nucleus in majority of cases has 2 lobes. Cytoplas is packed by large retractive granules which are well stained by eosin stain to red or orange. There are two types of granules: 1) specific acidophilic, which contain proteolitic enzymes, peroxydase, major basic protein, histaminase and ets. 2) non-specific azurophil granules.

Functions:

1. Participation in allergic reactions, as deactivation of mast cells and others.

2. Destroying of bacterial toxins.
3. Antihelminth (antiparasite) immunity.
4. Antioncogenic (anticancer) effect.

Basophiles.

Count: around 0.5% of total leukocyte number. The life span of basophiles is about 10 days.

Origin: they develop from myeloid tissue of red bone marrow too.

Morphology: they are about a same size as neutrophils are. Nucleus is segmented and divides into 2 lobes. About half of them has nucleus which is very irregular in shape. The cytoplasm is packed by basophil-stained granules and non-specific azurophil granules. Basophilic granules encapsulate histamine, heparine, chondroitine sulphate and other enzymes.

Functions:

1. Migration to a tissue and formation of mast cells.
2. Participation in allergic reaction.
3. Regulation of capillary permeability.
4. Phagocytosis.
5. Stimulation of smooth muscle contraction in small intestine, in bronchi and so on.

During allergic reaction the number of basophils in blood increases. This condition may lead to rapid release of histamine from abundance of basophils and cause anaphylactic shock.

Lymphocytes in blood.

They are main cells of immune system. Their number is 25-35% of total leukocyte number. They persist in blood for a limited time on a migration way to lymph nodes or other lymphoid organs. But they can return to a blood to participate in immune response. The life span of lymphocytes vary from couple hours to many years. There are small (6 mcm), medium (8 mcm) and large (10 mcm) lymphocytes. In blood we can find mostly small lymphocytes. They have round shaped nucleus, small circle of cytoplasm around, few organelles of general purpose (EPR, ribosomes, mitochondria). Small lymphocytes are differentiated lymphocytes from thymus or red bone marrow, but they are not active in immunological aspect. They become ative after blastransformation reaction

in lymphoid organs. They enlarge in size and become medium and large lymphocytes.

There are T-lymphocytes, B-lymphocytes, NK-lymphocytes and "0"-lymphocytes. We can distinguish them only immunologically. But they are functionally different.

T-lymphocytes are differentiated in thymus gland. They are subdivided into T-killer (to kill foreign or cancer cell), T-helpers (to activate immune response), T-suppressors (to suppress immune response) and T-memory lymphocytes (to remember infectional agent until next meeting with it).

B-lymphocytes are differentiated in red bone marrow, but birds have special organs for their differentiation – bursa Fabricius – that is why they are called B-lymphocytes. In tissues they transform to plasma cell, which produce antibodies. Among B-lymphocyte population there are B-memory cells.

NK-lymphocytes (or natural killers) contain in cytoplasm secretory granules. This population is also called large granular lymphocytes. They are 10% of total lymphocyte count and only function of them is participation in anticancer immunity.

"0"-lymphocytes are cells without markers of T- or B-lymphocytes. Their function is unclear.

Monocytes

Their number is 6-8% of total leukocyte number. They appear from red bone marrow. The main place where they work is tissues. So in blood they only travel to their destination point. But by the way, they may participate in immune reactions if it is necessary. They have small azurophil granules, well developed cytoskeleton, which provides good motility. The have big nucleus with large amount of cytoplasm. When they come to a tissue, they transform to macrophages. Each tissue has own macrophages. But all together they form Mononuclear Phagocyte System.

Functions:

1. Phagocytosis.
2. Processing and presentation of antigens for other immune cells.
3. Anticancer immunity.
4. Regulation by cytokines synthesis.
5. Participation in tissue homeostasis maintaining.

Lymph

It is a product of interstitial fluid. It is filtrated to lymph vessels. Lymph consists of lymph plasma and lymph formal elements. The composition of lymph plasma is close to blood plasma. Formal elements of lymph are lymphocytes (95%), granular leukocytes (4%) and monocytes (1%).

Funtions:

1. Transport of products from tissues.
2. Distridution of body fluid.
3. Immune reactions.
4. Returning proteins back to a blood.

The hemogramm, the lymphogramm, the leukocyte count

The hemorgamm is integrated index that shows quantitative structure of blood. We can say that hemogramm is blood count. But it will be not fully correct because hemogramm also includes such indexes as sedimentation rate, hemoglobin concentration, hematocrit, and leukocyte count.

There is an example of normal hemogramm without leukocyte count, which will be listed below.

Erythrocytes (10^12/liter)	Hemoglobin (gram/liter)	Reticulocytes (%)	Sedimentation rate (mm/hour)	Platelets (10^9/liter)	Lekocytes (10^9/liter)	Hematocrit (%)
4-5.5	130-160	0.5-1	4-9	200-400	3-8	40/60

The leukocyte count present relative composition of whole leukocyte pool. The typical leukocyte count is presented below.

Basophils	Eosinophils	Neutrophils			Lymphocytes	Monocytes
		Juvenile	Stab	Segmentead		
0.5-1	3-5	0-0.5	3-5	60-65	20-35	6-8

Age changes of blood

During human ontogenesis the blood composition always changes. So the physicians of any spatiality mast know these changes.

Erythrocytes. The erythrocytes count of newborns is about 6-7*10^12/liter. To 2-week age it reaches adult level and continues falling down. The lowest physiological count is on a 3-6th month of life (physiological anemia). The newborns have significant reticulocytosis (increased number of reticulocytes). The definite state of blood count is reached in puberty. Elders may have decreased number of erythrocytes.

Leukocytes. The newborns have physiological leukocytosis (up to 10-30*10^9/liter). The definite state of leukocyte count is reached in puberty. There are physiological cross points between granular and agranular leukocytes. The newborn has ratio between these types, which is similar to adult (73/30). But number of granular leukocytes falls and at the 4th day of life we have first cross point where number granular and agranular leukocytes is equal (50/50). The granular leukocyte number continues falling and at the age of 1-2 year, we face following ration: 25% of granular and 75% of agranular. Than, number of granular leukocytes start to rise and at the age of 4 years we face second cross point. This process continues and leukocyte count reaches its definite state in puberty.

Chapter 7: Nervous tissue

General morphofunctional characteristics

Nervous tissue is spetializated tissue. In phylogenesis it appeared later than tissues of general purpose. The impact for it appearance was that animals aquired new and more complicate behavior. It performs an important function – reactivity. It is based on ability of neurons to percept irritaations, to induce impulses and to cause responsive reactions.

The source of development for nervous tissue is nervous plate. It is a part of ectoderm (neuroectoderm). It gives two main buds – nervous tube and ganglionic plates. Tissue elements of nervous tissue are two cell types: neurons and glial cells. Neurons are leading cells of nervous tissue and they are responsible for performing all functions of nervous tissue. Glial cells are accessorial cells for neurons. They perform nutritive, defense, supportive, and regulatory functions. Neurons of the adult have no undifferentiated precursors. All cells are subject to irreversible differentiation after birth. The neurons can not divide. That is why the regeneration occurs only on intracellular level by hypertrophy of neighbor cells. The variant of intracellular regeneration is regeneration of nervous fibers after injury. The only exclusion from this rule is olfactory neurons.

They are subject to cellular regeneration. Glial cells can divide because they have cambial cells. Nervous tissue has good blood supply.

Sources of development and histogenesis of nervous tissue

The source of development for nervous tissue is neuroectoderm – it is part of dorsal ectoderm, which lies above a chorda. It is called *nervous plate*. The determination of neural plate cells is induced by chorda region during second gastrulation phase. The process, which is called neurulation, has following steps. Almost as soon as it formed the neural plate becomes depressed along its middle to form the *neural groove* and elevated along its two edges to form two neural folds. Near the crest of each fold, below the line along which the thickened ectoderm of the plate becomes continuous with the ordinary ectoderm of the back, some thickened ectoderm bulges laterally; these bulges on each side constitute what are termed *neural crest* (ganglionic plates). Next, the edges of two neural folds come together. This entails three fusions: 1) the edges of thickened ectoderm of neural groove fuse to convert the groove to the *neural tube*, 2) the two neural crests fuse, but only temporally, because they soon become separated again, 3) the edges of ordinary ectoderm fuse over the neural tube separating it from environment and sinking it deep to mesoderm. In cranial part of embryo, the ectoderm enlarges and form neurogenic placodes.

Neural tube and neural crest are major buds for nervous system development. Neural tube gives rise to neurons and macroglia of central and peripheral nervous system. Neural crest gives rise to neurons and macroglia of spinal and autonomic ganglions, to adrenal medulla, to melanocytes and to cells of diffuse endocrine system. Neural placodes give rise to olfactory and gustatory neurons, to neurons of organ of balance and internal ear and to neurons of V, VII, IX, X cranial nerves ganglions.

Neural tube has 5 layers: 1) internal borberline membrane, 2) ependymal layer, 3) mantle layer, 4) lateral veil, 5) external borberline membrane. Ependymal layer consists of germinal cells, which actively divide. After division cells move to mantle layer, however, some cells remains here and serve as a source for development ependymal glial cells. In mantle layer cells are involved into two differentiation lines: neurogenic and gliogenic. Neurogenic line results in neurons formation, whereas gliogenic line results in macroglia cells formation (except ependymal cells). The lateral veil is made of cellular processes from two previous layers.

The stages of neurons development are the following: medulloblast of ependymal layer → neuroblast → proneurocyte → neurocyte (neuron). The transforming to neuroblast occurs by influence of *neuromodulin* GAP-43. The neuromodulin is a protein specific to acsons. The appearance of the neuromodulin shows the beginning of differentiation. There are several processes of cell on early stage of development. Each is apt to be either acson or dendrite. The accumulation of GAP-43 in one of them let it to be acson.

Neuroblast is characterized by having acson and well developed organelles of protein synthesis. The synthesis of neurofibrills actively takes place. Neuroblasts migrate to strictly determined locations. **Proneurocyte** rapidly rises in volume. It forms a lot of dendrites and synapses with other cells. **Mature neurocyte** structure will be discussed below.

Neurocytes

Classification. There are several principles, which were laid down to the classification core.

1. Morphological classification (by number of processes and perycaryon shape).

1.1 Unipolar neurocyte. It has only one acson, which may branch on several branches.

1.2 Bipolar neurocyte. It has two processes – one acson and other dendrite.

1.3 Pseudounipolar neurocyte. It has one narrow processus leaving a body, but soon after that it branches on two.

1.4 Multipolar neurocyte. It has many processes. One of them is acson, others – dendrites. This is most common type of neurons.

Unipolar neurons are very rare in our body. They are presented by amacrine neurons in retina. Bipolar neurons are found in retina, spiral ganglion, vestibular ganglion. Pseudounipolar neurons localization is spinal ganglions. As bipolar as pseudounipolar are sensory neurons or may be sometimes intercalated neurons as bipolar neurons in retina.

2. Functional classification. It concerns neurons functions.

2.1 Motor (efferent) neurons. They carry signals to working organs (muscles, glands).

2.2 Sensory (afferent) neurons. They can generate impulse as response on irritation and carry it to CNS.

2.3 Intercalated (associative) neurons. They connect neurons.

2.4 Neurosecretoral neurons. They secrete hormones.

3. Neurotransmitter classification. Neurotransmitter – is a chemical substance, which is used to transmit signals from one neuron to another.

3.1 Cholinergic neurons (transmitter is acetylcholine).

3.2 Aminergic neurons (transmitters are biogenic amines).

a) adrenergic neurons (adrenaline).

b) serotoninergic neurons (serotonin).

c) dopamineergic neurons (dopamine).

3.3 Purinergic neurons (transmitters are ATP and other purine bases).

3.4 Peptidergic neurons (transmitters are different petides).

3.5 GABAergic neurons (transmitter is GABA, gamma aminobutyric acid).

Structure of neurocyte

Neurocyte – is a nervous cell with all it's processes and terminal branches – terminal endings. The processes can be of two types – acson and dendrites. The acson carries impulse from cell body to periphery. The dendrite carries impulse from periphery to cell body. Neurocytes can have only one acson, but several dendrites.

Nucleus is big with large nucleolus. The euchromatin prevails in the nucleus. There is Barr's body in female cells, which is really is deactivated X-chromosome. Such structure of nucleus is typical fro cells with high protein production activity.

The cytoplasm is subdivided into perykaryon (part which surrounds nucleus) and acsoplasm (cytoplasm of processes). Basic stains stain perykaryon very strongly. This staining called basophilic Nissl bodies. They are present in perykaryon and in dendrites, but they are absent in acson. The structure of basophilic Nissl bodies can be changed during cell living. For example, they become invisible while cell regeneration. With help of electronic microscope, it was revealed that basophilic Nissl bodies are well developed rough EPR. Their function is protein biosinthesis.

If we stain neuron by argentums salts, we can reveal neurofibrills. They are components of cytoskeleton, which come in various directions in cell body and processes. Due to this staining, they become aggregated and visible for us. With help of electronic microscope, it was shown that cytoskeleton of neuron is presented by microtubules (neurotubules), microfilaments and intermediate filaments (neurofillaments). Microtubules andmicrofillaments have the same structure as in other cells. Neurotubules

with help of kinesin are connected with cell organelles and thus participate in acson flow.

Apart from listed above, neurons have a lot of mitochondria, well developed Golgi complex and smooth EPR. The centrioles are located between nucleus and dendrites. In aging cell we can see lipid and pigment inclusions, especially lipofuscin. In some neurons there are melanin inclusions. Lysosomes are well developed here. They can be of various sizes. They participate in digestion of aged elements of cytoplasm, in cell renewing.

Dendrites. They extended from the various surfaces of multipolar cell like branches from a trunk of a tree. They allow neuron to get information from other cells. The smallest branches form small buds in a place of contact with other cell. They are called *gemmules*. They are very labile. They are constantly destroyed and rebuilt. They become especially abundant in case of functional load on a cell. There are all types of organelles in the place where dendrite leaves the body, but they decrease in number to periphery.

Acson. It carries an impulse from cell body to periphery. It may be 1.5 meter long and contain about 99% of cytoplasm. It arises from a special part of a periphery of cell body called *acson hillock*. There is complex Golgi, but Nissl bodies are absent. Here, the generation of nerve impulse takes place. The cytolemm of acson hillock is rich in ion channels, which are necessary for depolarization. The bundles of neurofillaments lie centrally, whereas neurotubules and microfilaments with organelles are located on a periphery.

Acson flow. The proteins are mostly produced in perykaryon. The main organelles are also located there. In processes, the synthetic processes are retarded. This dictates the necessity to transport proteins along acson. There are two types of acson flow: anterograde and retrograde. The anterograde acson flow is transport of substances from body of cell to periphery. The retrograde acson flow is conversely process – transport from periphery to cell body. There are slow and rapid acson flows. The slow acson flow has a speed 1-5 mm per day and it helps in transporting elements of acsoplasm with enzymes and cytoskeleton elements. The rapid acson flow has a speed 50 -2000 mm per day and it serves for transmitter and organelles transportation. The retrograde acson flow has a speed 200 mm per day. It serves for transportation of waste products, products of glial cells, synaptic vesicles back to the body. The aged organelles are also transported back to the body to be destroyed by it's lysosomes. There are two main mechanisms of acson flow. First is actin – myosin mechanism.

The principle of its work is the same to muscle. The second is tubulin – kinesin (dinein) mechanism. The kinesin molecul is attached from one end to organelle or to a vesicle. By the other end it jumps along peripheral cytoskeleton components of acson. The glial cells also help in acson flow. They surround acson and they always produce waving movements. It helps to push substances forward along acson.

Plasmolemm. It is plasma membrane of neuron. It has the ssame structure as in other cells, but functionally it has some special properties. It contains a lot of ion pumps, which always transport ions forming membrane charge. While excitation, the ion concentration is rapidly changed, it cause impulse generation. The impulse is generated in the acson hillock.

Neuroglia

Gliocytes are accessory cells of nervous tissue. They arise from nervous bud (nervous tube and nervous crest). The term "glia" means "glue" from Greek. The early scientists believe that gliocytes glue neurocytes to whole. Glial cells, in compare with neurocytes, can divide. They may form glial scars in case of injury of nervous system. Also they can give rise for malign tumors.

Glial cells perform nutritive, supportive, barrier, defensive, secretoral functions. They also participate in conducting of nerve impulse and they take part in producing of hemato-encephalic barrier.

CLASSIFICATION:

Macroglia			Microglia
Astrocytes	Oligodendrocytes	Ependymocytes	Glial macrophages
1. Fibrous 2. Protoplasmic	1. Mantle oligodendrocytes 2. Lemmocytes 3. Free oligodendrocytes of CNS 4. Oligodendrocytes of nervous endings.	1. Ependynocytes of central canal 2. Ependynocytes of brain ventricles 3. Tannicytes 4. Choriod glia 5. Radial glia	

Ependymal glia. It makes the lining of spinal canal and of brain ventricles. It resembles simple epithelium. Inner surface of a cell has villia. There are processes arising from basal side of a cell. They extend through all width of spinal cord or brain. They unite with each other on external surface, forming external glial bordering membrane. They join with each other by their side walls.

There is another type of ependymal glia, which is in the regions of vascular plexuses. It is choriod glia. The cells have cuboidal shape and they cover the protrusions of pia matter. Apical surfaces have many villia, whereas basal surfaces form many pseudopodia, which make basement labyrinth. They join with each other by their side walls.

Tannicytes lies in the walls of 3rd ventricle. They have cuboidal or columnar shape. Inner surface of a cell has villia. There is one processus leaving the cell from basal side. It comes to capillary and form a plate on it.

Radial glia. They are very important in embryogenesis. They direct moving and growing of neuroblasts to their definite locations.

Functions of ependymal glia: support, defense, nutrition, secretion (of liquor), barrier.

Astrocyte glia. It makes the support frame of brain and spinal cord. The marker of astrocytes is Glial Fibrillar Acid Protein. The intermediate filaments are made of it. There are two types of astrocytes: fibrous and protoplasmic. The protoplasmic astrocytes prevail in grey matter, whereas fibrillar in white matter. Protoplasmic astrocyte has short and thick processes, which are rich in cytoplasm with glycogen inclusions and various organelles. The concentration of intermediate filaments is low. Fibrillar astrocyte has long and narrow processes with many intermediate filaments. The processes of gliocytes make support and barrier structures in white matter. BY their processes astrocytes contact not only between themselves, but also with ependymocytes and oligodendrocytes. Protoplasmic astrocytes participate in formation of blood-brain barrier.

Functions of astrocytes: support, defense, barrier, transportation, nutritive, metabolic and plastic (formation of glial scar after brain injury). Astrocytes can phagocytate bacteria and present antigens for other immune cells. They can secrete mediators of immune reactions.

Oligodendrocyte glia. This type of glia has cells with few processes. The cells body is small and triangular in shape. They surround neurons and their processes. By this all oligodenrogliocytes are subdivided into several groups:

1. **Mantle** or **satellite** glia. It surrounds neurons bodies. Cells are flattened in shape with small nucleus.
2. Lemmocytes or Schwann cells. They form glial covering of neurons processes and participate in formation nerve fibers.
3. Free oligodendrocytes of CNS.
4. Oligodendrocytes of nervous endings, which participate in formation of nerve endings (variant of lemmocytes).

Functions of oligodendroglia: 1) barrier, 2) defense, 3) isolation of nervous fibers and producibng of myelin, 4) participation in nervous impulse conducting, 5) regulation of neuron metabolism.

Microglia. It is made of glial macrophages. It has origin from blood monocytes. The cells are small with dense cytoplasm and thin branched processes. There are a lot of lysosomes in cytoplasm. Glial macrophages move along the tissue and phagocytate dieing neurons and nerve fibers. If it is irritated, it loose its processes and becomes oval in shape. Such cells are often called granular spheres.

Nervous fibers

Nervous fiber – is a processus of nerve cell, surrounded by glial covering. The processus of nerve cell is called axial cylinder. There are two types of nervous fibers: **myelinated** and **nonmyelinated.**

In nonmyelinated fibers, the processes of nerve cells are in invagination of Schwan cell. Thus the process is surrounded by its own plamalemm and by plasmolemm of lemmocyte. It is suspended on the duplication of lemmocyte plasmalemm, which is called mesoaxon. Nonmyelinated fibers contain several axial cylinders (up to 20). They resemble electric cable by their structutre. That is why they are called nerve fibers of cable type. The nerve fiber is enclosed in basement membrane. Some investigators point out that there are "naked" nerve fibers without glial membrane in CNS. But they are found only during embryogenesis. The conducting speed is low about 1-5 meters per second. This type of fibers is mostly localized in autonomic nervous system (postganglionic fibers).

Myelinated nervous fibers are made of nerve cell processus and lemmocytes. The processus is surrounded by myelin sheets. They are the spiralized processes of oligodendrocytess (Schwann cells). The myelin coat is made of circles of plasmalemm duplication of lemmocyte and of nevrilemma (cytoplasm of lemmocyte). Myelin coat contains many lipids, and therefore it is well stained by osmic acid.

There are Ranvier nodes along nervous fiber. It is the place where myelin coat is absent. Inthis regions the acson cytolemm expands and contains lot of ion canals. The Schwan cells contact with each other by interdigitations. The abundance of mirotubules provides tight connection between Schwan cells and acson.

The speed of signal transmitting along myelinated nervous fibers is around 10-120 meters per second. The way of transmitting is called saltatory conduction. When an impulse travels down along acson it does not proceed uniformly along the length of the axis cylinder, but umps from on node to the next. In nonmyelinated nervous fibers it has to travel all way down a nerve fiber without jumping. It is much slower than saltatory conduction and consumes more energy.

Regeneration of nervous fibers

Physiological regeneration of nervous fibers is related with regenerative processes in axial cylinder and in olygodendrocytes. It is performed on intracellular level in axial cylinder, whereas aged oligodendrocytes may be substituted by new cells.

After injury of nervous fiber the degeneration of axial cylinder on both sides from the place of injury takes place. It is called Wallerian degeneration. Perycaryon looses Nissl bodies – chromatolysis of Nissl bodies. The proximal part degenerates on a small distance, whereas distal part degenerates all the way down to the working organ. Microglial cells and macrophages clean the space by phagocitating of degradation products. Than oligodendroglial cells multiply, move along acson and form endoneurial tubes. The growth bulb appears on proximal end of axial cylinder.

The growth bulb enters the endoneurial tube and grows along it with speed 2-4 mm/day until it reaches innervating organ. During this process the axial cylinder branches, an each branch grow in separate endoneurial tube. 4-6 weeks after the function of neuron fully recover. The Nissl bodies appear in cytoplasm. When growing bulb reaches innervating organ, the lemmocytes form myelin covering of fiber.

Succesful regeneration depends on several factors. Some factors suppress regeneration. They are the following: 1) presence of died tissues in injury place, they induce scar formation, 2) large distance between parts of injured nervous fiber, 3) failure of nerve blood supply. If scar connective tissue has been formed, the nerve can grow in it. It causes formation of amputation nevroma. Such nevroma can cause phantom pains

and require surgical treatment. The regeneration can be stimulated by Nerve Growth Factor, anabolic hormones, vitamins, folic acid, and ets.

In central nervous system the regeneration of nervous fibers do not occur. It is due to fast formation of glial scar, whereas neurocytes have ability to regeneration of processes.

Chapter 8: The nerve endings

Nerve endings are terminal branches of nerve cells. In the terminal the impulses are generated or are transmitted to another cell. There are three types of endings:

1. Efferent (transmit signal to working cells: muscle or glands).
2. Afferent (transmit signal from the place where the impulse is generated).
3. Interneuronal (transmit signal between neurons).

Efferent nerve endings

Efferent nerve endings can be of two types: 1) muscular 2) secretoral. Muscular nerve endings are divided into endings in skeletal muscular tissue and in smooth muscles. Muscular nerve ending in skeletal muscle called **motor end plate**. It was generally accepted that the acson on approaching muscle fiber and before it branched into terminal twigs, looses its myelin coat. The sarcolemm that forms the floor of a gutter is thrown into numerous folds, called junctional folds, which extend toward the nerve ending. The acsolemm that covers each expanded nerve termination does not come into direct contact with crests of junctional folds, instead of two cell membranes, one (of nerve ending) called **presynaptic membrane**, another ((of muscular fiber) called **postsynaptic memebrane**, are always separated by the space about 200Å wide and termed the **synaptic cleft**.

The neuromuscular junction is the synapse between a nerve and a muscle cell. A nervous impulse arriving at an end plate causes the release of acetylcholine from some of the vesicles, which presumably are filled by chemical mediator. The acetylcholine is released into the synaptic cleft, where it affects the considerable amount of membrane receptors of the muscular cells. The acetylcholine here seems to act by reducing the permeability of the sacolemma to sodiumion, and this in turn initiates a wave of depolarization that sweeps over the fibers via the system of

transverse tubules. The acetylcholine liberated in response to nervous impulse is promptly inactivated by acetilcholinesterase.

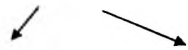
In smooth muscle nerve ending terminate by several alveolar expansion with mediator, which is released to the matrix.

Secretoral nerve endings terminate on secretoral cells. They release the neurotransmitter to secretoral cells. It activates cell membrane and facilitates release of secretoral vesicles.

Afferent nerve endings

Classification:

1) According to the place where the irritation is recepted.
A. Exteroreceptors (from outside).
B. Interoreceptors (from inside).
C. Proprioreceptors (from organs of locomotion).
2) According to the type of recepted irritation.
A. Mechanoreceptors (physical irritation).
B. Chemoreceptors (chemical irritation).
C. Termoreceptors (for temperature).
D. Nocireceptors (for pain).
3) By way of reception.
A. Distant.
B. Contact.
4) Morphological classification.
4.1 Naked (bare) nerve endings.
4.2 Covered nerve endings



incapsulated non-incapsulated

Morpholgy of afferent nerve endings

Bare (naked) nerve endings. They are mostly presented in the skin. They are mechanoreceptors in hair follicles, nocireceptors in epithelium. They are widly presented in stratified squamous non-keratinized epithelia. Morphologically, they are just terminal branches of pseudounipolar neurons of spinal ganglia. They are for pain and pressure recepting.

