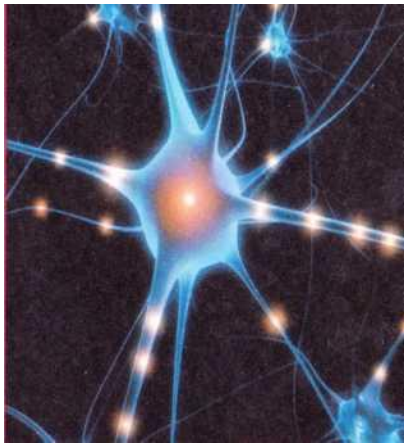
HISTOLOGY

CYTOLOGY

EMBRYOLOGY



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Recommended

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ISBN 978-617-579-260-5

This text contains the concise thorough presentation of Cytology, Embryology, General and Special Histology, based on modem information of functional morphology of cells, tissues, different organs and systems.

This text was created on the basis of the systematized lecture course on Histology, Cytology and Embryology which is delivered at the Histology, Cytology and Embryology Department of State institution «Lugansk State Medical University)) for the students of the Faculties of Medicine and Dentistry.

Edition is oriented to the effective learning or revision of course of Cytology, Embryology, General and Special Histology and meant for the students in the health professions and advanced undergraduates.

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ABBREVIATIONS

AIDS	acquired immune deficiency syndrome
ACTH	adrenocorticotropic hormone
ADH	antidiuretic hormone
APC	antigen-presenting cell
A PUD	amine precursor uptake decarboxylase
ATP	adenosine triphosphate
BFII	burst-forming unit
CFC	colony-forming cell
CFU	colony-forming unit
CNS	central nervous system
CRH	corticotrophin-realising hormone
DNA	deoxyribonucleic acid
ECF-A	eosinophil chemotactic factor of anaphylaxis
FSH	follicle-stimulating hormone
fill	growth hormone
GHRH	growth hormone-realising hormone
Hb	hemoglobin
hcc;	human chorionic gonadotropin
IIIV	human immunodeficiency virus
IiPt	Human placental lactogen
Iᴋ	immunoglobulin
IL	interleukin
IVF	in vitro fertilization
LH	luteinizing hormone
LPH	lipotropic hormone
MHC	ma or histocompatibility complex
MSH	me anocyte-stimulating hormone
NETs	neutrophil extracellular traps
NK	natura killer
NPC	nuclear pore complex
PALS	periarterial lymphatic sheath
PNS	peripheral nervous system
PP	pancreatic polypeptide
PRL	prolactin
PTH	parathyroid hormone (parathormone')
RER	rough endoplasmic reticulum
RNA	ribonucleic acid
SER	smooth endoplasmic reticulum
SR	sarcoplasmic reticulum
T,	triiodothyronine
T_4	tetraiodothyronine
TNF	tumor necrosis factor
TRH	thyrotropin-releasing hormone
TSH	thyroid-stimulating hormone
VIP	vasoactive intestinal peptide

PREFACE

This text is based on the content of lecture course on Histology, Cytology and Embryology which is delivered at the Histology, Cytology and Embryology Department of State establishment «Lugansk State Medical TJniversity» for the students of the Faculties of Medicine and Dentistry.

Histology, the study of cellular and tissue structure, is the key to integrating all of cell biology, anatomy with physiology, and biochemistry and the foundation of pathology.

Purpose: The purpose of this textbook is to provide the students with an understanding of basic histological structure and function. It also provides the students with an appreciation of the interaction of cells within and among the various tissues and organ systems. Such an understanding will lead to a better comprehension of the processes that occur in pathology and pathological physiology.

Audience: The book was written tor the students which are taught in accordance with the ***credit module educational system*** in the health professions, clinical interns, graduate students and doctors of different specialities.

Features: The chapters of this text are in appropriate order, starting with the basic tissues of the body ana proceeding to each of tne organ systems. The textbook includes an introductory chapter on laboratory methods used for the study of tissues, including the most important types of microscopy ("Histology and its method of study"). Separate chapters focus on the cytoplasmic and nuclear compartments of the cell ("Cell. Cell membrane. Cytoplasm. Organelles. Inclusions" and "Nucleus. Cell cycle. Cell division"), followed by chapters on the four basic tissues of the body. Individual chapters are devoted to the bases of general embryology and human embryology and also to each of the organ systems.

More than 300 illustrations which are contained in a book include schematic diagrams, photomicrographs and electron micrographs. Expanded legends that accompany each figure emphasize important points and eliminate the need to jump from image to text. Figures and their legends include key points to facilitate preview or review study of a chapter.

Because of medical orientation of course all of information is expounded as it applies to a human.

Terms used are fully consistent with the new ***Terminologia Histologica: International Terms for Human Cytology ami Histology*** and with standard usage in both clinical and basic sciences.

Clinical correlations explain the clinical relevance of each chapter.

Good Luck on your journey to really Understanding Histology, Cytology and Embryology!

£□ CHAPTER 1

HISTOLOGY AND ITS METHOD OF STUDY

Histology is the study of the microscopic anatomy of cells and tissues. Histology is an essential tool of biology and medicine.

Subdivisions of histology

Cytology is a science which is about the structure and functions of cells and their derivatives, their reproduction and interactions.

General histology examines the composition of each of the tissue types, including the nature of its cells and extracellular matrix.

Special histology is a science which is about the structure of organ systems.

Embryology is a science which is about the development of an embryo from the fertilization of the ovum to the fetal stage.

Fundamental theoretical problems of histology:

> studying of laws of cyto- and histogenesis, structures and functions of cells and tissues;

> studying of laws of a differentiation and regeneration of tissues;

y finding out of role of nervous, endocrine, immune systems of organism in regulation of processes of cells, tissues and organs and their functioning;

> research of age changes of cells, tissues, organs;

> research of adaptation of cells, tissues and organs to action of various biological, physical, chemical and other factors;

> studying of processes of morphogenesis in system mother - fetus;

> research of features human embryogenesis.

The ***cell theory*** refers to the idea that cells are the basic unit of structure in every living thing. Development of this theory' during the mid 17th century was made possible by advances in microscopy. This theory is one of the foundations of biology. Credit for developing cell

theory is usually given to three scientists: ***Theodor Schwann***, ***Matthias Jakob Schleiden,*** and ***Rudolf Virchow.***

Cell theory states:

> that the cell is the basic unit of living systems;
> that all organisms consist of at least one cell;
> that cells in multicellular organisms are often specialized;
> that all cells come from previous cells.

Cell

The ***cell*** is the structural and functional unit of the organism. Except for cells, in an organism there are their derivative, which have no the cellular structure (***intercellular matrix, postcellular structures, symplast, syncytium).***

Extracellular matrix (ECM) is produced by cells and excreted to the extracellular space within the tissues, serving as a scaffolding to hold tissues together and helping to determine their characteristics.

Postcellular structures are derivatives of cells which during a differentiation (more often owing to loss of a nucleus and a part of organelles) have lost the major signs of cells, but have got a number of the properties necessary for execution by them the specialized functions. The postcellular structures at human are erythrocytes, platelets, horny cells of epidermis.

Symplasts are the structures formed as a result of cell fusion with loss of their borders and formation uniform cytoplasmic mass in which there are nucleuses. Symplasts are osteoclasts of bone, an external layer of trophoblast, and fibers of a skeletal muscular tissue.

Syncytium is the structure arising owing to incomplete cytotomia at cell division with preservation of connection between elements of cells by means of cytoplasmic bridges (seminiferous epithelium in the seminiferous tubules of testis).

0 Overview of methods used in histology

Modern histology has the wide arsenal of various methods of research. All these methods are connected by the requirement of

application of the special device - microscope, and all of they are microscopic methods.

Light microscopy

Conventional light, phase contrast, polarizing, confocal, and fluorescence microscopy are all based on the interaction of photons and tissue components.

With the light microscope, stained preparations are usually examined by transillumination. The microscope is composed of both mechanical and optical parts (fig. 1.1).

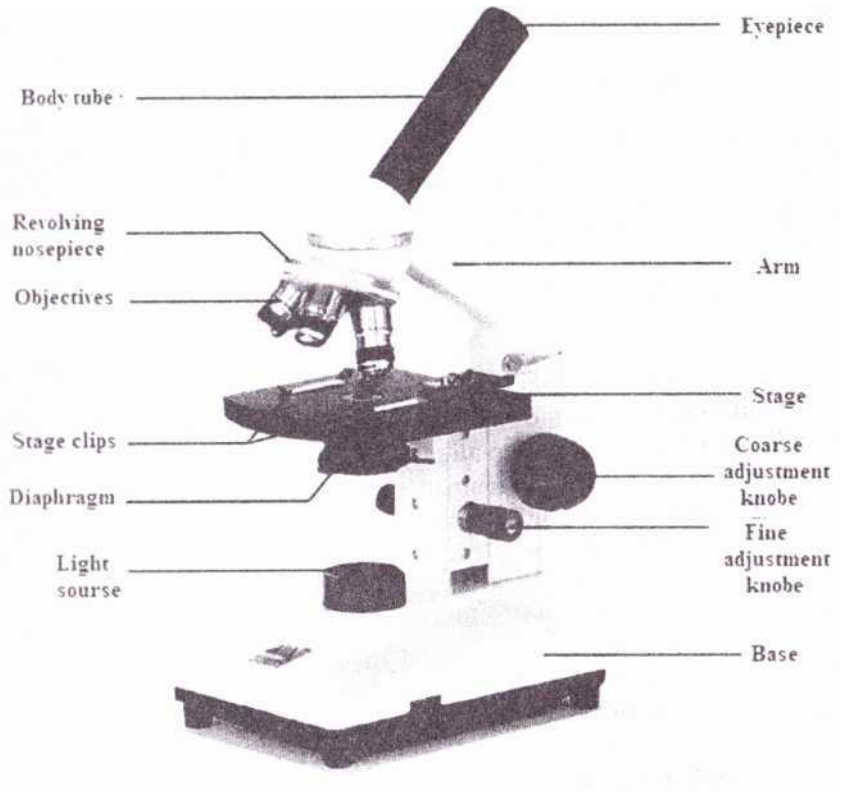

Figure 1.1. Parts of light microscope.

The optical components consist of three systems of lenses: condenser, objective, and ocular. The ***condenser*** collects and focuses the illumination to produce a cone of light that illuminates the object to be observed. The ***objective*** lens enlarges and projects the illuminated image of the object in the direction of the ocular lens. The ***ocular*** lens (eyepiece) further magnifies this image and projects it onto the viewer's retina or a photographic plate. The total magnification is obtained by multiplying the magnifying power of the objective and ocular lenses.

The critical factor in obtaining a crisp, detailed image with the microscope is its ***resolving power,*** that is, the smallest distance between two particles at which they can be seen as separate objects. The maximal resolving power of the light microscope is around 0.1 pm; this permits good images magnified 1000-1500 times. Objects smaller than 0.1 pm cannot be distinguished with this instrument.

The quality of the image - its clarity and richness of detail - depends on the microscope's resolving power. The ***magnification*** is independent of its resolving power and is of value only when accompanied by high resolution. The resolving power of a microscope depends mainly on the quality of its objective lens. The ocular lens only enlarges the image obtained by the objective; it does not improve resolution.

Phase contrast microscopy

Unstained biologic specimens are usually transparent and difficult to view in detail, since all parts of the specimen have almost the same optical density. Phase contrast microscopy, however, uses a lens system that produces visible images from transparent objects.

The principle of phase contrast microscopy is based on the fact that light changes its speed and direction when passing through cellular and extracellular structures with different refractive indices. These changes cause the structures to appear lighter or darker relative to each other. Differential interference optics produces an apparently three- dimensional image of living cells and tissues.

Polarizing microscopy

When normal light passes through a polarizing filter, it exits vibrating in only one direction. If a second filter is placed in the

microscope above the first one, with its main axis perpendicular to the first filter, no light passes through, resulting in a dark field effect. If, however, tissue structures containing oriented molecules (such as cellulose, collagen, microtubules, and microfilaments) are located between the two Polaroid filters, their repetitive, oriented molecular structure allows them to rotate the axis of the light emerging from the polarizer. Consequently, they appear as bright structures against a dark background. The ability to rotate the direction of vibration of polarized light is called birefringence and is present in crystalline substances or substances containing oriented molecules.

Confocal microscopy

This type of microscopy uses lasers and computers to produce three-dimensional images of living cells and tissue slices. Because of the way in which the image is produced, the investigator can visually dissect through the specimen, observing structures above or below others. Storing information from each visual plane of the section in a computer allows a three-dimensional image to be reconstructed.

Fluorescence microscopy

When certain fluorescent substances are irradiated by light of a proper wavelength, they emit light with a longer wavelength. In lluorescence microscopy, tissue sections are usually irradiated with ultraviolet light so that the emission is in the visible portion of the spectrum. The fluorescent substances appear as brilliant, shiny particles on a dark background. A microscope with a strong ultraviolet light source is used, and special filters that eliminate ultraviolet light are used after the objective lens to protect the observers' eyes.

Some naturally fluorescent substances are normal constituents of cells, e.g., vitamin A, vitamin B_2, and porphyrins. Other fluorescent compounds that have an affinity for tissues and cells are used as fluorescent stains. Acridine orange is most widely used, because it can combine with DNA and RNA. When observed in the fluorescence microscope, the DNA-acridine orange complex emits a yellowish-green light, and the RNA-acridine orange complex emits a reddish-orange light. It is thus possible to identify and localize nucleic acids in the cells.

Fluorescence spectroscopy is a method of analyzing the light emitted by a fluorescent compound in a microspectrophotometer. It can be used to characterize several compounds present in cells and is of particular importance in the study of catecholamines. The development of fluorescent probes (substances that react specifically with cell components) has permitted highly sensitive assays for various substances within cells.

Electron microscopy

Both ***transmission*** and ***scanning electron microscopy*** are based on the interaction of electrons and tissue components.

The electron microscope is an imaging system that permits high resolution (0,1 nm). In practice, however, a resolution of 1 nm in tissue sections is considered satisfactory. This by itself permits enlargements to be obtained up to 400 times greater than those achieved with light microscopes.

The electron microscope functions on the principle that a beam of electrons can be deflected by electromagnetic fields in a manner similar to light deflection in glass lenses. Electrons are produced by high-temperature heating of a metallic filament (cathode) in a vacuum. The emitted electrons are then submitted to a potential difference of approximately 60-100 kV or more between the cathode and the anode. The anode is a metallic plate with a small hole in its centre. Electrons are accelerated from the cathode to the anode. Some of these particles pass through the central opening in the anode, forming a constant stream (or beam) of electrons. The beam is deflected by electromagnetic lenses in a way roughly analogous to what occurs in the optical microscope. Thus, the condenser focuses the beam at the object plane and the objective lens forms an image of the object. The image obtained is further enlarged by one or two projecting lenses and is finally seen on a fluorescent screen or is projected onto photographic plates.

Because electron microscopy requires a much thinner section (0.02-0.1 pm), embedding is performed with a hard epoxy plastic. The blocks thus obtained are so hard that glass or diamond knives are usually necessary to section them. Since the electron beam in the microscope cannot penetrate glass, the extremely thin sections are collected on small

metal grids. Those portions of the section spanning the holes in the mesh of the grid can be examined in the microscope.

Scanning electron microscopy

A variant of electron microscopy, ***scanning electron microscopy***, and permits pseudo-three-dimensional remembered that the observed product is the end result of a series of processes that considerably distort the image observable in living tissue, mainly through shrinkage. This shrinkage is produced mainly by the heat (60°C) needed for paraffin embedding; it is virtually eliminated when specimens are embedded in resin. As a consequence of these processes, the spaces frequently seen between cells and other tissue components are artefacts. Furthermore, there is a tendency to think in terms of only two dimensions when examining thin sections, when the structures from which the sections are made actually have three dimensions. In order to understand the architecture of an organ, it is therefore necessary to study sections made in different planes and to reason accordingly.

Another difficulty in the study of microscope preparations is the impossibility of differentially staining all tissue components on only one slide. It is therefore necessary to examine several preparations stained by different methods before a general idea of the composition and structure of any type of tissue can be obtained.

Radioautography

Radioautography permits the localization of radioactive substances in tissues by means of the effect of emitted radiation on photographic emulsions. Silver bromide crystals present in the emulsion act as microdetectors of radioactivity. In radioautography, tissue sections from animals previously treated with radioactive compounds are covered with photographic emulsion and stored in a lightproof box in a refrigerator. After various exposure times the slides are developed photographically and examined. All silver bromide crystals hit by radiation are reduced to small black granules of elemental silver, which reveal the existence of radioactivity in the tissue structures in close proximity to these granules. This procedure can be used in both light and electron microscopy.

By localizing radioactivity in tissue components it is possible to

obtain data on the sequence of events occurring in tissues. Thus, if a radioactive protein precursor (amino acid) is given to a protein- synthesizing cell, its pathway can be followed in the cell after varying periods of time. Furthermore, the intensity of the process is proportional to the number of granules formed over the tissue components.

Iinunohistochemical methods

The ***immunohistochemical methods*** are based on the reactions antigen-antibody. Every cell of organism has specific antigen composition which is determined by proteins mostly. It is possible to get by immunization specific antibodies proper to the antigens. Antibodies contact with fluorochromes or enzymes. After processing of the explored histological specimens in the places of localization of the proper antigens the molecules of the marked antibodies, which expose either thanks to luminescence (luminescent microscopy), or on the basis of laying of the products of histochemical reaction (light microscopy), are concentrated. By this method it is possible to identify any cells or substances produced by those or other cells, for example, hormones.

Diagnostic immunohistochemical markers

Immunohistochemistry is an excellent detection technique and has the tremendous advantage of being able to show exactly where a given protein is located within the tissue examined. It is also an effective way to examine the tissues .This has made it a widely-used technique in the neurosciences, enabling researchers to examine protein expression within specific brain structures. Its major disadvantage is that, unlike immunoblotting techniques where staining is checked against a molecular weight ladder, it is impossible to show in immunohistochemistry that the staining corresponds with the protein of interest. For this reason, primary antibodies must be well-validated in a Western Blot or similar procedure. The technique is even more widely used in diagnostic surgical pathology for typing tumors.

Cytospectrophotometry is method of the quantitative measuring of maintenance of different substances in a cell on the basis of study of spectrums of absorption by them light rays.

The method of running cytometry enables to analyse characteristics of cells in suspension which are crossed by focusing laser ray. The proper device is called cytofluorograph. By means this method it is possible to determine sizes and shape of cells, their viability, to divide the cells of initial suspension on subpopulations.

0 Tissue preparation

Fixation

Chemical fixation with formaldehyde or other chemicals

Chemical fixatives are used to preserve tissue from degradation, and to maintain the structure of the cell and of sub-cellular components such as cell organelles. The most common fixative for light microscopy is 10% neutral buffered formalin. For electron microscopy, the most commonly used fixative is glutaraldehyde, usually as a 2.5% solution in phosphate buffered saline. These fixatives preserve tissues or cells mainly by irreversibly cross-linking proteins. The main action of these aldehyde fixatives is to cross-link amino groups in proteins through the formation of CH_2 (methylene) linkage, in the case of formaldehyde, or by a C_5HIO cross-links in the case of glutaraldehyde. This process, while preserving the structural integrity of the cells and tissue, can damage the biological functionality of proteins, particularly enzymes, and can also denature them to a certain extent. This can be detrimental to certain histological techniques. Further fixatives are often used for electron microscopy such as osmium tetroxide or uranyl acetate.

Frozen section fixation

Frozen section is a rapid way to fix and mount histology sections. It is used in surgical removal of tumors, and allows rapid determination of margin (that the tumor has been completely removed). It is done using a refrigeration device called a cryostat. The frozen tissue is sliced using a microtome, and the frozen slices are mounted on a glass slide and stained the same way as other methods. It is a necessary way to fix tissue for certain stain such as antibody linked immunofluorescence staining. It can also be used to determine if a tumour is malignant when it is found incidentally during surgery on a patient.

Processing

The aim of tissue ***processing*** is to remove water from tissues and replace with a medium that solidifies to allow thin sections to be cut. Biological tissue must be supported in a hard matrix to allow sufficiently thin sections to be cut, typically 5 pm thick for light microscopy and 80- 100 nm thick for electron microscopy.

For light microscopy, paraffin wax is most frequently used. Since it is immiscible with water, the main constituent of biological tissue, water must first be removed in the process of dehydration. Samples are transferred through baths of progressively more concentrated ethanol to remove the water. This is followed by a hydrophobic clearing agent (such as xylene) to remove the alcohol, and finally molten paraffin wax, the infiltration agent, which replaces the xylene. Paraffin wax does not provide a sufficiently hard matrix for cutting very thin sections for electron microscopy. Instead, resins are used. Epoxy resins are the most commonly employed embedding media, but acrylic resins are also used, particularly where immunohistochemistry is required.

Thicker sections (0.35pm to 5pm) of resin-embedded tissue can also be cut for light microscopy. Again, the immiscibility of most epoxy and acrylic resins with water necessitates the use of dehydration, usually with ethanol.

Embedding

After the tissues have been dehydrated, cleared, and infiltrated with the embedding material, they are ready for external embedding. During this process the tissue samples are placed into molds along with liquid embedding material (such as agar, gelatine, or wrn) which is then hardened. This is achieved by cooling in the case of paraffin wax and heating (curing) in the case of the epoxy resins. The acrylic resins are polymerised by heat, ultraviolet light, or chemical catalysts. The hardened blocks containing the tissue samples are then ready to be sectioned.

Because formalin-fixed, paraffin-embedded (FFPE) tissues may be stored indefinitely at room temperature, and nucleic acids (both DNA and RNA) may be recovered from them decades after fixation, making FFPE tissues an important resource for historical studies in medicine.

Sectioning

For light microscopy, a steel knife mounted in a microtome (fig. 1.2) is used to cut 10-micrometer-thick tissue sections which are mounted on a glass microscope slide. For transmission electron microscopy, a diamond knife mounted in an ultramicrotome is used to cut 50-nanometer-thick tissue sections which are mounted on a 3- millimeter-diameter copper grid. Then the mounted sections are treated with the appropriate stain.

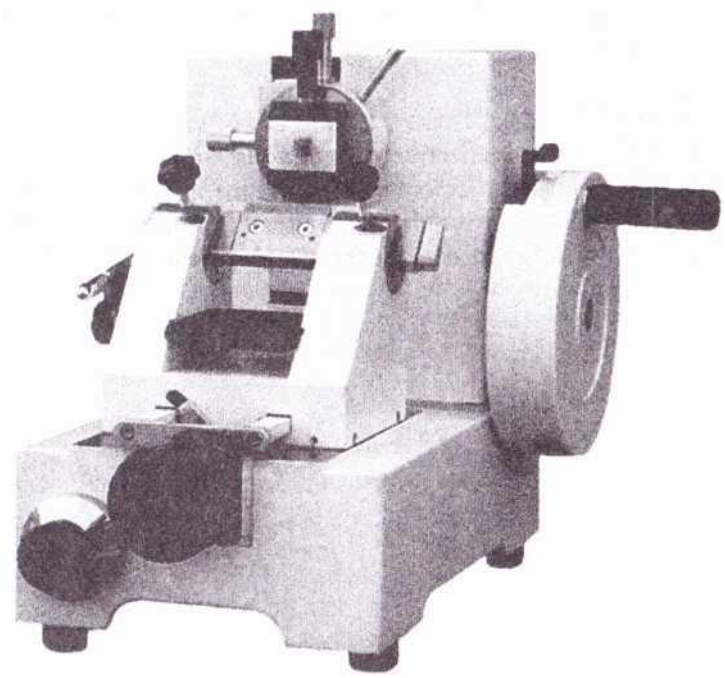

Figure 1.2. Microtome.

Frozen tissue embedded in a freezing medium is cut on a microtome in a cooled machine called a cryostat.

Staining

Biological tissue has little inherent contrast in either the light or electron microscope. Staining is employed to give both contrasts to the tissue as well as highlighting particular features of interest. Where the underlying mechanistic chemistry of staining is understood, the term histochemistry is used.

Hematoxylin and eosin (H&E stain) is the most commonly used light microscopical stain in histology and histopathology. Hematoxylin, a basic dye, stains nuclei blue due to an affinity to nucleic acids in the cell nucleus; eosin, an acidic dye, stains the cytoplasm pink. Uranyl acetate and lead citrate are commonly used to impart contrast to tissue in the electron microscope.

Special staining: There are hundreds of various other techniques that have been used to selectively stain cells and cellular components. Other compounds used to colour tissue sections include safranin, Congo red, fast green FCF, silver salts, and numerous natural and artificial dyes that were usually originated from the development dyes for the textile industry.

CELL. CELL MEMBRANE. CYTOPLASM. ORGANELLES. INCLUSIONS

0 Overview of cell structure

The ***cell*** is limited by an active membrane, well-organized structured system of the biopolymers forming a nucleus and cytoplasm, participating in the united aggregate of metabolic and power processes carry ing out maintenance and reproduction of all system as the whole.

The cell is composed of 3 basic parts:

> plasma membrane,
> cytoplasm and
> nucleus.

0 Cell membrane

Chemically cell membrane consists of lipids, proteins, and oligosaccharides (fig.2.1).

Under the electron microscope (EM) cell membrane consists of 2 densely stained layers separated by a lighter zone.

The basic structure of membrane is the arrangement of phospholipids' molecules that constitute the basic framework of the membrane. Each molecule consists of:

> enlarged polar hydrophilic head and
> thin non-polar hydrophobic tail.

Lipids are most stable when organized into a double layer with their non-polar tails directed toward the center of the membrane and their polar heads directed outward.

In addition to molecules of phospholipids the cell membrane contains several proteins.

Integral proteins either completely (integral proteins proper), or partly ***{semiintegral)*** are embedded in the lipid bilayer.

Peripheral proteins form a looser association with inner or outer membrane surface.

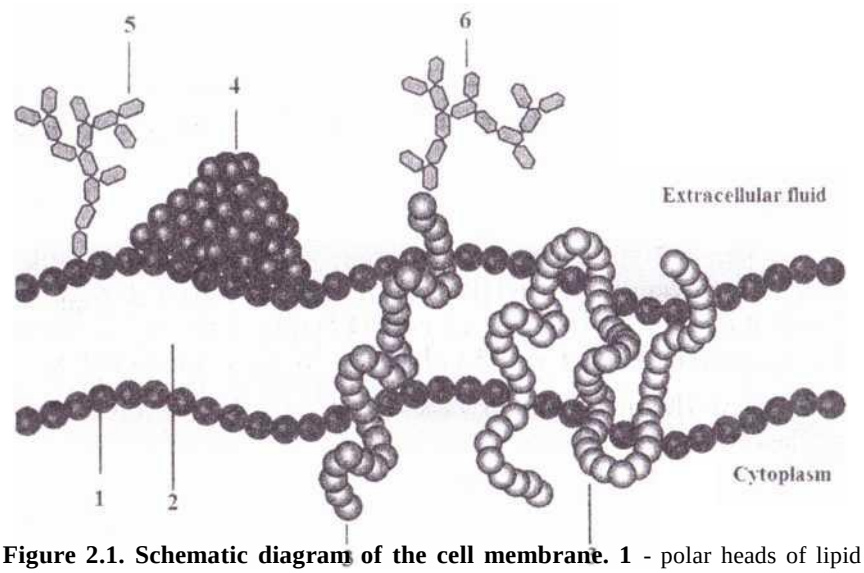

Figure 2.1. Schematic diagram of the cell membrane. 1 - polar heads of lipid molecule, 2 - non-polar tails of lipid molecule, 3 - integral proteins, 4 - peripheral protein, 5 - sugar chain of glycolipid, 6 - sugar chain of glycoprotein

The carbohydrate layer ***(glycocalyx)*** is formed on the external surface of the membrane. It is formed by carbohydrates, which form connections with proteins ***(glycoproteins***) or lipids ***(glycolipids).***

Glycocalyx help establish extracellular microenvironments at the membrane surface that have specific functions in metabolism, cell recognition, and cell association and serve as receptor sites.

The theory of structure of cell membrane called ***fluid mosaic- model*** proposed by ***S.J. Singer*** and ***G. Nicolson.***

Functions of the cell membrane:

1. Maintaining the structural integrity of the cell.
2. Regulating of cellular interactions.
3. Recognition of antigens and foreign cells.
4. Interaction between the cytoplasm and the external environment.
5. Movements of the cell (formation of cilia, flagella).
6. Transport of substances into and from the cell.

Endocytosis

Some substances (consisting of small molecules) pass through the passive channels. Larger molecules enter the cell by invagination of a part of the cell membrane, which first surrounds the molecule and then separates to form endocytosis vesicle.

Endocytosis is the process of engulfing by cell macromolecules, particulate matter, and other substances from the extracellular space.

Endocytosis is divided into 2 categories: ***phagocytosis*** and ***pinocytosis*** (fig.2.2).

Phagocytosis (cell eating) is the cellular process of engulfing solid particles by the cell membrane to form an internal phagosome. Phagocytosis is involved in the acquisition of nutrients for some cells, and, in the immune system, it is a major mechanism used to remove pathogens and cell debris. Bacteria, dead tissue cells, and small mineral particles are all examples of objects that may be phagocytised.

Pinocytosis (cell drinking) is the cellular process of engulfing of fluid and small protein molecules usually smaller than 150 nm in diameter.

Exocytosis is extrusion of materials from the cell (fig.2.3).

0 Cell junctions

Cell junctions are the types of structures that exist within the tissue of a multicellular organism. They consist of protein complexes and provide contact between neighbouring cells, between a cell and the extracellular matrix. Cell junctions are especially abundant in epithelial tissues.

There are three major types of cell junctions:

> Adherens junctions and desmosomes (anchoring junctions)
> Gap junctions (communicating junction)
> Tight junctions (occluding junctions)

Adherens junctions provide strong mechanical attachments between adjacent cells. They hold cardiac muscle cells tightly together as the heart expands and contracts. They hold epithelial cells together. Adherens junctions are built from (fig.2.4): ***cadherins*** - transmembrane proteins whose extracellular segments bind to each other and whose

ntracellular segments bind to ***catenins.*** Catenins are connected to ***actin filaments.***

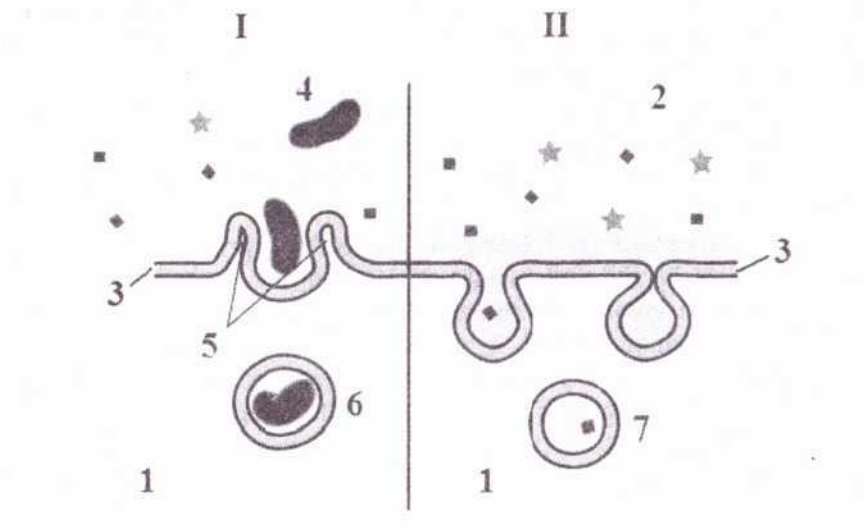

Figure 2.2. Schematic diagram of phagocytosis (I) and pinocytosis (II). 1 - cytoplasm, 2 — extracellular fluid, 3 — plasma membrane, 4 — solid particle, 5 —
pseudopodium, 6 — phagosome, 7 —

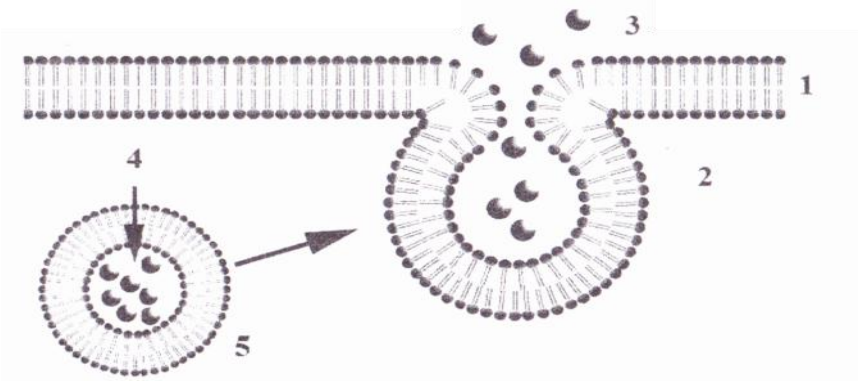

Figure 2.3. Schematic diagram of exocytosis. 1 - plasma membrane, 2 — cytoplasm, 3 - extracellular fluid, 4 - material for secretion, 5 - secretory vesicle

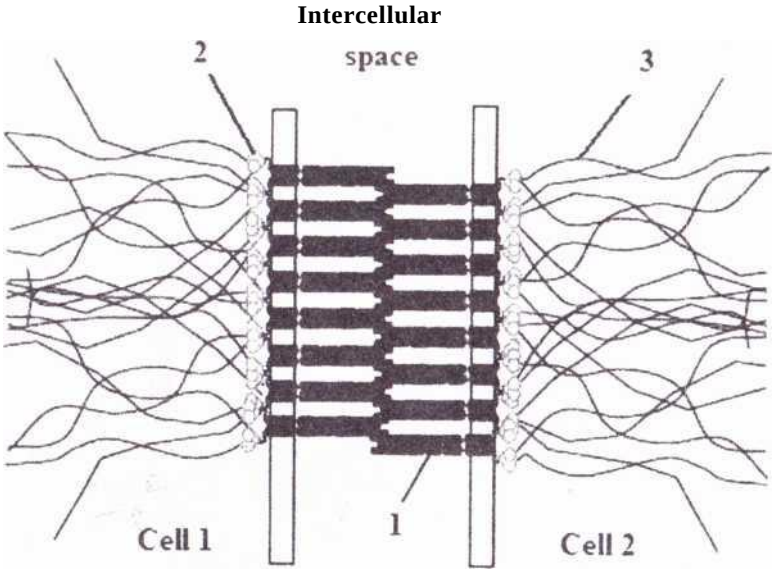

Figure 2.4. Schematic diagram of adherens junction. 1 - cadherins, 2 - catenins, 3 - actin filaments

Desmosomes (fig.2.5) are molecular complexes of cell ***adhesion proteins*** and ***linking proteins*** that attach the cell surface adhesion proteins to intracellular ***intermediate filaments.*** Desmosomes help to resist shearing forces and are found in simple and stratified squamous epithelium. The intercellular space is very wide (about 30 nm). Desmosomes are also found in muscle tissue where they bind muscles cells to one another.

Hemidesmosomes are the cell-matrix junctions, which mediate adhesion between the basal cells and the basement membrane.

Gap junctions (fig. 2.6) are intercellular channels, which are involved in cell-cell communication. The gap junctions form a pathway for passive diffusion of nutrients, metabolites, ions, and small signalling molecules between adjacent cells. Structurally, each gap junctional channel is composed of pair of ***connexons*** (hemichannels), which leave a narrow intercellular gap between the neighbouring cell membranes.

Each connexon is composed of 6 ***connexin*** proteins lining the transmembrane channel.

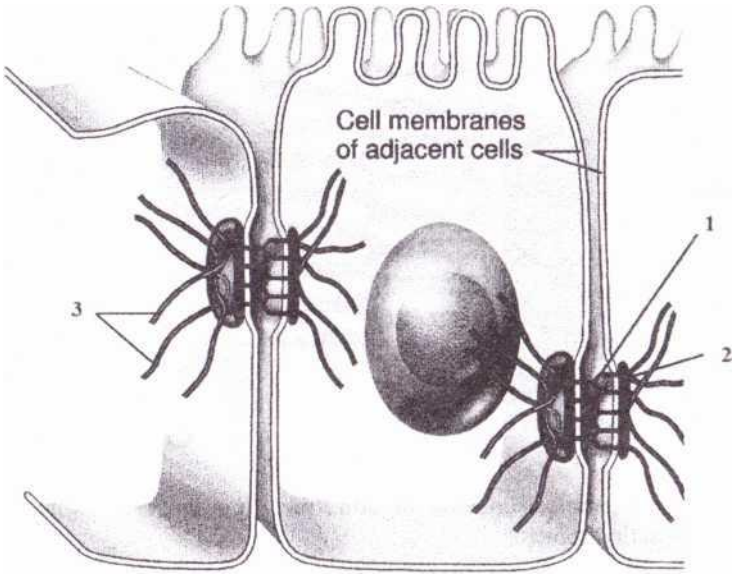

Figure 2.5. Schematic diagram of desmosome. 1 — adhesion proteins, 2 — linking proteins, 3 - intermediate filaments

Tight junctions, or ***zonula occludens*** (fig. 2.7) are the closely associated areas of two cells whose membranes join together. These junctions act as barrier that prevents the movement of molecules into intercellular spaces.

Tight junctions are composed of a branching network of sealing strands, each strand acting independently from the others. Each strand is formed from a row of transmembrane proteins embedded in both plasma membranes, with extracellular domains joining one another directly.

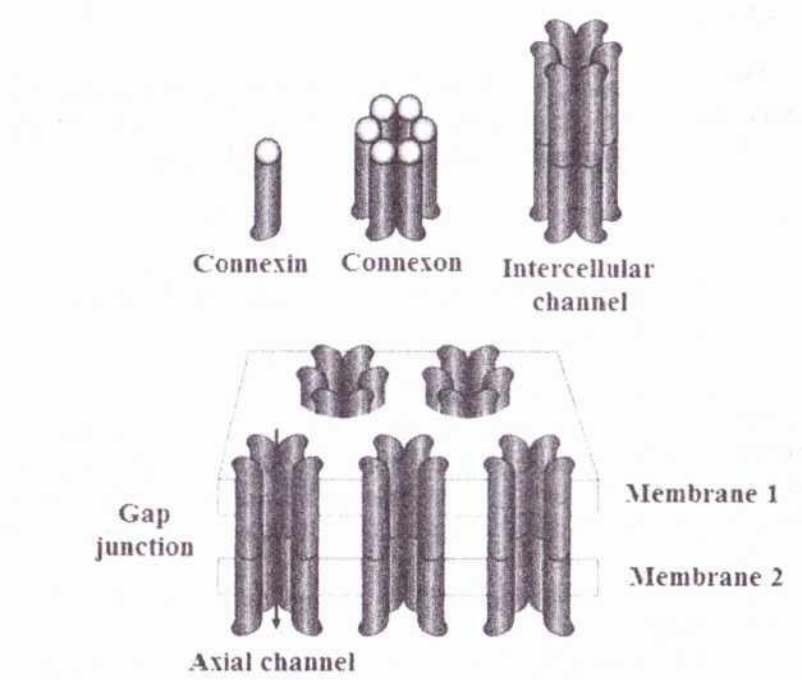

Figure 2.6. Schematic diagram of gap junction.

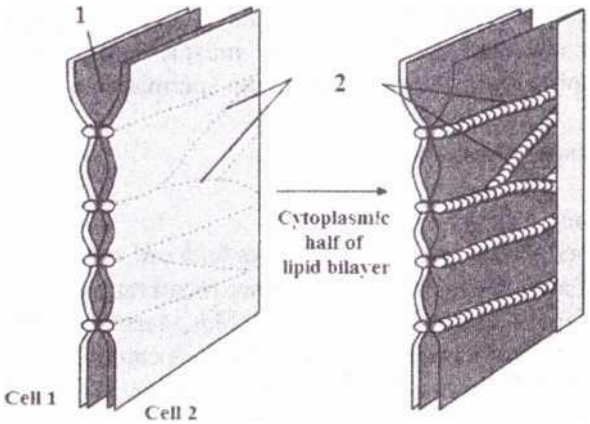

Figure 2.7. Schematic diagrams of tight junctions. 1 - intercellular space, 2 - group of tight junction proteins

0 Cytoplasm

The ***cytoplasm*** is the part of the cell lying between the cell membrane and nucleus. It consists of matrix, in which several components such as ***organelles*** and ***inclusions*** are embedded.

0 Organelles

The ***organelles*** are the specialized subunits within a cell that have specific functions.

Classifications of the organelles

1) . On the basis of their structure the organelles are subdivided on ***membranous*** (mitochondria, endoplasmic reticulum, Golgi complex, lysosomes, peroxisomes) and ***nonmembranous*** (ribosomes, microtubules, microfilaments, intermediate filaments, centrioles, cilia and flagella).

2) . On the basis of their functions the organelles are subdivided on ***general*** and ***special.***

General organelles such as ribosomes, mitochondria, endoplasmic reticulum, Golgi complex, lysosomes, peroxisomes, and centrioles are in any cell.

Special organelles are in specialized cells (neurofibrils and Nissl bodies - in neurons, myofibrils — in muscle cells, cilia in cells of respiratory epithelium, flagella - in human spermatozoa).

0 Membranous organelles

Mitochondria

Mitochondria are spherical or cylindrical organelles, which are composed of an outer membrane and inner membrane (fig.2.8).

The inner membrane projects folds, termed ***cristae,*** into the interior of the mitochondrion. The space located between the two membranes, is termed the ***intermembrane*** space. The other space, the ***matrix,*** space, is enclosed by the inner membrane. Matrix contains mitochondrial DNA, ribosomes, tRNA, and the enzyme system that

generate ATP by means of the citric acid cycle, oxidative phosphorylation, and P-oxidation of fatty acids.

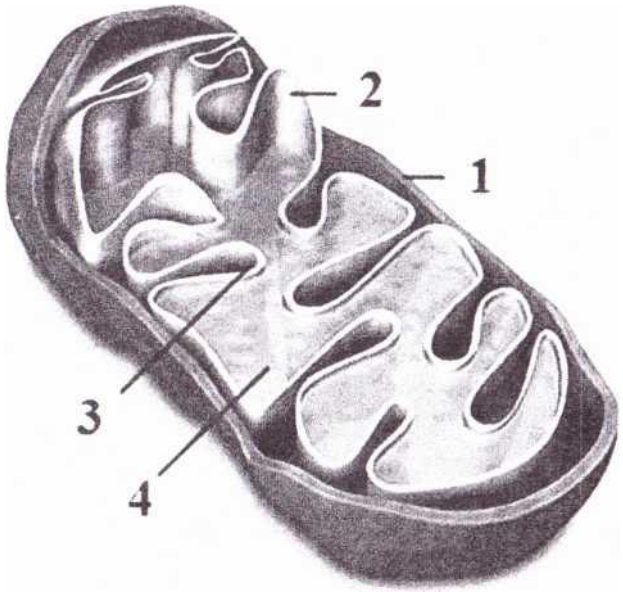

Figure 2.8. Schematic diagram of mitochondrion. 1 - outer membrane, 2 - inner membrane, 3 - cristae, 4 — matrix space

The end result of these reactions, which take place in the mitochondrial matrix, is the production of $C0_2$, water, and heat and the accumulation of energy in high-energy compounds such as ATP.

Endoplasmic reticulum

The ***endoplasmic reticulum*** (ER) is the site of the lipid and carbohydrate synthesis, protein segregation from the cytoplasm.

With light microscope endoplasmic reticulum appears as deep blue staining particles usually concentrated in the basal part of the cells.

With electron microscope it appears as a rich network of membrane bound flattened tubules and sacs.

There are two types of endoplasmic reticulum: ***rough*** and ***smooth*** (fig.2.9).

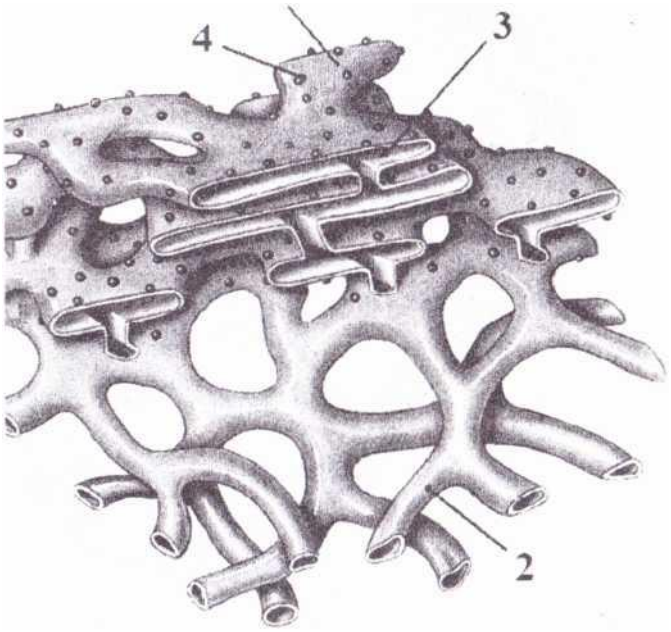

Figure 2.9. Schematic diagram of endoplasmic reticulum. 1 - rough endoplasmic reticulum, 2 - smooth endoplasmic reticulum, 3 - lumen of smooth reticulum, 4 - ribosomes

Rough (granular) endoplasmic reticulum (RER) is prominent in cells specialized for the protein secretion, such as pancreatic acinar cells (digestive enzymes), fibroblasts (collagen), plasma cells (immunoglobulin). The rough endoplasmic reticulum consists of tubules and flattened cisterns. On the cytoplasmic surface of the endoplasmic reticulum there are polyribosomes, giving them granular appearance.

The principal function of the rough endoplasmic reticulum is to synthesis and segregate proteins destined for export or intracellular use.

Smooth (agranular) endoplasmic reticulum (SER) is the membranous network within the cell. These are devoid of ribosome

granules. Its cisterns are more tubular and more likely to appear as a profusion of interconnected channels of variable size s and shape. They are concerned with steroid synthesis, lipid metabolism and detoxication processes.

Golgi apparatus

Golgi apparatus is composed of a series of stacked, flattened, membrane-limited sacs or cisternae and tubular extensions. Small vesicles are seen in association with the cisternae (fig.2.10).

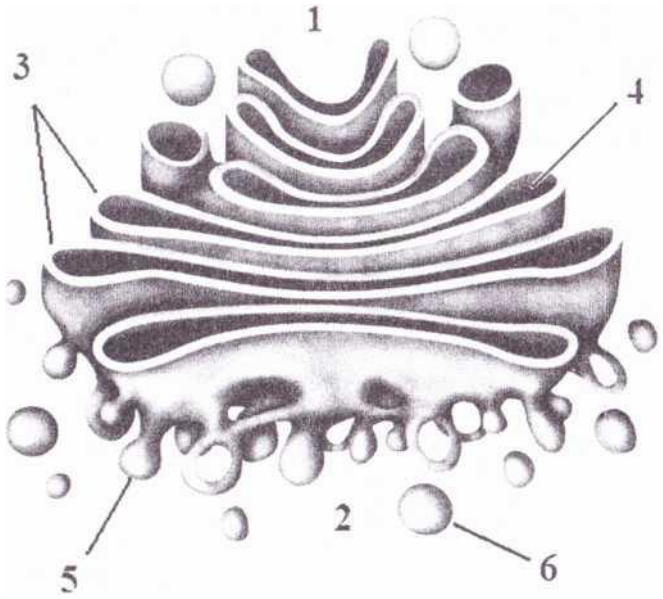

Figure 2.10. Three-dimensional model of the Golgi apparatus. 1 - cis (forming) face, 2 - trans (maturing) face, 3 ~ cistemae, **4** - lumen, 5 - newly forming vesicle, 6 - secretory vesicle

The Golgi apparatus is polarized both morphologically and functionally.

Through transport vesicles that fuse with the Golgi cis face, the complex receives several types of molecules produced in the rough

endoplasmic reticulum (RER). After Golgi processing, these molecules are released from the Golgi trans face in larger vesicles to constitute secretory vesicles, lysosomes, or other cytoplasmic components.

Proteins, which are synthesized in endoplasmic reticulum, migrate to Golgi apparatus, where they are stored and condensed into granular for secretion.

Lysosomes may also be produced in the Golgi apparatus.

Lysosomes

The ***lysosomes*** are sites of intracellular digestion and turnover of cellular components (fig.2.11). Lysosomes are membrane-limited spherical vesicles that contain a large variety of hydrolytic enzymes (more than 40). Lysosomes are present in almost all cells, but they are particularly abundant in cells with phagocytic activity (macrophages, neutrophilic leukocytes).

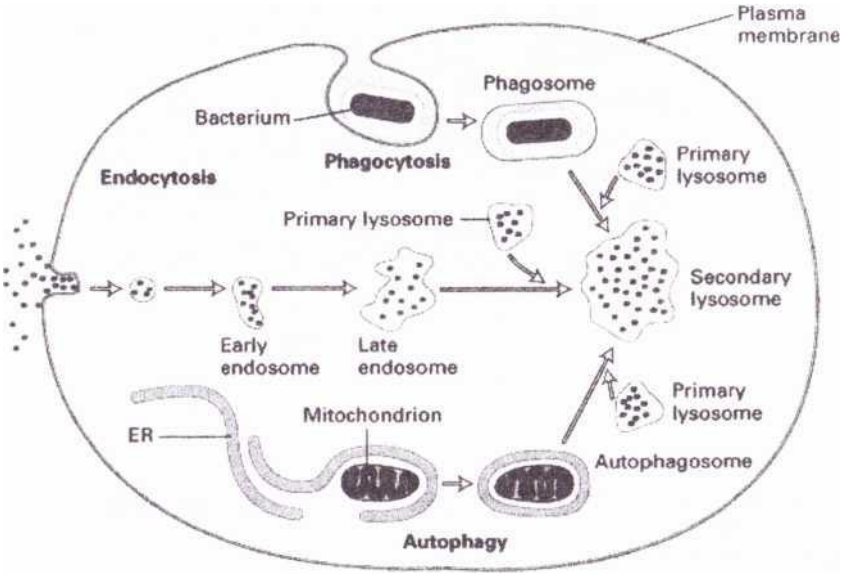

Figure 2.11. Schematic diagrams of the lysosomes.

Lysosomes that have not entered into a digestive event are called as ***primary lysosomes.***

Secondary lysosomes are those in which digestion occurs.

Secondary' lysosomes result from the fusion of endocytosis material with primary lysosomes to form phagosome. Secondary lysosome is also known as a ***phagolysosome.***

Following digestion of the contents of the secondary lysosome, nutrients diffuse through the lysosomal membrane and enter the cytoplasm.

Undigestable compounds are retained within the vacuoles, which are now called ***residual bodies.***

Another function of the lysosomes concerns the turnover of cytoplasmic organelles. Primary lysosomes fuse with this structure and initiate the lysis of the enclosed cytoplasm. The resulting secondary lysosomes are known as ***autophagosomes.***

Peroxisomes

Peroxisomes are small (0,5 jam diameter) spherical membrane- limited organelles that contain oxidative enzymes, particularly ***catalase*** and other peroxidative enzymes. The oxidative enzymes react with other substances to form hydrogen peroxide (H_2O_2). Hydrogen peroxide is toxic substance. Catalase decomposes hydrogen peroxide to water and oxygen ($_2H_2O_2$ —$+_2H_2O + O_2$). Peroxisomes protect the cell from the effects of hydrogen peroxide, which could cause damage to many important cellular constituents.

0 Nonmembranous organelles

Ribosomes

Ribosomes are present in relation to rough endoplasmic reticulum. They may also lie free in the cytoplasm. They may be present singly (monosomes) or in groups (polysomes). “Free” ribosomes synthesize proteins that will remain in the cell as cytoplasmic structural or functional elements. Polysomes of the rough endoplasmic reticulum synthesize proteins for export from the cell and integral proteins of the plasma membrane.

Each ribosome consists of proteins and ribonucleic acid (RNA). Ribosome consists of 2 subunits of different size (fig.2.12). Ribosomes play an essential role in protein synthesis.

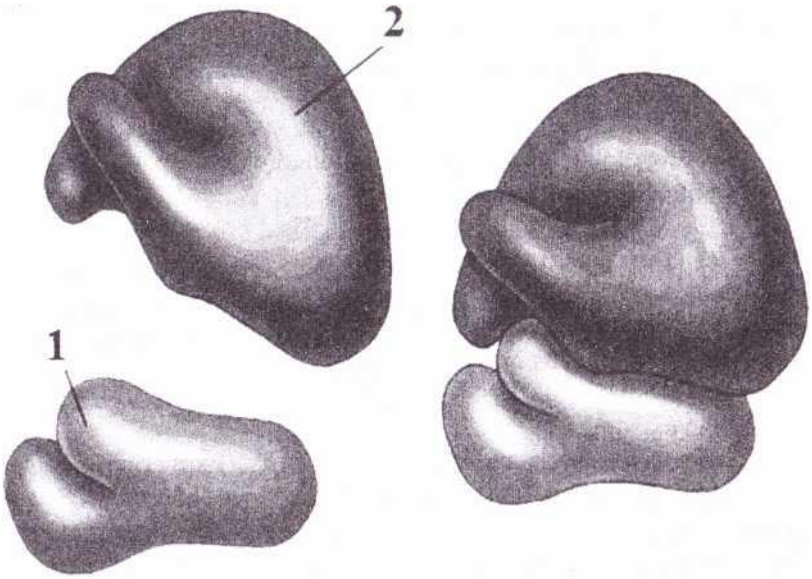

Figure 2.12. Schematic diagram of ribosome. 1 - small subunit, 2 - large subunit

The cytoskeleton

The cytoplasmic matrix contains a complex network of ***microtubules***, ***microfilaments,*** and ***intermediate filaments.***

These structural proteins not only provide for the form and shaping of cell but also play an important role in cytoplasmic and cellular movements.

Microtubules

Microtubules are thin elongated elements of cell cytoplasm; they are circular in cross section (fig.2.13) with diameter of 24 nm.

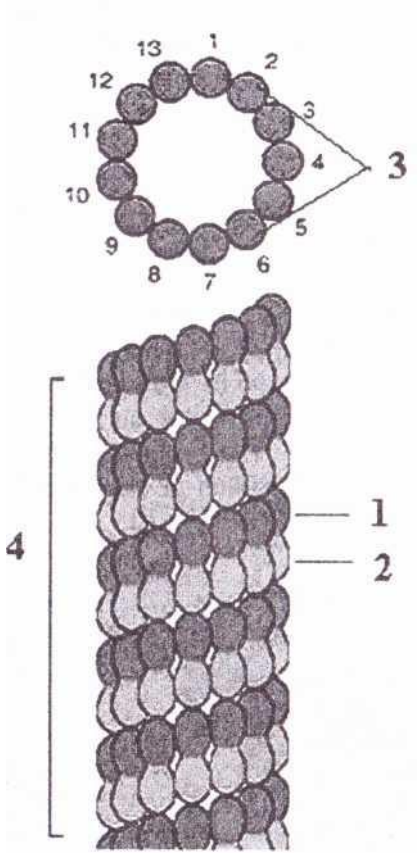

Figure 2.13. Schematic representation of microtubule. 1 - a-tubuiin molecules, 2 - p-tubulin molecules, 3 - subunits, 4 - microtubule

The subunit of ***a*** microtubule composed of a- arid P-tubulin molecules. Under appropriate conditions tubulin subunits polymerize to form microtubules. A total of 13 subunits are present in one complete turn of the spiral.

Microtubules provide the basis of several complex of cytoplasm components, including ***centrioles, basal bodies***, ***cilia,*** and ***flagella.***

Centrioles are cylindrical structures which composed of highly organized microtubules (fig.2.14). Centrioles lie at right angles to each other. Each centriole is composed of 9 triplets of microtubules (9x3 +
0) . Centrioles play important role in the formation of the mitotic spindles of dividing cells.

Cilia (fig. 2.15) and ***flagella*** are motile processes with a highly organized microtubular core; they extend from the surface of some cell types.

Ciliated cells usually possess a large number of cilia that range 2 to 10 (.im in length. Flagellated cells normally have only 1 flagellum, which ranges in length from 100 to 200 |im. The core of these structures consists of 9 pairs of microtubules surrounding 2 central tubules (doublets) (9 x-2 + 2).

At the base of each cilium or flagellum is a ***basal body.*** This body is identical to a ***centriole*** (9 x-3 + 0).

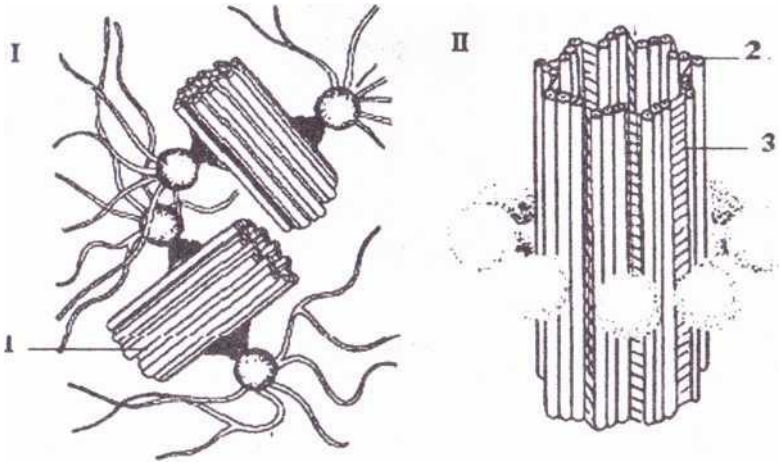

Figure 2.14. Schematic diagram of cell centre (I) and centriole (IT). 1 - centriole, 2 - microtubule triplet, 3 - protein links (from ***EbiKoe*** *B.JJ.*, 2007)

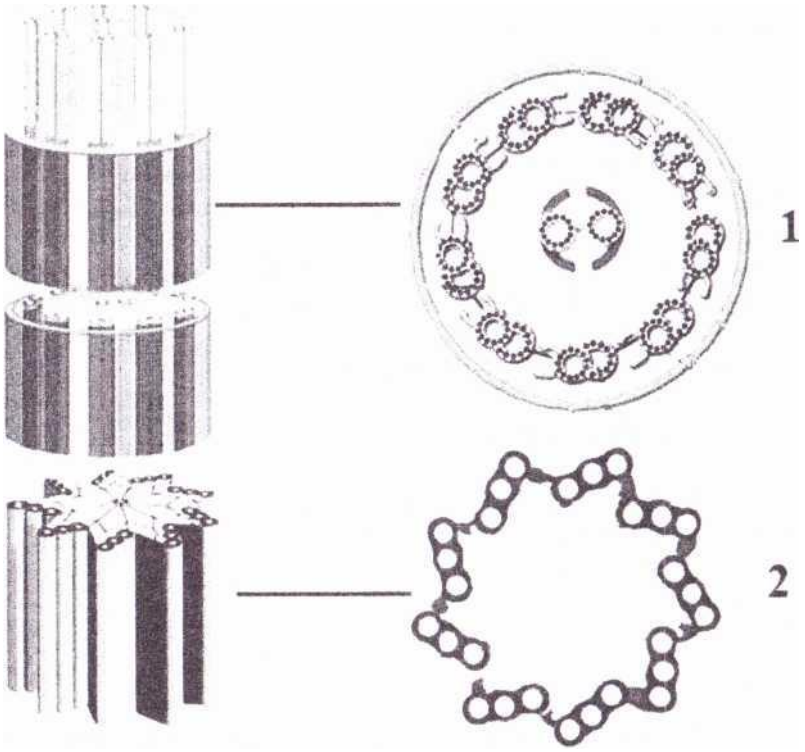

Figure 2.15. Schematic diagram of cilium. 1 - axoneme **(9** x 2 + 2), 2 - basal body (9x-3 + 0)

Microfilaments

Microfilaments are the thin protein fibers. The protein forming microfilaments are called ***actin*** (5-7 nm in diameter).

Microfilaments can be organized in many forms:

> in skeletal muscle they integrate with thick (16 nm) myosin filaments;

> in most cells microfilaments are present as a thin sheath just beneath the plasmolemma.

These filaments appear to be associated with membrane activity such as endocytosis, exocytosis, and cell migratory activity (pseudopodial processes).

Intermediate filaments

The cells contain a class of intermediate-sized filaments with diameter of 8-12 nm. Intermediate filaments occur in the cells of many tissues:

> ***vimentin*** filaments are characteristic of cells of mesenchymal origin.

> ***desmin*** is found in smooth muscle and in the Z disks of skeletal and cardiac muscle;

> ***cytokeratins*** are found in most epithelia.

0 Cytoplasmic inclusions

Inclusions are temporary components of the cytoplasm, mainly composed of accumulated metabolites or deposits of varied nature. Cytoplasmic inclusions are subdivided in

> trophic,

> secretory,

> excretory,

> pigment.

The ***trophic inclusions*** are lipid droplets in adipose tissue, adrenal cortex cells, and liver cells; carbohydrate accumulations in several cells in the form of glycogen.

The ***secretory inclusions*** are protein secretory granules in glandular cells.

The ***excretory inclusions*** are similar with secretory, they contain the metabolic substances.

The ***pigment inclusions*** are often found in the cells. They may synthesize by the cell: ***lipofuscin,*** a yellow-brown substance in neurons and cardiac muscle; ***melanin*** in the epidermis of the skin, in the pigment layer of the retina. The pigment inclusions may come from outside the body (e.g., carotene).

0 Clinical correlations

Abnormalities in microtubules and filaments. Tau proteins are proteins that stabilize microtubules. They are abundant in neurons in the central nervous system. Tau proteins interact with tubulin to stabilize microtubules and promote tubulin assembly into microtubules. When tau proteins are defective, the microtubules disintegrate, collapsing the neuron's transport system. This may result first in malfunctions in biochemical communication between neurons and later in the death of the cells. It can result in dementias, such as Alzheimer's disease - incurable, degenerative, and terminal disease.

Lysosomal storage diseases are a group of inherited metabolic disorders that result from defects in lysosomal function. Lysosomal disorders originate from an abnormal accumulation of substances inside the lysosome. When the lysosome doesn't function normally, excess products destined for breakdown and recycling are stored in the cell. Lysosomal storage diseases affect mostly children and they often die at a young age. The symptoms of lysosomal storage disease can include developmental delay, movement disorders, seizures, dementia, deafness and/or blindness. Some people with lysosomal storage disease have enlarged livers (hepatomegaly) and enlarged spleens (splenomegaly), pulmonary and cardiac problems, and bones that grow abnormally.

Mitochondrial diseases are a group of disorders caused by dysfunctional mitochondria. Mitochondrial diseases are often caused by mutations to mitochondrial DNA that affect mitochondria function. Symptoms include poor growth, loss of muscle coordination, muscle weakness, visual problems, hearing problems, learning disabilities, mental retardation, heart disease, liver disease, kidney disease, gastrointestinal disorders, respiratory disorders, neurological problems, autonomic dysfunction, and dementia.

NUCLEUS. CELL CYCLE. CELL DIVISION

The ***nucleus*** is an essential component of the cells; it takes a deep base stain.

The nucleus is usually spherical; but oval in columnar cells; flattened in squamous cells; rod shaped in smooth muscle cells.

The nuclei are centra! in most cells; basal in mucous cells; peripheral in skeletal muscle fibers.

Most cells have one nucleus. Occasionally binucleate cells are found in urinary bladder epithelium, liver and cardiac muscle. Skeletal muscle fibers are multinucleated.

The functions of the nucleus

1. Keeping of the genetic information (in the molecules of DNA).
2. Realization of the genetic information.
3. Reproduction and transfer of the genetic information (during the cell division).

The structure of the nucleus

The interphase nucleus has 4 parts: ***nuclear envelope, chrotnadn, nucleolus,*** and ***nuclear matrix*** (fig.3.1).

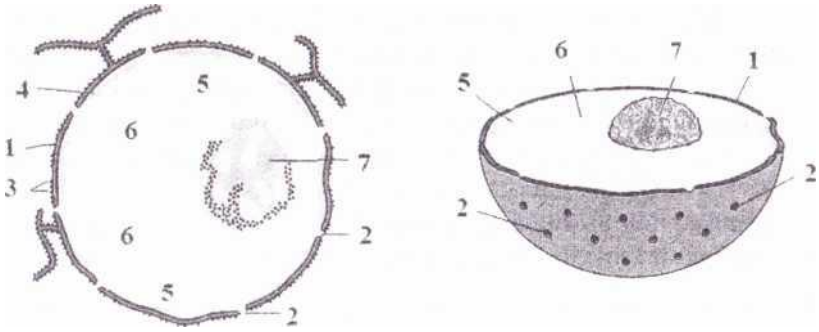

Figure 3.1. Schematic diagram of structure of a nucleus. 1 - nuclear envelope, 2 - nuclear pores, 3 - ribosomes, 4 - nuclear fibrous lamina, 5 - heterochromatin, 6 - euchromatin, 7 - nucleolus

Nuclear envelope

The nucleus is surrounded by 2 parallel unit membranes separated by a narrow space called ***perinuclear cisternal space.*** Together, the paired membranes and intervening space make up the ***nuclear envelope.***

The outer layer of the nucleus membrane is continuous with the endoplasmic reticulum.

Closely associated with the inner membrane of the nuclear envelope is a protein structure called ***fibrous lamina.*** The fibrous lamina forms part of the nuclear matrix.

Around the nuclear envelope, at sites where inner and outer membranes fuse, there are circular gaps, the ***nuclear pores.***

The nuclear pore function is bidirectional nucleocytoplasmic transport.

The ***nuclear pore complex*** (NPC) (fig.3.2) consists of an assembly of eight spokes arranged around a central channel.

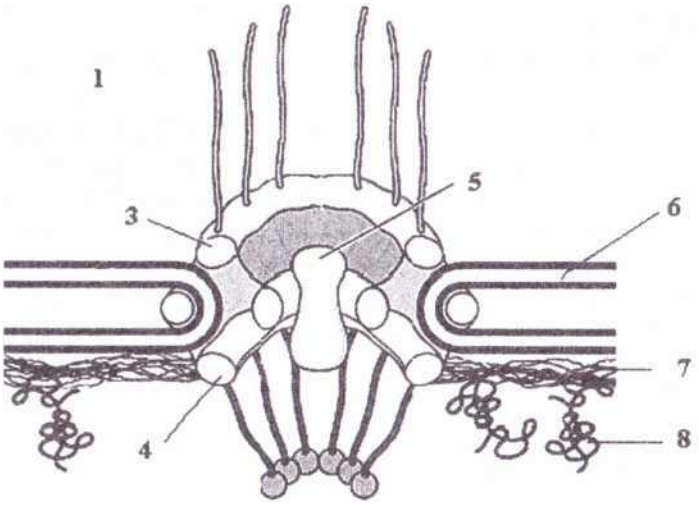

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Figure 3.2. Schematic cross-section of the nuclear pore complex. 1 — cytoplasm, 2 - nucleus, 3 - cytoplasmic ring, 4 - internuclear ring, 5 - central granule, 6 - nuclear envelope, 7 - nuclear lamina, 8 - chromatin

The spokes are connected to rings at the nuclear and cytoplasmic surfaces, and the spoke-ring assembly is anchored within the nuclear envelope at sites of fosion between the inner and outer nuclear membranes. Protein filaments extend from both the cytoplasmic and nuclear rings, forming a distinct basketlike structure on the nuclear side.

The central channel is approximately 40 nm in diameter, which is wide enough to accommodate the largest particles able to cross the nuclear envelope. It contains a structure called the central transporter, through which the active transport of macromolecules is thought to occur.

The nuclear pore complex provides a channel for transport of substances between the nucleus and the cytoplasm. There are roughly 3000 NPCs situated in the nuclear envelope. Smaller molecules that are less than 9 nm in diameter, like ions and metabolites, may freely diffuse through the NPC between the nucleus and the cytoplasm. Larger molecules, between 9 and 28 nm in diameter, must be actively transported through the NPC in a controlled process that is selective and energy dependent.

Chromatin is little blue staining particles within the nucleus. Chromatin (fig.3.3) is composed mainly of coiled strands of deoxyribonucleic acid (DNA) bound to basic proteins (histones). The basic structural unit of chromatin is the ***nucleosome.*** It consists of a core of 8 histone molecules. Approximately 2 loops of DNA are wrapped around the core octamer. A long strand of nucleosomes is coiled to produce a unit ***chromatin fibril*** about 30 nm in diameter.

In dividing cells chromatin is condensed and organized into discrete bodies called ***chromosomes.***

2 types of chromatin can be distinguished with both the light and electron microscopes.

Heterochromatin is coiled segments of chromosomes and stain deep blue. It forms the chromatin particles of interphase nucleus, and is inert and inactive.

Euchromatin is uncoiled segments of chromosomes and stain poorly or not at all. it is active and directs the cell activities in the production of protein.

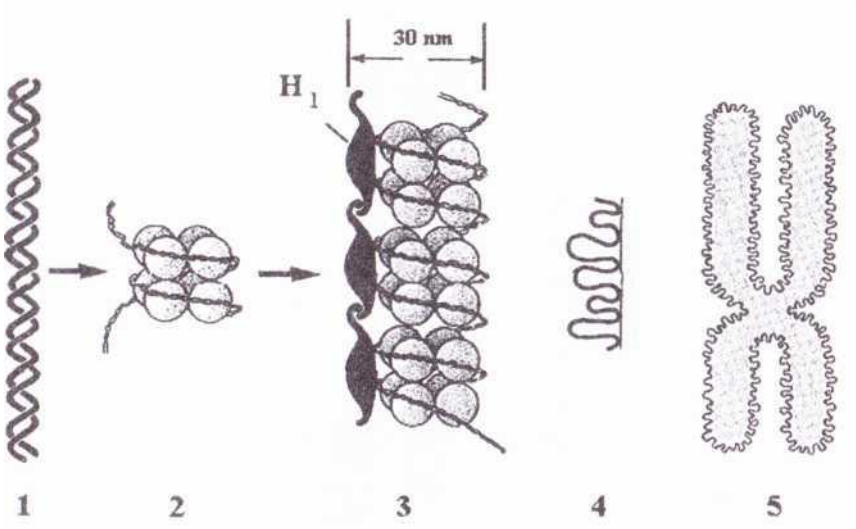


Figure 3.3. Orders of chromatin packing. 1 - DNA double helix chain, 2 — nucleosome, 3 — nucleosomes are linked by elongated molecules of histone H|, 4 - loops of the 30 nm fiber, 5 - metaphase chromosome (from *Junqueira L.C. and CarneiroJ.*, 2005)

Chromosomes are little rod-like bodies in the nucleus, which take a deep basic stain (fig.3.4).

Each chromosome is formed by 2 ***chromatids*** that are joined together at a point called the ***centromere.*** Each chromatid has 2 ***arms,*** one on either side of the centromere. Each chromosome differs from one another in total length and in the relative length of the two arms.

The chromosome pattern of an individual is known as ***karyotype*** (fig-3.5).

Human chromosomes have been classified into 7 groups A to G, and each has been given a number mainly on the length of chromosomes and the position of the centromere: group A- 1 to 3; B- 4 and 5; C- 6 to **12** and X; D- 13 to 15; E-16 to 18; F- 19 and 20; G-21, 22, and Y.

Chromosomes control the heredity and activities of the cell.

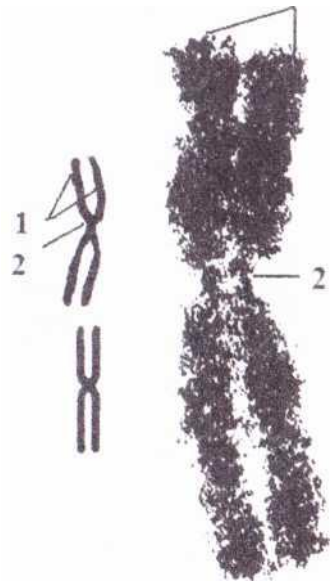


Figure 3.4. Structure of chromosome. 1- arms. 2 - centromere (from *fOII.A^anacbea, H.AKJpwia u dp.,* 1999)

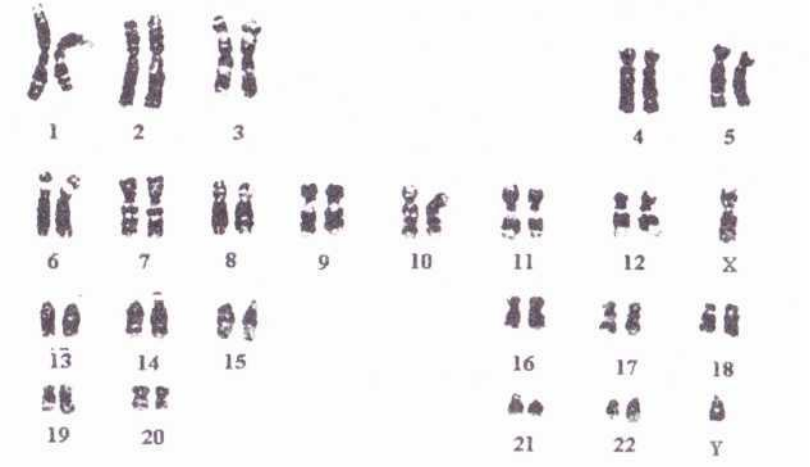


Figure 3.5. Human karyotype.

Nucleolus

The ***nucleolus*** is a spherical structure, usually basophilic when stained with hematoxylin and eosin (flg.3.6).

The nucleolus consists of:

1) densely packed ribonucleoprotein fibers, the ***pars fibrosa***, which is composed of primary transcripts of rRNA genes, and is situated mainly in the central part of nucleolus;
2) the ***pars granulosa***, consisting of granules (maturing ribosomes);
3) nucleolar organizer DNA.