Covered non-incapsulated nerve endings. They are presented by Merkel disks and nerve endings in connective tissue. They are widely

located in derma. Their morphological structure is in following. There are sensitive Merkel cells in epidermis. They contain a lot of vesicles with neurotransmitters. If they are irritated by touching, they release their neurotransmitters and evoke signal on nerve ending, which lies closely to Merkel cell. They are for pressure reception.

Nerve endings in connective tissue loose their myelin coat and make close connections with other glial cells forming symmetrical structure. When condition of the matrix is changed, the nerve endings are stimulated. They are for pressure reception.

Covered incapsulated nerve endings. All of them have similar general structure plan. Nerve ending is surrounded by inner capsule of glial cells, which in turn is surrounded by connective tissue capsule. There are several types of such endings: Vater-Pacinian corpuscles, Meissner's corpuscles, Krause's end-bulbs, genital Dogel's corpuscles, corpuscles of Ruffini, neuromuscular spindle, neurotendinous organ.

Let's describe them.

Vater-Pacinian corpuscles are very spread in human body. They are of oval shape. They have outmost capsule presented by LICT. In inner capsule, there are glial cells of two types: special flat gliocytes that cover nerve ending and branching glioytes that are place inbetween flat gliocytes. By their branches they touch nerve ending. When corpuscle is irritated by pressure, the outer capsule of it slides along inner capsule. Cells of inner capsule change their position. It irritates nerve ending and evoke nerve impulse. Having two capsules helps to increase irritation power. It helps in recognizing very quiet signals from environment. They are for pressure reception.

Meisner's corpuscles. They are of oval shape. Nerve fiber comes to the capsule and than it comes up spirally. Gliocytes lie with right angle to it. They are for pressure and touch reception

Krause's end-bulbs. They are of sphere shape. They are localized generally in the skin. Gliocytes make kind of network with nerve endings embedded between them. They are for temperature reception.

Genital Dogel's corpuscles. They are located in the most sensitive regions of skin (so called erogenic zones). They look like Krause's en-bulbs, but several nerves give their termination to Dogel's corpuscle, whereas only one enters Krause end-bulb. It allows enhancing irritation.

Ruffini corpuscle. They are in connective tissue and in joints capsule. They recept touch and pressure. They are of spindle shape. Nerve ending enters to it and branches. The terminal branches have bulbs on their ends.

In smooth muscles afferent nerve endings are also incapsulated. They contact a group of smooth myocites.

In skeletal muscle tissue afferent nerve endings called neuromuscular spindles. Normal muscular fibers are called extrafusal fibers. There are regions, which are made of intrafusal muscular fibers. Intrafusal muscular fibers can be of two types: a) nuclear chain type and b) nuclear bag type.These fibers are surrounded by afferent nerve endings of two types:

1. Annulospiral endings, which surround the nuclear bag fibers and nuclear chain fiers in a spiral fashion. They start stretching reflex.
2. Flower spray endings. They are on the nuclear chain fibers only. They start relaxation reflex.

There are motor end-plates of γ-motoneurons of spinal cord on intrafusal muscular fibers.

The way how it works: Any stretching or relaxation of muscle leads to irritation of annulospiral and flower spray endings. That excites dendrite and we receive information about our muscles state. Motor end-plates of γ-motoneurons of spinal cord are needed to maintain intrafusal muscular fibers in tonus all day long.

The neurotendinous organ has approximately the same structure and working pattern.

Interneuronal synapses

Interneuronal synapses are connetions between nervous cells.

Classification:

1) By mechanism of signal transmitting.
    a) Chemical.
    b) Electricla.
    c) Mixed
2) By morphology.
    a) Axo-somatic
    b) Axo-dendritic
    c) Axo-axonal
    d) Dendro-dendritic
    e) Dendrosomatic
    f) Soma-somatic
3) By psysiological effect.
    a) exciting
    b) supressive
4) By releasing neurotransmitter.

a) cholinergic (acetylcholine)
b) adrenergic (adrenaline)
c) aminergic (dopamine, serotonime)
d) purinegic (ATP)
e) GABA-ergic (gammaaminobutiric acid)
f) peptidergic and so on.

Structure.

Every synapse consists of three parts: presynaptic membrane, synaptic cleft (or gap) and postsynaptic membrane.

Electric synapses. They are made of nexuses. The pre- and postsynaptic membranes lie close together. They are tightly connected by connexin. Connexin allows passing the exitation (depolarization) wave from one ending to another. Such synapses are located in molecular layer of brain cortex.

Chemical synapses. Here, the impulse is transmitted with help of neurotransmitter. The neurotransmitter is produced mainly in cell body. Than, it is transported to the acson termination with help of axon flow. The neurotransmitters are stored in nerve termination until request. When the wave of excitation reach the acson termination, the neuromediator is released through, so called, active zones of presynaptic membrane. It travels through synaptic gap and binds with receptor on postsynaptic membrane. This binding cause depolarization of postsynaptic membrane and the excitation wave continue its way along neuron process.

The destiny of neurotransmitter can be different:

1. Recycling (pumping back to presynaptic pole).
2. Degradation by glial cells.
3. degradation by specific enzymes (acetylcholinesterase).
4.

Reflex arcs

Reflex arc is the chain a neurons, which provide impulse carrying from receptor to effector. The reflex arcs can be simple and complex. The simple reflex arc consists of only 2 neurons: afferent and efferent. The complex reflex arc consists of more than two neurons due to having one or several association neurons.

The complete structure of complex reflex arc is presented below.

Receptor → dendrite of sensory neuron → perycaryon → acson of sensory neuron →synapse of sensory neuron with association neuron→ dendrite of association neuron→ perycaryon → acson of association

neuron → synapse of association neuron with effector neuron → dendrite of effector neuron →perycaryon →acson of effetor neuron → motor end-plate.

Statements of neuron theory

The neuron theory was suggested by Spanish histologist S. Ramon-i-Kahal in the beginning of XX century. For this theory he was awarded by Nobel Prize in 1906.

The statements of neuron theory are following:

1. The structural, functional, morphological, metabolic unit of nervous system and nervous tissue is neuron.
2. The neuron is a cell having perycaryon, acson, dendrites and terminal branches.
3. The neuron functioning is possible only with integration with glial cells.
4. Neurons interact with each other with help of synapses – spetializated intercellular junctions.
5. Several neurons connected by synapses form reflex arcs – main substrate of nervous system.
6. The exitation in synapses and in reflex arcs may be transmitted one way only.

Chapter 9: The introduction to the histology of organs

Histology of organs or microscopic anatomy – is the special part of histology core, which studies microscopic structure of various organs in our body.

Organ is hierarchic system, the part of organism, which has a specific structure, and which made of several close connected tissues. Any organ of the organism is originated from several embryonic layers. Organ is anatomically and functionally organized. Organ has several tissues in its structure, but one of them is a leading tissue. This leading tissue is responsible for main function of organ. Organs perform various functions and have very different histological structure. But generally we can find some similarities in their structure. All the organs are classified on several types:

1. **Organs of parenchymal type.** The tissues, which are in these organs, are divided into two functional groups. One group provides main function of the organ and that why it is called

parenchyma. Parenchymal cells of the organ usually have one source of development and common functions. Different tissues can be parenchymal tisues. For example, in skeletal muscle the parenchymal tissue is skeletal muscle tissue, in brain – nervous tissue, in tendon – dense regular connective tissue and so on.

Another group serves as supportive and nutritive base. It brings vessels and nerves to the organ. It is called stroma. The stroma of parenchymal organs is made of enclosing capsule (dense connective tissue) and septas (loose irregular connective tissue). The stroma is very important for the organ. It contains undifferentiated cells, defense cells, blood and lymph vessels, nerves.

The examples of parenchymal organs are liver, pancreas, kidney, brain, spinal cord and so on. The parenchhymal organs have some particular features in their structure. That is why we can distinguish several types of parenchymal organs:

a) parenchymal lobular organs.

b) parenchymal zonal organs.

c) parenchymal fascicular organs.

The parenchyma in parenchymal lobular organs is divided on structural and functional units of different shape – lobes. The lobes have common structural plan and functions. The examples of such organs are liver, pancreas. Parenchymal zonal organs are such organs, which are divided into different functional zones. For example, the kidney has cortex and medulla. The same we can say about adrenal gland and cartilage. The parenchymal fascicular organs are muscles, nerves, tendons, spinal cord. In these organs, the structural elements make bundles, which are separated by LICT. Some organs can combine signs of lobular and zonal organs. In thymus gland we can see lobular structure, but every lobe has cortex and medulla.

2. **Organs of lamellar type**. This type includes all hollow organs. The tissues of these organs are not divided on parenchyma and stroma. These organs structurally made of coats (tunica). There are internal coat, medial coat and external coat of vessels. There are mucosa, submucosa, muscular and serous coats in organs of alimentary canal. Each coat is made of one tissue type, but it is not obligatory. It may include several tissue types. The coats may include vessels and nerve in their structure. The one is referred as lamellar organ too.
3. **Mixed organs**. Some organs may combine features of parenchymal and lamellar organs. The examples are the heart

and uterus. In these organs, the tunica media is so strong, that we can identify parenchyma (cardiomiocytes and smooth miocytes) and stroma (LICT) in it.

4. **Organs of atypical structure**. They have unique organization. They can not be referred either parenchymal or lamellar organs. The examples of such organs are vestibular organ and cochlea.

Each organ has systems of blood and lymph circulation and innervation. The microcirculatory vessels are adapted to structure and functions of an organ. It is especially obvious in liver, spleen, lungs ets. The capillaries of microcirculatory flow take part in formation of structural-functional units, histohematic and hematoparenchymal barriers.

Almoust all organs are innervated. By this their growth, functioning and regeneration are regulated. Efferent innervation of all internal organs is performed by autonomic nervous system. Afferent innervation is performed by pseudounipolar neurons of spinal ganglia.

Structural-functional elements of organs

The structural-functional element of organ – is particular part of the organ, the smallest unit, which has definite structure and able to perform main functions of the organ. The modern view suggests that the structural-functional elements of the organ have 4 following components.

1. Working part – is the system of specific cells of the organ, which perform its main functions. For example, in liver it is system of hepatocytes.
2. Loose irregular connective tissue – it is a part of organ, which serve for maintaining of working part (in parenchymal organs it is stroma).
3. Nervous component. It innetrvates working part and vessels as well.
4. Microcirculatory unit – it is integrity of microvessels, which provides optimal blood flow, substance transport, gases exchange through vessels wall.

The structural-functional elements of different organs may vary in structure. Thus, the structural-functional element of the liver is lobe, whereas in kidney it is nephron. There are two structural elements in pancreas. The acinus – for exocrine part, and Langherhans islet for endocrine part.

The histohematic and hematoparenchymal barriers

The concept about histoparenchymal (histohematic) barrier is closely connected to the concept about structural-functional element of the organ. It is a barrier between blood and working cells of the organ. The barrier includes the following components:

1. Endothelium of capillaries, which supply working part. The endothelium can be of continuous, fenestrated and sinusoid type.
2. Basement membrane of endothelium. It may absent or interrupted.
3. LICT, which surrounds microvessels. It contains immune cells, including macrophages, which are capable to phagocytosis.
4. Basement membrane of working part.

In spite of general principle of histoparenchymal barrier structure, each organ has own particular barrier. The differences may involve each part of the barrier. In some organs some structures are absent, but in others the barrier may be equipped by additional structures (like glial cells in hemotoencephalic barrier).

The function of histohematic barriers is in following:

1. regulatory function. They take part in homeostasis regulation of organ.
2. selective transport of substances.
3. defense function.

The organ is not an independent structure. Each organ is connected with other organs to perform general fundamental function. Thus, organs make systems of organs: nervous, endocrine, respiratory, digestive and others systems. Each organ depends from other organs in the system. The failure in working of one organ results in disturbance of other organs.

Chapter 10: The brain and cerebellum

Brain cortex

The big hemispheres consists of white and grey matter. Grey matter lies outside and forms the brain cortex. The width of cortex varies from 1.3 to 4.5 mm.

Functions. The brain cortex is phylogenetically youngest and most complicate part of the brain. It is nerve center of plane type. Here, the processing of sensory information, response formation, formation of effectory commands and integration of complex behavior take place. It is

responsible for higher nervous activity (thinking, conscience, memory, creation).

The intensive growth of cortex in higher mammalians in limited space of cranium resulted in formation of many brain convolutions. Perhaps, the surface of brain cortex was significantly increased. The square of brain cortex is 2200 cm^2, whereas total volume of the brain is 300 cm^3. There are 10^9 - 10^10 neurons and in 10 times more glial cells on this surface.

Neurons of the cortex. All neurons of the cortex are multipolar. They are divided into two groups: pyramidal and no-pyramidal. The no-pyramidal neurons are spindle-shaped, star-shaped and others.

1. Pyramidal neurons. The main feature of them is having pyramidal cell body. The apical dendrite leaves the cell body from the top. It is ranched in molecular layer as letter "T". About 20 dendrites leave from side surfaces of the cell. They branch within the same layer, where the cell body is. Apical and lateral dendrites have a lot of synapses with other neurons. The acson leaves the cell from the bottom of it. It leaves the cortex within downward pathways or travel toward others zones of the cortex. The acson gives collateralizes which go back to the pyramidal layer and connect with other pyramidal neurons.

2. Star-shaped neurons. They are located almost in all cortical layers. They are smaller than pyramidal neurons, vary in shape, have short branched dendrites and acsons. There are several type of such cells: cell-candelabrum, суд with double dendrite set and others. It is considered that star-shaped neurons work as suppressive neurons. Their processes are terminated on strategically important parts of other neurons: acson hillock, starting segment of acson, where the impulse is generated. The other part of star-shaped neurons activates pyramidal neurons.

3. Spindle-shaped neurons. They have long acson, which may go in vertical and horizontal direction as well.

Cytoarchitecture. The cell bodies and processes of listed above neurons have particular localization in brain cortex. The cortex is nervous center of plane type and that why all structures are located in different layers. Brain cortex of mammalians has 6 horizontal layers.

1. *Molecular layer* – it is outmost layer of cortex. There is tight tangential plexus of nervous fibers in it. The fibers are placed along the brain cortex surface. The main part of these fibers is apical dendrites of pyramidal neurons from underlying layers. In this layer there are thalamo-cortical fibers from thalamus nuclei, which regulate level of excitation of cortical neurons. The neurons of molecular layer are assotiated spindle-shaped neurons (cells of Ramon-i-Kahal). Their acsons also participate in

tangential plexus formation. Their dendrites make the synapses with thalamo-cortical fibers. There are glial cell also.

2. *Outer granular layer*. It is consist of star-shaped neurons. The lower part of this layer also contains small pyramidal neurons. All cells of this layer give up dendrites to the molecular layer, where they form synapses with thalamo-cortical fibers. Some dendrites make the synapses with neighboring cells within this layer. The acsons go to the 3rd, 5th and 6th layer of cortex and interact with neurons of these layers. Acsons can give up collateralizes which go back to the molecular layer. The layer is mainly responsible for association functions and it is well developed in associative zones of cortex.

3. *Pyramidal layer*. It is made of pyramidal neurons of medium size. They give apical dendrite to the molecular layer and lateral dendrites, which make the ynapses within the layer. Acsons make associative nervous fibers which either go to the underlying layers of cortex or go to the neighbor regions of cortex and make synapses with cells of the same layer. There are different no-pyramidal neurons here.

4. *Internal granular layer*. It contains a lot of star-shaped neurons and a few of small pyramidal cells. It is called sensory layer, because neurons of this layer are sensory in function. They have many associative connections with neurons of different types. The thalamo-cortical fibers give collateralizes to this layer. This collateralizes make dense bundles, which are called *outer line of Baillarger*. This layer is well developed in optic and hearing zones of cortex and t is almost absent in motor zones.

5. *Ganglionic or internal pyramidal layer*. In one part of the cortex, called the motor area, the pyramidal cells of this layer are huge; they are called *Betz cells*. Their apical dendrites go up to the molecular layer. Lateral dendrites make a close network of synapses with neighboring neurons of the layer. Acsons go to the white matter and form cortico-spinal (pyramidal) fibers. Acsons may give up collateralizes to the other Betz cells.

6. *Layer of polymorphous cells*. The cells of this layer have many shapes. The dendrites of these cells go to the molecular layer. The acsons of these cells make efferent fibers, which leave the cortex (cortico-thalamic fibers). The cells of Martinotti have an opposite location in compare with other cells oa the cortex. Their acsons go to the molecular layer, whereas dendrites make synapses within the layer. These cells work as suppressive neurons.

The whole cortex has 6th layer plan of structure. But expression of different layers is different in various regions. Having in mind this

principle, K. Brodman suggested division of brain cortex to the 50 architectural areas. In sensory areas, the pyramidal layers are badly developed, whereas granular layers are well developed. This type of cortex called *granular type*. In motor areas, the granular layers are badly developed, whereas pyramidal layers and layer of polymorphous cells are well developed. This type of cortex called *agranular type*.

The neurons of the cortex perform variety of functions. Some of the function results from having different transmitters. That is why in the cortex we can find more than 10 different types of neurons with different transmitters, like acetylcholine, serotonine, dopamine, noradrenaline, VIP, somatostatine and others.

Mieloarchtecture. It is pattern of nervous fibers distribution in the brain cortex. The nerve fibers are divided into:

1) projectional, which connect brain cortex with nuclei of underlying brain regions (efferent and afferent).

2) associative, which connect different regions of rain cortex in one hemisphere.

3) commissural, which connect both brain hemispheres.

These thre types of nervous fibers make three main plexuses in the cortex.

1. Tangential plexus. It lies in the molecular layer. It is made of dendrites of neurons from underlying layers and of thalamo-cortical fibers.

2. Outer line of Baillarger. It is made of thalamo-cortical nervous fibers. It is localized in internal granular layer.

3. Inner line of Baillarger. It is made of collateralizes of acsons from fifth layer and of projectional nerve fibers. It is located in the ganglionic layer.

Among listed above plexuses, some investigators include line of Kez-Bechterev. It lies in outer granular layer and it is made of associative and commissural nervous fibers.

Columnar (module) organization of brain zones. In 1957 American scientist V. Mauntcasle, analyzing responses of nervous cells in motor zone of cat on impulses of different mode, stated that if electrode is inserted athwart to the brain surface, all cell, which interact with electrode, give a response in one mode. But if electrode is inserted slantwise to the brain surface, cells, which interact with it, give responses with different mode. Having in mind that findings, V. Mauntcasle made a conclusion that cortex is made of elementary morphofunctional units – columns or modules. He thought that column is elementary block, structural and

functional unit of the cortex, where initial information processing takes place.

Than, D. Hueble and T. Vizel showed columnar organization of optical cortex. The neuron composition of column was described by Hungarian scientist D. Setagotai. For these works, all listed above scientist receive Noble Prize in 1981.

Today, it is considered that each column of sensomotor cortex consist of several micromodules including several closely located neurons. There are several pyramidal cells with closely lying dendrites in the micromodule. The dendrites make dendritic bundle. In this bundle there are electotonic impulses, which provide synchronic work of the micromodule. There are star-shaped neurons close to pyramidal cells. They contact with thalamo-cortical and cortico-cortical fibers. Some of them activate, other suppress working of neighboring neurons. Acson of pyramidal cells give up collateralizes, which also can be either stimulating or suppressive in function. Several micromodules are united by horizontal branches of thalamo-cortical fibers and by star-shaped neurons to the macromodule with diameter 1000 mcm. The macromodule is integral unit within which all neurons have one mode of responding. Thus, the column has three main department: 1) **entrance**, it is thalamo-cortical fibers or cortico-cortical fibers. They bring information from thalamus (which is main collector of sensory information) or from other regions of cortex. 2) **zone of information processing**, it is a system of pyramidal and star-shaped cells connected with each other by stimulating and suppressive synapses. 3) **exit**, it is acsons of pyramidal cells. The acsons of outer pyramidal layer make connections mainly with neighboring columns and with columns of opposite hemisphere. The acsons from inner pyramidal layer together with acsons from sixth layer go to the subcortical centers and to the spinal cord making efferent exits of cortex.

All zones of the cortex have columnar principle of organization. Structural columns may unite to the functional column. One functional column is responsible for one type or reflex activity. Human education or training are based on formation of new columns responsible for new activity types.

Blood-brain barrier (hematoencephalic barrier). It is a barrier between blood and brain cells. It performs following functions:

1. It prevents harmful substances diffusion to the nervous cells. Immune cells migration is also suppresd by it because that cell can induce autoimmune response.

2. It facilitates diffusion of nutritive substances to the nervous cells.

Blood-brain barrier consists of following structures:

- Endothelial cells of capillaries of continious type.
- Basement membrane of these capillaries.
- Externa glial borderline membrane. It is made of astrocyte glia processes.
- Microglia cells.
- Coat around neurons, which is made of mantle oligodendrocytes and processes of astrocytes.

Cerebellum

Functions: 1) It is a center of balance, of complex movement control; 2) it maintains a muscular tonus; 3) it regulates articulation; 4) it is included into suprasegmental autonomic nervous centers – it regulates working of hair erector muscle, of pupil reflex muscles, it receives sensory information from all internal organs. Cerebellum plays role of controlling organ. It trace every movement, calculates its trajectory and strength. It integrates all information from spinal cord, vestibular nuclei, reticular formation, brain cortex. Signals from locomotory apparatus enter cerebellum through spinal-cerebellar fibers (from neuromuscular spindles), through olivo-cerebellar (from muscular receptors) and ets. The main exit pathway is rubrospinal fibers. It carries impulses to motor neurons of spinal cord and regulates their activity.

Cerebellum has two hemispheres and connecting part called vermix. It has three pair of peduncles (superior, middle and inferior) though which it is connected with outher parts of the brain. It has white and grey matter. Grey matter is cerebellar cortex and three pairs of nuclei lying in white matter.

Cerebellum cortex has convolutions. Cortex is over white matter and has three layers.

1. Molecular layer. It is superficial layer. It contains nervous fibers, which are located along surface of the cortex. They are made of acsons granular cells and of dendrites and acsons of other cells. Basket cells lies in the bootomof molecular layer. They have long acsons, which travels to flask-shaped cells of ganglionic layer and they form many synapses on them. These multiply connections look as baskets around neurons. One basket cell may have contacts with 240 flask-shaped cells. There are star-shaped neurons over the basket cells. They can be of two types: star-shaped neurons with short acsons (they make synapses with dendrites of flask-shaped cells) and star-shaped neurons with long acsons (they make synapses not only with dendrites of flask-shaped neurons, but also can

direct acson to the cell body and participate in basket formation around cell body). Dendrites of basket and star-shaped cells make synapses with acsons of granular cells from granular layer. Basket and star-shaped cells work as associative neurons.

2. Ganglionic layer. It is made of monolayer of suppressive flask-shaped Purkinje cells. The perykarions of the cell measure 60x35 mm. The acson leaves the bottom of the cell and go to the basal nuclei and vestibular nuclei. The acsons of Purkinje cells is the only exit from cerebellum cortex. They can give collateralizes back to the neighbor Purkinje cells. The dendrites leave the top of the cell and than they branch to secondary and tertian dendrites. The dendrites have a lot of synaptic connections with cells of molecular and granular layer. The perykaryons of the Purkinje cells are surrounded by basket of fibers from other neurons. The following structures take part in basket formation: 1) acsons of basket cells, 2) acsons of star-shaped cells with long acson, 3) climbing fibers. One Purkinje cell may concentrate about 40000 synapses.

3. Granular layer. The main cell type here is granular cells. They are most numerous cells of cerebellum. Their total number is about 10^10 - 10^11. The cell has 3-6 dendrites, which branch. Acson of granular cell go to the molecular layer and T-shaped branches. The branches go along convolution and make multiply synapses with dendrites of Purkinje cells, and also with dendrites of basket and star-shaped neurons. The mossy fibers come to the granular cells and make synapses with them as cerebellum glomerulus. Granular cells stimulate Purkinje cells.

There are Golgi cells of three types among gromerular cells in the glomerular layer.

1. Star-shaped Golgi cells with short acsons. Their dendrites go to the molecular layer and make there synapses with acsons of granular cells. Their acsons have synaptic connections with dendrites of granular cells. The cells can block impulses incoming through mossy fibers.

2. Star-shaped Golgi cells with long acsons. Their function is to provide connections between different zones of cerebellum cortex. The dendrites make synapses with cells of granular layer, whereas acsons go to the white matter and than turn back to the cortex.

3. Horizontal Golgi cells. Their dendrites terminate in granular and ganglionic layer, whereas acsons go to the white matter giving collateralizes to granular layer. It is considered that all Golgi cells are suppressive cell, which suppress activity of Purkinje cells.

Afferent fibers or cerebellum entrance. The information can enter cerebellum through 3 fiber types.

1. Mossy fibers. They are from olivo-cerebellar and ponto-cerebellar pathways. They are terminated on dendrites of granular cells.

2. Climbing fibers. They are from spino-cerebellar and vestibule-cerebllar pathays. They make synapses with bodies and dendrites of flask-shaped Purkinje cells.

3. Adrenergic fibers, which come from blue spot in midbrain. They are to regulate excitement of cerebellar neurons.

Purkinje cells are suppressive cells. They suppress functions of neuronf in cerebellum nuclei. Thus they regulate locomotion activity. The movements become smoother and more precise. The Purkinje cells are activated by mossy and climbing fibers. In the first case the excitement pathway looks this way: mossy fiber → granular cell → its acson → contact with dendrites of Purkinje cell in molecular layer → Purkinje cell body → neurons of cerebellum nuclei (supression). In the second case the excitement pathway is shorter and looks this way: climbing fiber → Purkinje cell body → neurons of cerebellum nuclei (supression). There are also suppressive pathways among stimulating pathways. They include star-shaped and basket cells of molecular layer. The pathways are following: mossy fibers → granular cell → its acson → contact with dendrites of star-shaped and basket cells → their bodies → synapses of these cells on Purkinje cells → Purkinje cells suppression. It results in activation of cerebellum nuclei. The transmitters of activating synapses are glutamate and aspartate, whereas in suppressive – GABA.

Glia of cerebellum.

1. Fibrous astrocytes in white matter and protoplasmic in gery matter.
2. Mantle oligodendrogliocytes and lemmocytes.
3. Microglia.
4. Fiber-cells of Bregman or epithelial Golgi cells. They lie between perykaryons of Purkinje cells. The cell bodies give up processes, which go through the cortex and form glial borderline membranes on the cortex surface.

Chapter 11: The autonomic nervous system

Functions: The autonomic nervous system (ANS, vegetative nervous system) is spread all over the body as vascular system. Even skeletal muscles, which are innervated by somatic nervous system, contain vessels with autonomic nerves. This wide distribution is connected with functional load.

ANS performs the most important function – maintaining of homeostasis in all its aspects: energetic, structural, metabolic, temperature, immune and ets. The ANS directs so important processes as metabolism, secretion, excretion, absorption, cell division, cell death, smooth muscle contraction and others. It innervates internal organs, blood and lymphatic vessels. It regulates processes of respiration, blood supply, temperature regulation, reproduction and others.

In spite of the name, the autonomic nervous system isn't totally autonomic. It is the part of integral system and it is close connected with somatic nervous system, it has common structures and it is tightly regulated by CNS. The centers of somatic and autonomic nervous system on a level of brain trunk and brain hemispheres correspond with each other. The examples of close relationships between autonomic and somatic nervous systems are somato-visceral and viscero-somatic reflexes.

Development. The sources of ANS formation are nervous tube and neural crest. The suprasegmental and segmental centers of ANS develop from nervous tube. Their development, generally, doubles the development of spinal cord and brain. The peripheral part of ANS develops from neural crest. The neurons of sympathetic part of ANS arise from 8-28 somites, whereas neurons of parasympathetic part arise from 1-7 somites and from somites located caudally from 28th somite. The cells of neural crest migrate laterally to form autonomic ganglia and nerves. The cells migrate at different time, so we can observe heterochrony of migration. Firstly, the ganglia of first grade are founded (paravertebral), than they are followed by second grade ganglia (perevertebral). Finally, the third grade ganglia (para- and intraorganic) are founded. There are three stages in ganglia development.

1. Stage of primary ganglia. The cells of neural crest migrate to the zone of future ganglion and concentrate there. Thus, the primary ganglia are formed.

2. Stage of concentration. Several primary ganglia fuse with each other and form continuous cellular bar.

3. Stage of definitive ganglia. The segmentation of continuous bar takes place. The ganglia acquire definite structure and after that they are called secondary ganglia.

The nervous fibers of ANS also appear in different time. The pre-ganglionic fibers are subject to myelinization, whereas post-ganglionic aren't.

The ANS is divided into two systems by morphofunctional features: sympathetic and parasympathetic. Some investigators mark

metasympathetic system. Sympathetic and parasympathetic systems have central and peripheral parts.

Stimulation of sympathetic nervous system results in increasing heart rate and force, increasing of breathing rate, vessels contraction in majority of internal organs, increasing of blood pressure, dilatation of heart, brain and skeletal muscle vessels, bronchi dilatation, pupil dilatation. The smooth muscle tonus in alimentary canal is decreased (excluding sphincters). Sympathetic nervous system stimulates glycogen and lipids breakdown in storages. It acts in adaptive and trophic manner on tissues and stimulates metabolic exchange in them.

Stimulation of parasympathetic nervous system results in mainly opposite effects: decreasing of heart rate and force, decreasing of breathing rate, decreasing of blood pressure, smooth muscle contraction in bronchi, increasing of bowel peristaltic movement, sphincters relaxation, pupil dilatation. The processes of digestion in alimentary canal are activated. The blood supply of intestine is increased. The vessels in skeletal muscle are dilatated. The synthesis of lipids and glycogen is activated in liver.

D GANGLIA

1 **Spinal/dorsal root ganglion** (no synapse involved)

1 Has a collagenous connective tissue investment.

2 Many *bundles* of thick, myelinated, nerve fibres separate

3 *groups* of large, round-bodied nerve cells.

4 Each neuron has a thin CT capsule like an endoneurium.

5 Between capsule and neuron is a layer of small *satellite cells* of a glial nature.

6 *Neuron* has only one process (not a dendrite) branching into two near to the soma. The thinner axon runs centrally via a dorsal root into the spinal cord, the thicker runs peripherally to a nervous receptor.

2 **Autonomic ganglion** (compared with a spinal ganglion)

1 *Fewer myelinated fibers* are present.

2 Neurons and fibers are *interspersed.*

3 Neurons are smaller and have *dendrites*, with preganglionic fibres synapsing upon them.

4 Many of the neurons' own axons (post-ganglionic fibers) are *unmyelinated.*

In a cross-sectional view, several unmyelinated fibers share one Schwann cell, lying in many deep invaginations of its membrane. In the gut, enteric glia take the place of Schwann cells.

2 Postganglionic autonomic nerve fiber terminals

1 *Control* smooth muscle contraction and exocrine glandular secretion, or go to the heart muscle and adrenal medullary cells.

2 Axons lie against, or sometimes within, invaginations of the muscle fibres or glandular cells, making mostly *en passant* contacts,

3 but specialized sarcolemmal structures comparable with a motor end-plate's are not present.

4 The nerve fibers are, however, widely dispersed as a *plexus* between the smooth muscle fibers, and contain many *vesicles* concentrated periodically.

5 These vesicles may contain one of the two principal transmitter substances - *acetylcholine* (ACh) and *norepinephrine (Ne)/noradrenaline*, along with other chemicals, e.g., peptides. Some neurons and fibers are neither cholinergic nor adrenergic. A chemical mapping of the PNS (crucial to pharmacology) is under way, including the sensory pathways to autonomic ganglia.

3 Origin of autonomic nerve fibers

1 *Parasympathetic*

Cranial nerves: III,VII,IX,X and sacral pelvic nerves have parasympathic preganglionic fibers (ACh)

These run near or into the organ to be controlled before synapsing with *local* parasympathetic ganglion neurons (e.g., of Auerbach's plexus), whose own short post-ganglionic fibers (ACh) innervate the muscle or glandular tissue.

2 *Sympathetic*

Thoraco-lumbar outflow has sympathetic preganglionic fibres (ACh) synapsing with neurons of the *sympathetic ganglion chain* along the vertebral bodies or going farther to ganglia, e.g., coeliac, serving a visceral or cranial region. Sympathetic post-ganglionic fibers (usually Ne) thence pass to the muscle or gland to be controlled. (Ac - acetylcholine is the transmitter substance; the fiber is called *cholinergic*. Ne - norepinephrine is the transmitter substance; the fiber is called *adrenergic*.)

Beware. There can be more than one transmitter, for example, ATP can be a cotransmitter for both sympathetic and parasympathetic neurons, making these also *purinergic*.

Chapter 12: The cardiovascular system

The circulatory system consists of a closed system of vessels, which main function is to transport blood to all cells and tissues of the body. The

three components of circulatory system are heart, blood vessels and lymph vessels. The heart and blood vessels are included to cardiovascular system.

Functions: 1. Transport
1.1 trophic
1.2 respiratory
1.3 excretory
2. Integration
3 Regulation
4 Participation in immune reactions

Development.

- Primary angiogenesis. It is vessels formation from mesenchyme in the yolk sac on 3rd week of embryonic development.
- Secondary angiogenesis. It is the formation of new vessels from already existed vessels. It may take place in embryo (embryonic period) and in child (postembryonic period).
- Heart develops from mesenchymal tubes (endocardium) and from myoepicardial plate, which is a part of visceral layer of splanchnotom (myocardium and epicardium).

Heart

It has features of parenchymal and lamellar organs as well. It has three coats: endocardium, myocardium and epicardium. In myocardium we can distinguish parenchime (cardiac muscle) and strome.

Functions: 1 Blood pump
2 Endocrine function (Na uretic factor)
3 Information coding in form of arterial pressure and ECG parameters.

Structure. **Endocardium.** It resembles blood vessel structure. It has 4 layers: endothelial → presented by endothelial cells, subendothelial → LICT, muscular-elastic → smooth myocites and elastic fibers, ecternal connective → LICT. Endocardium forms the heart valves. The blood vessels are only in external connective layer. All other layers get nutrition by diffusion from heart lumen.

Myocardium. It is the main heart coat. It is presented by cardiac muscle tissues as parenchyma and by LICT as stroma. Cardiomyocites can be of 3 types:

1. Working or contractive or typical.
2. Conductive or atypical.
3. Secretory myocites.

Working cardiomyocites. They are of irregular square shape. They are separated one from another by intercalated disks. Intercalated disk has 3 zones: zone of nexuses, zone of desmosomes and zone of myofibril attachment. Nexuses are direct contacts between cells, which provide excitement conduction from one cell to another. They have a lot of myofibrils and organelles of general purpose.

Atypical cardiomyocytes. The main function of them is to generate impulse. They form impulse-conductive system of heart. Among them we can distinguish 3 types:

- ✓ P-cells – pacemakers. They are in sinu-atrial node (S-A node).
- ✓ Intermediate cardiomyocites. They are in atrio-ventricular node (A-V node). They contain more myofirills than P-cells.
- ✓ Cells –of Purkinje fibers. They form His bundles and Purkinje fibers.

The signal is genetrated in S-A node than it is transmitted to A-V node and after that it travels along His bundles and Purkinje fibers until it reaches working cardiomyocytes. Atypical cardiomyocites contain more glycogen in cytoplasm. That is why they look paler on slides.

Secretoral cardiomyocites. They are in the atrium wall. The main function of them is to produce Na-uretic factor – the hormone, which regulates Na+ excretion by kidney. They have less myofibrils than working cardiomyocytes, but they have well developed organelles of protein synthesis (rough EPR, Golgi complex).

Epicardium. It is external wall of the heart. It has two layers: internal (LICT) and external (mesothelium).

Blood supply of the heart is performed through coronary arteries, which are branched from the beginning of aorta. The blood from the heart is collected to coronary veins, which enter to coronary sinus.

Innervation. The heart has sympathetic and parasympathetic innervation.

Sympathetic innervation: Preganglionic neurons are located in Th1-Th5 segments of spinal cord in lateral horn.

Postganglionic neurons are located in ganglion stellatum.

Parasympathetic innervation: Preganglionic neurons are in nuclei nerve vagus.

Postganglionic are located in intramural ganglia of the heart.

Age changes. In elderly heart acquires the following features:

1) myocardium becomes flabby due to atrophia and distrophia processes.

2) nuclear/cytoplasmic ratio decreases, number of damaged chromosomes rises, lipofuscin is accumulated.

3) basement membrane and sarcolemm become wider.

4) stroma of organ gradually develops causing cardiosclerosis.

Regeneration. It is possible only on intracellular level (hypertrophy and hyperplasia of organelles).

Blood vessels

Vessels have three coats: internal, middle (muscular), external (adventitial).

Vessels are of three types: 1) arteries (they carry blood from the heart). 2) veins (they carry blood to the heart). 3) microcirculatory vessels.

Arteries

There are three kinds of arteries. Although all of them conduct blood, each perform different and important functions. And their structure is adopted to perform this specific function.

1) Elastic arteries.

2) Muscular arteries.

3) Mixed arteries.

Elastic arteries. They are aorta and pulmonary arteries. The main function of these arteries is to transport blood from the heart and move it along vascular path. The presence of increased amount of elastic fibers in their wall allows elastic arteries to expand during heart contraction and blood ejection to their lumen. During heart relaxation, the expanded elastic arteries recoil. This effect forces the blood to move forward along vascular path and it maintains the necessary arterial pressure. Thus arterial pressure becomes less variable.

Structure. As every vessel, they have three coats.

1) Internal coat. It has three layers:

A) endothelial layer – made of endotheliocytes.

B) subenditheliallayer – LICT with elastic fibers.

C) layer of elastic fibers – abundance of elastic fibers.

2) Middle coat. It is consists mainly from elastic elements, which form 50-70 layers of fenestrated laminas. There are smooth myocytes and LICT adjusted between fenestrated laminas.

3) Outer coat. It is adventitial coat with vessels, LICT and fibers. The nerves are also presented.

Muscular arteries. They are arteries of medium and small diameter. The pulse wave is significantly decreased here. The most developed coat is middle one. They are like switchers. They distribute blood between different organs. They also give the resistance for the blood stream – that is why they are called resistive vessels.

Structure. Internal coat is the same as in elastic arteries, but it is narrower. Muscular coat is well developed. Smooth myoctes are located spirally. This position helps to pump down the blood. The endotheliocytes and myocytes have close connections. It helps to regulate diameter of the vessel in response to functional load. External coat is adventitial. It structure is similar to elastic arteries.

Structure and functions of mixed arteries are the same as muscular arteries. They are on intermediate position between elastic and muscular arteries.

Veins

There are two types of veins: muscular and no-muscular.

Veins of no-muscular type are in placenta, bones, pia mater, retina, spleen, central veins of liver. Here, the blood flow is not regulated by muscles. They have only two coats (internal and external).

Muscular veins. They have muscular coat in their structure. They may be of several types.

1) Veins with slight development of muscular elements. They are the veins of upper part of the body. The middle coat has a few smooth myocites. They may form bundles. The regions between these bundles can be expanded for blood storage.

2) Veins with intermediate development of muscular elements. The internal coat of such veins forms valves. It contains some smooth myocites. Middle coat is made of smooth myocites, which are located spirally along the vein. But it is narrower than muscular coat of artery of the same diameter. The external coat is in 2-3 times wider than in artery of the same diameter. It is made of LICT.

3) Veins with strong development of muscular elements. Smooth myocites can be found in any coat of the vein. They are the veins of lower part of the body. The maximal distribution of myocites is in external coat. Muscle contraction helps blood to move to the heart.

Differences between arteries and veins:

1. In veins subendothelial layer is less developed than in arteries.
2. Internal and external elastic membranes are absent in veins.
3. Veins have less developed muscular component.

4. The width of the wall in vein is lee than the diameter of the vein, whereas in arteries it is overwise.
5. The coats of veins are less separated one from another than in arteries.
6. Veins have wider adventitial coat.
7. The veins have wider range of changes in structure that arteries do.
8. Many veins have valve, whereas arteries don't.

Microcirculatory Net

It includes: 1. Arterioles
2. Precappilaries.
3. Capillaries
4. Postcappilaries.
5 Venules.
6. Arterio-venular anastamoses.

It performs following functions: 1) nutrition and respiration, 2) blood storage, 3) drainage, 4) regulation of blood flow in the organ, 5) transportation.

Arterioles. Their diameter is about 50-100 mcm. They have all three coats in their structure as arteries do. But these coats are less developed. The smooth myocites of middle coat contact with each other as well as with endotheliocites. Thus endotheliocites regulate vessel's tonus in response to functional load on vessel.

The place, where the capillary is branched off from artery, is called **precappilary.** It has the sphincter and may regulate blood flow in capillaries.

Capillaries. They are the smallest vessels. The internal layer is presented by endothelial cell, whereas external layer by perycites. The basement membrane separates these two layers. The nerve terminations are located in it. There are differentiated and cambial endotheliocytes. Differentiated endothelocites are very active cells. The can produce and secrete a long list of biologically active substances. We can distinguish the following types of capillaries with help of electronic microscope:

1. Somatic type (without interruptions or continuous) – they are in the muscles, brain, spinal cord. They have continuous basement membrane and endothelial layer.
2. Visceral type (fenestrated) – they are located in internal organs and endocrine glands. They have small windows in endothelial layer and continuous basement membrane.

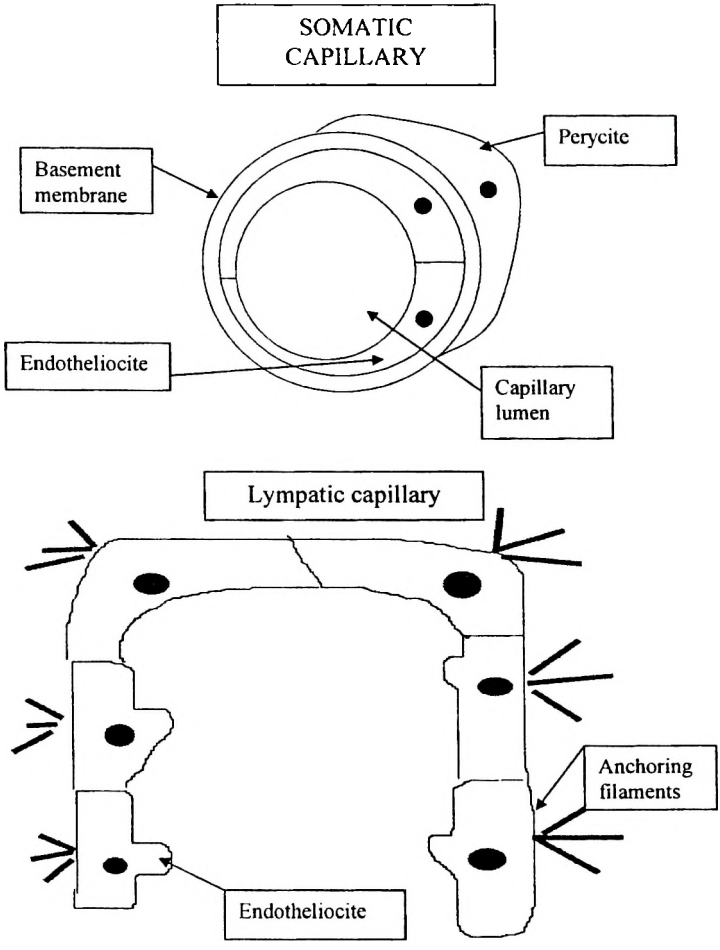
3. Sinusoid type – they are in liver, red bone marrow, spleen. Endothelial layer and basement membrane both have windows.

Venules. They are divided into postcapillary, collective and muscular. The regions between capillary and postcappilary venule is called postcapillary. It is continued by postcapillary venule. It has the same structure as capillary but it is wider in diameter (up to 30 mcm). Collective venules are result of fusing of several postcapillary venules. They have two layers (internal and external) and diameter 30-50 mcm. Muscular venules are the smallest venules with smooth myocites.

Anastamoses. They are the vessels, which allow blood to escape capillaries and come directly from arteries to veins. All anastamoses are divided into typical and atypical. Typical anastamoses have two variants: simple and complex. In simple anastamoses there aren't muscular elements in structure. The blood flow in them is regulated by sphincter, which are located in the place where anastamoses are branched off from the artery. They look like venules. The complex anastamoses contain contractive elements in their wall to regulate blood flow in them. Atypical anastamoses have no contractive elements and blood flow in them is not regulated. Even venous blood can be injected into their lumen. So, atypical anastamoses contain mixed blood. Anastamoses play important role in blood redistribution, arterial pressure regulation and thermoregulation.

Lymphatic vessels

Lymphatic system brings the lymph from tissues to venous flow. It consists of lymphatic capillaries and lymphatic vessels. Lymphatic capillary begins from tissues. Their wall has only endothelial layer. Basement membrane as usually is absent or it is very slightly expressed. To keep capillaries always open there are anchoring filaments. By one end they are attached to endotheliocite, by other end they are attached to LICT structures. The diameter of lymphatic capillary is about 20-30 mcm. They work as drainage; they accept intercellular fluid from tissues to their lumen. Lymphatic vessels may be intraorganic and extraorganic. They may be of small, middle and large caliber. In vessels of small caliber there is not muscular coat. Internal coat has endothelial and subendothelial layers. Vessels of middle and large caliber have muscular coat and structurally they resemble veins. In large vessels there are elastic membranes. There are lymphatic nodes along the way of lymphatic vessels.



Chapter 13: The skin and appendages

Skin is the largest organ in the body, both by weight and surface area. In adults, the weight of your skin accounts for about 16% of your total

body weight. Normally the skin separates the internal environment from the external. However skin diseases and infections can compromise that barrier. Infections and diseases also affect the nails and hair.

Functions of the skin:

1. Defense.
2. Immunological – Here, in the skin, are a lot of immune cells, which can perform various immune reactions (i.d. Langherhans cells).
3. Reception – it is a place for many sensory nerve terminations.
4. Osmotic pressure regulation – 30% of excreted fluid are evaporated or excreted by sweat glands. This fluid lost can change osmotic pressure in the vessels.
5. Temperature regulation.
6. Respiratory function – 2% of total gases exchange takes place through the skin.
7. Participation in metabolic exchange.
8. Excretion. Sweat and adipose glands can excrete urea and other substances.
9. Blood storage. Skin accumulates up to 1 liter of blood.
10. Haemopoietic function during embryogenesis.
11. Endocrine function. Skin is a place, where vitamin D transforms into active form. Keratinocytes also produce factors, which can activate thymus and regulate proliferation of keratinocytes.
12. Function of communication – releasing of smelling substances, which help different animals to recognize each other.
13. Cosmetic and elastic function.

The skin is composed of several layers. The lowest layer is called the dermis. This layer is composed of connective tissue, blood vessels, nerve endings, hair follicles, and sweat and oil glands.

The outermost or top layer of skin is called the epidermis. This is the layer of skin which we see. This layer rests on top of the dermis.

Epidermis

The thickness of the epidermis varies with your age, your sex, and the location on the body of the skin. For example, the epidermis on the underside of the forearm is about 5 cell-layers thick. On the sole of the foot, the epidermis might be 30 cell-layers thick. The epidermis is for the most part impermeable to water. This water-impermeable skin is one of the features that allows us to live on land.

Epidermis has 5 layers. But in the regions with narrow skin, the number of layers decreases to 4. Traditionally, those layers are called strata.

The deepest layer is **stratum basale**. It is made up of a single layer of columnar cells that rest on a basal lamina. The basal layer contains stem cells that undergo mitosis to give off cells called keratinocytes. The basal keratinocytes have all organelles of general purpose, a few melanosomes and tonofibrils. Tonofillaments and tonofibrils make up a 3-dimentional frame that carries out supportive function. Melanosomes contain melanin granules, which have their origin from melanocytes. Melanin protect keratinocytes from UV (ultraviolet) radiation. Cells of basal layer lie on a basement membrane to which they are attached by semidesmosomes.

There are some other cell types in stratum basale.

- **Melanocytes**. They are the cells with many processes. They contain DOPA-oxydase enzyme. This enzyme enables them to produce melanin. They give out melanin granules to keratinocytes. Different people have different melanin concentration. This concentration provides skin color. Melanin absorbs harmful ultraviolet (UV) light before the UV radiation can reach the nucleus. Melanin protects the DNA in the nucleus from UV radiation damage. When melanin is produced and distributed properly in the skin, dividing cells are protected from mutations that might otherwise be caused by harmful UV light. Differences in skin color are due mostly to differences in the types and amount of pigment in our keratinocytes. Skin darkening (tanning) from sun exposure is caused by the movement of existing melanin into keratinocytes, and by increased production of melanin by the melanocyte. During embryonic development these cells migrate from the neural crest into the skin.
- Langherhans cells. They are intraepidermal macrophages. They are dendritic shape. They are derived from monocytes of red bone marrow. They contain Birbeck's bodies (or granules), lysosomes and organelles of protein synthesis. It is bielived that they play important role in skin protecting against viral and bacterial infection. They take up antigens in the skin, represent it on surface and bring it to lymphoid tissue, where an antigen stimulates T-lymphocytes differentiation. They also take part in regularion of growth rate in epidermis.
- Merkel cells. They are especially abundant in the skin of palms and soles. They are larger than keratinocytes and contain more

organelles of protein synthesis. Many of them make synapses with Merkel disks (widening of dendrite of pseudounipolar neuron of spinal ganglion). One main function of them is perception of touching. Other functions are not fully clear. It is believed that they take part in immune reactions. These cells are also referred as a part of APUD-system (amine precursors uptake and decarboxilation).

- ❖ Greenstein cells. They are derived from monocytes as well as Lengherhans cells. They are intaepidermal macrophages too. However, in compare with Langherhans cells, while interaction with T-lymphocytes in lymphoid tissue they suppress immune reactions. Thus, system of Langherhans and Greenstein cells regulate immune response in the skin by "plus-minus" mechanism.
- ❖ Intraepidermal lympocytes.

Stratum spinosum. Keratinocytes of this layer have dendritic shape. Keratinocytes are connected with each other by desmosomes. In cytoplasm the organelles of general purpose, melanosomes, Odland's granules and tonofibrils are found. Stratum basale and stratum spinosum form, so called, germinal layer of Malpigi.

Stratum granulosum. There are a few (1 to 5) layers of flattened cells. The granules of keratohyaline appear in keratinocytes. Keratohyaline is intermediate metabolite for keratin synthesis. There are Odland's granules. They are modified lysosomes. They secrete their content between cells. This content adjust adjoin cells one to another and makes a barrier for external influences. It is rich in lipids. Thus, it forms hydrophobic barrier for the water. Here, the synthesis of keratolinine and fillagrine starts.

Stratum lucidum. It is visible only in light microscope. This layer is so called because it appears homogenous, the cells boundaries being extremely indistinct.

Stratum corneum. This layer is acellular, It is made up of flattened scale-like elements (squames). They are full filled by keratin filaments, keratolinine, which make cells surface more resistant, and by fillagrine, which aggregates tonofilaments.