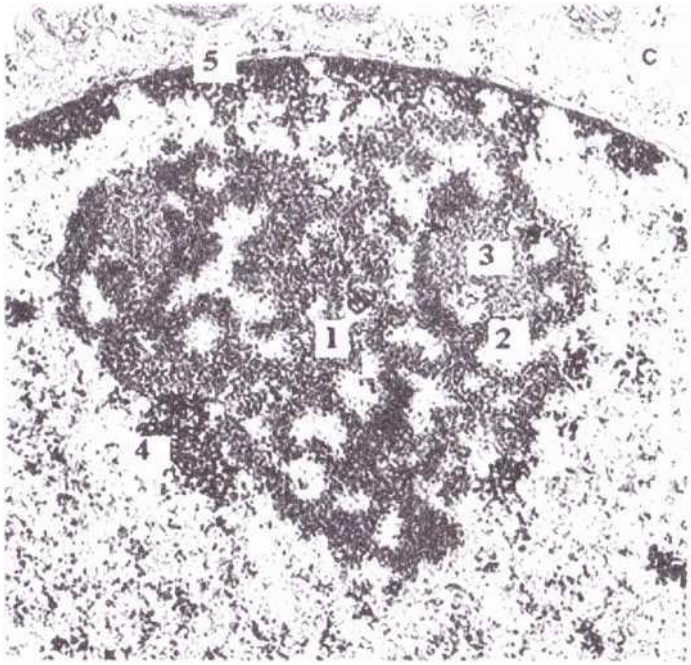


Figure 3.6. Electron micrograph of a nucleolus. 1 - pars fibrosa, 2 - pars granulose, 3 - nucleolar organizer DNA, 4 - nucleolus-associated chromatin, 5 - nuclear envelope (from *Junqueira L.C. and Carneiro J.*, 2005)

Proteins, synthesized in the cytoplasm, become associated with rRNA in the nucleolus; ribosome subunits then migrate into the cytoplasm.

Nuclear matrix

The nuclear matrix is the component that fills the space between the chromatin and the nucleoli in the nucleus. It is composed mainly of proteins (some of which have enzymatic activity), metabolites, and ions. The fibrous lamina of the nuclear envelope is a part of the nuclear matrix.

E3 Cell division

The ***cell division*** or mitosis can be observed with the light microscope. During this process, the parent cell divides, and each of the daughter cells receives a chromosomal karyotype identical to that of the parent cell.

Mitosis

Mitosis (fig.3.7) is characterised by a series of changes in which there is equal division of nuclear material ***(kuryokinesis),*** followed by the division of the cell ***(cytokinesis).***

Phases of mitosis are prophase, metaphase, anaphase, telophase

Prophase

The nuclear membrane and the nucleolus disappear. The chromatin granules resolve into chromosomes. As a prelude to mitosis each chromosome is duplicated, each of which is called a ***chromatid*** The paired chromatids lie side by side and are united at one point only termed the ***centromere.*** The centrioles divide, move in the opposite direction and finally take up positions at opposite poles of the cell. The centrioles are connected by microtubules forming ***mitotic spindle.***

Metaphase

The chromosomes migrate to the equatorial plane of the cell, where each divides longitudinally to form two chromatids (***metaphase plate).***

Anaphase

The centromere divides and the two chromatids become completely separated from each other. The spindle tubules pull the separated group of chromatids to opposite poles. Two groups of chromatids, now chromosomes are identical.

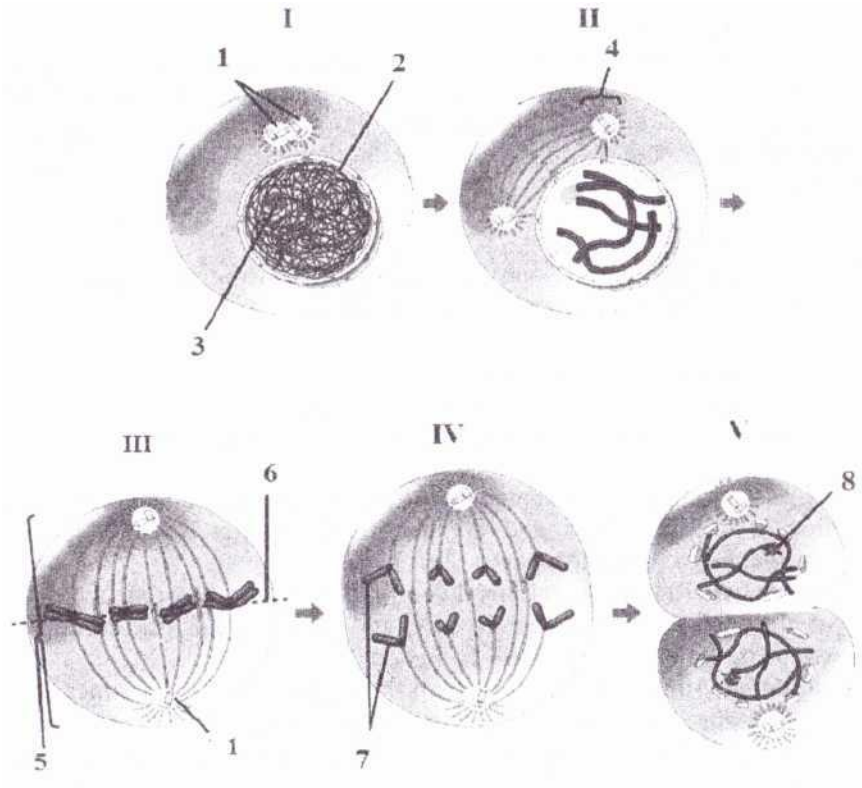


Figure 3.7. Schematic diagram of phases of mitosis. I - interphase: **1 -** centrosome, 2 - chromatin, 3 — nucleolus; II - prophase: 4 — aster; III - metaphase; 5 - spindle, 6 - metaphase plate; IV — anaphase: 7 - daughter chromosomes, V - telophase: 8 - nucleolus forming

Telophase

Constriction develops at the equator of the elongated cell. It deepens and divides the cell into two daughter cells. In each daughter cell, the chromosomes lose their identity, become uncoiled to varying extent and are seen as chromatin particles. The nucleoli and the nuclear membrane have reformed.

F>ndomitosis

Endomitosis is a process by which chromosomes replicate without the division of the cell nucleus.

Polyploidy

Polyploidy is the state of having greater than the diploid content of DNA, has been recognized in a variety cells (liver cells, megakaryocytes of red bone marrow). Polyploid cells are larger than diploid ones; not surprising in view of the increased amount of DNA in their nucleus.

Meiosis

Meiosis occurs only in sex cells during maturation, and comprises of first and second meiotic divisions.

The first meiotic division

1. ***Prophase*** is divided into 4 substages:

> ***leptoten:*** chromosomes become prominent and stain deeply with basic dyes;

y zygotene; 23 pairs of genetically homologous chromosomes become attracted to each other and lie side by side; this Is called pairing (conjugation) of chromosomes;

> ***pachytene*** (tetrad formation and coiling): each chromosome splits into two chromatids except at centromere, and forms ***tetrads,*** the chromatids become partially coiled around each other;

> ***diplotene*** (interchange of segments): homologous chromosomes move apart except at ***chiasmata*** Chiasmata are points of contact, where exchange of genetic material takes place between two chromatids. At the chiasmata parts of two chromatids (one from each homologous pair) break and then join diagonally. This is called crossover, which results in redistribution of genetic material. Finally the chromosomes (with two chromatids) uncoil and slip apart ***(diakinesis);***

2. ***Metaphase:*** chromosomes with paired chromatids arrange themselves at the equator;

3. ***Anaphase: centromeres do not divide*** and each member of homologous chromosomes, consisting of a pair of chromatids, is dragged to opposite poles of the spindle;

4. ***Telophase:*** cell divides into two containing one half (haploid) chromosomes.

The second meiotic division follows closely after the first meiotic division with practically no resting stage. This is exactly like

mitosis but the phases are much shortened. Four cells are derived from the two cells of 1st meiotic division. Each has haploid number of

chromosomes and each has its own particular share of the genetic material.

0 Cell cycle

The alternation between mitosis and interphase is known as the ***cell cycle*** (fig.3.8).

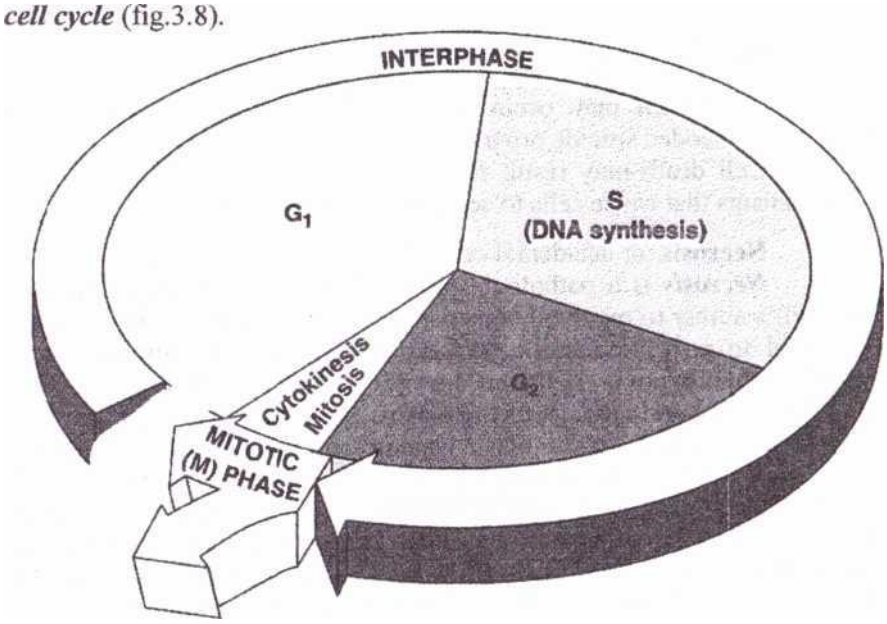


Figure 3.8. Schematic diagram of cell cycle.

It can be divided into two stages: ***mitosis,*** consisting of four phases already described ***(prophase, metaphase***, ***anaphase***, and ***telophase),*** and ***interphase.***

Interphase is divided into three phases: Gi (presynthetic), S (DNA synthesis), and G_2 (post-DNA duplication).

It is during the G, ***phase*** that RNA and protein synthesis occur and the cell volume, previously reduced to one-half by mitosis, is restored to its normal size.

In cells that are not continuously dividing, the cell cycle activities may be temporarily or permanently suspended. Cells in such a stage of development (e.g., muscle, nerve) are referred to as being in a ***Gg phase.***

Synthesis and replication of DNA and centrioles take place in the ***S phase.***

Processes that occur during the ***G*2 *phase*** are the production and accumulation of energy to be used during mitosis and the synthesis of tubulin to be assembled in microtubules during mitosis.

0 Cell death

Cell death may occur as a result of acute cell injury or an internally encoded suicide program.

Cell death may result from accidental cell injury (necrosis) or mechanisms that cause cells to self-destruct (apoptosis).

Necrosis, or accidental cell death.

Necrosis is a pathologic process. It begins with impairment of the cell's ability to maintain homeostasis. Necrosis occurs when cells are exposed to an unfavourable physical or chemical environment (e.g., hypothermia, hypoxia, radiation, low pH, cell trauma) that causes acute cellular injury and damage of the plasma membrane. Under physiologic conditions, damage to the plasma membrane may also be initiated by viruses, substances such as complement, or proteins called perforins.

As a result of cell injury, damage to the cell membrane leads to an influx of water and extracellular ions. Intracellular organelles, such as the mitochondria, rER, and nucleus, undergo irreversible changes that are caused by cell swelling and cell membrane rupture (cell lysis). As a result of the ultimate breakdown of the plasma membrane, the cytoplasmic contents, including lysosomal enzymes, are released into the extracellular space. Therefore, necrotic cell death is often associated with extensive surrounding tissue damage and an intense inflammatory response.

Apoptosis

Apoptosis also referred to as programmed cell death. In Greek, apoptosis translates to the "dropping off" of petals or leaves from plants or trees.

Apoptosis represents as a physiologic process. Apoptosis is a mode of cell death occurs under normal physiologic conditions. During apoptosis, cells that are no longer needed are eliminated from the organism. This process may occur during normal embryonic development or other normal physiologic processes, such as follicular atresia in the ovaries. Cells can initiate their own death through activation of an internally encoded suicide program. Apoptosis is characterized by controlled autodigestion, which maintains cell membrane integrity; thus, the cell "dies with dignity" without spilling its contents and damaging its neighbours.

Cells undergoing apoptosis show characteristic morphologic and biochemical features (flg.3.9) such as DNA fragmentation decrease in cell volume, membrane blebbing without loss of membrane integrity, and formation of apoptotic bodies, causing cell breakage. Apoptotic bodies are later removed by phagocytic cells without inflammatory reactions.

0 Clinical correlations

Dysregulation of p53

The ***tumor-suppressor protein p53*** accumulates when DNA is damaged due to a chain of biochemical factors. p53 prevents the cell from replicating by stopping the cell cycle at Gi, or interphase, to give the cell time to repair, however it will induce apoptosis if damage is extensive and repair efforts fail. Any disruption to the regulation of the p53 will result in impaired apoptosis and the possible formation of tumors.

HIV progression

The progression of the human immunodeficiency virus infection to AIDS is primarily due to the depletion of T-helper lymphocytes, which leads to a compromised immune system. One of the mechanisms by which T-helper cells are depleted is apoptosis.

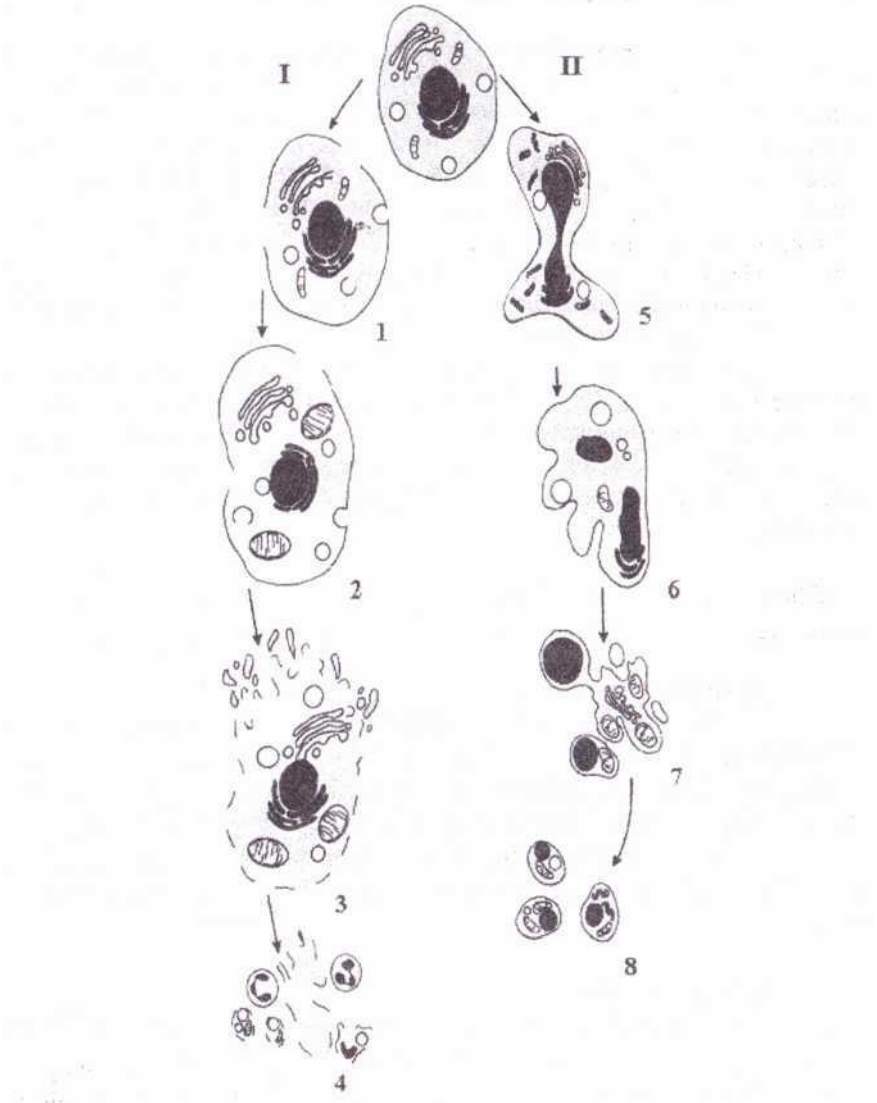


Figure 3.9. Changes occurring during necrosis and apoptosis. I - necrosis: **1** - injury at cell membrane, 2 — swelling, 3 - membrane breakdown, 4 — disintegration and inflammation; **II**- apoptosis: 5 - DNA fragmentation, 6 - decrease of cell volume, 7 - membrane blebbing, 8 - formation of apoptotic bodies.

BASES OF GENERAL EMBRYOLOGY

Embryology is a science which is about the formation, early growth, and development of an embryo from the fertilization of the ovum to the fetus stage.

Embryogenesis is the process by which the ***embryo*** is formed and develops, until it develops into a ***fetus.***

0 Structure of the spermatozoon

The human male sexual cell - ***spermatozoon*** is 60 pm long, actively motile.

Spermatozoon is divided into 3 main parts (fig.4.1):

> ***head***,
> ***neck*** (or ***connecting piece),*** and
> ***tail*** or ***flagellum.***

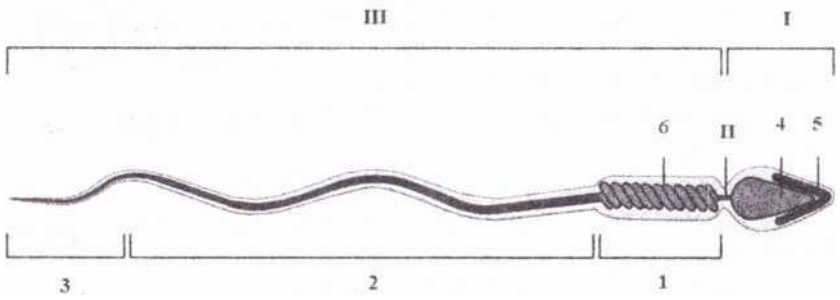


Figure 4.1. Structure of a spermatozoon. I - head, II — neck (connecting piece), III - tail: 1 — middle piece, 2 - principal piece, 3 - end piece; 4 — nucleus, 5 - acrosome, 6 — mitochondrial sheath

Flattened ***head*** of spermatozoon includes:

> a small dense ***nucleus*** with a haploid set of the chromosomes surrounded anteriorly by

> an ***acrosome***, which contains enzymes as hyaluronidase, corona penetrating enzyme used for penetrating the female egg; acrosome is derivative of Golgi complex.

The ***neck (connecting piece)*** is narrow, contains proximal ***centriole.***

The ***tail*** consists of ***middle piece, principal piece*** and ***end piece.***

The ***middle piece*** contains a ***distal centriole,*** a central ***axoneme*** with many ***mitochondria*** spiralled around it (helical ***mitochondrial sheath),*** used for ATP production for sperm motility. ***Axoneme*** consists of parallel microtubules in a characteristic "9x2+2" pattern, which is surrounded by the longitudinal dense fibers.

The ***principal piece*** constitutes most of the tail and consists of the ***axoneme*** surrounded by a sheath of fibers.

The ***end piece*** consists of the ***axoneme*** only and is the narrowest part of the sperm.

0 Structure of the ovum

The ***ovum (oocyte)*** is generally spherical, nonmotile gamete with yolky cytoplasm and enclosed in one or more egg envelopes (fig.4.2).

Size of ovum varies in different animals and depends upon the amount of yolk from 10 micrometers to a few centimetres. Largest sized egg is of ostrich and is about 170 x 135 mm.

The ***nucleus*** of an ovum is large, has haploid set of chromosomes.

The ***cytoplasm*** contains yolk inclusions, is differentiated into outer, smaller and transparent ***exoplasm*** or ***egg cortex*** and inner, larger and opaque ***endoplasm*** or ***ooplasm.***

Egg cortex is with some cytoskeletal structures like microtubules and microfilaments, and ***cortical granules*** of mucopolysaccharides.

Endoplasm is with cell organelles, informosomes tRNAs, histones, enzymes etc. ***Yolk granules*** contain proteins, phospholipids and carbohydrates used for a feed of a germ.

The side of ovum with nucleus is called ***animal pole,*** while the opposite side is called ***vegetal pole.***

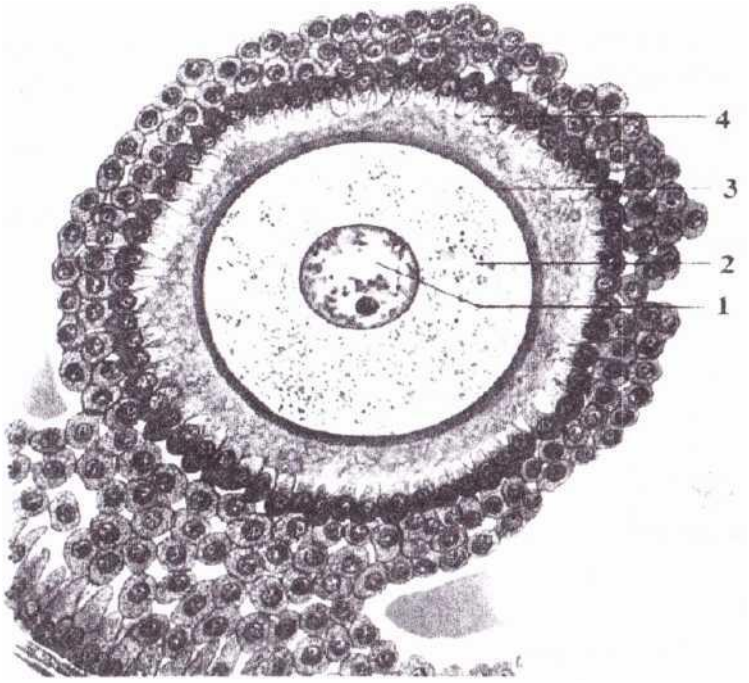


Figure 4.2. Structure of oocyte. 1 — nucleus, 2 - yolk inclusions in the cytoplasm, 3 — zona pellucida, 4 — follicular (corona) cells

Classification of the oocytes

Classifications of the oocytes are based on amount and distribution of a yolk (lecithos) in the cytoplasm.

Oocyte classification by amount of the yolk (fig.4.3):

> ***micro/ecithal.*** oligolecithal (very little yolk):
  - primary (amphioxus, sea urchin);
  - secondary (secondary yolk reduction) (placental mammals);

> ***mesolecithal*** (medium amount of yolk) (frog);

> ***macrolecithal***, polylecithal (with large amount of yolk) (bird).

Oocyte classification by distribution of the yolk (fig.4.4):

> ***telolecithal*** (y olk is distributed in gradient, concentrated at one pole of the egg, usually vegetal) (bird);

> ***isolecithal*** (yolk is evenly distributed throughout egg cytoplasm of microlecithal oocytes) (human);

> ***centrolecithal*** (the placement of the yolk in the centre of the cytoplasm of the oocyte).

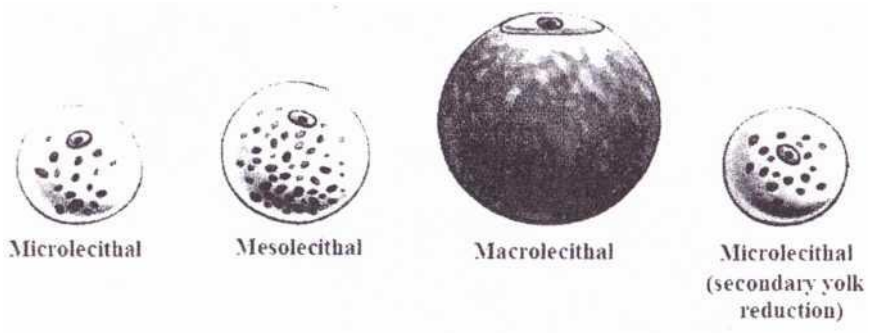


Fig. 4.3. Types of the oocytes by amount of the yolk.

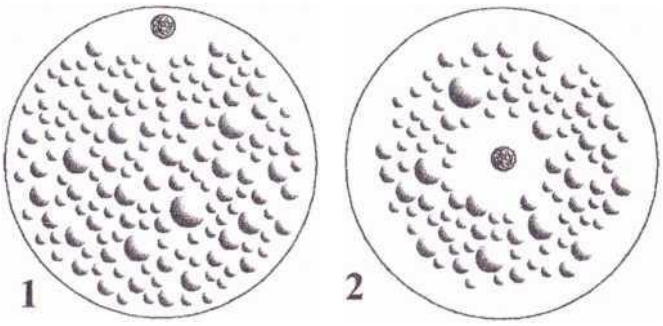


Fig. 4.4. Types of the oocytes by distribution of the yolk. - telolecithal, 2 - centrolecithal

0 Fertilisation

The ***fertilisation*** is the fusion of male and female sexual cells therefore it is restored diploid set of chromosomes, and arises 52

qualitatively new cell — ***a zygote*** (impregnated oocyte, or a monocelled germ) (fig.4.5). Fertilization of the ovum occurs in the ampulla of the uterine tube.

During fertilisation distinguish three phases:

1) chemotaxis;
2) sperm activation/acrosomal reaction;
3) sperm/egg adhesion.

1) . ***Chemotaxis*** is provided by the specific factors, secreted by sexual cells (hamons). During the time the sperm spend in the female reproductive tract, while swimming towards the oocyte, they acquire the capacity to fertilise it - a process called ***capacitation***.

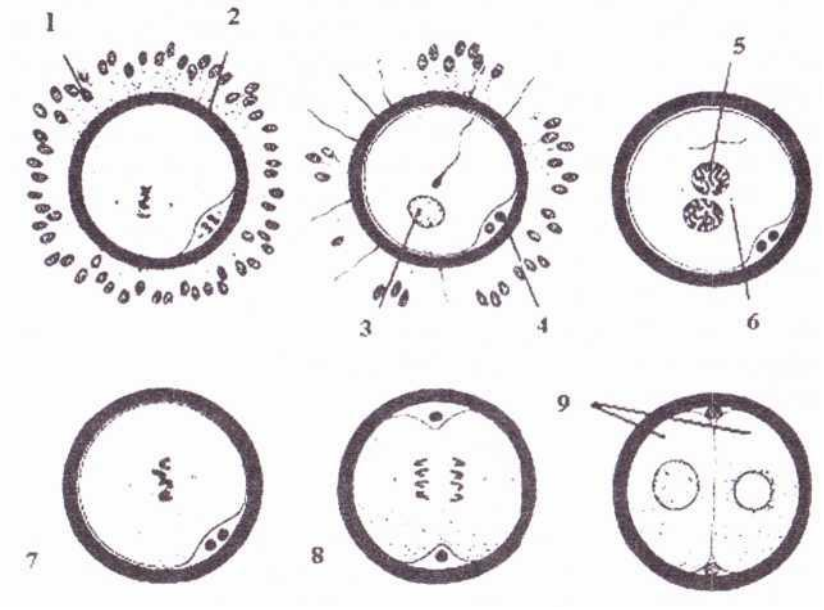


Figure 4.5 Fertilisation and beginning of cleavage. 1 - follicular cells, 2 - zona pellucida, 3 - female pronucleus, 4 -polar bodies, 5 -male pronucleus, 6 - centrosome, 7 - synkaryon, 8 - formation of spindle of chromosomes, 9 - twocell stage (from T. W. Sadler, 2004)

2) . When the sperms reach the corona cells of the oocyte they become hyperactivated - they start beating their tails.

The sperms disperse the cumulus oophorus and when they reach the oocyte, they first bind to the zona pellucida. A chemical is released here by the sperms in a process called the ***acrosomal reaction*** in which the acrosome is removed.

The acrosomal enzymes dissolve the zona pellucida. At this time, the oocyte transforms the zona to an ***impenetrable barrier***, thus preventing other sperm from entering it (***monospermia***).

The contact of the sperm with the oocyte surface results in the ***cortical reaction.***

The cortical reaction is exocytosis of the egg's cortical granules. When the fertilizing sperm contacts the egg plasma membrane, it causes calcium to be released from storage sites in the egg, raising the intracellular free calcium concentration. This triggers fusion of the cortical granule membranes with the egg plasma membrane, liberating the contents of the granules into the extracellular space. Fusion begins near the site of sperm contact, and then as the wave of calcium release sweeps around the egg, a wave of cortical granule fusion results.

3) The genetic material of the sperm (the male pronucleus) and the genetic material of the egg (the female pronucleus) then fuse - to form an embryo.

The ***results of fertilization*** are:

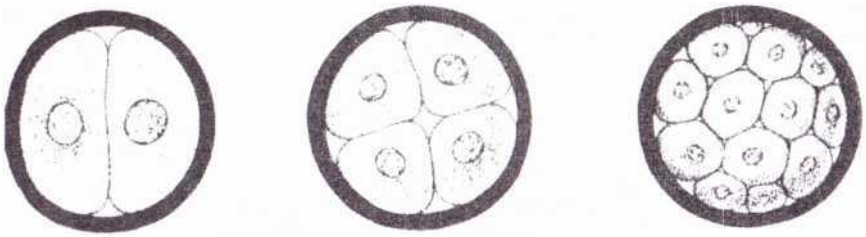
> restoration of diploid set of chromosomes;
> determination of the sex of new individual;
> beginning of the cleavage.

0 Cleavage

The ***cleavage*** is mitotic division of diploid cell (zygote) with increase the number of cells without increase of their total volume. These cells (***blastomeres)*** become smaller with each cleavage division.

Cleaving cells have a modified cell cycle, in which two phases, G| and G_2, are completely omitted. The cells cycle rapidly between M and S phases.

As a result of cleavage the multicellular germ, which looks like a mulberry or a dense congestion of cells (***morula***) (fig.4.6), and then as a bubble with a small cavity ***(blastula)*** is formed.



1 **2** **3**

Figure 4.6 Cleavage. 1 - two-cell stage, 2 - four-cell stage, 3 - morula (from T. W. Sadler, 2004)

Blastula has a wall - ***blastoderm*** and a ***cavity,*** filled with a liquid - a product of secretion blastomeres. In blastoderm distinguish the ***roof*** formed due to the shattered material of animal pole, ***a bottom*** — from a material of a vegetal pole and the ***regional zones*** located between them (fig-4.7).

The pole of the egg with the highest concentration of yolk is referred to as the ***vegetal pole*** while the opposite is referred to as the ***animal pole*** (fig. 4.8).

Type of cleavage

The pattern of cleavage is determined by the ***amount of yolk*** in the egg, which was fertilized (fig.4.8 4.9).

Depending mostly on the amount of yolk in the egg, the cleavage can be ***holoblastic*** (total or entire cleavage) or ***meroblastic*** (partial cleavage).

In the absence of a large concentration of yolk, ***holoblastic*** cleavage can be observed in ***isolecithal*** cells (cells with a small even distribution of yolk) or in ***mesolecithal*** cells (moderate amount of yolk in a gradient).

In the presence of a large amount of yolk in the fertilized egg cell, the cell can undergo ***partial***, or ***meroblastic***, cleavage.

In eggs with less yolk, cleavage is ***equal,*** and the resulting blastomeres are of similar size. If the yolk is localized, such as in frog eggs, then cleavage is ***unequal*** - the cells derived from the yolky region

(the vegetal pole) are larger than those derived from the region without yolk (the animal pole) (fig. 4.8).

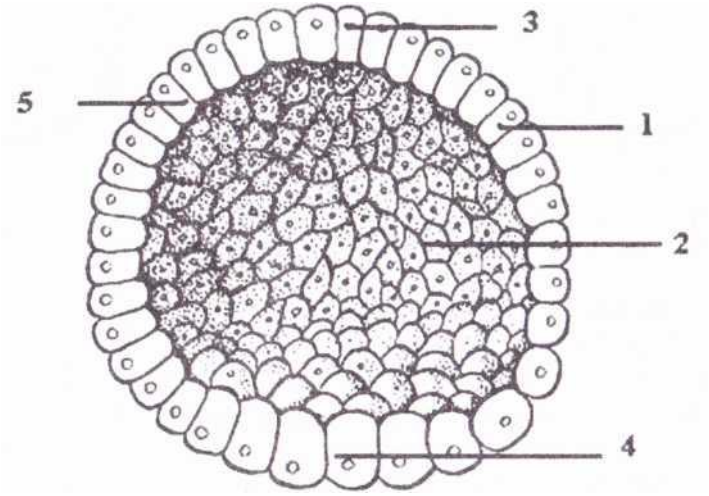
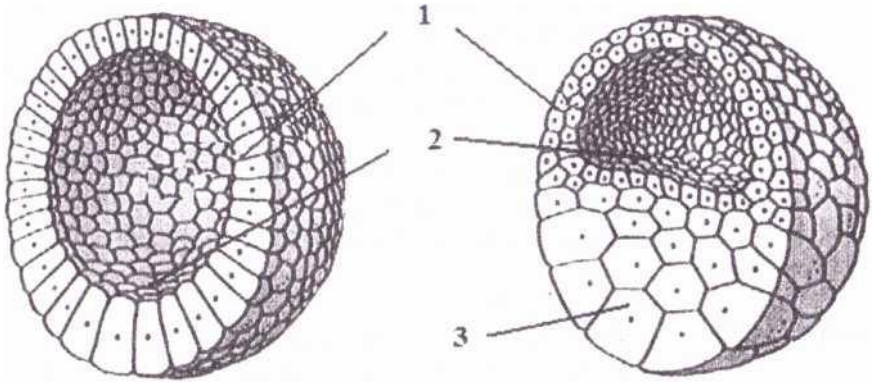


Figure 4.7 Schematic diagram of blastula. 1 - blastoderm, 2 -cavity, 3 - roof, 4 - bottom, 5 - regional zone



I **II**

Figure 4.8 Schematic diagrams of blastulae. I - sea urchin (equal cleavage); IT — frog (unequal cleavage); 1 - blastoderm, 2 — blastocoele, 3 — vegetal pole

In the very yolky - ***telolecithal*** - eggs (of fish and birds), the cleavage is slowed, or even blocked, by the presence of the yolk. Complete divisions are restricted to the least yolky region of the egg, and the embryo forms as a cap of cells sitting on top of the yolk (fig. 4.9).

Primary microlecithal isolecithal oocytes (sea urchin) divide full and in regular intervals - ***holoblastic*** (total) ***equal cleavage.***

In ***mesolecithal oocytes*** cleavage is total, but unequal in a vegetal pole where the yolk is concentrated. Such type of cleavage is termed as ***holoblastic*** (total) ***unequal.***

Macrolecithal oocytes have ***meroblastic cleavage*** (only a part of oocyte divides at animal poles).

Secondary microlecithal oocytes of placental mammals have ***holoblastic unequal asynchronous cleavage.***

E3 Gastrulation

The ***gastrulation*** is complex process of chemical and morphogenetic changes, accompanying with reproduction, growth, directed moving and differentiation of cells therefore germ layers are formed: external ***(ectoderm),*** middle ***(mesoderm)*** and internal ***(endoderm)*** — sources of tissues and organs, complexes of axial organs.

Types of gastrulation

Four basic types of gastrulation are distinguished: ***delamination, immigration, invagination***, and ***epiboly.*** The result of gastrulation is formation of the ***gastrula.***

> ***Delamination*** (fig. 4.10 - 1) is the process in which the cells split, converting the one-layered wall of the embryo to a two-layered one - external ***ectoderm*** and internal ***endoderm.***

> In ***immigration***, or settlement, (fig. 4.10-2) certain cells move to the interior of the embryo and settle under the superficial layer, forming a middle layer - ***mesoderm***; immigration may be unipolar (settlement from one place) or multipolar (from various places).

> ***Invagination***, or intrusion, (fig. 4.10 - 3) is the process by which the wall of a one-layered embryo gradually turns inward and forms external layer - ***ectoderm*** an internal layer - ***endoderm.***

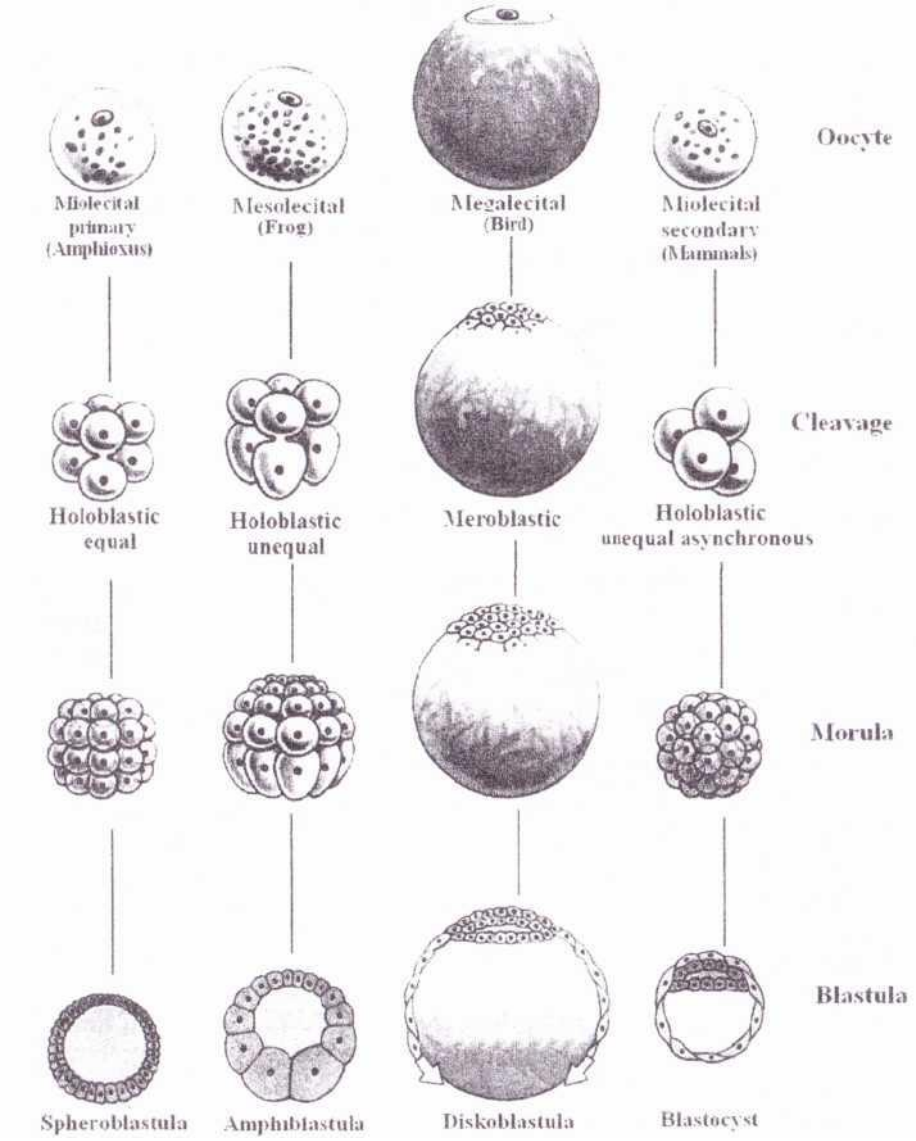


Figure 4.9. Schematic diagrams of the types of cleavage, blastulae, and gastrulae

> In ***epiboly,*** or overgrowth, (fig. 4.10 - 4) relatively large cells (macromeres) rich in yolk are overgrown by the small ones (micromeres) and find themselves inside, forming an internal layer.

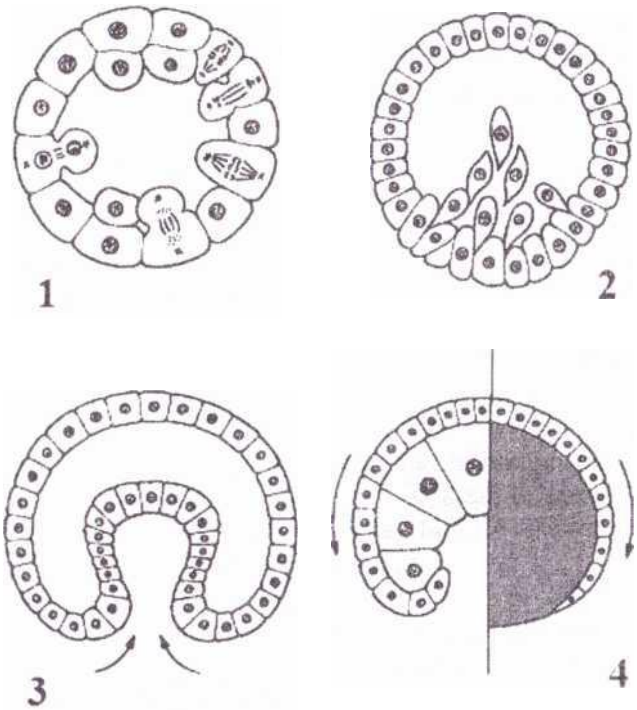


Figure 4.10. Schematic diagrams of ways of gastrulation. 1 - delamination, 2 - immigration, 3 - invagination, 4 - epiboly

13 Differentiation of the embryonic layers

Differentiation of the ectoderm

Ectoderm is subdivided into:

> extraembryonic being by a source of formation of amnion and
> intraembryonic.

Intraembryonic ectoderm gives rise to:

• neural tube (brain and spinal cord);

- prechordal plate (epithelium of oral cavity, oesophagus, respiratory tract);
- placodes (the internal ear);
- neural crests (neurons of the sensory spinal and autonomic ganglia; cells of the adrenal medulla; pigment cells of the skin);
- skin ectoderm (epidermis and its derivatives, epithelium of cornea, enamel of teeth, epithelium of vagina and the anal canal of the rectum).

At a differentiation of the ***ectoderm*** germ parts - skin ectoderm, neuroectoderm, placodes, notochord, and extraembryonic ectoderm, being by a source of formation amnion, are formed.

The smaller part of ectoderm, located above a notochord ***(neuroectoderm),*** gives rise to a differentiation ***of a neural tube*** and ***neural crests.***

Neural tube gives rise to the brain and spinal cord.

Neural crests give rise to the neurons of the sensory spinal ganglia and V, VII, VIII, IX, X cranial nerves; the neurons of sympathetic ganglia; the cells of the adrenal medulla; chromaffin tissue; the pigment cells of the skin.

The most part of intraembryonic ectoderm is formed ***skin ectoderm,*** giving rise of the stratified squamous epithelium of skin (epidermis) and its derivatives, epithelium of cornea, epithelium of organs of a mouth, enamel of teeth, epithelium of the anal canal of the rectum, epithelium of vagina.

Placodes give rise to epithelial structures of the internal ear.

Most of ***notochord*** disappears, but parts of it persist in the region of each intervertebral disc as the ***nucleus pulposus.***

Differentiation of endoderni

The differentiation of ***endoderm*** results to formation in a body of an embryo of an ***intestinal tube*** and to formation ***extra-embryonic endoderni***

From endoderm of an intestinal tube develops simple epithelium of a stomach, intestines and those glands, epithelium of a liver and a pancreas.

Extra-embryonic endoderm gives rise to epithelium of yolk sac and allantois.

Differentiation of mesoderm

The intra-embryonic mesoderm is subdivided into 3 parts.

1. The ***paraxial mesoderm*** - the cells, on either side of the notochord.

The ***paraxial mesoderm*** is segmented into cubical masses called ***somites.*** Somites are differentiated on 3 parts:

> ***myotome,*** giving rise a skeletal muscular tissue,

> ***sclerotome,*** being a source of development bone and cartilage tissues, and also

> ***dermatome,*** forming dermis of a skin.

Process of segmentation of the paraxial mesoderm and formation of the somites begins in a head part of an embryo and is quickly distributed in caudal direction.

More laterally, the mesoderm forms a thinner layer called the ***lateral mesoderm*** It is not segmented, and split on two parts - ***visceral*** or ***splanchnopleuric*** (giving rise of heart, adrenal cortex, stroma of testes and ovary, connective and smooth muscle tissues of internal organs and blood vessels) and ***parietal,*** or ***somatopleuric*** (giving rise of serous membranes).

Between these two, there is a longitudinal strip of mesoderm called ***intermediate mesoderm*** (giving rise of the organs of urogenital system).

Mesenchyme

The ***mesenchyme*** is the undifferentiated connective tissue found in the early embryo between the embryonic layers and axial organs. Most mesenchyme is derived from mesoderm.

Mesenchyme consists of small stellate (star) shape cells containing large oval nuclei with prominent nucleoli. Processes of mesenchymal cells extend and contact those of other cells to form a three dimensional cellular network (fig.4.11). A semi-fluid ground substance fills the extracellular spaces. Fibers are present, but are very fine and sparse.

Mesenchymal cells are multipotential cells that can be transformed into other types.

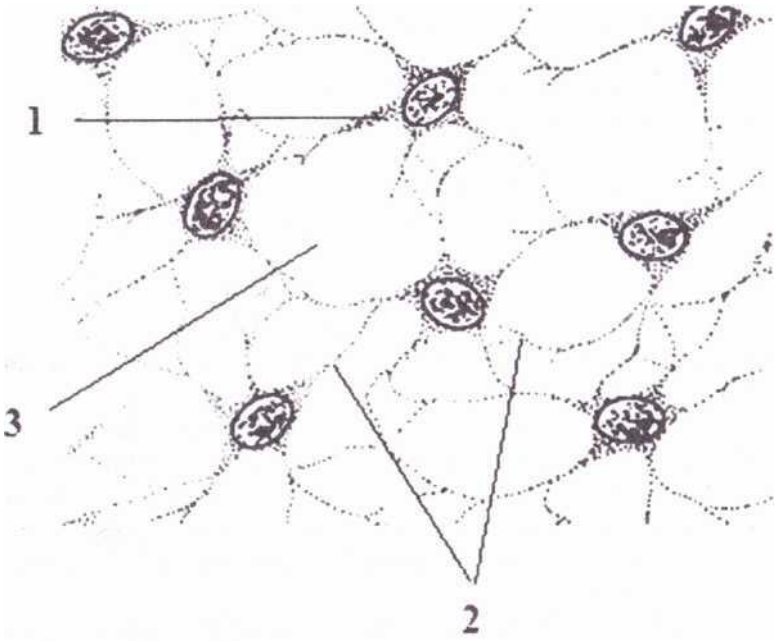


Figure 4.11. **Mesenchyme.** 1 - nuclei of mesenchymal cells, 2 - processes of mesenchymal cells, 3 - matrix

Mesenchyme gives rise to all the connective tissues of the body, as well as to some other tissue:

> connective tissues;
> walls of blood vessels;
> cells of blood and lymph;
> smooth muscle tissue;
> microglia of nerve tissue.

0 Fetal organs

The ***fetal organs*** develop in process of embryo development outside of its body; carry out the different functions providing growth and development of the germ.

These are ***yolk sac, amnion, allantois umbilical chord, chorion, and placenta.***

Yolk sac

The ***yolk sac*** is a membranous sac attached to an embryo, providing early nourishment in the form of yolk.

The yolk sac develops from extra-embrvonic endoderm and extra-embryonic mesoderm (fig.4.12).

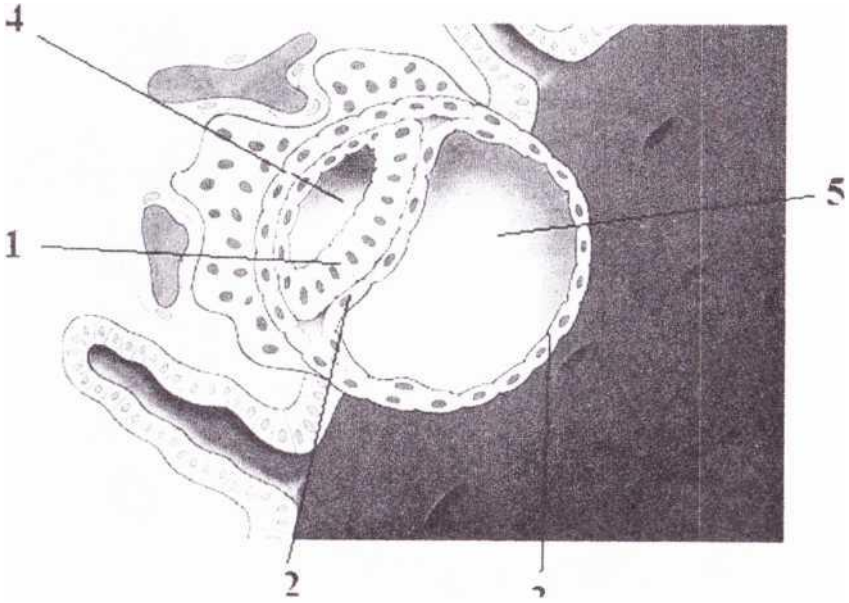


Figure 4.12. Formation of the yolk sac and amnion. 1 - ectoderm, 2 - endoderm, 3 - extra-embryonic endoderm, 4 - amniotic cavity, 5 - yolk sac

Yolk sac carries out trophic and hematopoietic functions (primitive blood cells begin to form first in the yolk sac).

Amnion

The ***amnion*** is a membrane building the amniotic sac that surrounds and protects an embryo. The primary function of this organ is the protection of the embryo for its development. It stems from parts of the mesoderm on the outer side and the ectoderm on the inner side (fig.4.12). ***Amnion*** contains amniotic fluid in which there is a fetus.

Allantois

The ***allantois*** is a small endodermal diverticulum arises from the yolk sac near the caudal end of the embryo. This diverticulum grows into the extra-embryonic mesoderm (fig.4.13). Allantois helps the embryo exchange gases and handles liquid waste.

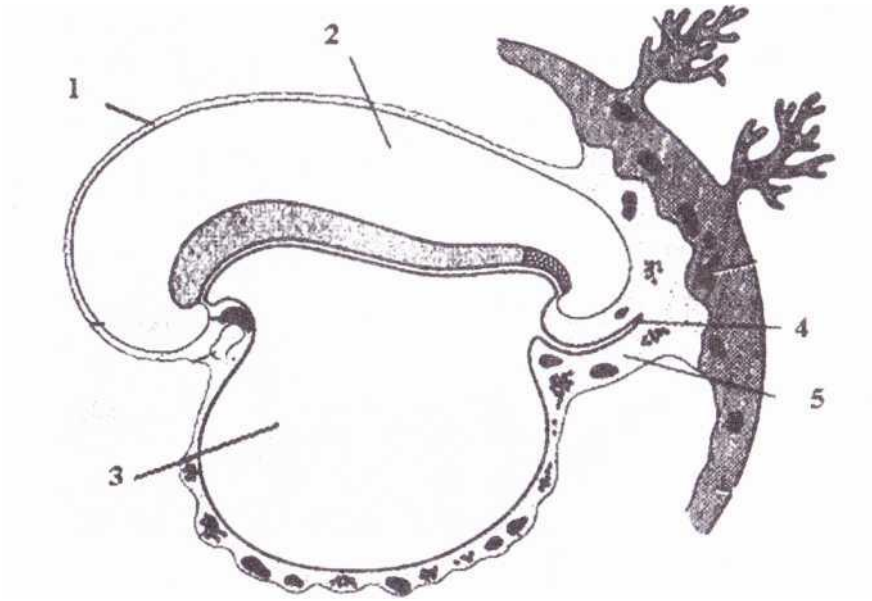


Figure 4.13. Formation of the allantois. 1 — amnion, 2 - amniotic cavity, 3 — yolk sac, 4 - allantois, 5 — connecting stalk of the extra-embryonic mesoderm

Chorion

The ***chorion*** is one of the membranes that exist during pregnancy between the developing fetus and mother. It is formed by extraembryonic mesoderm and two layers of trophoblast (syncytiotrophoblast and cytotrophoblast) and surrounds the embryo and other membranes. The chorionic villi emerge from the chorion, invade the endometrium, and allow transfer of nutrients from maternal blood to fetal blood.

Placenta

The ***placenta*** is an organ that connects the developing fetus to the uterine wall to allow nutrient uptake, waste elimination, and gas exchange via the mother's blood supply.

Functions of placenta

> Nutrition, gas exchange, waste elimination.

> Endocrine (placenta secretes hormone that are important during pregnancy human chorionic gonadotropin, human placental lactogen, estrogen, progesterone, relaxin).

> Protective

HUMAN EMBRYOLOGY. PLACENTA

In the development of an individual organism which is termed the ***ontogeny,*** distinguish two main periods: ***prenatal*** and ***postnatal*** development.

Prenatal development is the period from the time of fertilisation until birth.

Postnatal development is the period beginning immediately after the birth of a child and extending for about six weeks.

Human prenatal development can be divided into three stages:

> ***initial*** (1-st week of development),
> ***embryonic*** (2-8 week of development),
> ***fetal*** (since 9-th week of development till a birth of the child).

Duration of human prenatal development is nine months (38- 40 weeks or 266-280 days).

The ***initial stage*** begins with ***fertilization.*** The fertilized egg (a zygote) moves toward the uterus. Cell division of a zygote begins approximately 24 to 36 hours after fertilization. Cell division continues at a rapid rate and the cells then develop into a ***blastocyst*** Blastocyst is attached to the uterine wall (***implantation***).

The ***embryonic stage (embryogenesis)*** begins after implantation and continues until cell differentiation into the various body systems has been mostly completed. Structures, including the placenta and umbilical cord, important to the support of the embryo, develop.

Embryogenesis consists of the main stages:

> fertilization and zygote formation;
> cleavage and blastocyst formation; ***y***

implantation;

> gastrulation (formation of the germ layers);
> histogenesis (formation of different tissues from undifferentiated cells, which are constituents of three primary germ layers);
> organogenesis (period of human development during which the embryo is becoming a fully functional organism capable of independent survivia);
> systemogenesis (formation of the the functional systems).

0 Structure of a mature spermatozoon

Human male sexual cell - ***spermatozoon*** is 60 pm long, actively motile.

Spermatozoon is divided into 3 main regions ***(head, neck*** (or ***connecting piece),*** and ***tail*** or ***flagellum);*** it is covered by plasmolemma which contains a receptor in a forward department, providing of the recognizing of receptors of oocyte (fig.5.1).

Flattened ***head*** of spermatozoon includes:
> small dense ***nucleus*** with a haploid set of the chromosomes (22 +X or 22 +Y; 50% of them have 22 +X chromosomes, 50% - 22 + Y chromosomes) surrounded anteriorly by
> an ***acrosome,*** which contains enzymes as hyaluronidase, corona penetrating enzyme used for penetrating the female egg; acrosome is derivative of Golgi complex.

The ***neck*** (***connecting piece***) is narrow, contains proximal ***centriole.***

The ***middle piece of the tail*** contains a ***distal centriole,*** a central ***axonema*** with many ***mitochondria*** spiralled around it, used for ATP production for for sperm motility. ***Axonema*** consists of parallel microtubules in a characteristic ***"9x2+2"*** pattern. This pattern describes 9 outer microtubule doublets (pairs) surrounding 2 central singlet microtubules. The motor protein dynenin move the outer microtubules with respect to the central pair, bending the flagella and generating motility. ***Axonema*** is surrounded by the longitudinal dense fibers.

The ***principal piece of the tail*** constitutes most of the tail and consists of the ***axoneme*** surrounded by a sheath of fibers.

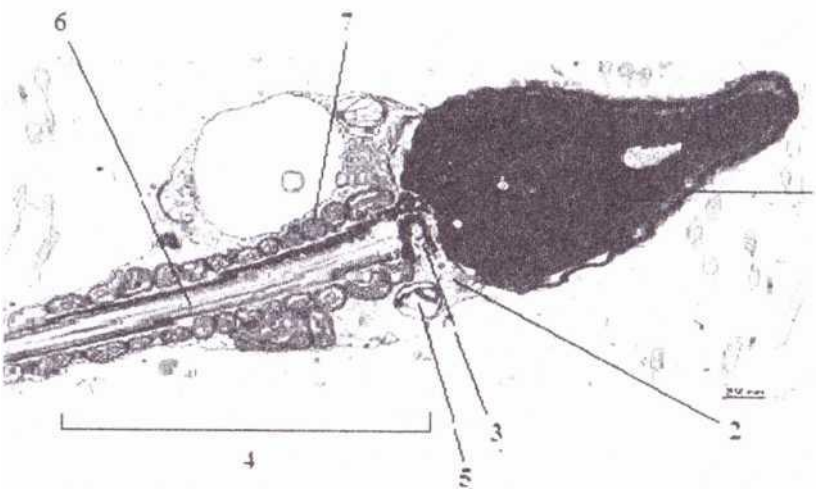


Figure 5.1. Electron micrograph of a spermatozoon.] - head, 2 - neck (connecting piece), 3 - proximal centriole, 4 - middle pieceof the tail, 5 - distal centriole, 6 - axonema, 7 - mitochondrial sheath

The ***end piece of the tail*** consists of the ***axoneme*** only and is the narrowest part of the sperm.

Human spermatozoa are formed during all active sexual period in plenty. Duration of spermatozoon development makes about 72 days.

At research of sperm in clinical practice carry out calculation of various forms of spermatozoa in painted smears, counting up their percentage.

According to the World Health Organization (WHO), normal characteristics of human sperm are the following parameters: concentration of 20-200 million per ml, the contents more than 60 % of normal forms. Among the spermatozoa should contain live cells of 75 % and more, and actively mobile - 50 % and more.

In sour environment spermatozoa quickly lose ability to movement and fertilization.

0 Structure of the ovum

Formation of female sexual cells (oogenesis) is made in the ovary cyclically, thus during ovarian cycle each 24-28 days, as a rule, one primary oocyte is formed.

Human female sexual cell - ***oocyte*** or ***ovum*** is large spherical cell, has no ability to move.

The nucleus of the human oocyte contains 23 chromosomes; one of them is a sexual X-chromosome.

Human oocyte is ***secondary miolecithal isolecithal*** with a small even distribution of yolk and large amount of cytoplasm (fig.5.2). Presence of small quantity of a yolk in oocyte is caused by development of a germ in an organism of mother. Yolk granules contain proteins, phospholipids and carbohydrates.

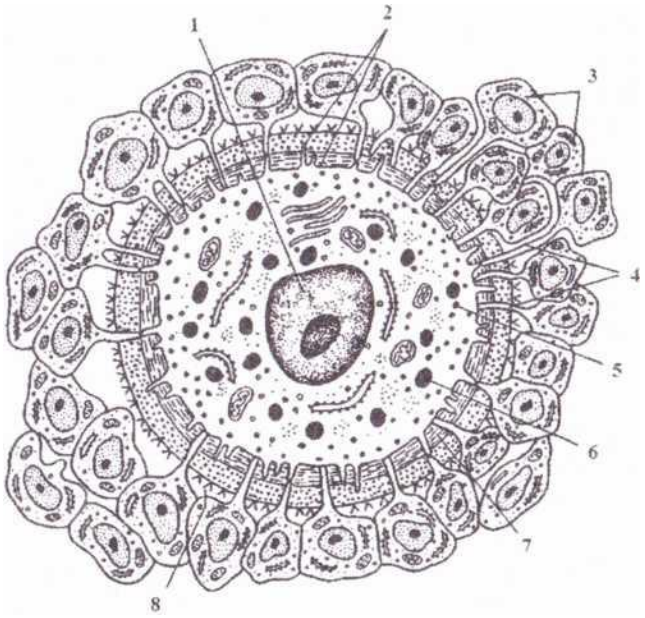


Figure 5.2. Structure of the human ovum. 1 — nucleus, 2 - cytolemma, 3 - follicular epithelium, 4 - corona radiata, 5 - cortical granules, 6 - yolk inclusions, 7 - zona pellucida, 8 - receptors (from *lO.H.Afpmacbee, H.A JOpuna u dp.*, 1999)

Human ovum is surrounded by a number of egg envelopes:

> ***Vitelline membrane*** is inner, thin, and transparent and is secreted by ovum itself.

> ***Zona pellucida*** is middle, thick, transparent and noncellular, composed of glycoproteins.

> ***Corona radiata*** is outer, thicker coat formed of stratified follicular epithelium. The processes of follicular cells penetrate through a zona pellucida, going to ova. Follicular cells carry out trophic and protective functions.

Between the vertiline membrane and zona pellucida, there is a narrow ***perivitelline space.***

Ef Fertilisation

Female gamete (***oocyte***) is produced during the menstrual cycle and expelled during the ***ovulation.*** During each ovarian cycle, only one follicle with an oocyte reaches full maturity. At the 14th day in an average 28-day cycle this follicle bulges on the surface of the ovary. Immediately before the ovulation, the oocyte and some surrounding cells 0***cumulus oophorus)*** detach from the interior of the follicle. Also, shortly before the ovulation the fimbriae of the oviduct start covering the surface of the ovary. During ovulation, follicle bursts and the oocyte is expelled into the uterine tube.

The expelled secondary oocyte is surrounded by the ***zona pellucida*** and several layers of the ***follicular cells*** arranged as the ***corron a radiata.*** Male gametes are produced during the spermatogenesis and stored in the epididymis. Upon ejaculation into the female genital tract, the spermatozoa are not capable of fertilizing the oocyte. They must undergo a ***capacitation*** period that lasts approximately 7 hours, during which the glycoprotein coat and seminal proteins are removed from the surface of the sperm acrosome by the action of the substances secreted by uterus or uterine tubes. When capacitated spermatozoa come into contact with the corrona radiata surrounding the secondary oocyte, they undergo the ***acrosomal reaction.*** This process includes release of the acrosomal vesicles enzymes that helps the sperm digest its way to the oocyte plasma membrane in order to fuse with it.

Fertilization, the process by which the male and female gametes fuse, marks the beginning of the pregnancy. It lasts 24 hours and occurs in the ampullar)' region of the uterine tube. The first event is the scattering of the corrona radiata cells by the released contents of the acrosomal vesicle (hyaluronidase), tubal mucosa enzymes and sperm tail movements. Penetration of the zona pellucida is enabled by the action of other enzymes released from the acrosome (acrosin and neuraminidase). When the first sperm passes through the zona pellucida, enzymes of cortical granules diffuse into the zona pellucida and ***zona reaction*** make it impermeable to other sperms. This mechanism ensures that each oocyte is fertilized by only one sperm.

When the sperm enters the oocyte, it leaves its plasma membrane behind. After the sperm entry, the secondary oocyte finishes its second meiotic division, forming an ***ovum*** and a second polar body. The nucleus of the mature oocyte is known as the ***female pronucleus. Male pronucleus*** is formed by the enlarging of the nucleus in the head of the sperm. During the growth of the pronuclei they replicate their DNA. Fertilization ends with the fusion of female and male pronucleus and formation of the ***zygote.*** Within 24-48 hours after fertilization, early pregnancy factor (EPF) can be detected in the maternal serum.

E3 Clinical correlations

Infertility

Infertility is a problem for 15% to 30% of couples.

Male infertility may be a result of insufficient numbers of sperm and/or poor motility. Normally, the ejaculate has a volume of 3 to 4 ml, with approximately 100 million sperm per ml. Males with 20 million sperm per ml or 50 million sperm per total ejaculate are usually fertile.

Infertility in a woman may be due to a number of causes, including occluded oviducts (most commonly caused by pelvic inflammatory disease), hostile cervical mucus, immunity to spermatozoa, absence of ovulation, and others.

In vitro fertilization (IVF)

In vitro fertilisation is a process by which egg cells are fertilised by sperm outside the uterus, in vitro. IVF is a major treatment in infertility when other methods of assisted reproductive technology have failed.

Follicle growth in the ovary is stimulated by administration of gonadotropins. Oocytes are recovered by laparoscopy from ovarian follicles with an aspirator just before ovulation when the oocyte is in the late stages of the first meiotic division. The egg is placed in a simple culture medium and sperm are added immediately. Fertilized eggs are monitored to the eight-cell stage and then placed in the uterus to develop to term. Fortunately, because preimplantation-stage embryos are resistant to teratogenic insult, the risk of producing malformed offspring by in vitro procedures is low.

A disadvantage of IVF is its low success rate; only 20% of fertilized ova implant and develop to term. Therefore, to increase chances of a successful pregnancy, four or five ova are collected, fertilized, and placed in the uterus. This approach sometimes leads to multiple births.

The first successful birth of a "test tube baby", Louise Brown, occurred in 1978. Louise Brown was born to Lesley and John Brow'n, who had been trying to conceive for nine years, but without success because of Lesley's blocked fallopian tubes. On 10 November 1977, Lesley Brown underwent the procedure developed by Patrick Steptoe and Robert Edwards in Oldham, Greater Manchester, UK.

Edwards was awarded the 2010 Nobel Prize in Physiology or Medicine "for the development of in vitro fertilization".

E3 Cleavage

After the fertilization, the zygote undergoes a series of rapid divisions called ***cleavage*** (fig. 5.3).

Cleavage of human zygote is ***holoblastic unequal asynchronous.***

The zygote first divides into two cells known as ***blastomeres*** (30 hours after fertilization). Three days after the fertilization, a rapid

increase in the number of the cells results in the formation of a solid ball of 12-16 cells, the ***morula.***

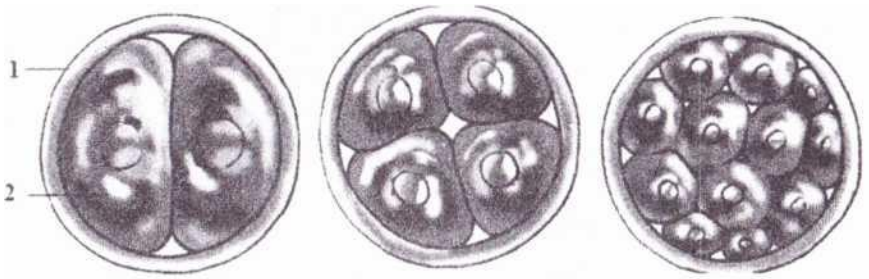


Figure 5.3. Human cleavage. I - two-cell stage: 1 - zona pellucida, 2 - blastmere; II - four-cell stage; III - morula

These repeated mitotic divisions happen during the zygote's passage through the uterine tube toward the uterus. Four days after fertilization, when the morula enters the uterus, fluid-filed spaces between the blastomeres appear and fuse into a central cavity called the ***blastocoele.*** At this stage of the development, the conceptus is called a ***blastocyst.***

The blastocyst (tlg.5.4) consists of ***inner cell mass (embryoblast)*** and ***outer cell mass (trophoblast).*** Embryoblast gives rise to the embryo and a part of the amnion. The trophoblast cells form most of the extraembryonic membranes, i.e., the bulk of the placenta.

During the 6th day after fertilization, the blastocyst attaches to the endometrial epithelium with its embryonic pole. This triggers the differentiation of the trophoblast into an inner ***cytotrophoblast*** and an outer ***syncytiotrophoblast.*** By the end of the first week, the blastocyst is superficially implanted. At about seven days a flattened layer of cuboidal cells, called ***hypoblast (endoderm),*** appears on the surface of the embryoblast.

In 5-5, 5 days blastocyte gets in a uterus. During about 2 days (with 5 for 7 day) the germ passes a stage of ***free blastocyte.***

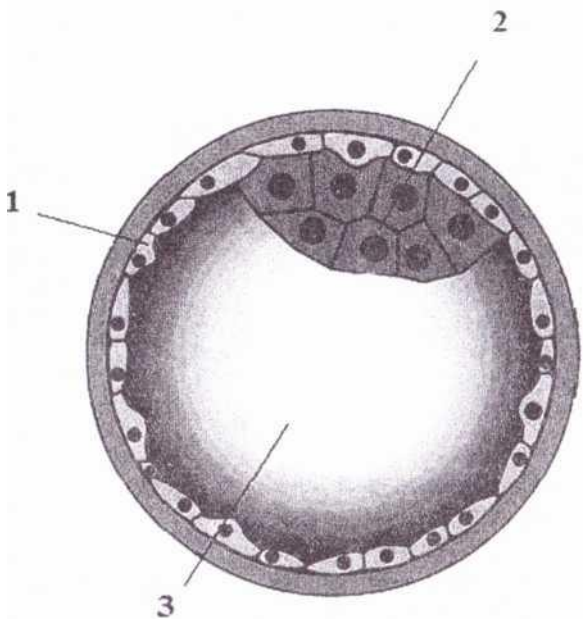


Figure 5.4. Schematic diagram of human blastocyst. 1 - trophoblast, 2 - inner cell mass (embryoblast), 3 - blastocyst cavity (blastocoele)

0 Implantation

The blastocyst usually implants on the posterior uterine wall. The ***implantation*** begins on the day 7 post-fertilization and and continues during about 40 hours.

Two stages of implantation distinguish: ***adhesion*** and ***invasion*** (***penetration***).

> At the ***first stage*** (day 7 post-fertilisation) the trophoblast of the blastocyst attaches to the endometrial epithelium (fig. 5.5).

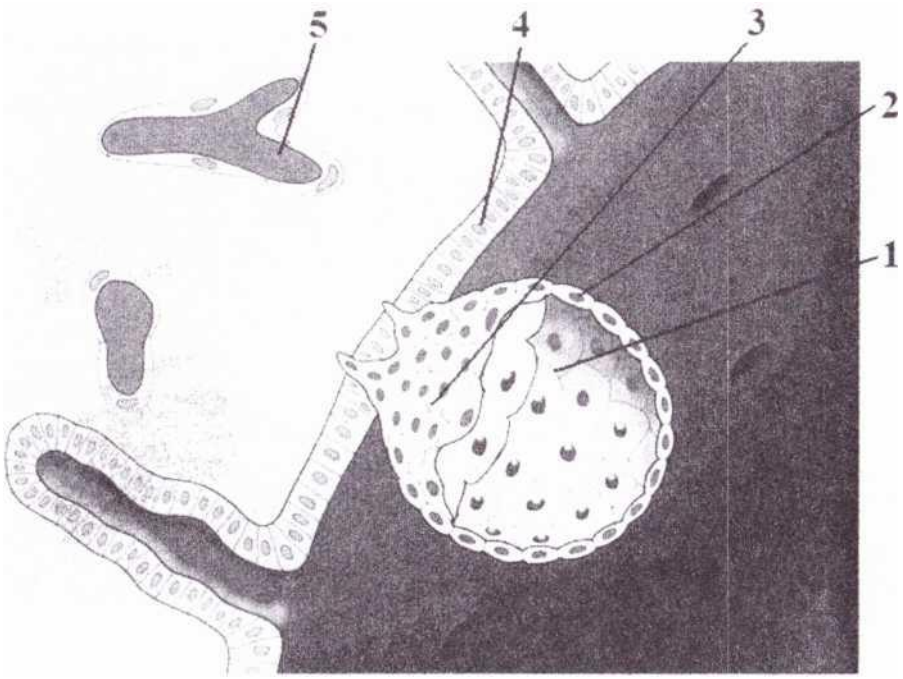


Figure 5.5. Implantation. Phase of adhesion. Day 6 post-fertilisation. 1 - blastocyst, 2 — trophoblast, 3 - inner cell mass, 4 - epithelium of endometrium, 5 - uterine vessels

During implantation, the trophoblast forms two layers - an outer ***syncytiotrophoblast*** and an inner ***cytotrophoblast.*** The inner cell mass becomes organised into a two-layered plate of cells called the ***embryonic disc,*** with the amniotic cavity above and the yolk sac below. These layers are ***ectoderm*** and ***endoderm*** (fig. 5.6).

> During the ***second stage*** syncytiotrophoblast, producing enzymes destroys the endometrium of the uterus (fig.5.7). Thus formed villi of trophoblast, invading in the uterus, consistently destroy its epithelium, then the connecting tissue and walls of vessels, and trophoblast enters direct contact to blood of mother vessels.

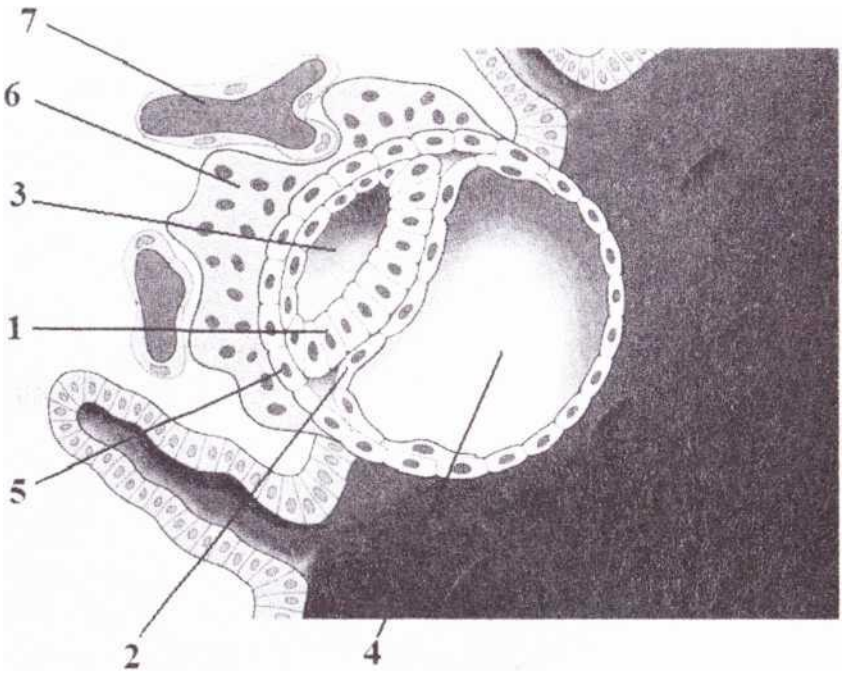


Figure 5.6. Implantation. 1 - ectoderm, 2 — endoderm, 3 — amniotic cavity, 4 — yolk cavity, 5 - cytotrophoblast, 6 - syncitiotrophoblast, 7 - uterine vessels

At the beginning of the second week the blastocyst is embedded in the endometrial stroma. The endometrial cells around the early conceptus enlarge and accumulate glycogen and lipids. These cellular changes, together with the vascular and glandular alterations in the endometrium, are called the ***decidual reaction.***

Three different regions of the ***decidua*** are identified according to the implantation site. The ***decidua basalis*** is the portion of the endometrium that underlies the implantation site. The decidua basalis torms a compact layer, called the ***decidual (basal) plate.*** The ***decidua capsularis*** is a thin portion of the endometrium that overlies the conceptus. The ***decidua parietalis (vera)*** includes the remaining endometrium of the uterus and the cervix (fig.5.8).