Keratinization process

It starts in the cells of basal layer from cytokeratin synthesis. Cytokeratin is the protein, which is insoluble even in strong dilutants. It makes up tonofibrills. This process continues in stratum spinosum. Here the synthesis of fillagrine starts. On being made, fillagrine glues

tonofibrills. Fillagrin synthesis is significantly enchanced in stratum granulosum and it is accompanied by keratolinine synthesis. Keratolinine lies internal surface of keratinocytes membrane preserving it from lysosomal enzyme destruction. In stratum lucidum, activated lysosomes digest nucleus and organelles. Thus, there are only cell frames in stratum corneum. They are full filled by keratin filaments. Odland's granules release their content, which provide strong adhesion of cells to each other.

Epidermal proliferative unit

It is a functional unit of epidermis. It is a group of organized columns of keratinocytes lying over each other. The basement cell of central column interacts with Langherhans cell. It can regulate proliferation rate of stem cells in basal layer. The basement cell of central column is stem cell. It can repair whole structure of the unit. The basement cells of peripheral columns are semistem cells. The cells of basal layer lie on a basement membrane. It is made of collagen IV, reticular fibers and glicoseaminoglicans. It's functions are support, transportation and barrier.

Dermis

Dermis is made of connective tissue. Just below the epidermis the connective tissue is loose and constitutes the papillary layer. Deep to this there is a network of thick fibers that constitutes the reticular layer of skin.

Papillary layer is presented by LICT. The papillae are best developed in the thick skin of palms and soles. Each papilla contains a capillary loop. Some papillae contain tactile corpuscles.

Reticular layer is presented by dense irregular connective tissue. It consists of collagen fibers bundles and considerable number of elastic fibers. The dermis rests on a superficial fascia through which it is attached to deeper stractures.

Hypoderm. It is made of adipose tissue, which underlies the dermis. It is important for thermoregulation, nutrition storage and water storage.

Skin appendages

Nails, hairs and skin glands are referred as skin appendages.

Hairs

All hairs are divided into coarse hairs (head, armpit, moustache) and vellus hairs (cover most of the body's surface).

Each hair consists of a part is seen on the surface of the body (shaft) and a part in the thickness of the skin (root). The shaft and root of coarse hairs consists of medulla, cortex and cuticle.

Cuticle – is external coat of a hair. It is made of keratinized pigmentless cells. They come from cambial cells of hair bulb. While growing, the cells become flattened and overlap each other making scales. Cells contain hard keratin that makes them elastic.

Cortex – consists of several layers of cells derived from cambial cells of hair bulb. In the bulb they are square shape cells with tonofibrills and melanin granules. There are melanocytes in-between the cells. The cells accumulate hard keratin while keratinization.

Medulla – is in the center of a hair. It comes from the entral part of the hair bulb. Medulla is made of soft keratin. Cells contain granules of trichohyaline.

The hair is surrounded by follicle, which consists of external and internal sheath. The follicle is surrounded by connective tissue.

Inner root sheath has three layers:

1. external Henle's layer
2. medial Huxley's layer
3. cuticle of internal root sheath.

The keratinization in internal root sheath has direction from external layer to internal layer.

External root sheath. The cells of external root sheath are not subject to keratinization. It is presented by double folded epithelium, in which germinative layer looks out. The external root sheath bulges out forming a bolster for muscle erector villi attachment. There are no antigen-presenting cells in this bolster. If they appear, it may results in alopecia (baldness).

Hair bulb. The cells of hair bulb surround papilla as a cap. The cell, which are on a top of papilla, are cambial cells fro hair growth. Lateral cells are for growth of hair sheath and cuticle.

Hair papilla is presented by LICT with blood vessels providing blood supply.

Nails

The nail plain consists of body and root. Nail's boy is visible. Nail's root is embedded. Into the tissue. The nail is placed on a nail's bed. Cells of nail's bed are called onichoblasts. They form nail matrix. The Langherhans and Merkel cells are also present. The nail grows in width and in length as well.

Sweat glands

These are simple tubular glands. Each one consists of secretory part and excretory part. The secretory part is placed just below the dermis in the subcutaneous tissue. The secretory cells are called sudoriferrocytes. They may be of 2 types: dark and light. The sudoriferrocytes are surrounded by myoepitheliocytes. The excretory duct consists of dermal and epidermal parts. The mechanism of secretion is merocrine and apocrine.

Sebaceous glands

These are simple alveolar branched glands. Mechanism of secretion is holocrine. They are all over the body's surface excluding soles and palms. The cells of these glands are sebocytes. The secrete fat that can serve as thermoisolation, barrier for bacteria, prevent formation of erosions. These glands are involved in skin regeneration.

Chapter 14: The endocrine system 2

ADRENAL GLANDS

Functions:

1. Production of mineralocorticoid hormones (aldosterone and deoxycorticosterone), which influence the electrolyte and water balance of the body, and also activate inflammatory and immune reactions. Mineralocorticoid hormones activate Na^+ reabsorption in kidney, which leads to water accumulation and blood pressure rising.

2. Production of glucocorticoid hormones (cortisone, dihydrocortisone). These hormones increase blood glucose level by stimulating glucose synthesis from fats and proteins. These hormones suppress inflammatory and immune reactions, which is widely used in medicine for treating autoimmune, allergic reaction, for preventing graft rejection and so on. Glucocorticoids production and secretion are enhanced during stress reaction. This process is stimulated by anterior pituitary hormone – ACTH.

3. Production of sex hormones, mainly androgens (dehydroepiandrosterone, androstendione). They have weak androgenic effect, but their releasing while stress reaction stimulates muscle growth. Androgen producing is controlled by ACTH.

4. Adrenal medulla produces catecholamines – adrenalin (epinephrine) and noradrenalin (norepinephrine). They are released during stress reaction and have similar effects, which were called by American

physiologist W. Kennon as "providing fight and running". These substances recruit all organism resources to save the life in complicate circumstances. It is the result of following effects. The heart rate, heart contraction ability and blood pressure are raised. Fat and glycogen storages are converted to glucose to supply muscles. The vessels of inner organs become collapsed whereas vessels in muscles expand diameter. The sense organs become activated. Breathing rate rises and diameter of air passages expands. At the same time with adrenaline and noradrenalin the growth factors and enkephalins are released from the cells. The growth factors are involved during long-tern stress to prevent excess of katabolic reaction. Enkephalins suppress pain, which may occur during life saving.

Thus, the adrenal glands are very important organs. Their removal or pathological destruction may cause death of the body.

Development. The development of adrenal glands can be subdivided into 7 phases.

1. The laying oa primary adrenal glands. Adrenal cortex develops from visceral splanchnotome in-between primary kidneys bud. Firstly, on the 4-5th week of development the primary cortex is formed from cells with oxyphylic cytoplasm. The adrenal gland source of development is located near gonads bud, which explains its ability to produce sex hormones.
2. Entering of ganglionic plates to adrenal bud with formation of chromaffinoblasts in subcapsular zone looking as "medulla spheres". They are the elements of future medulla (6-7th week of development).
3. Splitting of primary cortex to fetal cortex (located centrally) and definitive cortex (located aside) (7th week of embrigenesis).
4. Growing of definitive cortex (8th week).
5. Medulla formation anв differentiation of chromaffinoblasts to A- and H-cells (7-10th week).
6. Definitive cortex differentiation on zones. Zone glomerulosa is formed on 4th month, zone fasciculata is formed on 7th month, zone reticularis is developed after birth.
7. Formation of definitive adrenal gland. Adrenal glands continue their development after birth. Destroying fetal cortex exist up to 3rd year. At the same tine the zone reticularis is formed. The adrenal glands acquire their definite structure at the beginning of puberty.

Thus, the two parts are united in one whole in adrenal gland, but genetically and functionally they are two different glands.

Structure.

Adrenal glands are paired parenhymal organs of zonal type. They are covered by capsule from dense fibrillar irregular connective tissue. It gives linings to the center of organ, which are called trabecules. There are smooth myocytes, autonomic ganglia, adipose cells, nerves and vessels in the capsule. Capsule and trabecules together make the stroma of the organ. The parenchyma of adrenal gland is made of two cell types: corticocytes (in cortex) and chromaffinocytes (in medulla). As it was said above the adrenal gland has two separate zones: cortex and medulla.

The cortex consists of several zones.

1. Zona subcapsularis. It is made of small, undifferentiated corticocytes, which play cambial role for the cortex.
2. Zona glomerulosa. It presents 10% of cortex. It is made of small corticocytes, which are organized in glomeruli. They have moderate developed smooth EPR – place of steroid hormone production, Golgi complex, mitochondria. There are a few lipid droplets having mainly cholesterol, which is needed for steroid hormone synthesis. The function of zona glomerulosa is to produce mineralcorticoids. But there are some interesting features of this process. In compare with corticocytes of zona fasciculata the corticocytes of zona glomerulosa have less developed organelles of steroid hormone synthesis and they have less lipid droplets. It is due to that fact that corticocytes of zona glomerulosa perform only last steps of steroid hormone synthesis. They acquire precursors from zona fasciculata, where there are made.
3. Zona sudanofobic. It is the narrow zone between zona glomerulosa and zona fascicilata. It was named because its cells aren't stained by specific stain – sudan. The cells of this zone are small and they are able to mitotic division. The function of the zone is cortex regeneration. Nowadays, the zona subcapsularis and zona sudanofobic are included into zona glomerulosa.
4. Zona fasciculata. It presents 75% of cortex. It is made of large oxyphilic corticocytes, which make fascicles. There are sinusoid capillaries in narrow LICT linings between fascicles. There are two types of fascicular corticocytes: light and dark. It is one cell type but in different functional state. The cytoplasm of corticocytes looks like having many vacuoles. It is due to having many lipid droplets, which are taking away while slide processing. That is why cells resemble the sponge, and sometimes they are called spongeocytes. On ultrastructural level the corticocytes of this zone have some features. They have large and giant mitochondria with well developed cristae of tubular structure (in compare with lamellar structure in other organs).

Mitochondria participate in some stages of steroid hormone biosynthesis. There are well developed free ribosomes, Golgi complex and smooth EPR (main place of steroid homone biosynthesis). The dark cells have less lipid droplets in compare with light cells. The function of zona fasciculata is to produce glucocorticosteroids.

5. Zona reticularis. It presents 10-15% of cortex. It is made of small cells, which are organized in the form of a net. There are a few lipid droplets, well developed EPR, Golgi complex, mitochndria in the cells. There are also a lot of lysosomes and lipofucin granules. It is suggested that in the zona reticularis there is destroying of aging corticocytes, which migrate here from upper layers. That is why they have a lot of lysosomes. It is revealed many corticocytes undergoing to apoptosis.

In the zona reticularis glucocorticoids and androgens are produced. The very light producing of female sex hormones also takes place. Androgens of adrenal glands have weaker androgenic effect, but they preserve anabolic effect. It has very important value for adaptation.

Adrenal hormones are lipid soluble substances. They easily pass cell membrane. That is why there are no secretory granules in the corticocytes.

Sometimes, there are rests of fetal cortex on the border with adrenal medulla. The cells of fetal cortex have strong oxyphilic properties.

Morphological changes of adrenal cortex after long and repeated stress influence. The size of zona fasciculata is significantly increased. The quantity of lipid inclusions is decreased, which shows the activation of hormone synthesis. There is significant enlargement of smooth EPR, mitochondria. The concentration of ascorbic acid falls down. The size of zona reticularis is also increased. The producing of adrogens is stimulated, which leads to the muscle growth. It helps to resist stress reactions.

Adrenal medulla. It separated from the cortex by thin LIST capsule. It is made of chromaffinocytes (chromaffin cells) congregation. There are named so, because of very good staining by chromium salts. The cells are divided to the two groups: 1) large light cells, which produce adrenaline (epinephrine) (A-cells), containing granules with moderate electron density; 2) small dark cell (NA-cells), containing a lot of dense granules surrounded by light circle, noradrenalin producing cells. A-cells and NA-cells are difficultly distinguisher on the routine slides. They can be distinguished on the chromium stained slides. Aside to catecholamines, the secrettory granules of chromaffin cells contain proteins and polypeptids: chromogranins, enkephalins, growth factors, immunomodulators (IL-1),

ATP and lipids. It is beleaved that chromogranins provide osmotic stabilization oa secretory granules.

There are also autonomic neurons and support cell (kind of neuroglia) in the adrenal medulla.

Blood supply. The entering arteries branch off to the small arteries and capillaries of fenestrated and sinusoid types in the cortex. The capillaries pass through the cortex and enter medulla, where the change to the wide sinusoids. They unite to the venules, which form venous plexux of medulla. There are separate arteries, which go directly to medulla from subcapsular plexus.

Innervation. The sensory innervation is provided by pseudounipolar neurons of thoracic and upper lumbal spinal ganglia and by Dogel cells of II type of para- and intraorganic ganglia of autonomic nervous system. Efferent innervation is provided by both sympathetic and parasympathetic nervous system. The cortex is innervated by sympathetic postganglionic non-myelinated fibers, which mainly act as vessels contractors. The medulla is innervated by sympathetic preganglionic myelinated fibers, which make the synapses on chromaffin cells playing role of postganglionic neurons. The stimulation of sympathetic nervous system enhances catecholamine output. Parasympathetic innervation is provided by nervus vagus. The parasympathetic innervation is absent in medulla. But secretory effect of parasympathetic innervation is not described.

Regeneration.

1. Physiological regeneration. It is provided by mitotic division of cambial cells of subcapsular and sudanophobic zones. There are two theories on adrenal gland regeneration. 1) migration theory of corticocytes. It suggests that newly formed corticocytes migrate inside differentiating to the appropriate corticocytes of following zones. In the end of zona reticularis they die by apoptosis. 2) zonal theory. It suggests that every zone has independent regeneration of corticocytes.

2. Reparative regeneration. Posttraumatic regeneration of medulla is not investigated. The cortex has high regenerative potential. It is evident on example of enucleation – total removing of adrenal gland from the capsule. After this operation there are only small pieces of zona subcapsularis and zona glomerularis. Survived cells divide very actively and migrate centrally. At the beginning all cells have similar structure, however later they are differentiated. This observation backs migration theory.

THYROID GLAND

Functions. The thyroid gland produces the following line of hormones.

1. Thyroid hormones – tetraiodthyronine (T_4) and triiodthyronine (T_3). They regulate fasting metabolism and processes of growth, development and tissue differentiation. They increase the breakedown rate of protein (with simultaneous activation of its synthesis), lipids and carbohydrates. They increase the oxygen uptake by cells. The target cells for the thyroid hormones are almost all cells of the organism. The mechanism of action is based on entering to the cell nucleus and influence on gene transcription. They also act on mitochondria preventing accumulation of energy in ATP. As result of this the energy is spread as heat maintaining the body's temperature. That is why the role of thyroid hormones is very important in cold conditions. They play important role in nervous system differentiation during embryonic development. If there is hormone insufficiency during embryonic development, it may result in cretinism formation.
2. In the thyroid gland there are cells producing following hormones: calcitonin, somatostatin and serotonin. Calcitonin is the product of calcitonin genes family. The products of the genes of this family are also catacalcin and peptide α. Thyro-calcitonin and catacalcin are functional antagonists of parathohormone. The decrease blood calcium level by stimulation of bone forming cells (osteoblasts). This results in calcium accumulation in bones and increased mineralization. At the same time thyro-calcitonin stimulates calcium excretion by kidneys. Peptide α isn't produced in normal thyroid gland. It is expressed in CNS neurons and in a line of peripheral organs, especially in vessels. This peptide participates in pain perception, vessel tonus regulation and food behavior. Somatostatin suppresses cell growth and division, secretion of several other glands. Serotonin has various effects: regulate functions of several endo- and exocrine glands, microcirculation, immune reactions ets.

Development. The thyroid gland bud forms on a 4^{th} week of embryogenesis as bulge of ventral wall of throat gut between 1^{st} and 2^{nd} couple of branchial sockets. This bulge converts to the epithelial lining. At the beginning the thyroid gland resembles exocrine gland and has analogue

of excretory duct. However, later the epithelial lining, which resembles excretory duct degrades and distal part of the thyroid bud is divided into two parts. Epihelial cells form separate follicles. The cells of neural crest also migrate to the thyroid bud and convert to the C-cells (light cells, calcitoninocytes).

Structure. The thyroid gland is parenhymal lobular organ. The stroma is made of capsule (dense irregular connective tissue) and trabecules (loose irregular connective tissue). There are intralobular supportive LICT frame with nerves and vessels, which is also referred as stroma. The trabecules separate the gland to lobules. The parenchyma is made of follicles and interfollicular islets.

The follicle is structural-functional unit of the thyroid gland. It is made of two cell types. The main cells are thyrocytes. Apart from them there are also parafollicular C-cells. Both cell types lie on a basement membrane, but C-cells don't reach the follicle lumen. There is colloid in the follicle lumen. The colloid is oxyphylic substance representing storage form of thyroid hormones.

The shape of the thyrocytes depends on functional state of the gland. If functional activity of the gland is normal, the shape of the thyrocytes is square and there are moderate amount of resorption regions in colloid. If functional activity of the gland is less than normal (hypofunction), the shape of the thyrocytes is flatten and there are no resorption regions in colloid. If functional activity of the gland is higher than normal (hyperfunction), the shape of the thyrocytes is columnar and there are a lot of regions of resorption in the colloid.

The thyrocytes have well developed organelles of protein synthesis: routh EPR, Golgi complex, mitochondria. There are several types of vacuoles in the cytoplasm: 1) *secretory* – contain non-iodinated thyroglobuline, they are separated from Golgi complex and transport made thyroglobuline to the follicle lumen; 2) *banded* – contain immature, non-iodinated thyroglobuline, which is taken from follicle lumen to be iodinated; 3) *endocytotic* – contain mature iodinated thyroglobulin, which is taken from follicle lumen to be degraded by lysosomes to release thyroid hormones. Apical surface of the thyrocytes has many microvilli. Basement surface has cytolemm folds. The number of cytolemm folds increases while hyperfunction. The microvilli and folds increase the cell surface, which is needed for transport purposes. The thyrocytes are tightly connected to each other by their lateral sides.

Secretory cycle of thyrocytes. There are 3 phases in the secretory cycle.

1. Biosynthesis of thyroglobuline
2. Thyreoglobuline output to the follicle lumen, iodination of organic frame of thyroid hormones and thyreoglobuline storage in follicle.
3. The hormone release to the blood.

The secretory cycle starts from tyrosine (biochemical precursor of thyroid hormones) absorption from the blood and it's accumulation in rough EPR. In rough EPR the polypeptide chain is made. Than it is transported to the Golgi complex, where it is added y carbohydrate components (glicosilation). Due to glicosilation the thyroglobulin has glycoprotein nature. The secretory vesicles transport thyroglodulin to the apical side of a cell, from where it is released to the follicle lumen, where it is converted to colloid. Then the iod ions are transported to the apical pole of the thyrocyte. Here, the thyroperoxydase enzyme converts them to the atomic iod. Then, the iod binds the tyrosine molecule, which are in the thyroglobuline molecule. Before this non-mature thyroglobuline is taken by thyrocyte villi from the follicle lumen with formation banded vesicles. Two thyrosine molecules adjust one to another by condensation. It results in thyroid hormones formation, which are still in thyroglobuline molecule. Thus thyroglobuline becomes matured. It is stored in the follicle lumen. Where it is necessity, the mature thyroglobulin is taken from colloid and is degraded by lysosomes. The thyroid hormone molecules are separated from thyroglobuline and are released to the blood.

The thyroglobuline is autoantigen. That means that if the thyroid gland is damaged and thyroglobulin is released to the blood, it may cause autoantibodies formation. It results in Hashimoto's thyroiditis.

Parafolliular cells (C-cells) comprise about 0,1% from total number of parenhymal cells in the gland. They are referred to the APUD-system. They produce such hormones as thyrocalcitonin, somatostatin and serotonin. These cells may be included to the follicle, but they don't reach follicle lumen by their apical sides. Beside that, these cells are included to the interfollicular islets. They also can be just as single cells. The cells have triangular shape, and they look paler when stained by hematoxylin-eosin ("light" cells). The granules are stained by argentums nitrate. C-cells have well developed EPR (however, lesser than in thyrocyte), Golgi complex and secretory granules.

Interfollicular islets – it is thyrocytes congregations without lumen. They produce thyroid hormones in small amount. If there is functional load on the thyroid gland, the islets can be transformed to the follicles. Thus,

the islets are reserve for new follicle formation. There C-cells among thyrocytes of islets.

Vascularization and innervation. The thyroid gland receives good blood supply. The feeding arteries are well branched, and their branches enter the interlobular connective tissue. The interlobular arteries give off interfollicular arteries, which make the network around follicles. The capillaries around follicles make a "basket". Human "baskets" are independent structures, which are not connected with other. After capillary "baskets" the blood goes to the interfollicular veins, than to interlobular veins and finaly to the thyroid veins.

Sensory innervation of the thyroid gland is provided by pseudounipolar neurons of spinal ganglia. Efferent signals are provided by symparthetic and parasympathetic system as well. Acsons from C VIII and upper thoracic segments go to the cervical sympathetic ganglia, where the second neurons are located. Their acsons make postganglionic nerve fibers, which go to the parenchyma of the organ. They make synapses on the thyrocytes and blood vessels. The stimulation of sympathetic system results in stimulation of hormones synthesis and secretion accompanied vasoconstriction. The parasympathetic innervation is provided by nervus vagus. Activation of nervus vagus results in suppressing function of thyroid gland. It is important to note that nervous influence on the thyroid gland has less effect than hormonal stimulation. The sympathetic system stimulates C-cells, whereas parasympathetic system suppresses them.

Regeneration. Physiological regeneration of the thyroid gland is on a high level due to thyrocytes division. There are two variants of regeneration: 1) intrafollicular – it is characterized by that in some place of follicle the wall of it bulges inside and forms intrafollicular islet; 2) extrafollicular - it is characterized by that in some place of follicle the wall of it bulges outside and forms daughter follicle. New follicle may have their origin from interfollicular islets. Posttraumatic regeneration is also on a high level. The saved follicles give out microfollicles, which grow up to the normal sizes. The subtotal resection gives us another picture. At the beginning the formation of new interfollicular islets takes place on the account of cellular proliferation. Than interfollicular islets are transformed to the new follicles.

PARATHYROID GLANDS

Function – hormone secretion.

1. Parat- hormone. It is antagonist of thyrocalcitonin. It rises up calcium level in the blood by two ways: 1) by activation bone

resorption through osteoclasts actovation; 2) by activation of vitamine D_3 formation, which enhances calcium absorption in the intestine.

2. Biogenic amines.
3. Calcitonin.

Development. The source of development is 3rd and 4th pairs of branchial sockets. On 5-6th week of embrygenesis they form 4 buds, which are separated from branchial sockets and become parathyroid glands. They can be covered by one capsule together with thyroid gland. While surgery on a thyroid gland, parathyroid glands can be mistakenly removed, which lead to the patients death.

Structure. It is organ of parenhymal type. The parenchyma has trabeculi. There are two cell types in parathyroid gland (parathyrocytes): main or basophilic, and oxyphilic. Main cells are subdivided into two subgroups: light and dark. This division id based on a functional state of parathyrocytes. The dark cells are active cells. They contain well developed EPR and Golgi complex. There are a lot of secretory granules up to 400 nm in size in cytoplasm. These granules contain parat-hormone. The light cells are les active. They contain more lisosomes, glycogen, lipid inclusions and secretory granules of small size (150-200 nm). They number in 3-5 times exceeds the number of dark cells. The secretion of these cells is regulated by biological feedback on calcium concentration in blood.

Oxyphilic cells are organized either as single cells spread all over the organ or as small cell congregations. There are a lot of mitochondria, moderately developed EPR and Golgi complex. There are no secretory granules. The number of the cells rises with age. Newborns have no such cells. Earlier, the cells were discussed as degenerating cells. But today this point of view is doubtful, because significant number of organelles shows active functionally state of these cells. Some researches refer these cells to APUD system. There are data that these cells produce biologically active amines, and some of the cells produce calcitonin.

The stroma of the gland is made of capsule with trabeculi, which are presented by LIST. The trabeculi do not separate the organ on the lobes. There are many vessels and lipid congregations in stroma.

Vascularisation and innervation. The feeding arteries branch off on plenty capillary network surrounding parathyrocytes. Capillarie don't make anastamoses with each other. They join to the venosus network, which enter subcapsular venosus plexus.

The sensory innervation of the parathyroid gland is provided by neurons of spinal ganglia. The efferent innervation is sympathetic and parasympathetic. The nerve terminals make "basket-like" plexus around oxyphilic cells. Nervous system regulates only vascular tonus. It has no effect on a secretion rate in the gland. How nervous system affect function of oxyphilic cells is still unclear.

SINGLE HORMONE PRODUCING CELLS

These cells in total are defined as diffuse endocrine system. This system includes two independent groups.

1. Cells of APUD system. Famous English histologist Pears thought that all cells of the system are derivates of ectoderm. Now this point of view is reconsidered and it is believed that cells of the system can be derivates of all three embryonic layers. The Merkel cells of skin, brain and epiphysis are derived from neuroectoderm. The cells of gastroenteropancreatic system (endocrine cells of intestine mucosa and Langherhans islets) are derived from endoderm. The apudocytes of respiratory tract mucosa are also derived from endoderm (prechordal plate). The endocrinocytes of urinary passages are derived from mesoderm. The cells of APUD system have specific structure. They have moderately developed rough EPR, Golgi complex and agirophilic granules on basal pole. Perhaps agirophilic granules, the cells are easily revealed in light microscope after silver impregnation. The cells of APUD system can actively uptake biogenic amines precursors and decarboxilate them. And the abbreviation APUD goes from it – amine precursor uptake and decarboxilation. The biogenic amines presenting in cells make possible to identify the cell with help of luminescent methods. The APUD cells of epithelium can be classified into two classes: open type and closed type. The open type cells are the cell, which reach surface of epithelium. The closed type cells are the cells, which are buried in the epithelium and don't reach surface. Cells of APUD system perform chemical analysis of food, air, urine and others and reply on it by secreting hormones and biologically active substances. So, APUD cells are both sensory and effectory cells. They regulate motor function of hollow organs, blood vessels diameter, secretion, exretion, absorption, cell number in cell population and others. The main mechanism of such influences is paracrine, but hormones may also act as endocrine hormones. The cells of APUD system may give malignant growth – apudoms.