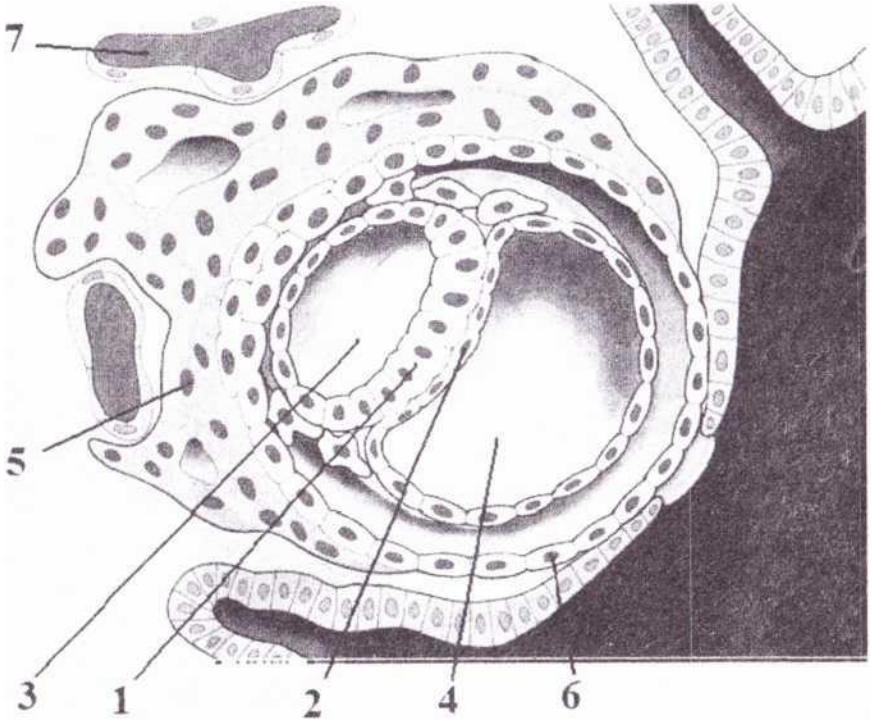


Figure 5.7. Implantation. Phase of invasion. Day 9 post-fertilisation. 1 - ectoderm, 2 — endoderm, 3 - amniotic cavity, 4 - yolk cavity, 5 - syncitiotrophoblast, 6 -cytotrophoblast, 7 — uterine vessels

Nutrition of the conceptus is initially ***histiotrophic*** - the uptake of oviductal and uterine secretions by the trophoblast.

Later, it switches to ***haemotrophic*** nutrition - exchange between the maternal and fetal circulations within the placenta.

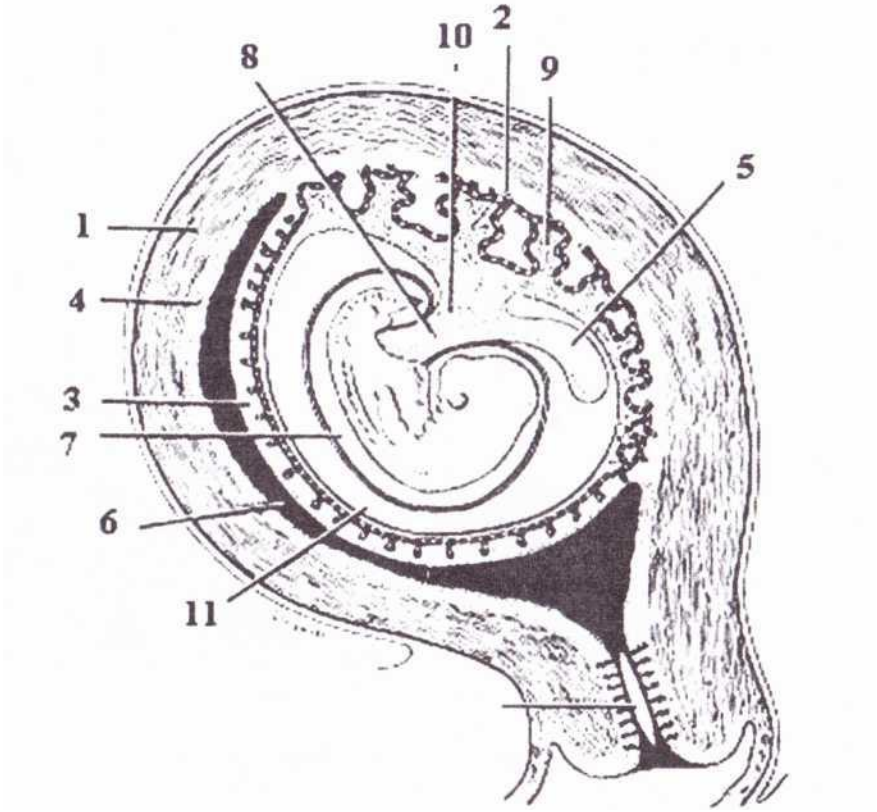


Figure 5.8. **The regions of the decidua.** 1 — myomertrium, 2 — decidua basalis, 3 - decidua capsularis, 4 - decidua parietalis, 5 - yolk sac, 6 - uterine cavity, 7 - amniotic cavity, 8 - umbilical cord, 9 - chorionic villi, 10 - allantois, 11 - chorionic cavity

0 Clinical correlations

Ectopic implantation

The embryo may be arrested during its migration through the uterine tube and implant in its wall. Previous pelvic inflammation damages the tubal epithelium and may predispose to such delay in tubal transport. Ectopic pregnancy may cause rupture of the uterine tube and catastrophic intraperitoneal haemorrhage.

Multiple pregnancy (fig.5.9)

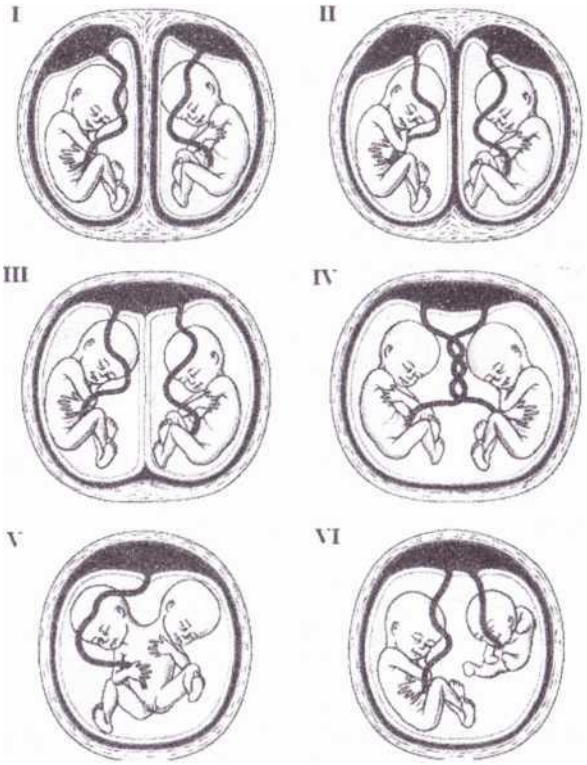


Fig. 5.9. Relationships of the extraembryonic membranes in different types of twinning. I- diamnionic, dichorionic separated; i.e. separation of the first two blastomeres results in separate implantation sites; II - diamnionic, dichorionic fused: the chorionic membranes are fused, but the fetuses occupy separate choria; III -diamnionic, monochorionic: reduplication of the inner cell mass can result in a single placenta and chorionic sacs, but separate amniotic cavities; IV - monoamnionic, monochorionic: duplication of the embryonic axis results in two embryos sharing a single placenta, chorion and amnion; V - incomplete separation of the embryonic axis results in conjoined twins; VI - unequal division of the embryonic axis or unequal division of the blood supply may result in an acardiac monster (from Gray's Anatomy, 2008)

Dizygotic twins are derived from two zygotes that were fertilized independently (i.e., two oocytes and two spermatozoa).

Consequently, they are associated with two amnions, two chorions, and two placentas, which may (65%) or may not (35%) be fused. Dizygotic twins are only as closely genetically related as any two siblings.

Monozygotic twins (30%) are derived from one zygote that splits into two parts. This type of twins commonly has two amnions, one chorion, and one placenta. If the embryo splits early in the second week after the amniotic cavity has formed, the twins will have one amnion, one chorion, and one placenta. Monozygotic twins are genetically identical, but may have physical differences due to differing developmental environments (e.g., unequal division of placental circulation).

0 Gastrulation

Gastrulation is complex process of formation of three germ layers of the embryo: ***ectoderm***, ***mesoderm,*** and ***endoderm.***

Human gastrulation occurs in two phases.

The ***first phase*** of the gastrulation precedes implantation or goes during it (day 7 post-fertilisation). This phase occurs by ***delamination,*** thus the inner cell mass (embryoblast) differentiate into two layers: the ***hypoblast,*** consisting of small cuboidal cells, and the ***epiblast,*** consisting of high columnar cells (fig. 5.7).

The two-layered plate that will differentiate into the embryo is called the ***embryonic disc.*** The epiblast forms the floor of the amniotic cavity and is peripherally continuous with a thin epithelial layer of the ***amnion.*** Flattened cells probably originating from the hypoblast form an ***exocoelomic membrane (Hauser's membrane).*** This membrane and the hypoblast form the lining of the ***exocoelomic cavity (primitive yolk sac).***

Cells derived from the yolk sac form the ***extraembryonic mesoderm*** and fill the space between the trophoblast externally and the amnion and the exocoelomic membrane internally . Large cavities within 80

the extraembryonic mesoderm become confluent and form the ***extraembryonic coelom.*** The extraembryonic coelom splits the extraembryonic mesoderm into two layers: the ***extraembryonic somatic mesoderm***, lining the trophoblast and amnion, and the ***extraembryonic splanchnic mesoderm,*** covering the yolk sac. The extraembryonic somatic mesoderm and two layers of trophoblast constitute the ***chorion.*** The extraembryonic somatic mesoderm and the extraembryonic part of the ectoderm constitute the amnion.

The endodermal germ layer produces additional cells which form a new cavity, known as the secondary or definitive ***yolk sac.*** The extraembryonic coelom expands to form a large chorionic cavity, within which the embryo and the attached amniotic and yolk sac are suspended by the ***connecting stalk.***

The ***second phase*** of the gastrulation begins on day 14-15 and continues about day 17 post-fertilisation. The second phase of gastrulation occurs by way of ***immigration.*** The germ gets a three-layer structure.

The second phase of the gastrulation begins with the formation of the ***primitive streak.*** The ***primitive streak*** is a linear band of thickened epiblast that first appears at the caudal end of the embryo and grows cranially. At the cranial end its cells proliferate to form the ***primitive (Hensen's) node.*** With the appearance of the primitive streak it is possible to distinguish cranial (primitive node) and caudal ends of the embryo (fig.5.10).

The cells that proliferate in the region of the ***primitive streak*** pass sideways, pushing themselves between epiblast and hypoblast. These ceils form ***intra-embryonic mesoderm.***

The cells that enter through the ***primitive (Hensen's) node*** will become the midline cellular cord known as the ***notochordal process.*** The notochordal process transforms into the notochord will eventually become the nucleus pulposis of each intervertebral disk.

The notochordal process grows cranially until it reaches the ***prechordal plate***, the future site of the mouth, in this area the ectoderm is attached directly to the endoderm without intervening mesoderm. This area is known as the ***oropharyngeal membrane,*** and it will break down

to become the mouth. At the other end of the primitive streak the ectoderm is also fused directly to the endoderm; this is known as the ***cloacaI membrane***, or primordial anus.

The spaces between the germ layers are filled with ***mesenchyme.***

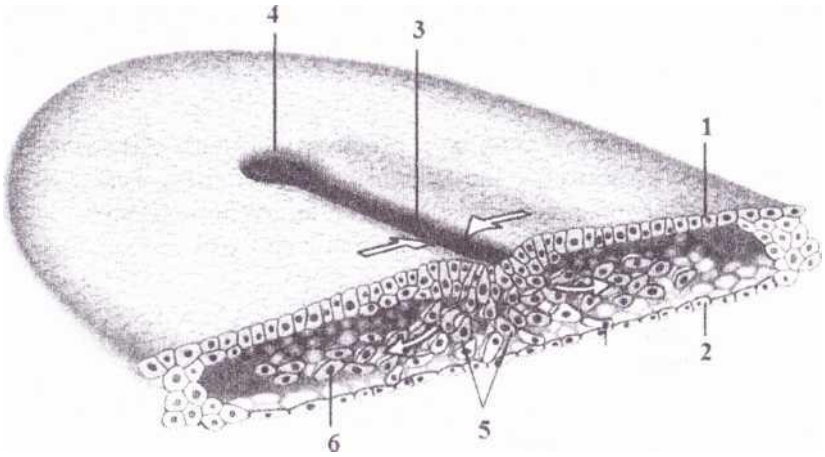


Figure 5.10. Schematic diagram of embryo during the second phase of the gastrulation. 1 - epiblast, 2 — hypoblast, 3 - primitive streak, 4 — primitive (Hensen's) node, 5 - migrating cells, 6 - mesoderm

Folding of the embryo (fig.5.11)

The folding of the flat trilaminar embryonic disc into a cylindric embryo establishes the general body form.

Folding occurs by differential growth of tissues. Neural ectoderm grows faster than the surrounding skin ectoderm and consequently folds to form a neural tube. Similarly, skin ectoderm grows faster than the underlying mesoderm and endoderm, and this differential growth causes folding of the trialminar disc and gives shape to the embryo.

Folding in the ***medial plane*** produces the ***head*** and ***tail folds,*** and results in the incorporation of part of the yolk sac into the embryo and the formation of the foregut and hindgut.

These are not three separate folds but occur simultaneously and merge into one another. The notochord, neural tube and somites stiffen the dorsal axis of the embryo.

Folding of the embryo in the ***horizontal plane*** produces the ***lateral folds*** and the formation of the lateral and ventral body walls. Part of the yolk sac is incorporated into the embryo as the midgut.

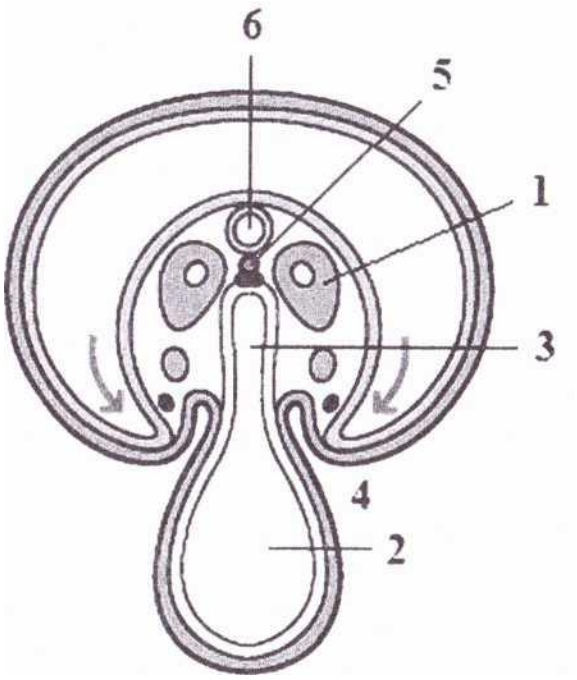


Figure 5.11. Folding of the embryo. 1 - intermediate mesoderm, 2 - yolk sac, 3 - gut, 4 - intraembryonic coelom, 5 - notochord, 6 - neural tube

Differentiation of the germ layers

Derivatives of the ectoderm

Ectoderm gives rise to:

> the central nervous system;
> the peripheral nervous system;

> the sensory epithelium of the ear, nose and eye;
> the epidermis, hair and nails; and
> the subcutaneous, mammary;
> pituitary gland;
> the enamel of teeth.

Neural crest cells give rise to the cells of ganglia andensheating cells of the peripheral nervous system, pigment cells of the dermis, muscles, connective tissue and bone of the branchial arches, suprarenal medulla and meninges.

Derivatives of the endoderm

Cranio-caudal and lateral folding of the embryo causes the incorporation of the part of the yolk sac into the body cavity and the formation of a tube-like ***gut.*** This layer gives rise to the epithelial lining of the:
> gastrointestinal system,
> repiratory system,
> urinary bladder and urethra,
> tympanic cavity and auditory tube, and
> the parenchyme of the tonsils, thyroid, parathyroid, thymus, liver and pancreas.

Derivatives of the mesoderm

Initially, the thin sheath of mesodermal layer proliferates and forms the ***paraxial mesoderm*** medially and ***lateral plate*** laterally. They are connected by the ***intermediate mesoderm.*** The lateral plate divides into two layers: ***somatic (parietal)*** and ***splanchnic (visceral) mesoderm.***

The paraxial mesoderm breaks into segmented blocks, the ***somites*** (42-44 pairs). The epithelial cells forming the somites lose their epithelial shape and migrate in the direction of the notochord and the spinal cord to form the ***sclerotome*** (future vertebral column). The dorsal wall of the somite differentiates into the ***myotome*** (furute muscles) and the ***dermatome*** (iuture dermis).

The ***intermediate mesoderm*** forms nephrotomes cranially and nephrogenic cord caudaily, both developing into the excretory units of kidneys, gonads, ducts and accessory' glands.

0 Placenta

The ***placenta*** is a temporary organ required for the development of the embryo and fetus.

Functions of placenta >***Nutrition, gas exchange, waste elimination***

Perfusion of the intervillous spaces of the placenta with maternal blood allows the transfer of nutrients and oxygen from the mother to the fetus and the transfer of waste products and carbon dioxide back from the fetus to the mother.

> ***Endocrine***

Placenta secretes hormone (secreted by syncytiotrophoblast of chorionic villi) that is important during pregnancy:

1) ***human chorionic gonadotropin*** (hCG) suppresses the maternal immunologic response so that placenta is not rejected.

2) ***human placental lactogen*** (hPL) promotes mammary gland growth in preparation for lactation in the mother. It also regulates maternal glucose, protein, fat levels so that this is always available to the fetus.

3) ***estrogen*** contributes to the woman's mammary gland development in preparation for lactation and stimulates uterine growth to accommodate growing fetus.

4) ***progesterone*** is necessary to maintain endometrial lining of the uterus during pregnancy. This hormone prevents preterm labor by reducing myometrial contraction.

5) ***relaxin*** is produced by decidua cells; softens the cervix and pelvic ligaments in preparation for childbirth.

> ***Protective***

1) IgG antibodies can pass through the human placenta, thereby providing protection to the fetus.

2) Cloaking from immune system of mother (***immune tolerance in pregnancy***).

The placenta and fetus may be regarded as a foreign allograft inside the mother, and thus must evade from attack by the mother's

immune system. For this purpose, the placenta uses several mechanisms. It secretes neurokinin B containing phosphocholine molecules. This is the same mechanism used by parasitic nematodes to avoid detection by the immune system of their host. Also, there is presence of small lymphocytic suppressor cells in the fetus that inhibit maternal cytotoxic T cells by inhibiting the response to interleukin 2.

3) Placenta forms a "protective barrier" against infectious agents. Nevertheless, there are some infections that can cross this barrier:

> ***The rubella virus*** may be responsible for a miscarriage during pregnancy (before the first month), for embryopathies or for fetopathies.

> ***Toxoplasmosis*** (caused by a protozoic parasite) is harmless for the mother, but can cause severe anomalies in the fetus.

>• ***Listeriosis*** (traced back to a gram-positive Listeria monocytogenes) can be responsible for intrauterine death or neonatal sepsis.

> The ***cytomegalovirus*** is generally can be responsible for miscarriages, microcephaly and growth retardation.

> With ***herpes simplex genitalis*** a risk of neonatal contamination exists through infection in the birth canal.

> ***HIV*** infection can also be transmitted from an infected mother to her offspring.

In addition, the placenta also presents an incomplete barrier against certain injurious effects of drugs: ***antibiotics*** and ***corticoids*** can pass through the placental barrier.

The same is true for certain ***medications*** the teratogenic effects of which are today well documented. Thalidomide, mainly responsible for phocomelia (prescribed in the 60 !s), as well as Roaccutane (retinoic acid, commonly used for treating acne), are highly teratogenic.

The consumption of ***barbiturates, drugs*** and ***alcohol*** during pregnancy are also to be avoided.

Development of placenta

The placenta begins to develop upon implantation of the blastocyst into the maternal endometrium (fig.5.5, 5.6, 5.7). The outer layer of the blastocyst becomes the ***trophoblast*** which forms the outer layer of the placenta.

Day 7 post-fertilisation: Trophoblast of the blastocyst proliferates and differentiates into inner ***cytotrophoblast*** and outer ***syncytiotrophoblast*** (a multinucleate continuous cell layer which forms as a result of differentiation and fusion of the underlying cytotrophoblast cells). Nutrition is by diffusion and erosion of maternal tissues (histiotrophic type). Syncytiotrophoblast secretes enzymes to invade maternal tissues. ***Day 8 post-fertilisation.*** Finger-like processes of syncytiotrophoblast continue to invade. Secretion of hCG begins. Uterine stroma cells become ***decidua cells*** (glycogen/lipid-laden) around blastocyst. Inner cell mass forms bilaminar disc. Amniotic cavity appears at embryonic pole; a layer of epiblast cells is displaced toward the embryonic pole by fluid that has begun to collect between epiblast cells. These cells, now called amnioblasts, differentiate into a thin membrane that separates the new cavity (amnion) from the cytotrophoblast. Hypoblast cells give rise to layer of cells (exocoelomic membrane) lining lower cavity, called exocoelomic cavity (to be primary yolk sac).

Day 9 post-fertilisation: Cells from hypoblast give rise to loosely arranged tissue, called ***extraembryonic mesoderm*** that surrounds amnion and primary yolk sac. ***Lacunae*** appear in syncytiotrophoblast. Endometrial capillaries rupture, glands erode. Syncytiotrophoblast has spread to totally surround blastocytst.

Day 10 post-fertilisation: Lacunae in syncytiotrophoblast fill with maternal blood and glandular secretions. Maternal capillaries anastomose with lacunae - ***uteroplacental circulation*** starts. Embedding of embryo is completed.

Day 11-12 post-fertilisation. Epithelium of endometrium completely regenerated.

Day 13 post-fertilisation: Chorion consists of 2 layers of trophoblast and extraembryonic somatic mesoderm.

Day 14 post-fertilisation: The chorionic villi are formed as elongated projections from the surface of the trophoblast. The ***primary villi*** (fig-5.12-1)consist of only c syncytyotrophoblast covering.

Day 16 post-fertilisation. Secondary villi (fig.5.12-11) form when mesoderm pushes into primary villi. Secondary' villi cover all of

chorionic sac. ***Tertiary villi*** (fig.5,12-HI) form when mesenchymal cells in villi differentiate into blood vessels.

Day 21 post-fertilisation. Embryonic blood begins to flow through capillaries of chorionic villi. Diffusion of nutrients/'wastes between maternal and embryonic circulations through walls of villi begins.

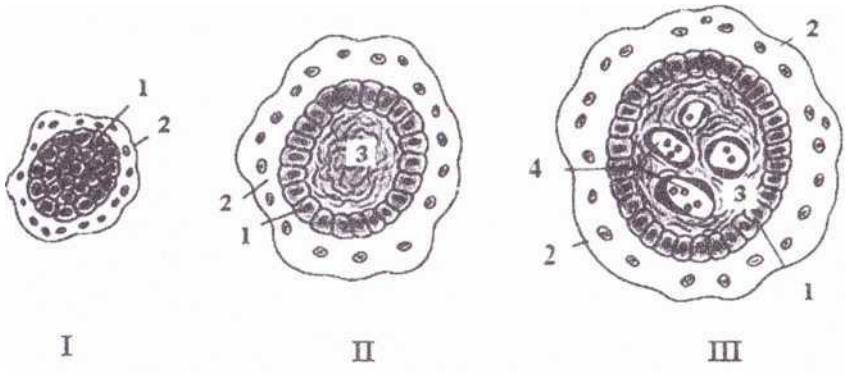


Figure 5.12. Formation of the chorionic villi. I - primary villus, II - secondary villus, III - tertiary villus, 1 - cytotrophoblast, 2 - syncytiotrophoblast 3 — mesodermal core, 4 - capillaries of the villus (fetal capillaries)

Chorionic villi cover the whole placenta. As chorion grows, villi associated with decidua capsularis are compressed and their blood supply is reduced. By the eighth week, the villi under the decidua capsularis have begun to degenerate and leave ***smooth chorion (chorion laeve***). Meanwhile, villi near decidua basalis increase in number, branch profusely and enlarge to form ***villous chorion (chorion frondosum).***

Structure of placenta

Human placenta is of ***haemochoreal, discoid, of type II.***

In humans, the placenta has a circular shape and measures about 15 to 20 cm in diameter, 2-2,5 cm in thickness, weighing 500 to 600 g.

It has a dark reddish-blue or maroon color. It connects to the fetus by an ***umbilical cord.***

The placenta consists of***fetal part*** and ***maternal part*** (fig.5.13).

The ***fetal part***, the ***chorion,*** consists of:

> branching ***chorionic plate***, portion of the chorion in the region of its uterine attachment, it consists of the mesoderm and is covered by

> ***amniotic membrane',***

> ***chorionic villi*** which are bathed with maternal blood from the lacunae of the decidua basalis.

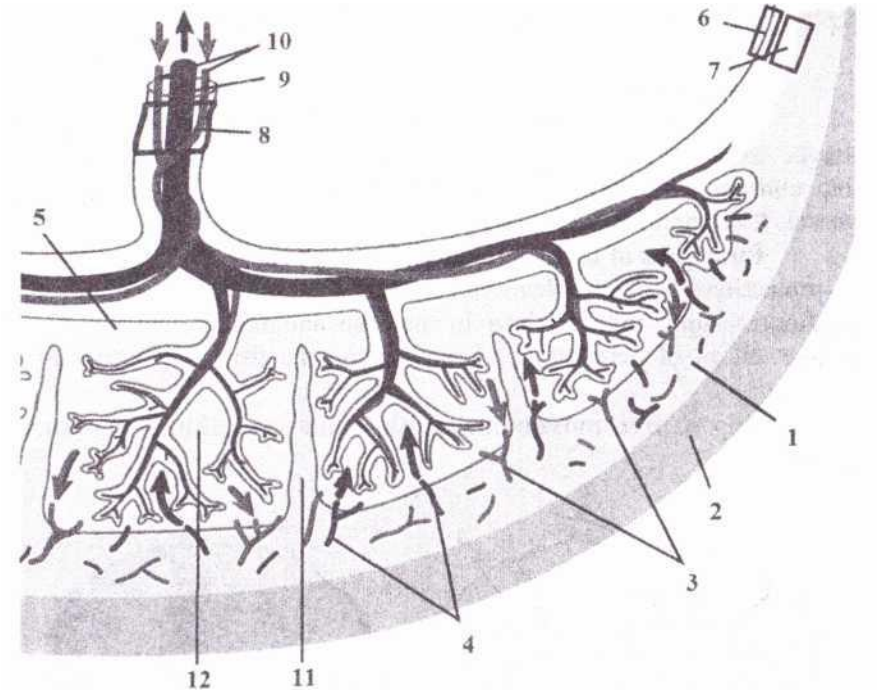


Figure 5.13. Schematic diagram of the placenta. 1 - decidua, 2 - myometrium, 3 - endometrial veins, 4 — endometrial arteries, 5 — villus paremchyma, 6 - amnion, 7 - chorion, 8 - umbilical cord, 9 - umbilical, 10 - umbilical areteries, 11 - connective tissue septa, 12 - lacune with maternal blood

The ***maternal part*** of the placenta consists of:

> modified ***basal lamina*** of endometrium (decidua basalis),

> ***lacunae*** filled with maternal blood and

> connective tissue ***septae,*** separating cotyledons from each other.

Cells from the connective tissue stroma of the decidua basalis form the ***decidual cells.*** These cells are large; they produce prolactin and other biologically active substances.

Structural and functional unit of the placenta is ***cotyledon,*** formed of chorionic villus both its secondary and tertiary branchings. ***Cotyledons*** are compartments of placenta, which are separated by the septae. The total of cotyledons in a placenta reaches 30-50 (fig.5.14).

Umbilical cord

The ***umbilical cord*** is elastic tube of approximately 55-60 cm in length, connecting germ (fetus) with a placenta. It is covered by amnion and consists of mucous connecting tissue (Warton's jelly) and blood vessels (two umbilical arteries and one vein) (fig.5.15).

Functions of the umbilical cord:

> protection of the umbilical vessels from compression, providing thus continuous supply of an embryo by nutrients and oxygen;

> prevention of penetration of harmful agents from a placenta to an embryo;

> ensuring of free movements of the embryo within the amniotic cavity.

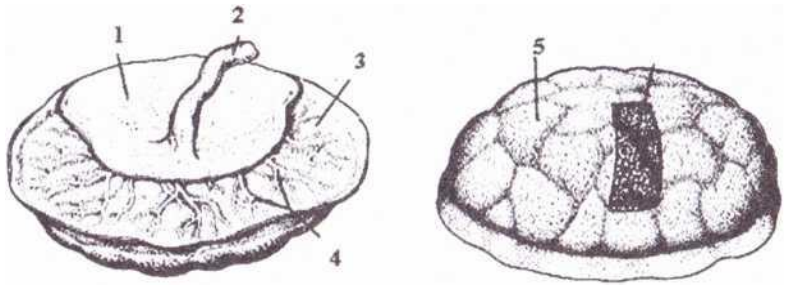


Figure 5.14. Schematic diagram of the cotyledon. 1 — amnion, 2 - umbilical cord, 3 - chorionic plate, 4 - chorionic vessels, 5 - cotyledon

0 Clinical correlations

Cord blood banking is a procedure performed on the umbilical cord at birth to collect stem cells from it. There can be up to 18 mL of blood, filled with stem cells that can mature and differentiate to about 200 cell

types. In humans these cells originate from the blastocyst, the mass of cells found 4-5 days after fertilization has occurred. There are public umbilical cord banks that store and save baby's cord so it can used when needed to save or prolong someone's life. Those stem cells inside the cord can be transplanted into the body of patients that have a damaged tissue for different reasons. Stem cells are used to treat certain illness such as leukemia and sickle cell anemia, and more diseases may be treated with cord blood in the future.

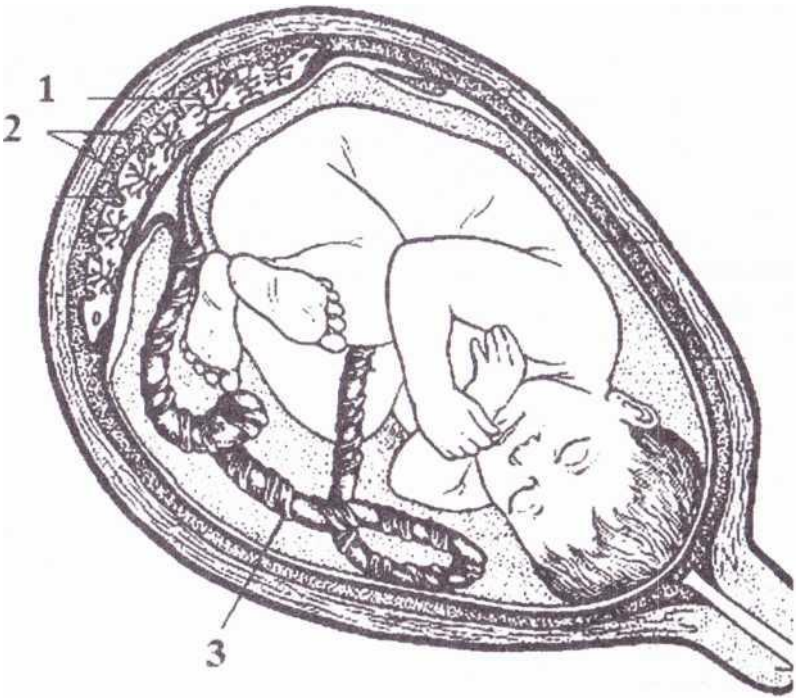


Figure 5.15. **Schematic section through the uterus.** 1 - chorionic villi, 2 - placenta, 3 - umbilical cord

Placental barrier

Fetal blood and maternal blood do not mix. The fetal blood is isolated by structures of the ***placental barrier:***

> endothelium of the fetal capillaries,

> basal lamina of these capillaries,
> mesenchyma of the interior of the villus,
> basal lamina of the cytotrophoblast,
> syncytiotrophoblast.

However through the placental barrier from blood of mother alcohol, narcotics, medicinal substances, nicotine, and also many hormones will easily penetrate into blood of the embryo.

E9 Classifications of the placentae

The placentae of all eutherian (placental) mammals provide common structural and functional features, but there are differences among species in gross and microscopic structure of the placentae.

1. Classification based on ***layers between fetal and maternal blood***

Just prior to formation of the placenta, there are a total of six layers of tissue separating maternal and fetal blood:

> fetal vessels endothelium,
> extraembryonic mesenchyme,
> cytotrophoblast,
> uterine epithelium,
> maternal vessels endothelium,
> connective tissue of the endometrium.

Distinguish four types of placentae (fig.5.16):

> ***epithelioehoreal,***
> ***desmocltoreal,***
> ***endotheliochoreal,***
> ***haemochoreal***

In ***epitheliochoreal*** placentae chorionic villi, growing into apertures of uterine glands, contact with epithelium of these glands (camel, horse, pig).

In ***desmochoreal*** placentae chorion partly destroys epithelium of uterine glands and villi of chorion grow into connecting tissue of lamina propria, for example at ruminant artiodactyl mammal (cow, sheep).

In ***endotheliochoreal*** placentae villi of chorion destroy epithelium and connective tissue and contact with the endothelium of blood vessels (cats, dogs).

Haemochoreal placenta destroys a wall of uterus vessels and villi of chorion contact directly to parent blood (Humans, rodents).

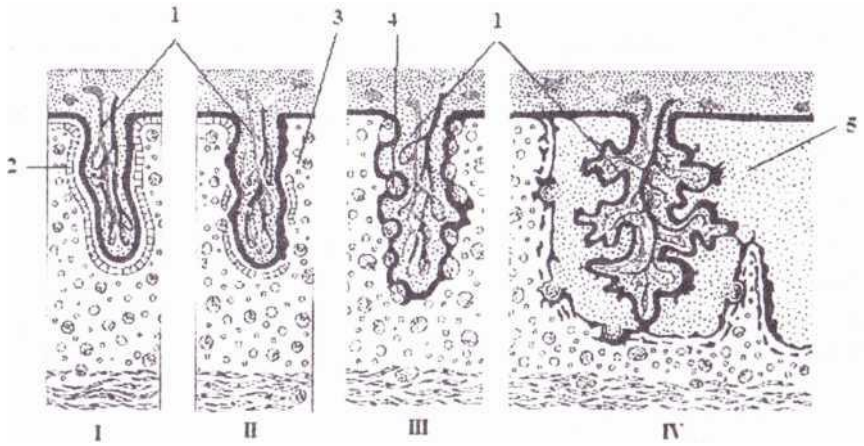


Figure 5.16. Types of placentae. I - epitheliochoreal, II - desmochoreal, III - endotheliochoreal, IV - haemochoreal placenta; 1 - chorionic villi, 2 - epithelium of uterine glands, 3 - connective tissue of lamina propria of endometrium, 3 - blood vessels of endometrium. 4 - parent blood (from *K). //. A(panacbea, H.A.lOpuna u dp.*, 1999)

II. Classification based on a ***character of trophic***

In a placenta of ***type I*** chorion absorbs from mother tissues proteins and splits them up to amino acids, synthesis of embryo proteins occurs in a liver of an embryo.

In placentas of ***type II*** chorion acquires from parent tissues mainly amino-acids and synthesizes embryo-specific proteins; the embryo receives thus ready proteins which uses for construction of own tissues.

Synthesis of proteins of embryo at animals having 2-nd type of placenta occurs mainly in chorion and consequently with a birth the level of synthetic processes sharply decreases. Naturally, those germs

after a birth rather long time metabolize only parent milk also are unable to eat independently.

III. Classification based on ***placental shape***

Examination of placentae from different species reveals striking differences in their shape and the area of contact between fetal and maternal tissue:

> In a placenta of ***diffuse type*** almost the entire surface of the chorion is involved in formation of the placenta (horses and pigs).

> In a placenta of ***cotyledonary type*** multiple, discrete areas of attachment called ***cotyledons*** are formed by interaction of patches of allantochorion with endometrium (ruminants).

> Placenta of ***zonary type*** takes the form of a complete or incomplete band of tissue surrounding the fetus (carnivores like dogs and cats, seals, bears, and elephants).

> ***Discoid type:*** single placenta is formed and is discoid in shape (primates and rodents).

The system mother - fetus

The ***system mother - fetus*** arises during pregnancy and includes two subsystems - an organism of mother and an organism of a fetus, and also a placenta being a link between them.

Interaction between an organism of mother and an organism of a fetus is provided by neurohumoral mechanisms.

Organisms of mother and fetus are dynamic system of homological organs. Damage of any organ of mother conducts to disturbance of development of the same organ of a fetus.

0 The critical periods of development

Individual development proceeds from the formation of germ cells (sperm and egg) through fertilization, embryonic and fetal development, infancy, early childhood, and adolescence. Specific events during each of these broad developmental stages may create sensitivity to environmental influences. Damage from environmental exposures may occur and manifest itself immediately or may not appear until subsequent stages of development or after development is complete.

Such periods in human ontogenesis are:

1) development of sexual cells (oogenesis and spermatogenesis);
2) fertilization;

3) implantation (7-8 days);
4) development of axial organs, differentiation of germ layers, and formation of a placenta (3-8 weeks);
5) stage of strengthened growth of a brain (15-20 weeks);
6) formation of the main functional systems of an organism and a differentiation of the sexual organs (20-24 weeks);
7) birth;
8) period till 1 year;
9) puberty (11 - 16 years).

Many factors such as chemical substances, including many medicinal, an irradiation (for example, X-ray in diagnostic dozes), hypoxia, starvation, drugs, nicotine, viruses, etc can be damaging in the critical periods.

0 Clinical correlations

Problems during prenatal development

Genetic problems

> ***Down Syndrome*** (trisomy 21) is the most common genetic anomaly during prenatal development. Down syndrome is caused by and extra copy of the 21 chromosome and impacts approximately 1 out of every

1,0 infants. Typical features of Down syndrome include flattened facial features, heart defects, and mental retardation. The risk of having a child with Down syndrome increases with maternal age.

> ***Inherited diseases*** are a number of illnesses can be inherited if one or both parents carry a gene for the disease. Examples of inherited diseases include ***Sickle-cell anemia, cystic fibrosis,*** and ***Tay-Sachs disease.*** Genetic tests can often determine if a parent is a carrier of genes for a specific disease.

> ***Sex-chromosome problems*** is a third type of genetic problems involves sex-chromosomes. These includes conditions such as ***Klinefelter's syndrome*** (an extra X-chromsome) and ***Turner syndrome*** (a single X-chromosome)

Environmental problems

Harmful environmental elements that can effects the fetus are known as ***teratogens.*** There a number of teratogens that can harm the fetus, including:

> ***Maternal drug use*** - The use of substances by the mother can have devastating consequences to the fetus. Smoking is linked to low birth weight, which can result in a weakened immune system, poor respiration, and neurological impairment. Alcohol use can lead to ***fetal alcohol syndrome,*** which is linked to heart defects, body malformations, and mental retardation. The use of illicit drugs such as cocaine and methamphetamine is also Linked to low birth weight and neurological impairment.

> ***Maternal disease*** - Maternal diseases can negatively impact the fetus, including herpes, rubella, and AIDS. Herpes virus is one of the most common maternal diseases and can be transmitted in the fetus, leading to deafness, brain swelling, or mental retardation. Women with herpes virus are often encouraged to deliver via cesarean to avoid transmission of the virus.

Early pregnancy testing

hCG produced by the syncytiotrophoblast can be detected in maternal blood or urine as early as day 10 of pregnancy and is the basis for pregnancy tests.

Placenta previa

The embryo implants in the ***lower part of the uterus towards the cervix.*** This makes it easy for the placenta to tear, and the mother can die from hemorrhage, or the placenta may grow to obstruct the cervical canal. This is diagnosed with ultrasound, and the baby is delivered via Cesarean section.

GENERAL PRINCIPLES OF ORGANIZATION AND CLASSIFICATIONS OF THE TISSUES EPITHELIAL TISSUES (EPITHELIA)

0 Overview of the tissues

The ***tissue*** is the system of the cells and the extracellular matrix, which specialized on the execution of the definite functions.

The human body is composed of ***four basic types of tissue:***

> epithelial,
> connective (tissues of the internal environment of the organism),
> muscle,
> nerve.

Structural and functional elements of tissues are:

1. ***Cells*** are the main elements of all tissues which are determining their basic properties.
2. ***Intercellular substance*** is the cumulative product of activity of cells of the tissue.
3. ***Postcellular structures*** is the derivatives of cells which during a differentiation have lost the major signs, characteristic for cells (more often owing to loss of a nucleus and part of organelles), but have got a number of the properties necessary for performance by them specialized functions (erythrocytes and platelets, dead cells of the epidermis, hair and nails).
4. ***Symplasts*** are the structures formed as a result of cell fusion with loss of their borders and formation uniform cytoplasm mass in which there are nuclei (osteoclasts, an external layer of trophoblast - symplastotrophoblast, fibers of a skeletal muscular tissue).
5. ***Syncytium*** is the structure arising as a result of incomplete cytotomia at cell division. The connections between elements of cells are preserved by means of cytoplasmic bridges (spermatogenic epithelium of convoluted seminiferous tubules of testis).

Differentiation is process during which cells of the tissue pass a number of stages of development, gradually getting structural and functional properties of mature elements.

Differon is set of all cells making the given line of a differentiation - from the least differentiated ***(stem)*** up to the most mature differentiated. Many tissues contain several cellular differons which cooperate with each other.

Stem cells are the least differentiated cells of the given tissue being a source of development of its other cells.

0 Epithelial tissues (epithelia)

Epithelial tissues are widespread throughout the body. They form the covering of all body surfaces, line body cavities and hollow organs, and are the major tissue in glands.

Functions of epithelium

1. ***Protection,*** protect underlying tissues from mechanical injury, harmful chemicals, invading bacteria and from excessive loss of water.
2. ***Absorption***: certain epithelial cells lining the intestine absorb nutrients from the digestion of food.
3. ***Secretion,*** in glands, epithelial tissue is specialised to secrete specific chemical substances such as enzymes, hormones and lubricating fluids.
4. ***Excretion,*** epithelial tissues in the kidney excrete waste products from the body and reabsorb needed materials from the urine. Sweat is also excreted from the body by epithelial cells in the sweat glands.
5. ***Sensation***: sensory stimuli are detected by specialized epithelial cells; specialized epithelial tissue containing sensory nerve endings is found in the skin, eyes, ears and nose and on the tongue.
6. ***Diffusion,*** simple epithelium promotes the diffusion of gases, liquids and nutrients; because they form such a thin lining, they are ideal for the diffusion of gases (e.g. walls of capillaries and lungs).
7. ***Contraction*** e.g., myoepithelial cells have ability to contract.
8. ***Cleaning:*** ciliated epithelium assists in removing dust particles and foreign bodies which have entered the air passages.

General morphological signs of epithelial tissues

1) Cells are closely packed together.
2) Intercellular substance is reduced to a minimum.
3) Cells rest on the basal lamina.
4) Polarity of epitheliocytes (in the epitheliocytes there are apical and basal poles).
5) All epithelia have no blood vessels. They derive their nutrition from the blood vessels of underlying connective tissue.
6) Availability of intercellular junctions.
7) High ability to regeneration.

Basal lamina. Basement membrane

The ***basal lamina*** connects the epithelium and subjacent connective tissue. With electron microscope the ***basal lamina*** consists of 2 layers: inner ***lamina lucida*** (thin amorphous layer of glycoprotein) and outer ***lamina densa*** (thick network of collagen fibrils) (fig.6.1).

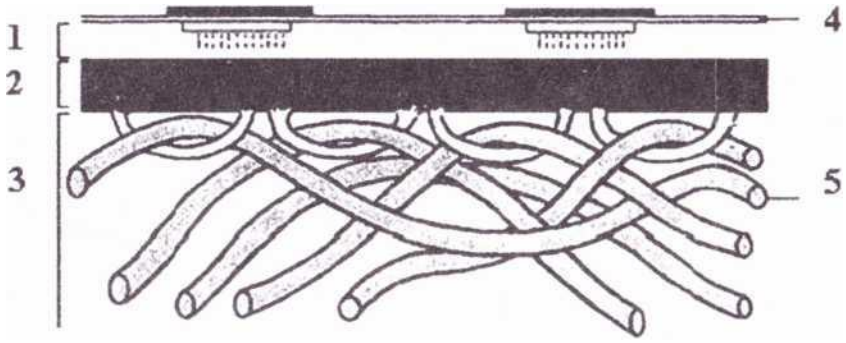


Figure 6.1. Schematic diagram of the basement membrane. 1 - lamina lucida, 2 - lamina densa, 3 - reticular lamina, 4 - plasmolemma of the basal surface of the epitheliocytes, 5 — collagen fibers (from *EbiKoe B.J1.*, 2007)

Outside the basal lamina is associated with the ***reticular lamina***; it consists of delicate reticular fibres.

The combination of basal lamina and the layer of reticular fibres appear as a single membrane under the optical microscope termed the ***basement membrane.***

0 Classifications of the epithelia

1. Histogenetic classification of the epithelia

Histogenetic type of epithelium	**Embryonic sources**	**Examples**
1. **Epidermal**	Ectoderm	Epithelia of the • skin • nasal cavity • mouth cavity • anal canal • cornea
2. **Enterodermal**	Endoderm	Epithelia of the • alimentary systems •respiratory systems
3. **Celoneph rodermal**	Celom, nephrotome	Epithelia of the • nephron • genital ducts • ovary • testis • prostate gland • renal cortex • mesothelium
4. Angiodermal	Mesenchyme	• Endothelium
5. **Ependymoglial**	Neuroectoderm	• Ependymal cells that line the cavities of the CNS

2. Morphofunctional classification of the epithelia

Epithelia are classified according to the structure and functions into 2 main groups:

- ***covering (integumentary) epithelia,***
- ***glandular epithelia.***

0 Covering epithelia

Covering epithelia are tissues whose cells are organized in the layers that cover the external surface or line the cavities of the body.

Covering epithelia are classified according to the number of cell layers and morphology of the cells in the surface layer:

1- ***Simple epithelia*** consist of only one layer of cells.

2- ***Stratified epithelia*** contain more than one layer.

There are four types of simple epithelia.

1.1 ***Simple squamous epithelium*** (fig.6.2) composed of flattened and irregularly-shaped cells.

It is found in:

- alveoli of lung,
- parietal layer of Bowman's capsule,
- descending limb of Henle's loop,
- blood and lymph vessels
- serous cavities.

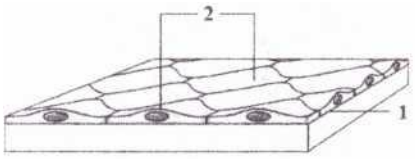


Figure 6.2. Simple squamous epithelium.
1 - basal lamina, 2 — squamous cells

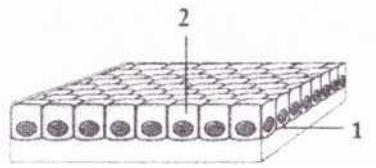


Figure 6.3. Simple cuboidal epithelium.
1 - basal lamina, 2 — cuboidal cell

1.2***Simple cuboidal epithelium*** (fig.6.3) consists of one layer of cuboidal cells.

It is found in:

- follicles of thyroid gland,
- proximal and distal convoluted tubules,
- respiratory bronchioles,
- pigment layer of retina,
- germinal epithelium of ovary,
- ducts of many glands.

1.3***Simple columnar epithelium*** (fig.6.4) consists of one layer of columnar cells.

It is found in:

- stomach,
- small intestine,
- most of large intestine,
- ducts of pancreas and gallbladder,
- oviducts.

1.4***Pseudostratified columnar ciliated epithelium*** (fig.6.5) is a true simple epithelium, because all cells lie on the basal lamina, but cells are of various types, tall and short. Nuclei of the cells are at different levels. Free surfaces of tall cells have cilia.

It is found in:

- trachea and bronchi,
- nasopharynx.

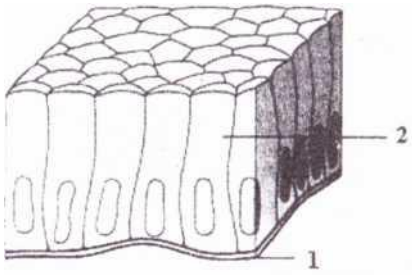


Figure 6.4. Simple columnar epithelium. 1 — basal lamina, 2 — columnar cell

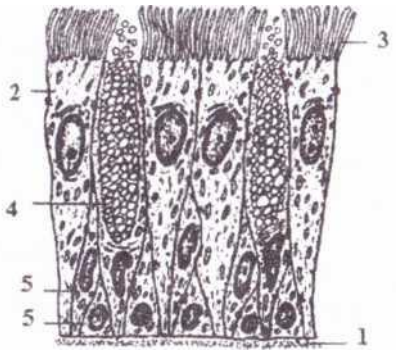


Figure 6.5. Pseudo-stratified columnar ciliated epithelium. 1 - basal lamina, 2 — ciliated columnar cell, 3 - cilia, 4 - goblet cell, 5 — basal cell

There are three types of stratified epithelia:

2.1 ***Stratified squamous non-keratinised epithelium*** (fig.6.6) consists of 3 layers:

> ***Stratum hasale*** contains a single layer of columnar or cuboidal cells resting on the basal lamina.
> ***Stratum spinosum*** consists of polygonal cells.
> ***Surface layer*** consists of squamous cells.

It is found in:

- mouth cavity,
- esophagus,
- cornea,
- vagina.

2.2 ***Stratified squamous keratinised epithelium*** (fig.6.7) consists of 5 layers of keratin-producing cells (keratinocytes):

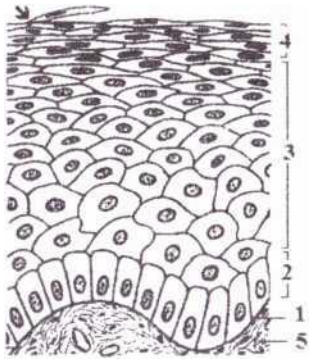


Figure 6.6. Stratified squamous non-keratinised epithelium. 1 - basal lamina, 2 - stratum basale, 3 - stratum spinosum, 4 — surface layer

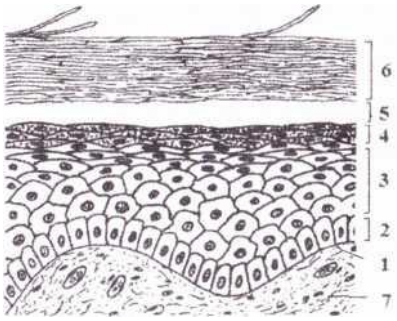


Figure 6.7. Stratified squamoas keratinised epithelium. 1 - basal lamina, 2 - stratum basale, 3 - stratum spinosum, 4 - stratum granulosum, 5 - stratum lucidum, 6 - stratum comeum, 7 — connective tissue

> ***Stratum hasale (stratum germinativum)*** consists of a single layer of basophilic columnar or cuboidal cells resting on the basal lamina.
> ***Stratum spinosum*** consists of polygonal cells with a central nucleus and a cytoplasm whose processes are filled with bundles of filaments.

> ***Stratum granulosum*** is characterized by 3 to 5 layers of flattened polygonal cells with the cytoplasm filled with coarse basophilic granules called ***keratohyalin granules.***

> ***Stratum lucidum*** is thin layer of flattened eosinophilic cells. The ceils are dying or already dead and contain droplets of eleidin.

> ***Stratum corneum*** consists of 15-20 layers of flattened cornified plates or dead cells consisting keratin (scleroprotein).

It is found in:

- epidermis of skin.

2.3 ***Transitional epithelium (urothelium)*** (fig.6.8) it is highly specialized to give a degree of stretch, so it is found only in the urinary tract. Cells are arranged in 3 to 5 layers. In the relaxed state of the organ, the surface cells are large, rounded and bulge into the lumen. With stretching the surface cells become flattened.

It is found in:

- urinary tract from the pelvis of the kidney to the beginning of the urethra.

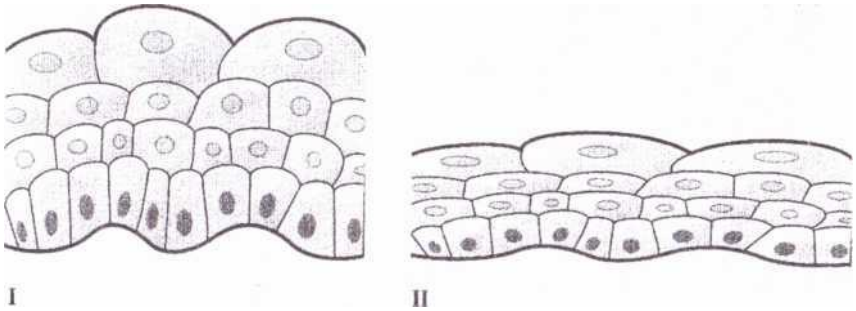


Figure 6.8. Diagram of transitional epithelium. I -relaxed, **II** - stretched

0 Glandular epithelia

The cells of ***glandular epithelia*** are specialized to produce a fluid secretion.

Glands are classified according to their mechanism of secretion.

> ***Exocrine glands*** secrete their products via ducts onto the apical (or epithelial) surface (fig.6.9-I).

> ***Endocrine glands*** release their secretion directly into blood or lymph vessels. These glands have no ducts (ductless glands) (fig.6.9-II).

> ***Paracrine glands*** are similar to endocrine glands but secretions reach target cells by diffusion through the extracellular space to affect neighbouring cells.

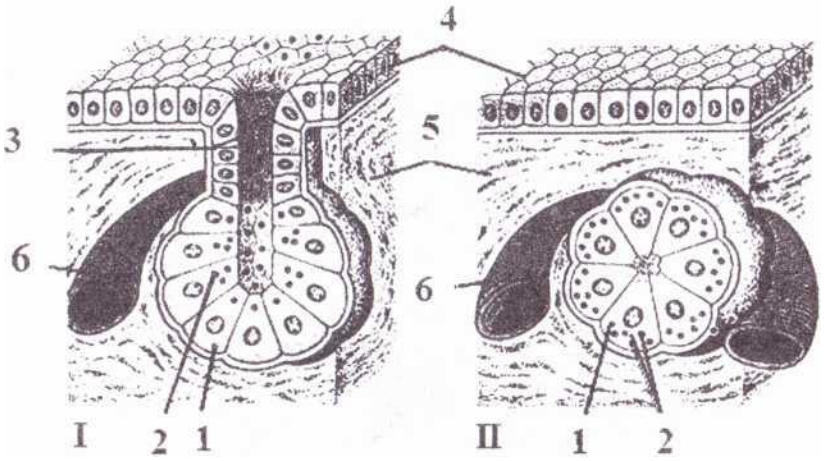


Figure 6.9. **Structure of the exocrine and endocrine glands.** I - exocrine gland, II - endocrine gland; 1 - secretory portion, 2 - secretory granules, 3 - duct of the exocrine gland, 4 - covering epithelium, 5 — connective tissue, 6 — blood vessel (from *IO. I f A(jiaiiachea, H.A JOpima u dp.,* 1999)

Morphology of secretory cycle (fig. 6.10)

Process of secretion in glandular cells proceeds cyclically and includes 4 phases:

I. ***Phase of absorption of initial substances:*** substrates for synthesis of secretion come from blood through plasmolemma of basal pole of a glandular cell.

II. ***Phase of synthesis of a secretion,*** processes of a transcription and translation in rough endoplasmic reticulum (RER) and Golgi complex (for protein secretions), smooth endoplasmic reticulum (SER) (for steroid substances).

III. ***Phase of accumulation of the synthesized product',*** increase of the maintenance of secretory granules in cytoplasm of glandular cells.

IV. ***Phase of extrusion of a secretion:*** exocytosis of contents of secretory granules.

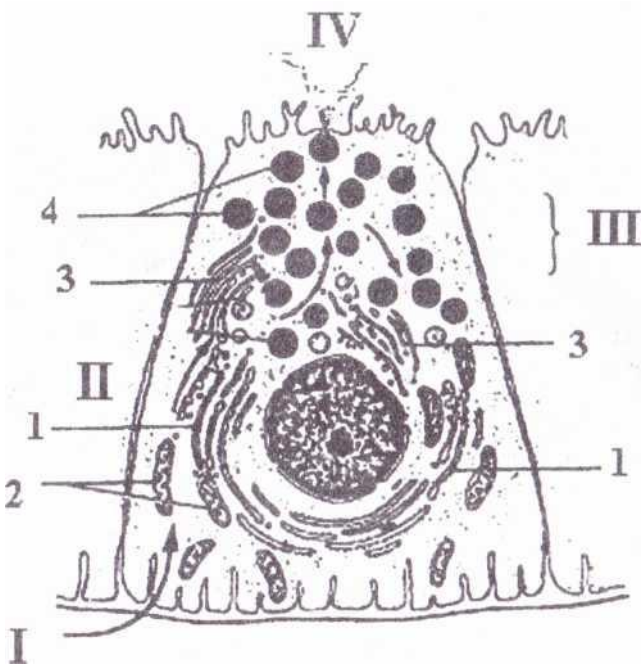


Figure 6.10. Structural organization of the glandular cell during secretory cycle. I - phase of absorption of initial substances, II- phase of synthesis of a secretion, III - phase of accumulation of the synthesized product, IV - phase of removing of a secretion, 1 - rER, 2 - sER, 3 - Golgi complex, 4 - secretory granules (from ***Ефимов В.Л.,*** 2007)

Morphological characteristic of the exocrine glands

Exocrine glands consist of two parts (fig.6.11):

I. The ***secretory portion,*** which contains the cells responsible for the secretory process;

II. The ***duct system,*** which transport the secretion to the exterior of the gland.

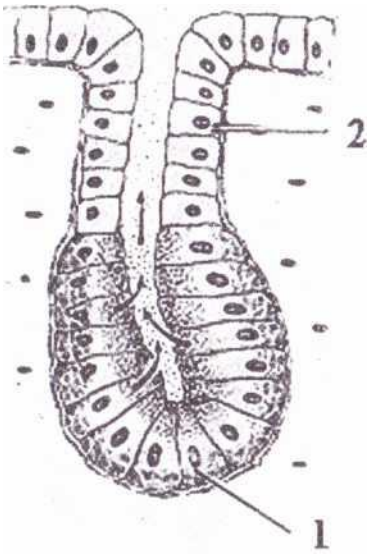


Figure 6.11. Structure of the exocrine gland. 1 — secretory portion, 2 — duct (from *Junqueira L.C., Carneiro,/.*, 2005)

Exocrine glands are classified based on six different morphological criteria.

1. ***Number of secretory cells***

> ***Unicellular glands*** (goblet cells) (fig.6.12) are mucus-secreting cells. They are found in the epithelium of trachea, bronchi, small and large intestine.

> ***Multicellular glands*** consist of many cells.

2. ***Location of the secretory cells in relation to the epithelium***

> ***Intraepithelialglands*** are goblet cells; described above.

> ***Extraepithelial glands*** are all large exocrine glands.

3. ***Nature of secretion***

> ***Mucous glands*** contain mucous-secreting cells (e.g.. lingual glands);

> ***Serous glands-,*** the secretory portions contain only serous cells (e.g., parotid gland, pancreas);

> ***Mixed glands (serous-mucous),*** the secretory portions contain both mucous and serous cells and the secretion is mixed (e.g.. submandibular, sublingual salivary glands).

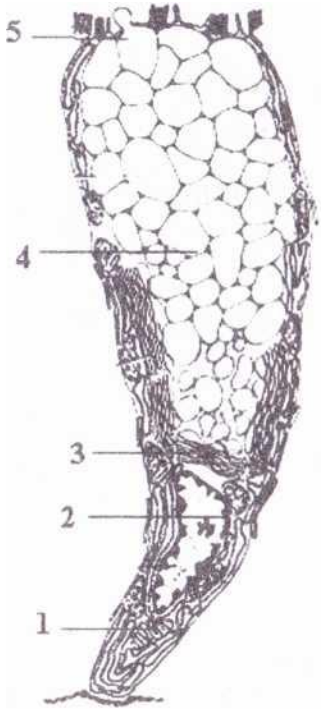


Figure 6.12. Diagram of uniceliuiar mucous gland. 1 — rER, 2 - nucleus, 3 — Golgi complex, 4 - accumulation of glycoprotein granules, 5 - exocytosis (from *Junqueira L.C., Carneiro./.*, 2005)

4. ***Mechanism of secretion*** (fig.4.13)

> ***Merocrine:*** No part of the cell is lost, only the secretory product is expelled by the process of exocytosis. It is the most common mode of secretion and is seen in serous, mucous, and mixed glands.

> ***Apocrine.*** Part of the apical cytoplasm of the cell is lost. Secretion is discharged within free, unbroken, membrane-bound vesicles (apocrine sweat glands and mammary gland).

> ***Holocrine:*** The entire secretory cell is lost (discharged within the lumen of the duct) (sebaceous glands).

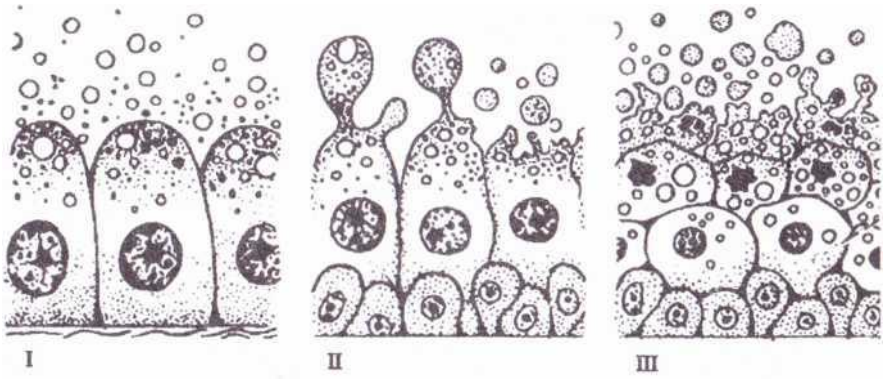


Figure 6.13. Types of glandular secretion. I - merocrine, II — apocrine, III - holocrine (from *10. KAcpaiiacbee, H.AJOpuna u dp.,* 1999)

5. ***Shape of secretory portions*** (fig. 6.14)

> ***Tubular:*** An elongated group of secretory cells with a lumen shaped like a tube.

> ***Acinar*** (or ***alveolar***): sac-like group of secretory cells arranged about a small lumen.

> ***Tubulo-acinar:*** lumen of secretory units has both of the above listed shapes.

6. ***Arrangement (branched or not) of duct system*** (fig. 6.14)

> ***Simple glands-.*** Glands of this type have an unbranched duct into which the cells secrete. Each secretory portion empties separately on an epithelial surface.

> ***Branched glands:*** Several secretory units empty into an unbranched excretory duct.

> ***Compound glands:*** These glands have a highly branched duct system. Secretory portions empty into an elaborate branched duct system, which, in turn, drain into larger ducts.

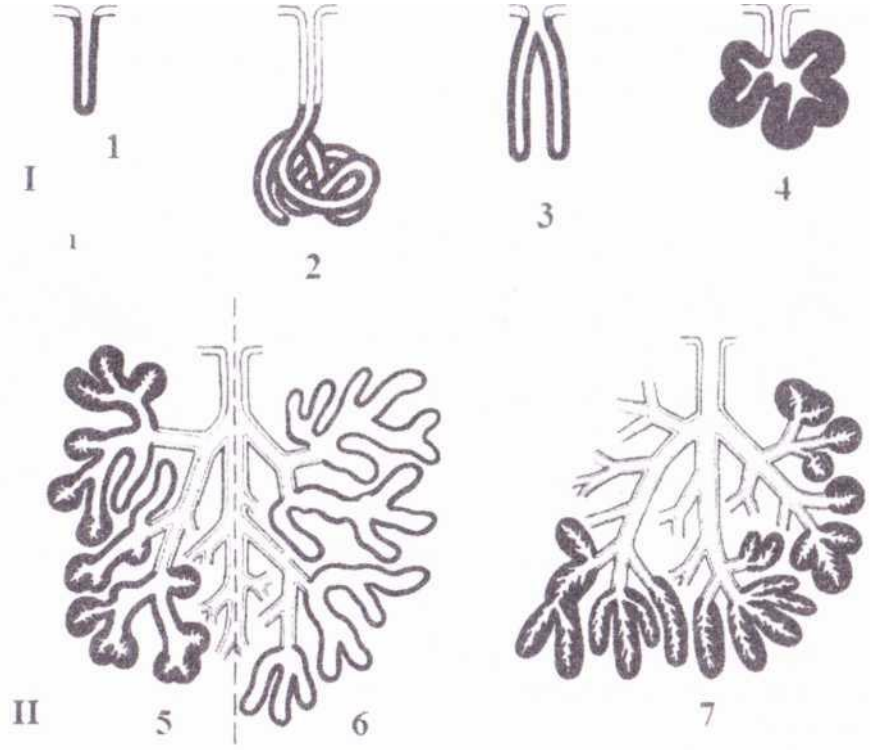


Figure 6.14. Principal types of exocrine glands. I - simple, II - compound; 1 — simple tubular, 2 — simple coiled tubular, 3 — simple branched tubular, 4 - simple branched acinar, 5 — compound tubuloacinar, 6 - compound tubular, 7 - compound acinar

BLOOD. LYMPH

0 Overview of the blood

Blood is a specialized type of connective tissue in which the fluid intercellular substance is called ***plasma***

Quantity of the blood of an adult man is 5 - 6 litres, of an adult woman - 4-5 litres, about 7% of the body weight.

The functions of blood

> ***Transportation*** of dissolved gases (oxygen and carbonic dioxide), nutrients, hormones, and metabolic wastes, medicines.

> ***Regulation*** of the pH and ion composition of interstitial fluids.

> ***Restriction*** of fluid losses at injury sites.

> ***Defense*** against toxins and pathogens. Blood transports white blood cells, specialized cells that migrate into peripheral tissues to fight infections or remove debris. Blood also delivers antibodies, special proteins that attack invading organisms or foreign compounds.

> ***Stabilization*** of body temperature. Blood absorbs the heat generated by active skeletal muscles and redistributes it to other tissues.

Components of the blood

I. ***Formed*** (cellular) ***elements*** constitute 40-45% of the total volume of blood:
   1. Erythrocytes;
   2. Leukocytes;
   3. Platelets.

II. ***Plasma*** constitutes 55-60% of the total volume of blood.

0 **Plasma**

The **components of the plasma** are:
90% - water,
9% - organic compounds,
1 % - inorganic salts.

The main components of organic substances are ***proteins.***

Three primary classes of plasma proteins are: ***albumins, globulins,*** and ***fibrinogen.*** These three classes make up over 99% of the plasma proteins. The remainder consists of circulating enzymes, hormones, and prohormones.

Albumins constitute 60 percent of the plasma proteins. ***Albumins*** are the main component and have a fundamental role in maintaining the osmotic pressure of the blood. Albumins are also important in the transport of fatty acids, thyroid hormones, some steroid hormones, and other substances.

Globulins account for approximately 35 percent of the proteins in plasma. Examples of important plasma globulins include ***antibodies*** and ***transport globulins.*** Antibodies, also called immunoglobulins, attack foreign proteins and pathogens. Transport globulins bind small ions, hormones, or compounds that might otherwise be lost at the kidneys or that have very low solubility in water.

Fibrinogen functions in clotting. Under certain conditions, fibrinogen molecules interact, forming large, insoluble strands of fibrin. These fibers provide the basic framework for a blood clot.

Origins of the plasma proteins

The liver synthesizes and releases more than 90 percent of the plasma proteins, including all albumins and fibrinogen, most globulins, and various prohormones. Antibodies are produced by plasma cells that are derived from lymphocytes.

Staining of blood cells

Blood cells are studied in the smears. The smears are prepared by spreading a drop of blood in a thin layer on a microslide (fig.7.1).

Blood smears are stained with special mixtures of red (Eosin) and blue (Azur II) dyes by Romanowsky- Giemsa.

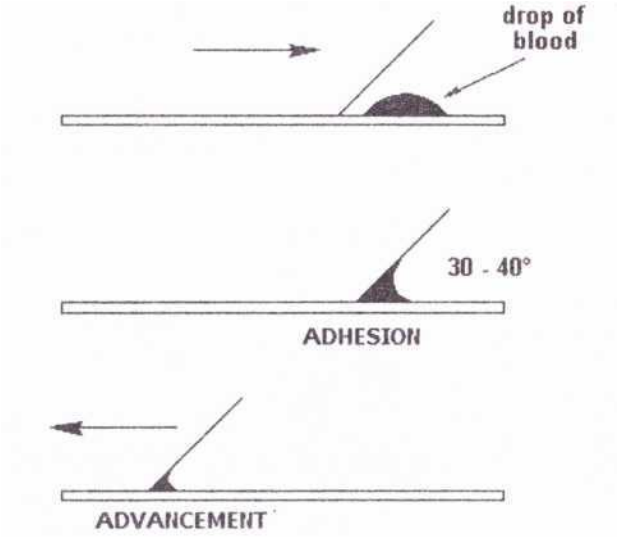


Figure 7.1. **Making the smear.**

E3 Erythrocytes

Erythrocytes (red blood cells) are postcellular structures which have no nuclei. These cells give whole blood its deep red colour. The erythrocyte is highly adapted for its principal ***function*** - oxygen and carbon dioxide transport. Erythrocyte consists of only an outer plasma membrane enclosing the iron-containine; respiratory protein ***hemoglobin (Hb),*** which binds and transports oxygen, and carbon dioxide, and the limited number of enzymes necessary for maintenance of gaseous transport function.

Each Hb molecule has a complex quaternary shape. The Hb molecule has two alpha chains and two beta chains of polypeptides. Each individual chain is a globular protein subunit. Each Hb chain contains a single molecule of ***heme,*** a pigment complex.

Erythrocytes are circular biconcave discs; biconcave shape increases the surface area (fig.7.2).

The normal concentration of erythrocytes in blood is 3,7- 4,9x1 $()^{12}$/L in women and 3,9-5,5xlO^{12}/L in men.

The ***hematocrit*** is the percentage of whole blood occupied by cellular elements. The normal hematocrit in adult males is 40-54; in adult females is 37-47.

The gender difference of erythrocytes reflects the fact that androgens (male hormones) stimulate red blood cell production, whereas estrogens (female hormones) do not.

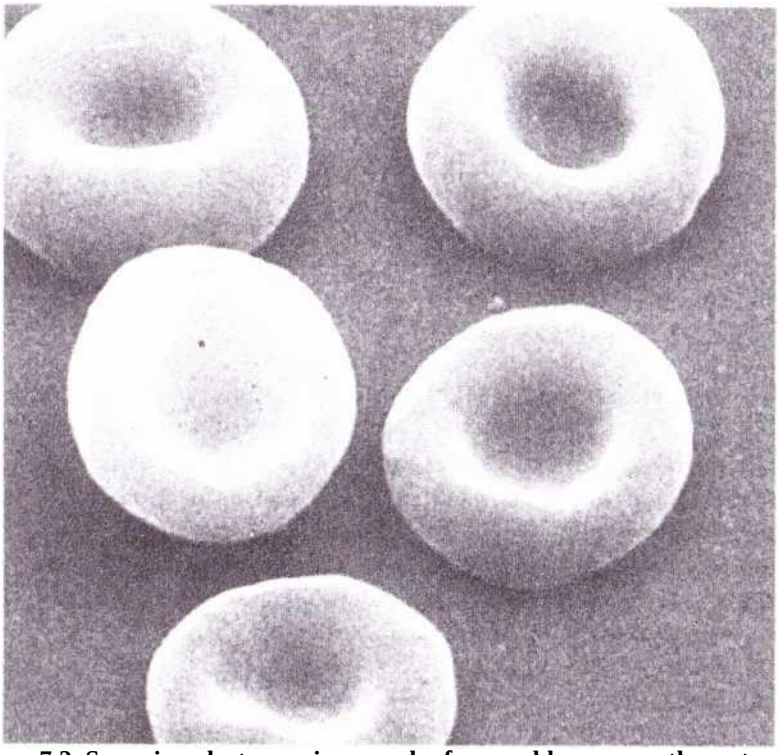


Figure 7.2. Scanning electron micrograph of normal human erythrocyte.

Human erythrocyte has 7,5 micrometers (pm) in diameter, 2,6 pm thick at the rim, and 0,8 pm thick in the centre.

Erythrocytes with diameter than 9 pm are called ***macrocytes*** and those diameters less than 6 pm are called ***microcytes.*** Change of sizes of erythrocytes is called ***anisocytosis.***

Lifetime

Human erythrocytes survive in the circulation for about 120 days. Worn-out erythrocytes are removed from the circulation mainly by microphages of the spleen and bone marrow.