2. Second group of single hormone producing cells – it is cells congregations, which are not referred to APUD system. They are glandulocytes of testis (produce androgens), follicular cells of ovarium (produce female sex hormones), reticuloepitheliocytes of thymus, juxtaglomerular cells of renal body (produce renin) and ets.

Chapter 15: The digestive system 2

SMALL INTESTINE

Functions:

1. **Digestive function.** It is in digestion of chime. It is performed by pancreatic enzymes and by own enzymes (dipeptidases). The proteins are digested by enterokinase, trypsin, erepsin; the carbohydrates by amylase, maltase, saccharase, lactase; the lipids by lipase, the nucleic acids by nuclease. There are both types of digestion: parietal digestion and central digestion.
2. **Absorptive function.** The most of nutrients are absorbed in small intestine. There is *striated border* to increase absorptive surface.
3. **Motor-evacuation function.** It is in propelling the chime down along alimentary canal.
4. **Secretory function.** It is in producing mucosa and intestinal juice containing water, mucosa, minerals, and some enzymes. The secretion is performed by cells of mucosa and duodenal glands in duodenum.
5. **Excretory function.** Some of terminal products of metabolism are excreted through small intestine.
6. **Endocrine function.** It is in hormone secretion by single hormone producing cells along alimentary canal.
7. **Barrier – defense function.** It is performed by mucosa, undamaged epithelium, solitary and aggregated lymphatic follicles, spread immune cells. They form so called **intestine assotiated lymphoid tissue.**

Development: The epithelium of small intestine is developed on 5^{th} week of embryogenesis. On the 8^{th} week it transforms from single cuboidal to single columnar. The system of crypts and villi is formed on the 3^{rd} month. All types of cells appear in epithelium. The mesenchyne gives rise to smooth muscles and connective tissues of intestinal coats. The visceral part of splanchnotone gives mesothelium of serous coat.

Structure.

The small intestine is dividedinto three parts: duodenum, jejunum, and ileum. All of them are organs, which is made by layers and all of them contain 4 coats: mucous, submucosa, muscularis, and serous or (alternatively) adventitial coat. In spite of common structure, they have some differencies, which are in following:

- The highest villi are in duodenum and their height is gradually falls to ileum.
- The widest villi are in duodenum and its width is gradually falls to ileum.
- The number of villi is biggest in duodenum and it is gradually falls to ileum.
- The aggregated lymphatic nodes are mainly located in ileum, but can be occasionally found in jejunum and duodenum.
- The duodenal glands are present only in duodenum.

Mucous coat (or mucose membrane) is made up of a) liling epithelium, b) lamina propria, c) muscularis mucosae. Mucous membrane has villi, crypts, circular folds of Kerkring, which increase surface of intestine. The villi are, typically, finger like projections consisting of a core of reticular tissue covered by a surface epithelium. The connective tissue core contains numerous blood capillaries forming a plexus. The endothelium lining of capillaries is fenestrated thus allowing rapid absorption of nutrients into the blood.

Each villus contains a central lymphatic vessel called a ***lacteal.*** Distally, the lacteal ends blindly near the tip of the villus; and proximally it ends in a plexus of lymphatic vessels present in the lamina propria. Occasionally, the lacteal may be double. Some muscle fibres derived from the muscularis mucosae extend into the villus core.

In some situations the villi, instead of being finger like, are flattened and leaf like, while in some other situations they are in the form of ridges. The villi are greatest and most numerous (for a given area) in the duodenum. They progressively decrease in size, and in number, in proceeding caudally along the small intestine. It has been estimated that the presence of villi increases the surface area of the epithelial lining of the small intestine about eight times. The cells lining the villi are described below.

There is a phenomena of *physiological villi rejection.* Some villi are rejected and stay alone for a while in an intestine lumen. New villi appear on their place. The meaning of this phenomena is still under investigation. It is suggested that it is manifestation of physiological regeneration of

intestine. Furthermore, rejected villi participate in parietal digestion as being additional source of membranes.

The crypts (of Lieberkuhn) are tubular invaginations of the epithelium into the lamina propria. They are really simple tubular ***intestinal glands*** that are lined by epithelium. The epithelium is supported on the outside by a basement membrane. The cells lining the crypts are considered below.

The circular folds are also called the ***valves of Kerkring.*** Each fold is made up of all layers of the mucosa (lining epithelium, lamina propria and muscularis mucosae). The submucosa also extends into the folds. The folds are large and readily seen with the naked eye. They are absent in the first one or two inches of the duodenum. They are prominent in the rest of the duodenum, and in the whole of the jejunum. The folds gradually become fewer and less marked in the ileum. The terminal parts of the ileum have no such folds.

Apart from adding considerably to the surface area of the mucous membrane, the circular folds tend to slow down the passage of contents through the small intestine thus facilitating absorption.

The *Epithelial Lining*

The epithelium covering the villi, and areas of the mucosal surface intervening between them, consists predominantly of columnar cells that are specialized for absorption. These are called ***enterocytes.*** Scattered amongst the columnar cells there are mucous secreting goblet cells. The crypts (intestinal glands) are lined mainly by undifferentiated cells that multiply to give rise to absorptive columnar cells and to goblet cells. Near the bases of the crypts there are ***Paneth cells*** that secrete enzymes. Endocrine cells (bearing membrane bound granules filled with various neuroactive peptides) are also present. The various cells mentioned above are briefly described below.

Absorptive Columnar Cells

Each cell has an oval nucleus located in its lower part. When seen with the light microscope the luminal surface of the cell appears to be thickened and to have striations in it, perpendicular to the surface. With the EM this ***striated border*** is seen to be produced by microvilli arranged in a very regular manner. The presence of microvilli greatly increases the absorptive surface of the cell.

Each microvillus has a wall of plasma membrane within which there are fine filaments. These filaments are continuous with a plexus of similar filaments present in the apical part of the cell and it is called the ***terminal web.*** The surface of each microvillus is covered by a layer of fine fibrils and mucous ***(glycocalyx).***

The plasma membrane on the lateral sides of absorptive cells shows folds that interdigitate with those of adjoining cells. Adjacent cells are united by typical junctional complexes and by scattered desmosomes. Intercellular canals may be present between adjacent cells. The cytoplasm of absorptive cells contains the usual organelles, including lysosomes and smooth ER. These cells are responsible for absorption of amino acids, carbohydrates, and lipids present in digested food.

Goblet Cells

A goblet is literally a drinking glass which is broad above, and has a narrow stem attached to a base. Goblet cells are so named because of a similar shape.

Each goblet cell has an expanded upper part that is distended with mucin granules. The nucleus is flattened and is situated near the base of the cell. Goblet cells are mucous secreting cells. In consonance with their secretory function these cells have a well developed Golgi complex and abundant rough endoplasmic reticulum. The luminal surface of the cell bears some irregular microvilli. In haematoxylin and eosin stained preparations, the mucin content of goblet cells appears to be unstained. It stains brightly with the PAS technique. Mucous cells increase in number as we pass down the small intestine, being few in the duodenum and most numerous in the terminal ileum.

Undifferentiated Cells (nonstriated cells).

These are columnar cells present in the walls of intestinal crypts. They are similar to absorptive cells, but their microvilli and terminal webs are not so well developed. The cytoplasm contains secretory granules.

Undifferentiated cells proliferate actively by mitosis. The newly formed cells migrate upwards from the crypt to reach the walls of villi. Here they differentiate either into typical absorptive cells, or into goblet cells. These cells migrate towards the tips of the villi where they are shed off. In this way, the epithelial lining is being constantly replaced, each cell having a life of only a few days. The term ***"intermediate cells"*** has been applied to differentiating stem cells that show features intermediate between those of stem cells and fully differentiated cells.

Zymogen Cells (Paneth Cells)

These cells are found only in the deeper parts of intestinal crypts. They contain prominent eosinophilic secretory granules. With the EM Paneth cells are seen to contain considerable rough endoplasmic reticulum. Other organelles and some irregular microvilli are present. The cells are rich in zinc.

They are known to produce lysozyme which destroys bacteria. They also produce dipeptidases. They produce substances, which neutralize hydrochloric acid.

Endocrine Cells

Cells containing membrane bound vesicles filled with neuroactive substances are present in the epithelial lining of the small intestine. They are most numerous near the lower ends of crypts. As the granules in them stain with silver salts these cells have, in the past, been termed argentaffin cells. Some of them also give a positive chromaffin reaction. They are, therefore, also called ***enterochromaffin cells.*** With the introduction of immunohistochemical techniques it has now been demonstrated that these cells are of various functional types, and contain many amines having an endocrine function.

Apart to that cells, there are two more cell types in the mucous membrane: **M- cells (follicle-assotiated) and granular neutrophils.** M-cells are in the epithelial covering of lymphoid follicles. They have deep cytolemm invaginations and numerous microvilli on their apical surface. The basal part of cytollem forms deep pockets for lymphocytes. Function of the cells is to uptake antigen and to present it to lymphocytes. Granular leucocytes migrate to epithelium from lamina propria and they are natural killers – cells of immune system, which trace and kill malignant cells.

Lamina propria is presented by LICT. It contains many reticular fibres, eosinophils, plasma cells. There are solitary and aggregated lymphoid follicles.

Muscularis mucosae consists of two layers of smooth myocytes: longitudinal and circular.

Submucosa is made of LICT and contains adipose tissue. There are vascular and neural plexuses. In the duodenum there are complex branched tubular glands (glands of Brunner). They produce mucous neutralizing hydrochloric acid and dipeptidases.

Muscularis coat is made of 2 layers of smooth muscular tissue. They have spiral direction. They are separated by LICT, where vascular and neural plexuses are located. The function of the coat is peristaltic movement of intestine and pushing chime down to the end of alimentary canal.

Serous coat is made of LICT and mesothelium lining.

Vascularisation. The arteries make 3 plexuses in the wall of intestine: intermuscularis, submucous, and musous. The mucous plexus give up capillaries forming network around crypts and villi. The viens make 2 plexuses: mucous and submucous.

Innervation. Afferent innervation is provided by pseudounipolar neurons of spinal ganglia and by Dogel cells II. Efferent innervation is made by sympathetic and parasympathetic nerves. The sympathetic centres are in lateral horns of spinal cord, the parasympathetic centre is nucleus nervi vagi. In the intestine wall there are well developed intermuscular and submucous nervus plexuses, which have Dogel cells I and II.

Histophisiology of digestion and absorption

There are two types of digestion: parietal and central. The central digestion is the digestion in the intestinal lumen. It is facilitated by enzymes of digestive glands and of bacteria. The parietal digestion is more significant. It takes place on striated border of enterocytes. The distance between two villi is less than bacteria size. That is why parietal digestion takes place in aseptic environment. The main structure, which provides digestion and absorption in the small intestine is villus, however, the crypts are also participate in the process of digestion. The villus always does repeated movements: contraction – relaxation. It acts as a pump. The lipid absorption can be described as following. In the intestinal lumen the complex lipids are emulgated by bile. The small drops of lipids surrounded by bile acids adsorb on the enterocyte surface. Here, they are subject to the lipases action. They are degraded to glycerin and fatty acids. These components can be easily absorbed through enterocyte membrane. The new lipids are formed in the cell. These lipids are specific only for this organism. The newly formed lipids bind proteins and carbohydrates and become. This process takes place in the Golgi complex. The glicolipoproteins are packed to the granules surrounded by membrane (chylomicrones). They are secreted to intercellular matrix and than enter lymph capillaries.

The carbohydrates are absorbed when they degraded to monosaccharids. These molecules are actively transported with help of transmembrane proteins GLUT-5. Than, the monosaccharids are released to the matrix with help of another transmembrane protein GLUT-2. Enterocytes with striated border can even produce glycogen from monosaccarids, if they are in excess. The proteins are degraded to amino acids. The amino acids are absorbed and are released to the matrix with help of transporter proteins in the membrane.

Histophisiology of "villus-crypt" system

Villus and crypt together are the whole system in the mucous membrane of intestine. This system can be discussed as structural-functional unit of small intestine. They both are covered by similar

epithelium, however, the cellular composition of the epithelium is different. The predominant cells in villi and in cryts are absorptive columnar cells. But the cells in villi are higher, and they have wider striated border, than in crypts. The crypts are less active in absorption processes. The villi are more active in absorption. They have contractive apparatus, which also facilitate absorption.

From the other side, the crypt carries out other functions. Here is the place, where undifferentiated cells are mainly localized. They are hidden from harmful influences by their position deep in the crypt. These cells give rise to any cell of crypt or villus. The Paneth cells are present only in the crypt, but the secretion of the cells is important for whole musous membrane.

Regeneration. The small intestine has cambial renewing tissues and good blood supply. The regeneration either physiological or reparative is very good. Incase of perforating wound, all layers of intestine can be repaired. In case of intestine resection, the length of the intestine is not restored, but diameter and villi number are increased.

THE LARGE INTESTINE

The Colon

The structure of the colon conforms to the general description of the structure of the gut. The following additional points may be noted.

The mucous membrane of the colon shows numerous crescent-shaped folds. There are no villi. The mucosa shows numerous closely arranged tubular glands or crypts similar to those in the small intestine. The mucosal surface and the glands are lined by an epithelium made up predominantly of columnar cells with a striated border. Their main function is to absorb excess water and electrolytes from intestinal contents. Many columnar cells secrete mucous and antibodies (IgA). The antibodies provide protection against pathogenic organisms. Numerous goblet cells are present, their number increasing in proceeding caudally. The mucous secreted by them serves as a lubricant that facilitates the passage of semisolid contents through the colon. Paneth cells are not present. Some endocrine cells, and some stem cells, are seen.

The epithelium overlying solitary lymphatic follicles (present in the lamina propria) contains M-cells similar to those described in the small intestine. Scattered cells bearing tufts of long microvilli are also seen. They are probably sensory cells.

The submucosa often contains fat cells. Some cells that contain PAS-positive granules, termed ***muciphages,*** are also present. These are most numerous in the rectum.

The longitudinal layer of muscle is unusual. Most of the fibres in it are collected to form three thick bands, the ***taenia coli.*** A thin layer of longitudinal fibres is present in the intervals between the taenia. The taenia is shorter in length than other layers of the wall of the colon. This results in the production of ***sacculations*** (also called ***haustrations)*** on the wall of the colon.

The serous layer is missing over the posterior aspect of the ascending and descending colon. In many situations the peritoneum forms small pouch-like processes that are filled with fat. These yellow masses are called the ***appendices epiploicae.***

The Vermiform Appendix

The structure of the vermiform appendix resembles that of the colon (described above) with the following differences.

1. The appendix is the narrowest pan of the gut.
2. The crypts are poorly formed.
3. The longitudinal muscle coat is complete and equally thick all round. Taenia coli are not present.
4. The submucosa contains abundant lymphoid tissue which may completely fill the submucosa. The lymphoid tissue is not present at birth. It gradually increases and is best seen in children about 10 year old. Subsequently, there is progressive reduction in quantity of lymphoid tissue.

The Rectum

The structure of the rectum is similar to that of the colon except for the following.

1. A continuous coat of longitudinal muscle is present and there are no taenia.
2. Peritoneum covers the front and sides of the upper one-third of the rectum; and only the front of the middle third. The rest of the rectum is devoid of a serous covering.
3. There are no appendices epiploicae.

The Anal Canal

The anal canal is about 4 cm long. The upper 3 cm are lined by mucous membrane, and the lower 1 cm by skin. The area lined by mucous

membrane can be further divided into an upper part (15 mm) and a lower part (15 mm).

The mucous membrane of the upper 15 mm of the canal is lined by columnar epithelium. The mucous membrane of this part shows six to twelve longitudinal folds that are called the ***anal columns.*** The lower ends of the anal columns are united to each other by short transverse folds called the ***anal valves.*** The anal valves together form a transverse line that runs all round the anal canal: this is the ***pectinate line.*** The mucous membrane of the next 15 mm of the rectum is lined by nonkeratinized stratified squamous epithelium. This region does not have anal columns. The mucosa has a bluish appearance because of the presence of a dense venous plexus between it an the muscle coat. This region is called the ***pecten*** or ***transitional zone.*** The lower limit of the pecten forms the ***white line (of Hilton).***

The lowest 8 to 10 mm of the anal canal are lined by true skin in which hair follicles, sebaceous glands and sweat glands are present.

Above each anal valve there is a depression called the ***anal sinus.*** Atypical (apocrine) sweat glands open into each sinus. They are called the ***anal (or circumanal) glands.***

The anal canal is surrounded by circular and longitudinal layers of muscle continuous with those of the rectum. The circular muscle is thickened to form the ***internal anal sphincter.*** Outside the layer of smooth muscle, there is the ***external anal sphincter*** which is made up of striated muscle. For further details of the anal musculature see a book on gross anatomy.

Prominent venous plexuses are present in the submucosa of the anal canal. The internal haemorrhoidal plexus lies above the level of the pectinate line, while the external haemorrhoidal plexus lies near the lower end of the canal.

THE LIVER

Introductory Remarks

The liver may be regarded as a modified exocrine gland that also has other functions. It is made up, predominantly, of liver cells or ***hepatocytes.*** Each hepatocyte is a large cell with a round open faced nucleus, with prominent nucleoli.

The liver substance is divisible into a large number of large lobes, each of which consists of numerous lobules. The exocrine secretion of the liver cells is called ***bile.*** Bile is poured out from liver cells into very delicate ***bile canaliculi*** that are present in intimate relationship to the cells.

From the canaliculi bile drains into progressively larger ducts which end in the ***bile duct.*** This duct conveys bile into the duodenum where bile plays a role in digestion of fat.

All blood draining from the stomach and intestines (and containing absorbed food materials) reaches the liver through the portal vein and its branches. Within the liver this blood passes through sinusoids and comes into very intimate relationship with liver cells. The liver is thus able to 'screen' all substances entering the body through the gut. Some of them (e.g., amino acids) are used for synthesis of new proteins needed by the body. Others (e.g., glucose, lipids) are stored in liver cells for subsequent use; while harmful substances (e.g., drugs, alcohol) are detoxified. The need for intimate contact between blood in the sinusoids, and liver cells, thus becomes obvious. The portal vein also brings blood from the spleen to the liver. This blood contains high concentrations of products formed by breakdown of erythrocytes in the spleen. Some of these products (e.g., bilirubin) are excreted in bile, while some (e.g., iron) are stored for re-use in new erythrocytes.

In addition to deoxygenated blood reaching the liver through the portal vein, the organ also receives oxygenated blood through the ***hepatic artery*** and its branches. The blood entering the liver from both these sources passes through the hepatic sinusoids and is collected by tributaries of hepatic veins. One such tributary runs through the centre of each lobule of the liver where it is called the ***central vein.***

Branches of the hepatic artery, the portal vein, and the hepatic ducts, travel together through the liver. The tributaries of hepatic veins follow a separate course as described below.

Basic Histology of the Liver

In sections through the liver, the substance of the organ appears to be made up of hexagonal areas that constitute the ***hepatic lobules.*** In some species (e.g., the pig) the lobules are distinctly demarcated by connective tissue septa, but in the human liver the connective tissue is scanty and the lobules often appear to merge with one another. In transverse sections each lobule appears to be made up of cords of liver cells that are separated by sinusoids. However, the cells are really arranged in the form of plates (one cell thick) that branch and anastomose with one another to form a network. Spaces within the network are occupied by sinusoids.

Along the periphery of each lobule there are angular intervals filled by connective tissue. These intervals are called ***portal canals,*** the 'canals' forming a connective tissue network permeating the entire liver substance. Each 'canal' contains (a) a branch of the portal vein; (b) a branch of the

hepatic artery, and (c) an interlobular bile duct. These three structures collectively form a ***portal triad.*** Blood from the branch of the portal vein, and from the branch of the hepatic artery, enters the sinusoids at the periphery of the lobule and passes towards its centre. Here the sinusoids open into a ***central vein*** which occupies the centre of the lobule. We have already seen that the central vein drains into hepatic veins (which leave the liver to end in the inferior vena cava).

The vessels in a portal triad usually give branches to parts of three adjoining lobules. The area of liver tissue (comprising parts of three hepatic lobules) supplied by one branch of the portal vein is regarded by many authorities as the true functional unit of liver tissue, and is referred to as ***a portal lobule*** (in distinction to a hepatic lobule described above). A still smaller unit, the ***portalacinus*** has also been described. It consists of the area of liver tissue supplied by one hepatic arteriole running along the line of junction of two hepatic lobules. Two central veins lie at the ends of the acinus.

The liver is covered by a connective tissue ***capsule*** (Glisson's capsule). This connective tissue extends into the liver substance through the portal canals (mentioned above) where it surrounds the portal triads. Sinusoids are surrounded by reticular fibres. Connective tissue does not intervene between adjoining liver cells.

Bile is secreted by liver cells into ***bile canaliculi.*** These canaliculi have no walls of their own. They are merely spaces present between plasma membranes of adjacent liver cells. The canaliculi form hexagonal networks around the liver cells. At the periphery of a lobule the canaliculi become continuous with delicate ***intralobular ductules,*** which in turn become continuous with larger ***interlobular ductules*** of portal triads. The interlobular ductules are lined by cuboidal epithelium. Some smooth muscle is present in the walls of larger ducts.

Further Details of Liver Structure

1. The cytoplasm of liver cells contains numerous mitochondria, abundant rough and smooth endoplasmic reticulum, a well developed Golgi complex, lysosomes, and vacuoles containing various enzymes. Numerous free ribosomes are present. These features are to be correlated with the high metabolic activity of liver cells. Stored glycogen, lipids, and iron (as crystals of ferratin and haemosidrin) are usually present. Glycogen is often present in relation to smooth ER. Many hepatocytes show two nuclei; or a single polyploid nucleus.

2. Although the liver performs numerous functions all liver cells look alike. Each cell is probably capable of performing all functions. However,

the cells at the periphery of a lobule receive more highly oxygenated blood than those nearer the centre of the lobule. Functional differences exist between hepatocytes in these regions.

3. We have seen that liver cells are arranged in the form of anastomosing plates, one cell thick; and that the plates form a network in the spaces of which sinusoids lie. In this way each liver cell has a sinusoid on two sides. The sinusoids are lined by an endothelium in which there are numerous pores (fenestrae). A basement membrane is not seen. Interspersed amongst the endothelial cells there are hepatic macrophages ***(Kupffer cells).*** The surface of the liver cell is separated from the endothelial lining of the sinusoid by a narrow ***perisinusoidal space*** (of Disse). Microvilli, present on the liver cells, extend into this space. As a result of these factors hepatocytes are brought into a very intimate relationship with the circulating blood. Some fat cells may also be seen in the space of Disse.

4. Blood vessels and hepatic ducts present in portal canals are surrounded by a narrow interval called the ***space of Mall.***

5. The surface of a hepatocyte can show three kinds of specialization.

(a) ***Sinusoidal surface:*** As mentioned above the cell surface adjoining sinusoids bears microvilli that project into the space of Disse. The cell surface here also shows many coated pits (see page 8) which are concerned with exocytosis. Both these features are to be associated with active transfer of materials from sinusoids to hepatocytes, and ***vice versa.*** About 70% of the surface of hepatocytes is of this type.

(b) ***Canalicular surface:*** Such areas of cell membrane bear longitudinal depressions that are apposed to similar depressions on neighbouring hepatocytes, to form the wall of a bile canaliculus. Irregular microvilli project into the canaliculus. On either side of the canaliculus, the two cell membranes are united by junctional complexes. About 15% of the hepatocyte surface is canalicular.

(c) ***Intercellular surface-.*** These are areas of cell surface where adjacent hepatocytes are united to each other just as in typical cells. Communicating junctions allow exchanges between the cells. About 15% of the hepatocyte surface is intercellular.

Functions of the Liver

The liver performs numerous functions. Some of these are as follows.

1. We have seen that the liver acts as an exocrine gland for the secretion of bile. However, the architecture of the liver has greater resemblance to that of an endocrine gland, the cells being in intimate relationship to blood in sinusoids. This is to be correlated with the fact that

liver cells take up numerous substances from the blood, and also pour many substances back into it.

2. The liver plays a prominent role in metabolism of carbohydrates, proteins and fats. Metabolic functions include synthesis of plasma proteins fibrinogen and prothrombin, and the regulation of blood glucose and lipids.

3. The liver acts as a store for various substances including glucose (as glycogen), lipids, vitamins and iron. When necessary the liver can convert lipids and amino acids into glucose ***(gluconeogenesis).***

4. The liver plays a protective role by detoxifying substances (including drugs and alcohol). Removal of bile pigments from blood (and their excretion through bile) is part of this process. Amino acids are deaminated to produce urea, which enters the blood stream to be excreted through the kidneys. The macrophage cells (of Kupffer) lining the sinusoids of the liver have a role similar to that of other cells of the mononuclear phagocyte system. They are of particular importance as they are the first cells of this system that come in contact with materials absorbed through the gut. They also remove damaged erythrocytes from blood.

5. During fetal life the liver is a centre for haemopoiesis.

EXTRAHEPATIC BILIARY APPARATUS

The extrahepatic biliary apparatus consists of the gall bladder and the extrahepatic bile ducts.