0 Leukocytes

Leukocytes (white blood cells) include a variety of cells specialized for immune defense against foreign material or organisms.

The normal concentration of leukocytes in blood is 6-9x10$^{'J}$/L. The number of leukocytes in the blood varies according to age, sex, and physiologic conditions. An increase in the number of leukocytes over the upper limits is called ***leukocytosis,*** and a decrease below the lower limit is called ***leukopenia.***

On the basis of the presence and type of the granules in their cytoplasm and the shape of the nucleus, white blood cells are classified into two groups: ***granulocytes*** and ***agranulocytes.***

The term ***granulocyte*** is due to the presence of granules in the cytoplasm of these cells. In the different types of granulocytes, the granules are different and help us to distinguish them. In fact, these granules have a different affinity towards neutral, acid or basic stains and give the cytoplasm different colours. So, granulocytes distinguish themselves in neutrophils, eosinophils (or acidophil) and basophils.

Classification of the leukocytes

> ***granulocytes*** (polymorphonuclear leukocytes):
  - ***neutrophils,***
  - ® ***eosinophils,***
  - ® ***basophils,***

> ***agranulocytes*** (mononuclear leukocytes):
  - ***lymphocytes,***
  - ***monocytes.***

Granulocytes contain specific granules in cytoplasm; their nuclei have two or more lobes (fig. 7.3).

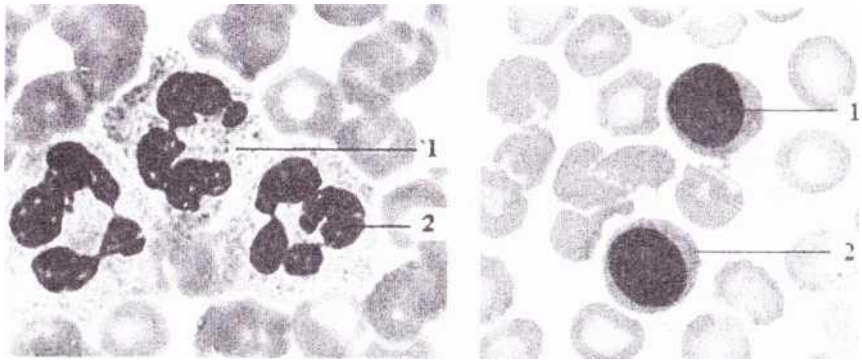


Figure 7.3. Photomicrograph of granulocytes. 1 — gianules, 2 — lobated nucleus

Figure 7A **photomicrograph of agranulocytes. 1**-nucleus. 2 - cytoplasm

Agranulocytes have no specific granules and contain non- lobated nuclei (fig.7.4).

1. Granulocytes

1.1 **Neutrophils**

Neutrophils constitute 65 - 75 % of circulating leukocytes. Neutrophils granulocytes have an average diameter of 10-12 micrometers (jam) in peripheral blood smears.

Nuclei of neutrophils are lobated, having 2-5 lobes. The lobes are connected by thin threads of chromatin (fig.7.5).

On a degree of a maturity distinguish neutrophils with the various shapes of the nuclei (fig.7.6):

> ***young*** (***metamyelocytes)*** have kidney-shaped nuclei, constitute 0,5%,

> ***band cells*** have nonsegmented horseshoe-shaped nuclei, constitute 1-6%,

> ***mature*** have segmented nuclei, constitute 47-72%.

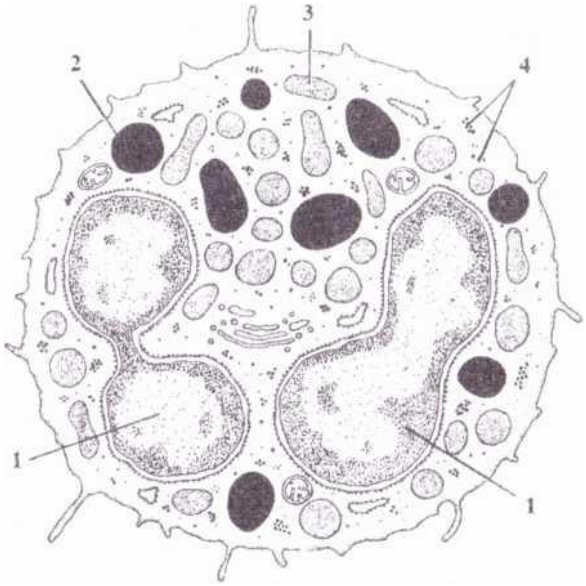


Figure 7.5. **Schematic representation of neutrophilic granulocyte.** 1 - lobes of nucleus, 2 - primary azurophilic granule, 3 - secondary specific neutrophilic granule, 4 - glycogen

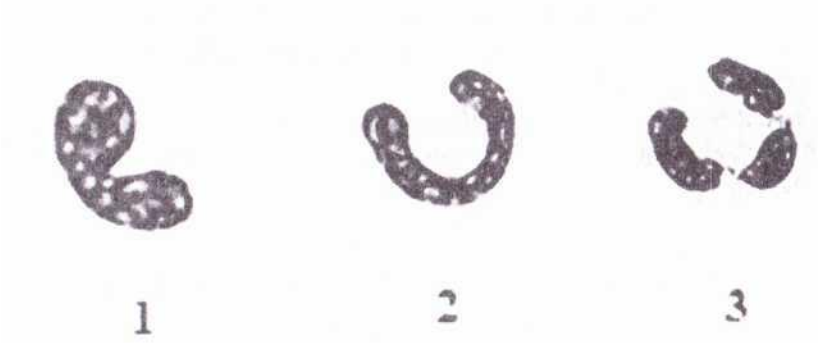


Figure 7.6. Types of neutrophils. 1 - young (metamyelocytes), 2 - band cell, 3 - segmented

In female, the inactive X chromosome appears as a drumsticklike appendage on the one of the lobe of the nucleus ***(Barr body)*** (fig-7.7).

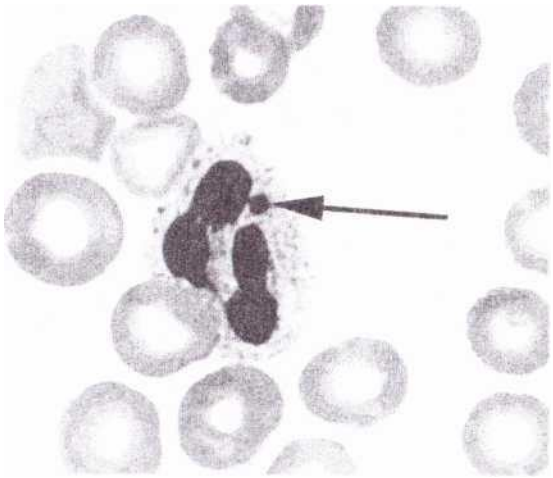


Figure 7.7. Barr body of neutrophil nucleus.

Cytoplasm contains two types of granules (fig.7.5): ***y primary azurophilic granules***, which are primary lysosomes and contain the enzymes (acid phosphatase, elastase, collagenase, cationic antibacterial proteins).
> ***secondary specific neutrophilic granules***, which are small, contain various enzymes (alkaline phosphatase, collagenase, lactoferrin, lysozyme).

Lifetime

Neutrophils are short-lived cells w'ith a half-life of 6-7 hours in blood and of 1 -4 days in spleen and other tissues.

Function

Neutrophils are phagocytes, capable of ingesting microorganisms or particles. They are called ***microphages.*** Neutrophils

constitute a defense against invasion by microorganisms, especially bacteria.

Chemotaxis is the process which is responsible for the migration of the neutrophils towards the infection or inflammation site. The receptors present at the surface of the cell, helps the neutrophils to detect

the chemical gradients of interleukin-8 (IL-8), interferon gamma (IFN- gamma), and C^a (fragment released from complement component C5). These molecules are responsible for directing the path of migration.

Being highly motile, neutrophils quickly congregate at a focus of infection, attracted by cytokines.

Neutrophils have three strategies for directly attacking micro-organisms:

> phagocytosis,

> release of granule proteins and

> generation of neutrophil extracellular traps (NETs) (NETs provide a high local concentration of antimicrobial components and bind, kill microbes independent of phagocytic uptake; in addition, NETs may serve as a magical barrier that prevents further spread of pathogens).

1.2Eosinophils (fig.7.8)

Eosinophils constitute 2 - 5 % of circulating leukocytes. Eosinophil granulocytes have an average diameter of 10-12 pm in peripheral blood smears. Eosinophils also have lobated nuclei (2-4 lobes).

Cytoplasm contains two types of granules:

> ***primary azurophilic granules,*** which are primary lysosomes and contain the enzymes

>■ ***specific eosinophilic granules*** are large and elongated; contain ***crystalline cores*** oriented parallel to the long axis of the granules.

Specific eosinophilic granules contain the major basic protein, cationic protein, eosinophil-derived neurotoxin and peroxidase.

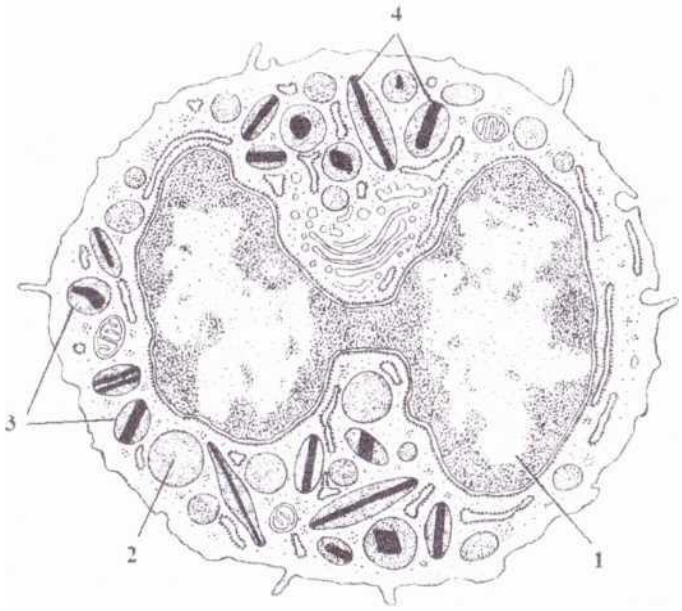


Figure 7.8. Schematic representation of eosinophilic granulocyte. 1 - lobe of nucleus, 2 - primary azurophilic granule, 3 - secondary specific eosinophilic granule, 4 - crystalline core

Lifetime

Eosinophils circulate for 4-5 hours in the blood, then migrate into the tissues (skin, mucosa of digestive, respiratory and reproductive tracts) and function 8 - 1 2 days.

Functions

> Participation in immune (allergic) reaction .

> Destruction of parasites (e.g. enteric nematodes) by the toxic basic protein.

> Limited ability to participate in phagocytosis.

> Diapedesis (eosinophils can migrate from the blood stream into the body tissues, in a process called diapedesis; this allows the leukocytes to fight localized infections in the tissues directly).

1.3 Basophils (fig.7.9)

Basophils constitute 0 - 1 % of circulating leukocytes.

Basophils have an average diameter of 12-15 pm in peripheral blood smears.

They have lobated (2-3 lobes) or S-shaped nuclei.

Cytoplasm contains two types of granules:

> ***primary azurophilic granules,*** which are primary lysosomes and contain the enzymes.

> ***specific basophilic granules*** which stain metachromatically with the basic dye of the usual blood stains.

Metachromasia is a property of cells to be painted in other colour distinguished from colour of dye.

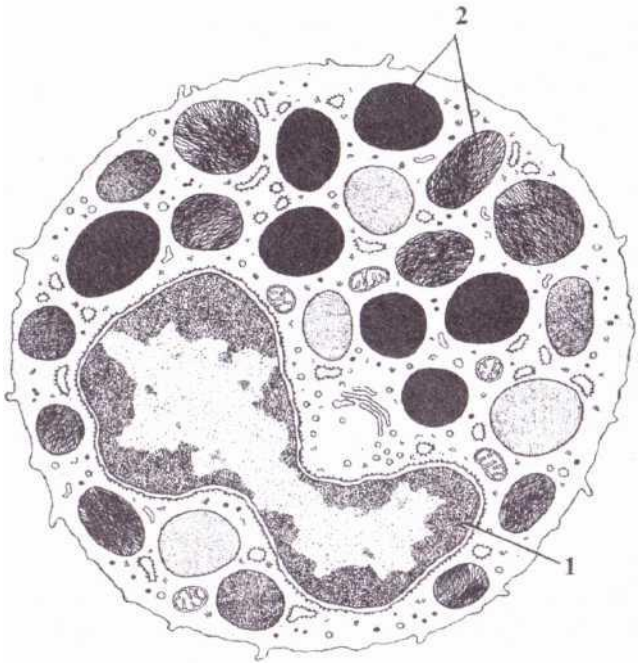


Figure 7.9. Schematic representation of basophilic granulocyte. 1 — lobe of nucleus, 2 - specific basophilic granules

Basophilic specific granules contain:

- heparin (anticoagulant) and
- histamine (dilatation of blood vessels and increase of their permeability).

Lifetime

Basophils circulate for a few hours in the blood, then migrate into the tissues and function for a few days.

Functions

Basophils appear in many specific kinds of ***inflammatory reactions.***

Basophils contain anticoagulant ***heparin,*** which prevents blood from clotting too quickly. They also contain the vasodilator ***histamine,*** which promotes blood flow to tissues.

They can be found in unusually high numbers at sites of ***ectoparasite infection.***

They are found in tissues where allergic reactions are occurring and probably contribute to the severity of these reactions.

Basophils have protein receptors on their cell surface that bind IgE, an immunoglobulin involved in macroparasite defense and allergy.

1. Agranulocytes

2.1**Monocytes** (fig.7.10)

Monocytes constitute 6 - 8 % of circulating leukocytes.

Basophils have an average diameter of 12-20 um in peripheral blood smears.

Nuclei are oval, horseshoe- or kidney-shaped, and eccentric in position.

Cytoplasm is basophilic, contains fine azurophilic granules (lysosomes).

Lifetime

Monocytes circulate in the bloodstream for about one to three days and then typically move into tissues throughout the body.

Function

In the tissues monocytes mature into tissue resident ***macrophages*** or ***dendritic cells.***

Monocytes, macrophages and dendritic cells have three main functions in the immune system:

> phagocytosis,
> antigen presentation,
> cytokine production.

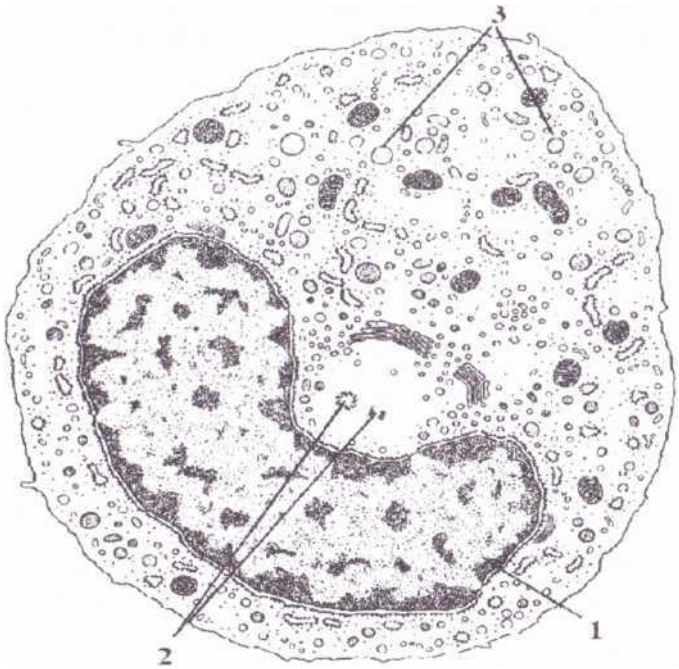


Figure 7.10. Schematic representation of monocyte. 1 - kidney-shaped nucleus, 2 — centrioles, 3 - azurophilic granules (lysosomes)

Phagocytosis is the process of uptake of microbes and particles followed by digestion and destruction of this material.

Microbial fragments that remain after such digestion can serve as antigen. The fragments can be incorporated into MHC molecules and then traffic to the cell surface of macrophages. This process is called ***antigen presentation*** and it leads to activation of T lymphocytes, which then provide a specific immune response against the antigen.

Other microbial products can directly activate monocytes and this leads to production of ***cytokines*** (tumor necrosis factor (TNF), interleukin- 1 (IL-1) and interleukin-12 (IL-12)).

A majority of macrophages are stationed at strategic points where microbial invasion or accumulation of dust is likely to occur.

Each type of macrophage, determined by its location, has a specific name:

jName of cell	**1 Location**
fDust cells/alveolar macrophages (pulmonary alveolus of lungs	
{Histiocytes	| connective tissue
Kupffer cells	| liver
jMicroglia	**J** neural tissue
jOsteoc lasts	fbone
jsinusoidal lining cells	| spleen

2.2**Lymphocytes** (fig.7.11)

Lymphocytes constitute 20-35 % of circulating leukocytes.

Lymphocytes can be classified into several groups according to their ***sizes***:

> small lymphocytes have diameter - 6-8 pm,
> medium-sized lymphocytes - 8-9 pm, and
> large lymphocytes - 10-18 pm.

The small lymphocytes are predominant in the blood. Lymphocytes have are large, spherical ***nuclei*** often indented on one side; very dense and dark blue due to heavy chromatin mass. ***Cytoplasm*** as a thin rim around the nucleus is slightly basophilic.

Lymphocytes can be classified into several groups according to ***functional significance.***

The three major types of lymphocyte are:

> T cells,
> B cells and
> natural killer (NK) cells.

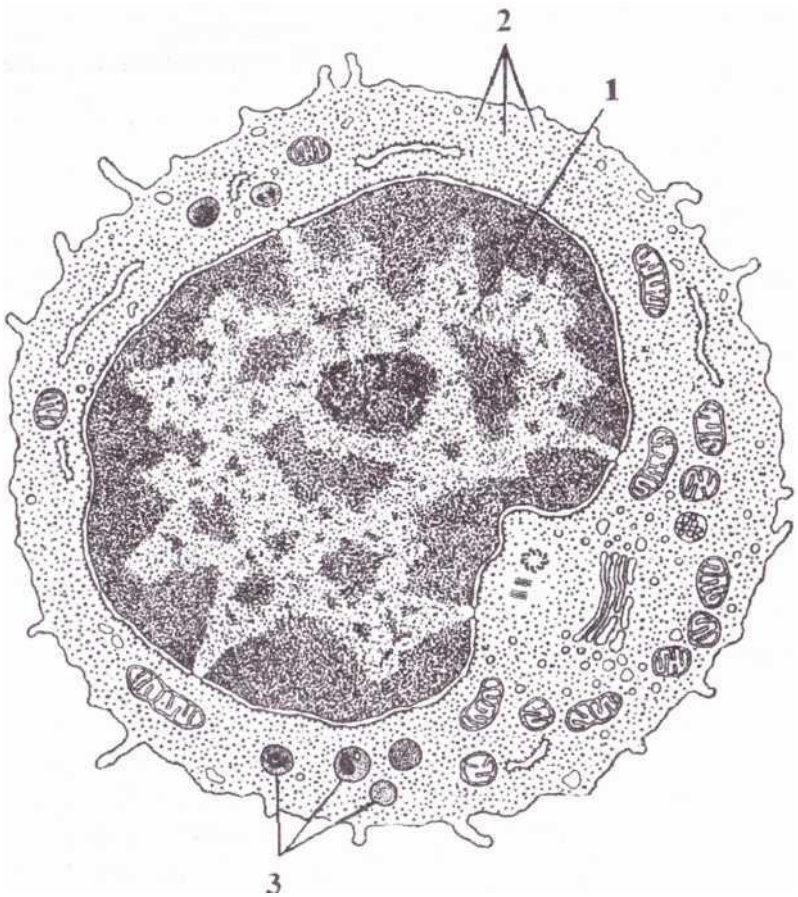


Fig. 7.11. Schematic representation of lymphocytes. 1 - nucleus, 2 — ribosomes, 3 - lysosomes

Characteristic of T lymphocytes (T cells)

T cells represent 60-80% of blood lymphocytes. They have a long lifespan and are involved in cell-mediated immunity.

These cells originate in the bone marrow and migrate to the thymus, where they differentiate into immunocompetent cells. Initially, lymphocytes are genetically programmed to recognize a single antigen out of virtually an infinite number of possible antigens. This process is termed antigen-independent proliferation and differentiation. Then immunocompetent cells migrate to the blood, lymph, and special T- regions of peripheral (secondary) lymphoid organs where they undergo antigen-dependent activation and differentiation into effector lymphocytes (cytotoxic cells, helpers, and suppressors) and memory cells. T memory cells react rapidly to the reintroduction of the same antigens.

Characteristic of B lymphocytes (B cells)

B- cells are named so because they were first recognized in the bursa of Fabricius in birds. They have variable lifespan and are involved in humoral immunity by production and secretion of circulating antibodies (immunoglobulins).

B cells represent 20-30 % of blood lymphocytes derive from ***bursa-equivalent organs*** (red bone marrow and GALT in mammals) where they undergo ***antigen-independent proliferation and differentiation.*** Then these cells migrate to the blood, lymph, and special B-regions of peripheral (secondary) lymphoid structures where they proliferate and differentiate into the ***effector lymphocytes*** (antibody- secreting plasma cells) and ***memory cells*** which react very rapidly to reintroduction of the same antigen. This process is called ***antigen- dependent activation and differentiation.***

Characteristic of natural killer (NK) cells

NK cells constitute about 5-10% of circulating lymphocytes. NK cells develop from the same precursor cells as T and B cells. These cells genetically are programmed to recognize transformed cells (tumor cells or infected with a virus). Following recognition of antigens, NK cells release proteins ***[perforins*** and ***fragmentins***) that open holes in foreign cell membranes, with consequent self-destruction (a process known as apoptosis) or cell lysis.

Lifetime

Lymphocytes vary in life span; some live only a few days, while others survive in the circulating blood for many years.

0 Blood platelets (thrombocytes)

The ***platelets*** are small (2-4 pm in diameter), irregular, discshaped non-nucleated membrane-bound cell fragments of giant polyploid cells of the bone marrow - megakaryocytes that contain substances important to the process of clotting.

Platelet count

There are normally 150 - 450 xlO^9 platelets in each liter of blood. Of the total quantity of platelets in the body, 70% are present in the circulation and 30% in the spleen.

Platelet is divided into four zones (fig.7.12) based on structure and function.

> ***Peripheral zone*** consists of cell membrane covered by a glycocalyx. The membranes of the platelet are rich in glycoproteins, which serve as receptors in platelet function.

> ***Structural zone*** is beneath the peripheral zone and is the framework of the platelet, the cytoskeleton. This zone consists of microtubules, actin filaments, myosin. They are circumferentially arranged and responsible for maintaining the platelet's dick shape as well as the contractile system that, upon activation, allows shape change, pseudopod extension.

> ***Organelle zone*** consists of the granules and cellular components, such as lysosomes, peroxisomes, mitochondria. The ***alpha granules*** contain adhesive proteins, such as fibrinogen, coagulation factors, plasminogen, etc. The ***delta (dense) granules*** contain adenosine triphosphate (ATP), adenosine diphosphate (ADP), serotonin, and calcium. The ***lambda granules*** are similar to lysosomes and contain proteolytic enzymes.

> ***Membrane zone*** includes two types of membrane channels. The platelet has a surface-connected system of channels called the ***open canalicular system.*** Through the open canalicular system, plasma

substances enter the interior of the platelet and platelet products exit. The ***dense tubular system*** originates from rough endoplasmic reticulum, serves as a storage site for calcium ions.

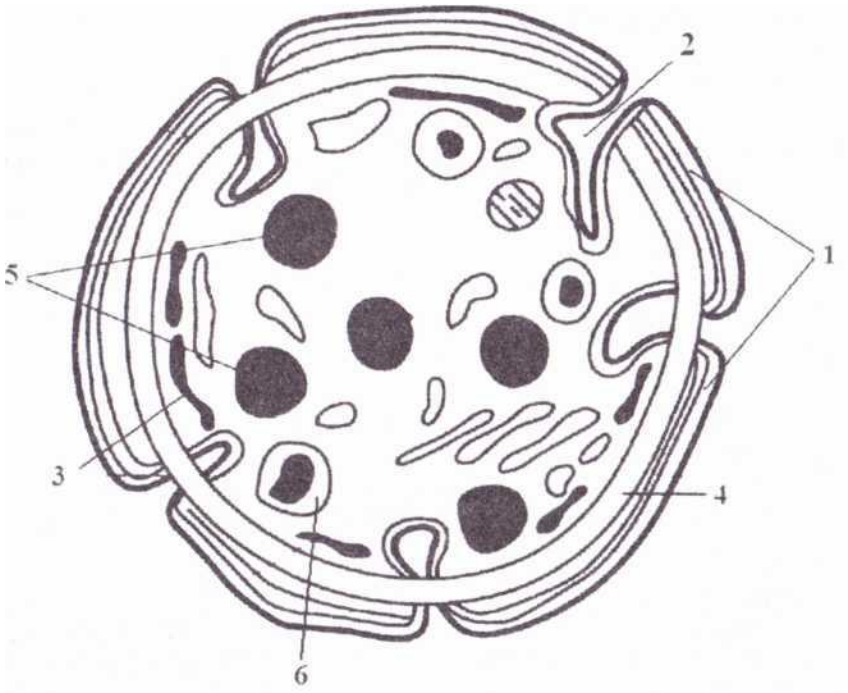


Figure 7.12. Schematic diagram of the human platelet. 1 - cell membrane, 2 - open canalicular system, 3 - dense tubular system, 4 - microtubules, 5 - delta (dense) granules, 6 - alpha granules

Lifetime

The average lifetime of a platelet is normally just 5 to 9 days.

Function

The function of platelets is the maintenance of hemostasis by the formation of thrombi, when damage to the endothelium of blood vessels occurs.

0 Hemogramm. Leukocytic formula

Hemogramm reflects contents of separate formed elements per 1 liter of blood:
Erythrocytes - 3, 9-5, 5xl0^{12} /L in women and 4. 1 -6x 10^{12} /L in men.
Leukocytes - 6 - 9x 1 ()^{g} /L.
Platelets - 150-450x10^{g}/L.

Leukocytic formula of peripheral blood (tab 1.7.1) reflects relative contents of different leukocytes as regards total quantity of leukocytes accepted for 100%.

Table 7.1. Leukocytic formula.

Basophils	Eosinophils	Neutrophils			Lympho cytes	Mono-cytes
		65 - 75 %:				
		young	band cells	Segmented cells		
0 -1 %	1 - 5 %	0-0,5 %	1-6%	47-72 %	19-37%	3-8 %

Age-dependent features of blood

Number of ***erythrocytes*** at newborn is 6-7x10^{-2}/L.

Number of leukocytes at newborn is 10-30 x 10^{9}/L;

By /***4th day*** it is equal to the indexes of the grown man.

On ***3-6th*** months there is physiological anaemia (decrease of number of erythrocytes and hemoglobin). It is related to the transfer of the growth factor of erythrocytes (erythropoietin) synthesis from the liver to kidneys.

New-born

> neutrophils 65-75 %;
> lymphocytes 20-35 %.

4-5 day - the first white blood cross

> neutrophils 45 %;
> lymphocytes 45 %.

2 years:

> neutrophils 25 %;
> lymphocytes 65 ***%.***

4-5 years - the second white blood cross

> neutrophils 45 %;
> lymphocytes 45 %.

14-17 years:

> neutrophils 65-75 %;
> lymphocytes 20-35 %.

0 Lymph

Lymph is a part of the interstitial fluid, the fluid which is in the interstices of all body tissues. Interstitial fluid becomes lymph when it enters a lymph capillary. The lymph then travels to at least one lymph node before emptying ultimately into the right or the left subclavian vein, where it mixes back with blood.

Lymph is a clear to yellowish watery fluid. Lymph contains the same proteins as in plasma of blood, but in smaller amounts.

Volume of lymph in the human body is 1-2 liters.

Functions of the lymph

> Return of protein and fluid from the tissues to the circulation.
> Absorption and transport of fat from the small intestine.
> Immunological - circulation of immune cells such as lymphocytes and dendritic cells, removal of bacteria.

Composition of lymph

Lymph consists of:

> plasma and
> formed elements.

Concentration of formed elements in the lymph is $2\text{-}20 \times 10^9$/L.

Formed elements of lymph

Lymphocytes constitute 90%;
Monocytes constitute 5%;
Eosinophils constitute 2%;
Neutrophils constitute 1%;
Other cells constitute 2%.

0 Clinical correlations

Because the liver is the primary source of plasma proteins, ***liver disorders*** can alter the composition and functional properties of blood.

For example, some forms of liver diseases can lead to uncontrolled bleeding due to the inadequate synthesis of fibrinogen and other proteins involved in clotting.

Erythrocyte disorders

> ***Anemia*** is a hemoglobin level below its normal range.
> ***Polycythemia*** is an over-production of erythrocytes.

Leukocyte disorders

> ***Leukopenia*** is a decrease in the number of leukocytes found in the blood, which places individuals at increased risk of infection.

> ***Leukocytosis*** is a raised leukocyte count above the normal range in the blood.

An increase in eosinophils is called an ***eosinophilia,*** and is typically seen in people with a parasitic infestation of the intestines, a ***collagen vascular disease*** (such as rheumatoid arthritis), ***malignant*** diseases such as Hodgkin's disease, etc.
The number of eosinophils increases dramatically if an ***allergic reaction*** is occurring.

An increase in basophils is called a ***basophilia.*** It is typically seen in people with ***viral infections, myeloproliferative disease, inflammatory processes, endocrine causes*** (hypothyroidism, increased estrogen). _____ _____

Monocytes (macrophages) are involved in many diseases of the immune system. For example, they participate in the formation of granulomas, inflammatory lesions that may be caused by a large number of diseases.

Macrophages are the predominant cells involved in creating the progressive plaque lesions of ***atherosclerosis.***

Macrophages also play a role in ***Human Immunodeficiency Virus (HIV) infection.*** Like T cells, macrophages can be infected with FflV, and even become a reservoir of ongoing virus replication throughout the body.
Macrophages are believed to help cancer ceils proliferate as well. They are attracted to oxygen-starved (hypoxic) tumor cells and promote chronic inflammation. Inflammatory compounds such as Tumor necrosis factor (TNF) released by the macrophage activates the gene switch nuclear factor-kappa B. NF-κB then enters the nucleus of a tumor cell and turns on production of proteins that stop apoptosis and promote cell proliferation and inflammation.

Platelet disorders

If the number of platelets is too low, excessive ***bleeding*** can occur. However, if the number of platelets is too high, blood clots can form (***thrombosis***), which may obstruct blood vessels and result in such events as a ***stroke, myocardial infarction, pulmonary embolism*** or the ***blockage of blood vessels*** to other parts of the body, such as the extremities of the arms or legs.

HEMOPOIESIS 0 Overview of

the hemopoiesis

Mature blood cells have a relatively short life span, and consequently the population must be continuously replaced by the progeny of stem cells produced in the ***hemopoietic*** organs.

Hemopoiesis is development of the blood cells. Distinguish ***embryonic (prenatal) hemopoiesis*** which descends in embryonic life and results in development of a blood as tissue, and a ***postembryonic (postnatal) hemopoiesis*** which represents process of physiological regeneration of a blood.

Development of erythrocytes name ***an erythropoiesis,*** development of granulocytes - a ***granulopoiesis,*** thrombocytes -a ***thrombopoiesis,*** development of monocytes - a ***monopoiesis,*** development of lymphocytes and immunocytes - a ***lympho-*** and ***immunopoiesis.***

At the adult person the hemopoiesis descends in the bone marrow of bone of a skull, ribs, sternum, spondyles, pelvic bones, and epiphyses of the lengthy bones. In the prenatal period the hemopoiesis serially descends in several developing organs.

0 Prenatal hemopoiesis

1. ***Yolk sac (megaloblastic) phase***

During 2-3 week of development in the wall of the ***yolk sac*** the clumps of mesenchymal cells - ***blood islands*** - are formed (fig.8.1). Cells on periphery of each island form the endothelium of primary blood vessels. The cells of the central part of an island form the first blood cells

- ***primary erythroblasts*** - the large cells containing a nucleus and embryonic hemoglobin (Hb).

Leucocytes and thrombocytes at this stage are not present.

On 12-th week the hemopoiesis in a yolk sac comes to an end.

Within the second month of development hemopoietic stem cells invade a liver, a lien a thymus and lymph nodes and in these organs different types of blood cells are formed.

2 ***Hepatic phase***

In a liver the hemopoiesis begins on 5-6 week of development. Granulocytes, thrombocytes and erythrob lasts, and erythrocytes (denuclearized cells) are form here. By the end of 5-th month intensity of a hemopoiesis in the liver decreases.

3. ***Splenic phase***

The hemopoiesis in the spleen is most expressed with 4 for 8 month of prenatal development. Here erythrocytes and a small amount of granulocytes and thrombocytes are formed. Directly before of a birth the main function of the spleen the formation of lymphocytes becomes.

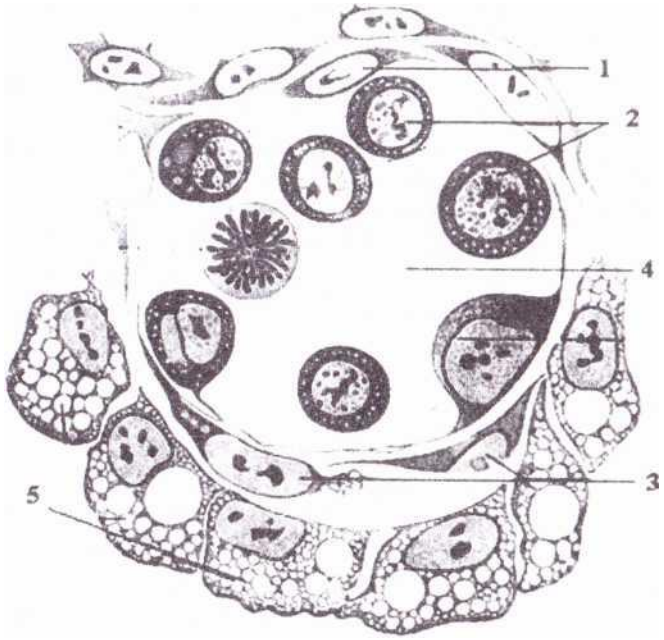


Figure 8.!. Cross section of the blood island. 1 - endothelium of the wall of blood vessel, 2 - primary blood cells, 3 - mesenchymal cells, 4 - lumen of blood vessel, 5 — eridodermal epithelium

4. ***Hemopoiesis in the thymus***

On 7-8 week of development in thymus T-lymphocytes are formed.

5. ***Hemopoiesis in the lymph nodes***

On 9-10 week of development lymph nodes can produce erythrocytes, granulocytes and megakaryocytes.

6. ***Bone marrow phase***

Within 5-th month of development a hemopoiesis begins in the bone marrow where all types of blood cells are formed. By the moment of a birth, after a birth and at the adult the hemopoiesis is limited to the bone marrow and the lymphoid tissue.

When the bone marrow is not capable satisfy the increased inquiry about formation of the blood cells, hemopoietic activity of a liver, spleen and lymph nodes can be reduced.

0 Theory of a hemopoiesis

Now it is proved, that as the common source of development of all formed elements of the blood is ***pluripotential stem cell*** This position for the first time is formulated by professor A.A.Maksimov in the beginning of XX century in the ***monophyletic (Unitarian) theory of the hemopoiesis***

Stem cells

Stem cells can produce all blood cell types, because these cells are called ***pluripotential.*** Stem cells look like small lymphocytes.

Stem cells are concentrated at the adult person mainly in the red bone marrow, however are found out in the blood, circulating in which they get in other organs of a hemopoiesis.

The basic properties of stem cells:

> ***Self-renewal*** - the ability to go through numerous cycles of cell division while maintaining the undifferentiated state.

> ***Potency*** - the capacity to differentiate into specialized cell types.

Pluripotential stem cells can differentiate into nearly all cells.

Multipotential stem cells can differentiate into a number of cells, but only those of a closely related family of cells.

Oligopotenial stem cells can differentiate into only a few cells, such as lymphoid or myeloid stem cells.

Unipotential cells can produce only one cell type.

The study of stem cells in bone marrow is possible because of experimental techniques that permit analysis of hemopoiesis.

In vivo techniques include injecting the bone marrow of normal donor mice into lethaily irradiated mice whose hemopoietic cells have been destroyed.

In these animals, the transplanted bone marrow cells develop ***colonies of hemopoietic cells in the spleen (colony-forming cells - CFC)***

In vitro investigation of hemopoiesis is made possible through the use of a tissue culture medium made with a layer of cells derived from bone marrow stroma. This medium creates microenvironmental conditions for hemopoiesis.

Data from an experiments show that under these suitable microenvironmental conditions, stimulation by growth factors influences the development of the various types of biood cells.

Bask compartments of the hemopoietic cells (fig.8.2)

I - pluripotential stem cell;
II - multipotential stem cells;
III - uni- or bipotential progenitor cells;
IV - precursor cells (blasts),
V - maturing cells,
VI - mature cells.

Pluripotential stem cell (I) proliferates and forms one cell lineage that will become lymphocytes (***lymphoid cells),*** and another lineage that will form the ***myeloid cells*** that develop in bone marrow (granulocytes, monocytes, erythrocytes, and megakaryocytes). Both these types of stem cells are called ***multipotential stem cells.***

The proliferating ***multipotential stem cells*** (II) form daughter cells with reduced potentiality: ***uni-*** or ***bipotential progenitor cells*** (III).

Cells forming colonies of specific cell types are called ***colony- forming cells (CFC),*** or ***colony-forming units (CFU).*** The convention in naming these various cell colonies is to use the initial letter of the cell each colony produces. Thus, MCFC denotes a monocyte-colony-forming cell, CFC-Eo produces eosinophils, and CFC-MG produces monocytes and granulocytes, and so on.

Progenitor cells (III) have high mitotic activity, self-renewing, common in marrow and lymphoid organs.

Uni- or ***bipotential progenitor cells*** generate ***precursor cells (blasts)*** (IV).

Precursor cells (IV) have high mitotic activity, not self- renewing, common in marrow and lymphoid organs, unipotential.

From each ***progenitor cell*** there is a formation of a concrete kind of cells. The maturing of each kind of cells passes series of stages which in aggregate form compartment of maturing cells (V). Mature cells represent last compartment (VI). All cells of V and VI compartments morphologically can be identified.

Hemopoietic cytokines

The differentiation pluripotential cell in unipotential is determined by action of some ***hemopoietic cytokines,*** erythropoietin, granulocyte colony-stimulating factor, granulocyte-macrophage colony- stimulating factor, monocyte colony-stimulating factor, thrombopoietin, interleukins etc. Cytokines are glycoprotein hormones and stimulating factors that regulate all stages of hemopoiesis.

Hemopoietic cytokines are produced by stromal components of hemopoietic tissues and organs. They are produced also by epithelial cells of a thymus, macrophages, T-lymphocytes, cells of an endothelium, and also the cells which were outside of hemopoietic tissues (for example, erythropoietin) is produced by the cells of liver and kidney.

0 Postnatal hemopoiesis

In the postnatal period the hemopoiesis is carried out in the special ***hemopoietic tissues - myeloid*** and ***lymphoid.***

The ***myeloid tissue*** is functionally leading tissue of ***the red bone marrow,*** which in lumens of tubular and flat bones.

The myeloid tissue contains stem cells and is a place of formation of erythrocytes, granulocytes, monocytes, thrombocytes, B- lymphocytes, precursors of T- lymphocytes and NK-cells (natural killer cells).

The ***lymphoid tissue*** is found in ***lymphoid organs*** - a thymus, a spleen, lymph nodes, tonsils, Peyer's patches, vermiform appendix and the numerous lymphoid formations available in a wall of organs of various systems. In it there is formation T-and B-lymphocytes, and also plasma cells which provide development of immune responses.

0 Erythropoiesis

Eryihropoiesis (fig.8.2) is process of formation and a maturing of the erythrocytes, occurring in ***myeloid tissue.***

Erythron is erythroidal differon, representing set of the cells - from stem cells up to mature erythrocytes.

BFU - burst forming unit - is named so on the ability to form quickly on semisolid medium colony of erythroidal cells size of some hundreds elements.

The first recognizable cell in the erythroid series is the ***proerythroblast.*** It is a large cell, its cytoplasm is basophilic.

The next stage is represented by the ***basophilic erythroblast*** with a strongly basophilic cytoplasm and a condensed nucleus. The basophilia of these two cell types is caused by the large number of polyribosomes involved in the synthesis of hemoglobin. During the next stage, polyribosomes decrease and areas of the cytoplasm begin to be filled with hemoglobin. Staining at this stage causes several colours to appear in the cell - the***polychromatophilic erythroblast.***

In the next step, the nucleus continues to condense and no cytoplasmic basophilia is evident, resulting in a uniformly acidophilic cytoplasm - the ***orthochromatophilic erythroblast.***

This cell puts forth a series of cytoplasmic protrusions and expels its nucleus, encased in a thin layer of cytoplasm. The remaining cell still has a small number of polyribosomes that, when treated with the survival dye brilliant cresyl blue, aggregate to form a stained network. This cell is the ***reticulocyte***, which soon loses its polyribosomes and becomes a mature red blood cell ***(erythrocyte).***

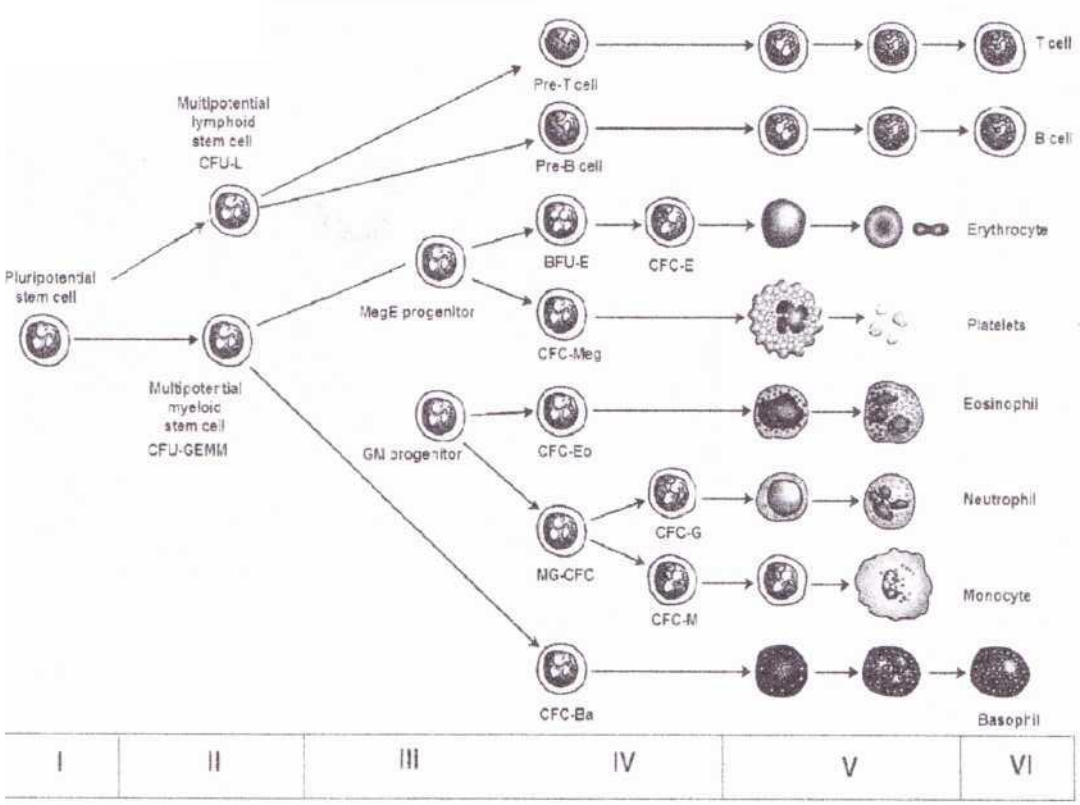


Figure 8.2. Scheme of hemopoiesis. I-VI- compartments of hemopoietic cells.

Process of development of erythrocytes is described by sequence:

Pluripotential stem cell => ***multipotential myeloid stem cell (CFU- GEMM) burst forming unit-erythrocyte (BFU-E)*** => ***colony forming unit-erythrocyte (CFU-E)*** => ***proerythroblast*** => ***basophilic erythroblast*** => ***polychromatophilic erythroblast*** => ***orthochromatophilic erythroblast*** ^ ***reticulocyte*** => ***erythrocyte.***

Process of a differentiation of precursors of erythrocytes into mature formed elements is accompanied by several gradual changes (fig-8.3):

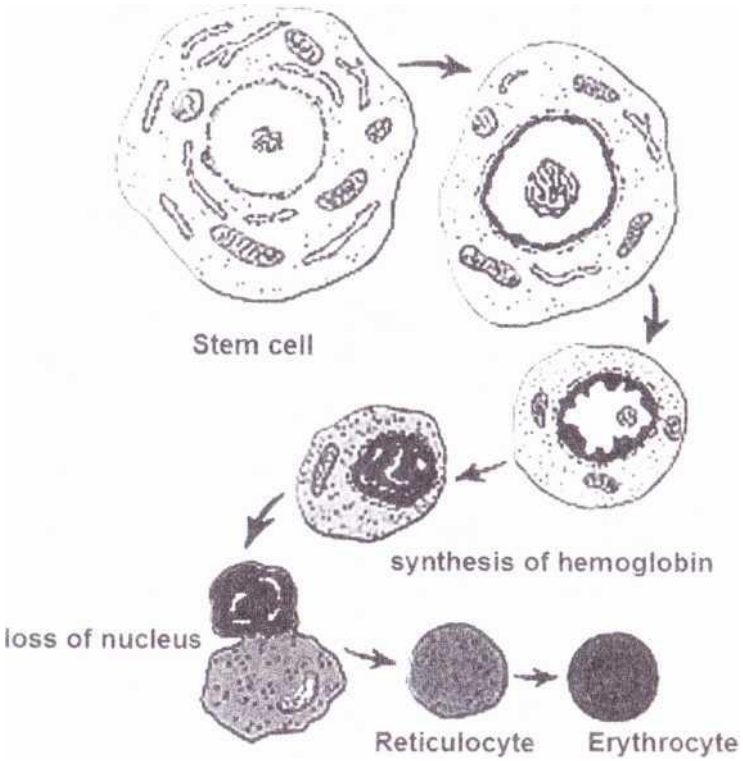


Figure 8.3. Schematic diagram of erythropoiesis.

> decrease in cell size and loss of cellular organelles,
> decrease of basophilia in cytoplasm due to loss of polysomes,
> increase of acidophilia in cytoplasm due to hemoglobin accumulation,
> decrease in nuclear size and increase in chromatin density (nucleus is eventually extruded),
> loss of ability to divide.

Regulation of erythropoiesis

For erythropoiesis to proceed normally, the red bone marrow must receive adequate supplies of amino acids, iron, and vitamins (including and folic acid) required for protein synthesis. For example, we obtain vitamin Bn from dairy products and meat, and its absorption requires the presence of intrinsic factor produced in the stomach. If vitamin $B|_2$ is not obtained from the diet, normal stem cell divisions cannot occur and pernicious anemia results.

Erythropoiesis is stimulated directly by the peptide hormone ***erythropoietin*** and indirectly by several hormones, including thyroxin, androgens, and growth hormone.

0 Granulopoiesis

Granulopoiesis (fig.8.2, 8.4) is formation and a differentiation of granulocytes, occurs in the red bone marrow.

Process of the differentiation of precursors of granulocytes into mature cells is accompanied by several gradual changes (similar to erythropoiesis):

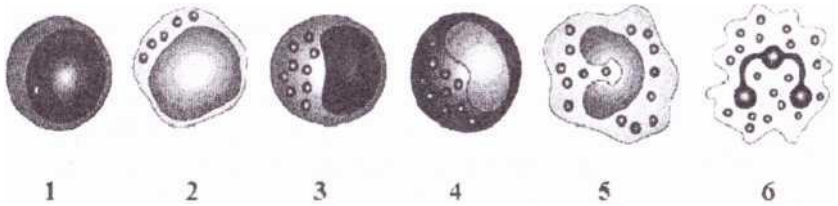


Figure 8.4. Schematic diagram of granulopoiesis. 1- myeloblast, 2 — promyelocyte, 3 — myelocyte, 4 - metamyelocyte, 5 - band cell, 6 - segmented granulocyte

> decrease in cell size,

> change of the shape of a nucleus - from spherical and kidney- shaped to and S- or horseshoe-shaped, its segmentation,
> decrease in amount of azurophilic granules, appearance and increase of specific granules,
> loss of ability to divide.

Sequence of the initial stages of development of granulocytes:

a) neutrophilic:

Pluripotential stem cell => multipotential myeloid stem cell (CFJJ- GEMM) => ***bipotential monocyte-granulocyte-colony-forming cell (MG-CFC)*** => ***granulocyte-colony-forming cell (CFC-G);***

b) basophilic:

Pluripotential stem cell => ***multipotential myeloid stem cell (CFU- GEMM) => basophil-colony-forming cell (CFC-Ba);***

c) eosinophilic:

Pluripotential stem cell => ***multipotential myeloid stem cell (CFU- GEMM)*** => ***eosinophil-colony-forming cel! (CFC-Eo);***

The subsequent stages of development of granulocytes precede for all three types of cells the same:

Myeloblast => ***promyelocyte*** => ***myelocyte => metamyelocyte*** => ***band celI*** => ***segmented granulocyte.***

0 Monopoiesis

Monopoiesis (fig.8.2) is formation and a differentiation of monocytes, occurs in the red bone marrow.

Process of development of erythrocytes is described by sequence:

Pluripotential stem cell => ***multipotential myeloid stem cell (CFU- GEMM) bipotential monocyte-granulocyte-colony-forming cell (MG-CFC) => monocyte-colony-forming cell (CFC-M)*** => ***monoblast*** => ***promonocyte*** => ***monocyte.***

Process of transformation of monoblasts into monocytes includes:

> increase in the sizes of a cell mainly due to increase of volume of cytoplasm;
> decrease of basophilia of cytoplasm;

> accumulation in cytoplasm of azurophilic granules;
> change of the shape of a nucleus which becomes kidney-shaped.

0 Thrombopoiesis

Thrombopoiesis (fig.8.2) is formation of platelets in the red bone marrow by fragmentation of the cytoplasm of mature ***megakaryocytes.***

Process of development of erythrocytes is described by sequence:

Pluripotential stem cell => ***multipotential myeloid stem cell (CFU- GEMM)*** => ***megakaryocyte-colony-forming cell (CFC-Meg)*** => ***megakaryoblast*** => ***megakaryocyte*** => ***platelets.***

The ***megakary oblast*** is 15-50 pm in diameter and has a large ovoid or kidney-shaped nucleus. The nucleus becomes highly polyploid (it contains up to 30 times as much DNA as a normal cell).

The ***megakaryocyte*** is a giant cell (35-150 pm in diameter) with an irregularly lobated nucleus. With maturation of the megakaryocyte, numerous invaginations of the plasma membrane ramify throughout the cytoplasm, forming the ***demarcation membranes.*** This system defines areas of the megakaryocyte cytoplasm that will be shed as platelets.

0 Lymphopoiesis

Lymphopoiesis (fig.8.2) is formation and a differentiation of lymphocytes, occurs in the red bone marrow and lymphoid organs.

Process of development of erythrocytes is described by sequence:

Pluripotential stem cell => ***multipotential lymphoid stem cell (CFU- L)*** => ***lymphoblast*** => ***lymphocytes.***

CONNECTIVE TISSUES 0 Overview of

the connective tissues

The ***connective tissues*** are the complex of derivatives of the mesenchymal origin, consisting of cellular differons and the extracellular substance, participating in maintenance of a homeostasis of the internal environment of an organism.

Functions of connective tissue

> ***Metabolic functions.*** All the metabolites from the blood pass from capillary beds and diffuse through the adjacent connective tissue to cells and tissues. The adipose tissue serves as an energy store and also provides thermal insulation.

> ***Regulative.*** Connective tissues regulate the activity of other tissues by means of biologically active substances and contact interactions.

> ***Defensive functions.*** Various components of the connective tissue play roles in the defense or protection of the body (plasma cells, lymphocytes, neutrophils, eosinophils, basophils, mast cells). Macrophages are important in tissue repair as well as defense against bacterial invasion. The fibroblasts of connective tissue proliferate in respoase to in jury of organs and migrate to and deposit abundant new collagen fibers, resulting in the formation of fibrous scar tissue.

> ***Structural support*** The connective tissues serve several functions, of which the most prominent function is structural support to enable maintenance of anatomical form of organs and organ systems. Examples include the connective tissue capsules surrounding organs. The loose connective tissue acts to fill the spaces between organs. The tendons and the elastic ligaments are examples of specialized orderly forms of connective tissue.

Classification of the connective tissues

1. Fiber connective tissue (connective tissue proper)
    1.1 Loose (areolar) connective tissue
    1.2 Dense connective tissue
        1.2.1 Regular
        1.2.2 Irregular
2. Connective tissues with special properties
    2.1 Adipose tissue
    2.2 Reticular tissue
    2.3 Mucous tissue
    2.4 Pigment tissue
3. Supporting connective tissue
    3.1 Cartilage
    3.2 Bone

General principle of organization of connective tissue

Connective tissue consists of:

> connective tissue cells,
> extracellular matrix:
    - ground substance,
    - protein fibers (collagen, reticular, elastic).

0 Types of connective tissue proper (fiber connective tissue)

Loose (areolar) connective tissue

The loose connective tissue (fig.9.1, 9.2) is characterized by low maintenance of fibers in intercellular substance, great volume of the ground substance, numerous cellular compositions.

This tissue is the more abundant in organism.

Loose connective tissue is found out in all organs - it forms their ***stroma***, fills in spaces between function elements of other tissues, accompanies with nerves and pots, is part of a skin and mucosa.

Loose connective tissue has a delicate consistency; it is flexible, well vascularised.

Loose connective tissue consists of cells and extracellular matrix.

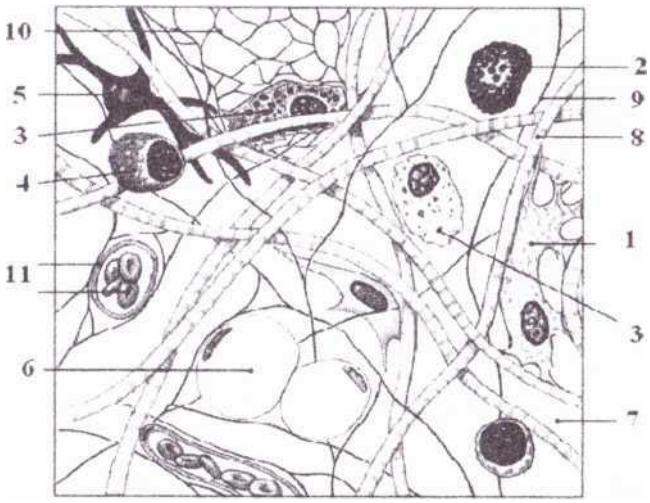


Figure 9.1. Schematic diagrams of loose connective tissue. 1 — fibroblast, 2 - mast cell, 3 - macrophage, 4 - leukocyte, 5 - pigment cell, 6 - adipocyte, 7 - extracellular matrix, 8 - collagen fibers, 9 - elastic fibers, 10 - reticular fibers, 11 - blood vessel (from *Ross M.H.*, 2003)

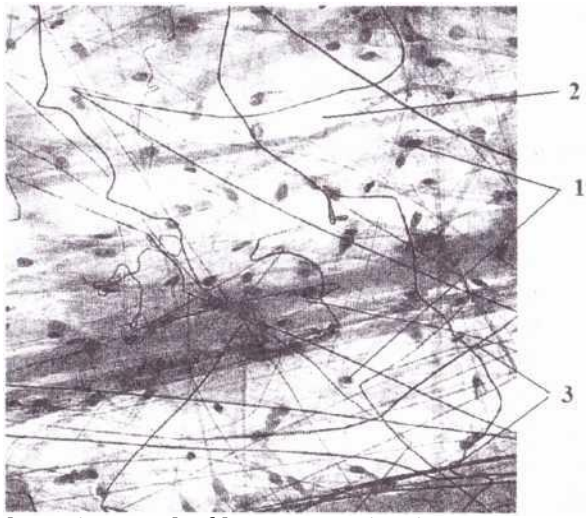


Figure 9.2. Photomicrograph of loose connective tissue. 1 - cells, 2 - extracellular matrix, 3 - fibers

The cells of loose connective tissue are fibroblasts, fibrocytes. macrophages, mast cells, plasma cells, fat cell (adipocytes), pigment cells, leukocytes, pericytes, and adventitional cells.

Collagen, elastic, reticular fibers appear in this tissue, although the portion of reticular fibers is small.

Connective tissue cells

1. ***Fibroblast differon*** includes ***fibroblasts*** and ***fibrocytes*** (fig.9.3). ***Fibroblasts*** are the dominant cells of the connective tissue. It is responsible for the synthesis of fibers and components of intercellular matrix.

The ***fibroblast*** is elongated cell with an ovoid nucleus. The cytoplasm is rich in rough endoplasmic reticulum, Golgi complex is well developed. The ***fibrocyte*** is spindle-shaped. It is more mature, small cell with dark elongated nucleus.

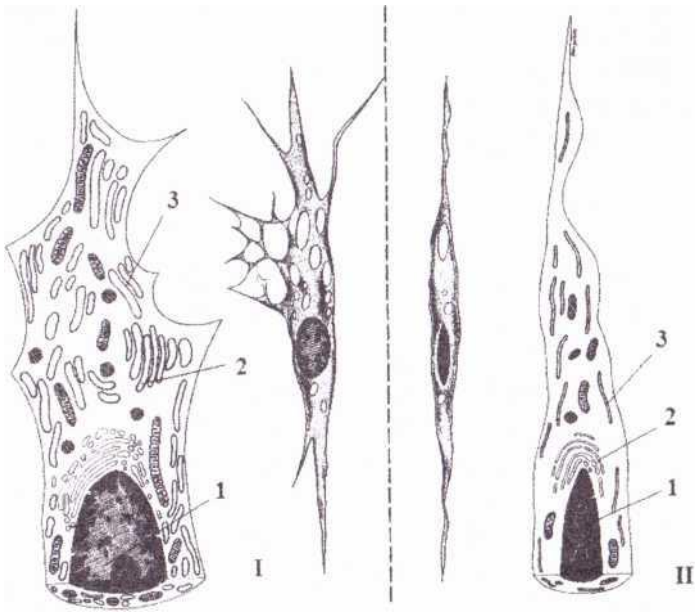


Figure 9.3. Diagram of the fibroblast and fibrocyte. I - fibroblast, II - fibrocyte, 1 — nucleus, 2 - Golgi complex, 3 - rough endoplasmic reticulum (from *Junqueira L.C., Cameiro J.*, 2005)

The ***myofibroblast*** is a cell with features of both fibroblast and smooth muscle. These cells contain of actin and myosin microfilaments. The activation of myofibroblasts descends at damage of a connective tissue. They participate in reparative processes. Myofibroblasts are found out in a myometrium of a uterus at pregnancy.

The ***fibroclasts*** are the cells, specialized on the destructions of intercellular substance of connective tissue. In their cytoplasm there are numerous vacuoles containing of lytic enzymes. These cells provide rearrangement and an involution of connective tissue.

2. ***Macrophages (histiocytes)*** are characterized by their phagocytic capacity. ***Macrophages*** derive mainly from precursor cells from the bone marrow that divide, producing ***monocytes*** that circulate in the blood. In a second step, these cells migrate into the connective tissue and are called ***macrophages.***

Macrophages, which are distributed throughout the body, are present in most organs and constitute the ***mononuclear phagocyte system.*** In certain regions, macrophages have special names, e.g., ***Kupffer cells*** in the liver, ***microglial cells*** in the central nervous system, and ***osteoclasts*** in bone tissue.

The macrophages are large irregular cells with processes. They have a well-developed Golgi complex, many lysosomes, and a prominent rough endoplasmic reticulum (fig. 9.4).

3. ***Mast cells*** are oval to round connective tissue cells, whose cytoplasm is filled with basophilic granules. The small and spherical nucleus is centrally situated (fig. 9.5).

Mast cell granules are stained ***metachromatically*** (purple after toluidine blue staining) because they contain glycosaminoglycans, histamine, neutral proteases, and eosinophil chemotactic factor of anaphylaxis (ECF-A).

Metachromasia is a property of cells to be stained in other colour distinguished from colour of dye.

The principal function of mast cells is the storage of chemical mediators of the inflammatory response.

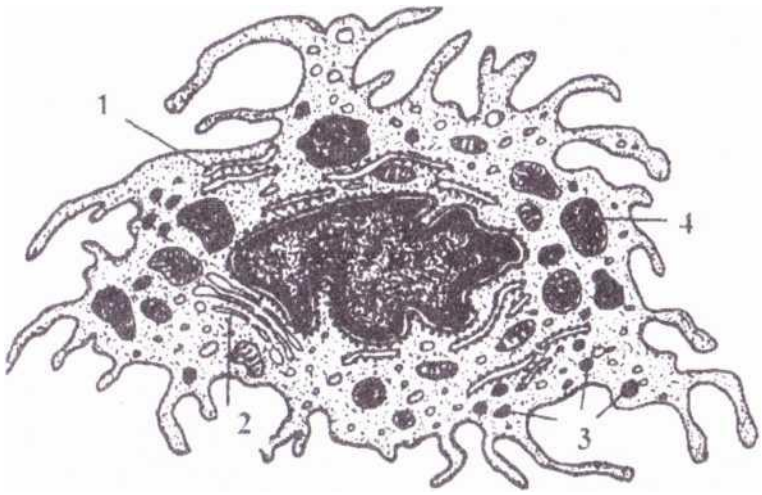


Figure 9.4. Schematic diagram of the macrophage (histiocyte). 1 - rough endoplasmic reticulum, 2 - Golgi complex, 3 - lysosomes, 4 - phagolysosomes (from *EbiKoe B.JI.*, 2007)

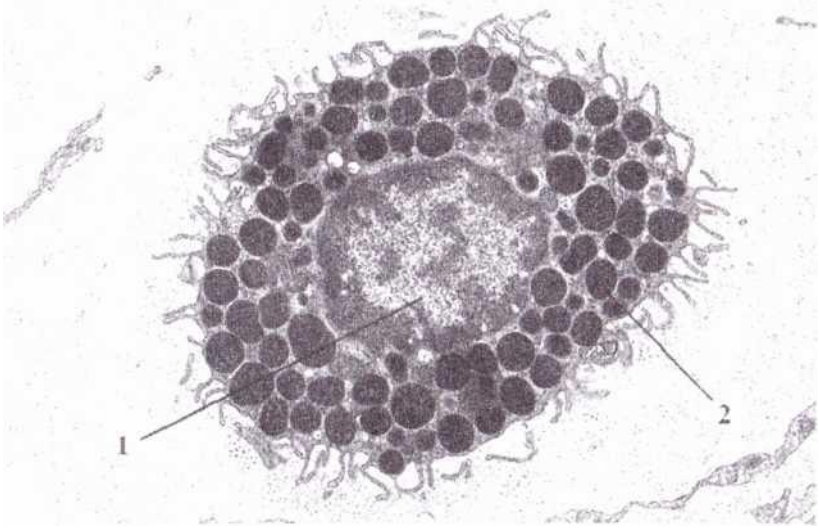


Figure 9.5. Electron micrograph of mast cell. 1 - nucleus, 2 - granules

Types of the mast cells

There are two populations of mast cells in connective tissues.

One type is called the ***connective tissue mast cell*** (dermis and stroma of different organs), in which the proteoglycan in the granules is mainly heparin, a substance with anticoagulant activity.

In the second type, termed ***mucosal mast cells*** (lamina propria of mucosa); the granules contain chondroitin sulfate instead of heparin.

Mast cells originate from stem cells in the bone marrow.

The surface of mast cells contains specific receptors for IgE, a type of immunoglobulin produced by plasma cells.

4. ***Plasma cells*** (fig. 9.6) are large with an eccentric round nucleus. Nucleus contains the chromatin clumped in a characteristic ''clock face" pattern. Cytoplasm is basophilic, which filled with rough endoplasmic reticulum. Rough endoplasmic reticulum is concentrically located around of a nucleus. Well developed Golgi complex displaces the nucleus to one side of the cell (perinuclear halo).

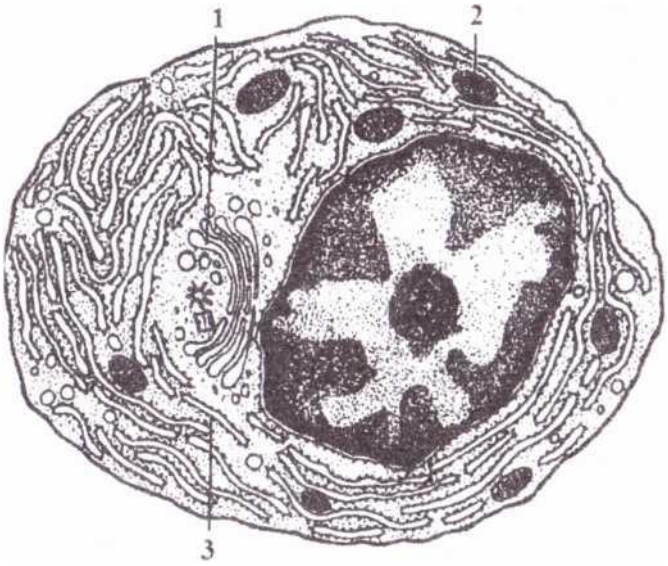


Figure 9.6. Schematic diagram of plasma cell. 1 - Golgi complex, 2 — mitochondria, 3 - rough endoplasmic reticulum (from ***ЕbiKOft*** *B.JT.,* 2007)

Plasma cell is a final stage of development of B-lymphocyte. ***Function:*** maintenance of humoral immunity by synthesis of antibodies.

5. ***Fat cells (adipocytes)*** are round with peripheral nuclei. Cytoplasm forms a thin peripheral layer around the central droplet of fat. Adipocytes also are called ring cells (fig. 9.7).

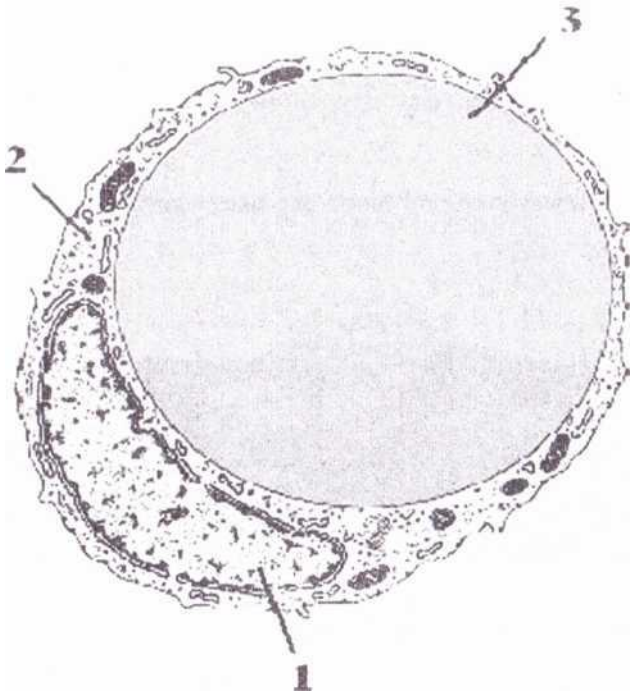


Figure 9.7. Schematic diagram of the adipose cell. 1 - nucleus, 2 — cytoplasm, 3 — fat droplet (from *T. L. Lentz, 1971)*

Functions:

> storage of neutral fats (food material);
> producing of heat.

6. ***Leukocytes*** are frequently found in connective tissue. They migrate across capillary and venule walls from the blood. There is a continuous movement of leukocytes from blood to connective tissue, and this process (diapedesis) increases greatly during inflammation.

7. ***Pigment cells (melanocytes)*** are stellate with long branching processes and small round nucleus, cytoplasm contains melanin granules.

8. ***Adventitional cells*** are the cells accompanying blood vessels. During a differentiation can turn in fibroblasts, myofibroblasts and adipose cell.

9. ***Pericytes*** surround blood capillaries and are the part of their wall (fig.9.8).

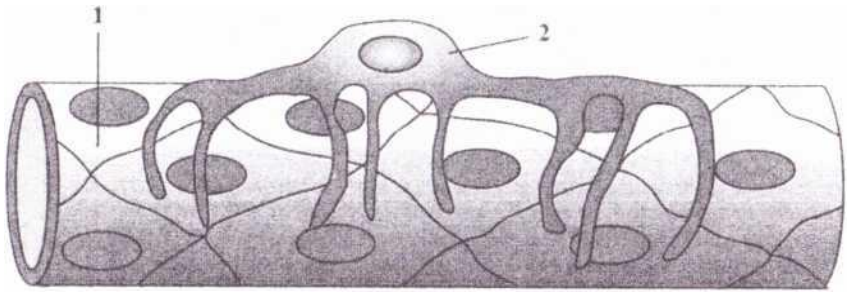


Figure 9.8. Schematic diagram of the pericyte. 1 — capillary, 2 - pericyte

Ground substance

The amorphous ***intercellular ground substance*** is colourless, transparent, and homogeneous; it varies from soft jelly to semisolid in consistency. It fills the space between cells and fibers of the connective tissue. The ground substance is formed mainly by two classes of components: ***glycosaminoglycans and glycoproteins.***

Fibers

Connective tissue ***fibers*** are long, slender protein polymers that are present in variable proportions in the different types of connective tissue.

There are three main types of connective tissue fibers: ***collagen***, ***reticular***, and ***elastic.***

Collagen and reticular fibers are composed of the protein ***collagen***, and the elastic fibers are composed of the protein ***elastin.***

1. ***Collagen fibers*** are the most numerous fibers in connective tissue.

With the light microscope collagen fibers are seen in bundles. The bundles may be straight or wavy. The bundles often branch, or anastomose with adjacent bundles, but the individual fibers do not branch.

Collagen fibrils are thin, elongated structures with diameter 20- 90 nm. They have transverse striation with a periodicity of 64 nm (fig.9.9). The transverse striations of the collagen fibrils are determined by the overlapping arrangement of the subunits tropocollagen molecules.

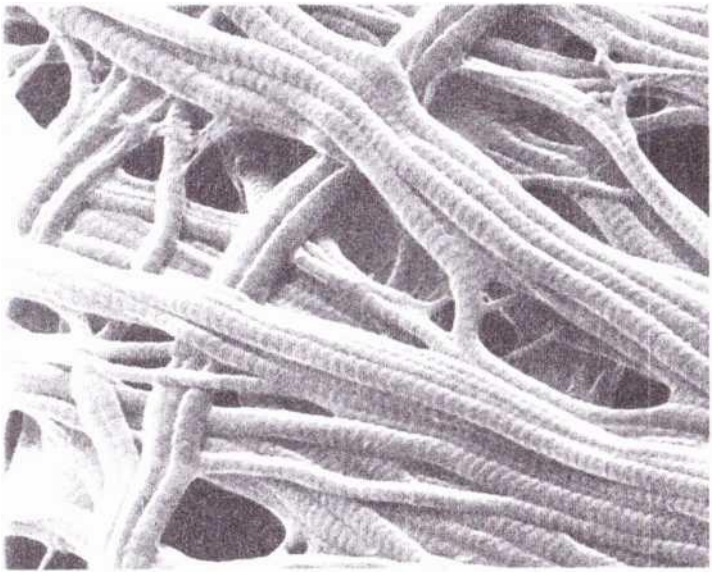


Figure 9.9. Electron micrograph of collagen fibers.

Formation of collagen fibers (fig.9.10)

Collagen is synthesized with fibroblasts.

Intracellular stage includes ***y*** synthesis of polypeptide alpha chains on polyribosomes of rough endoplasmatic reticulum from amino acids (***glycin, prolin,*** and ***hydroxyprolin***);

> 3 alpha chains wrap around each other to form a triple helix except at the terminals where the polypeptide chains remain uncoiled; the resultant molecule is soluble ***procollagen*** monomer excreting from a cell.

Extracellular stage

> procollagen is converted into ***tropocollagen*** by cleavage of terminal propeptides by specific procollagen peptidases;

> tropocollagen then spontaneously self-assembles into multimolecular aggregates, which are aligned end-to-end to form banded fibrils;

y crosslinks are formed between specific amino acids, which stabilize the collagen fibril and provide tensile strength.

Localization of collagen fibers: tendon, aponeurosis, intervertebra 1 disks.

2. ***Reticular fibers*** are thin, with a diameter 0, 5-2, 0 jam. They form an extensive network in certain organs. They are not visible in haematoxylin-eosin specimens but can be stained black by impregnation with silver salts.

Chief distribution of reticular fibers: smooth muscle, endoneurium, and the framework of hematopoietic organs (spleen, lymph nodes, red bone marrow).

3. ***Elastic fibers*** have diameter 0,2-10,0 j^m, branch and anastimose with each other, shaping three-dimensional networks; they do not form bundles.

Elastin is the main protein component of elastic fibers.

Elastic fibers can be demonstrated by staining with ***orcein.*** Elastic fibers can be stretched and return to their original length when tension is released.

Localization of elastic fibers: lungs, fibrocartilage, skin, and wall of aorta.