The Gall Bladder

The gall bladder stores and concentrates bile. This bile is discharged into the duodenum when required. The wall of the gall bladder is made up of a mucous membrane, a fibromuscular coat, and a serous layer that covers part of the organ.

The mucous membrane of the gall bladder is lined by a tall columnar epithelium with a striated border. The mucosa is highly folded. The folds are called ***rugae.*** In sections, the folds may look like villi. [Because of this resemblance to villi students sometimes mistake sections of the gall bladder for those of the intestines. The two are easily distinguished if it is remembered that there are no goblet cells in the epithelium of the gall bladder. The folds may branch and anastomose with one another to give a reticular appearance.

The fibromuscular coat is made up mainly of connective tissue containing the usual elements. Smooth muscle fibres are present and run in various directions.

The serous layer has a lining of mesothelium resting on connective tissue.

With the EM the lining cells of the gall bladder are seen to have irregular microvilli on their luminal surfaces. Near the lumen the lateral margins of the cells are united by well developed junctional complexes. More basally the lateral margins are separated by enlarged intercellular spaces into which complex folds of plasma membrane extend. Numerous blood capillaries are present near the bases of the cells. These features indicate that bile is concentrated by absorption of water at the luminal surface of the cell. This water is poured out of the cell into basal intercellular spaces from where it passes into blood. Absorption of salt and water from bile into blood is facilitated by presence of Na^+ and K^+ ATPases in cell membranes of cells lining the gall bladder.

Inflammation of the gall bladder is called ***cholecystitis.*** Stones may form in the gall bladder ***(gall stones; cholelithiasis).*** In such cases surgical removal of the gall bladder may be necessary ***(cholecystectomy).***

The Extrahepatic Ducts

These are the right, left and common hepatic ducts; the cystic duct; and the bile duct. All of them have a common structure. They have a mucosa surrounded by a wall made up of connective tissue, in which some smooth muscle may be present.

The mucosa is lined by a tall columnar epithelium with a striated border.

At its lower end the bile duct is joined by the main pancreatic duct, the two usually forming a common ***hepato-pancreatic duct*** **(or** ***ampulla)*** which opens into the duodenum at the summit of the major duodenal papilla. The mucosa of the hepato-pancreatic duct is highly folded. These folds are believed to constitute a valvular mechanism that prevents duodenal contents from entering the bile and pancreatic ducts.

Well developed smooth muscle is present in the region of the lower end of the bile duct. This muscle forms the ***sphincter of Oddi.*** From a functional point of view this sphincter consists of three separate parts. The ***sphincter choledochus*** surrounds the lower end of the bile duct. It is always present, and its contraction is responsible for filling of the gall bladder. A less developed ***sphincter pancreaticus*** surrounds the terminal part of the main pancreatic duct. A third sphincter surrounds the hepato-pancreatic duct (or ampulla) and often forms a ring round the lower ends of both the bile and pancreatic ducts. This is the ***sphincter ampullae.*** The sphincter ampullae and the sphincter pancreaticus are often missing.

Blockage of the bile duct (by inflammation, by a gall stone, or by carcinoma) leads to accumulation of bile in the biliary duct system, and within the bile capillaries. As pressure in the passages increases bile passes into blood leading ***to jaundice.*** The sclera, the skin, and the nails appear to be yellow in colour, and bile salts and pigments are excreted in urine. Jaundice occurring as a result of such obstruction is called ***obstructive jaundice.*** Jaundice is seen in the absence of obstruction in cases of hepatitis.

A gall stone passing through the bile duct can cause severe pain. This pain is ***biliary colic.***

PANCREAS

Pancreas is a one from big digestive glands.

Development: Pancreas is developed from entoderm of body's gut at the end of third week of embryogenesis. The gut makes two invaginations, which give rise for head, body and tail of pancreas. On a third month pancreatic stem differentiates into exocrine and endocrine parts. Capsule and interlobular septa is formed from mesenhyme.

Functions:

1. Exocrine function – it is to secrete pancreatic juice – a mixture of digestive enzymes such as trypsin (for proteins digestion), carboxipeptidase (for peptid digestion), amylase (for starch, gliycogen), lipase (for lipids), phospholipase (for phospholipids), nucleases (for nucleic acids) and others. Other components of pancreatic juice are water, bicarbonate ions and mucus.
2. Endocrine function – it is to produce a line of hormones. Among them we can find insulin (for glucose utilization in tissues), glucagons (for recruiting glucose from storages), somatostatine (it suppresses cell division and glands secretion in alimentary canal), VIP (vasoactive intestinal peptide for smooth muscles relaxation and stimulating pancreatic bicarbonate secretion), pancreatic polypeptide (PP for inhibition of pancreatic bicarbonate and protein secretion).

Structure: Pancreas is parenhymal lobular organ. Stroma is presented by capsule and septa. Both is made of LICT. Parenchyma is presented by acini, ducts and Langherhans islets.

Exocrine part is major with many serous acini and some ducts. Structural unit is acinus. It is made from acinocytes and centrocinocytes. Acynocytes lie on basement membrane. Pyramidal epithelial cells line the

acini; are rich in basal granular ER (deeply basophil); have a prominent supranuclear Golgi complex and apical zymogen granules (precursors of several digestive enzymes). These enzymes are to be activated only in duodenum. Centroacinocytes are not reffered to secretoral part. They are a pale duct cell (or a pair), which may be seen intruded into the centre of the acinus. They are the part of intercalated duct and some authors consider them as cambial element for pancreas.

Ducts. Commence as narrow *intercalated ducts* within the acini, although varies of section plane result in one finding centroacinar cells in only some acini. Cells of intercalated ducts produce bicarbonates for acid neutralization in duodenum. Beyond the intercalated ducts, ducts have pale cuboidal cells, with few organelles and some microvilli, changing to columnar epithelial cells in the larger ducts. Ducts are less often seen than in the serous parotid gland, and probably actively change the secretions only in the smaller, early ducts. Ducts are accompanied by less connective tissue than in the salivary glands, which are exposed to masticatory forces.

Endocrine part is minor: many small clusters of cells staining palely (with HE) - islets of Langerhans. Its are made from isulocytes of different types:

- Alpha cells, 20 per cent, and large - produce the hormone, glucagon, which raises the blood's glucose level.
- Beta cells, 75 per cent, smaller - produce insulin, which promotes the glucose uptake and glycogen storage, thereby lowering the glucose level of the blood.
- Delta cells, 5 per cent, with large argyrophil granules; form somatostatin, which inhibits insulin and glucagon release.
- Delta1 cells, contain granules with VIP, which stimulates production of pancreatic juice and ddecrease blood pressure.
- F cells/PP cells, in islets and among exocrine cells, making pancreatic polypeptide (PP), acting centrally on the brainstem to influence the vagal control of GI functions, and on the liver.

Islets are rich in capillaries with a fenestrated endothelium.

Blood supply: Pancreas is fed by superior mesenterial artery. Cappilarie in acini are of usual type, but those in islets have fenestrated endothelium. Venous blood is drainaged to vena porta system.

Innervation: Pancreas has afferent and efferent innovation. Afferent innervation is the same as in other internal organs. Efferent innervation is performed by autonomic nervous system by both its divisions: sympathetic and parasympathetic. Activated sympathetic part suppresses activity of

exocrine part but stimulates insulin secretion. Parasympathetic part acts overwise.

Regeneration: regeneration is performed with help of centroacinar cells, which are cambial cells. They can be differentiated to acinar and islet cell, as well.

Table 10 - Argentaffin Cells

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Peer Review Status: Externally Peer Reviewed

Cell	Location	Product	Function
D	Stomach, jejunum, ileum, colon	Somatostatin	Inhibition of other endocrine glands
D_1	Stomach, jejunum, ileum, colon	Vasoactive intestinal polypeptide	Increases intestinal motility, ion, and water secretion
EC	Stomach, jejunum, appendix	Serotonin, substance P	Increased intestinal activity
ECL	Stomach	Histamine	Vasodilator, gastric secretion
G	Stomach, duodenum	Gastrin	Stimulates gastric secretion, neurotransmitter
GRP	GI System	Gastrin-releasing peptide	Releases gastrin
I	Jejunum, ileum	Cholecystokinin	Pancreatic exocrine secretion, gallbladder contraction
K	Jejunum, ileum	Gastrin, inhibitory peptide	Inhibits gastric acid secretion
L	Jejunum, ileum, colon	Glucagon-like	Hepatic glycogenolysis substances
Mo	Jejunum, ileum	Motilin	Increases gut motility
N	Ileum	Neurotensin	Myenteric plexus

			transmitter
P	Stomach, jejunum	Unknown	Unknown
PP	Stomach, colon	Pancreatic polypeptide	Pancreatic exocrine secretion
S	Jejunum, ilium	Secretin	Pancreatic and bile secretion
TG	Jejunum	C-terminal gastrin immunoreactivity	Neurotransmitter
X	Stomach	Unknown	Unknown

Some names associated with the digestive system follow: von Ebner was a nineteenth-century Vienna histologist; Paneth, a nineteenth-century German physician; Lieberkühn, an eighteenth -century German anatomist; Brunner, a seventeen th-cen tury Swiss anatomist; Meissner, a nineteenth-century German anatomist, Auerbach, a nineteenth-century German anatomist; Glisson, a seventeenth -century English anatomist; von Kupffer, a nineteenth-century German anatomist; Schiff, a twentieth-century German chemist working in Florence, and Zenker, a nineteenth-century German pathologist.

Chapter 16: The haemopoietic system

Continuous formation of the cells, corpuscles, and platelets of the blood is necessary to keep their numbers relatively constant as they wear out or are lost from the body. The formation is called *haemocytopoiesis* or *haemopoiesis* for short.

Embrionic haemopoiesis

It is a process of blood formation as a tissue during embryonic development. It is divided into 3 periods depending on time and place where it happen.

1. Extraembrionic period – 1-2 months of ebriogenesis.
2. Hepato-thymo-lienal period – 2-5 months.
3. Medullo-thymo-lymphatic period – 5-10 months of embryogenesis.

The first period occurs in extraembrionic mesoderm of yolk sac. Here, blood clasters appear. Their cells are differentiated into two directions: angioblasts, which lie laterlally and form endothelium cells of primary vessels, and primary blood cells, which lie centrally and form stem cells of blood. The majority of primary blood cells transforms to primary

erythroblast of huge size – megaloblasts. Megaloblasts divide by mitosis and are subject to differentiation. They accumulate free ribosomes. Due to this their cytoplasm becomes basophilic. Free ribosomes start to produce embryonic hemoglobin $\zeta_2\varepsilon_2$. The hemoglobin has oxyphilic staining. Due to having both hemoglobin and free ribososmes the cells are stained either basophilic and oxyphilic stains. Such cells are called polychromatophilic megaloblasts. Further differentiation leads to hemoglobin accumulation. The cells become more oxyphilic and are named oxyphilic megaloblasts. The cells give up megalocytes, which may have nucleus or haven't it, as well. The process of megalocyte formation is named as megaloblastic erythropoiesis. It is typical for embryonic hemopoiesis. It can be found in adults only during pathological condition called pernicious anemia. Such anemia is connected with vitamin B_{12} deficiency. At the same time, there is normoblastic erythropoiesis in the yolk sac. Small amount of normal sized erythrocyte are formed inside of blood vesels.

Erythroppiesis is accompanied by granulocytopoiesis. It takes place extravascular. It gives eosinophilic and netrophilic leucocytes. Part of stem cells stays in undifferentiated condition. They wait until blood vessels will be formed. Than they travel to other hemopoietic organs and become cells of hemopoietic tissue or connective tissue.

Further, yolk sac is subject to reducing and on 12 week of development the hemopoiesis in the yolk sac is terminated.

Thus, the features of extraembrionic hemopoiesis are:

1. The clsters of hemopoiesis are localized outside of the embryo.
2. The concentration of hemopoiesis in the one organ.
3. The narrow range of hemopoiesis: prevalence of erythropoiesis.
4. The prevalence of intravascular hemopoiesis.
5. The hemopoiesis regulation is performed mainly by inductive influences of yolk ectoderm and by few humoral factors. The integrating systems as nervous, endocrine and immune, do not take part in regulation.

The second period starts on 5-6 week of embryogenesis. During second month of development the stem cells settle liver, spleen and thymus. The hemopoiesis starts in the organs.

In the liver mesenchyme, the normocytes, granulocytes, megakaryocytes are formed extravascular. The liver hemopoiesis is terminated gradually to birth, but it may exist during first month after delivery in small volumes.

Hemopoiesis in spleen is most significant from 4^{th} to 8^{th} month of embryogenesis. On 4^{th}-5^{th} month the spleen is universal organ of

hemopoiesis, where hemopoiesis of all blood cells takes place. It is extravascular hemopoiesis. The peak of erythropoiesis and myelopoiesis is on 5th month. Than their rate is gradually decrease. After birth, the main function of spleen is lymphopoiesis.

Hemopoiesis in thymus starts on 7-8 week of embryogenesis. At this time the first lymphocytes appear in the epithelial stroma of the organ. Later, their number is gradually increased. Lymphocytes acquire specific receptors. The different forms of T-lymphocytes are formed here. This formation is regulated by thymus hormone – thymosin and probably by other hormones, which are produced by reticuloepithelial cells. The maximal development of thymus occurs at the end of embryonic period and it lasts until 3 year. Than it process becomes stable, but after 20 years it gradually decreases. But even in old age it preserves in a small volume.

Lymph nodules hemopoiesis. The majority of lymph nodes is founded at 8-10 week of embryogenesis. At the same time they are settled by blood hemopoietic stem cells. These cells are differentiated to erythrocytes, all types of granulocytes and megakaryocytes. The naïve lymphocytes from thymus enter T-depended zones of lymph nodes. The maximum of the settlement is on 16-17 week of embryonic development. The other clusters of hemopoiesis are suppressed by lymphoid hemopoiesis.

The listed above organs are main organs of hemopoiesis in the second period. But some part of hemopoiesis may take place in connective tissue, embryonic skin, lungs, and kidneys.

Thus, the features of second period of hemopoiesis are:

1. Widening of hemopoietic range.
2. Prevalence of extravascular hemopoiesis.
3. Allocation of hemopoiesis to various organs.
4. Interchange from difuse hemopoiesis to more concentrated one.
5. Appearance of transitional universal organ of hemopoiesis – spleen.
6. Gradual increasing of hemopoiesis regulation mechanisms.

The third period is medullo-thymo-lymphatic. It starts on 5th month. The red bone marrow becomes the universal organ of hemopoiesis. The hemopoiesis is divided to myeloid and lymphoid hemopoiesis. The mesechyme of red bone marrow gradually transforms to reticular tissue. The reticular tissue maintains erythropoiesis, granulopoiesis, monocytopoiesis, megakaryocytopoiesis and B-lymphopoiesis. The prevalating majority of blood stem cells are concentrated in red bone marrow. The formation of all cell types excluding lymphocytes is called myelopoiesis. At the same time in thymus, spleen, lymph nodes the lymphopoiesis take place.

Thus, the features of third period of hemopoiesis are:

1. Appearance of defenitive universal organ of hemopoiesis – red bone marrow.
2. Splitting of hemopoiesis to two branches: myelopoiesis and lymphopoiesis.
3. Termination of hemopoietic function of transitional hemopoietic organs. But aloocation of hemopoiesis in different organs preserves.
4. Solely extravascular type of hemopoiesis.
5. Definite setting of regulatory mechanisms.

Postembryonic hemopoiesis

Postembryonic hemopoiesis or physiological (and of course reparative) regeneration of blood is performed throughout the individual's life. It takes place in myeloid and lymphoid tissue, which make the core of hemopoietic organs.

Myeloid tissue is included into red bone marrow. It's total weight is about 2 kg. Red bone marrow is located inside of bone cavity. The precursors of all blood and connective tissue cells are formed here. Than, the early precursors of lymphoid cells migrate to lymphoid organs, where they continue the differentiation.

Lymphoid tissue is located in lymphoid organs: thymus, spleen, lymph nodes, solitary and aggregated lymphoid follicles, tonsil. The total weight of lymphoid tissue is approximately equal to the weight of myeloid tissue. The lymphoid tissue produces T- and B-lymphocytes and plasmocytes (as terminal point of B-lymphocyte differentiation).

Myeloid and lymphoid tissues are variants of connective tissue. They have two cell lines: 1) cells of hemopoietic tissue and 2) reticular cells.

Reticular tissue is a type of connective tissue with specific properties. As all tissues derived from mesenchyme it has cells and intercellular substance. The cells are fibrolasts, macrophages and undifferentiated cells. The intercellular substance is made of reticular fibers and amorphous substance. Reticular tissue makes an environment for hemopoietic cells. It includes support, nutrition, defense, regulation, secretion (of hemopoietic factors and interleukins).

Hemopoietic tissue. The term includes all cells of hemopoietic line from stem cell to terminally differentiated cell. Hemopoietic cells arise from stem cell under reticular cells controlling by hemopoietins.

Properties of stem cells

1. Structurally stem cell resembles small lymphocyte: it has small size, high nucleus/cytoplasm ratio, a few organelles of general purpose to maintain metabolic rate on a small level.
2. They may subject to mitotic division. But are divided very rare. Stem cells can perform about 1000 divisions. But it was shown that to maintain blood composition during 70 years it is required 53 divisions of one embryonic stem cell. So, blood stem cells give up huge reserve of hemopoiesis. Theoretically it is enough to maintain blood composition during 22600000000 years!
3. Blood stem cells can maintain their cell number in population by two processes: 1) rare mitosis and 2) differentiation. After mitosis, the one cell is subject to differentiation, whereas another stays in G_0 phase (resting position). When it is needed the resting cell can be differentiated.
4. Blood stem cell as autosynthetic metabolism. It means that cell produce substances only for itself.
5. They are polypotent cells. So, they can become any blood cell.
6. They are more resistant to harmful factors due to having condenced heterochromatin in the nucleus and duet to deep localization inside of bone.
7. In spite of red bone marrow localization, the blood stem cells can migrate to other organs with blood flow.

THEORETICAL CONSIDERATIONS OF HAEMOPOIESIS

1 Granular leucocytes and RBCs are specialized *end products* in being unable to divide, and living for only a few weeks. Since their numbers in the blood stay constant, new cells must be forming from less specialized ones.

2 Bone marrow, stained as for a blood smear, has cells, construed from their granularity, eosinophilia, nuclear morphology, etc, as members of developmental sequences, apparently starting with a large, undistinguished weakly basophil, primitive cell, and ending as one of the clear-cut specialized kinds.

3 If all the primitive marrow cells multiplied and then turned into blood cells, when the blood cells were spent, no primitive ones would exist to replace them. Thus, the primitive cells must act as stem cells able to divide, and with two possible fates: some *to stay* as primitive stem cells, others *to differentiate* into special forms.

4 Since there are several specialized blood cells, are there separate, but histologically indistinguishable, stem cells: one for each blood cell type? - The *polyphyletic theory* of committed progenitors for each lineage. Yes, but the *monophyletic* theory also survives, because rare multipotent/*pluripotent stem cells* exist, and can replenish the restricted stem cells, e.g., those for erythropoiesis.

5 CFU-S denotes the pluripotent cell in mouse, and forms the basis for naming progenitor cells in humans. *Colony-forming unit - spleen/CFU-S* was the cell that could give rise to an island/colony of complete haemopoiesis in the spleen of the mouse, after splenic and other sites of haemopoiesis had been totally destroyed by irradiation. Where, then, did the rescuing cell come from to form the colony? The CFU-S was obtained from infant mice and injected just after the irradiation. (A convenient human source for equivalent stem cells is blood from the umbilical cord.)

6 All cell divisions and differentiations need controlling growth factors (cytokines), not only to maintain the stem cell population, but to persuade some of them to fill precisely the ranks of the various blood cells.

7 After a stem cell becomes a *committed precursor*/progenitor for a certain cell line, a period elapses when histology, without immunostaining, cannot identify the line. Later, perceptible morphological changes make the cell a recognizable precursor, say a pro-erythroblast. Thereafter, the development of the cell is divided into named stages, each based on a significant change in appearance from the previous stage.

The potential for confusion exists, since workers have differed in the number of stages chosen, e.g., omitting pre-stages, and their names for a given cell type, e.g., rubriblast/normoblast for erythroblast.

8 The ability of the few stem cells to divide does not preclude proliferation by committed precursors, and by cells at later, recognizable, stages of development, for continued *amplification* of cell numbers.

CHANGES IN DEVELOPING BLOOD CELLS

I Erythrocytes

1 Large, weakly basophilic *pro-erythroblast* increases the free ribosomes in its cytoplasm to become a *basophil erythroblast.*

2 Cell size decreases, and organelles are lost.

3 *Nucleus,* initially large and pale, with nucleoli, gets smaller and stains more darkly.

4 *Cytoplasm* acquires *haemoglobin* at the expense of ribosomal ribonucleprotein (RNP) - thus its staining affinity changes from basophilia

to acidophilia; the mixed-hued halfway stage is the *polychromic/polychromatophil erythroblast.*

5 Small cell, with orange cytoplasm and a round dark nucleus, is the *orthochromic erythroblast/normoblast.*

6 Nucleus, in a little cytoplasm, is *extruded* for phagocytosis.

7 *Reticulocyte/polychromatophil erythrocyte* is an RBC that is released into the blood still with RNP in its cytoplasm. Supravital staining with brilliant cresyl blue causes this material to clump as a blue network (reticulum) in around 2 per cent of the RBCs of normal blood.

2 Granulocyte

1 *Myeloblast*/granuloblast develops into a

2 *promyelocyte* synthesises non-specific azurophil granules (lysosomes) in the cytoplasm, and with its nucleus getting smaller and darker.

3 *Myelocyte*, after a pause, then makes additional granules *specific* for one of the three kinds of granulocyte in their staining affinity.

4 Nucleus elongates and indents, and chromatin becomes coarser, giving the *metamyelocyte* (now unable to divide).

5 More granules form and the nucleus becomes sausage-shaped - *band*/juvenile granulocyte. Then the nucleus starts segmenting, as the cell becomes the mature granulocyte.

3 Platelets

1 *Haemocytoblast* enlarges to become a *megakaryoblast.*

2 The nucleus experiences several rounds of DNA replication, but each time with reassembly of a single nuclear envelope and no segregation into separate nuclei. Thus the nucleus takes on a distinctive *lumpy, polyploid* form. (The single, large, lumpy nucleus is the criterion for distinguishing megakaryocytes from nearby osteoclasts in bone sections.)

3 Fine cytoplasmic azurophil granules accumulate as the cell becomes a very large granular *megakaryocyte.*

4 Many paired membranes of smooth ER (*demarcation membranes*) appear and contribute plasmalemma to the formation of

5 *pseudopodia*, which are extended into the lumen of a sinusoid, where they cast off in the blood as *platelets.*

6 Megakaryocyte cytoplasm might also serve as a transcellular migration pathway for some new leucocytes passing from the marrow into the blood.

4 Agranular leucocytes

1 In developing, they do not become so strikingly different from their stem cells as do granulocytes and RBCs.

2 Monocytes form from monoblast/pre-monocyte precursors in bone marrow.

3 Lymphocytes develop from lymphoblasts in bone marrow and lymphoid organs.

4 Some circulating lymphocytes appropriately stimulated can also become lymphoblasts.

BONE MARROW

1 The naked-eye appearance of fresh, unstained marrow may be *red* from many developing RBCs, or *yellow* from mainly fat cells.

2 Red marrow has many elements,

- (a) *Blood sinusoids* are lined by *endothelial cells* on an incomplete BL. *Collagen fibrils* (reticular fibres) support these, and
- (b) adventitial *stromal/reticular cells*, similar to fibroblasts, but extending processes between, and greatly influencing, the haemopoietic cells.
- (c) *Macrophages* cleanse blood, and detect and destroy worn-out RBCs and other elements. The iron recovered is stored, combined with protein as ferritin granules, before release to the labile pool and reuse.
- (d) *Blood cells* develop extravascularly, are stored, then released through the sinusoidal wall into the circulation.
- (e) *Megakaryocytes* form and release platelets.
- (f) *Fat cells* are present, large and empty of fat in embedded sections.
- (g) *Bone surface cells* act as an enclosing sac for the marrow.

3 *Microscopic methods for marrow* include sections, and smears of aspirated sternal marrow stained with a blood stain.

3 Some factors affecting blood cell formation

1 *Bacterial infection* increases the number of circulating granulocytes (a *leucocytosis*) and their rate of formation.

2 *Erythropoietin* is a humoral factor, released from the kidney in response to hypoxia, that increases RBC production. *Thrombopoietin* controls platelet formation, but has multiple sources, including liver and kidney.

3 RBC formation requires adequate *dietary elements*, e.g., folic acid, iron, vitamin B_{12}.

4 Androgenic *steroid hormones* stimulate erythropoiesis.

5 *Stromal cells* release cytokines and, with the matrix, create a microenvironment favourable for haemopoiesis.

Chapter 17: The immune system 1

A multicellular organism has to contend with *three related problems*:

- some of its cells have short lives and their remains must be disposed of;
- foreign non-living matter may enter, e.g., dust and grit, and has to be eliminated or made harmless;
- foreign living matter may gain entrance, carrying the additional hazard that the intruder may poison or proliferate and overwhelm its host.

The immune system helps to cope with these problems.

Immunity – is defense of an organism from anything which is genetically foreign, likewise: foreign biopolymers, microorganisms, foreign cells, own malignant cells. The immunity is provided by specific and non-specific immunity factors. Non-specific defense mechanisms are also called inherited. It is group of factors which either prevent antigen entering or destroy entered antigens. The following factors are involved to non-specific defense:

1. Mechanical barriers. It is mainly epithelial barriers of skin, mucose membranes and ets.
2. Chemical factors. The most of secreting materials have low pH. Skin surface has pH 5.5, gastric juice has pH about 2. Mucosa cells produce line of enzymes which have bactericidic effect on bacteria.
3. Cellular factors. Among them there are macrophages, neutrophils, basophils and other cells which can destroy foreign agents by phagocytosis.