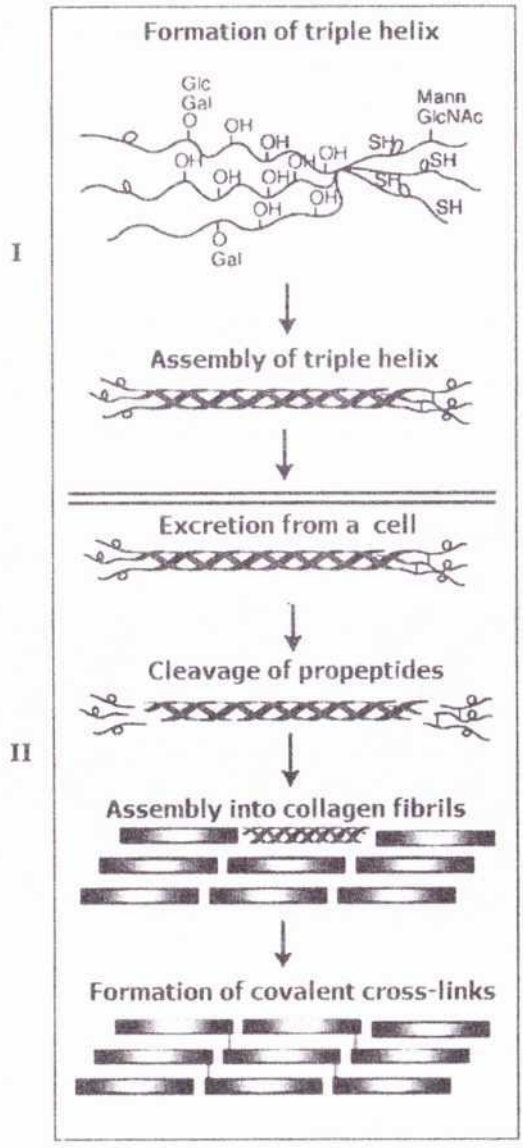


Figure 9.10. Schematic representation of collagen synthesis. I - intracellular stage, II - extracellular stage (adapted from *Myllyharju,/. and al,,* 2004)

Dense connective tissue

Dense connective tissue consists of same components found in loose connective tissue but there are fewer cells and clear predominant collagen fibers.

The main property dense connective tissue - very high mechanical strength - it is caused by presence of potent bundles of collagen fibers. Orientation of these fibers corresponds to a direction of action of forces, which cause deformation.

Dense irregular connective tissue has the collagen fibers that are arranged in bundles without a definite orientation. The collagen fibers form a three-dimensional network in this tissue and provide resistance to stress from all directions (fig.9.11). This type of tissue forms the dermis.

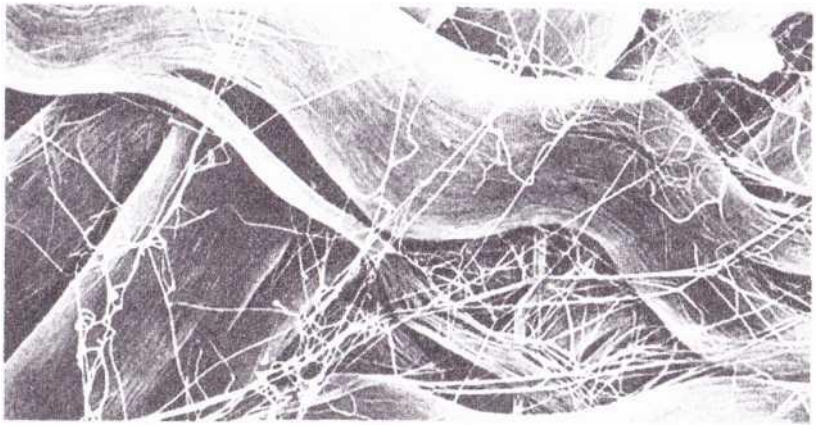


Figure 9.11. Electron micrograph of dense irregular connective tissue.

Dense regular connective tissue

The collagen bundles of ***dense regular connective tissue*** are arranged according to a definite pattern.

Tendons are the most common example of dense regular connective tissue. Tendons are cord-like structures that attach muscle

to bone. Tendons (fig. 9.12) consist of parallel bundles of collagen fibers separated by a small quantity of amorphous intercellular substance. Rows of fibroblasts (***tendinocytes***) are situated between these bundles. Their flbrocytes contain elongated nuclei parallel to the fibers.

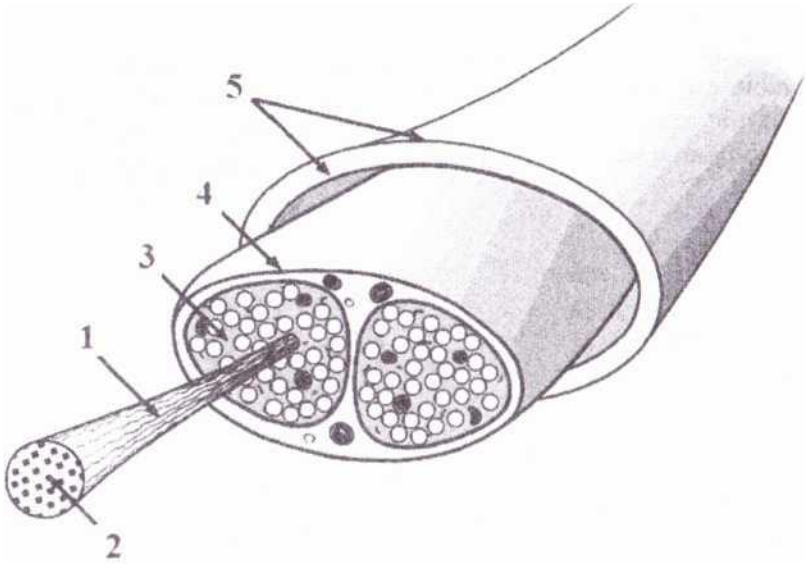


Figure 9.12. Dense regular connective tissue of tendon. 1 - collagen fibres. 2 - tendinocytes, 3 - endotenon, 4 - epitenon, 5 - synovial sheath

The collagen bundles which are situated between the tendinocytes are called ***primary bundles.*** Primary- bundles aggregate into larger bundles ***(secondary bundles***) that are enveloped by loose connective tissue containing blood vessels and nerves (***endotenon***). The substance of tendon is surrounded by a thin connective tissue capsule, the ***epitenon.*** Some tendons are also surrounded by a specialized synovial sheath.

0 **Connective tissue with special properties**

1. **Adipose tissue**

There are two types of the adipose tissue:

> *white* **(unilocular, or yellow),**
> *brown* **(multilocular).**

White (unilocular) adipose tissue **(fig.9.13) contains cells, each contain only one large fat droplet (ring cells). White adipose tissue is found in subcutaneous, omentum & mesentery regions. Unilocular adipose tissue subdivided into lobules by a partition of connective tissue.**

Figure 9.13. White (unilocular) adipose tissue. 1 -adipose cell, 2 - cytoplasm, 3 - nuclei

Functions of adipose tissue:

> *trophic,*
> *supporting, protective and plastic* **- adipose tissue surrounds organs and fills in spaces between them; softening impacts, it protects them from mechanical traumas; it substitutes a tissue of some organs after their involution (thymus, mammary gland, bone marrow);**

> *energy storage*: food that is excess to requirements is converted into fat and stored within adipose tissue;
> *heat-insulating* - adipose tissue has properties heat-isolator due to what it interferes with excessive heat waste by an organism;
> *heat-forming* - the part of the energy formed owing to oxidation of power-intensive lipid molecules turns to heat;
> *depot* of liposoluble vitamins (A, D, E, K) and serves large depots of steroid hormones;
> *endocrine* - synthesizes estrogens and hormone, which regulate consumption of food -*leptin.*

Brown (multilocular) adipose tissue is a specialized form of adipose tissue in hibernating and newborn mammals. It is greatly reduced in adulthood.

Brown adipose tissue is mainly found in subscapular, interscapular, and mediastinal areas (figure 9.14).

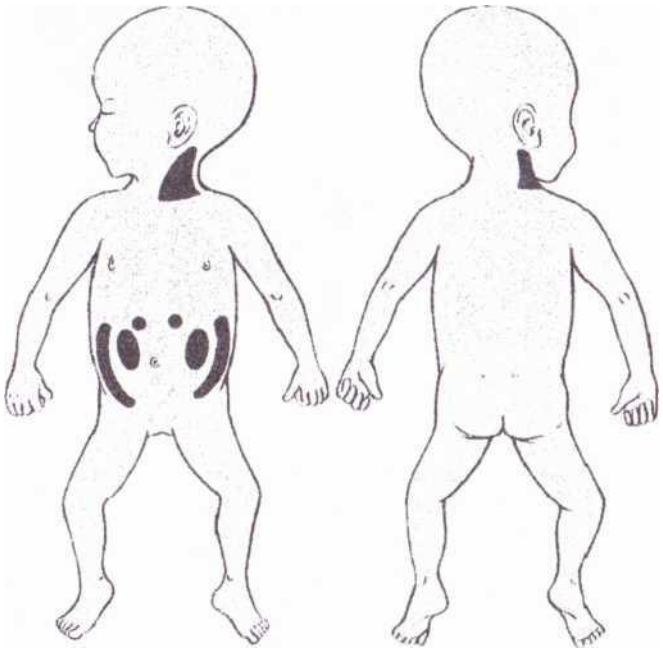


Figure 9.14. Distribution of brown adipose tissue (from ***Junqueira L.C., Carneiro J***., 2005)

Cells ot the ***brown (multilocular) adipose tissue*** have several fat droplets and many mitochondria, are rich in heme-containing cytochromes (fig.9.15).

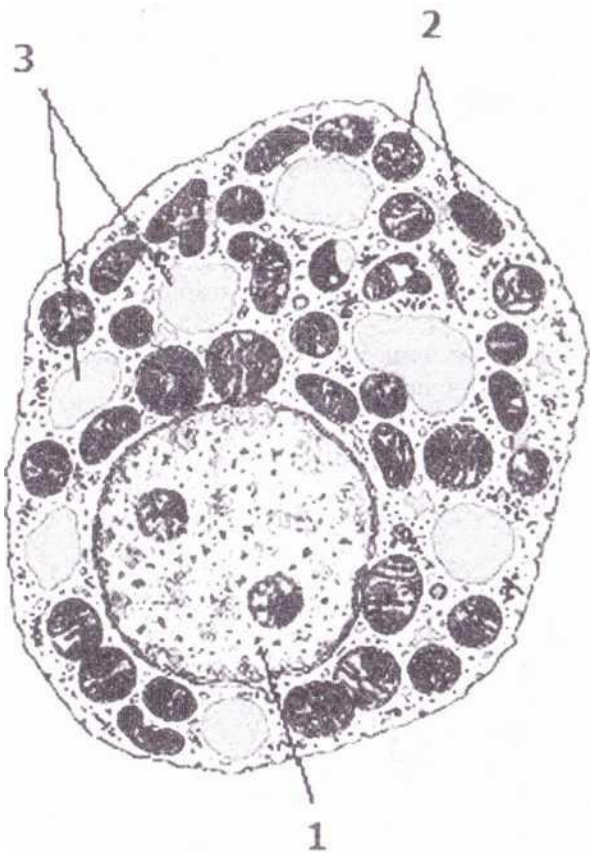


Figure 9.15. Schematic diagram of brown adipose tissue cell. 1 - nucleus, 2 - mitochondria, 3 - fat droplets (from *T. L. Lentz, 1971)*

This specialized tissue can generate heat by “uncoupling" the respiratory chain of oxidative phosphorylation within mitochondria.

1he function of this tissue in humans appears to be of importance mainly in the first months of postnatal life, when it produces heat and thus protects the newborn against cold.

2. **Reticular tissue**

The ***reticular tissue*** is a specialized loose connective tissue that provides the architectural framework of the myeloid (bone marrow) and lymphoid (lymph nodes, spleen) hematopoietic organs.

Reticular tissue consists of reticular cells and branched reticular fibers (fig.9.16). Cells and fibers form supporting network for hematopoietic cells.

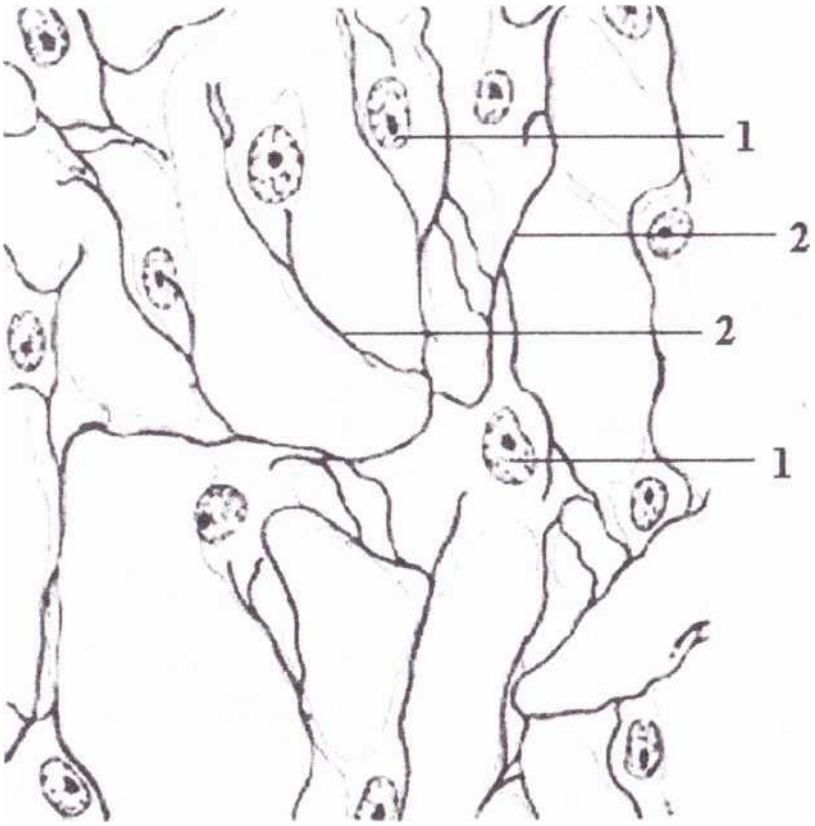


Figure 9.J6. Reticular tissue. 1 - reticular cells, 2 - reticular fibers (from ***Junqueira L.C., CarneiroJ.,*** 2005)

3 Mucous tissue

The ***mucous tissue*** has an abundance of ground substance composed of hyaluronic acid. It is a .jelly like tissue containing very few fibers. The cells in this tissue are mainly fibroblasts (fig.9.17).

Mucous tissue is the principal component of ***Wharton's jelly*** of the umbilical cord.

4 Pigment tissue

The ***pigment connective tissue*** reminds loose connective tissue, however contains numerous ***pigment cells (melanocytes)*** (fig.9.18).

Function of melanin of pigment cells is to protect the organism against the damaging effects of nonionizing ultraviolet irradiation.

Localization, in humans, melanin is the primary determinant of skin colour. It is also found in hair, the pigmented tissue underlying the iris of the eye, and the stria vascularis of the inner ear. In the brain, tissues with melanin include the medulla and zona reticularis of the adrenal gland, and pigment-bearing neurons within areas of the brainstem, such as the locus coeruleus and the substantia nigra.

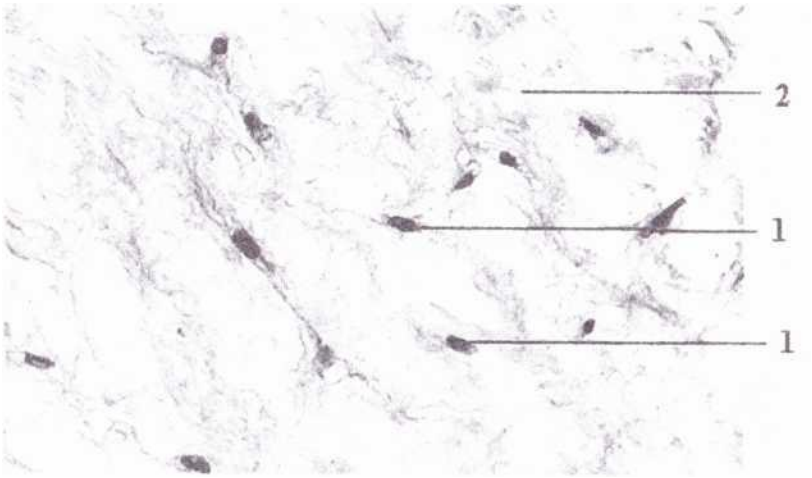


Figure 9.17. Photomicrograph of mucous tissue. 1 - fibroblasts, 2 - ground substance

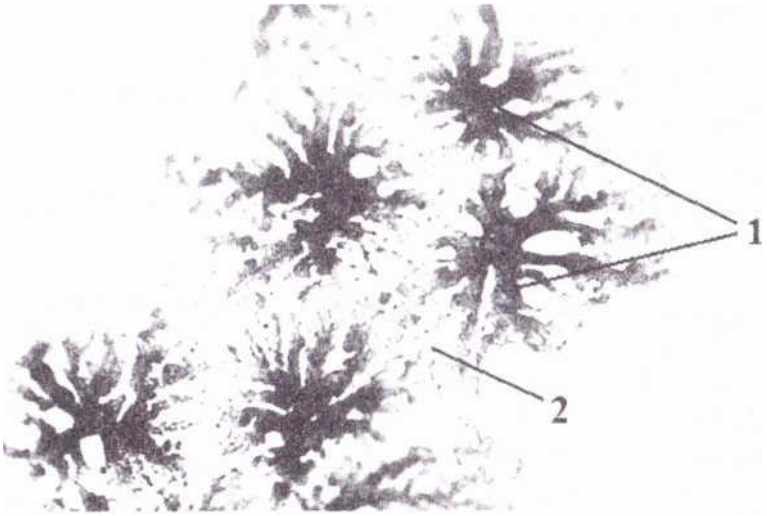


Figure 9.18. Pigment tissue. 1 - pigment cell, 2 — ground substance, 3 - fibers

Types of melanin

Eumelanin is found in hair, areola, and skin. In humans, it is more abundant in people with dark skin. There are two different types of eumelanin: black and brown. Black eumelanin is mostly in non- Europeans and aged Europeans, while brown eumelanin is in mostly young Europeans. A small amount of black eumelanin in the absence of other pigments causes grey hair. A small amount of brown eumelanin in the absence of other pigments causes yellow (blond) color hair.

Pheomelanin is also found in hair and skin and is both in lighter and darker skinned humans. Pheomelanin imparts a pink to red hue and, thus, is found in particularly large quantities in red hair. Pheomelanin is concentrated in the lips, areola, nipples, glans of the penis, and vagina. Pheomelanin also may become carcinogenic when exposed to the ultraviolet rays of the sun.

Neuromelanin is the dark pigment present in pigment bearing neurons of four deep brain nuclei: the substantia nigra, the locus coeruleus ("blue spot"), the dorsal motor nucleus of the vagus nerve (cranial nerve X), and the median raphe nucleus of the pons.

0 Clinical correlations

Collagen diseases (collagenopathies) are diseases associated with defects in collagen.

Stickler syndrome is a group of genetic disorders affecting connective tissue, specifically collagen. The syndrome is thought to arise from a mutation of several collagen genes during fetal development.

Stickler syndrome is characterized by distinctive facial abnormalities, eye problems, hearing loss, and joint problems.

Many people with Stickler syndrome are very nearsighted (having high myopia). People with eye involvement have increased pressure within the eye (ocular hypertension) which could lead to detachment retina of the eye.

People with this syndrome have arthritis, vertebrae abnormality, and curvature of the spine, scoliosis, and joint pain.

Stickler syndrome is thought to be associated with an increased incidence of mitral valve prolapse of the heart, although no definitive research supports this.

Kniest dysplasia is a subtype of collagenopathy that is disorder of bone growth. The condition is characterized by dwarfism, enlarged joints, and other skeletal abnormalities, and problems with vision and hearing.

Spondyloperipheral dysplasia is an autosomal disorder of bone growth. The condition is characterized by flattened bones of the spine (platyspondyly) and unusually short fingers and toes (brachydactyly). Some affected individuals also have other skeletal abnormalities, short stature, nearsightedness (myopia), hearing loss, and mental retardation. *Albinism.* Some individual animals and humans have very little or no melanin in their bodies, a condition known as *albinism.*

Although the functional nature of neuromelanin is unknow'n in the brain, it may be a byproduct of the synthesis of monoamine neurotransmitters for which the pigmented neurons are the only source. The loss of pigmented neurons from specific nuclei is seen in a variety of neurodegenerative diseases. In *Parkinson's disease* there is massive loss of dopamine-producing pigmented neurons in the substantia nigra.

SKELETAL (SUPPORTING) TISSUES

Classification of the skeletal tissues

Cartilage

- > hyaline,
- > elastic,
- > fibrocartilage

Bone

- > primary, immature, or woven bone,
- > secondary, mature, or lamellar bone

0 Cartilage

The ***cartilage*** is a flexible connective tissue that consists of specialized cells called ***chondroblasts*** that produce a large amount of extracellular matrix composed of collagen fibers, abundant ground substance rich in proteoglycan, and elastic fibers. Unlike other connective tissues, cartilage does not contain blood vessels. The chondrocytes are supplied by diffusion, helped by the pumping action generated by compression of the articular cartilage or flexion of the elastic cartilage.

Cartilage functions

> Movement (cartilage joins bones firmly together in such a way that a certain amount of movement is still possible between them).

> Support (maintain shape of the organs: the C-shaped cartilaginous rings in the trachea and bronchi assist in keeping those tubes open).

> Growth (hyaline cartilage is responsible for the longitudinal growth of the long bones).

0 Histogenesis of cartilage tissue (chondrification, chondrogenesis)

In embryogenesis, the skeletal system is derived from the mesoderm germ layer.

Chondrification (also known as ***chondrogenesis***) is the process by which cartilage is formed from condensed mesenchymal cells, which differentiates into chondroblasts and begins secreting the molecules that form the extracellular matrix.

Steps in chondrification (fig. 10.1)

1 - early stage of the ***chondrification centres*** formation from the mesenchymal cells;

2 - late stage of the ***chondrification centres*** formation: mesenchymal cells lose processes, become rounded and form densely packed cellular masses;

3 - differentiation of mesenchymal cells into cartilage-forming cells, ***chondroblasts,*** which begin to secrete the components of the extracellular matrix of cartilage;

4 - formation of ***isogenous groups of chondrocytes.***

Growth of the cartilage

Two types of growth can occur in cartilage: ***appositional*** and ***interstitial.***

> ***Appositional growth*** results in the increase of the diameter or thickness of the cartilage. The new cells derive from the perichondrium and occur on the surface of the cartilage model.

> ***Interstitial growth*** results in an increase of cartilage mass and occurs from within. Chondrocytes undergo mitosis within their lacuna, but remain imprisoned in the matrix, which results in clusters of cells called ***isogenous groups.***

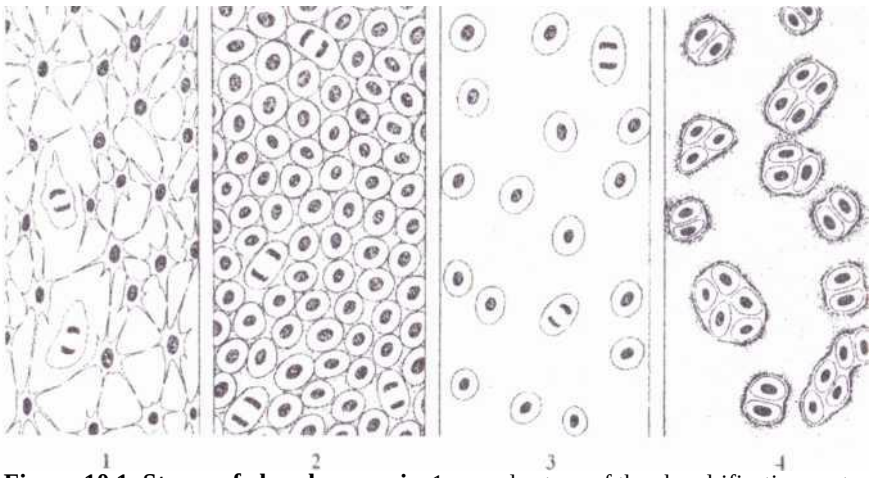


Figure 10.1. Stages of chondrogenesis. 1 — early stage of the chondrification centre formation, 2 - late stage of the chondrification centre formation, 3 - differentiation of mesenchyme cells into chondroblasts. 4 - formation of isogenous groups of chondrocytes (from *Junqueira L.C., Carneiro*2005)

Repair of cartilage

Once damaged, cartilage has limited repair capabilities. Because chondrocytes are bound in lacunae, they cannot migrate to damaged areas. Also, because hyaline cartilage does not have a blood supply, the deposition of new matrix is slow. Damaged hyaline cartilage is usually replaced by fibrocartilage scar tissue.

Common plan of cartilage tissue structure

Cartilage consists of ***y***

Cells are:

•chondroblasts

•chondrocytes

> Extracellular matrix is composed of:

•fibers

•ground substance **Cells of**

cartilage tissue

Chondroblasts are young cartilage precursor cells, capable to a proliferation and synthesis of intercellular substance of a cartilage. Cytoplasm of chondroblasts contains well-developed rough and smooth cytoplasmic reticulum, Golgi apparatus.

Chondrocytes occur singly or in groups called ***isogenous groups*** within spaces called ***lacunae.*** Chondrocytes are responsible for the secretion and maintenance of the matrix.

Differon of cartilage cells

Chondroblasts and chondrocytes are derived from ***chondroprogenitor cells*** (mesenchymal stem cell that can undergo mitotic division and differentiate into a chondroblast). ***Chondroprogenitor cell*** => ***chondroblast*** => ***chondrocyte***

Extracellular matrix

The majority of the wet weight of cartilage, ranging anywhere 65-80%, consists of water. The matrix is mainly composed of proteoglycans, which are large molecules with a protein backbone and glycosaminoglycans (GAG) side chains. Glycosaminoglycans are

polysaccharides. This molecule fills all the spaces between the collagen fibers and holds water, thus plumping out the extracellular matrix and giving cartilage its resistance to compression and its resilience (ability to spring back into shape after load). The most common types of GAGs in cartilage are chondroitin sulfate and keratin sulfate.

1 he matrix immediately surrounding the chondrocytes is referred to as the territorial matrix, or capsule, and stains darker than the interstitial matrix during slide preparation.

Cartilage covering

At the periphery of mature cartilage is a zone of dense connective tissue, ft is rich in collagen and contains numerous fibroblasts with cartilage-forming potential. This zone is called ***perichondrium.***

Functions of the perichondrium:

1. trophic;
2. growth of the cartilage;
3. maintenance of the cartilage.

Types of cartilage

There are three different types of cartilage, each with special characteristics adapted to their function.

0 Hyaline cartilage

Hyaline cartilage (fig. 10.2) is the most abundant type of cartilage. The name hyaline is derived from the Greek word ***hyalos,*** meaning ***glass.*** This refers to the translucent matrix or ground substance.

Hyaline cartilage is found in the wall of respiratory passages (nose, larynx, trachea, and bronchi), lining bones in joints (articular cartilage or, commonly, gristle) and is also present inside bones, serving as a center of ossification, or bone growth. In addition, hyaline cartilage forms most of the embryonic skeleton.

Structural features of the hyaline cartilage:

> presence of isogenous groups of chondrocytes;

> ground substance contains a dense network of ***collagen fibers',***
> possesses a perichondrium.

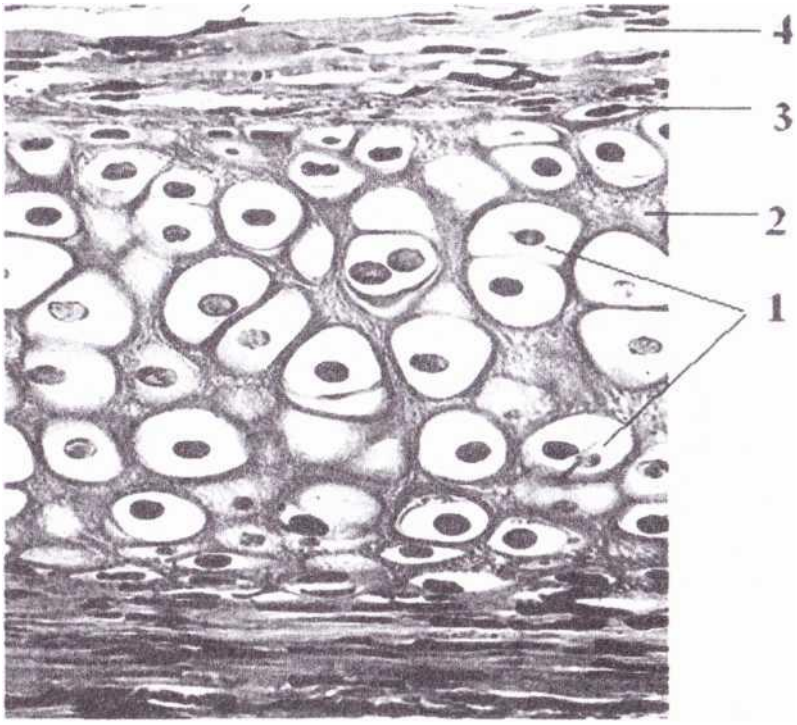


Figure 10.2. Hyaline cartilage. 1 - isogenous groups of chondrocytes, 2 — matrix, 3 - inner layer of perichondrium, 4 - outer layer of perichondrium

0 Elastic cartilage

Elastic cartilage (fig. 10.3), also called yellow cartilage, is found in the pinna of the ear and several tubes, such as the walls of the auditory (Eustachian) tubes, larynx, and especially in the epiglottis (keeps food from entering the airways).

Elastic cartilage is similar to hyaline cartilage but contains elastic fibers scattered throughout the matrix. Elastic fibers can be demonstrated by standard elastin stain (orcein).

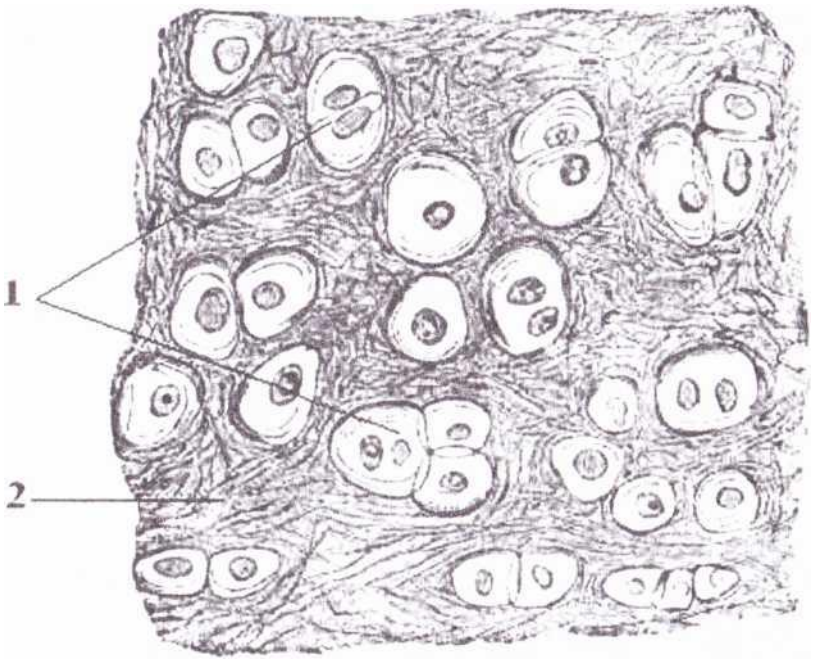


Figure 10.3. Elastic cartilage. 1 - isogenous groups of chondrocytes, 2 - elastic fibers

Structural features of the elastic cartilage:

> presence of singly chondrocytes or isogenous groups of chondrocytes;

> ground substance contains a dense network of branching and anastomosing elastic fibers;

> possesses a perichondrium.

0 Fibrocartilage

Fibrocartilage is a specialized type of cartilage found in areas requiring tough support or great tensile strength, such as between the

intervertebral discs, between the hip and pelvis bones, and at sites connecting tendons or ligaments to bones.

Fibrocartilage has characteristics intermediate between those of dense connective tissue and hyaline cartilage.

Structural features of the fibrocartilage (fig. 10.4):

> presence of singly chondrocytes or isogenous groups of chondrocytes arranged in long rows;

> ground substance contains a great number of ***collagen fibers*** oriented in the direction of the functional stresses;

> perichondrium is absent.

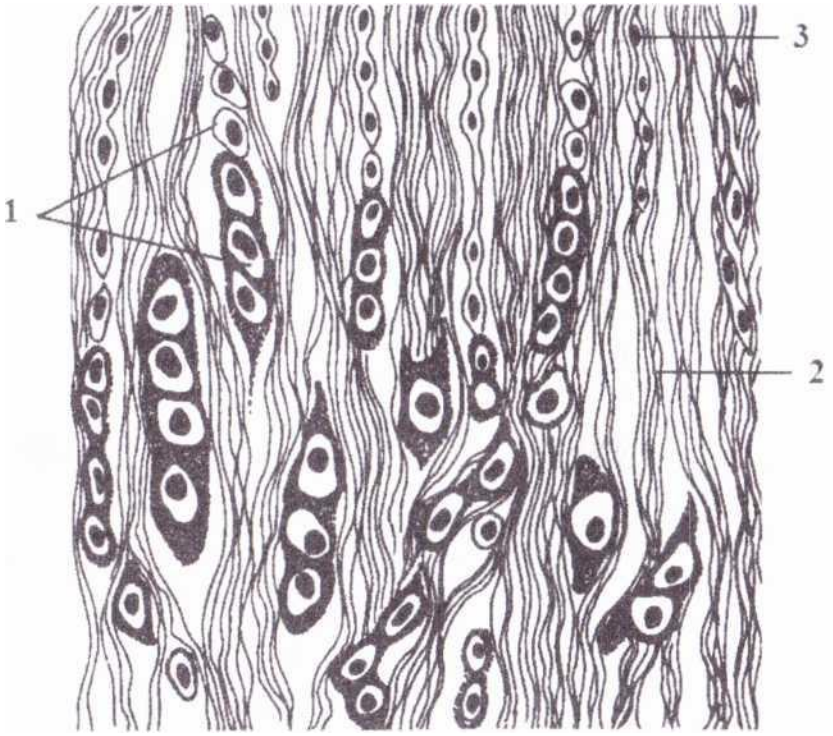


Figure 10.4. Schematic representation of the fibrocartilage. 1 - chondrocytes, 2 - bundles of collagen fibers, 3 — fibrocytes

Intervertebral discs

The ***intervertebral discs*** (fig. 10.5) lie between the articular surfaces of adjacent vertebral bodies. The disc consists of

> annulus fibrosus,

> nucleus pulposus.

Annulus fibrosus consists of concentric layers of fibrocartilage; ***nucleus pulposus*** consists of a few rounded cells embedded in an amorphous viscous substance rich in hyaluronic acid and collagen fibrils.

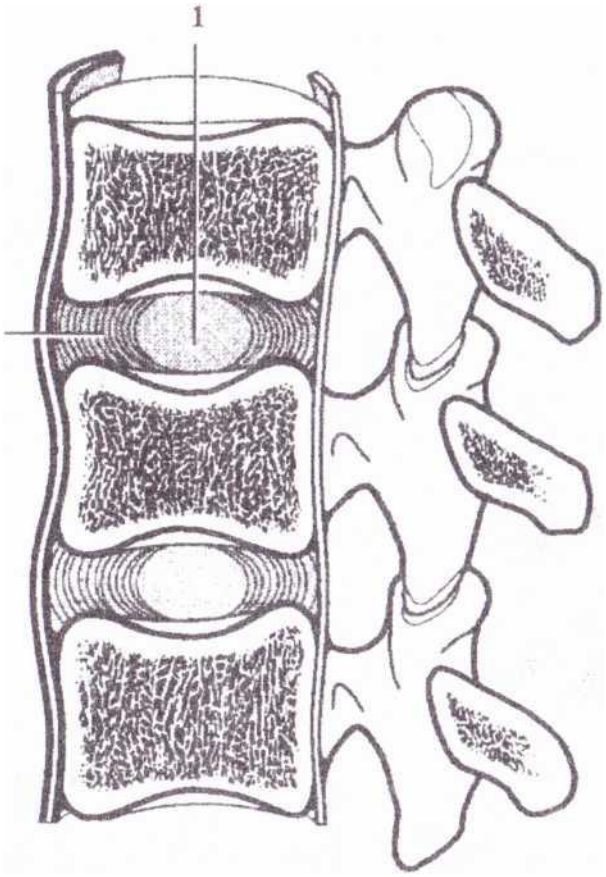


Figure 10.5. Schematic diagram of intervertebral disc. 1 - nucleus pulposus. 2 - annulus fibrosus

Nutrition of cartilage

Cartilage is avascular.

Hyaline and elastic cartilages get nutrition from the blood vessels of the perichondrium; fibrocartilage - from blood vessels of surrounding connective tissue, articular cartilage from synovial fluid.

0 Bone

Bone tissue is a specialized type of connective tissue and is the main element of the skeleton. It is composed of cells and an extracellular matrix in which fibers are embedded.

Bone tissue is unlike other connective tissues in that the extracellular matrix becomes calcified.

Functions of the bone tissue

> formation of the adult skeleton;
> participation in the movements of body;
> protection of the vital organs of the cranial and thoracic cavity;
> reservoir of ionic calcium essential for many cellular processes of the body; bone has several metabolic functions especially in calcium homeostasis.
> protection of the hematopoietic bone marrow.

Common plan of structure and functions of bone tissue

Like other connective tissues, bone consists of cells and extracellular matrix (fibers, and ground substance) but differs because the extracellular matrix is calcified.

Bone is composed of:

> Cells:
    - •osteoprogenitor cells;
    - •osteoblasts;
    - •osteocytes;
    - •osteoclasts;
> Matrix:
    - •organic component (osteoid) - 50%;
    - »in organic component - 25%;
    - •water - 25%.

Cells of bone tissue

Osteoprogenitor cells are mesenchymal stem cell that can undergo mitotic division and differentiate into osteoblasts. Osteoprogenitor cells are located in the inner cellular layer of the periosteum (periostal cells), the endosteum and lining canals of the osteons. These cells are most active during bone growth.

Osteoblasts are derived from osteoprogenitor cells and are responsible for the synthesis of the organic components of bone matrix, which is called ***osteoid.*** Osteoblasts are associated with growing surface of bone.

When the cells are active they have a cuboidal appearance (fig. 10.6); and when their activity declines, they flatten. The cells have cytoplasmic processes that bring them in contact with neighbouring cells.

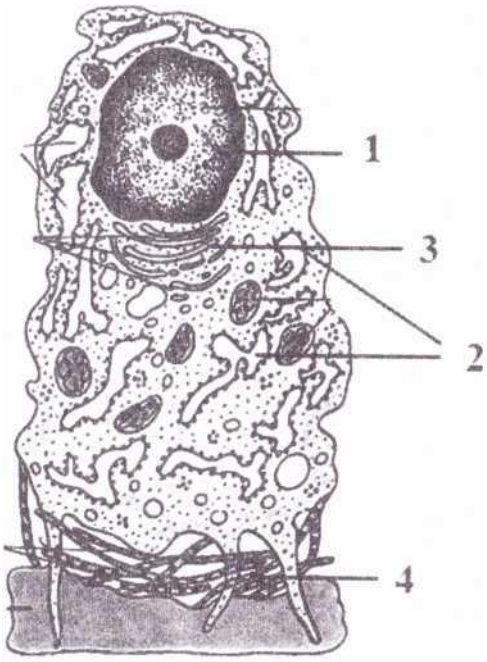


Figure 10.6. Schematic diagram of the osteoblast. 1 - nucleus, 2 - rough endoplasmic reticulum, 3 — Golgi complex, 4 — synthesized fibres

Their organelles are typical of protein secretory cells: they contain extensive rough ER, well developed Golgi complex and numerous secretory vesicles.

Osteocytes are the flat, almond-shaped cells of mature bone (fig. 10.7, 10.8). They reside in the ***lacunae*** of bone, only one osteocyte is found in each lacuna. Thin cylindrical spaces that house cytoplasmic processes are called ***canaliculi.*** Processes of adjacent cells make contact via gap junctions, which allow ions and small molecules to travel from cel! to cell. Canaliculi also contain extracellular fluid carrying nutrients to nourish the osteocytes.

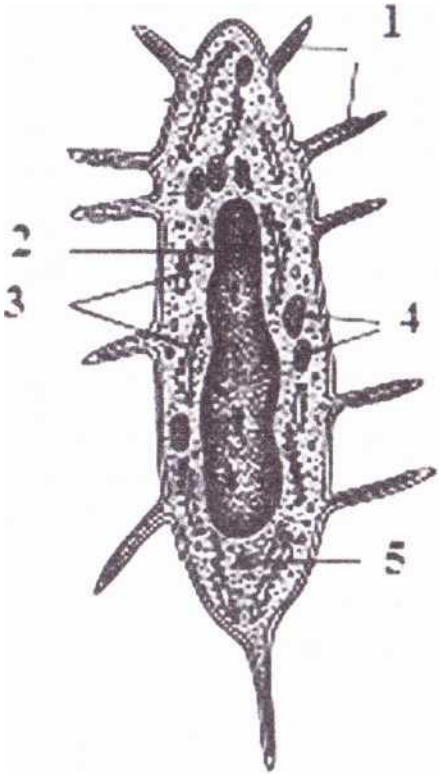


Figure 10.7. Schematic diagram of osteocyte. 1 - processes, 2 — nucleus, 3 — rough endoplasmic reticulum, 4 - mitochondria, 5 - Golgi complex

Osteocytes have flattened nuclei and eosinophilic cytoplasm with small amount of rough endoplasmic reticulum and Golgi complex. ***Function of osteocytes*** is maintenance of bone matrix.

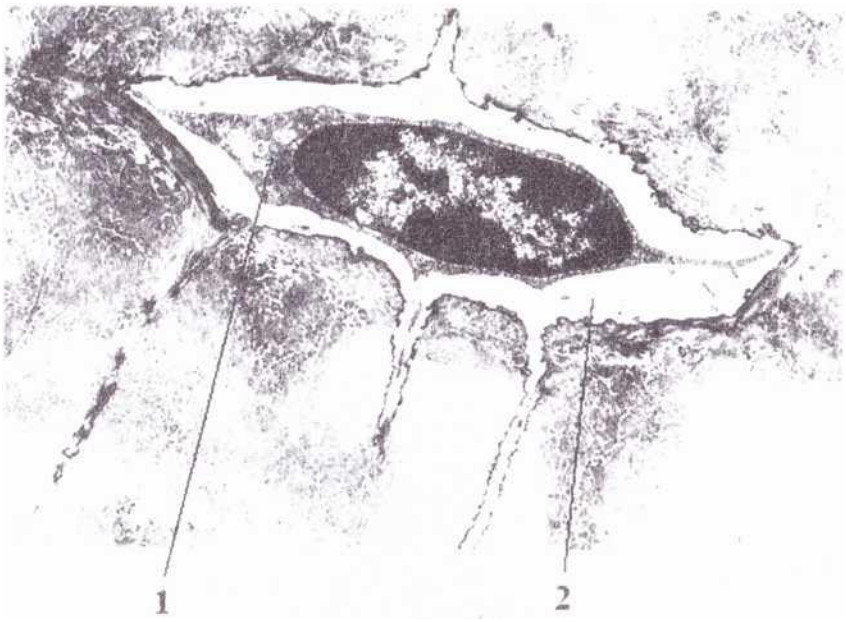


Figure 10.8. Electron micrograph of osteocyte. f- osteocyte, 2 - lacuna

Osteoclasts (fig. 10.9) are very large, motile, multinucleated, bone-resorbing cells. ***Osteoclasts*** are derived from blood monocytes of the blood. They contain 5-50 nuclei and acidophilic, foamy cytoplasm with the high maintenance of lysosomes, mitochondria, well- development Golgi complex and some rough endoplasmic reticulum. Osteoclasts lie in a small cavity called ***lacunae***, formed from the digestion of the underlying bone.

Function of the osteoclasts is maintenance of the calcium homeostasis (lysosomal enzymes are released by exocytosis and degrade the organic components of bone).

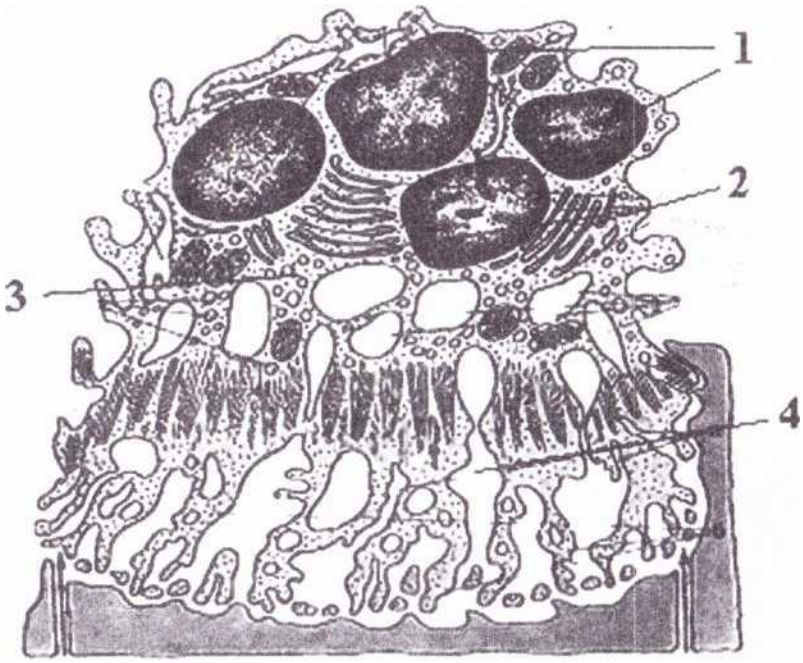


Figure 10.9. Schematic diagram of osteoclast. 1 - nuclei, 2 - Golgi complex, 3 - lysosomes, 4 — area of destruction of bone

Two hormones affect osteoclastic activity:

> ***Parathyroid hormone*** produced by the parathyroid gland that increases osteoclastic activity and results in ***elevated blood calcium levels.***

> ***Calcitonin*** produced by the thyroid gland that decreases osteoclastic activity and results in ***reduced blood calcium levels.***

Differons of bone cells

1. Osteoblasts and osteocytes are derived from ***osteoprogenitor cells*** (mesenchymal stem cell that can undergo mitotic division and differentiate into an osteoblast).

Osteoprogenitor cell => ***osteoblast*** => ***osteocyte***

2. Osteoclasts are derived from the fusion of blood-derived monocytes and thus belong to the mononuclear phagocyte system.

Pluripotential cell => myeloid multipotential cell => ***monocyte-colony- forming cell*** => ***promonocyte*** => ***monocyte*** => ***osteoclast***

Bone matrix

The ***bone matrix*** has two main components:

> ***Inorganic component*** (70%) is composed mainly of calcium and phosphorus in the form of hydroxyapatite (C«$_{/w}$ $(P0_4)_b(0H)_2$) crystals.

> ***Organic component*** (30%): collagen makes up over 90% of the organic component, which is called ***osteoid***; collagen forms collagen fibers.

Bone coverings

> ***Periosteum*** is the external covering of bone. Periosteum consists of two layers:

1) ***outer fibrous layer*** that contains many blood vessels. Branches of the blood vessels penetrate the inner layer of periosteum to enter Volkmann's canals and eventually communicate w'ith the vessels in the Haversian canals;

2) ***inner cellular layer*** that contains osteoprogenitor cells that have osteogenic potential.

'> ***Endosteum*** is thin layer of osteoprogenitor cells, osteoblasts and a small amount of connective tissue that lines all internal surfaces of cavities within bone including the Haversian canals and marrow spaces.

Functions of periosteum and endosteum

1. Nutrition of bone tissue
2. Repair or growth of bone
3. Mechanical, supporting (periosteum provides mechanical connection of the bone with tendons and muscles).

Types of bone tissue

1. Primary, immature, or woven bone

Primary, immature, or ***woven bone*** is the first type of bone formed during fetal development, bone repair, and tissue turnover.

r

Characteristics of primary bone are abundant osteocytes, a low mineral content, and an irregular organisation of collagen fibers (fig. 10.10). Woven bone is mechanically weak.

It is temporary and is replaced by secondary bone tissue.

Localization.

> embryo skeleton:
> suture of the flat bones of the skull (in adults),
> tooth sockets (in adults),

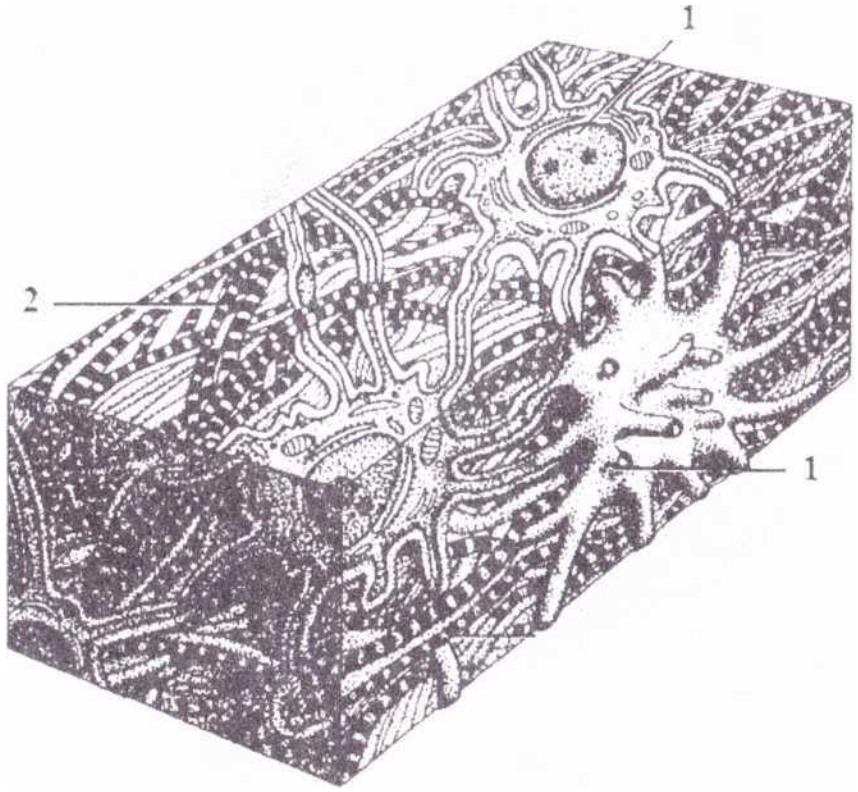


Figure 10.10. Schematic representation of the primary bone. 1 - osteoeytes, 2 — collagen fibers of the matrix (from ***fO KAc/jauacbee, H.A.JOpuna it dp.,*** 1999)

2. **Secondary, mature, or lamellar bone**

Secondary bone characteristically contains collagen fibers arranged in lamellae that are parallel to each other or concentrically organized around a vascular channel (fig. 10.11).

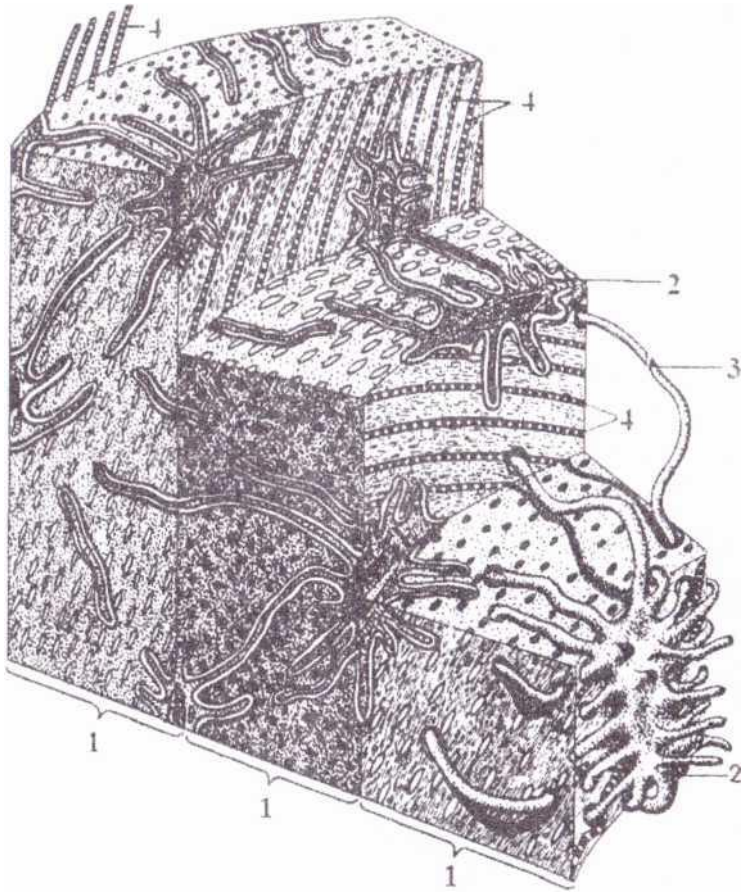


Figure 10.11. Schematic diagram of structure of secondary bone. I - lamellae, 2 - osteocytes, 3 - processes of osteocytes, 4 - collagen fibers of matrix (from ***1(1 M. Ar/xmacbee, H.A.IOpma u dp.,*** 1999)

Mineralized matrix of lamellar bone consists of the *lamellae,* each of which contains collagen fibers that are parallel to each other. Fibers of the next lamellae lay under an angle to each other. The lamellae contain *lacunae* housing osteocytes, which are nourished by diffusion of nutrients that travel through canaliculi from the marrow cavity.

Lacunae contain osteocytes, are found between and sometimes within the lamellae.

Canaliculi house cellular processes belonging to osteocytes and permit communication between lacunae and with the Haversian canals.

Bone consists of dense areas without cavities - *compact hone* - and areas with numerous interconnecting cavities - *cancellous (spongy) bone.*

In *long bones,* the bulbous ends - *epiphyses* - are composed of *spongy hone* covered by a thin layer of *compact bone.* The cylindrical part - *diaphysis* - composed of *compact bone.*

Short bones have a core of *spongy bone* surrounded by *compact bone.*

Compact bone consists of cylindrical units called *osteons* or *Haversian system* (fig. 10.12) comprising of:

> *Haversian canals* are tubes located in the center of osteons, run parallel to the long axis of the bone, and are united to other canals. Canals contain blood vessels and nerves.

> *Concentric bony lamellae* surround the Haversian canal. The lamellae consist of fine collagen bundles in calcified matrix.

> *Osteocytes* are located in the lacunae and their processes extend into canaliculi.

> *Volkmann's* (*perforating*) *canals* are vascular canals containing blood vessels, and connect Haversian canals with periosteum and marrow cavity.

In compact bone (e.g., the diaphysis of long bones) the lamellae exhibit a typical organization consisting of (fig. 10.12): *y outer circumferential lamellae* that are deep to the periosteum and form the outermost region of the diaphysis,

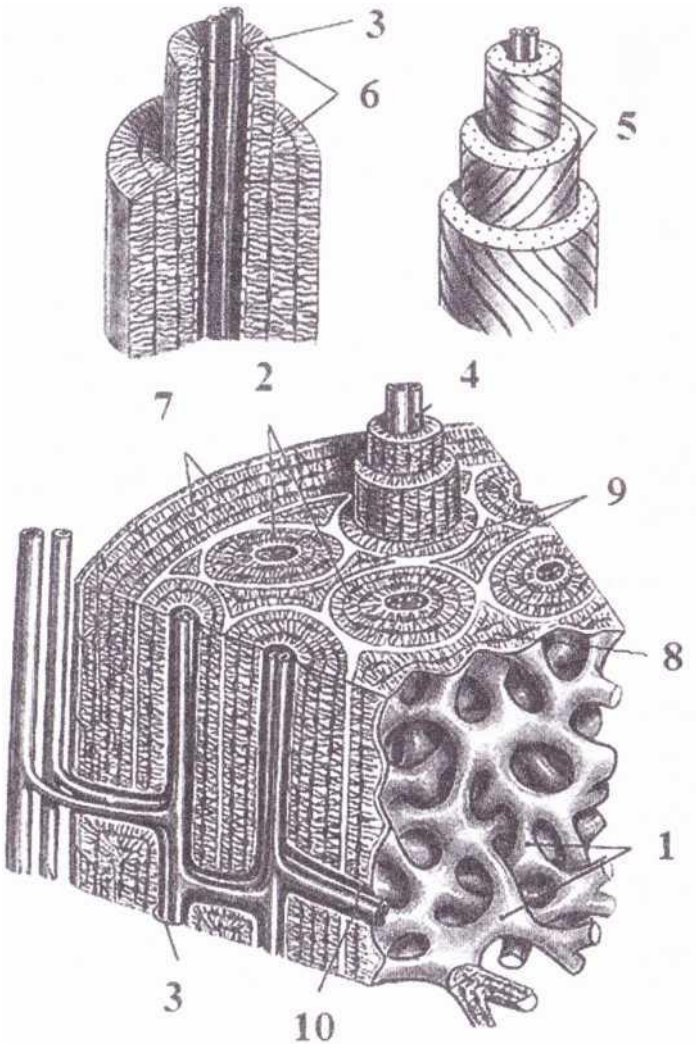


Figure 10.12. Diagram of structure of diaphysis of long bone. 1 - spongy bone, 2 - osteons, 3 - central canal, 4 - blood vessels, 5 - collage fiber orientation, 6 - concentric lamellae, 7 - outer circumferential lamellae, 8 - inner circumferential lamellae, 9 - interstitial lamellae, 10 - Volkmann's canals

> *haversian systems* (lamellae arranged around an osteonie (Haversian) canals),
> *interstitial lamellae* that lie between osteons,
> *inner circumferential lamellae* that completely encircle the marrow cavity.

Spongy bone consists of branching bone trabeculae project out from the internal surface of compact bone into the marrow cavity.

Spongy bone typically does not contain osteons. Trabeculae are only a few cell layers thick and contain irregularly arranged lamellae.

0 Histogenesis of bone (ossification)

Bone can be formed in two ways:

> by direct mineralization of matrix secreted by osteoblasts *(intramembranous ossification),*

y by deposition of bone matrix on a pre-existing cartilage matrix *(endochondral ossification).*

Intramembranous ossification

Intramembranous ossification is responsible for the formation of most flat bones.

Steps in intramembranous ossification (fig. 10.13) are:

1. *Development of ossification center* .

- mesenchymal stem cells proliferate and aggregate in richly vascularised connective tissue (the *primary ossification center),* where they differentiate into osteoblasts;
- osteoblasts secrete bone osteoid, some become surrounded and trapped by the newly formed matrix and are now called osteocytes.

2. *Calcification:*

- osteoid is calcifies to form spicules of spongy bone;
- inorganic salts carried in by the blood vessels;
- salts are deposited in an orderly fashion as fine hydroxyapatite crystals intimately associated with the collagen fibers;

collagen fibers in the developing spicules are randomly oriented (primary bone); remaining connective tissue among the spicules is penetrated by growing blood vessels and the undifferentiated mesenchymal cells give rise to bone marrow cells.

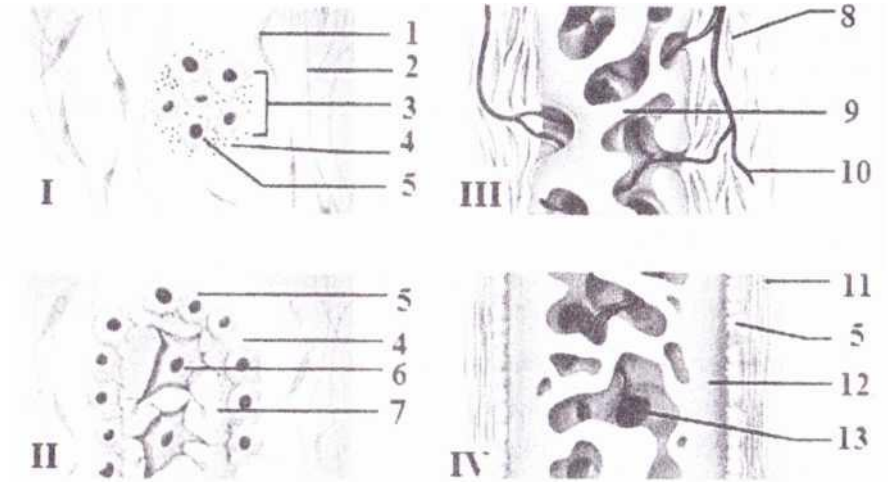


Figure 10.13. Intramembranous ossification. 1 - mesenchymal cells, 2 - collagen fibers, 3 — ossification center, 4 - osteoid, 5 - osteoblasts, 6 - osteocytes, 7 - newly calcified bone matrix, 8 - mesenchyme condensing to form the periosteum, 9 - trabeculae of primary bone, 10 — blood vessel, 11 - periosteum, 12 — plate of compact bone, 13 — cavities containing red bone marrow

3. ***Formation of trabeculae:.***
- spicules unite to form trabeculae;
- ossification centers grow radially and finally fuse replacing the original connective tissue.

4, ***Development of periosteum.***
- portion of bone that does not undergo ossification becomes the periosteum and endosteum.

Endochondral ossification

Endochondral ossification is responsible for the formation of short and long bones.

This process begins with a hyaline cartilage model whose shape resembles a small version of the bone to be formed.

Steps in endochondral ossification (fig. 10.14) are:

1 ***Development of cartilage model'.***

> process of endochondral ossification begins with a hyaline cartilage model whose shape resembles a small version of the bone to be formed.

2. ***Growth of cartilage model***

3. ***Development of the primary (diaphyseal) ossification cen ter:***

> formation of a thin woven bony collar ***(periosteal collar)*** around the diaphysis by intramembranous ossification;

> perichondrium of the template becomes the periosteum;

> invasion of the diaphysis by blood vessels that carry osteoprogenitor cells from periosteum that mature into osteoblasts;

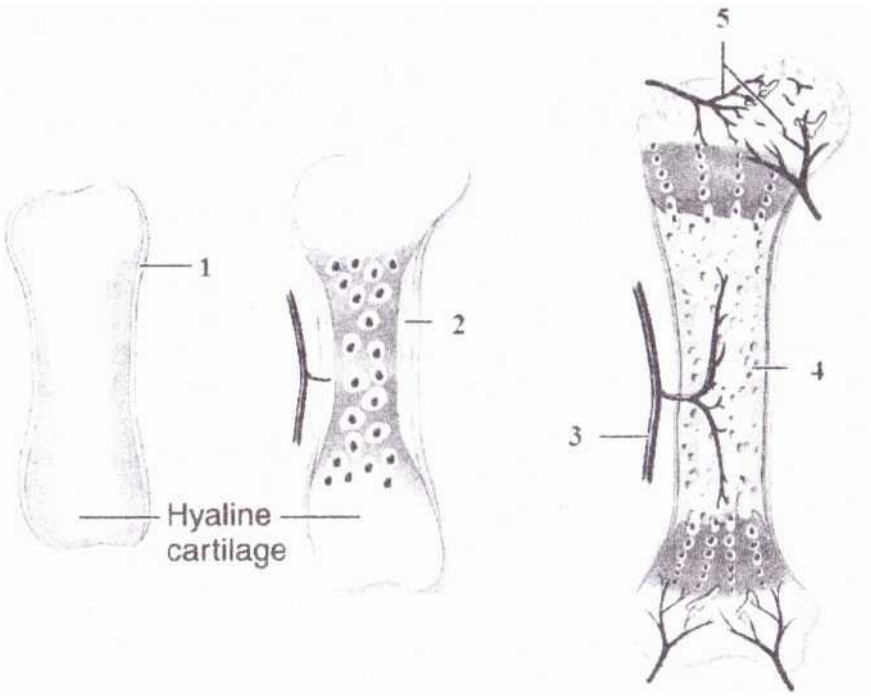


Figure 10.14. Endochondral ossification. 1 - perichondrium, 2 - periostal bone collar, 3 - invasion of the diaphysis by blood vessels, 4 - primary (diaphyseal) ossification center, 5 - secondary (epiphyseal) ossification center

> osteoblasts secrete osteoid, and cartilage matrix begins to calcify;
> chondrocytes hypertrophy and die (because there is no diffusion of nutrients across the bone matrix);
> osteoclasts form a primary marrow cavity, and incoming blood vessels carry in bone marrow cells;
> compact bone is formed.

4. ***Development of the secondary (epiphyseal) ossification center.***

> blood vessels infiltrate the epiphysis;
> chondrocytes of the epiphysis hypertrophy and die upon ossification;
> osteoblasts start building trabecular bone.

5. ***Formation of articular cartilage and epiphyseal plate .***

y cartilage remains in two places:

1) articular cartilage: hyaline cartilage covering joint surfaces that remains throughout life;

2) epiphyseal plate: the cartilage of the epiphyseal plate continues to grow and is continuously replaced by newly formed bone matrix resulting in elongation of bone.

The ***epiphyseal plate*** is divided into zones (fig. 10.15):

> ***resting zone:*** hyaline cartilage without morphological changes;
> ***zone of proliferation:*** chondrocytes dividing rapidly that from columns of stacked cells parallel to the long axis of the bone;
> ***zone of maturation / hypertrophy:*** large chondrocytes whose cytoplasm has accumulated glycogen and narrow areas of matrix between lacunae;
> ***zone of ossification:*** osteoprogenitor cells invade the area and differentiate into osteoblasts, which secrete bone matrix onto the calcified cartilage matrix. Chondrocytes here die when they can no longer receive nutrients via diffusion. This is because the calcified matrix is much less hydrated than hyaline cartilage.

Bone growth

> Bone length is dependent upon the activity that occurs in the epiphyseal plate. Bone growth stops when the cartilage of the epiphyseal plate ceases proliferation and bone development continues to unite the diaphysis and epiphysis.

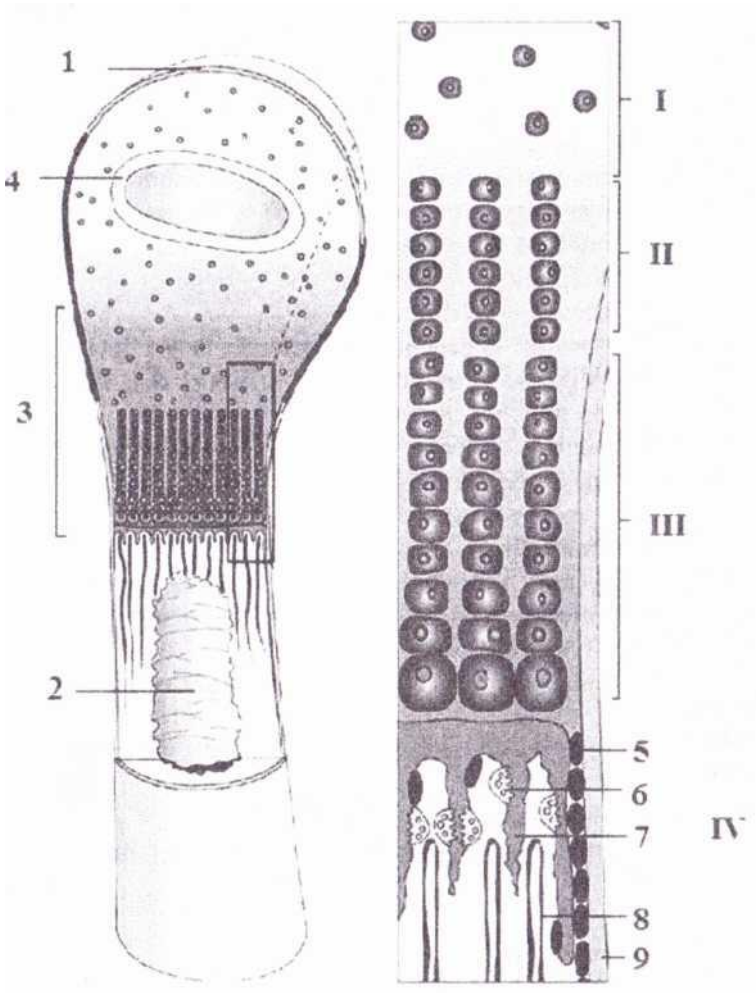


Figure 10.15. **Schematic diagram of epiphyseal plate.** I - resting zone, II - zone of proliferation. III - zone of hypertrophy, IV - zone of ossification; 1 - articular cartilage, 2 — bone marrow cavity, 3 - epiphyseal plate, 4 — secondary ossification, 5 - osteoblasts, 6 - osteoclasts, 7 — trabeculae, 8 — blood vessel, 9 — cortical bone

> An increase in bone width occurs by a process called appositional growth. Bone is produced by the periosteum (intramembranous ossification) on the external surface of the bone collar, and at the same time bone is removed from the internal surface causing the marrow cavity to increase in size.
> During infancy and childhood the most important stimulus of epiphyseal plate activity is growth hormone, which is released from the anterior pituitary gland. Excessive amounts of growth hormone result in excessive height (pituitary gigantism) and deficits of growth hormone result in diminished height (dwarfism).
> Normal bone growth is dependent on proper dietary intake of protein, minerals and vitamins. A deficiency of vitamin D prevents calcium absorption from the GI tract resulting in ***rickets*** (children) or ***osteomalacia*** (adults). Osteoid is produced but calcium salts are not deposited, so bones soften and weaken.

Bone remodelling

> In a growing person bone deposition exceeds bone resorption.
> In adulthood after the closure of the epiphyseal plates, bone deposition is balanced with bone resorption.
• Osteons are replaced by osteoprogenitor cells and osteoblasts from the periosteum.
• Trabeculae are replaced by osteoprogenitor cells and osteoblasts from the endosteum.
• Bone resorption is accomplished by osteoclasts.
• If bone resorption exceeds bone deposition then ***osteoporosis*** will occur.

Fracturc repair

> The bone matrix is destroyed and the bone cells adjoining the fracture die.
> The damaged blood vessels form a blood clot.
> The blood clot, damaged bone matrix, and dead cells are removed by macrophages.
>" Granulation tissue forms in the site of the blood clot and condenses into connective tissue and later into a fibrocartilaginous callus.

> At the same time, osteoprogenitor cells of the periosteum are activated and become osteoblasts that begin to deposit new bone. The new bone, which is a meshwork of trabeculae of primary bone, forms a bone callus around the fracture site.
> A similar activation of cells of the endosteum results in deposition of bone around the fibrocartilaginous callus that is slowly eroded away and replaced by bone (endochondral ossification).
> The spongy bone uniting the bones is transformed into compact bone by osteoblastic deposition of bone matrix, which gradually obliterates the spaces among the trabeculae.
> Resorption of excess bone by osteoclasts re-establishes the marrow cavity and the normal surface contours of the bone.

0 Clinical correlations

Cartilage disorders

Chondrocalcinosis is calcification in hyaline and/or fibrocartilage. In this metabolic disorder, calcium pyrophosphate dihydrate crystals accumulate in the cartilage of joints, usually the knee is affected. The symptoms include: joint swelling, joint stiffness, and joint pain.

Osteochondrodysplasia is a general term for a disorder of the development (dysplasia) of bone and cartilage. ***Achondroplasia*** is a type of autosomal dominant genetic disorder that is a common cause of dwarfism. Achondroplastic dwarfs have short stature, with an average adult height of 131 cm for males and 123 cm for females.

Chondromalacia patella is abnormal softening of the cartilage of the under the kneecap (patella). Chondromalacia patella is the most common cause of chronic knee pain. Chondromalacia patella results from degeneration of cartilage due to poor alignment of the kneecap as it slides over the lower end of the thigh bone (femur).

Bone disorders

Osteomalacia is the softening of the bones due to defective bone mineralization. Osteomalacia in children is known as ***rickets.*** It may show signs as diffuse body pains, muscle weakness, and fragility

of the bones. A common cause of the disease is a deficiency in vitamin D, which is normally obtained from the diet and/or sunlight exposure.

Osteoporosis is a condition characterized by a decrease in the density of bone, decreasing its strength and resulting in fragile bones (fig. 10.16). In osteoporosis the bone microarchitecture is deteriorating, and the amount and variety of proteins in bone is altered.

Osteoporosis is a disease of bones that leads to an increased risk of fracture. Osteoporosis is most common in women after menopause ***(postmenopausal osteoporosis).***

Senile osteoporosis occurs at age 75 years and older and is seen in both females and males. Other type of osteoporosis is a result of chronic or prolonged use of certain medications and the presence of predisposing medical problems or disease states.

Therefore, osteoporosis may also develop as a result of medications, specifically glucocorticoids, when the disease is called ***steroid-*** or ***glucocorticoid-induced osteoporosis.***

Bone loss can be prevented with lifestyle changes, vitamin supplements and sometimes medication.

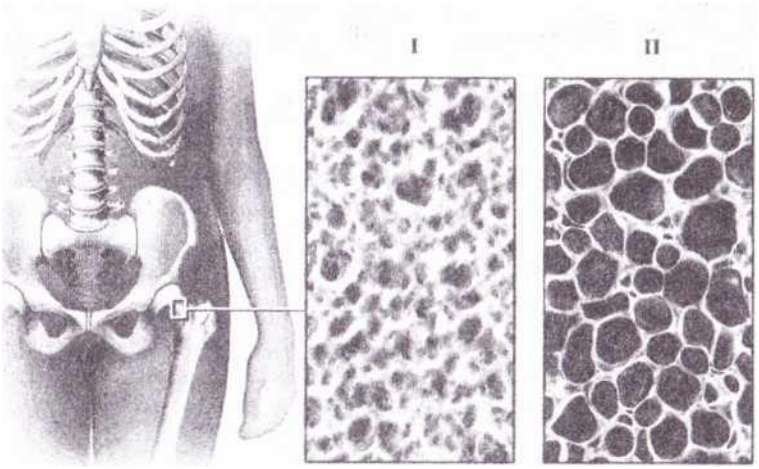


Fig.10.16. Schematic representation of normal bone matrix (1) and osteoporosis (II).