Specific immunity (acquired immunity). It is started after first contact with antigen. It include specific response formation, which can be either antibodies formation (humoral immunity) or formation of immune competent cells (cellular immunity). Both types lead to antigen elimination.

According to immune mechanism the imunity can be *active* or *passive*. *Active imunity* is an immunity, which is formed during active production of defense components as response on antigen entering. It can be either after disease (*natural active immunity*) or after vaccination by microorganisms containing vaccines (*artificial active immunity*). Passive immunity is when an organism takes already made defense components. It can take it with mother's milk (*natural passive immunity*) or while injection already made serum or immune cells (*artificial passive immunity*).

Immune system includes: 1) immune competent organs; 2) immune competent tissues; 3) immune competent cells.

All organs of immune system are divided to central and peripheral. Central organs of immune system are red bone marrow, bursa Fabricius (in birds), thymus. The function of central immune organs is antigeindpendent differentiation of immune cells. It results in formation specific surface receptors on immune cells. Peripheral organs of immune system are spleen, lymph nodes, tonsils, appendix vermiformix, solitary and aggregated lymphoid follicles. The main function of the organs is antigendependent differentiation of immune cells. It results in formation of immune cells directed on elimination of particular antigen.

Immune competent tissues are reticular tissue, llymphoid tissue, myeloid tissue and LICT.

Immune competent cells are macrophages, lymphocytes, granulocytes, mast cells, natural killers. They will be discussed below.

Functions of immune system: 1) Integration and regulation. Immune system is one from four regulatory systems (other are nervous, circulatory, endocrine). The cells of immune sytem can interact with almost all cells of an organism regulating their activity.

2) Maintaining of homeostasis. Immune system eliminate all foreign antigens, which were brought from outside or were formed inside.

3) Barrier-defense function. It is a protection of an organism from infectional (bacteria, viruses, parasites) and non-infectional antigens (malignant tumors, foreign grafts).

4) Regulation of cell division and cell apoptosis, cell regeneration and maintaining of tissue homeostasis.

Concept about antigens

Antigens – are foreign agents of compound organic nature, which can induce immune reactions. Most antigens are macromolecules such as proteins/ polysaccharides/ and occasionally lipids or nucleic acids. Molecules differ in their effectiveness in stimulating antibody production. Proteins and polysaccharides are generally good antigens/ whereas lipids and nucleic acids are rarely antigenic. Substances of low molecular weight (less than 10/000) do not make good antigens.

Antigens are usually foreign to the host and are recognized as such by the immune system. If this were not so/ an individual might respond immunologically against his or her own body constituents/ with the potential of producing tissue damage. If the body did not recognize foreign materials/ then bacteria and viruses could colonize the host and destroy it.

Antigens are large molecules. However, the immune response is not directed toward the entire antigen molecule but rather to specific chemical

groups on the molecule known as **antigenic determinants,** or **epitopes.** On large protein molecules, sequences of ten to twenty amino acids act as antigenic determinants. Complex structures such as most bacterial cell walls have 100 or more different antigenic determinants.

Sources of antigen, actual or potential, are:.. (a) viruses and microorganisms;.. (b) venoms;.. (c) inspired particles, e.g., fungi, pollen, dander;.. (d) foods;.. (e) semen;.. (f) the embryo;.. (g) transplanted tissues, e.g., skin;.. (h) altered autologous (own) cells, e.g., tumour products.. (i) some medicaments, e.g., penicillin.

Antibodies

Antibodies are proteins, which are produced in an organism as a response on antigens. They are able to selectively bind them and destroy them, thus providing humoral immunity. The antibodies are secreted by activated B-lymphocytes and plasma cells.

Plasma cells produce five kinds of immunoglobulins, which have the following characteristics:

1. IgG constitutes about 75 per cent of serum immunoglobulin, which provides binding sites for antigens. This immunoglobulin, produced by a mother, also provides protection for her newborn against infection because it can cross the placenta.
2. IgA is found in colostrum, saliva, tears, and nasal, bronchial, intestinal, prostatic, and vaginal secretions. It is synthesized by the mucosal epithelial cells. Another type of IgA and associated proteins are synthesized by plasma cells located in the mucosa of the digestive, respiratory, and urinary tracts.
3. IgM is important for early immune responses and may be bound to B lymphocytes, or it may circulate in the blood. The bound form (along with IgD) is a receptor for antigens, which leads to the differentiation of anti body- producing plasma cells. IgM can activate a group of plasma enzymes (complement) capable of lysing bacteria and other cells.
4. IgE is secreted by plasma cells and attaches itself to basophils and mast cells. When the antigen that induced IgE synthesis and secretion is once again encountered, the basophils and mast cells release their stored histamine, heparin, leucotrienes, and eosinophil chemotactic factor, resulting in an allergic reaction. Leucotrienes are important compounds mediating allergic reactions, such as in asthma, which are produced by mast and perhaps, other cells.

5. IgD is found on the surface membrane of B lymphocytes with IgM, but its function is uncertain.

Thus, of the immunoglobulins, IgM is considered the first line of defense. IgG has a long half-life and can cross the placenta, thus is ideally suited for passive immunization. IgA protects mainly the secretory surfaces (gastrointestinal tract and eyes) where there are nonvascular exposures to antigens and conditions that may interfere with the usual antibody activity, such as acid secretion, intestinal motility, and proteolytic enzymes. IgE is important in the release of pharmacologically active agents from mast cells and thus causes asthma and hayfever. It is also the major mechanism in the elimination of parasites. IgD is primarily a lymphocyte receptor, is the strongest binding antibody, and is important in directing antigen to B cell surfaces to accomplish initial immunization.

STRUCTURE OF ANTIBODIES (NEED TO BE INSERTED)

Immunocompetent cells

Immunocompetent cells are divided into several groups:

1. Antigen-presenting cells. (macrophages and monocytes, interdigitating cells, follicle-dendritic cells, some subpopulations of B-lymphocytes, M-cells of Peir's plaths)
2. Effectory cells. (T- and B-lymphocytes, NK-cells)
3. Regulatory cells. (T-helpers, T-supressors)
4. Accessory cells. (neutrophils, eosinophils, mast cells, NK-cells,)
5. Cells of immune memory. (long living T- and B-lymphocytes, interdigitating cells, follicle-dendritic cells)

DEFENSIVE CELLS AND MECHANISMS

1 Plasma cells (immunologically competent). 1 Develop from B lymphocytes via a transitional cell involved in rearranging its immunoglobulin genes for expression, first for the cell-surface, then for secretion.2 Synthesize and release specific *humoral antibodies* (immunoglobulins), after engagement with the presented antigens, and stimulations from helper T lymphocytes.3 *Immunoglobulins*:.. (a) bind and inactive the antigenic bodies;.. (b) neutralize toxins;.. (c) enhance phagocytosis;.. (d) trigger the activation of special blood proteins - *complement* factors - which amplify the immune response.4 Complement also binds to the antigen, potentiating the action of the bound antibody, and itself has lytic, signalling, and other effects. The three-part entity - antigen, antibody and complement - is an *immune complex*.

2 Lymphocytes (competent). 1 Start as stem cells of fetal haemopoietic tissue, but fall into two classes differing in where they were conditioned for distinct tasks.

- (a) *B lymphocytes* develop in the bone marrow from stock originating perhaps in the fetal liver, then populate germinal centres, and can proliferate and differentiate to become the sessile (non-moving) antibody-forming *plasma cells*;
- (b) *T lymphocytes* originate in marrow, develop and survive elimination in the thymus, are more mobile, and play many roles.

2 Both B and T lymphocytes seed out to populate the *secondary lymphoid organs*: spleen, nodes, and major mucosal lymphoid structures, and some lymphocytes then circulate. (Thymus, bone marrow, and fetal liver are primary lymphoid organs.)

3 *Roles* of the T lymphocyte

- (a) By gene rearrangement and selective expression, to offer a very broad range of T-cell receptors (one specific TCR per clone) for the diverse antigens that might be met.
- (b) Patrolling the body as a *naive* or virgin lymphocyte able to be stimulated by a new antigen taken up by macrophages or dendritic cells.
- (c) For some antigens, T lymphocytes *help* the humoral response of B lymphocytes.
- (d) Less often, they have a *suppressor* action on the B cell's response.
- (e) For certain antigens, e.g., virally-infected cells or foreign transplanted tissue, the stimulated lymphocyte proliferates, sending its progeny via the circulation as *cytolytic/cytotoxic* lymphocytes (CTLs) to attack the target cells at close range - the *cell-mediated response*.
- (f) *Cytolytic lymphocytes* /CTLs release substances that:
  - (i) lyse the target cells or organisms, e.g., *perforin*, which inserts uncontrollable pores into the target cell's membrane;
  - (ii) *Fas ligand* presented on the surface binds to the Fas/death receptor triggering apoptosis;
  - (iii) as *cytokines*, attract other leucocytes to the site of antigen,
  - (iv) activate naive lymphocytes and cause their proliferation,
  - (v) enhance leucocytes' phagocytic activity;
  - (vi) and trigger the release of histamine by basophils.

4 *Natural killer/NK cells* are marrow-derived lymphocytes that act early and independently of antigen presentation to attack tumour cells and infected cells, using membrane-damaging perforin, Fas ligand, and other agents.

5 Lymphocytes are classified by the reaction of certain of their surface glycoproteins to monoclonal antibodies. Thus, inducer/helpers are CD4+; cytolytic lymphocytes are CD8+; natural killer cells are CD3-, CD16+, CD56+; B lymphocytes are CD19+, etc. CD means *Cluster-of-Differentiation* antigens, and stems from the patterns of response of differentiating leucocytes to a great variety of monoclonal antibodies. It turns out that many kinds of cell aside from leucocytes express one or more of the antigens that the CD antibodies mark. These antigens only incidentally help characterize cells (e.g., marrow stem cells are CD34+), since they are working molecules - in adhesion and signalling, as enzymes, protective agents, etc.

6 Some T and B cells, having participated in an immune response to a certain antigen, patrol the body as long-lived *memory cells* ready to initiate an early and stronger secondary response, should the same antigen intrude again - the basis of *vaccination.*

7 The distinction between self- and non-self-recognition, and the acquisition of memory by lymphocytes, may be confounded by presentation of the antigen in high doses, by unusual routes, or in immaturity just after birth. The confused lymphocytes that result remember *to tolerate* an antigen, to which they should react. This tolerance is believed to be a byproduct of a normal mechanism, whereby all normal cells are telling circulating T lymphocytes, with receptors for the normal cells' materials, not to react, but to die.

3 Dendritic antigen-presenting cells (APCs) and Macrophages (accessory)1 APCs and macrophages/MOs concentrate some antigenic fragments on their surface, presenting them in a form more potent for stimulating lymphocytes.2 What is presented on the surface is a small peptide, derived by degradation from the antigen, bound to a *histocompatibility protein* (MHC class I or II depending on whether the antigen is of intracellular (self) or foreign/exogenous origin). Intracellular antigens presented in this way include materials that viruses have forced the cell to make.A non-sequitur: antigen-presentation is not limited to MOs and antigen-presenting cells. For example, B lymphocytes present antigen to T lymphocytes.3 Once activated by a particular antigen, lymphocytes and macrophages exchange cytokine messages to:.. (a) *recruit* more macrophages from the circulating monocytes;.. (b) *inhibit* macrophage migration to keep macrophages at hand;.. (c) *activate* macrophages to attack more vigorously the antigen by which the lymphocyte is activated, e.g., tuberculosis bacilli.(These cytokines convey simple 'doggy' orders: Come! Stay! Attack!) 4 Macrophages *phagocytose* toxins and cells killed

by other mmune actions, and make cytokine factors, e.g., chemotactic for neutrophils.5 Macrophages and other phagocytes liberate destructive enzymes and oxygen metabolites to lyse cells. They also digest matrix, e.g., by MO elastase, so that they themselves may move more freely. Enzymes may also be regurgitated in phagocytosis, or be spilled after death of the cell.To reduce the damage to surrounding tissues, extra-cellular degradative enzymes normally are neutralized by *protease inhibitors* in the plasma and tissues, such as *alpha l-antitrypsin.* 6 *'Tingible-body'* macrophages are in germinal centres. Their darkly stained (tingible) inclusion material is nuclear debris of apoptotic B lymphocytes that were selected against for not improving their affinity for antigen fast enough.

4 Granular leucocytes I *Neutrophils* respond in strength to certain bacterial and fungal infections, avidly ingesting, say, streptococci, dying, and often accumulating to become pus. 2 Neutrophils and eosinophils are attracted to immune complexes which they phagocytose, but the materials that they use to attack microbes and parasites also damage tissues, e.g., airway epithelium in allergies.

5 Mast cells I One kind of immunoglobulin (Ig) is already bound to their surface. Antigen entering the tissue bridges these *IgE* molecules, triggering the release of 2 *histamine*, which dilates vessels, increases their permeability and facilitates the exit of granular leucocytes, monocytes, antibodies, etc.3 *Heparin* may hold histamine and other factors ready for discharge; if released itself, it might, as a polyanion, bind and neutralize toxins. Among the many other mediators are bradykinin and factors attracting granulocytes - *chemokines.*4 The mast cell's reaction is an *immediate hypersensitive* one: the basis of allergies. An anaphylactic hypersensitive response in the airway lining is life-threatening, by overconstricting smooth muscle, and other effects.

Antigenindependent lymphocytopoiesis

It is a process of immune cell formation in central immune organs in absence of antigen. There are B- and T-antigenindependent lymphocytopoiesis. B-lymphocytopoiesis takes place in red bone marrow under influence of B-lymphopoietins, produced by stromal cells of red bone marrow. It has following stages: blood stem cell → CFU-Lymphocytes → pro B-lymphocyte → pre-pre B-lymphocyte → pre B-lymphocyte → immature B-lymphocyte → mature B-lymphocyte. The early stages are morphologically similar, the differences are in structure of surface antigens. The pre-B-lymphocyte starts to produce IgM. In immature B-lymphocyte Igm is expressed on cytolemm. In mature B-

lymphocyte IgD appears. Morphologially pre-pre and pre B-lymphocytes are similar to B-lymphoblast, whereas immature lymphocyte to small lymphocyte.

T-antigenindependent lymphocytopoiesis takes place in thymus. Pro T-lymphocyte leave bone marrow and travel to thymus. The hormone of thymus (thymosin) stimulates lymphocytopoiesis. It has following stages: blood stem cell → CFU-Lymphocytes →pro T-lymphocyte → pre T-lymphocyte → immature T-lymphocyte → mature T-lymphocyte. Pro-T-lymphocyte has no genome changes. It travels to thymus, where it is transformed to pre T-lymphocyte. Pre T-lymphocyte has activated genome and it expresses surface markers. Immature T-lymphocyte select surface markers and eliminate markers of immature cells. Thus it becomes mature t-lymphocyte. Morphologially pre T-lymphocytes are similar to T-lymphoblast, whereas immature lymphocyte to small lymphocyte.

Antigendependent lymphocytopoiesis

The lymphocytes, which are made after antigenindependent lymphocytopoiesis, are "naive" or inactive. Their further development takes place in peripheral immune organs in T- and B-dependent zones. This development is triggered by antigen and that is why this developmet called antigendependent lymphocytopoiesis or immunogenesis. After last-transformation reaacction naïve T-lymphocytes become T-immunoblasts, which are inclined to differentiation to effectory cells and memory cells.

T-dependent zones of peripheral immune organs are paracortical zone of lymph node, peryartherial zone of spleen, interfollicular zones in appendix, tonsils, Peyer's platelet. There are interdigitatig cells, macrophages in the zones. They make an environment for T-lymphocytes and transmit information about antigen to them. Moreover, there is special type of vessels in T-dependent zones – postcapillary venules with high endothelium. Here is the place of lymphocyte migration to/from blood. The height of endotheliocytes can be changed regulating rate of migration.

B-dependent zones of peripheral immune organs are the zones where antigenindependent differentiation of B-lymphocytes takes place. B-lymphocytes are subject to blasttransformation reaction and become either plasmoblast or B-lymphocytes of memory. There are also follicular dendritic cells, which make microenvironment for B-lymphocytes and transmit information to them. They also participate in immune memory.

General scheme of humoral immunity

1. Antigen enter B-dependent zones of peripheral lymphoid organs with blood or lymph.

2. Antigen is taken by macrophages or follicular dendritic cells.
3. These cells transform antigen to highly immune form and than express it on their surface binding to Major Histocompartibility Complex (MHC) molecules of class II. Highly immune antigen and IL-1 stimulate naïve B-lymphocytes and T-helpers type 2 (Th2).
4. Th2 produce IL-4, Il-10 and other interleukins, which are additional stimul for naïve B-lymphocytes.
5. Stimulated b-lymphocytes are subject to blasttransformation reaction. Blat cells are cells which are able to mitotic divisions. Thus the cell number rapidly increases.
6. The cells are subject to differentiation. As result if it we have B-lymphocytes of memory, plasma cells (plasmablast → proplasmacyte→ plasma cell), B-supressor cells. Plasma cells produce antibodies against that antigen, which have induced blasttransformation reaction.

General scheme of cell mediated immunity

In this case antigens are located on a surface a foreign or modified cell. These cells can get to lymphoid organs by their own and induce immune response. Moreover, the antigen can come off from their surface and induce response alone. The steps are the following:

1. Antigen travels to T-dependent zones of peripheral immune organs.
2. The macrophages and interdigitating cells take the antigen. They process the antigen and express it on their surface binding to Major Histocompartibility Complex (MHC) molecules of class II.
3. IL-1 and MHC-antigen complex stimulate Thelpers type 2 (Th2).
4. Th2 secretes IL-2, Tumor Necrosis Factor and γ-interferon.
5. Il-2 and antigen stimulate T-lymphocytes. This cause blasttransformation of T-lymphocytes. Thus the cell number rapidly increases.
6. As a result of the differentiation we have T-helpers/inductors, T-supressors/cytotoxic (transforming to T-killers), and T-lymphocytes of memory

THE WAY HOW IT WORKS NEED TO BE ADDED

The thymus

The thymus is one of the two primary lymphoid organs (the other being the bone marrow). The organ is also part of the neuroendocrine axis of the body, and it both influences and is influenced by the products of this axis. Its activity, therefore, varies throughout life under the influence of

different physiological states, disease conditions and chemical insults such as drugs and pollutants.

The thymus varies in size and undergoes structural alterations with age. It is largest in the early part of life up to the age of about 15, although it persists actively into old age. It undergoes rapid growth until the end of the second year, after which time the rate of growth slows until approximately the fourteenth year. After this, the thymus begins to involute or decrease in size, and, gradually, the lymphatic tissue is largely replaced by fat and connective tissue. In old age, very little thymic tissue may be present.

It is a soft, bilobed organ, its two parts lying close together side by side, joined in the midline by connective tissue which merges with the capsule of each lobe. Each lobe contains many lobules, which are 0.5 to 2 mm in diameter and which are incompletely separated from each other.

In children it is more pyramidal in shape and firmer than in later life, when its lymphoid content is reduced. In the fresh state it is deep red due to its rich vascular supply; with age it becomes thinner and greyer before yellowing as adipose tissue infiltrates the organ, a process which is independent of obesity.

Its weight also varies with age; at birth it is 10-15 g and rapidly increases to about 20 g, then remains at that level thereafter, although the amount of lymphoid tissue gradually decreases. Each of the two lobes is partially divided by the ingrowth of shallow septa so that superficially it appears lobulated; as fatty atrophy proceeds during ageing this lobulation becomes more distinct.

The older thymus can be distinguished from the surrounding mediastinal fat only by the presence of its capsule, although even within greatly atrophied glands there are usually greyer areas around blood vessels, formed by persistent lymphoid tissue. It is responsible for the provision of thymus-processed lymphocytes (T lymphocytes) to the whole body.

The thymus provides a unique microenvironment in which the T-cell precursors (thymocytes) undergo development, differentiation and clonal expansion; during this process, the exquisite specificity of T-cell responses is acquired, as also is their immune tolerance to the body's own components. These steps involve intimate interactions between thymocytes and other cells (mainly epithelial cells and antigen-presenting cells) and chemical factors of the thymic environment.

The thymus is derived from the number of sources, including epithelial derivatives of the pharyngeal wall, mesenchyme,

haemolymphoid cells and vascular tissue. These form distinctive components within the mature thymus, interacting functionally to create its unique immunological properties

The thymus is seen to consist of an outer cortex of densely packed cells mainly of the T-lymphocyte lineage, the thymocytes, and an inner medulla rich in connective tissue but with fewer lymphoid cells. The cortex consists of lymphocytes, which are densely and uniformly packed, obscuring the sparse reticular framework. The cortex lacks lymph nodules. Both lobes have a loose fibrous connective tissue **capsule**, from which **septa** penetrate to the junction of the cortex and medulla, to partially separate the irregular lobules, each 0.5-2.0 mm in diameter. A loose network of interconnected thymic epithelial cells permeates the cortex and medulla. In each lobule, the cortex has a superficial outer cortical region (subcapsular cortex) composed of a narrow band of cells immediately beneath the capsule, and the main cortex which is much more extensive.

The central core of both thymic lobes is composed of a **medulla** which is continuous from one lobule to the next. The lobulations are partially separated from each other by connective tissue septa that form a route of entry and exit for blood vessels, efferent lymphatics and nerves. Most cells enter or leave the thymus by this route. The medulla stains less intensely as a result of thinning of the concentration of lymphocytes, and it is here that reticular cells can be recognized. Hassall's thymic corpuscles, located in the medulla, are diagnostic for identifying the thymus. The diameter of Hassall's corpuscles varies from 20 to 150 μm. The origin and nature of Hassall's corpuscles is unknown but may represent degeneration residue.

Unlike other lymphoid structures, where the supportive framework is chiefly collagenous reticular tissue, the thymus is permeated by a network of interconnected epithelial cells (thymic epitheliocytes) between which lodge lymphoid and other cells of the organ.

There is only a little reticulin and few fibroblasts. By cell-cell contact and the release of soluble factors, the epitheliocytes create the microenvironments necessary for the thymocytes to develop.

Epitheliocytes vary in size and shape in the different positions within the thymus. Typically they have pale, oval nuclei, a rather eosinophilic cytoplasm and desmosomal attachments between cells. Intermediate (keratin) filament bundles lie within the cytoplasm. These cells form a continuous external lining to the thymus beneath its fibrous capsule, following its lobulated profile and investing the vessels which pass into it.

Other cortical epitheliocytes are branched, with large spaces between them, while those of the medulla tend to form more solid cords as well as the characteristic whorls of (often) partially keratinized stratified epithelium (thymic or Hassall's. corpuscles).

Lymphocytes lie within the meshes and cords formed by these various cells. There is much evidence that many distinctive functional roles are subserved by the epithelial cells, some of them related to the differentiation of T lymphocytes, others to the production of soluble thymic factors or hormones or to barrier and mechanically supportive functions. Of special significance, however, is their role in MHC restriction of T-cell immune responses

In the human thymus, the epitheliocytes have been divided morphologically into Types 1-6 and also characterized immunohistochemically. There is considerable heterogeneity within these classes, and the two methods of analysis give slightly different results. Immunological reagents generally distinguish subcapsular, cortical and medullary epitheliocytes as well as Hassall's corpuscles.

Some subcapsular and medullary cells share the same epitopes. According to the morphological classification, Type 1 epitheliocytes (subcapsular-perivascular) create the continuous monolayer around the perimeter of the thymus, extending along the septa to the corticomedullary boundary and forming an outer limit to the perivascular spaces.

Capillaries within the cortex are similarly en-sheathed, but medullary blood vessels are not. Type 1 cells are flattened, have a distinct basal lamina and are connected to adjacent cells by desmosomes.

Morphologically they are distinguished from Type 2 cells by their shape and the lower content of short lengths of granular endoplasmic reticulum, fewer small electron-dense granules and the presence of a distinctive tubular complex of unknown significance.

Like most other thymic epitheliocytes, Type 1 cells have MCCII-positive surfaces, apart from their capsule-facing aspects which are MHCII-negative. Type 1 cells secrete factors that attract stem cells to the thymus, and thymic hormones.

Type 2 cells extend from the outer cortex towards the medulla forming a series of cells in contact with Types 3 and 4 epithelial cells. Types 2 and 3 cells are large, with long cytoplasmic extensions (sometimes extending 100u.m from the nucleus). They are active cells with numerous cytoplasmic vesicles, several small Golji bodies and many small electron-dense granules.

Type 2 cells are more electron lucent than Type 3 cells which are, in turn, paler than the smaller very dense Type 4 cells. All cortical epitheliocytes are closely apposed to thymocytes, sometimes apparently engulfing them (emperiopoleisis). Large epitheliocytes with many associated thymocytes (50 or more) are called thymic nurse cells (TNC). These may be a special subset of Type 2 or 3 cells. They also contain mRNA for oxytocin and vasopressin, unlike most other cortical epithelial cells.

Type 5 cells are a small subset of medullary epithelial cells that appear to be relatively unspecialized. Type 6 cells are the commonest in the medulla, although several subsets may occur. Their forms range from spindle-shaped cells secreting thymic hormones to flattened cells forming Hassall's corpuscles.

Hassall's corpuscles are balls of flattened medullary epithelial cells from 30 to 100 μn in diameter which are characteristic features of the thymus. They start to form before birth and their numbers increase throughout life, often showing periods of increase or decrease. Their function is not clear, although in the past it has been suggested that they are graveyards for thymic cells, or regions where immunoglobulins are concentrated. The center of the corpuscle often contains cellular debris and sometimes eosinophils.

Some thymic epitheliocytes can be immunostained with antibodies against neuropeptides and in rodents, cell with phenotypic and biochemical markers for both neurons and epithelial cells have been described in thymic cultures.