During the formation and development of bones the bones may grow long and thin but not to the required width, becoming brittle so that they fracture easily. This condition is known as ***osteogenesis imperfecta.*** The individual may grow out of the condition in the middle twenties after suffering numerous fractures while growing up. A child thus afflicted cannot participate in games or other strenuous activities.

Paget's disease is characterized by a softening of the bones followed by an abnormal thickening of the bones. Its cause is unknown, and it manifests itself after the age of 30. It may cause pain in the thighs, knees, or legs, as well as backache, headache, and general fatigue. Symptoms include deafness, deformity of the pelvis, spine, and skull, and bowed legs. Although there is no known cure, Paget's disease is not usually fatal, but is eventually disabling.

Osteomyelitis is an inflammation of the bone caused by f ever-inducing bacteria or mold organisms. The invading microorganisms usually reach the bone through the bloodstream after entering the body through a wound or ulcer; the infection also can begin through a compound fracture or during surgery. The staphylococcus germ is most frequently the causative agent, and the most frequent site is the shaft of a long bone of a child. In adults, osteomyelitis usually occurs in the pelvis or spinal column.

MUSCLE TISSUES

0 Overview of the of the muscle tissues

Muscle tissues represent group of tissues of a various origin and a constitution, united on the basis of the common sign - ***contractile ability.*** Cytoplasm of muscle cells and muscle fibers contain ***actin*** and ***myosin***, two contractile proteins that generate force and produce movement.

The ***function*** of muscle tissue is to contract and thus produce motile forces that have two general consequences:

> movement and support of body parts,
> transport of materials within the body.

The cytoplasm of muscle cells is called ***sarcoplasm***, the smooth endoplasmic reticulum is called ***sarcoplasmic reticulum***, the cell membrane, or plasmalemma is called ***sarcolemma.***

Classifications of the muscle tissues

1. **Morphofunctional classification** (based on the structure and function of the muscle tissue)

> Striated muscle tissues
  - skeletal (somatic, voluntary) muscle;
  - cardiac muscle;

> Smooth (visceral) muscle

2. **Histogenetic classification** (based on the origin of muscle tissue)

1) muscle tissue of ***somatic type*** arises from myotomes of somites; forms a skeletal muscle, is cross-striated;

2) muscle tissue of ***coelomic type*** arises from the cardiogenic area of splanchnopleuric mesoderm; forms a cardiac muscle (myocardium), is cross-striated;
3) muscle tissue of ***mesenchymal type*** arises from a mesenchyme, forms a musculature of an internal organs and vessels, is smooth;
4) muscle tissue of ***ectodermic type*** arises from ectoderm, forms myoepithelial cells located in the alveoli of exocrine glands and muscles of the iris.

0 Skeletal muscle tissue

Skeletal muscle is a form of striated muscle tissue existing under control of the somatic nervous system.

Function of skeletal muscle tissue is the movement of the skeleton and organs.

Distribution of skeletal muscle tissue

Skeletal muscle tissue forms skeletal musculature, tongue, pharynx, upper $2/3^{rd}$ of esophagus, anal canal, and lower part of vagina.

Skeletal muscle tissue is made up of individual components known as ***muscle fibers*** or ***myosymplasts.***

Muscle fibers are ***morphofunctional unit*** of the skeletal muscle. Muscle liber is very long (up to 30 cm) cylindrical multinucleated fiber with a diameter of 10-100 (am.

Nuclei are oval in shape, reside along the cell periphery.

Each muscle fiber is surrounded by a basai lamina.

Skeletal muscle fibers are multinucleate structures that arise by fusion of mononucleate myoblasts.

Components of the muscle fiber.

1. Myosymplasts,
2. Mononucleate ***satellite cells*** associate with the muscle fiber and reside within the muscle basal lamina (fig. 11.1).

The sarcoplasm of a myosymplast contains all general organelles (except for centrioles) and some special organelles, and also inclusions. These structures form ***functional systems.***

1) contractile system,
2) conducting system,
3) supporting system,
4) system of energy production.

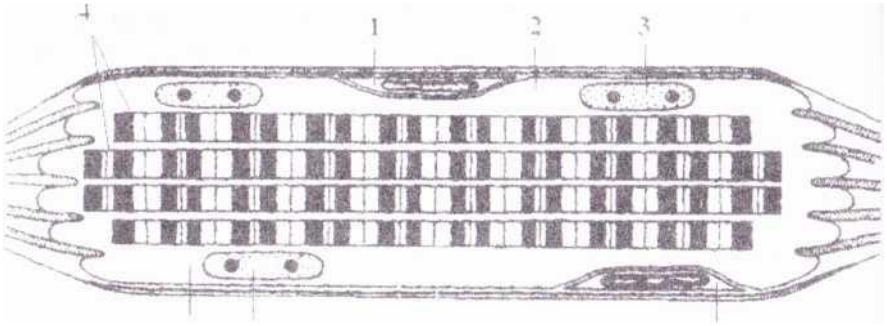


Figure 11.1. Schematic diagram of skeletal muscle fiber. 1 - satellite cells, 2 - sarcoplasm, 3 - nuclei of myosymplast, 4 - myofibrils (from *JO. fi.Acpanacbee, HA.IOpma u dp.,* 1999)

Contractile system

Muscle fibers contain many ***myofibrils***, running parallel to one another and to long axis of the muscle fibers.

Myofilaments are polymers of two types:

> ***thick filaments,*** which are composed principally of ***myosin,*** and

> ***thin filaments***, which are composed of ***actin',*** thin filaments also contain other proteins including ***tropomyosin*** and ***troponin,*** which regulate contraction.

The registered packing of many myofilaments produces the ***myofibril,*** which shows the striations that are visible by light and electron microscopy (fig.l 1.2).

Arrangement of thin and thick filaments in a myofibril Each skeletal muscle fiber exhibits along its length alternate dark bands (***anisotropic or A-bands)*** and light bands (***isotropic or l-bands)*** (fig. 11.3).

The ***sarcomere*** is the basic contractile unit of a myofibril. Each myofibril contains many sarcomeres in tandem.

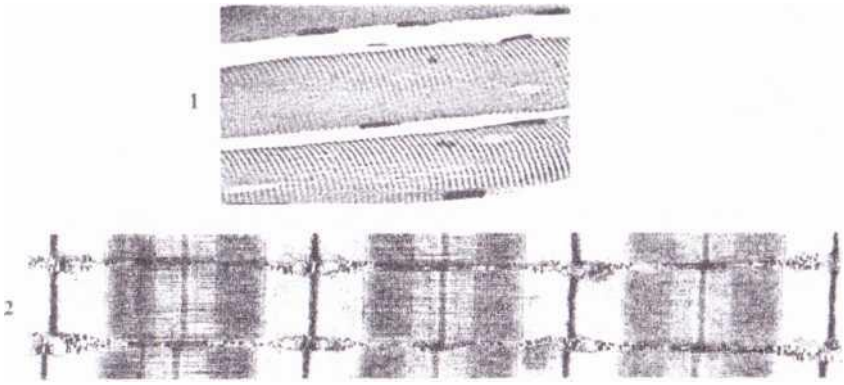


Figure 11.2. Skeletal muscle fibers. 1 - light microscopy, 2 - electron microscopy

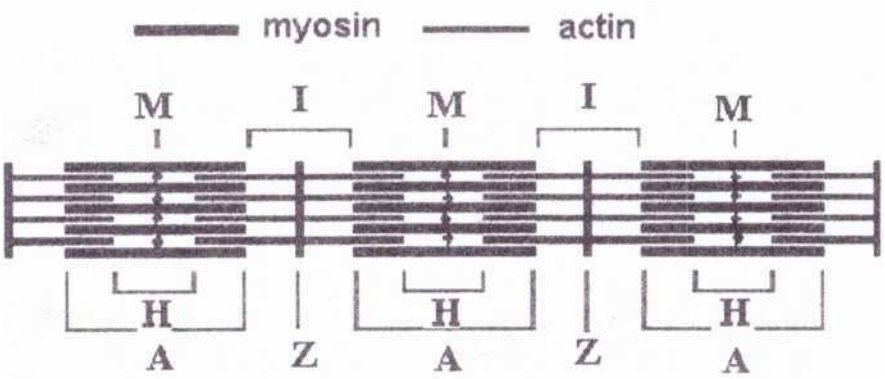


Figure 11.3. Diagram of contractile system of skeletal muscle fiber. M-M- line, Z - Z-iine, A - anisotropic or A-band. I - isotropic or 1-band

The thick filaments occupy the ***A-band,*** the central part of the sarcomere.

The thin filaments run between and parallel to the thick filaments. One of their ends attached to the ***Z- line.***

A- band has two parts:
- central part ***(H band)*** containing only myosin (thick) filaments: they are held together in the ***M- line*** situated in the center of ***H- band,***
- lateral parts containing both thick and thin filaments.

I-band consists of only actin (thin) filaments; the free ends of actin filaments extend into outer part of ***A- band.***

In cross section 6 thin filaments surround only 1 thick filament.

Muscle contraction results from the coordinated contraction of the sarcomeres. The contraction of sacromeres is mediated by the relative movement (sliding) of the thick and thin filaments.

Regulation of contraction

Contraction in skeletal muscle is regulated by the activities of two membrane systems ***(conducting system)*** (fig. 11.4).

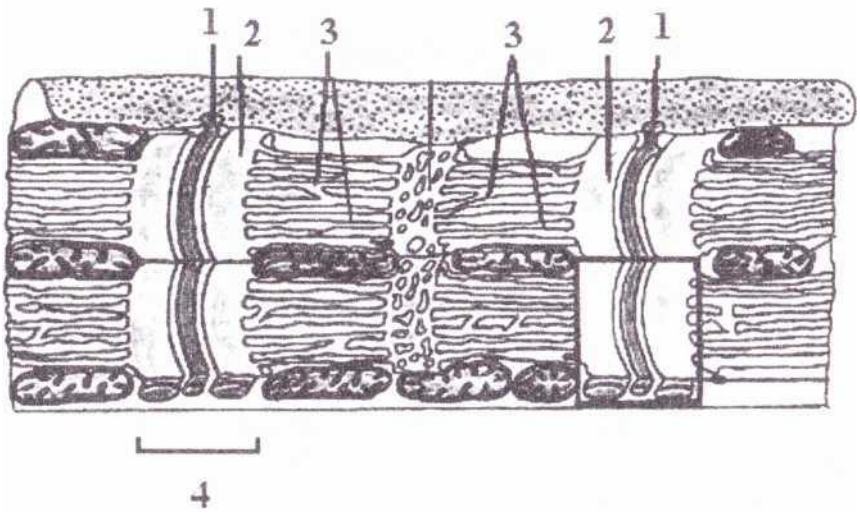


Figure 11.4. The conducting system. 1 -T-tubules, 2 - terminal cisterns, 3 - sarcoplasmic reticulum, 4 - triad

> ***T-tuhules*** (or ***transverse tubules)*** are transverse, deep tubular invaginations of the plasma membrane which surround myofibrils at the junction of the A and I band. They are responsible for synchronous contraction of all sarcomeres.
> The ***sarcoplasmic reticulum*** **(SR)** is a large membrane network derived from ER that surrounds each myofibril between the T-tubules.

The ***terminal cisternae*** are flat regions of the SR adjacent to the T-tubules. The SR serves as a calcium store.
T tubules together with two cytoplasmic cisterns form ***triads.***

Nerve-induced depolarization propagates into the cytoplasm by the T-tubule system inducing release of calcium from the terminal cisternae of the sarcoplasmic reticulum; this induces contraction through interactions with troponin, a regulator)' protein associated with the thin filaments. Subsequent uptake of calcium by the SR, in turn, results in relaxation.

Supporting system of a muscle fiber includes the ***special elements of cytoskeleton***, providing locating of myofibrils inside a fiber, and also a ***sarcolemma*** connected to them.

System of energy production includes
> ***mitochondria,*** which produce ATP, necessary for exercise of muscle work, and also
> ***trophic inclusions*** (glycogen) serve as a depot of energy that is mobilized during muscle contraction.

Mitochondria in a myosymplast settle down as chains under a sarcolemma and between myofibrils.

0 Histogenesis of skeletal muscle (myogenesis)

Skeletal muscle arises from the paraxial mesoderm that is present either side of the neural tube in two wide strips of loose unconnected cells or mesenchyme.

Skeletal myogenesis proceeds through three stages (fig.l 1.5):
> ***determination*** of precursor muscle cells, called ***myoblasts***;
> ***proliferation*** and in some cases ***migration*** of myoblasts; and
> ***differentiation*** of myoblasts into mature muscle.

Somites are collections of embryonic mesodermal cells, some of which become determined as ***myoblasts.*** After formation of the neural tube, each somite forms a dermamyotome, which gives rise to skin and muscle, and a sclerotome, which develops into skeletal structures. Myoblasts form at each edge of a dermamyotome. Lateral myoblasts proliferate and migrate to form ***premuscle nwsses*** in the limbs, where they differentiate into long, multinucleate skeletal muscle cells responsible lor muscle contraction, called ***myotubes.*** Axial myoblasts form the myotome. The dermatome gives rise to skin elements (dermis), and the myotome to axial muscle.

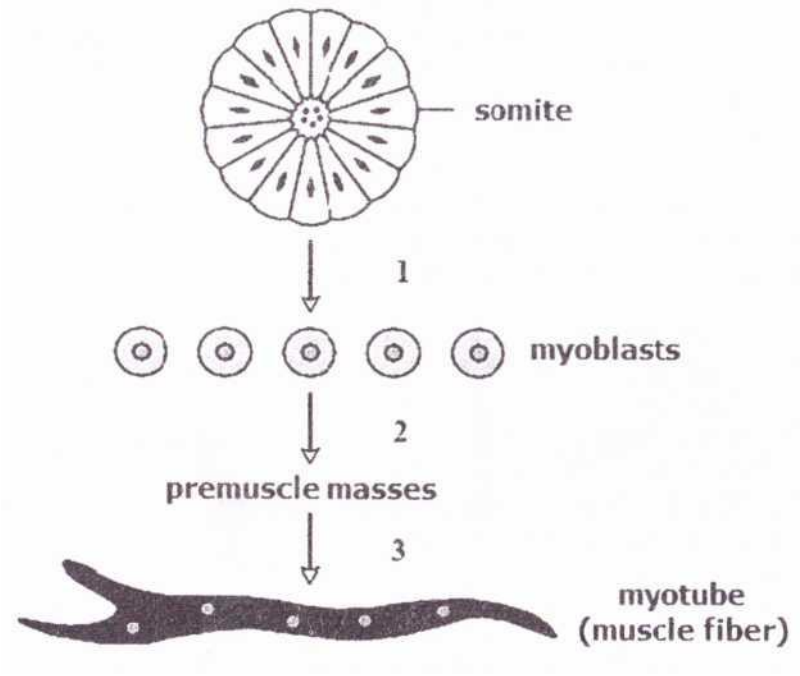


Figure 11.5. Schematic diagram of stages in development of skeletal muscle.
1 - myoblast determination, 2 - myoblast proliferation and migration, 3 — differentiation into muscle

0 Organization of skeletal muscle

The skeletal muscle consists of fascicles of the muscle fibers connected together by system of connective tissue components (fig. 11.6).

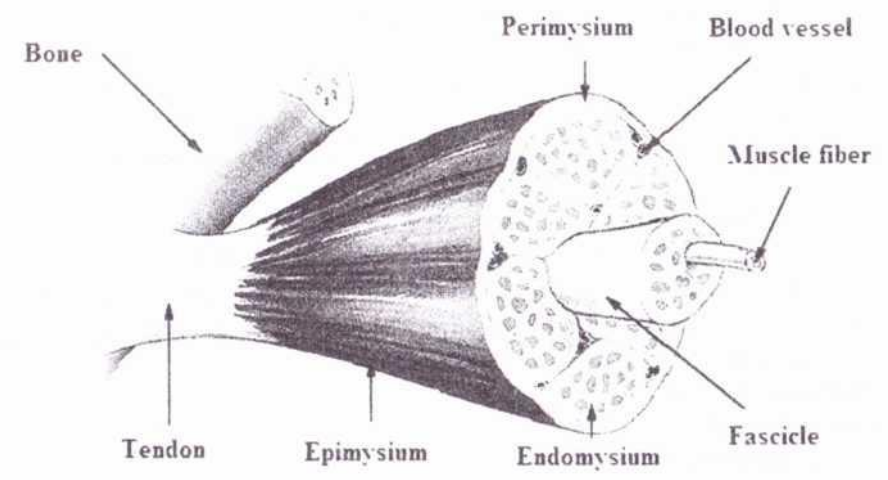


Figure 11.6. Organization of skeletal muscle.

System of connective tissue components:

Endomysium is delicate layer of loose connective tissue surrounded each muscle fiber.

Perimysium is loose connective tissue surrounded the groups of muscle tissue (fascicles).

Epimysium is connective tissue surrounded the muscle as a whole. **Innervation**

of skeletal muscle

Skeletal muscle has efferent (motor) and afferent (sensitive) innervation. A single nerve fiber (axon) can innervate one muscle fiber, or it may branch and be responsible for innervation 160 or more muscle fibers. A single nerve fiber and all the muscles it innervates are called a ***motor unit***

0 **Cardiac muscle tissue**

Cardiac muscle is a type of involuntary" striated muscle tissue found in the walls of the heart, specifically the myocardium.

Function of the cardiac muscle tissue

Coordinated spontaneous rhythmic contractions of cardiac muscle cells in the heart propel blood out of the atria and ventricles to the blood vessels of the left/body/systemic and right/lungs/pulmonary circulatory systems. This complex of actions makes up the systole of the heart.

Morph ofunctional unit is ***cardiac muscle cell.***

Cardiac muscle cells are long, cylindrical; they are 15 pm in diameter and 85-100 pm in length. Cardiac muscle cells have one or two pale-staining, centrally located nuclei. Sarcoplasm contains organelles and inclusions that form functional systems:

1) contractile system,
2) conducting system,
3) supporting system,
4) system of energy production.

Contractile system

The ends of the cardiac muscle cells are split into branches which form three-dimensional cytoplasmic network (fig. 11.7). Between the muscle cells delicate loose connective tissue have capillary network. Contractile systems of skeletal fibers and cardiac muscle cells have many structural similarities.

Conducting system

Conducting system of a heart contains:

1) ***sarcoplasmic reticulum*** is not well development, does not form terminal cisterns,

2) ***transverse (T) tubules*** are wide, together with elements of sarcoplasmic reticulum form ***diads*** composed of one T-tubule and one cytoplasmic cistern, which are found in range Z- lines.

Supporting system

The ends of adjacent cardiac cells are connected through an intercellular junctional complex called the ***intercalated disks.*** It provides anchorage for the myofibril and permits rapid spread of contractile stimuli. It is visible in the light microscope as a dense line and is comprised of several structural elements.

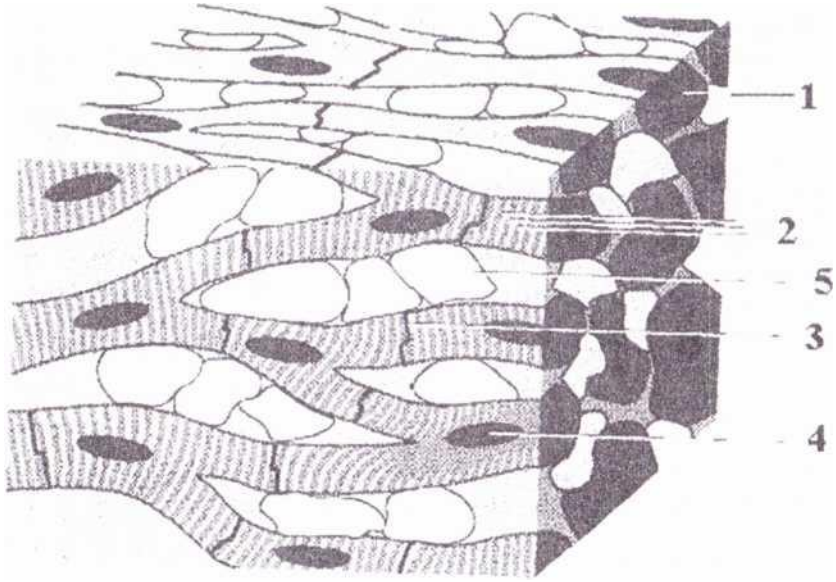


Figure 11.7. Cardiac muscle tissue. 1 - cardiac muscle cells, 2 - cross-striation, 3 - intercalated disk, 4 - nucleus, 5 - blood capillaries

The intercalated disc consists of three types of contacts (fig. **11.8):**

> ***transverse portion,*** which runs across the fibers at right angles:
  - ***fascia adherens***,
  - ***desmosomes***,
> ***lateral portion***, which runs parallel to the myofilaments:
  gap junctions (nexuses).

*

Fascia adherens and ***desmosomes*** carry out mechanical function; ***nexus*** carries out electrical connection of cardiac muscle cells. Nexuses provide fast conduction of impulses from cell to cell.

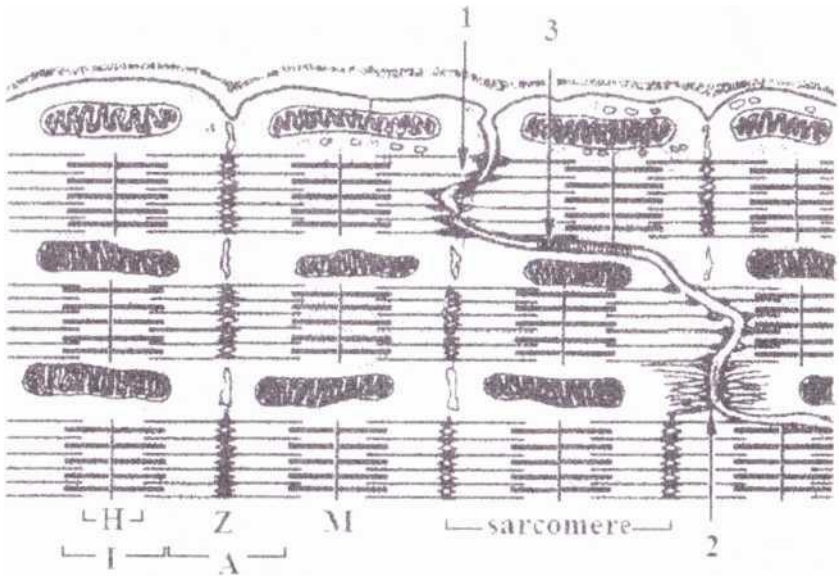


Figure 11.8. Schematic diagram of intercalated disk of cardiac muscle cell.
1 - fascia adherens, 2 - desmosome, 3 - gap junction

System of energy production

The ***system of energy production*** is submitted by mitochondria and inclusions (glycogen, triglycerides). Very numerous and large mitochondrion lay series between myofibrils, at poles of nucleus and under sarcolemma.

Types of the cardiac muscle cells

The cardiac muscle cells are subdivided on three types:

> ***contractile;***

> ***conducting;***

y secretory (endocrine).

1) ***Contractile cardiac cells*** form the basic part of a myocardium and are characterized highly developed contractile system (fig. 11.9);

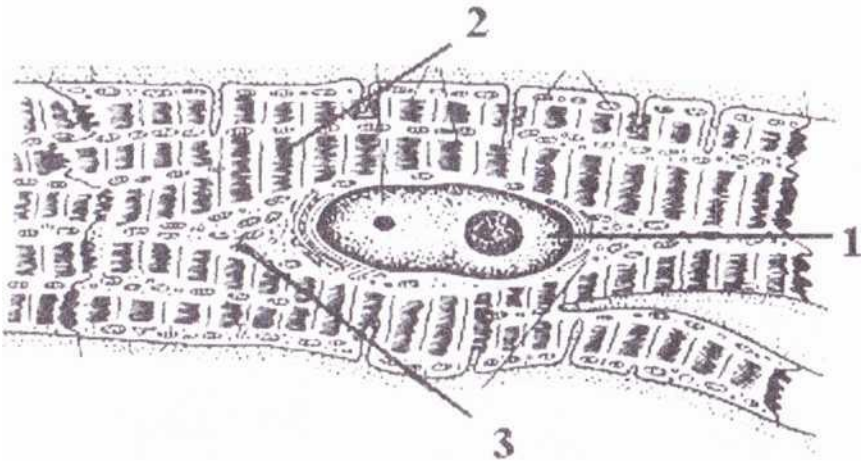


Figure 11.9. Contractile cardiac cell. 1 - nucleus, 2 - myofibrils, 3 - mitochondria

2) ***Conducting cardiac cells*** have ability to generation and conduction of electrical impulses through an ***impulse-generating and conducting system of a heart.*** They are characterized by weak development contractile system, a light sarcoplasm and large nucleus (fig. 11.10).

3) ***Secretory (endocrine) cardiac cells*** are found in right atrium and are characterized by weak development of contractile system. In their sarcoplasm near to poles of a nucleus there are granules containing hormone (***atrial natriuretic factor, auriculin,*** or ***atriopeptin).***

EZJ Histogenesis of cardiac muscle

The source of development of a cardiac muscle is the ***cardiogenic plate*** - thickening of ***splanchnopleuric mesoderm*** located at the cranial end of the embryo.

Cardiac precursor cells which lie in a horse-shoe shape configuration in the plate coalesce to form two endocardial tubes. These tubes are then forced into the thoracic region due to cephalic and lateral foldings where they fuse together forming a single. Cells of endocardial

tube can differentiate into endocardium which lines the heart chamber and valves and the myocardium which forms the musculature of the ventricles and the atria.

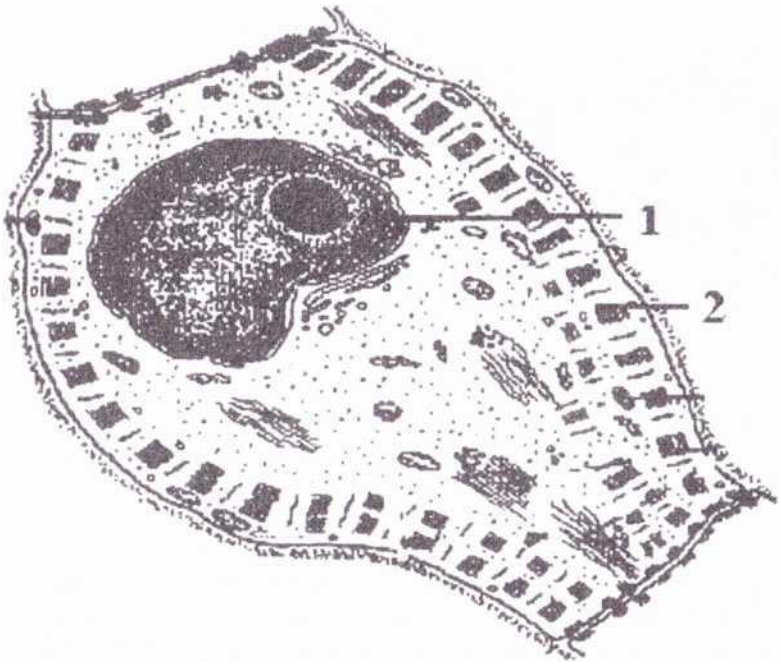


Figure 11.10. Conducting cardiac cell. 1 — nucleus, 2 - myofibrils

0 Smooth (visceral) muscle tissue

Smooth muscle is an involuntary non-striated muscle.

Function of smooth muscle tissue

Smooth muscle may contract spontaneously or as in the gut special pacemakers cells interstitial cells of Cajal produce rhythmic contractions. Contraction and relaxation can be induced by a number of physiochemical agents (e.g., hormones, drugs, neurotransmitters - particularly from the autonomic nervous system).

Location of smooth muscle tissue

Smooth muscle tissue found within:

> tunica media layer of large and small arteries (except large elastic arteries) and veins,
> urinary bladder,
> uterus and male and female reproductive tracts,
> gastrointestinal tract,
> respirator}' tract,
> ciliary muscle and iris of the eye.
> glomeruli of the kidneys contain a smooth muscle-like cell called the mesangial cell.

Smooth muscle is fundamentally different from skeletal muscle and cardiac muscle in terms of structure, function, excitation-contraction coupling, and mechanism of contraction.

Morphofunctional unit of the smooth (visceral) muscle tissue is ***smooth muscle cell*** (fig. 11.11).

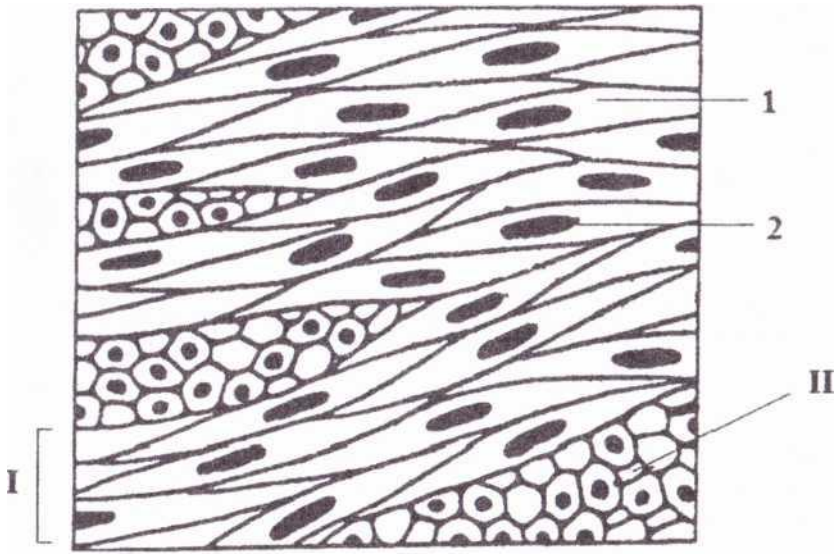


Figure 11.11. Schematic representation of the smooth muscle tissue. I - longitudinal section, **II -** cross section, 1 - smooth muscle cell, 2 - nucleus

Smooth muscle cell is long spindle-shaped cell ***Smooth muscle cell*** is from 20 pm in small blood vessels to 500 pm in the pregnant uterus in length; greatest diameter is about 6 pm.

Nucleus is single, rod-shaped, and central in position; in contracted condition of muscle the nucleus may become wrinkled.

Sarcoplasm contains concentrated at the pole of the nucleus mitochondria, polyribosomes, cisterns of rough endoplasmic reticulum, and Golgi complex.

Sarcoplasm consists of functional systems:

1) contractile system,
2) conducting system,
3) supporting system,
4) system of energy production.

Contractile system

Contractile system is submitted by ***thin actin*** and ***thick myosin*** filaments which not form myofibrils. The bundles of myofilaments crisscross obliquely through the cell, forming a lattice like network (fig. 11. 12). The myofilaments till most of the cytoplasm. They are not organized into sarcomeres. There is neither banding nor T tubules, however, smooth muscle cells do have a sarcoplasmic reticulum that can sequester and release calcium.

Each cell is surrounded by a connective tissue sheath.

Figure 11.12. Schematic diagram of the smooth muscle cell. I - relaxed smooth muscle cell, **II** - contracted smooth muscle cell; 1 - dense bodies, 2 - contractile filaments, 3 - nucleus, 4 - caveolae

r

Conducting system

Conducting system contains:

> ***sarcoplasmic reticulum*** which in these cells consists of system of vesicular and tubular structures, and also

> numerous flask-shaped invaginations of plasmolemma ***(caveo/ae).***

Caveolae contain high concentrations of calcium, they contact to elements of sarcoplasmic reticulum. T-tubules are absent.

Supporting system

Supporting system of smooth muscle cell of is submitted by its ***sarcolemma, a basal membrane, system of elements of cytoskeleton*** and connected with them ***dense bodies.***

The ***sarcolemma*** of each smooth cell is surrounded with ***basal membrane*** with thin reticular, collagen and elastic fibers;

Dense bodies are the oval structures laying along the lengthy axis of smooth cell loosely in its sarcoplasm or connected with inner surface of a sarcolemma.

System of energy production

System of energy production is submitted by mitochondria and inclusions (glycogen, lipids) which scission provides reception of energy. Small mitochondrion lay at poles of a nucleus and under a sarcolemma.

Innervation of smooth muscle tissue

Smooth muscle is innervated by both sympathetic and parasympathetic nerves of autonomic system. Nerve terminals are found out only on separate cells. Depolarization is transferred to the next smooth muscle cells by means of ***gap junctions.***

Histogenesis of smooth muscle tissue

The source of the development of smooth muscle is ***mesenchyme.***

On a measure differentiation cells elongate, in them proteins of contractile system and cytoskeleton start to be synthesized.

In immature smooth muscle cells are strongly advanced rough endoplasmic reticulum and Golgi complex.

0 Regeneration of muscle tissues

Three types of adult muscle exhibit varying potentials for regeneration after injury.

Cardiac muscle has no regenerative capacity beyond early childhood. Defects or damage (e.g., infarcts) in heart muscle are generally replaced by the proliferation of connective tissue, forming myocardial scars.

In ***skeletal muscle***, although the nuclei are incapable of undergoing mitosis, the tissue can undergo limited regeneration. The source of regenerating cells is believed to be the ***satellite cells.***

Smooth muscle is capable of an active regenerative response. Mononucleate smooth muscle cells and pericytes from blood vessels undergo mitosis and provide for the replacement of the damaged tissue.

0 Clinical correlations

Disorders of the muscular system can be due to genetic, hormonal, infectious, autoimmune, poisonous, or cancerous causes. But the most common problem associated with this system is ***injury*** from misuse. Skeletal muscle sprains and tears cause excess blood to seep into the tissue in order to heal it. The remaining scar tissue leads to a slightly shorter muscle. Muscular impairment and cramping can result from a diminished blood supply. Cramping can be due to overexertion. Poor blood supply to the heart muscle causes chest pain called angina pectoris.

Muscular system disorders related to the ***immune system*** include ***myasthenia gravis*** and ***tumors.***

Myasthenia gravis is characterized by weak and easily fatigued skeletal muscles, one of the symptoms of which is droopy eyelids. MG is caused by antibodies that a person makes against their own receptors; hence, MG is an ***autoimmune disease.*** The antibodies disturb normal stimulation to contract skeletal muscles.

Failure of the immune system to destroy cancerous cells in muscle can result in muscle tumors. Benign muscle tumors are called myomas; while malignant muscle tumors are called myosarcomas.

Contamination of muscle cells by infectious substances and drugs can also lead to muscular disorders.

Clostridium bacteria can cause muscle ***tetanus,*** which is a disease characterized by painful repeated muscular contractions.

In addition, some types of ***gangrene*** are due to bacterial infections deep in a muscle. Gangrene is the decay of muscle tissue in varying degrees; it can involve small areas of a single muscle or entire organs.

The poisonous substance, ***curare,*** blocks neuromuscular transmission in skeletal muscle causing paralysis.

And large doses of prolonged ***alcohol*** consumption can cause muscle damage, as well.

The most common type of muscular genetic disorder is muscular dystrophy of which there are several kinds.

Duchenne's muscular dystrophy is characterized by increasing muscular weakness and eventual death.

Becker's muscular dystrophy is milder than Duchenne's, but both are X-linked recessive ***genetic disorders.***

NERVE TISSUE

0 Overview of the of the nerve tissue

The ***nervous tissue*** is the main component of the nervous system - the brain, spinal cord, and nerves - which regulates and controls body functions. It is composed of the ***neurons***, which transmit impulses, and the ***neuroglial cells,*** which assist propagation of the nerve impulse as well as provide nutrients to the neuron.

Functions of the nervous system are sensory input, integration, controls of muscles and glands, homeostasis, and mental activity.

0 Development of nerve tissue (neuruiation)

The neuruiation (fig. 12.1) is the formation of the embryonic neural plate and its transformation into the neural tube.

Stages of neuruiation:

1 - ***formation of neural plate,*** cells of the neural plate can be distinguished as elongated cells in the dorsal region of the ectoderm (shaping); than the neural plate forms the ***neural folds*** (folding);

II - ***formation of neural groove:*** the dorsal edges of the plate thicken, forming the neural groove;

III - ***elevation*** and ***convergence*** **of** ***neural folds***,

IV - ***formation of neural tube:***

Neural tube gives arise to the central nervous system. Cells lateral to the neural groove from the ***neural crests*** (fig. 12.2).

Although derived from ectoderm, the neural crest has sometimes been called the “fourth germ layer” because of its importance.

Neural crest cells give rise to a variety of important structures in the adult body. As neuruiation proceeds and the neural tube begins to form, neural crest cells are groups of cells positioned on the top (dorsal) edges of the forming neural folds. Once the neural tube has formed and invaginated, the neural crest cells form a distinct population of cells resting on top of (just dorsal to) the neural tube.

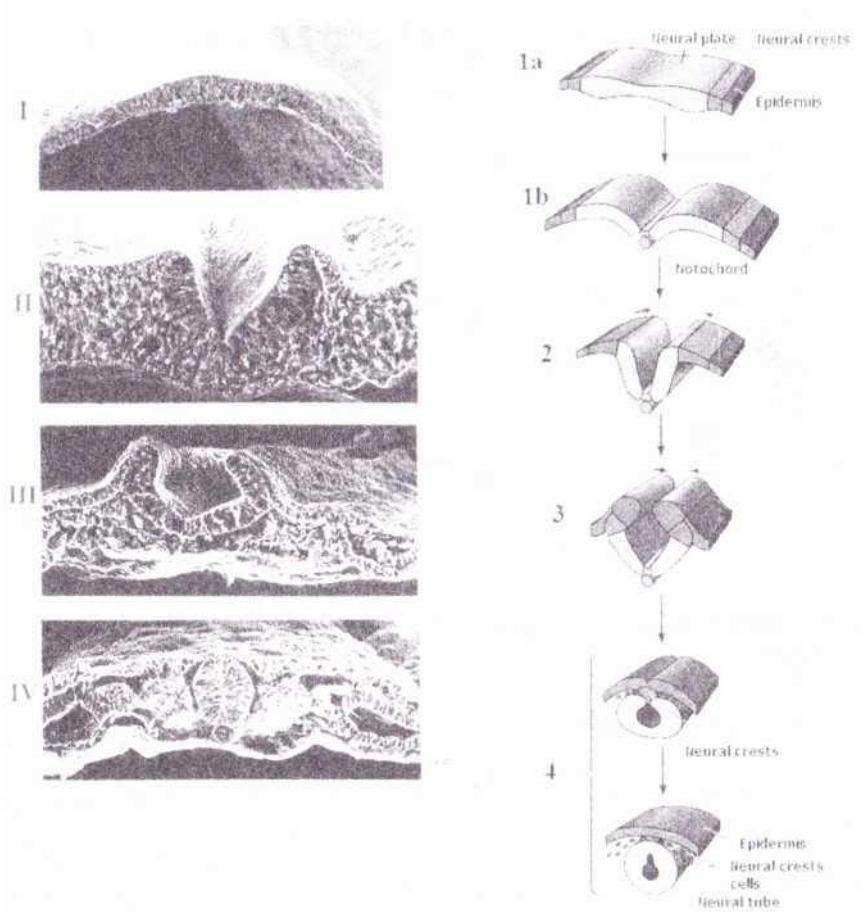


Figure 12.1. Schematic diagram of neurulation. I, 1 - formation of neural plate: la - shaping, lb - folding; II, 2 - elevation of neural folds; III, 3 — convergence of neural folds, IV, 4 - formation of neural tube

Cells of the ***neural crests*** undergo migration and give rise to:

> skin pigment cells (melanocytes);
> neurons of the dorsal root ganglia of spinal nerves;
> autonomic nervous system (both sympathetic and parasympathetic ganglia);

> Schwann cells responsible for myelination of peripheral nerves; *'y* adrenal medulla;
> some bones and cartilage in the lower jaw

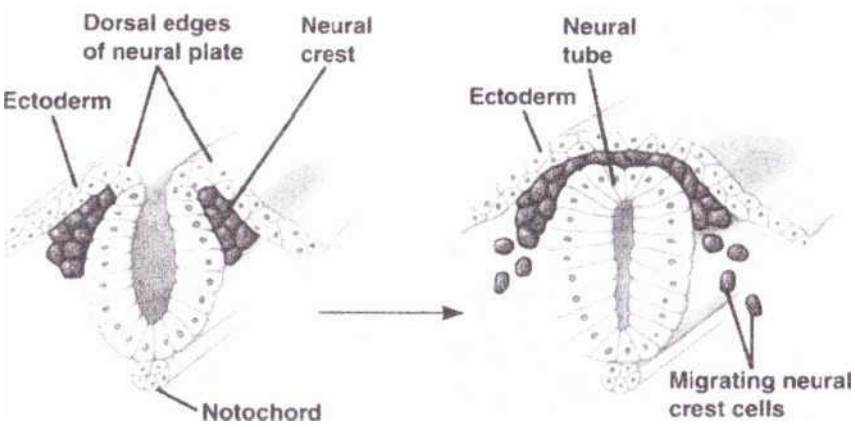


Figure 12.2. Schematic diagram of the neural crests (from *Campbell N.A et al.,* **2008)**

0 Neurons (nerve cells)

The ***neuron*** consists of (fig. 12.3):

1) ***cell body*** (perikaryon) containing the nucleus surrounded by cytoplasm;
2) processes:

> ***dendrites,*** which are multiple elongated processes specialized in receiving stimuli from the environment, sensory epithelial cells, or other neurons;
> ***axon*** which is a single process specialized in generating or conducting nerve impulses to other cells (nerve, muscle, and gland cells); all axons originate from a short pyramidal-shaped region, the ***axon hillock.***

Cell bodies are situated in grey matter of CNS, in sensory and autonomic ganglia outside PNS.

Neurons are very variable in size - from 5 pm in cerebellum to 130 |im in the anterior horn of spinal cord. They have rounded, oval,

star-shaped, or pyramidal shape. ***Nuclei*** of neurons are large, spherical, pale-staining and centrically placed with a prominent nucleolus. ***Cytoplasm*** contains ***Nissl bodies,*** neurofibrills, Golgi complex, mitochondria, inclusions.

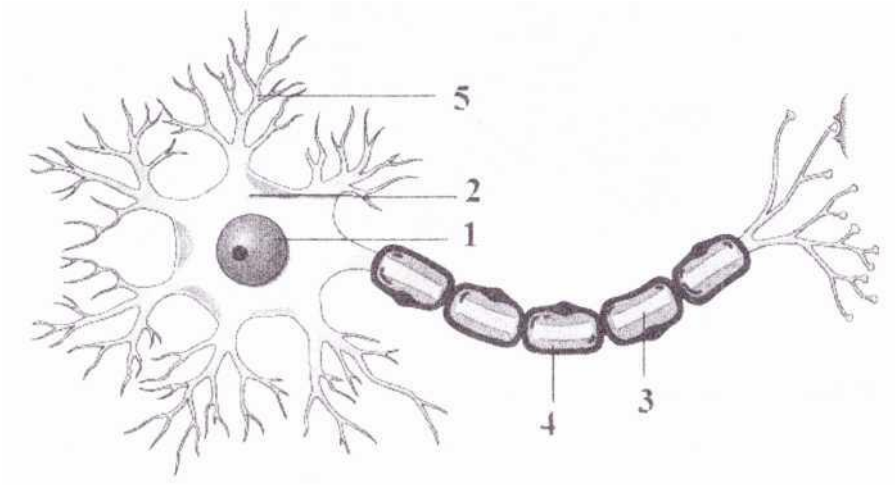


Figure 12.3. Structure of the neuron. 1 - nucleus, 2 - cell body, 3 - axon, 4 - myelin sheath, 5 - dendrites

The highly developed rough endoplasmic reticulum organized into aggregates of parallel cisterns and ribosomes between them appear under the light microscope as basophilic granules called ***Nissl bodies*** (fig. 12.4). Nissl bodies are present in cell body and dendrites, are absent in axon.

Neuroftbrils (stained by silver salts) (fig. 12.5) are cytoplasmic fibrils in the cell body where they form a branching network, and extend into all processes. Each microfibril consists of collections of ***neurofilaments.*** They provide mechanical support and stability to the cell.

Golgi complex is well development, perinuclear in position.

Mitochondria are numerous in the cytoplasm and extend into all processes.

Inclusions of pigment, such as iipofuscin, are residua! of undigested materia! by lysosome.

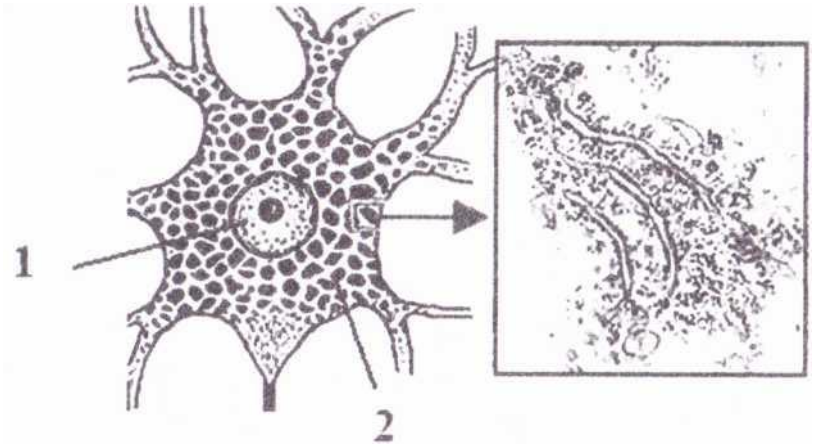


Figure 12.4. Nissl bodies in the neurons. 1 - nucleus, 2 —Nissl bodies

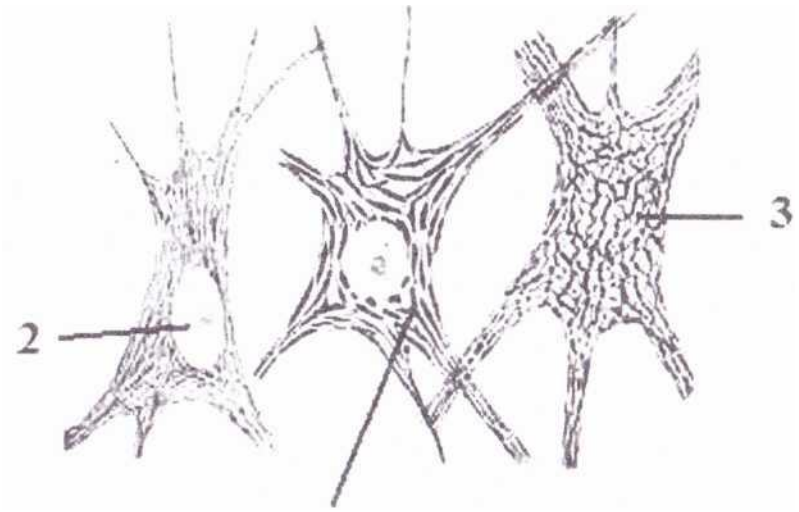


Figure 12.5. Neurofibrils in the neurons. 1 - cell body, 2 - nucleus, 3 - neurofibrills

Classifications of the neurons

Morphological classification is based on number of processes (fig. 12.6):

1. ***Unipolar*** (neuroblasts)
2. ***Pseudounipolar neurons*** have a single process, which then forms a T- shape.
   Location, sensory ganglia except vestibular and cochlea.
3. ***Bipolar neurons*** have one axon and one dendrite.
   Location: cochlear and vestibular ganglia, olfactory neuroepithelium, retina.
4. ***Multipolar neurons*** have more than two processes, one process being the axon and others dendrites.
   Location: either motor or interneurons.

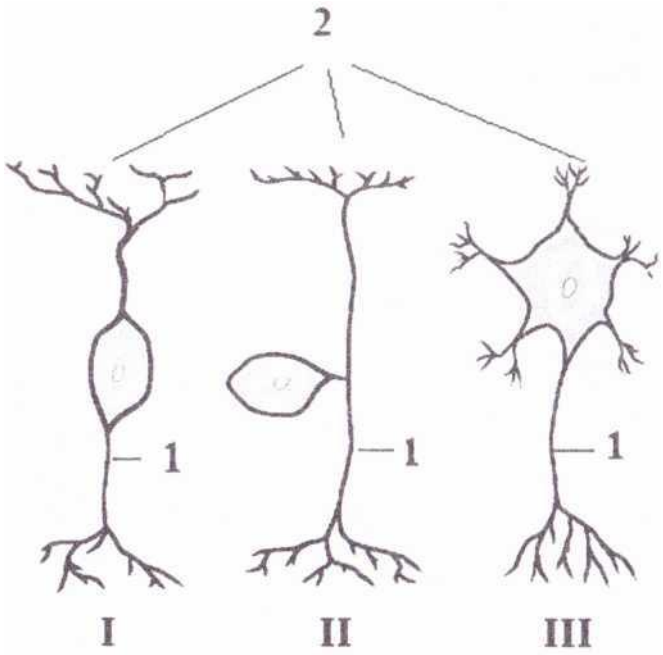


Figure 12.6. Main types of neurons. I - bipolar, **II** - pseudounipolar, **III** multipolar, 1 - axon, 2 - dendrite (dendrites)

Functional classification is based on functional relations.

1. Sensory (afferent) neurons are involved in the reception of sensory stimuli from the environment and from within the body. They are mostly pseudounipolar neurons; their cell bodies lie outside CNS in sensory ganglia.

2. Interneurons establish relationship among other neurons, forming complex functional networks.

3. Motor (efferent) neurons control effecter organs such as muscle fibers and exocrine and endocrine glands.

0 Glial cells

Nervous tissue has no intercellular matrix, and glial cells furnish a microenvironment suitable to neuronal activity.

Functions of the glial cells:

> supporting,
> delimitative,
> trophic,
> secretory,
> protective.

Classification of the glial cells

1. Macroglia:
   1.1 oligodendrocytes;
   1.2 astrocytes;
   1.3 ependymal cells.
2. Microglia

1. Macroglia

1.1 ***Oligodendrocytes*** produce the myelin sheath that provides the electrical insulation of neurons in the central nervous system. These cells have a few' small processes that wrap around axons (fig. 12.7). The same function is performed by Schwann cells in the peripheral nervous system.

Types of the oligodendrocytes in the peripheral nervous system:

> ***Schwann cells*** have the same function as oligodendrocytes but are located around axons in the peripheral nervous system;

> ***satellite cells of ganglia*** are flattened cells that form a capsule around each ganglion cell.

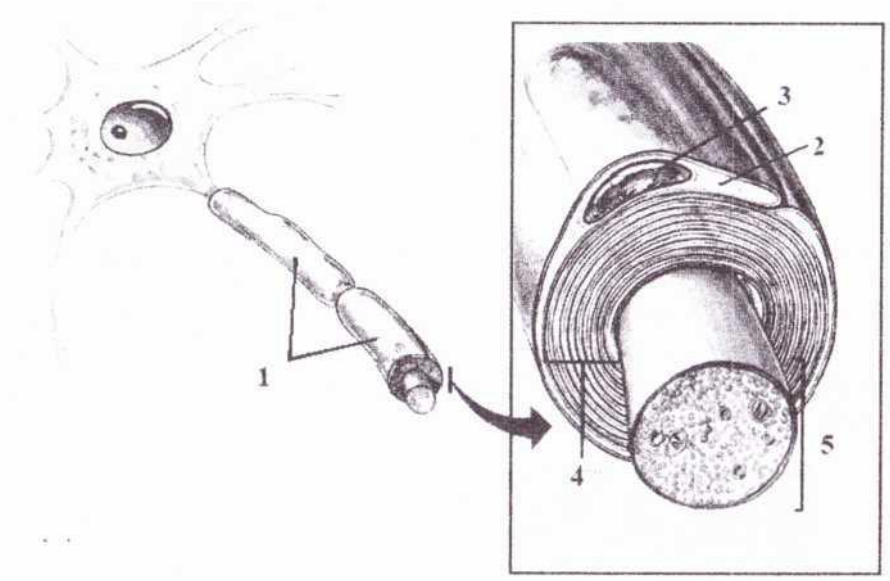


Figure 12.7. Oligodendrocyte. 1 - Schwann cells, 2 — neurolemma, 3 - nucleus of Schwann cell, 4 - myelin sheath, 5 - axon

1.2 ***Astrocytes***

Astrocytes are star-shaped cells with profuse branching processes, they contain large, pale, round nucleus.

Astrocytes with few long processes are called ***fibrous astrocytes***; they are located in the ***white matter*** (fig. 12.8). Processes are attached to capillaries by perivascular feet.

Protoplasmic astrocytes with many short-branched processes are found in the ***grey matter*** (fig. 12.9). Many of them processes are attached to pia mater; some extend to blood vessels and are termed perivascular feet.

1.3 ***Ependymal cells*** are low columnar ciliated epithelial cells that line the cavities of central nervous system (fig. 12.10).

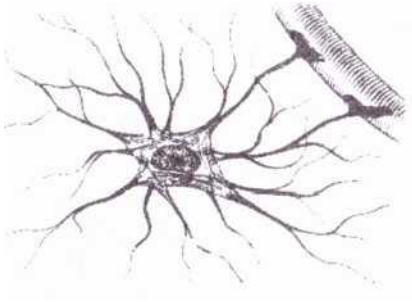


Figure 12.8. Fibrous astrocyte

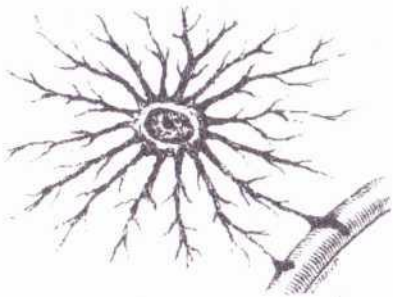


Figure 12.9. Protoplasmic astrocyte

Cilia of their apical surfaces circulate cerebrospinal fluid (CSF) around the central nervous system. Their apical surfaces are also covered with microvilli, which absorb CSF. Ependymal cells are CSF producing cells.

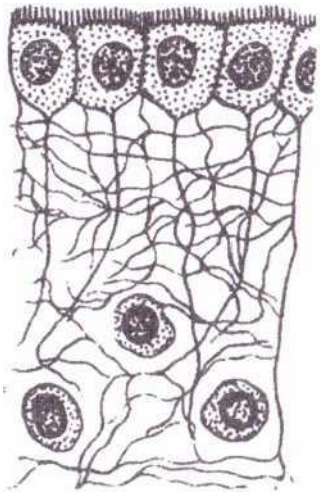


Figure 12.10. Ependymal cells

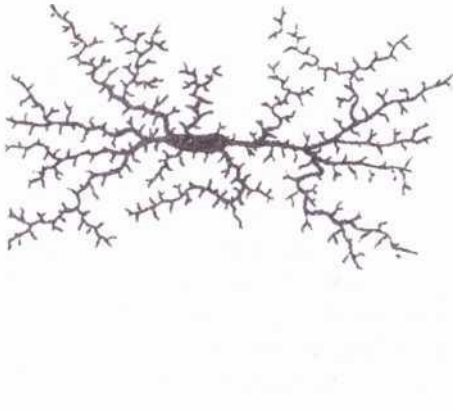


Figure 12.11.

Within the brain's ventricles, a population of modified ependymal cells and capillaries together form a system called the ***choroid plexus,*** which produces the CSF.

2. **Microglia**

Microglia is small elongated cells with short irregular processes (fig. 12.11). Microglia is phagocytic cells that represent the mononuclear phagocytic system in nervous tissue, are derived from precursor cells in the bone marrow. They are involved with inflammation and repair in the adult CNS.

Microglia acts as antigen-presenting cells; they secrete a number of immunoregulatory cytokines.

0 Nerve fibers

Nerve fibers consist of axons (***axial cylinders)*** enveloped by a special ***sheath*** derived from glial cells.

Classification of nerve fibers is based on the structure of their sheath.

Distinguish 2 types of the nerve fibers:

/. ***unmyelinated***,

2. myelinated.

Unmyelinated nerve fibers

Location: at the adult mainly in composition of autonomic nervous system. They are characterized ***by low speed*** of carrying out of nervous impulses (0.5-2 m/s).

Unmyelinated nerve fibers are formed by dipping the axial cylinder (axon) in cytoplasm of the Schwann cell (fig. 12.12).

Thus the plasmolemma of Schwann cell invaginates, surrounding an axon, and forms duplication - ***mesaxon.*** Quite often in cytoplasm of one Schwann cell there can be till 10-20 axial cylinders. Such fiber reminds an electrical cable and consequently refers to as a ***fiber of cable type.***

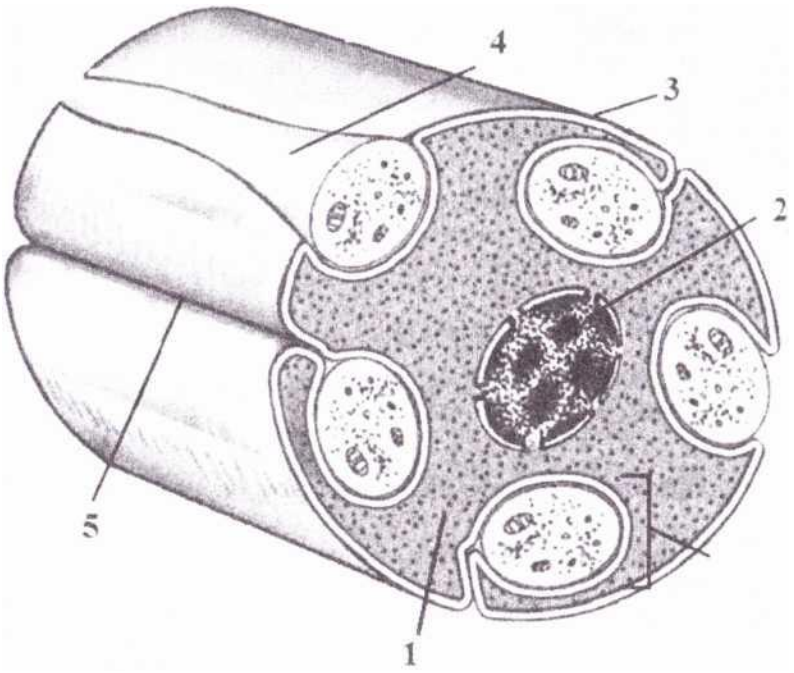


Figure 12.12. Schematic diagram of the unmyelinated nerve fiber. 1- cytoplasm of Schwann cell, 2 - nucleus of Schwann cell, 3 — cytolemma of Schwann cell, 4 — axial cylinders (axons), 5 — niesaxon

Myelinated nerve fibers

Location: at CNS and PNS and are characterized ***by high speed*** of carrying out of nervous impulses (5-120 m/s).

In myelinated nerve fiber the axial cylinder is surrounded with a ***myelin sheath*** around of which the thin layer including cytoplasm and a nucleus of Schwann cell - ***neurolemma*** (fig. 12.13).

The process of formation of myelin begins with the invagination of a single axon into a Schwann cell (fig. 12.14); a mesaxon is then formed. As myelination proceeds, the mesaxon rotates around the axon thereby enveloping the axon in concentric layers of Schwann cel! cytoplasm and plasma membrane. Thus ***myelin sheath*** is concentric layers of Schwann cell membrane.

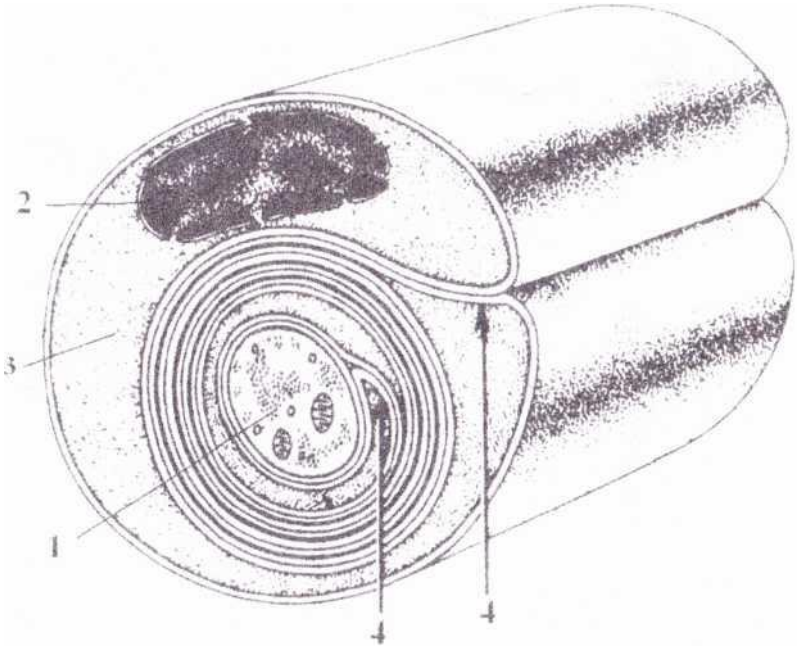


Figure 12.13. Schematic diagram of the myelinated nerve fiber. Cross section. 1 - axial cylinder (axon), 2 - nucleus of Schwann cell, 3 - cytoplasm of Schwann cell, 4 - mesaxon

An axon comes in contact with many Schwann cells along its length. Each Schwann cell forms myelin sheath over a short segment of the axon.

Between the Schwann cells there are short intervals at which the axon is not covering by a myelin. These points are ***nodes of Ranvier*** (fig. 12.15).

The distance between two nodes is called an ***internode*** and consists of one Schwann cell.

The action potential travels by jumping from node to node. This mode ol conduction is called ***salutatory conduction.***

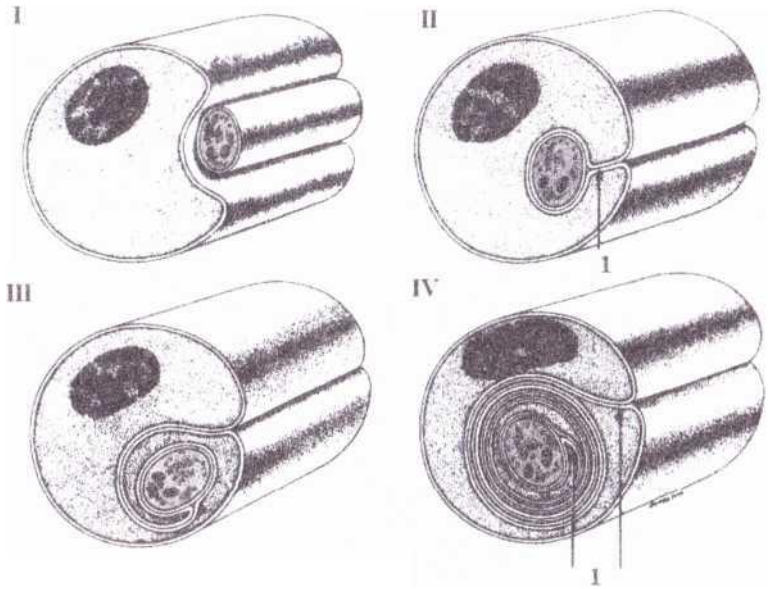


Figure 12.14, Consecutive phases of myelin formation in nerve fibers. I - invagination of a single axon into Schwann cell, **II** - formation of a mesaxon, **III** - rotation of the mesaxon around the axon, **IV** - enveloping the axon in concentric layers of Schwann cell cytoplasm and plasma membrane, 1 - mesaxon

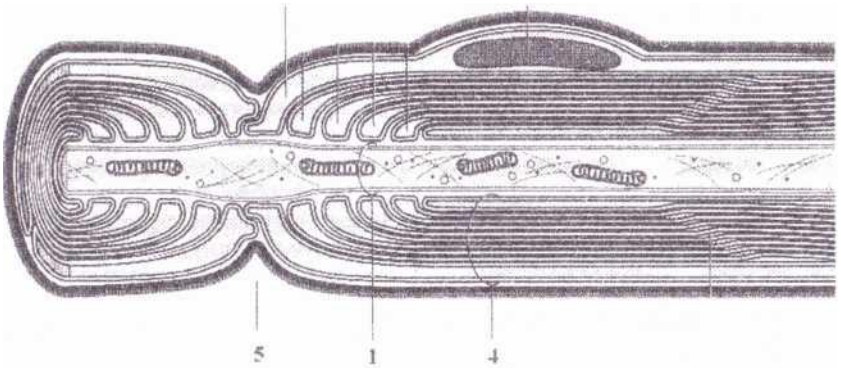


Figure 12.15. Myelinate nerve fiber. Longitudinal section. 1 - axial cylinder (axon), 2 - nucleus of Schwann cell, 3 - cytoplasm of Schwann cell, 4 - myelin sheath, 5 - node of Ranvier

0 Nerve endings

Nerves end either on some other neurons, or in some peripheral organs (skin, joint capsules, muscles and glands).

Nerve endings (terminals) are subdivided on three types:

> transneuronal contacts (synapses) provide a functional connection between neurons;

> receptor (sensory) endings accept stimuli from an external and an internal environment are on dendrites.

> motor (efferent) endings transfer signals from nervous system to organs (muscles, glands), are on axons.

Synapses

Synapse is the junction between neurons, where the nerve impulse passes from neurons to the next.

Synapses may be classified morphologically as

- axodendritic, occurring between axon and dendrites;
- axosomatic, occurring between axon and the cell body;
- axoaxonic, occurring between axon and axon;
- dendrodendritic, occurring between dendrite and dendrite.

Synapses also may be classified as ® ***chemical,*** in which conduction of impulses is achieved by the release of chemical substances (neurotransmitters);

- ***electrical,*** which contain gap junctions that permit movement of ions between cells and consequently permit the direct spread of electrical current from one cell to another.

Chemical synapse (fig. 12.16) consists of:

> axon terminal ***(presynaptic terminal***) that delivers the impulse;

> part of another cell where a new impulse is generated ***(postsynaptic terminal***);

> thin intercellular space (***synaptic cleft).***

Most synapses transmit the impulse by releasing ***neurotransmitters.*** These are chemical substances that induce the transfer of the nervous impulse to other neurons. Synapses which transmit nerve impulses through neurotransmitters are ***chemical synapses.***

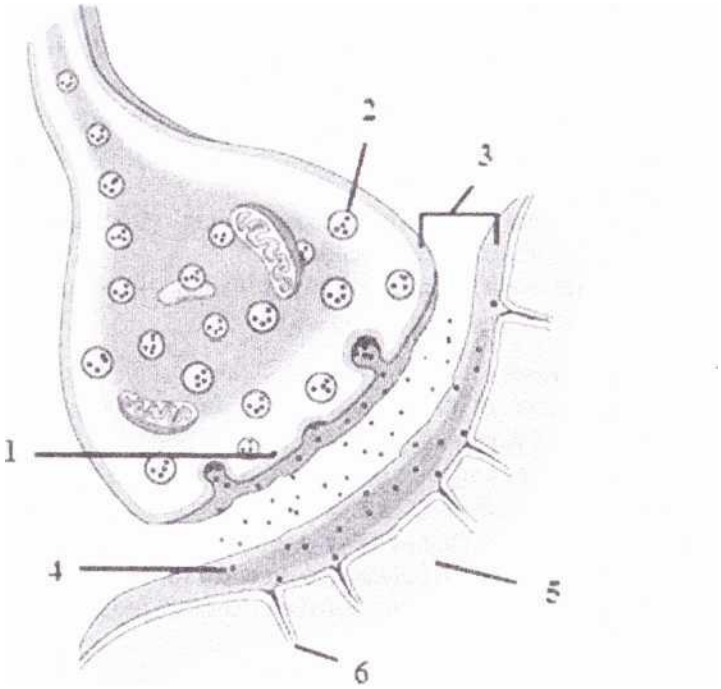


Figure 12.16. Schematic diagram of synapse. 1 - presynaptic membrane of axon. 2 - synaptic vesicles, 3 - synaptic cleft, 4 - neurotransmitter, 5 - postsynaptic terminal, 6 - receptors

Presynaptic terminal contains ***synaptic vesicles.*** Synaptic vesicles contain one of the neurotransmitter substances - acetylcholine, norepinephrine, dopamine, serotonin, glycine and gamma-amino-butyric acid (GABA).

Postsynaptic terminal contains postsynaptic web with ***receptors.***

Histophysiology of synapse

1. Depolarization of presynaptic membrane.
2. Opening of calcium channels.

3. Exocytosis of synaptic vesicles with neurotransmitter.
4. Release of neurotransmitter into synaptic cleft.
5. Reaction of neurotransmitter with receptors of postsynaptic region.
6. Depolarization of postsynaptic membrane.

Receptor (sensory) endings (terminations)

Receptor (sensory) nerve terminations accept signals from an external environment ***(exteroceptors)*** and an internals ***(interoceptors).***

Functional classification of sensory nerve endings is based on nature of stimuli:
mechanoreceptors,
chemoreceptors,
thermoreceptors,
pain receptors (nociceptors).

Morphological classification of sensory nerve endings is based on features of their structural constitution:

1 ***free,***
2. nonfree
- ***2.1 nonencapsulated,***
- ***2.2 encapsulated***

Free nerve endings

Free nerve endings are devoid of myelin and Schwann sheaths (fig. 12.17).
They receive pain, tactile and temperature sensations.

Distribution, epithelium and connective tissue of skin.

Nonfree nerve endings

Nonfree nonencapsulated nerve endings consist of dendrite branchings surrounded with Schwann cells.

Distribution. connective tissue of a skin (derma), lamina propria of

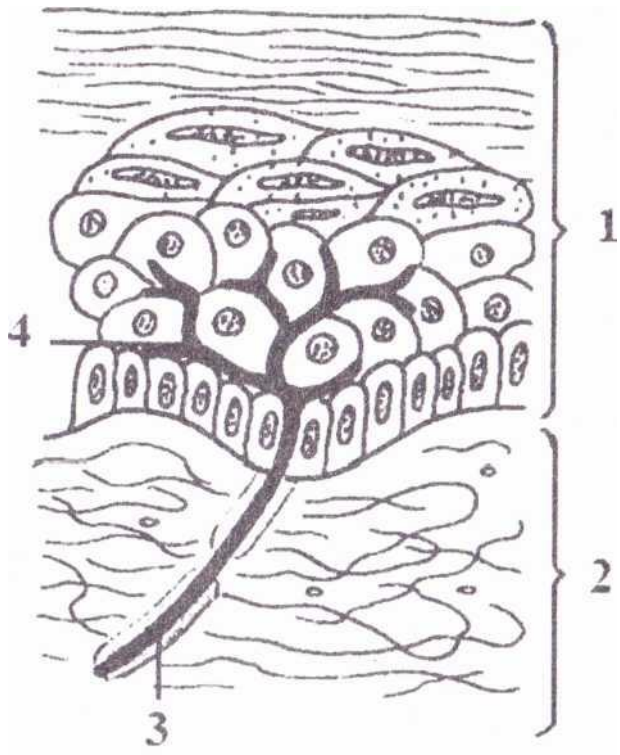


Figure 12.17. Schematic diagram of the free nerve ending. 1 — epithelium, 2 — connective tissue, 3 — myelin nerve fiber, 4 — tree nerve endings (from ***fO.*** *M.Acpanacbee, HA.JOpuna* ***u dp.,*** 1999)

The various types of nonfree encapsulated nerve endings are:

1) ***Pacinian corpuscle*** contains capsule consisting of concentrically arranged lamellae like the leaves of an onion (fig. 12.18). It receives pressure and vibration sensations.

Distribution: connective tissue of internal organs, skin.

2) ***Meissner's corpuscle*** is touch receptor, has elliptic shape, contains the spiral terminals of afferent axons, surrounding by flattened Schwann cells which form several irregular lamellae and thin capsule (fig. 12.19).

Distribution: papillary layer of dermis.