These include cells of the ***mononuclear phagocyte system, fibroblasts and myoid cells.***

Cells of the mononuclear phagocyte system (macrophage lineage cells). These are found as monocytes at the corticomedullary junction, as mature macrophages in the cortex and as interdigitating cells in the medulla. In rodents, two types of cortical macrophages have been described, one a phagocytic cell capable of engulfing duing (apoptotic) thymocytes, the other producing proliferative factors for thymocyte development. The interdigitating cells are antigenpresenting cells similar to those found in other lymphoid organs and are thought to be able to present antigens to the maturing T cells as they migrate from the cortex into the medulla, the medulla acting as a secondary lymphoid organ in this respect. Interdigitating cells are large, with characteristic infoldings of the plasma membrane and do not generally contain phagocytic inclusions.

Fibroblasts. They are found in the capsule, perivascular spaces; and medulla, but are infrequent in the cortex, except in involuted glands. Short-range or contact interactions between thymocytes) Class II MHC positive epitheliocytes and mesenchymal cells (or a fibroblast cell line) have been found to be necessary for the in vitro development of thymocytes.

Myoid cells. These cells are situated mainly in the medulla and at the corticomedullar junction. They are large, rounded cells, with a central nucleus surrounded by irregularly arranged bundles of myofilaments. In lower vertebrates, where myoid cells are often more numerous, these cells are joined to neighbouring medullary epithelial cells by desmosomes. Their functions are unknown, although it has been suggested that their contractions might aid the movement of lymphoid cells across or out of the gland.

Lymphocytic population, thymocytes

In the cortex, massive numbers of densely packed small thymocytes (thymic lymphocytes) predominate, occupying the interstices of the epithelial reticulum, which in histological sections they largely obscure, and forming about 90% of the total weight of the thymus.

A distinct subcapsular zone is present, housing the thymic stem cells, prothymocytes and lymphoblasts undergoing mitotic division. The first stem cells to enter the thymus in the embryo come from the yolk sac and liver during their haemopoietic phases, possibly, as in birds, being attracted by thymic chemotactic substances. During later periods it is probable that all thymic lymphocytes originate in the bone marrow, or at least have sojourned there, before passing in the bloodstream to the thymus.

The cortex has two rather ill-defined zones: an outer cortex with a framework of Types 1-3 epitheliocytes and a deep cortex where Type 4 cells occur. Thymocytes undergo mitosis in all cortical zones as the clones of differentiating T cells mature, gradually moving deeper in the cortex. In rodents, cell cycling times of 8 hours have been recorded in the outer cortex, but no estimates exist for the human thymus.

The appropriate conditions for the proliferation and differentiation of thymocytes appear to be produced by their close proximity to neighbouring epitheliocytes.

Although the nature of these interactions is not clear, it may involve the release from the epitheliocytes of soluble mitogenic and differentiation factors as well as induction of changes through intercellular contact. During this process, thymocytes differentiate along the T-cell line, acquiring the CD3 + marker and T-cell receptors, and also switching into

different subclasses of T cells. The great range of different T-cell receptor types, running into many millions, is also established here by the expression of variable genes and related mechanism

As time passes, the differentiating thymocytes enter the medulla, and migrate through the walls of venules and lymphatics to move into the circulation. Such cells (post-thymic thymocytes) are not immunocompetent within the cortex, and in general attain maturity only after entering the medulla or perhaps not until they reach their secondary lymphoid tissue destinations.

However, the existence of antigen presenting cells and plasma cells in the medulla indicates that T lymphocytes can be activated within the thymus, if not in large numbers.

Thymocyte classes. Four major lymphoid cell types are found in the thymic cortex, as determined by immunocytochemistry and flow cytometry; each of them has a different proportion of small, medium and large thymocytes. Firstly, there are cells which do not express the mature T-lymphocyte markers $CD4^-$ or $CD8^-$ (double negative cells) nor, initially, CD3. Most of these are large blast cells, which after undergoing mitosis become small, double negative thymocytes and begin to develop the T-cell receptor (TCR) complex and become $CD8^+$-positive. These blast cells are primarily located in the subcapsular cortex and around blood vessels, especially at the corticomedullary junction. Than, cells garadually develop components of TCR and at the same time become double positive by expressing CD4.

The majority of these double-positive cells are small cortical thymocytes comprising 80-90% of the total thymocyte population. It is thought that the functional abilities of the T-cell repertoire is determined at this stage, with 'undesirable' lymphocytes dying in great numbers by apoptosis.

The few that are rescued by the action of factors from the micro-environment (positive selection) become either CD4- or CD8-positive (i.e. single rather than double positives); these cells are found in the medulla and are slightly larger than cortical thymocytes.

Medullary single-positive thymocytes may either be cells about to be exported to the periphery where they will become fully immunocompetent, or recirculating activated T cells which have entered the medulla secondarily. In addition, a few single positive cells represent early cortical cells that transiently express either CD4 or CD8 before becoming double-positive early thymocytes, as noted above.

In addition to these T-cell products, the thymus is also to be responsible for generating natural killer cell lineages.

The thymus often contains some immature B lymphocytes in medulla or around blood vessels at the corticomedullary junction and mature B cells (plasmacytes) throughout the thymus are perivascular spaces. These cells are not formed in the thymus arrive by immigration through the vasculature.

Arteries supplying the thymus follow the connective tissue septa and give off branches that enter the lobular cortex and break up into capillaries, which supply the cortex.

Epithelial reticular cells sequester developing lymphocytes and form a sheath covering capillaries and lymphatic vessels. The sheathing forms what is called the blood-thymus barrier, preventing antigen contamination of developing and programmed T lymphocytes. The blood-thymus barrier is not found in the medulla, which appears to have a richer blood supply than the cortex. The capillaries terminate in thin-walled veins located in the connective tissue septa along with arteries. Lymphatic vessels arise within the thymic lobule and join to form larger vessels, which accompany the arteries and veins in the septa. In contrast to lymph nodes, the thymus contains no lymph sinuses or afferent lymphatic vessels.

Chapter 18: The excretory system

Excretion of terminal products of metabolic processes is fundamental function of a body. Failure to do so can result in organism death. The main part of excretion is performed by urinary excretion system. Some volume of terminal metabolic products is excreted by skin, lungs, and alimentary system, but they are incompetent to maintain homeostasis when kidneys are damaged. The respiratory system excretes carbon dioxide as terminal metabolic product. Urianry excretion system consists of kidneys and urinary passages: urinary calyces, ureter, urinary bladder, urethra.

Kidneys

Functions: 1. Urine formation and excreting. It is in filtration and reabsorption of urine from blood flow and excreting it to urinary passages. The formed urine contains terminal products of nitrogen exchange and xenobiotics.

2. Maintaining of acid-base homeostasis. The kidneys participate in maintaining of acid-base homeostasis by three ways: a) regulation of

HCO_3^- level in blood; b) regeneration of HCO_3^- ions; c) H^+ secretion into urine.

3. Regulation of ion-water exchange. The kidneys are particular important in Na^+ homeostasis maintaining. The deviation in Na^+ excretion even on 1% can results in heavy disturbances in volume of intracellular fluid. Beside Na^+ the kidneys excrete K^+, Ca^{2+}, Mg^{2+}, Cl^- and other inorganic anions and they maintain constant level of these minerals in an organism.

4. Regulation of arterial pressure. It is performed by regulation of Na^+ concentration in blood and by rennin-angiotesin-aldosterone system.

5. Endocrine function and synthesis of biologically active substances. Rennin, erythropoietin, erythrogenin, prostaglandins, biogenic amines, D_3 vitamin, kininogenin and some of interleukins are produced in kidneys. Rennin is a part of rennin-angiotesin-aldosterone system, which regulates Na^+ concentration and blood pressure. Erythropoietin stimulates proerythroblasts formation in bone marrow and release of erythrocytes from bone marrow. Erythrogenin facilitates conversion of erythropoietinogen to erythropoietin in blood plasma. Prostaglandins act as vasoconstrictors and regulate microcirculatory flow. Biogenic amines have the same effects. Kininogenin stimulates conversion of kininogens to kinins, which are vasodilatators. D_3 vitamin, after activation in kidney, increases calcium absorption in the intestine.

6. Participation in substances exchange, especially in protein and carbohydrates exchange. This function is very important for newborns. Due to having not fully developed digestion, the proteins are digested to oligopeptids (no to aminoacids). Oligopeptids have about 8-12 aminoacids in structure. They can be absorbed to the blood. The further degradation of oligopeptids occurs in proximal convoluted tubules. At the same time, the kidneys are important organ of gluconeogenesis.

7. Participation in blood coagulation system. It is concluded in production of urokinase (plasminogen activator) and factor of platelets activation.

All listed above functions show that kidney is vitally important organ. Lost of kidneys results in death.

Development. The kidney development is begun on 1st month of embryogenesis and is continued even after birth. The source of development is intermediate mesoderm – nephrotom. Human nephrotom is segmented in cranial part of embryo and it is not segmented in caudal part. This non-segmented part is called nephrogenic tissue. In kidney

development there are three stages: pronephros, mesonephros and metanephros.

The pronephros is developed from 8-10 anterior nephrotom segments. They form tubules – pronephridia (pronephric tubules). These tubules are opened to celomic cavity by ventral end and are connected with somites by dorsal end. They fuse with each other near somites forming so called pronephric ducts. It is transitory structure that regresses completely by week 5 of development and it not functional in humans.

On a second stage of embryogenesis, 25 pairs of nephrotom segments start to form primary kidney – mesonephros. These segments form S-shaped canalicules, called mesonephric tubules (or mesonephridia). Dorsal end of these tubules fuses with pronephric duct. After this fusing it is called mesonephric duct. Ventral end of these tubules extends toward vascular glomeruli, which are branched off from aorta. Tubules and vascular plexuses form renal body. Here, we have plasma filtration and partial reabsorption of it. But process of reabsorption is not well developed due to absent of specialized structures responsible for it. Mesonephros is active diuring 5 months of pregnancy, but than it reduces. But males use some of the mesonephric ducts for formation of some testis structures.

Metanephros (or definitive kidney) appears on 2^{nd} month of embryogenesis and it is functionally active on 5^{th} month. It is formed from non-segmented part of nephrotom – nephrogenic tissue and from mesonephric duct. Caudal end of mesonephral duct near entering a cloaca is branched on so called metanephritic diverticul. It enters nephrogenic tissue. Nephrogenic tissue is concentrated around the diverticul, forming nephrogenic blastema. Nephrogenic blastem is a source for formation of all nephron parts. The nephrogenic tissue preserves in children until 3 years old. It gives new nephrons. The metanephric diverticul gives rise to epithelium of collecting tubules, minor calyces, major calyces, renal pelvis, ureters. The vascular network of kidney and its connective tissue is originated from mesenchyme. The epithelium of different parts of urinary bladder has different origin: from allantois, mesonephric duct and partially from skin ectoderm.

Structure. The kidney is parenchymmal zonal organ. It is covered by capsule from dense connective tissue and by serous coat. Capsule gives up projections of LICT, which bringing vessels to the kidney parenchyma. Many mammalians have kidneys with lodes, but human's kidney is not divided into lobes. The kidney has cortex and medulla. The border between cortex and medulla isn't straight. Cortex enters medulla by columns of Bertin, whereas medulla by Ferreyn rays.

Cortex lies outside and it is divided by Ferreyn rays to separate regions. Medulla is made by medullar pyramids. They are separated one from another by columns of Bertin. The top of pyramid is called papilla. They look toward minor calyces, which than extends to major calyces and renal pelvis. Medullar pyramid and adjusted part of cortex is called renal lobe. Humans have about 10-18 lobes in the kidney.

Nephron histophysiology

Form of nephron and relations with cortex and medulla

Cortex

1 Renal corpuscle (round, 150-240 μm diameter) - *glomerulus* of epithelium-invested capillaries, and enclosed in a *Bowman's capsule*, opening out at the urinary pole into the 2 *proximal convoluted tubule*, which leads to the

Medulla

3 *descending limb* of the hairpin loop of Henle, 4 then the *ascending limb* of Henle's loop.

Cortex

5 *Distal convoluted tubule* follows, attached at one point to the renal corpuscle of origin; thence leading to an 6 *arched collecting/junctional tubule* joining a

Medulla

7 *straight collecting tubule*, receiving many branches and running down from a medullary ray through the medulla to a 8 *papillary duct of Bellini*, opening at the papilla of the pyramid. The papilla is cribriform from the many openings.

Thin segments and loops vary in length dependent on the position in the cortex of their glomeruli of origin. The appearance of the kidneys is dominated by the nephrons, since the connective tissue element (reticular fibres) is slight, and the very many small blood vessels follow the pattern of the nephrons, because the two work together.

3 Functional unit of the kidney. Consists of (a) nephron, (b) blood vessels, (c) interstitium, and (d) collecting tubule. The functions of the various parts of the unit are given briefly, so that all aspects of the finer structure can be presented together.

1 *Renal corpuscle*, with vascular glomerulus - ultrafiltration of arterial blood.

2 *Proximal convoluted tubule* - from the ultra-filtrate received from the corpuscle, the prompt massive recovery (reabsorption), by active transport,

cotransport, facilitated and downhill diffusion, of sodium, chloride, glucose, amino acids, etc, and of small proteins by endocytosis.
3 *Loop of Henle* - urine concentration by active and passive functions in a complicated counter-current osmotic multiplier interaction of loops of Henle, blood vessels, interstitium, and collecting tubules.
4 *Distal tubule* (partly in the loop) - continued active reabsorption of Na^+ under the control of aldosterone, and the secretion of potassium.
5 *Collecting tubule* - passive reabsorption of water to the blood, making the urine hypertonic, under the influence of pituitary antidiuretic hormone (ADH); and a variety of fine adjustments to electrolytes and acidity.
6 The nephron is controlled by hormones from other endocrine glands, but the kidney itself produces hormones that affect non-renal tissues.

4 Nephron cytology

1 *Glomerulus*

- (a) Blood is fed, via an *afferent arteriole*, under pressure into groups of capillaries, tufting out as loops from the vascular pole, and ensheathed in *visceral squamous epithelium.*
- (b) *Glomerular wall* of. (i) *fenestrated endothelium*, (ii) *thick basal lamina* (two laminae fused together), (iii) *podocytes' pedicels* (visceral epithelial cells' feet), separated by filtration slits of controllable width, permit
- (c) the *filtration* of water and solutes, with a molecular mass less than 30 kDa, into a *capsular space* between
- (d) glomerular/visceral epithelium and the parietal squamous epithelium and BL of Bowman's capsule.
- (e) The altered blood is collected from the capillary tufts, and passes out via the narrower *efferent arteriole.*
- (f) Between the capillaries at their base lie *mesangial cells*, synthesizing and maintaining the glomerular basal lamina, and also probably phagocytic and contractile. Mesangial cells are significantly involved in renal disease, e.g., in diabetes and glomerular nephritis.

2 *Proximal tubule* (40-50 μm diameter)

- (a) Most common of those tubules seen in the sectioned cortex, since it is longer than the distal tubule.
- (b) Simple, acidophilic, cuboidal, epithelial lining cells with: large round nuclei;
- (c) very many microvilli (brush border), and a surface glycoprotein coat containing peptidases to reduce polypeptides;

- (d) vesicles and lysosomes just below the microvilli, and involved in endocytotic protein uptake and breakdown to amino acids;
- (e) marked lateral membrane infoldings and interdigitation with adjacent cells,
- (f) to which they attach with junctional complexes.
- (g) The basal region has many membrane infoldings and long mitochondria (*basal striation*) for the provision of energy for active transport of Na^+, and with it glucose and amino acids, through the basolateral membrane,
- (h) basal lamina, and thence into adjacent capillaries, with their fenestrated endothelium.

3 *Thin segment* (15 μm diameter)

- (a) Squamous epithelial lining on a BL.
- (b) Cells are pale, tightly fastened, with small, short microvilli, and a few mitochondria scattered randomly.
- (c) The lack of red blood corpuscles in the lumen, and plumper nuclei, distinguish thin segments from capillaries.

4 *Distal tubule* (20-50 μm diameter)

- (a) Weakly acidophilic, cuboidal epithelial cells enclose large lumens.
- (b) No brush border is seen because only a few short microvilli are present.
- (c) Basal infoldings and interdigitations, with very many long mitochondria, give a basal striation.
- (d) Cells lie on a BL, also supporting fenestrated endothelial cells of the surrounding capillaries.
- (e) *Macula densa* is a specialized, more nucleated region of the epithelium, where it attaches to the arterioles of the glomerulus to form part of the juxtaglomerular apparatus. It senses the $[Cl^-]$ locally in the distal tubule and signals, via mesangial cells, for renin release, and arteriolar and mesangial contraction.

6 *Collecting duct* (40-200 μm diameter)

- (a) Pale cuboidal cells, with the lateral cell membranes prominent because lateral interdigitation is lacking, are of three kinds:
- (b) principal collecting-duct cells, and, set between them, alpha/A and beta/B intercalated cells, all differing in their ion-transport roles.
- (c) *Principal cells* have few microvilli, and few mitochondria, but are tightly connected by occluding junctions. *Aquaporin 2* constructs the channels making the luminal cell membrane permeable to water in the presence of vasopressin/ADH, so that the cells reabsorb water.

Basolaterally, a membrane Na,K-ATPase lets the cells secrete potassium, while absorbing sodium.

- (d) *Intercalated cells* have darker cytoplasm, and more and darker mitochondria, than principal cells. The number of vesicles is highly variable, because they function to insert or remove ion pumps into the cell membrane, in a similar way to the gastric parietal cell.
- (e) Type A intercalated cells bear a luminal-membrane H,K-ATPase to secrete hydrogen ions and reabsorb potassium; type B cells have a luminal Cl/HCO_3^- countertransporter to secrete bicarbonate and recover chloride.
- (f) A simple columnar epithelium lines the final papillary ducts of Bellini, and covers the papillae.

5 Renal interstitium

1 lies between the kidney tubules and vessels.

2 It comprises: (a) reticular fibres, (b) a little ground substance, and (c) interstitial fibroblasts, looking after the matrix and secreting erythropoietin.

3 The interstitial elements are more prominent in the medulla than the cortex.

6 Renal blood vessels

1 *Renal artery* branches to form

2 *interlobar arteries* (interpyramidal), extending to the cortico-medullary junction, where they branch and turn as arching

3 *arcuate arteries*, giving off outward branches called

4 *interlobular arteries*; from which

5 *intralobular arteries* provide

6 *afferent arterioles* to

7 *glomeruli*; from the capillaries of which the blood is taken via

8 *efferent arterioles* to serve one or both of

9 *two capillary beds* - around the convoluted tubules, and between the straight medullary tubules.

10 The blood collected in *stellate, deep cortical*, and *interlobular* veins, traces back the arterial path to the *renal vein.*

11 The sympathetic nervous supply to the kidney goes mainly to the renal vasculature, including the juxtaglomerular cells.

12 *Vasa recta* is a collective name for arteriolar, capillary, and venous *straight* blood vessels in the medulla. They participate in the counter-current exchange.

Juxtaglomerular apparatus

To make primary urine it is necessary to maintain blood pressure on level 70-90 mm of mercury. If it is lower than this, it may cause filtration failure and toxic products accumulation in an organism. That is why arterial pressure in renal vessels is strictly regulated. The mechanisms of arterial pressure maintaing are neiroendocrine. Among them one of most important is juxtaglomerular apparatus (JGA). This apparatus produce enzyme – rennin, which is needed to activate angiotensin II – the strongest vascular pressing factor. Rennin also stimulates producing of aldosteron in adrenal cortex. Aldosterone is needed for Na^+ reabsorption in distal tubules and collecting tubules. It causes increasing of circulating blood volume and consequently rising of arterial pressure. The described system of arterial pressure regulation is called rennin-angiotensin- aldosterone system.

There are following cell types in JGA:

1. Juxtaglomerular cells. They are cells of tunica muscularis of afferent or (lesser) defferent arterioles. They are muscular cells in nature, but secretory cells by function. They contain protein producing apparatus and rennin granules. The second feature of juxtaglomerular cells is having of barorecetive properties – the cells can recept AP fall lower necessary level. After this perception they secrete rennin to a blood.
2. Cells of macula densa. These cells (about 20-40) are cells of distal convoluted tubule adjusted to glomerulus. The basement membrane here is very thin or even absent. The cells have processes, which enter between juxtaglomerular and juxtamedullar cells. They are osmoreceptive cells. They percept and transmit information about Na^+ concentration in distal tubules to juxtaglomerular and juxtamedullar cells. If concentration exceeds the level, juxtaglomerular cells produce rennin, which stimulates aldosterone synthesis. Aldosterone activate Na^+ reabsorption, thus decreasing it's concentration in urine. By the way, signals from macula densa cells can reduce Na^+ filtration in Malpigian body.
3. Juxtavascular cells or cell of Goormatigh (lacis cells). They lie in triangular space between afferent and defferent arterioles. They contain rennin granules. It is considered that these cells start to secrete rennin when juxtaglomerular cells are depleted. They also can transmit information from macula densa cells to vessels of glomerulus.

4. Mesangial cells. Part of the can produce rennin when juxtaglomerular cells are depleted. Basing on this finding some authors also include them to JGA.

Stimulation of JGA. It is performed by followinf ways:

1. As result of activation of baroreceptors of juxtaglomerular cells while arterial pressure fall.
2. As result of activation osmoreceptors of macula densa cells on response of decreasing blood circulating volume.
3. As result of sympathetic system activation. The rennin secretion under sympathetic system influence takes place while hemorrhage and blood lost and while orthostatic reactions.
4. Accordinary to feedback principle, the rennin synthesis may be stimulated under influence of other components of rennin-angiotensin- aldosterone system, prostaglandins and bradikinin. The failure of regulatory mechanisms of rennin secretion may results in renal hypertension.

Apart to hypertension system, there is hypotension system in the kidney. It includes intersticial cells of medulla and light cells of collecting tubules. Interstitial cells have processes which surround capillaries of secondary network and nephron tubules. The population of interstitial cells is heterogeneous. Some of them produce bradikinin, which is strong vasodilatator. Another part of them and light cells of collecting tubules produce prostaglandins.

Other endocrine functions of kidneys. Apart to rennin and prostaglandins the kidney produces erythropoietin, which stimulates erythropoiesis. It is produced by (juxtaglomerular, juxtavascular cells and podocytes). The biogenic amines are also produced. Among them the important one is bradikinin, produced by interstitial cells of medulla. Vitamin D_3 is activated in kidney also. The cells of distal part of nephron produce kininogenin (kallekrein), which dilates vessels, increase blood flow in kidney and increase diuresis.

Innervation of kidneys. Sensory innervation is performed by Th10, 11, 12 and L1, 2 spinal ganglia and by sensory nucleus of nervus vagus. Efferent sympathetic innervation is performed by nuclei of lateral horns from lower thoracic and upper lumbal segments of spinal cord. Parasympathetic innervation is performed by nervus vagus and partially by intermediate nuclei of lateral horn of sacral part of parasympathetic nervous system. Nervous fibers surround renal tubules, glomerulus, components of JGA. It is important to emphasize that vessels of kidney have both sympathetic and parasympathetic innervation. Stimulation of

sympathetic nervous system leads to vessels constriction and JGA stimulation, whereas parasympathetic system has adverse effects.

Regeneration of kidney. *Physiological regeneration* of kidney is performed mainly on intracellular level, by hypertrophy of cellular organelles, because cells of proximal and distal parts have minimal proliferative activity. Overwise, cells of convoluted tubules can regenerate due to cell division. *Reparative regeneration* of kidneys is provided by the same mechanisms. When proximal and distal parts are damaged, the good intracellular regeneration is possible even if a very few cytoplasm stays safe. At the same time nephrocytes of the distal part can change enzymatic patern and take some functions of proximal part. If a nephron is totally damaged, the neighboring nephrons are enlarged and take their function. But new nephrons isn't formed (exception is young age of patient). If one kidney is removed, the second is subject to hypertrophy and take double load.

Allotransplantation of kidney. Nowadays, the alotransplantation of kidney is widely used in clinic. The indication for it is chronic renal failure. The kidney from close relatives or from cadavers is used for this purposes. This procedure should be accompanied by strict HLA testing of donor and recipient.

Urinary passages

The urinary passages are minor and major calyces, renal pelvis, ureter, urinary bladder, and urethra. All of them are organs which are made of coats. They contain 4 coats: mucosa, submucosa, muscular and adventitial (or serous). The epithelium and lamina propria mucosaee are thin in calyces, but they have maximal width in urinary bladder. Submucosa is absent in pelvis and calyces, but well developed in uterus and urinary bladder. Muscular coat is thin in calyces and pelvis and is presented but circular layer only. The upper two thirds of ureter have two muscular layers. The lower one third and urinary bladder have three layers of muscles.

Ureter. The wall of uterus consists of four coats. The mucosa has folds and lamina propria. It gradually merges to submucosa. The epithelium is transitional. The number of layers in transitional epithelium depends of functional state of the organ. When ureter is filled by urine, the epithelium is stretched and has only two layers. When ureter is empted, the epithelium is shrunken and has many layers. The transitional epithelium lining of urinary bladder is capable of withstanding osmotic changes

caused by variation in concentration of urine. It is also resistant to toxic substances present in urine.

Urinary bladder. The structure of coats is similar to ureters. The submucosa is made of LICT and has no glands. It is absent in the "triangle of urinary bladder". It is the region between mouths of ureters and mouth of urethra. Perhaps, the folds of mucosa are absent here. The muscular coat is made of three layers. The external coat is adventitial, excluding posterior and lateral surfaces, where it is serous.

Educational edition

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SELECTED THEMES OF HISTOLOGY, CYTOLOGY AND EMBRYOLOGY CORE
Studying manual

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