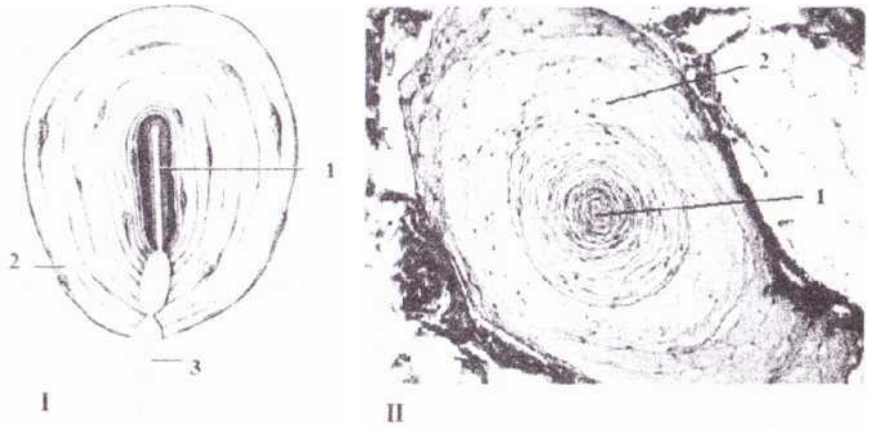


Figure 12.18. Pacinian corpuscle. 1 — schematic diagram, 11 - photomicrograph, 1 — single nerve fiber, 2 - concentrically arranged lamellae of capsule, 3 — myelin sheath

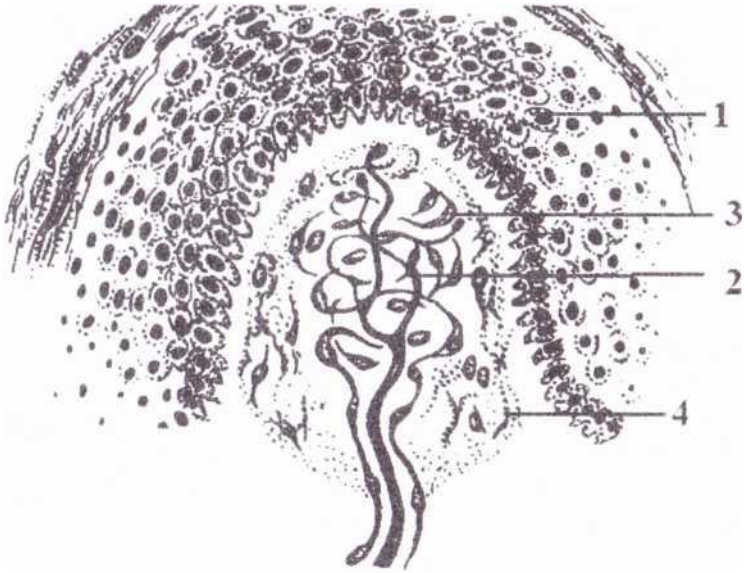


Figure 12.19. Meissner's corpuscle. 1 — dermal papilla, 2 — spiral terminals of afferent axon, 3 — tortuous Schwann cells, 4 — capsule

3) ***Ruffini corpuscles*** (fig. 12.20-1) are elongated, spindle-shaped capsular specializations are located deep in the skin, as well as in ligaments and tendons. The long axis of the corpuscle is usually oriented parallel to the stretch lines in skin; thus, Ruffini corpuscles are particularly sensitive to the cutaneous stretching produced by digit or limb movements. They account for about 20% of the receptors in the human hand, are sensitive to skin stretch, and contribute to the kinesthetic sense of and control of finger position and movement.

4) ***End-bulb of Krause*** (fig. 12.20-11) has round shape, contains glial cells and capsule. It receives cold sensation.
Distribution: papillary layer of dermis, lamina propria of mucosa of oral cavity.

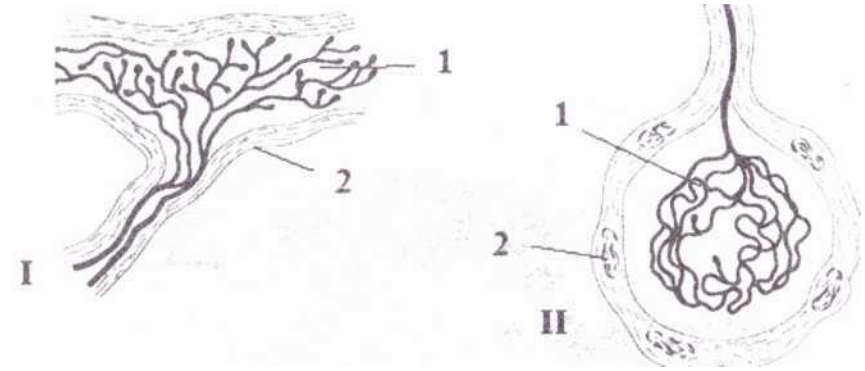


Figure 12.20. Nonfree encapsulated nerve endings. I - Ruffini corpuscle, II - end-bulb of Krause; 1 - terminal branches of afferent axon, 2 - capsule

5) ***Neuromuscular spindles*** (fig. 12.21) are sensory end organs in skeletal muscle. They consist of 6-14 modified skeletal muscle fibres called ***intraf usal fibres*** which are of two types - ***nuclear bag*** and ***nuclear chain*** fibres; they are supplied both by motor and sensory fibres. This complex of muscle and nerve is enclosed in a connective tissue capsule and is known as muscle spindle; they give information about the length of muscle.

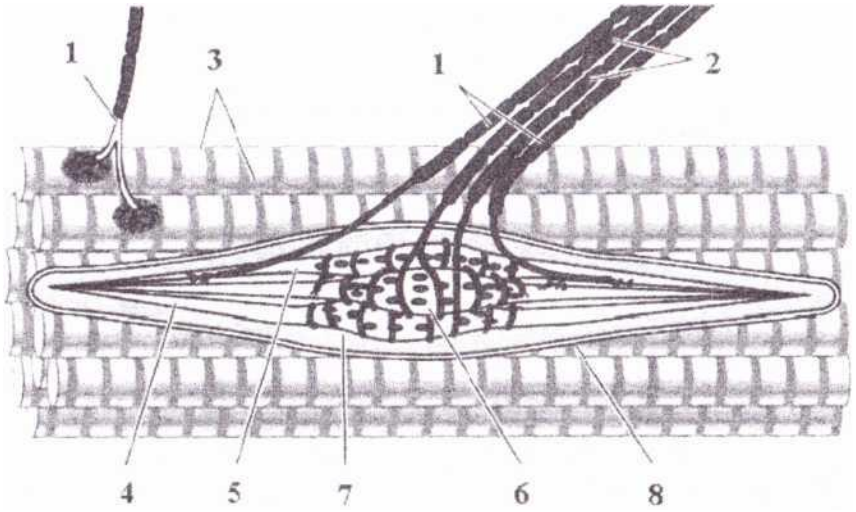


Figure 12.21. **Neuromuscular spindle.** 1 - axon of motor neurons, 2 - afferent axons, 3 - extrafusal muscle fibers, 4 - intrafusal muscle fibers, 5 - nuclear chain fibres, 6 - nuclear bag fibers, 7 - subcapsular space, 8 - capsule surrounding spindle

6) ***Neurotendinous organ of Golgi*** is spindle structure locating in region of connection of skeletal muscles fibers with collagen fibers of tendons. Exaltation of receptors arises at a distension of a tendon during a muscular contraction.

Motor (efferent) endings

The various types of motor (efferent) endings are:

1) ***Motor end plate*** (in skeletal muscle) (fig. 12.22) is the junctional area between the motor nerve terminal and the skeletal muscle. It consists of two parts, a nervous and a muscular, separated by a cleft; the relationship is a close apposition of axolemma and sarcolemma.

Each muscle fiber receives one motor end plate, but each axon by virtue of its branching supplies several muscle fibers. A motor neuron together with all the muscle fibers which it innervates is called a ***motor unit.***

2) In cardiac and smooth muscles, the nonmyelinated fibers end by one or more terminal knobs on the plasma membrane, whereas in gland cells they end among the epithelial cells.

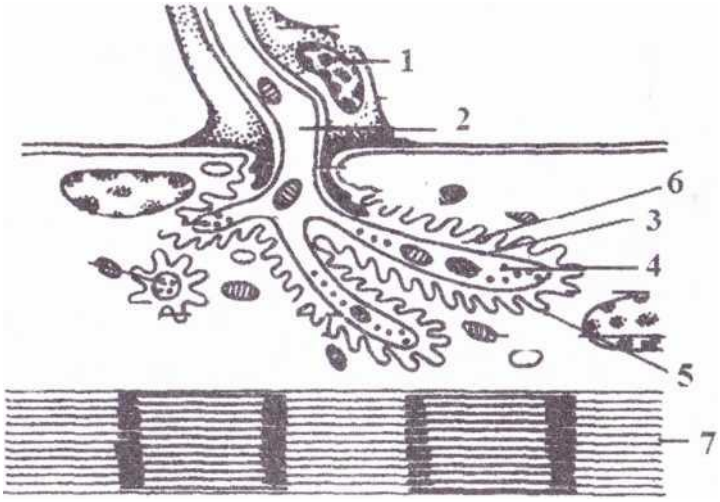


Figure 12.22. Schematic diagram of the motor end plate. 1 - Schwann cell, 2 - axon. 3 - presynaptic membrane, 4 - presynaptic vesicles, 5 - junctional folds of muscle cell, 6 - synaptic cleft, 7 - myofibril (from *[O.M.Atpanacbee, H A.IOpma u dp.*, 1999)

0 Clinical correlations

The ***motor neurone diseases*** are a group of neurological disorders that selectively affect motor neurones, the cells that control voluntary' muscle activity including speaking, walking, breathing, swallowing and general movement of the body. Symptoms include progressive weakness, muscle wasting, and muscle fasciculation, spasticity or stiffness in the arms and legs, and overactive tendon reflexes.

Parkinson's disease is a slowly progressive neurologic disorder caused by the loss of dopamine-secreting cells in the substantia nigra and basal ganglia of the brain. Symptoms include motor dysfunction (resting tremor in the limbs, especially of the hands; increased tone in all muscles; slowness of movements; loss of postural reflexes); autonomic dysfunction, cognitive and neurobehavioral problems, and sensory and sleep difficulties.

NERVOUS SYSTEM I. PERIPHERAL NERVE. GANGLIA. SPINAL CORD. CEREBELLUM 0 Overview of the nervous system

The nervous system is the most complex in the human body and is formed by a network of more than 100 million nerve cells, assisted by the glial cells.

Functions of the nervous system

> integration (consolidation of parts of an organism in a single whole);
> regulation and maintenance of homeostasis;
> coordination of function of various organs and tissues;
> interaction of an organism with our environment, both external and internal;
> mental activity including thought, learning, and memory.

Subdivisions of the nervous system

Anatomically nervous system is divided into:

> ***central nervous system (CNS)*** consisting of the brain and the spinal cord;
> ***peripheral nervous system (PNS)*** composed of nerve fibers, nerve ganglia, and nerve terminations.

Physiologically nervous system is divided into:

> ***somatic nervous system*** which controls mainly functions of an autokinesia;
> ***autonomic nervous system*** which controls activity of the smooth muscles of the viscera, blood vessels, cardiac muscle of the heart, and secretory cells of the exocrine and endocrine glands, thus helping to maintain homeostasis.

The autonomic nervous system is subdivided into two functionally different divisions:

1. The ***sympathetic nervous system*** responds to impending danger, and is responsible for the increase of one's heartbeat and blood pressure,

among other physiological changes, along with the sense of excitement one feels due to the increase of adrenaline in the system.

2. T he ***parasympathetic nervous system*** is evident when a person is resting and feels relaxed, and is responsible for such things as the constriction of the pupil, the slowing of the heart, the dilation of the blood vessels, and the stimulation of the digestive and genitourinary systems.

0 Development of the nervous system

Nervous system develops from ***neural tube*** and ***neural crests.***

Cranial part of the neural tube gives arise to the brain.

Trunk part of the neural tube gives arise to the spinal cord, ***Neural crests*** give arise to the spinal sensory ganglia, autonomic ganglia, and chromatin tissue of the organism.

0 Organization of the peripheral nervous system

Peripheral nerve

In the peripheral nervous system the nerve fibers are grouped in bundles to form the ***nerves.***

The individual nerve fibers are held together by connective tissue organized into three components (fig. 13.1, 13.2):

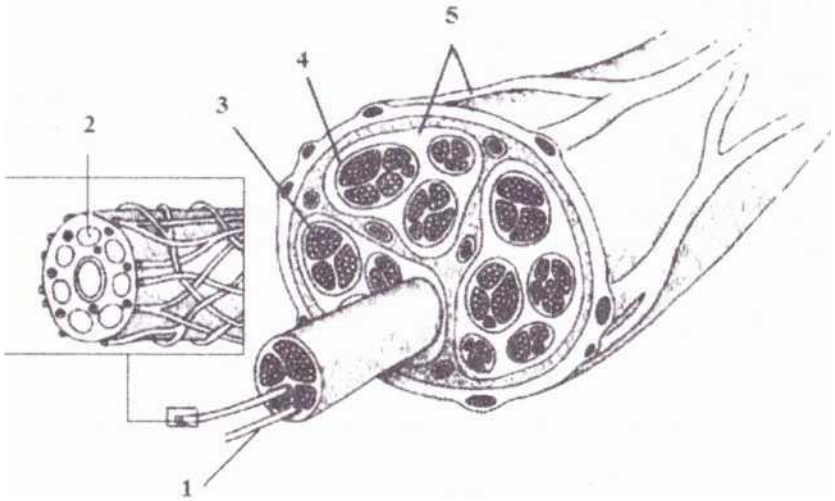


Figure 13.1. Schematic diagram of peripheral nerve. 1 - nerve fibers, 2 - axon, 3 — endoneurium, 4 — perineurium, 5 - epineurium

> ***endoneurium*** is a thin layer of loose connective tissue, surrounding each individual nerve fiber;
> ***perineurium*** surrounds each bundle of nerve fibers;
> ***epineurium*** includes the dense irregular connective tissue that surrounds a peripheral nerve.

The nerves establish communication between brain and spinal cord centers and the sense organs and effectors (muscles, glands, etc.).

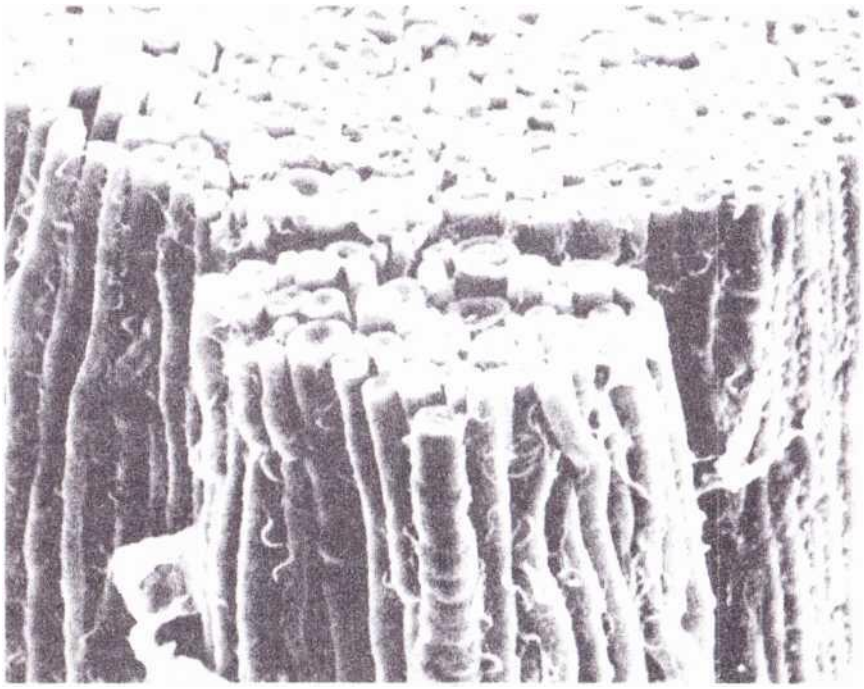


Figure 13.2. Electron micrograph of peripheral nerve.

Ganglia

The ***ganglia*** are aggregations of cell bodies of neurons located outside the CNS. There are two types of ganglia - ***sensory*** and ***autonomic.***

Sensory (dorsal root, spinal) ganglia

Sensory ganglia lie along the vertebral column by the spine (fig. 13.3), contain pseudounipolar cell bodies of sensory neurons.

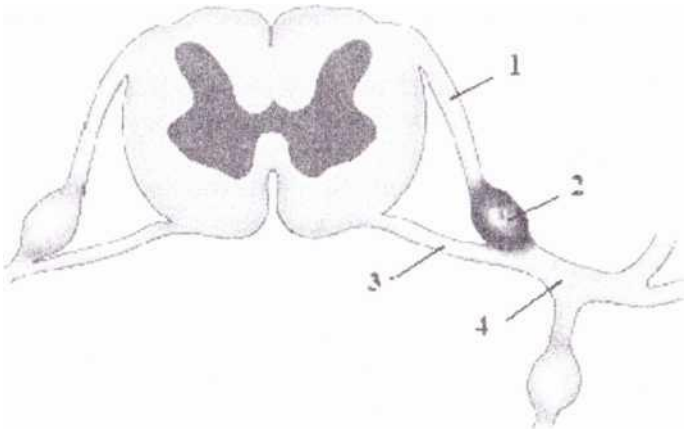


Figure 13.3. Location of sensory (dorsal root) ganglia. 1 — posterior root, 2 — sensory ganglion, 3 — anterior root, 4 - spinal nerve

Sensory ganglia of the spinal nerves are called ***dorsal root ganglia*** or ***spinal ganglia.*** Ganglia associated with cranial nerves are called ***cranial ganglia.***

Each ***spinal ganglion*** has a thin connective tissue capsule within which the nerve cells are peripherally placed (fig. 13.4).

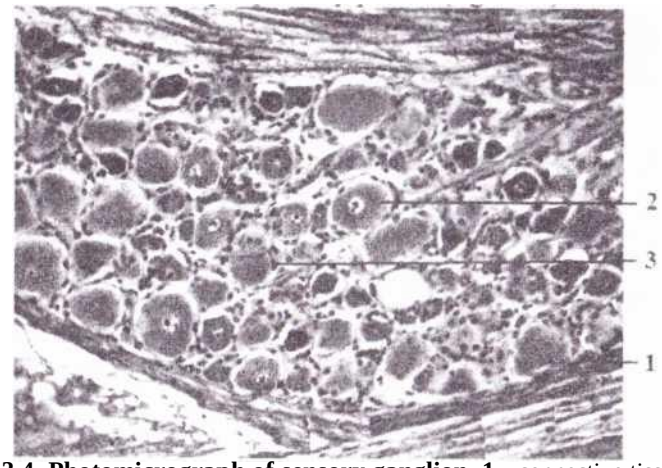


Figure 13.4. Photomicrograph of sensory ganglion. 1 - connective tissue capsule, 2 - sensory neurons, 3 - glial satellite cells

Each ganglion cell is surrounded by a single layer of flattened glial satellite cells.

0 Organization of the central nervous system

The ***central nervous system*** consists of spinal cord, cerebellum, and cerebrum.

The section of CNS shows regions of white ***(white matter)*** and grey (***grey matter).***

The ***white matter*** contains myelinated axons and the myelin- producing oligodendrocytes.

The ***grey matter*** consists of neuronal cell bodies, dendrites, the initial unmyelinated portions of axons and glial cells.

The grey matter is prevalent at the surface of the cerebrum and cerebellum, forming the ***cortex.*** White matter is present in more central regions.

Aggregates of neuronal cel! bodies forming islands of grey matter are called ***nuclei.***

0 Spinal cord

In ***spinal cord*** the grey matter is central and the white matter is peripheral. The grey matter has the shape of an H (fig. 13.5).

Grey matter

The ***gray matter*** is subdivided into ***horns.***

Anterior (ventral) horns are short, broad, directed forwards. Anterior horns contain motor neurons whose axons make up the ventral roots of the spinal nerves.

Posterior (dorsal) horns are narrow, elongated directed backwards. They receive sensory fibers from neurons in the spinal ganglia (dorsal roots) and contain cell bodies of small multipolar interneurons.

Lateral horns (in T_2 to L_t segments) contain small motor cells and give rise to preganglionic sympathetic fibers.

Spinal cord cytoarchitectonic

Depending on topography of axons spinal cord neurones are divided on:

1) ***radicular neurones,*** which axons form ventral roots;

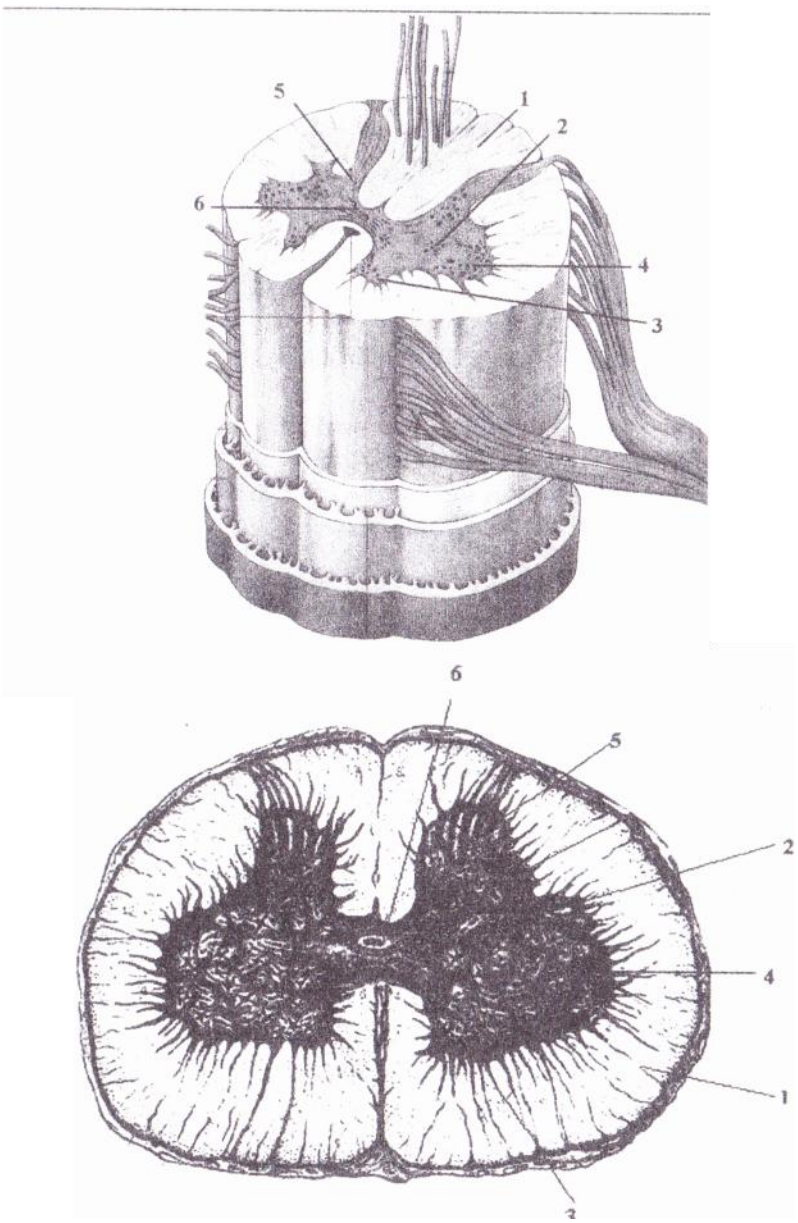


Figure 13.5. Spina! cord. 1 - white matter, 2 - grey matter, 3 - anterior horn, 4 - lateral horn, 5 - posterior horn, 6 - centra! canal

2) internal neurones, which processes come to an end within of grey matter of the spinal cord;

3) fascicular neurones, which processes form bundles of nerve fibers in white matter of the spinal cord.

The ***posterior horns*** contain some ***nuclei,*** formed by small multipolar interneurons. These neurons receive sensory' fibers from pseudounipolar neurons of the spinal ganglia (dorsal roots) and also fibers of descending paths from centers lying above (supraspinal centers). Posterior horns consist of dorsomarginal layer, substantia gelatinosa, nucleus proprius, and dorsal nucleus of Clarke.

The ***anterior horns*** contain the largest (100-150 pm) ***multipolar motoneurons.*** Motoneurons are aggregated in nuclei (anterolateral, anteromedial, posterolateral, retroposterolateral, and rosteromedial, central). Its axons form ventral roots.

The medial group of motoneurons is developed for spinal cord and innervates the muscles of a trunk.

The lateral group is in the region of cervical and lumbar enlargements and innervates the muscles of limbs.

The ***lateral horns*** are well expressed at the level of thoracic and sacral segments of spinal cord; they contain sympathetic and parasympathetic nuclei of autonomic nervous system.

Glial cells of the spina! cord

The central canal of spinal cord is covered by ***ependymal cells.***

Fibrous astrocytes are located in the white matter; ***protoplasmic astrocytes*** are found in the grey matter.

Oligodendrocytes form the myelin sheathes of nerve fibers.

Microglia are phagocytic cells, are found in the white and grey matter.

White matter

White matter consists of bundles of myelinated nerve fibers forming ascending and descending paths. Each half of white matter is divided into ***anterior, lateral*** and ***posterior*** regions ***[f uniculi***).

0 Reflex arc

Reflex arcs underlie of activity of nervous system. In reflex arcs the neurones are connected with each other by synapses, form three parts:

> ***receptor (afferent),***
> ***efferent*** and posed between them
> ***associative*** which in the elementary variant of an arc can be absent.

Somatic reflex arc (fig. 13.6)

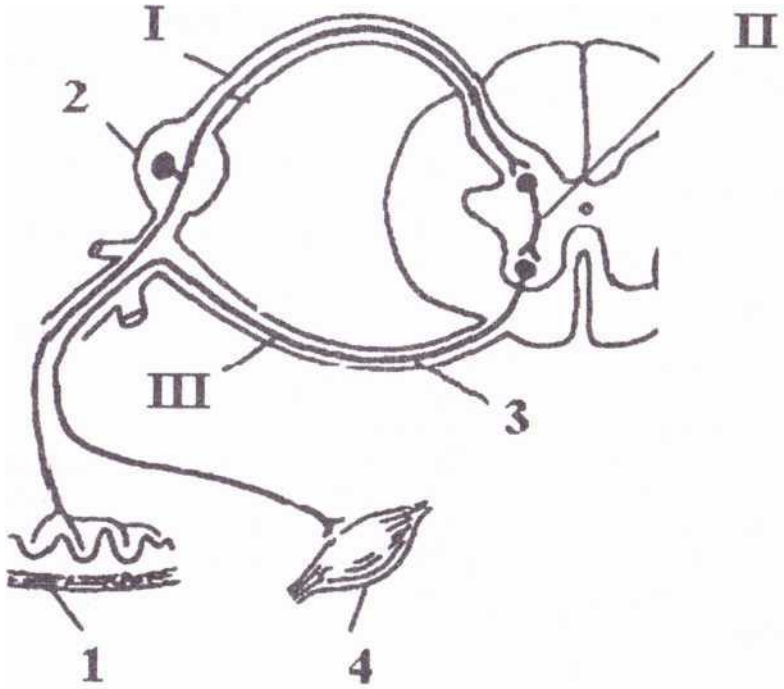


Figure 13.6. Schematic diagram of the somatic reflex arc. I - receptor part, ! - nerve terminations in a peripheral organ, 2 - spinal ganglion, **II** - associative part, III- effector part, 3 - axon of motoneuron, 4 - skeletal muscle

The ***receptor part*** is formed by ***afferent pseudo unipolar neurons*** which cell bodies are in ***spinal ganglia.*** Dendrites of these cells form nerve terminations in a skin. Axons enter a spinal cord in composition of ***dorsal roots*** and form synapses on cell bodies and dendrites of interneurons of ***posterior horns*** of its grey matter.

The associative part is submitted ***by multipolar interneurons.*** Their dendrites and cell bodies are in ***posterior horns*** of a spinal cord and axons terminate on cell bodies and dendrites of effector motoneurons of ***anterior horns*** of spinal cord.

The effector part is formed by ***multipolar motoneurons.*** Their bodies and dendrites are in ***anterior horns.*** Their axons leave a spinal cord in composition of ***ventral roots*** and terminate in skeletal muscles.

Cerebellum ***Cerebellum***

consists of:

> surface layer of ***grey matter*** - ***cerebellar cortex*** (fig. 13.7);
> central core of ***white matter*** (arbour vitae);
> cerebellar ***nuclei*** embedded in the white matter.

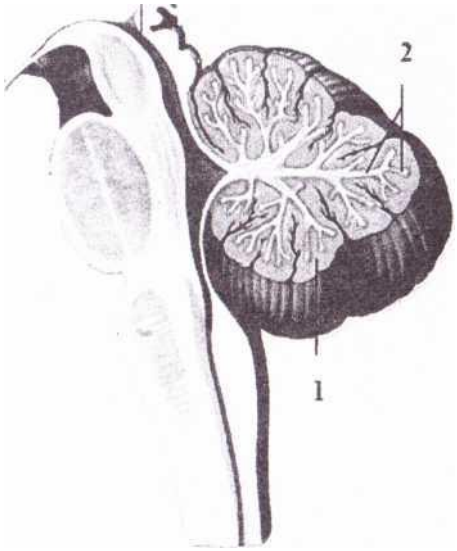


Figure 13.7. Schematic diagram of cerebellum. 1- grey matter, 2 - white matter (arbour vitae)

Cerebellar cortex is responsible for maintaining balance and equilibrium, muscle tone, and coordination of skeletal muscles.

The cerebellar cortex is divided into three layers (fig. 13.8. 13.9):

1. Outer ***molecular layer*** which contains superficially located ***stellate cells***, ***basket cells***, and the dendrites of Purkinje cells and the axons of granule cells but few cell bodies.

2. Middle ***Purkinje cell layer*** which contains a single layer of large, flask-shaped ***Purkinje cells*** (fig. 13.10). Their dendrites project into the molecular layer, and their myelinated axons project into the white matter. Each Purkinje cell receives hundreds of thousands of excitatory and inhibitory synapses that it must integrate to form the proper response. Purkinje neurons have a broad dendritic tree with its width oriented perpendicular to the long axis of the folium. The Purkinje cell is the only cell of the cerebellar cortex that sends information to the outside.

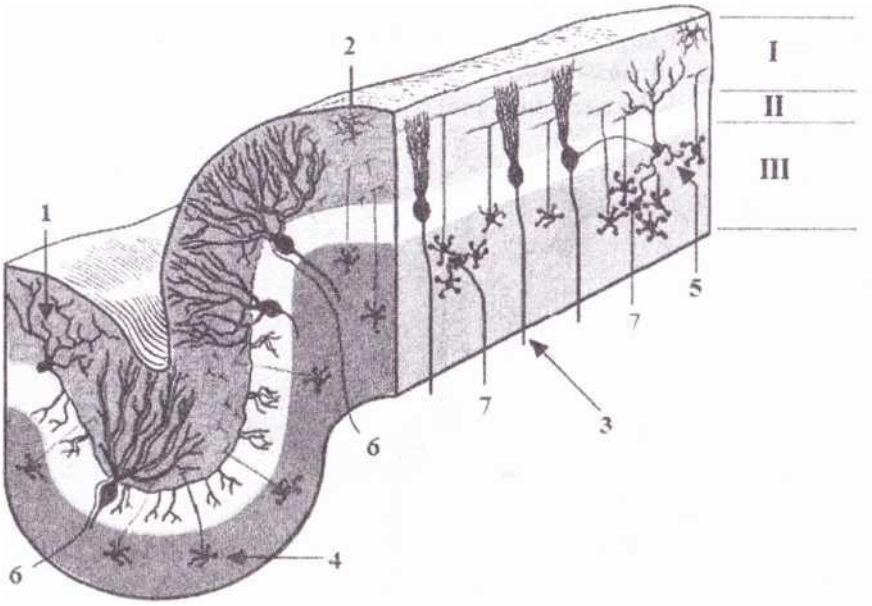


Figure 13.8. Schematic diagram of cerebellar cortex. I - molecular layer: **1** - basket cell, 2 - stellate cell; II - Purkinje cell layer: 3 - Purkinje cell; III - granule cell layer: 4 - granule cell, 5 - Golgi cell; 6 — climbing fiber, 7 - mossy fiber

3. Inner ***granule cell layer*** composed of vast numbers of very small neurons called ***granule cells*** and ***Golgi cells.*** Each granule cell has a few short dendrites within the granule cell layer. Each granule cell axon projects into the molecular layer and bifurcates into parallel fibers which extend parallel to the long axis of each layer.

Climbing fibers and ***mossy*** fibers enter the cerebellar cortex. Axons of Purkinje neurons leave the cerebellar cortex.

Climbing fibers are axons that originate in the inferior olive, ascend through the inferior cerebellar peduncle, and make terminal arborisations that invest the dendritic tree of Purkinje cells.

Mossy fibers are axons from the pontine nuclei that bring information into the cerebellum.

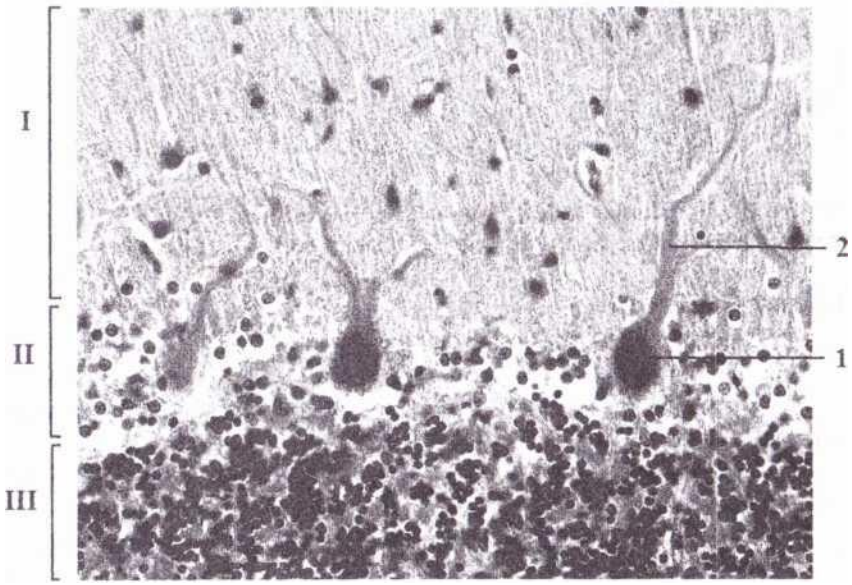


Figure 13.9. Photomicrograph of the cerebellar cortex. I - molecular layer, II - Purkinje cell layer, III - granule cell layer; 1 - Purkinje cell bodies, 2 — Purkinje cell dendrites

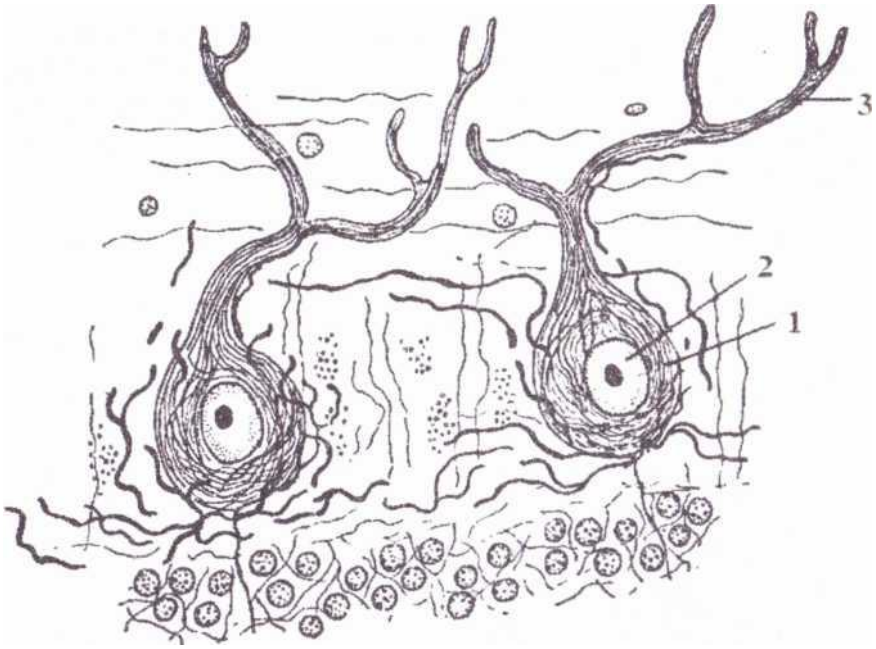


Figure 13.10. Schematic diagram of *Purkinje cells.* 1 - Purkinje cell body, 2 - nucleus of Purkinje cell, 3 - dendrites of Purkinje cell

0 Clinical correlations

Damage to the cerebellum can result in a number of motor defects.

Ataxia, a condition that involves lack of coordination between movements of body parts, is one of these deficits.

Another cerebellar condition is known as ***dysmetria,*** which is the inability to make a movement in the direction or distance that is desired.

Nystagmus, involuntary eye movements, is another dysfunction of the cerebellum. The final main cerebellar deficit is an action or intention tremor.

NERVOUS SYSTEM II. CEREBRAL CORTEX. MENINGES. AUTONOMIC NERVOUS SYSTEM

Cerebral cortex

The cerebral hemispheres consist of a convoluted cortex of grey matter. Central mass of white matter conveys fibers between different parts of the cortex and to and from other parts of CNS.

Cerebral cortex cytoarchitectonic

The neurons of the cerebral cortex are arranged in six layers (fig. 14.1):

I. Molecular layer is most superficial, mainly contains dendrites and axons of neurones originating in other layers of cortex; ***horizontal cells of Cajal.*** Axons of these cells form ***tangential plexus.***

II. External granular layer contains small ***pyramidal cells*** and ***stellate (granular) cells*** and also various axons and dendrites of neurons from deeper layers.

III. External pyramidal layer contains medium-sized ***pyramidal cells***, increasing in size deeper in the layer.

IV Internal granular layer is a thin layer characterized by densely packed ***stellate*** and ***pyramidal celts.***

V. Internal pyramidal (ganglionic) layer contains large ***pyramidal cells,*** and in the motor cortex the ***giant pyramidal neurons of Betz.***

VI. Multiform layer consists of cells of various shapes: numerous small ***pyramidal cells*** and ***cells of Martinotti,*** as well as ***stellate cells*** especially superficially, ***and fusiform cells*** in the deeper part.

Types of cerebral cortex

In the certain areas of a cerebral cortex connected to execution of different functions, development of those or its other layers dominates.

Therefore the cerebral cortex is divided into ***granular*** and ***agranular***

> ***Agranular type*** of cerebral cortex is characterized by the greatest development of III, V and VI layer at weak development of II and IV (granular) layers (***motor centers).***

> ***Granular type*** of cerebral cortex is characterized by weak development of the layers containing pyramidal cells (III, V) at greatest development of granular (II and IV) layers (***sensory centers).***

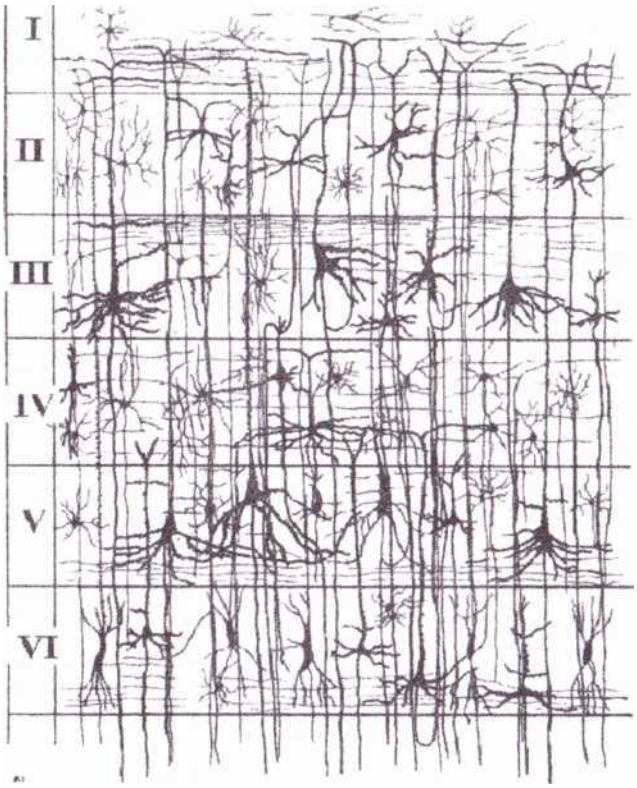


Figure 14.1. Schematic representation of the cerebral cortex. I — molecular layer, II - outer granular layer, III - pyramidal cell layer, IV - Inner granular layer, V - ganglionic layer, VI - multiform cell layer (from ***lO.M/UfxiHacbee,*** *H.AJOpuna u dp.*, 1999)

Modular principle of the cerebral cortex organization ***Modules*** are ***structural and functional units*** of cerebral cortex. They are disposed vertically and have the shape of cylinders in diameter 200-300 microns which are passing upright through all thickness of cortex (fig. 14.2). In cerebral cortex of the person about 2-3 million such columns is present, everyone contains approximately 5000 neurones.

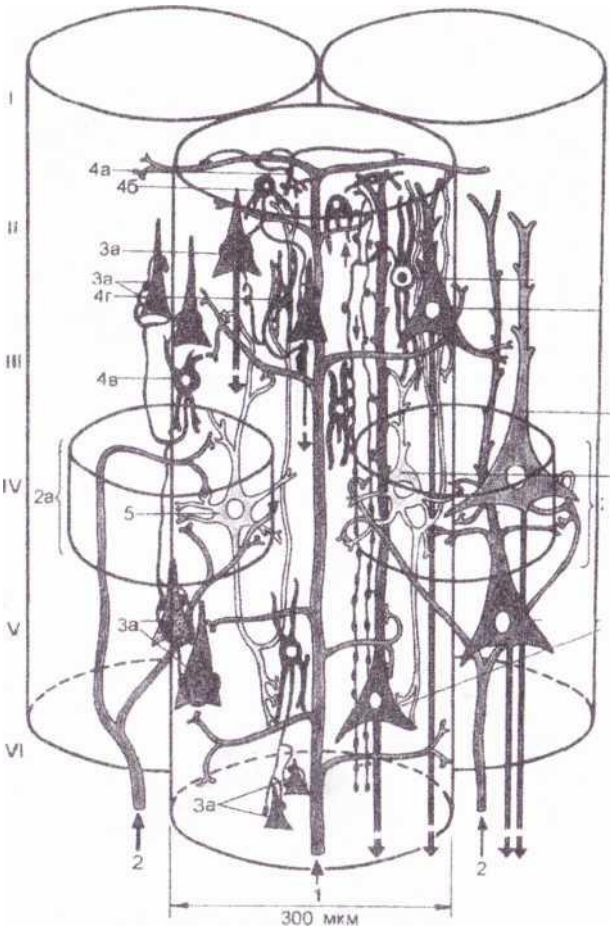


Figure 14,2. Module of the cerebral cortex (from *JO. KA(panacbee, H. A. lOpuHa u dp.*, 1999)

0 Meninges

The central nervous system is protected by the skull and the vertebral column.

Three connective tissue coverings of the brain and spinal cord are the ***meninges.*** The outermost layer of the meninges is

> ***dura mater,***
> intermediate layer is the ***arachnoid,*** and
> innermost or intimate layer of the meninges is the ***pia mater*** (fig. 14.3).

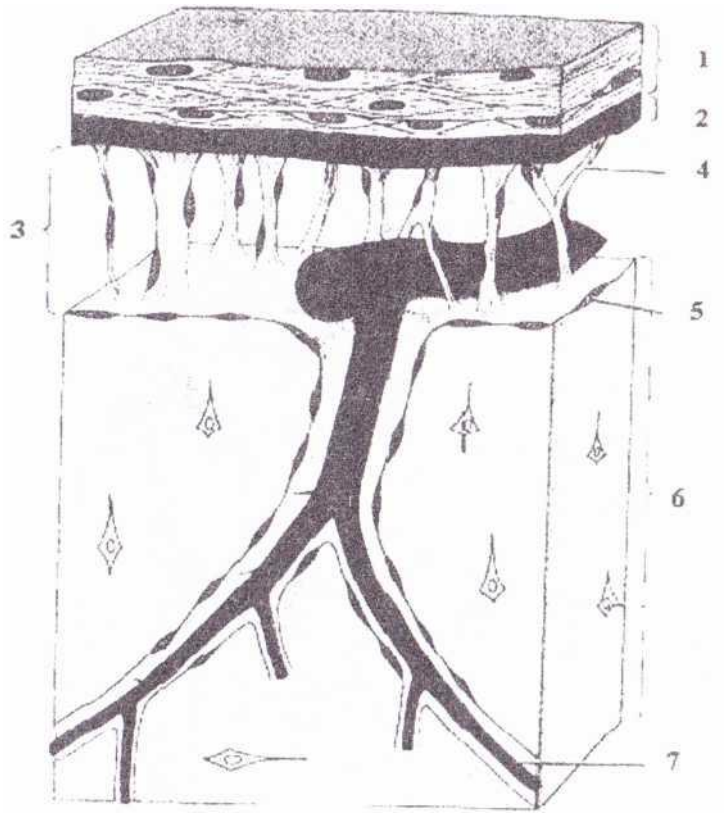


Figure 14.3. Schematic representation of the meninges. 1 — dura mater, 2 — arachnoid mater, 3 — subarachnoid space, 4 — arachnoid trabeculae, 5 — pia mater, 6 - cerebral cortex, 7 - blood vessels (from *Ross, Michael H*, 2003)

Dura mater

The ***dura mater*** is externa! iayer. It consists of dense connective tissue continuous with the periosteum of the skull.

The dura mater that envelops the spina! cord is separated from the periosteum of the vertebrae by the ***epidural space,*** which contains thin veins, loose connective tissue, and adipose tissue.

The dura mater is always separated from the arachnoid by the thin ***subdural space.*** The internal surface of all dura mater, as well as its external surface in the spinal cord, is covered by simple squamous epithelium of mesenchymal origin.

Arachnoid

The ***arachnoid*** is composed of connective tissue devoid of blood vessels.

The arachnoid has two components:

> layer in contact with the dura mater, and
> system of trabeculae connecting the layer with the pia mater.

The cavities between the ***trabeculae*** form the ***subarachnoid space,*** which is filled with cerebrospinal fluid and is completely separated from the ***subdural space.*** This space forms a hydraulic cushion that protects the central nervous system from trauma. The ***subarachnoid space*** communicates with the ventricles of the brain. There are large blood vessels in this space which branches supply a brain

Pia mater

The ***pia mater*** is a loose connective tissue containing numerous blood vessels. Although it is located quite close to the nerve tissue, it is not in contact with nerve cells or fibers. Between the pia mater and the neural elements is a thin layer of neuroglial processes, adhering firmly to the pia mater. It forms a physical barrier that separates the CNS from the cerebrospinal fluid.

Blood-brain barrier

Nowhere in the body is there more need for homeostasis than in the brain. The mechanism for maintaining this barrier function lies in the capillary' network supplying blood to the brain. Ion concentration levels in plasma may fluctuate abruptly. The blood- brain barrier protects the

brain against surging fluctuations in ion concentrations. It maintains homeostasis by restricting the entrances of potentially harmful chemicals from the blood, and by allowing the entrance of essential nutrients.

The concept of the blood-brain barrier was first introduced by Paul Ehrlich. He found that intravenous injection of dyes into the bloodstream stained all the tissues in most organs except the brain.

The ***blood-brain barrier*** consists of (fig. 14.4):

1. ***Endothelial cells of the capillaries*** connected with each other by tight junctions represent the main structural component of barrier.
2. ***Basal lamina*** of the endothelial cells of the capillaries.
3. ***Perivascular feet of astrocytes***, which surround by the blood capillaries.

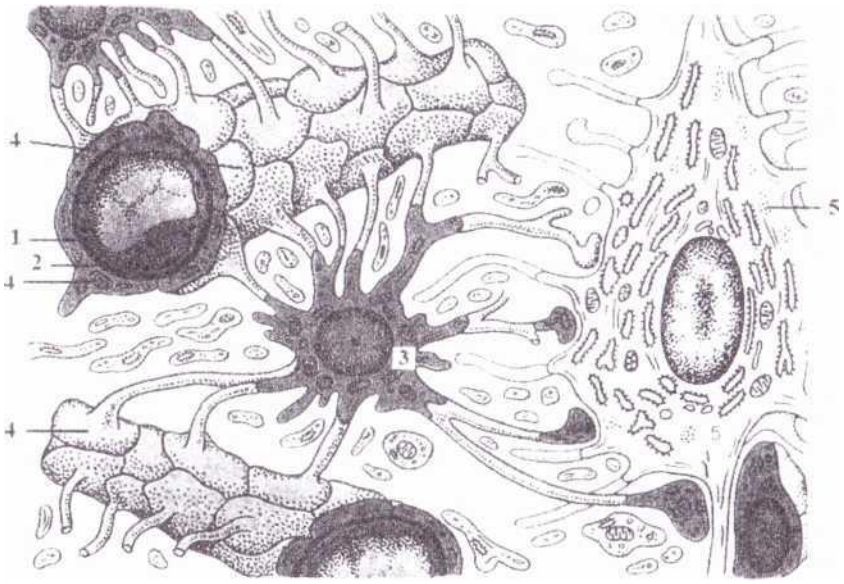


Figure 14.4. Schematic diagram of the blood-brain barrier. 1 - endothelial cells of blood capillary, 2 - basal lamina of the endothelial cells, 3 - cell body of the astrocyte, 4 — perivascular feet of astrocytes. 5 — neuron (from *{O.M.AcpciHacbea, H.A.IOpima u dp*1999)

As a result, only certain materials are allowed to pass from blood vessels to the brain. Substances such as O_2, glucose, H_20, CO_2, essential amino aids, and most lipid-soluble substances enter the brain readily. Other substances, such as creatine and urea (wastes transported in the blood), most ions (Na^+, K^+, CF), proteins, and certain toxins either have limited access or are totally blocked from entering the brain.

Unfortunately, most antibiotic drugs are equally blocked from entering, while other substances such as caffeine, alcohol, nicotine, and heroin readily enter the brain (because of their lipid solubility).

E3 Autonomic nervous **system**

The ***autonomic nervous system*** is related to the control of smooth muscle, the secretion of some glands, the modulation of cardiac rhythm, and to maintain a constant internal environment (homeostasis).

The autonomic nervous system is composed of two parts that differ both anatomically and functionally: the ***sympathetic system*** and the ***parasympathetic system.***

The ***autonomic reflex arc*** consists of such components (fig. 14.5):

I. ***Receptor part,*** as well as in a somatic reflex arc, is formed by ***afferent pseudounipolar neurons.*** Their cell bodies settle down in ***spinal ganglia;*** however dendrites of these cells form nerve terminations in the internal organs, vessels and glands.

Their axons enter a spinal cord in composition of ***dorsal roots*** and form synapses on cell bodies and dendrites of interneurons of ***lateral horns*** of gray matter.

II. ***Associative part*** is submitted ***multipolar interneuron*** Their dendrites and cell bodies are in ***lateral horns*** of a spinal cord. Axons ***(preganglionic fibers)*** leave a spinal cord in composition of ***ventral roots*** and terminate on dendrites and cell bodies of effector neurones of ***autonomic ganglia.***

III. ***Effector part*** is formed by ***multipolar neurons*** Their cell bodies are in ***autonomic ganglia,*** and axons ***(postganglionic fibers)*** terminate in the smooth muscles, glands, and heart.

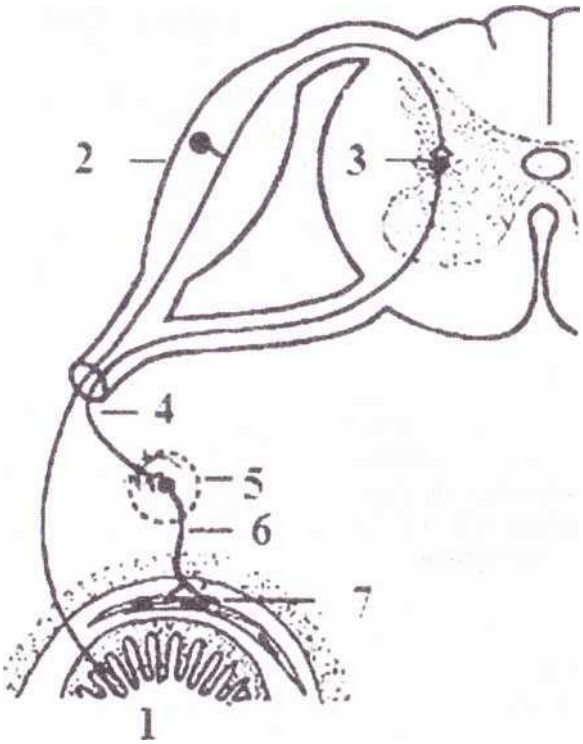


Figure 14.5. Schematic representation of the autonomic reflex arc. 1 - sensory nerve ending, 2 - spinal ganglion, 3 - lateral horns of spinal cord, 4 - preganglionic fibers, 5 — autonomic ganglion, 6 — postganglionic fibers, 7- effector nerve ending

Sympathetic system (fig. 14.6)

T he nuclei of the ***sympathetic system*** are in the thoracic and lumbar segments (Ti - L|) of the spinal cord. Therefore, the sympathetic system is also called the ***thoracolumbar division*** of the autonomic nervous system.

The axons of these neurons - ***preganglionic fibers*** - leave the central nervous system by way of the ventral roots to join the spinal nerve. After a short distance, the fibers leave the peripheral nerve, via 250

white rami communicates, to enter one of the ***sympathetic chain ganglia***, adjacent to the spinal cord, or the ***collateral ganglia***, along the abdominal aorta in the abdomen.

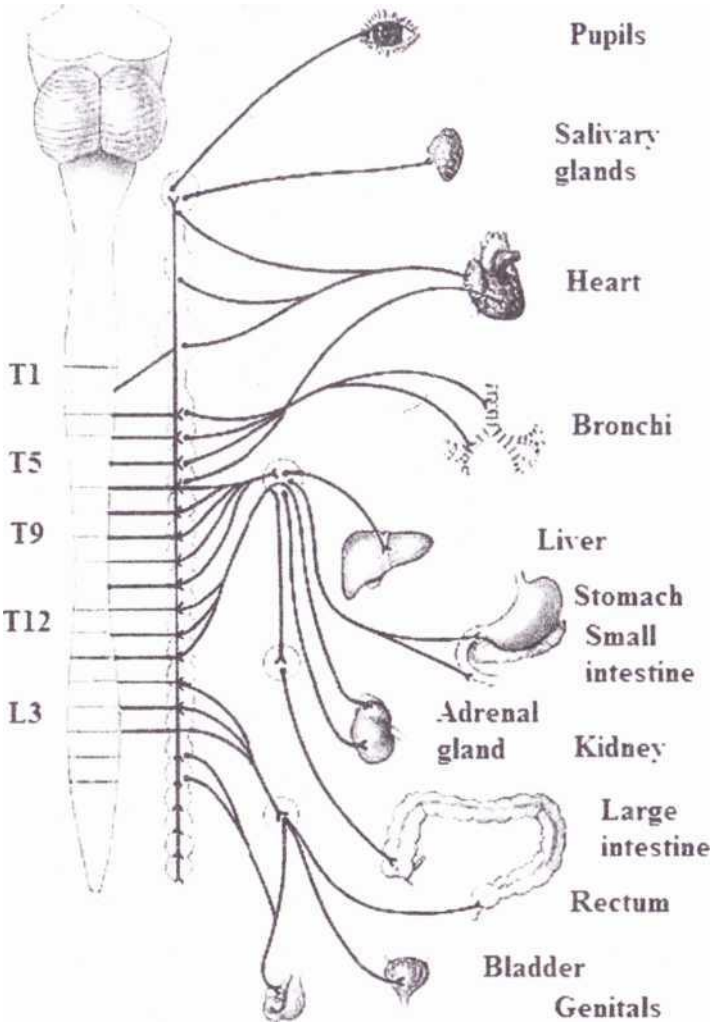


Figure 14.6. Schematic diagram of the sympathetic system.

Parasympathetic system (fig. 14.7)

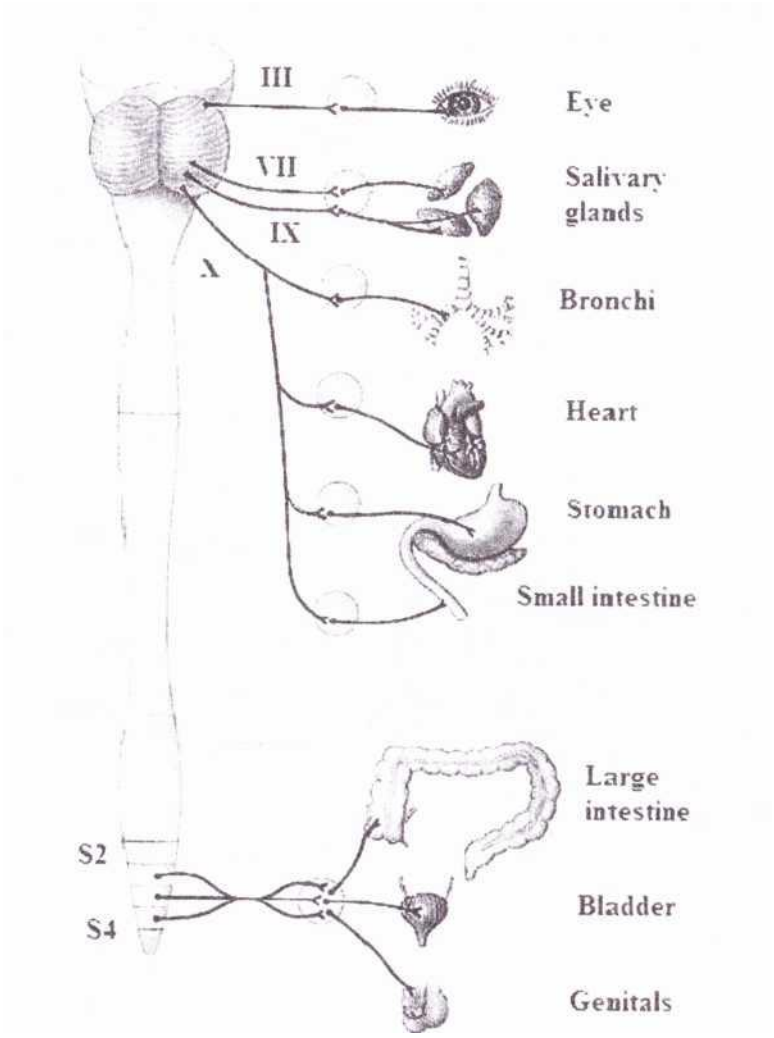


Figure 14.7. Schematic diagram of the parasympathetic system.

Nuclei of the ***parasympathetic system*** are located in the medulla, midbrain and in the sacral portion of the spinal cord.

The reganglionic fibers of these neurons leave through four of the cranial nerves **(III, VII, IX,** and **X)** and also through the **II, III,** and IV sacral spinal nerves. The parasympathetic system is therefore also called the ***craniosacral division*** of the autonomic system.

The second neuron of the parasympathetic system is found in ganglia which are always located near or within walls (intramural ganglia) of the effector organs (e.g., stomach, intestines).

Autonomic ganglia

Autonomic ganglion is covered by connective tissue capsule (fig. 14.8), contains multipolar neurons. The cell bodies of neurons are irregular-shaped; the nuclei of the ganglion cells are located eccentrically.

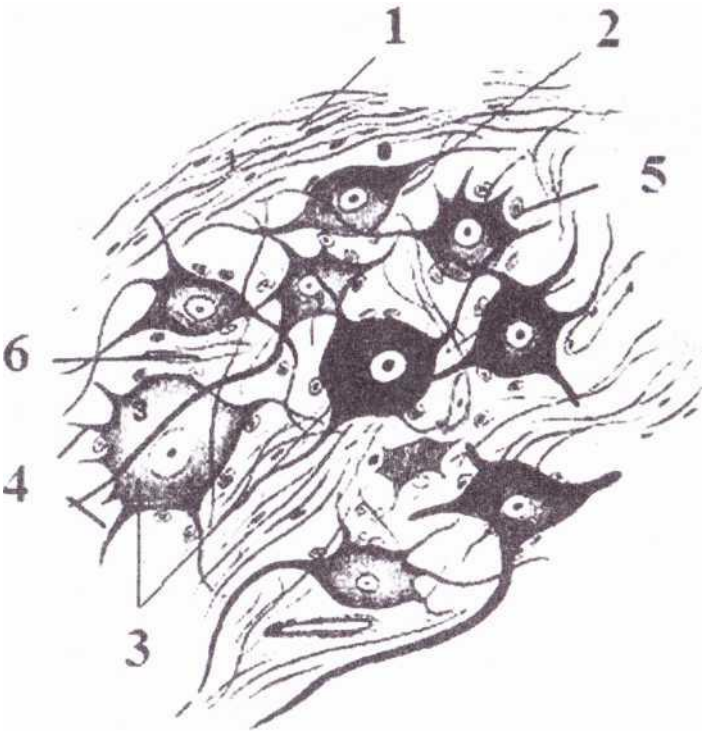


Figure 14.8. Autonomic ganglion. 1 - connective tissue capsule, 2 - neurons, 3 — perikaryon, 4 — process of neuron, 5 - glial cells, 6 — blood vessel

The neurons of autonomic ganglia are enveloped by a layer of satellite glial cells.

Intramural ganglia are devoid of connective tissue capsules, and their cells are supported by the stroma of the organ.

0 Clinical correlations

Demyelinating disease is any disease of the nervous system in which the myelin sheath of neurons is damaged.

Multiple sclerosis is an inflammatory disease in which the myelin sheaths around the axons of the brain and spinal cord are damaged, leading to demyelination and scarring as well as a broad spectrum of signs and symptoms. Multiple sclerosis affects the ability of nerve cells in the brain and spinal cord to communicate with each other.

Disorders of the autonomic nervous system Achalasia of the cardia is result of defect in the autonomic innervation of the esophagus.

Hypertension - high blood pressure - can result from overactive sympathetic vasoconstriction due to continual high levels of stress.

Raynaud's disease is characterized by constriction of blood vessels usually in the phalanges provoked by exposure to cold or by emotional stress.

SENSORY SYSTEM I. VISION: THE PHOTORECEPTOR SYSTEM

0 Overv iew of the sensory system

The ***sensory system*** is a part of the nervous system responsible for processing sensory information. Recognized sensory systems are those for ***vision***, ***hearing, somatic sensation*** (touch), ***taste*** and ***olfaction*** (smell). The senses are transducers from the physical world (heat, pressure, light, sound, etc) to the realm of the mind.

The human sensory system consists of the following sub-systems:

> visual system;
> auditory system;
> *somatosensory system (touch and proprioception) ;*
> gustatory system;
> olfactory' system.

Human sensory receptors are:

> chemosensors;
> mechanoreceptors (Pacinian corpuscles, Meissner's corpuscles, Merkel's discs, and Ruffini corpuscles);
> nociceptors;
> photoreceptors;
> thermoreceptors.

The sensory system consists of: ***y***
peripheral parts (sensory receptors),

> ***intermediate parts*** (neural pathways),
> ***central*** (parts of the brain involved in sensory perception).

Receptors are subdivided into:

> ***neuro-sensitive receptors*** are neurons which accept sensitive signals by the peripheral processes, transduce them to nervous impulses and

transfer in CNS by the central processes. They are part of the ***photoreceptor system*** and ***olfactory organ;***

> ***senso-epithelial receptors*** are the specialized epithelial cells which accept sensitive signals; the transmission of nervous impulses from them in CNS is carried out due to their connections with the endings of neurons. They are part of the ***vestibulocochlear apparatus*** and ***taste organ.***

0 Photoreceptor system

The ***photoreceptor system*** consists of the ***eyeball*** and ***accessory structures*** (conjunctiva, eyelids, and lachry mal apparatus).

Eyeball

The ***eye*** is complex and highly specialized organ of photoreception, a process which involves the conversion of different, quanta of light energy into nerve action potential.

The ***eyeball*** is composed of 3 layers (fig. 15.1):

> ***external layer*** (tunica fibrosa) that consists of ***sclera*** and ***cornea,***

> ***middle layer*** (vascular layer or uveal tract) which consists of the ***choroid, ciliary body,*** and ***iris;***

> ***inner layer*** of nerve tissue, which consists of an outer ***pigment epithelium*** and an inner ***retina propria.***

The ***lens*** of the eye is biconvex transparent structure, which is attached to the ciliary body by the suspensory ligament.

Partly covering the anterior surface of the lens is pigmented expansion of the middle layer called ***iris.*** The round hole in the middle of the iris is the ***pupil***

The eye contains 3 compartments:

> ***anterior chamber*** is space between the cornea and the iris and the lens;

> ***posterior chamber*** lies between the iris and the lens; ***y***

vitreous space.

Both the anterior and posterior chambers contain fluid called ***aqueous humor.***
The vitreous space is filled by a gelatinous substance called the ***vitreous body.***

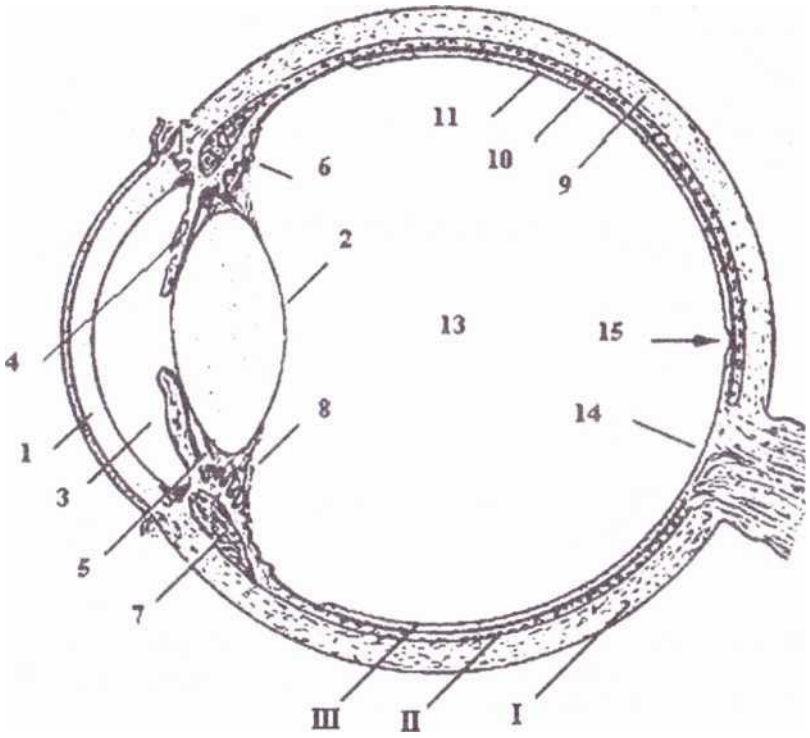


Figure 15.1. **Structure** of **the eyeball.** I - external layer, II — middle layer, III - inner layer, 1 - cornea, 2 - lens, 3 - anterior chamber. 4 - iris, 5 — posterior chamber, 6 — ciliary body, 7 — ciliary muscle, 8 - zonule fiber, 9 — sclera, 10 - choroid, 11 - retina, 12 - optic nerve, 13 - vitreous body, 14 - optic disc, 15 - fovea (from *BbiKoe B.JL*, 1999)

External layer

The ***external (corneoscleral) layer*** forms a fibro-elastic capsule which supports the eye. The posterior five-sixths, the ***sclera***, are opaque and provide insertion for the extra-ocular muscles. It consists of dense connective tissue made up of collagen bundles, a moderate amount of ground substance, and a few fibroblasts.

The anterior one-sixth, the ***cornea,*** is transparent and colourless. The cornea consists of 5 layers (fig. 15.2):

> epithelium,
> anterior elastic lamina (Bowman's membrane),
> stroma.
> posterior elastic lamina (Descemet's membrane),
> endothelium.

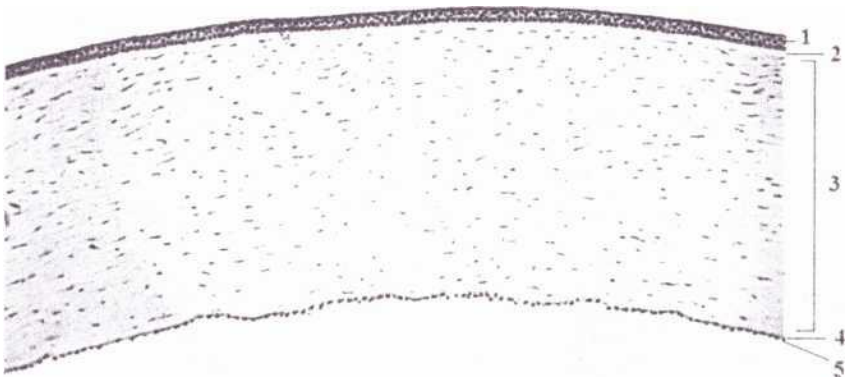


Figure 15.2. Photomicrograph of cornea. 1 — epithelium, 2 - anterior elastic lamina (Bowman's membrane), 3 - stroma, 4 - posterior elastic lamina (Descemet's membrane), 5 - endothelium

Corneal epithelium is stratified squamous non-keratinized, consists of 5-6 layers of cells.

Anterior elastic lamina (Bowman's membrane) is acellular thick homogeneous layer. It consists of densely packed collagen fibrils embedded in ground substance.

Stroma forms 90 % of cornea thickness. It consists of 200 - 250 layers of regularly organized collagen fibers. Collagen fibres within each layer will run parallel to each other but at large angles to collagen fibres in the next layer. Flattened fibrocytes are located between the layers of collagen fibres. The regular arrangement of the collagen fibres, their small diameter (20 - 60 nm) and absence of blood vessels result in the transparency of the cornea.

Posterior elastic lamina (Descemefs membrane) is a thick homogeneous structure composed of collagen fibers, intercellular matrix, and no cells.

Endothelium is simple squamous epithelium.

The corneo-scleral junction is known as the ***limbus.*** In the region of the limbus in the stromal layer, irregular endothelium-lined channels, the trabecular meshwork, merge to form the ***canal of Schlemm,*** which drains fluid from the anterior chamber of the eye. The canal of Schlemm communicates externally with the venous system.

Middle layer (vascular layer or uveal tract)

The ***middle layer*** consists of 3 components:

> choroid,
> ciliary body,
> iris.

Choroid

Choroid lies in the posterior five-sixths of the eye and contains:

> ***suprachoroidal lamina*** (the outer layer) is a layer of loose connective tissue rich in melanocytes;
> ***vascular lamina*** contains arteries and veins;
> ***choriocapillary lamina*** (the inner layer) is rich in small vessels. It has an important function in nutrition of the retina;
> ***basal (Bruch's) lamina*** separates the choriocapillary lamina from the retina. It consists of elastic and collagen fibers that are covered by the basal lamina of the capillaries of choriocapillary layer on one side and the basal lamina of the pigment epithelium on the other side.

Ciliary body

The ***ciliary body,*** an anterior expansion of the choroid at the level of the lens, thickened ring that lies at the inner surface of the anterior of the sclera. It forms a triangle in transverse section (fig. 15.3). Ciliary body contains:

> ***ciliary muscle*** is important in visual accommodation.
> ***ciliary processes*** are extensions of the ciliary body. They are the place of attachment of zonule fibers that insert into the capsule of the lens and anchor it.

Ciliary processes are covered by epithelium. The cells of this epithelium secrete ***aqueous humor*** into the posterior chamber.

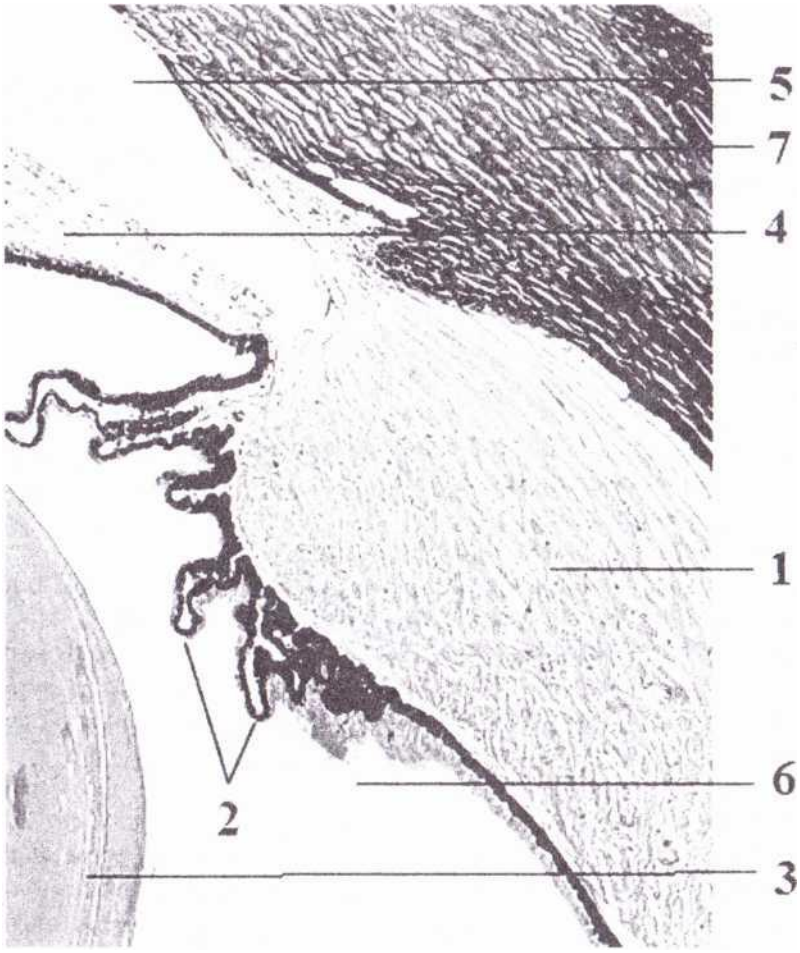


Figure 15.3. Eye (anterior lateral portion). 1 - ciliary body, 2 - ciliary processes, 3 - lens, 4 — iris, 5 - anterior posterior chamber, 6 — posterior chamber, 7 — sclera

Iris

The ***iris*** is an extension of the choroid in front of the lens. The aperture of the iris is called the ***pupil.***

The iris contains the ***dilator pupillae muscle*** and ***sphincter pupillae muscle*** which are formed by smooth muscle tissue.

The iris consists of 3 layers:

> anterior epithelium contains of pigment cells and fibroblasts;
> intermediate layer contains loose connective tissue rich in blood vessels, pigment cells;
> posterior epithelium consists of 2 layers of columnar cells.

The highly pigmented iris acts as an adjustable diaphragm with regulates the amount of light reaching the retina.

Lens

The ***lens*** is a transparent, colourless, plastic and biconvex disk which is kept by zonule fibers. The lens changes its curvature in dependence on tension of the zonule fibers and providing thus ability to focusing on a retina the subjects posed on various distance from an eye.

The lens has 3 principal components (fig. 15.4):

> ***lens capsule,***
> ***subcapsular epithelium,***
> ***lens fibers.***

1. ***Lens capsule*** is the thick homogeneous layer covering the lens outside, which contains glycoproteins and the network of microfilaments. It is a basement membrane of lens epithelium, serves as a place of attachment of zonule fibers.

2. ***Subcapsular epithelium*** consists of a single layer of cuboidal epithelial cells that are present only on the anterior surface of the lens.

3. ***Lens fibers*** are elongated and appear as thin flattened structures. They are highly differentiated cells derived from cells of the subcapsular epithelium. They eventually lose their nuclei and other organelles and become greatly elongated fibers. These cells are filled with proteins called ***crystalline.***

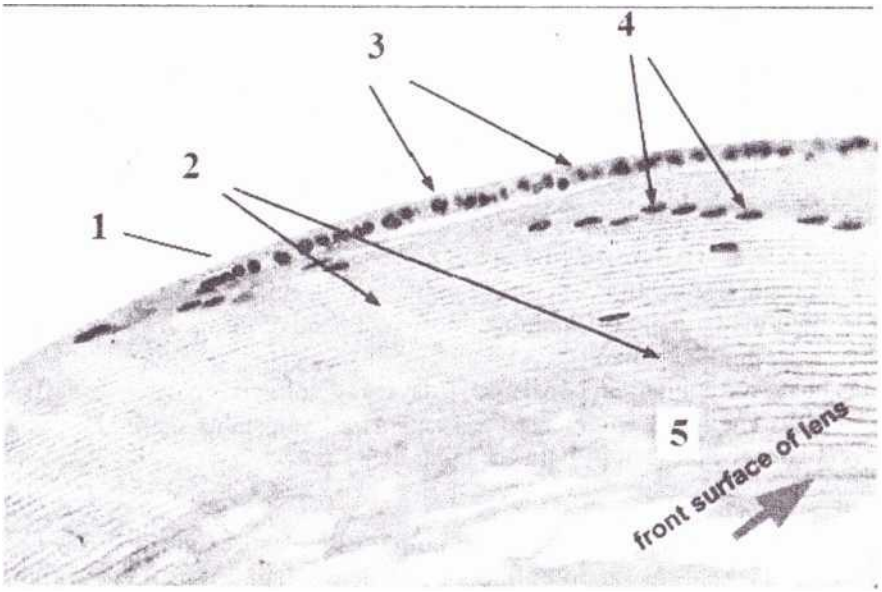


Figure 15.4. Photomicrograph of the lens. 1 - lens capsule, 2 - subcapsular epithelium, 3 — lens fibers, 4 - nuclei of the lens fibers, 5 - nucleus of lens

The lens is held in place by a radially oriented group of fibers, the ***zonule***, which inserts on one side on the lens capsule and on the other on the ciliary' body. Zonular fibers are similar to the microfibrils of elastic fibers.

This system is important in the process known as ***accommodation,*** which permits focusing on near and far objects by changing the curvature of the lens. When the eye is at rest or gazing at distant objects, the lens is kept stretched by the zonule in a plane perpendicular to the optical axis. To focus on a near object, the ciliary muscles contract, causing forward displacement of the choroid and ciliary body. The tension exerted by the zonule is relieved, and the lens becomes thicker, keeping the object in focus.

Vitreous body

The ***vitreous body*** occupies the region of the eye behind the lens. It is a transparent gel that consists of water (about 99%), collagen, and hyaluronic acid. The vitreous body supports the lens and retina.

Retina

The ***retina,*** the inner layer of the globe, consists of two portions:

> ***posterior (optic) part*** lines the inner surface of the eye posterior to the ora serrata, is photosensitive;

> ***anterior (nonvisual) part*** lines the inner aspect of the ciliary body and the posterior surface of the iris, located anterior to the ora serrata.

The structural components of retina are:

1) pigment epithelium,
2) supporting cells,
3) neurons.

1. The ***retinal pigment epithelium*** (fig. 15.5) shows a dark colouration due to the abundant melanin within the cell. Pigment cells are cuboidal or columnar cells, which form a single layer.

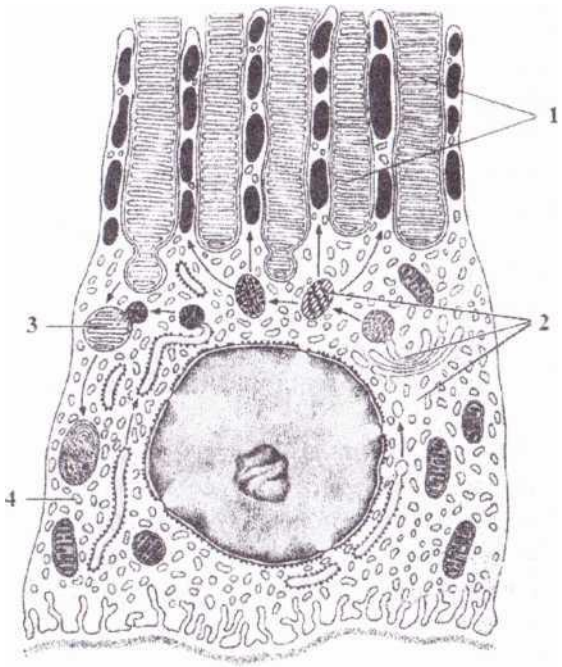


Figure 15.5. Schematic diagram of the retinal pigment cell. 1 - apical portions of photoreceptors, 2 - synthesis of melanin, 3 — lysosomes, 4 - vitamin A (from *Junqueira L.C. and CarneiroJ.*, 2005)

This dark pigment functions to absorb light that has already passed through the retina and did not interact with the photoreceptors. In this way, this dark layer reduces scatter by preventing light from bouncing around inside the eye, thus reducing interferences that would cause a distorted image to be formed. The cells of the pigment epithelium have lysosomes containing enzymes that digest phagocytised parts of the apical portion of photoreceptors that are continually shed.

2. ***Supporting (Muller's) cells*** or ***retinal gliocytes*** are elongated cell extending through all thickness of the retina perpendicularly to its layers, are analogous to the neuroglia of the CNS. Muller's cells provide structural support and may also mediate the transfer of essential metabolites such as glucose to the retinal neurones.

3. ***Neurones*** of a retina form three-part chain of radially posed cells, connected with each other by synapses (fig. 15.6):

> Photosensitive cells (the rods and cones);

> Bipolar neurons, which connect the rods and cones to the ganglion cells;

> Multipolar ganglion cells, which axons converge at the optic papilla, forming the ***optic nerve***

Photosensitive cells

> ***Rod cells*** are thin, elongated, cylindrical, bipolar cells consist inner and outer segments, a nuclear region, and a synaptic region (fig. 15.7 - A). The outer segment is separated from the inner segment by a constriction (***cilium***).

The ***outer segment*** is composed of numerous flattened membranous discs, which are not continuous with the plasma membrane. These discs contain ***visual purple rhodopsin.***

The ***inner segment*** contains mitochondria, smooth and rough endoplasmic reticulum, polyribosomes. Nucleus lies near the center of the inner segment.

Rod cells are found in peripheral parts of the retina, accept light signals of low intensity (twilight vision) and responsible for black-and-white vision. Human retina has 120 million rod cells.

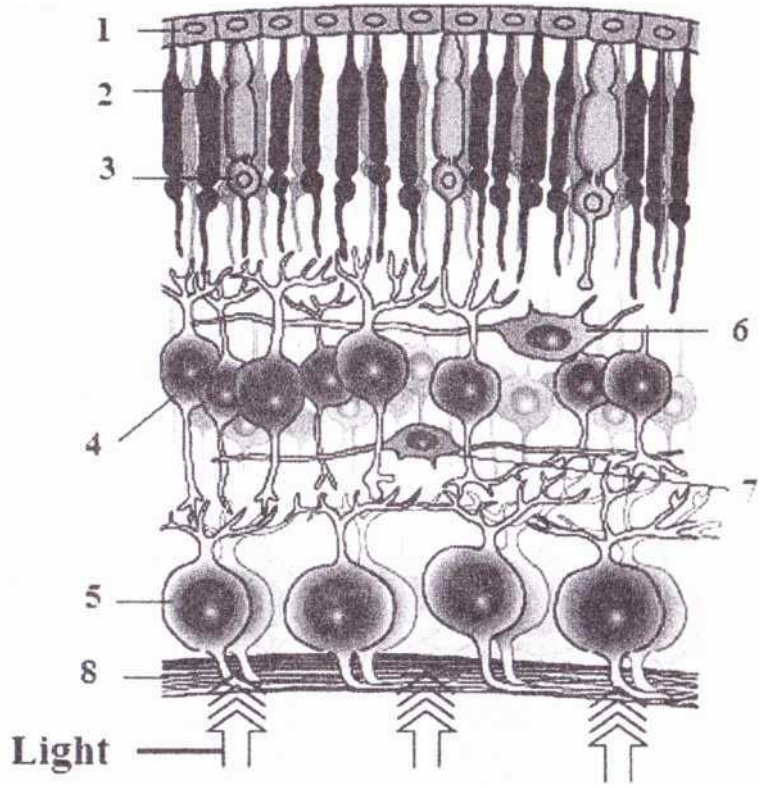


Figure 15.6. Schematic drawing of the retinal neurons. 1 — retinal pigment epithelium, 2 - rod cell, 3 - cone cell, 4 - bipolar cell, 5 — ganglion cell, 6 - horizontal cell, 7 - amacrine cell, 8 - optic nerve

> ***Cone cells*** are also elongated neurons but somewhat shorter and wider than rods. The structure of the cones is similar to that of the rods: the cone contains outer and inner segments, which are separated by cilium. Inner segment contains ***ellipsoid,*** which consists of lipid droplet and accumulation of mitochondria.

The cones differ from the rods in their form (conical) and the structure of their outer segments.

This region is also composed of stacked membranous disks; however, they are not independent of the outer plasma membrane but

arise as invaginations of this structure (fig. 15.7 - B). These discs contain *visual purple iodopsin.*

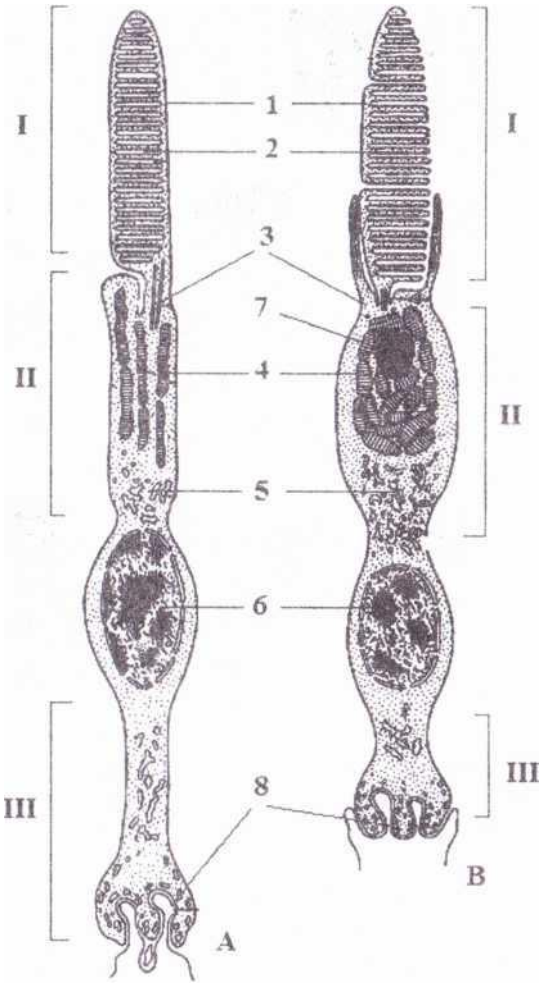


Figure 15.7. Schematic diagram of the photoreceptors. A - rod cell, B — cone cell, I — outer segment, II — inner segment, III - synaptic region; 1 — plasmolemma, 2 - membranous discs, 3 - cilium, 4 — mitochondria, 5 - Golgi complex, 6 — nucleus, 7 - ellipsoid, 8 - synapse (from *lO.KAfiaHacbee, H.A.lOpuna u dp.*, 1999)

Because humans usually have three kinds of cones with different photopsins, which have different response curves and thus respond to variation in colour in different ways (in the red, green, or blue region of the visible spectrum), they have trichromatic vision.

Cone cells are found in the central parts of the retina and are especially numerous in the ***fovea*** of a ***macula lutea***, in which retina has the ***maximum photoreceptor sensitivity.*** They react to light of high intensity, provide ***diurnal and colour vision.***

Human retina has 6-7 million cone cells.

Difference between rods and cones (tabl. 15.1).

Table 15.1. Comparison of human rod anti cone cells (from *Kandel, E. R.; Schwartz, J.H.etal.,* **2000)**

Rods	Cones
Scotopic vision the vision of the eye under low light conditions	Photopic vision (colour perception)
Very light sensitive; sensitive to scattered light	Not very light sensitive; sensitive to only direct light
Not present in fovea	Concentrated in fovea
Have more pigment than cones, so can detect lower light levels	Have less pigment than rods, require more light to detect images
Stacks of membrane-enclosed disks are unattached to cell membrane directly	Disks are attached to outer membrane
20 times more rods than cones in the retina	
One type of photosensitive pigment	Three types of photosensitive pigment in humans
Confer achromatic vision	Confer colour vision

Bipolar (associative) cells are connected by dendrites to axons of photosensitive cells, and their axons transfer nervous impulses to dendrites of ganglion cells.

Ganglion cells are typical multipolar nerve cells. Dendrites form connections with axons of bipolar cells. Axons, collecting together, form an ***optic nerve.***

Association neurons of retina (fig. 15.6)

1. ***Horizontal cells*** are associative multipolar neurons. They establish contact between different photoreceptors. It is possible that they act to integrate stimuli

2 ***Amacrine cells*** establish contact between the ganglion cells.

The retinal layers

10 layers of the retina from outside are (fig. 15.8):

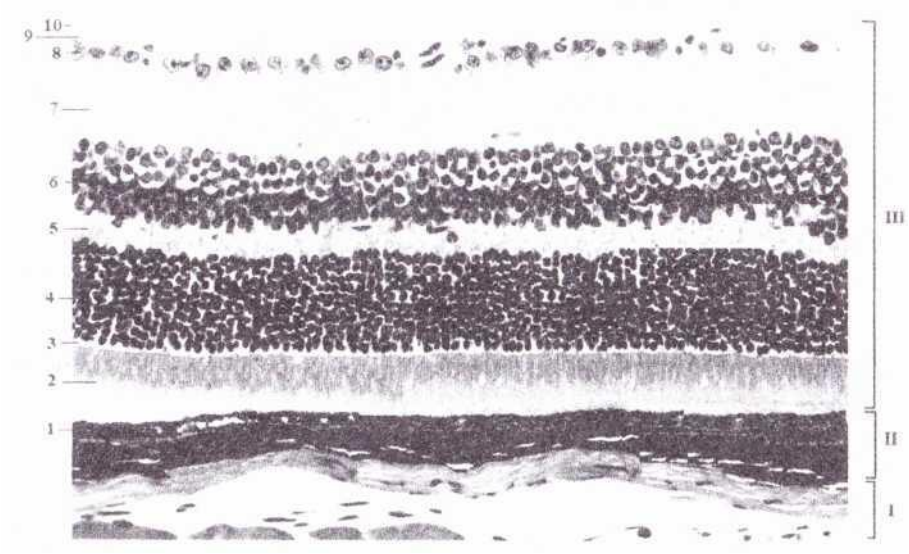


Figure 15.8. Photomicrograph of the human retina. I - sclera, II — choroid, III — retina: 1- retinal pigment epithelium, 2 — photosensitive layer (outer segments of rods and cones), 3 - outer limiting membrane, 4 - outer nuclear layer, 5 - outer plexiform layer, 6 - inner nuclear layer, 7 - inner plexiform layer, 8 - ganglion cells layer, 9 - layer of afferent fibers, 10 - inner limiting membrane

> ***pigment epithelium*** is a single layer, resting on Bruch's membrane which separated them from the choroid;
> ***photosensitive layer*** are the outer processes of the photoreceptor cells (rods and cones);
> ***outer limiting membrane*** formed by the outer ends of Muller's cells;
> ***outer nuclear layer*** contains cell bodies of rods and cones;
> ***outer plexiform layer*** is synaptic connections between the axons of the rods and cones and the dendrites of bipolar cells;
> ***inner nuclear layer*** contains cell bodies of bipolar, horizontal and amacrine cells;
> ***inner plexiform layer*** is synaptic connections between the axons of the bipolar cells and the dendrites of multipolar ganglion cells;
> ***ganglion celI layer*** contains the cell bodies of ganglion ceils;
> ***layer optic nerve fibers*** contains the axons of ganglion cells, which collecting together, form an ***optic nerve;***
> ***inner limiting membrane*** is formed by the inner ends of the Muller's cells.

The retina has two zones with ***special structural and functional characteristics.***

1. Fovea is a conical depression at the posterior pole of the optical axis (fig. 15.9). In the fovea (0,5 mm in diameter) retina is very[7] thin because the bipolar and ganglion cells accumulate in the periphery of this depression. In this area retina consists only of cone cells, and blood vessels are absent. Surround the fovea is an ovoid ye llow area called the ***macula lutea*** (1-2 mm in diameter).

Light falls directly on the cones in the fovea. In this area the retina has the ***maximum photoreceptor sensitivity.***

2. The afferent fibers from the retina converge at appoint medial to the fovea, the ***optic papilla*** or ***optic disc*** (fig. 15.10). The fibers then penetrate the sclera to form the optic nerve. Rods and cones are absent here. Optic disc is insensitive to light and is termed the ***blind spot.***

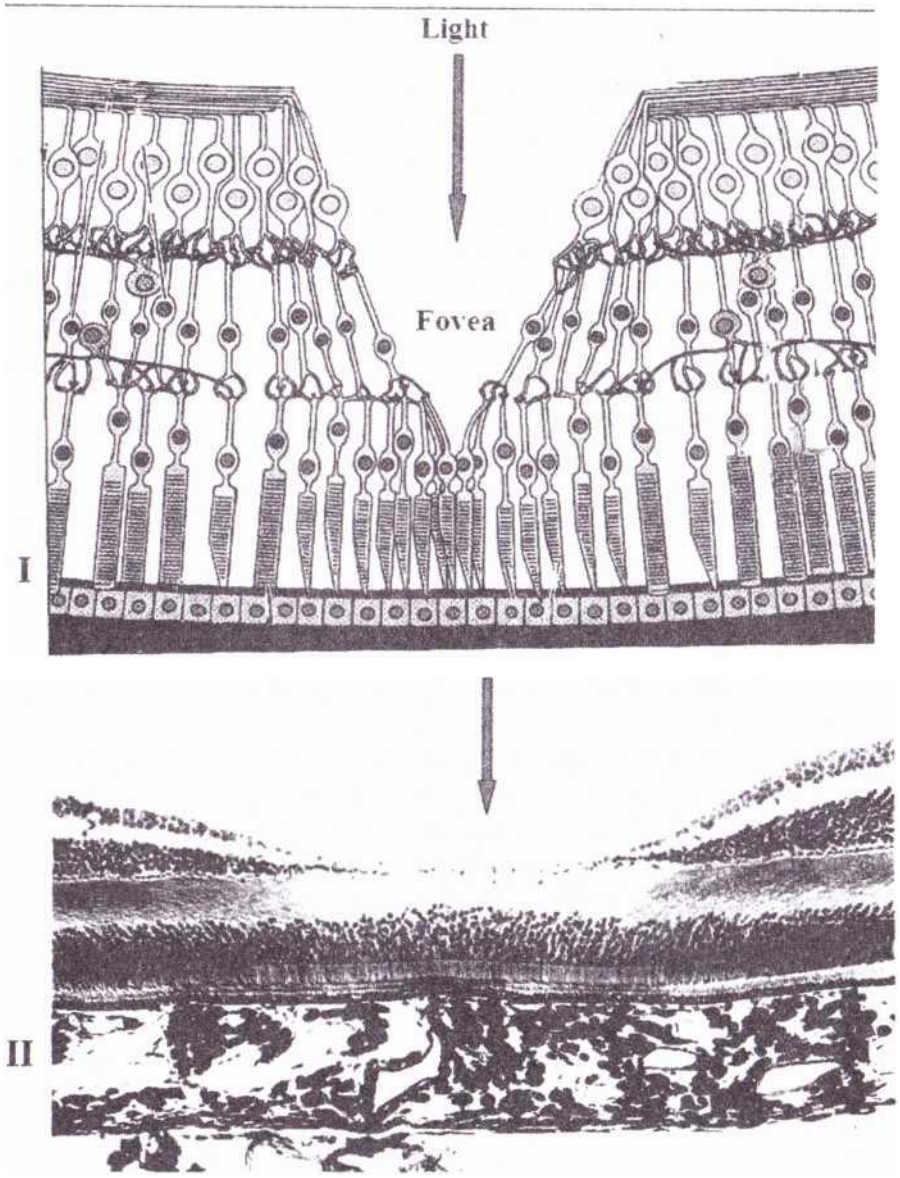


Figure 15.9. Fovea. I - schematic diagram, II - photomicrograph

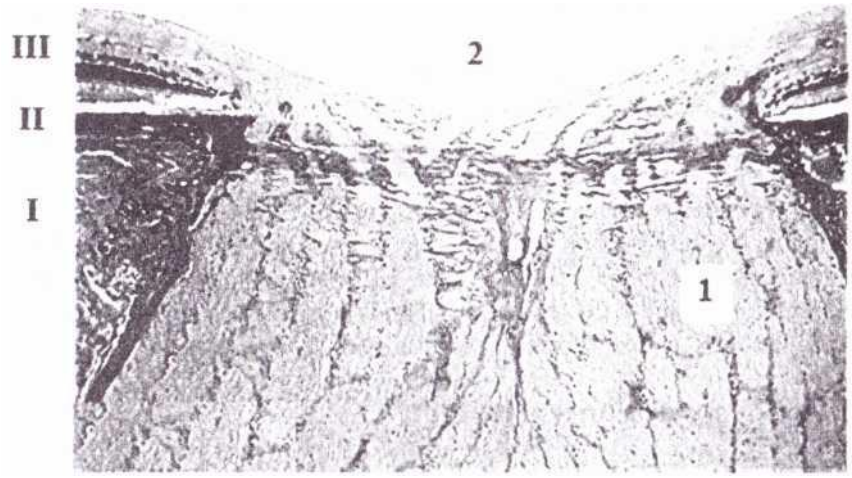


Figure 15.10. Optic disc. I - sclera, II - choroid, III- retina, 1 - layer of afferent fibers, 2 - optic disc

Functional systems of the eye

1. ***Refracting*** (dioptric) (the cornea, the aqueous humor, the lens, and the vitreous body) provides refraction light rays and a projection of observable subjects to the retina.
2. ***Accommodative*** (the iris, the ciliaty body, the lens) provides focusing the image on the retina by change of the form of the lens, regulates the intensity of lighting of the retina (owing to change of diameter of the pupil of iris).
3. ***Receptive*** (retina) provides perception and processing of light signals.

Retinal histophysiology

The conversion of the energy of light into nerve impulses is called ***phototransduction*** and involves two basic steps:

Step 1 is photochemical reaction that occurs in the outer segments of the rod and cone receptors. Photopigment contained in the disk membranes of the outer segment of rods and cones absorbs light energy (photons) and undergoes a ***biochemical changes.*** The visual pigment decomposes under influence of light. Visual pigment is a complex of two molecules: opsin and the chromophore. ***Opsin*** is a

protein; the ***chromophore*** is the part affected by light - called ***retinal*** (a derivative of retinol, i.e., vitamin A).

Absorbed light energy causes ***biochemical conformational changes*** in the chromophores.

Step 2 is ***changes in concentration of internal transmitters*** within the cytoplasm of the inner segment of the photoreceptors. These changes cause Na' channels (which are open in the resting state) to close. Closing Na^+ channels hyperpolarises the neuron. The hyperpolarisation of the outer segment spreads to the inner segment. Then the electrical signal is transmitted to the bipolar and then to the ganglion cells. The ganglion cells generate action potentials along their axons to the brain.

0 Accessory structures of the eye

1) ***Eyelids*** (fig. 15.11) are mobile folds of tissue that protect the eyes. Each eyelid consists of a dense fibro-elastic plate, the ***tarsus,*** covered externally by thin skin and on the internal aspect by conjunctiva.

Skeletal muscle of ***orbicularis oculi*** lies superficial to the tarsal plate. Within the tarsal plate lie some 12-30 sebaceous ***tarsal (Meibomian) glands.***

Associated with the eyelashes are sebaceous ***glands of Zeis*** and modified apocrine sweat ***glands of Moll.***

2) ***lachrymal apparatus*** consists of the lacrimal glands, canaliculi, lacrimal sac, and nasolacrimal duct.

Lachrymal glands are compound tubulo-alveolar. Alveoli are lined by cuboidal serous cells with basal myoepithelial cells.

Canaliculi are lined by stratified squamous epithelium.

Lachrymal sac and ***nasolacrymal duct*** are lined by pseudostratified epithelium.

3) ***Conjunctiva*** covers the anterior portion of the eye up to the cornea and the internal surface of the eyelids. It has stratified columnar with numerous goblet cells epithelium, its lamina propria consists of loose connective tissue.

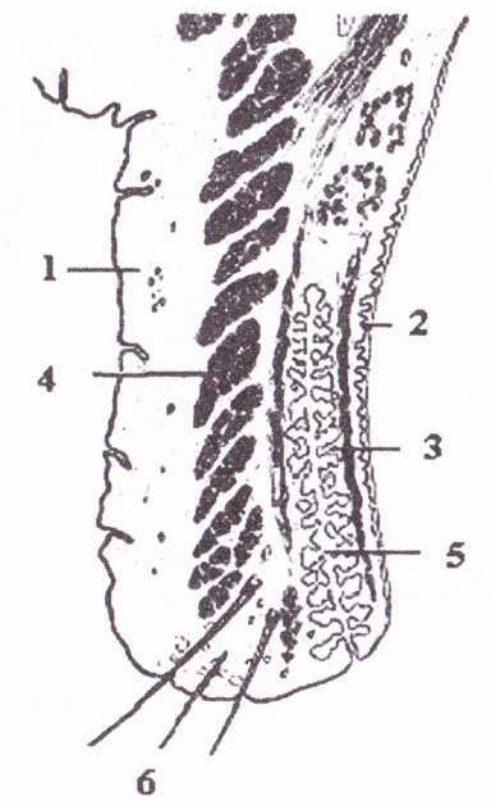


Figure 15.11. Eyelids. 1 - skin, 2 - conjunctiva, 3 — tarsal plate. 4 — orbicularis muscle, 5 — Meibomian glands, 6 - eyelashes

0 Development of the eye (fig. 15.12)

The eye develops from

1) ***ectoderm*** forms the ***lens pit***, which becomes deeper to form ***lens vesicle.*** Lens is formed from lens vesicle. Cornea is formed from ectoderm is over the lens vesicle.

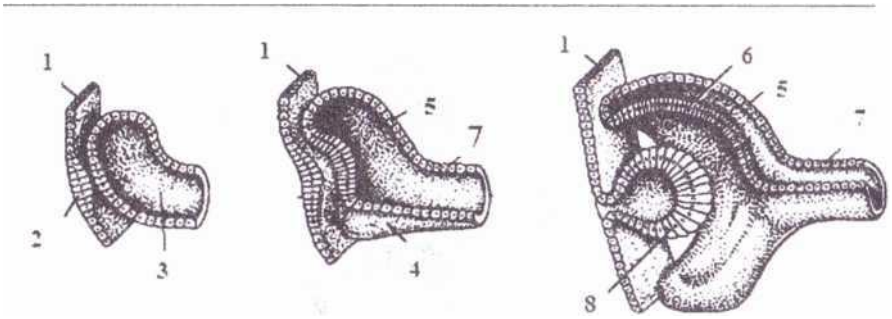


Figure 15.12. Development of eye. 1 - ectoderm (cornea), 2 — lens pit, 3 — optic vesicle, 4 - optic goblet, 5 - puter wall of the optic cup (layer of pigmented cells of the retina), 6 - inner wall of the optic cup (neurons of the retina), 7 - nerve stalk (optic nerve), 8 - lens vesicle (lens) (from ***IO.H.A(panacbee, H.A.IOpma к*** up., 1999)

1) ***neuroectoderm*** forms optic vesicle, which differentiates to form ***optic cup.*** Outer wall of the optic cup forms the layer of pigmented cells of the retina. Inner wall of the optic cup forms the neurons of the retina. ***Nerve stalk*** forms optic nerve.

2) ***mesechyma*** forms the other components of the eye.

Clinical correlations

Glaucoma is a disease in which the optic nerve is damaged, leading to progressive, irreversible loss of vision. The major risk factor for glaucoma is increased intraocular pressure. Intraocular pressure is a function of production of aqueous humour by the ciliary processes of the eye and its drainage through the trabecular meshwork. Any impediment to the drainage of aqueous humour results in an increase in intraocular pressure, causing glaucoma.

Advancing age reduces the elasticity of the lens, making accommodation for near objects difficult. This is a normal aging process ***{presbyopia***), which can be corrected by wearing glasses with convex lenses.

In older individuals, a brownish pigment accumulates in lens fibers, making them less transparent. When the lens becomes opaque, the condition is termed ***cataract.***

Pathologies of the retina

Age related macular degeneration involves a progressive deterioration of the central portion of the retina. The macula begins to get thinner as it suffers atrophy and bleeding may sometimes occur. As a result of loss of functioning in the photoreceptors of the macula, individuals with this disorder begin losing vision in their central field and in severe cases, most of the vision in a roughly 20° central field can be lost. ***Age related macular degeneration*** is a major cause of blindness in adult populations and while there is no cure, there are some treatments that can slow the progression of this disease.

Diabetic retinopathy develops in many individuals suffering from diabetes mellitus. Diabetes mellitus is an endocrine disorder that interferes primarily with glucose metabolism. Progressive degeneration, rupture, and excessive growth of abnormal blood vessels that invade the space between the retinal layers cause losses in visual acuity that are characteristic of diabetic retinopathy. Among some of the treatments for this disorder is laser therapy to seal leaking vessels and inhibit further growth of new vessels.

Colour vision deficiency (colour blindness) is the inability to distinguish certain shades of colour or in more severe cases, see colours at all. Colour vision is possible due to cones in the retina that have light sensitive pigments that enable to recognize colour. Found in the macula, each cone is sensitive to red, green or blue light. Normally, the pigments inside the cones register differing colours and send that information through the optic nerve to the brain enabling you to distinguish countless shades of colour. But if the cones lack one or more light sensitive pigments, eye will be unable to see one or more of the three primary colours thereby causing a deficiency in your colour perception. Red-green color blindness is one of the most frequent forms of colour blindness and is a sex-linked genetic disorder in which people cannot distinguish between red and green _____ _____ _____

Night blindness is the inability to see well at night or in poor light. The most common cause of night blindness is a disorder in which the rod cells in the retina gradually lose their ability to respond to the light. In X-linked congenital stationary' night blindness, from birth the rods either do not work at all, or work very little. Another cause of night blindness is a deficiency of retinol, or vitamin A, found in fish oils, liver and dairy products.

RetinaI detachment is a disorder of the eye in which the retina peels away from its underlying layer of support tissue. Initial detachment may be localized, but without rapid treatment the entire retina may detach, leading to vision loss and blindness. It is a medical emergency.

SENSORY SYSTEM II.
HEARING: THE AUDIORECEPTOR SYSTEM.
TASTE & SMELL: THE CHEMORECEPTOR SYSTEM

0 Ear

The ***ear*** consists of 3 parts:
1) ***external ear,*** which is responsible for reception of sound waves;
2) ***middle ear***, transmitting sound waves in vibrations of fluid (perilymph) in a cochlea;
3) ***internal ear*** in which vibrations of a perilymph are transformed to nervous impulses.

0 External ear

The ***external ear*** consists of:
> auricle (pinna),
> external auditory meatus,
> tympanic membrane.

Auricle is composed of elastic cartilage covered by skin. ***External auditory meatus***

The wall of the outer third of the canal is formed by cartilage; the inner two-thirds of the canal lie in the petrous part of the temporal bone. The canal is lined by hairy skin containing sebaceous glands and modified apocrine sweat glands which secrete a waxy material called cerumen.

Tympanic membrane separates external ear from the middle, is composed of 3 layers:
> outer surface lined by skin;
> middle fibrous layer consisting of collagen fibers,
> inner mucous layer, lined by simple squamous epithelium.

Sound waves impinging on the tympanic membrane are converted into mechanical vibrations which are then amplified by auditory bones.

0 Middle ear

The ***middle ear*** consists of:

> tympanic cavity,
> auditory ossicles,
> auditory tube.

Tympanic cavity is irregular space in the temporal bone lined by simple squamous epithelium. In the medial wall of the tympanic cavity are 2 membrane-covered regions: the oval and the round windows.

Auditory ossicles (the malleus, incus, and stapes) transmit the mechanical vibrations generated in the tympanic membrane to the inner ear. These bones are articulated by synovial joints and covered by simple squamous epithelium.

Auditory tube communicates the tympany cavity with the nasopharynx and permits equalization of pressure changes with the external environment.

0 Internal ear

The ***internal ear*** consists of a fluid-filled membranous labyrinth lying within a labyrinth of spaces in the temporal bone (the bone labyrinth). The membranous labyrinth is bound down to the walls of the bone labyrinth by thin strands of connective tissue in various places but in the main is separated from the bony walls by a fluid-filled space. The fluid within the membranous labyrinth is known as ***endolymph*** and the fluid in the surrounding perimembranous space is known as ***perilymph.***

The ***bone labyrinth*** may be divided into 3 main areas (fig. 16.1):

1) vestibule, housing the ***saccule*** and the ***utricle***;
2) behind this, three ***semicircular canals*** enclose the semicircular duct;
3) the anterolateral cochlea contains the ***cochlear duct.***

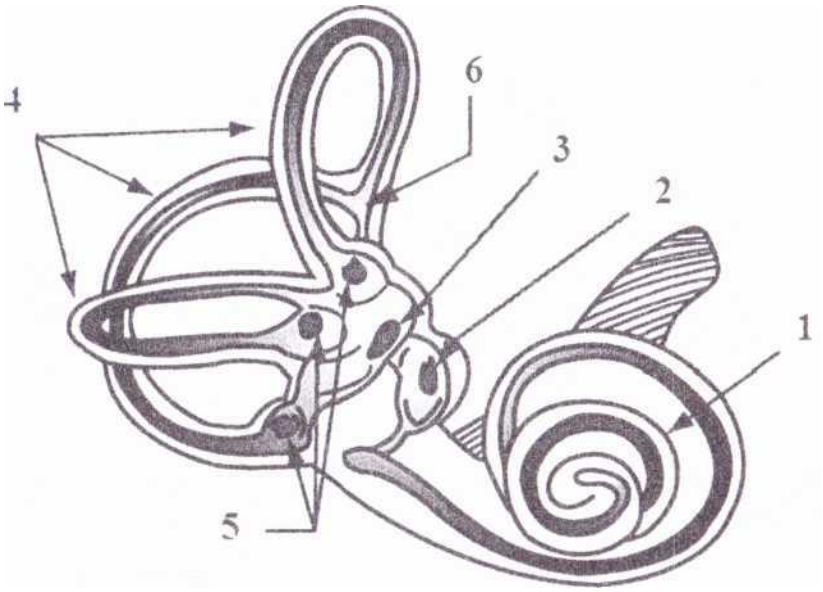


Figure 16.1. The osseous labyrinth. 1 - cochlea, 2 - saccule, 3 — utricle, 4,— semicircular canals, 5 - ampullae, 6 - tubular ducts containing endolymph

The cochlea, about 35 mm in length, makes two-and-one -half turns around a bony core - the ***modiolus*** (fig. 16.2).

Receptor organs of the saccule and utricle

The ***saccule*** and ***utricle*** are two dilated regions of the membranous labyrinth lying within the vestibule of the inner ear.

The saccule and utricle are lined by simple cuboidal epithelium but in each there is a region of highly specialised epithelium called the ***macula of the saccule*** and ***nmcula of the utricle.***

The maculae are made up of two basic cell types, ***sensory (receptor) cells*** and ***supporting cells*** (fig. 16.3).

1. The supporting cells are tall and columnar with basally-located nuclei and microvilli at their free surface.
2. The sensory cells (hair cells) lie between the support cells.

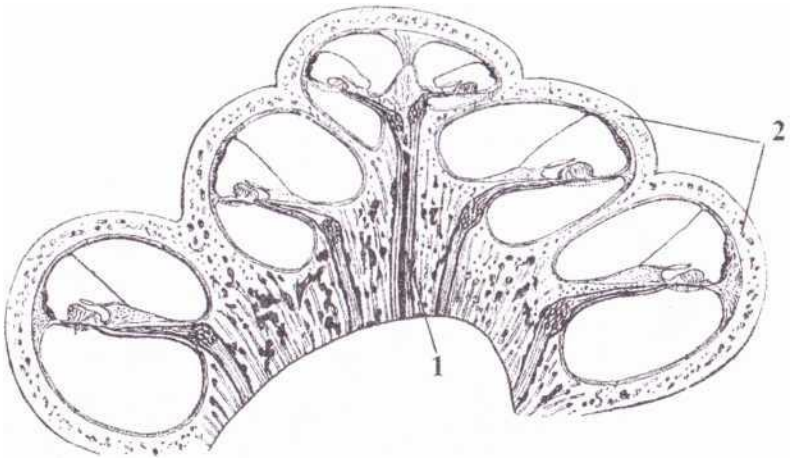


Figure 16.2. Schematic diagram of a cochlea. 1 - turns of cochlea, 2 - modiolus

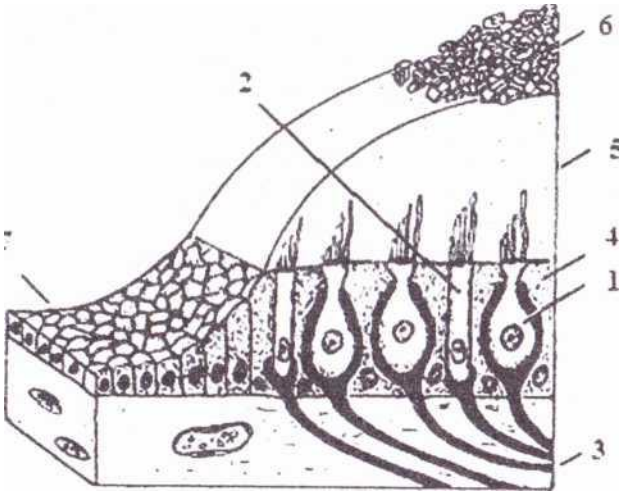


Figure 16.3. The structure of maculae. 1 - receptor type I hair cell, 2 - receptor type II hair cell, 3 - nerve endings, 4 - supporting cell, 5 - gelatinous layer (the otolithic membrane), 6 — otoliths, 7 — epithelium of membranous labyrinth (from ***EbiKoe*** *B.JI.,* 1999)

Each sensory (receptor) cell has a single large eccentrically- located ***kinocilium***, which is immotile and number of ***stereocilia*** (microvilli) projecting from its surface (fig. 16.4).

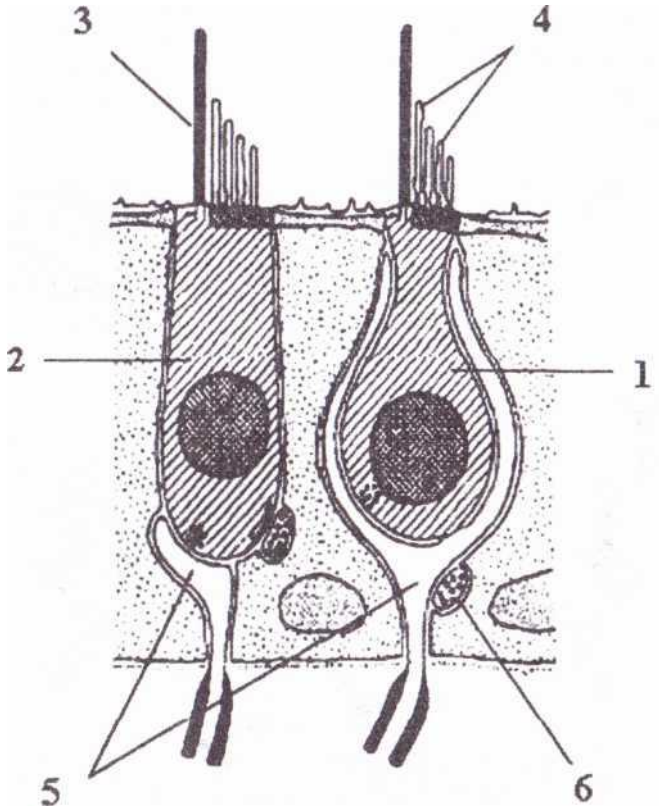


Figure 16.4. Sensory (receptor) hair cells. 1 - type **I** hair cell, 2 - type **II** hair cell, 3 - kinocilium, 4 - stereocilia, 5 - afferent nerve endings, 6 - efferent nerve endings

There are two different types of sensory cells.

Type I hair cells are bulbous in shape. They are invested by a meshwork of dendritic processes of afferent sensory neurons.

Type II hair cells have columnar shape. They have only small afferent nerve endings at their bases.

Both types have efferent nerve endings that are inhibitory.

Covering this epithelium is a thick, gelatinous glycoprotein layer (the otolithic membrane). At the surface of this membrane there is a mass of crystals mainly composed of calcium carbonate (***otoliths***) (fig. 16.5).

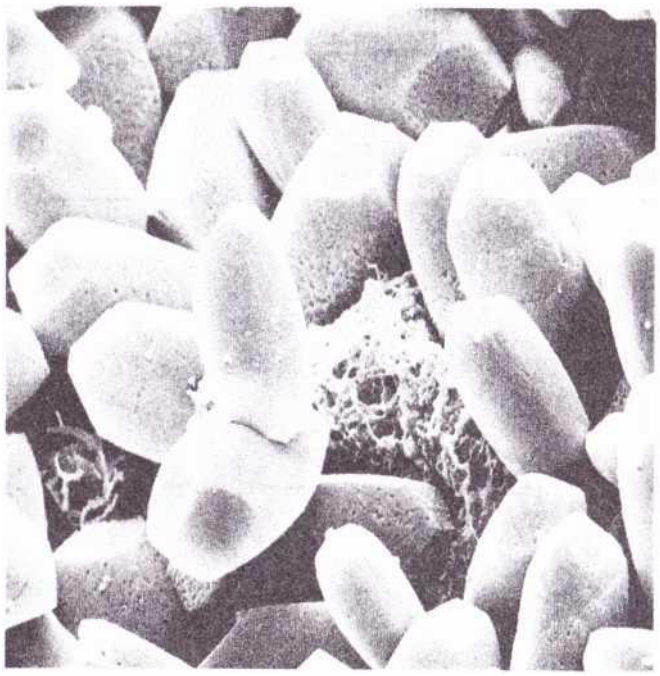


Figure 16.5. Scanning electron micrograph of the surface of the macula showing the otoliths.

Function of the maculae

The function of the maculae is to the ***maintenance of balance*** by providing sensory information about the static position of the head

in space. This is of particular importance when the eyes are closed, or in the dark or under water.

When the head is moved from a position of equilibrium, the otolithic membrane tends to move w'ith respect to the receptor cells, thus bending their stereocilia. When the stereocilia are bent in the direction of the cilium, the receptor cell undergoes excitation and, when the relative movement is in the opposite direction, excitation is inhibited.

Receptor cells of the semicircular canals

Three semicircular canals arise from the vestibule of the inner ear, each containing a membranous semicircular duct which opens at both ends into the utricle. At one end of each duct there is a dilated portion, the ampulla, which contains a receptor organ, called the ***crista ampullaris*** (fig. 16.6).

Each crista ampullaris is an epithelial structure situated on a ridge of supporting tissue.

The receptor cells are of two morphological types, one are flask-shaped and the other are more slender (columnar).

The receptor cells are supported by a single layer of columnar cells which is continuous with the simple cuboidal epithelium lining the rest of the membranous labyrinth.

Like those of the maculae, the receptor cells of the cristae have numerous stereocilia and a single cilium. The stereocilia and the cilia of the sensory receptors are embedded in a gelatinous glycoprotein layer; it is a conical shape called a ***cupula.*** The cupula does not contain otolithic crystals.

Function of the crista ampullaris

The crista ampullaris accept ***angle accelerations.*** When the head is moved in the plane of a particular semicircular canal, the inertia of the endolymph acts so as to deflect the cupula in the opposite direction. The stereocilia of the sensory cells are then deflected towards or away from the cilia, resulting in excitation or inhibition respectively.

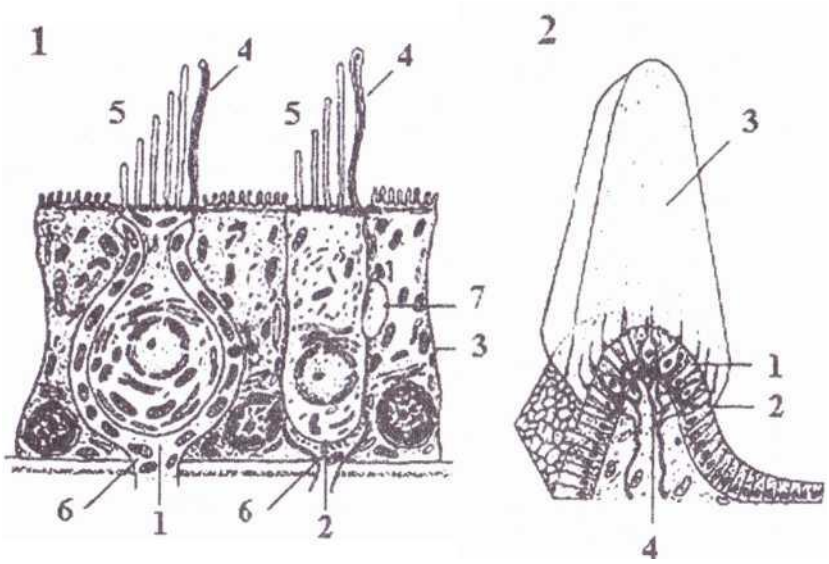


Figure 16.6 - 1. **infrastructure of sensory cells of crista ampullaris: 1** - type **I** hair cell, 2 - type **II** hair cell, **3** - supporting cell, **4** - kinocilium, 5 — stereocilia, 6 - - afferent nerve endings, 7 - efferent nerve endings (from ***EbiKoe*** *B.JI.*. 1999) **Figure** 16.6 - **2. Crista antpuliaris:** 1 - receptor hair cell, 2 - supporting cell, 3 - cupula, **4** - nerve endings (from *EbiKoe B.JI.*, 1999)

Cochlear duct

When observed in histological sections, the cochlea appears to be divided into 3 spaces (fig. 16.7):

> ***scala vestibule*** (above),
> ***scala media (cochlear duct***) in the middle,
> ***scala tympani*** (below).

The cochlear duct, which contains endolymph, ends blindly at the apex of the cochlea.

Other two scalae contain perilymph and are one long tube, beginning at the ***oval window*** and terminating at the ***round window.*** They communicate at the apex of the cochlea via an opening known as the ***helicotrema.***

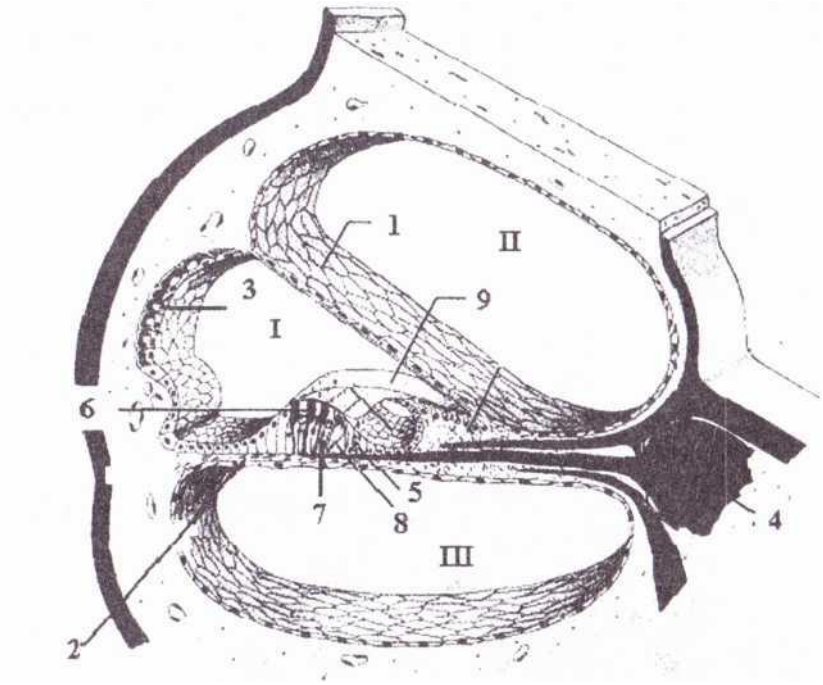


Figure 16.7. **Schematic diagram of the cochlea.** I - scala media, II - scala vestibule, III - scala tympani; 1 - vestibular membrane, 2 - basilar membrane, 3 - stria vascularis, 4 - spiral ganglion, 5 - inner hair cells, 6 - outer hair cells, 7 - pillar cells, 8 - inner tunnel, 9 - tectorial membrane

Histological structure of the cochlear duct

1) . ***Vestibular (Reissner's) membrane*** consists of two layers of squamous epithelium, one derived from the scala media and the other from the lining of the scala vestibuli.

2) . ***Stria vascularis*** is a vascularised epithelium located in the lateral wall of the cochlear duct. It consists of three types of cells: ***marginal***, ***intermediate***, and ***basal.*** Marginal cells are responsible for the characteristic ionic composition of endolymph.

3) . ***Basilar membrane*** separates the scala media and scala tympany and supports special auditory receptors is called the ***spiral organ of Cord;*** it contains hair cells that respond to different sound frequencies.

The basilar membrane is a thick layer of amorphous ground substance, containing fibrils.

Spiral organ of Corti

Organ of Corti consists of 2 types of cells (fig. 16.8):

1) ***sensory (hair) cells,***
2) ***supporting cells.***

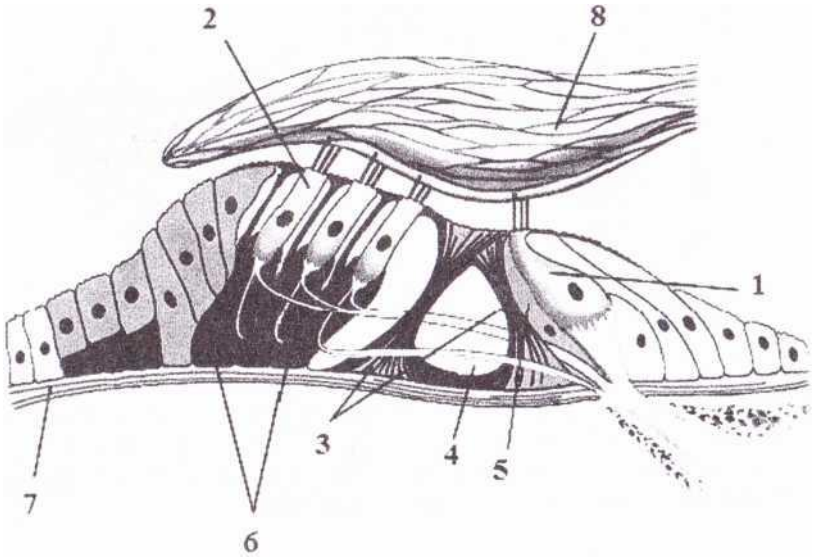


Figure 16.8. Schematic diagram of the spiral organ of Corti. 1 - inner hair cell, 2 - outer hair cells, 3 - pillar cells, 4 - tunnel of Corti, 5 - inner phalangeal cells, 6 - outer phalangeal cells, 7 - basilar membrane, 8 - tectorial membrane

At the centre of the organ is a triangular-shaped canal, the *inner tunnel* or *tunnel of Corti.* It is bounded on each side by a single row of tall columnar cells called *pillar cells.*

On the inner aspect of the inner row of pillar cells is a single row of flask-shaped cells called *inner phalangeal cells* which support a single row of *inner sensory (hair) cells.*

Beyond the outer row of pillar cells there are three to five rows of ***outer phalangeal cells*** which support the same number of rows of ***outer sensory (hair) cells.***

Both types of hair cells are columnar. The most characteristic feature of these cells is the V-shaped (outer hair cells) or liner (inner hair cells) (fig. 16.9) array of stereocilia.

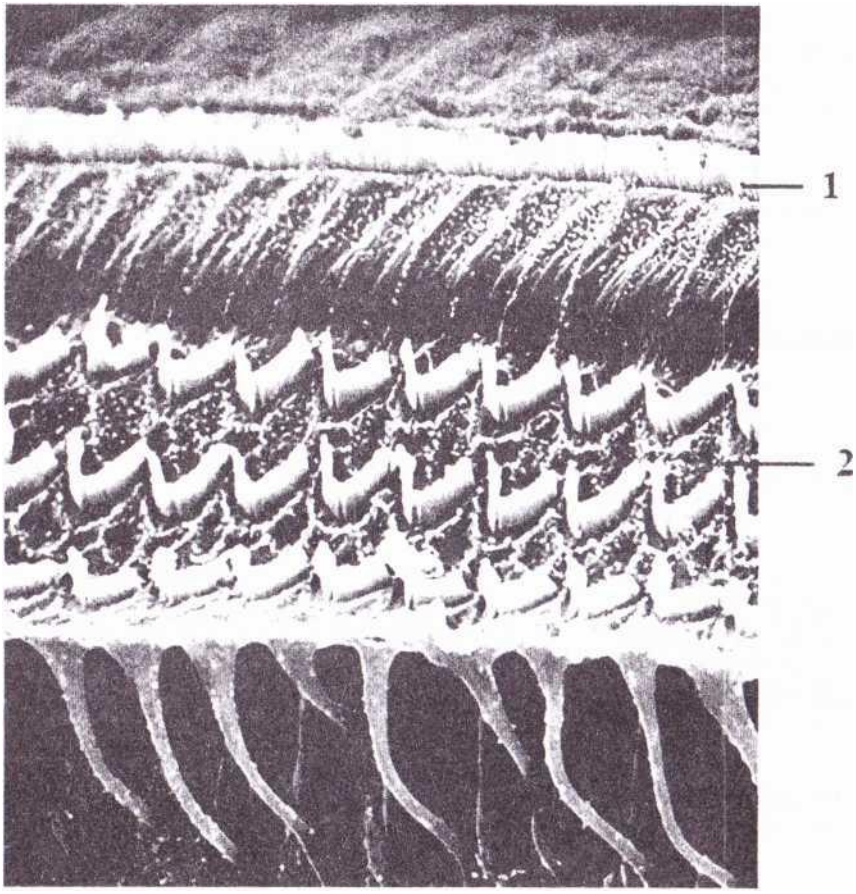


Figure 16.9. Scanning electron micrograph of the spiral organ of Corti. 1 single row of inner hair cells, 2-3 rows of outer hair cells

The tips of the stereocilia of the sensory cells are embedded in the gelatinous glycoprotein ***tectorial membrane.***

Function of the organ of Corti

Sound waves produce vibrations of a tympanic membrane. These vibratioas are transmitted to the auditory' ossicles transferring them on a perilymph and a basilar membrane.

The basilar membrane is thinnest at the base of the cochlear and thickest at the apex. It appears that, at every point on the spiral, the membrane is 'tuned' to vibrate to a particular frequency of sound waves reaching the ear.

The process of transduction of mechanical energy into electrochemical energy' probably results from deformation of the stereocilia of the sensory' cells.

An electric potential is transferred to the terminals of dendrites of bipolar cells of a spiral ganglion (their axons form a cochlear nerve).

More than 90 % of afferent nerve fibrils approach to inner hair cells and to more numerous outer hair cells - only 10 %.

Development of the membranous labyrinth of the ear

The membranous labyrinth is derived from a area of surface ectoderm overlying the developing rhombencephalon (hindbrain) (fig. 16.10). This area is called the ***optic placode.***

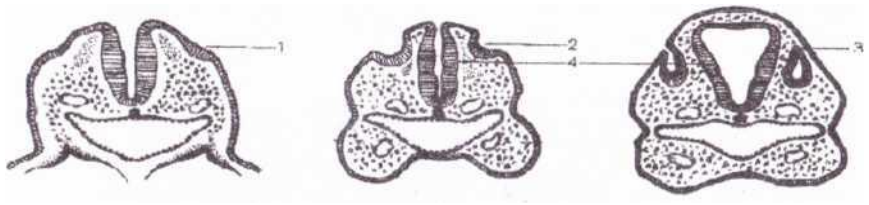


Figure 16.10. Development of the ear. 1 — otic placode, 2 - otic pit, 3 — 3 - otic vesicle, 4 - hindbrain (from ***K).KA(paHacbee,*** *H.A.fOpuna u dp.,* 1999)

The otic placode becomes depressed to form the ***otic pit.*** The pit then becomes rounded to form the ***otic vesicle,*** which separates from the surface ectoderm.

The otic vesicle is at first an oval structure. By differential growth of various parts of its wall, it gives rise to the comprising the membranous labyrinth.

Localized areas of the epithelium of the membranous labyrinth undergo differentiation to form specialized sensory end organs of hearing, and of equilibrium.

0 Taste

Taste is a sensation perceived by ***taste buds***, receptors located principally on the tongue and in smaller numbers on the soft palate and laryngeal surface of the epiglottis. Lingual taste buds are embedded within the stratified epithelium of the circumvallate, foliate, and fungiform papillae (fig. 16.11).

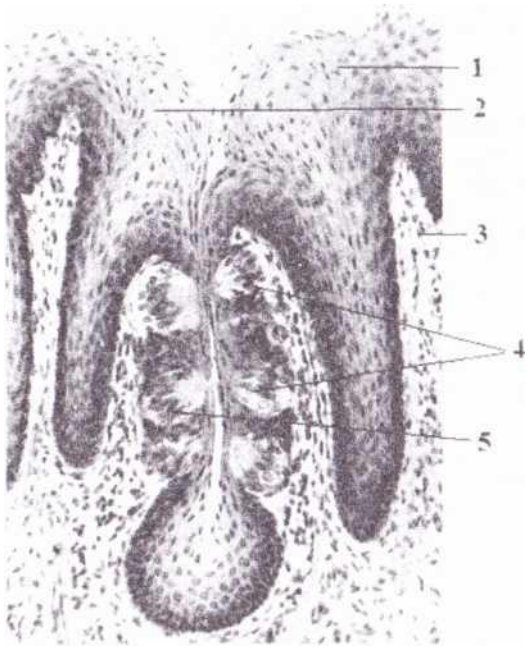


Figure 16.11. Papillae of the tongue. 1 - papilla, 2 - stratified epithelium, 3 — connective tissue, 4 - taste bud, 5 - gustatory cells of the taste bud

I here are about 3000 taste buds on the tongue of an adult person. There are four main tastes - sweet, salty, sour and bitter. These

four main tastes are felt by different portion of the tongue. The tip of our tongue senses salt and sweet. The taste buds at the sides detect sour taste. The rear portion of the tongue detects bitter taste.

The taste bud is a ban-el-shaped organ extending the full thickness of the epithelium and opening at the surface via ***taste pore*** (fig. 16.12).

Each taste bud contains 20-30 long spindle-shaped cells. 3 types of cells are described in the taste bud: ***y*** gustatory cells,

> supporting cells,

> basal cells.

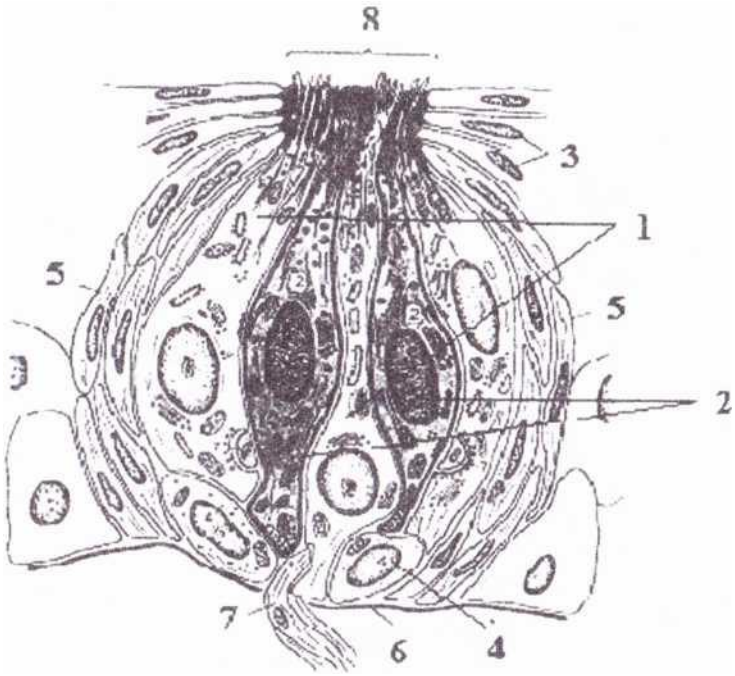


Figure 16.12. Structure of a taste bud. 1 - supporting cells, 2 - gustatory cells, 3 - epithelial cells of the tongue, 4 - basal cells, 5 — peripheral cells, 6 - basal membrane, 7 - nerve fibers, 8 - taste pore

Gustatory cells are fusiform cells and lie in the center of the bud. ***Supporting cells*** are crescent shaped and surround the gustatory cells. Both gustatory and supporting cells have long microvilli extending into the taste pore. ***Basal cells*** are precursors of one or both of the other cell types.

ESI Smell: the chemoreceptor system

The ***olfactory*** chemoreceptors are located in the ***olfactory epithelium*** in the nasal cavity. This is a pseudostratified columnar epithelium composed of 3 types of cells (fig. 16.13);

> ***supporting cells***,
> ***basal cells.***
> ***olfactory cells.***

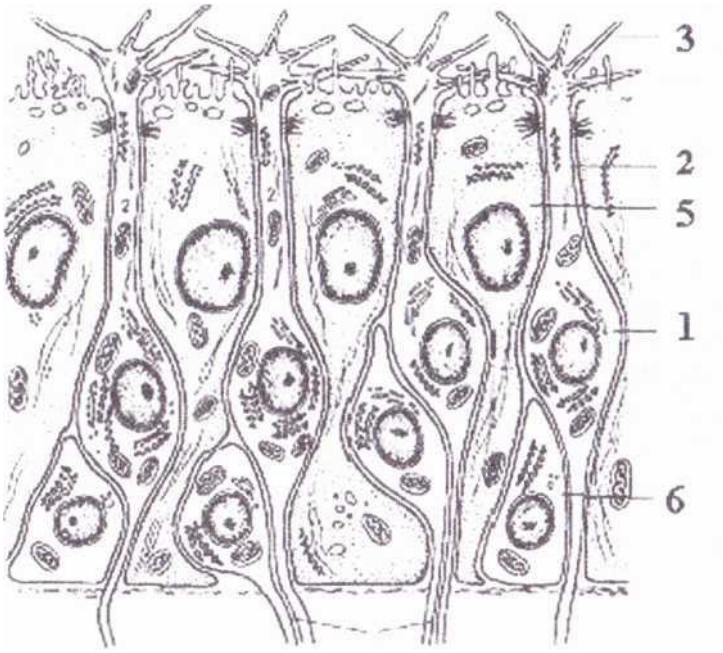


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Figure 16.13. Olfactory epithelium. 1 - olfactory cells, 2 — dendrites, 3 — olfactory cilia, 4 - axons, 5 - supporting cells, 6 - basal cells

The ***supporting cells*** have broad apexes and narrow bases. Their surface has microvilli. The cytoplasm contains yellow pigment that is responsible for the colour of the olfactory mucosa.

The ***basal cells*** are small, spherical or cone-shaped. Basal cells are precursors of both olfactory and supporting cells.

The ***olfactory cells*** are the bipolar neurons. Their apexes possess dilated areas from which arise 6-20 cilia. These cilia are long and immotile and are the structures that respond to odoriferous substances by generating a receptor potential. The axons of olfactory cells unite in small bundles directed toward the central nervous system.

0 Clinical correlations

Hearing loss is any degree of impairment of the ability to apprehend sound.

Sound energy passes through the air of the external ear (air conduction), the bones of the middle ear (bone conduction) and the liquid of the inner ear (water conduction to the organ of Corti).

It is then translated into nerve impulses, sent to the brain through nerves and interpretation by the brain as sound. Hearing can be interrupted at each of these steps. The external ear canal can be blocked with ear wax, foreign objects, infection, and tumors. Several conditions can diminish the mobility of the ossicles in the middle ear. Sensory hearing loss, refers to damage to the organ of Corti and the acoustic nerve.

Prolonged exposure to loud noise is the leading cause of sensory hearing loss. Brain infections like meningitis, drugs such as the aminoglycoside antibiotics (streptomycin, gentamycin, kanamycin, tobramycin), and Meniere's disease also cause permanent sensory hearing loss.

INTEGUMENTARY SYSTEM 0 Overview of

the integumentary system

The ***integumentary system*** comprises of the skin and its derivatives: hair, nails, sweat glands, sebaceous glands, mammary glands.

The skin is the largest organ of the body, constituting 15-20% of total body mass and, in adults, forming 1,2 - 2,3 m^2 of body surface.

Functions of the skin

1. ***Protection*** (mechanical, UV radiation, water conservation) and ***immune response*** (the skin is the first line of defence against pathogens and toxins in the environment).
2. ***Sensation***

Skin is sensitive and causes the body to react to heat, cold, sharp pain, and pressure. Skin can provide protection from injury.

3. ***Body temperature regulation***

Skin controls body temperature by contracting or expanding the blood vessels in the skin. Dilated blood vessels release heat from the body. Contracted blood vessels restrict heat loss. Increased perspiration cools the body while decreased perspiration keeps the body warmer,

5. ***Storage and nutrient synthesis***

Skin stores water, lipids, cholesterol and vitamins A, D, E and K. Interaction with UV light synthesis vitamin D.

6. ***Excretion***

The skin excretes urea and excess minerals.

7. ***Absorption***

The skin absorbs oxygen, carbon dioxide and nitrogen in small amounts. It also absorbs many of the chemicals that are in the environment such as pollution and chemicals from body care and cleaning products.

0 Organization of the skin

The ***skin*** is composed of the ***epidermis*** and the ***dermis*** The junction of dermis and epidermis is irregular, and projections of the dermis called papillae. Beneath the dermis lies the ***hypodermis.*** or subcutaneous tissue (fig. 17.1).

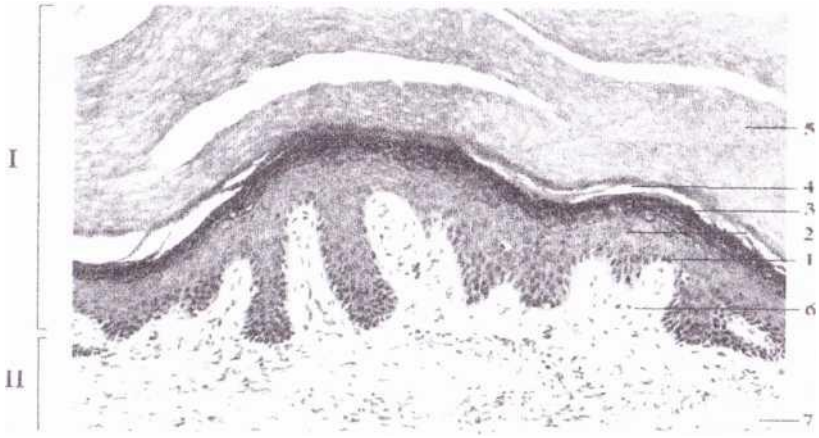


Figure 17.1. **Photomicrograph of human** thick **skin.** I - epidermis: 1 - stratum basale, 2 — stratum spinosum, 3 — stratum granulosum, 4— stratum lucidum, 5 - stratum comeum; II - dermis: 6 - papillary layer, 7 - reticular layer

Epidermis

The ***epidermis*** consists of stratified squamous keratinised epithelium and has 5 layers:

> ***Stratum basale*** consists of a single layer of basophilic columnar cells (keratinocytes) resting on the basal lamina at the dermal-epidermal junction.

> ***Stratum spinosum*** consists of polygonal cells joined to one another by cytoplasm processes. Mitosis occurs in both the above layers and such two layers together are called ***stratum germinativum.***

> ***Stratum granulosum*** consists of I or 5 layers of flattened polygonal cells. These cells contain ***kerotohyalin*** granules.

> ***Stratum lucidum*** is thin layer of flattened eosinophilic cells. The cells are dying or already' dead and contain droplets of ***eleidin,*** precursor of keratin.

> ***Stratum corneum*** consists of 15-20 layers of flattened anucleate keratinized cells whose cytoplasm is filled with scleroprotein, ***keratin.*** The most superficial cells are continuously lost and are replaced by proliferation of cells that arise from mitotic activity in stratum germinativum.

Regional differences if the skin

The epidermis of palm and sole are ***thick***, has 5 layers, is hairless.

Elsewhere, the skin possesses a much thinner epidermis ands is called ***thin*** It contains hair follicles. Its epidermis contains stratum basale, stratum spinosum, stratum granulosum, and a thin stratum comeum. Stratum lucidum is absent.

Cells of the epidermis

The cells of the epidermis consist of different types: ***keratinocytes*** and ***nonkeratinocytes.***

Keratinocytes are the predominant cell type of the epidermis. These cells originate in the basal epidermal layer. Their main functions are:

> production of the major structural protein of the epidermis, keratin;
> formation of the epidermal water barrier.

Nonkeratinocytes

1. Melanocytes are pigment-producing cells. These cells are derived from neural crest and produce ***melanin***, a dark brown pigment. The bodies of these cells are situated at the stratum basale, and highly branching processes are situated at the stratum spinosum (fig. 17.2).

2. Langerhans' cells are star-shaped cells, found mainly in the stratum spinosum of the epidermis. They are bone-marrow-derived macrophages that are capable of binding, processing, and presenting antigens to T lymphocytes. These cells have a significant role in immunologic skin reactions.

3. Merkel's cells generally present in the thick skin of palms and soles. Free nerve ending are present at the base of Merkel's cells. These cells may serve as sensory mechanoreceptors.

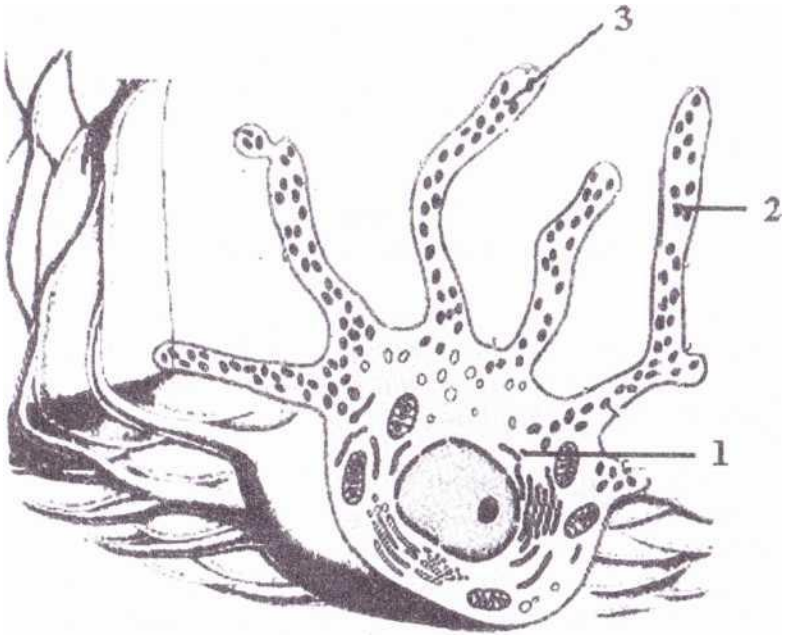


Figure 17.2. Schematic diagram of a melanocyte. 1 - cell body, 2 - processes, 3 - melanin granules (from ***Junqueira L.C., CarneiroJ.,*** 2005)

Dermis

The ***dermis*** is a connective tissue layer containing blood and lymphatic vessels, and nerves of the skin. It also contains hair follicles, sweat and sebaceous glands

The dermis contains 2 layers - the superficial ***papillary*** layer and the deeper ***reticular*** layer.

The thin ***papillary layer*** is composed of loose connective tissue; delicate collagen network contains predominately type 1 and type 111 collagen molecules; elastic fibers form an irregular network.

Sections of skin cut perpendicular to the surface reveal numerous finger-like connective tissue protrusions, dermal papillae that project into the undersurface of the epidermis. Epidermal ridges are epidermal protrusions that project into the dermis. The ridges and papillae are most prominent in the thick skin of the palmar and plantar

surfaces. Ridges form a distinctive pattern that is genetically unique to each individual. These patterns are the basis of the science of dermatoglyphics, or fingerprint or footprint identification.

The ***reticular layer*** is thicker, composed of irregular dense connective tissue. This layer contains thick, irregular bundles of mostly type I collagen and coarser elastic fibers. This elastic network is responsible for the elasticity of the skin. The collagen and elastic fibers form regular lines of tension in the skin, called Langer's lines. Skin incisions made parallel to Langer's lines.

Hypodermis (subcutaneous tissue)

The ***hypodermis*** consists of loose connective tissue that binds the skin to the subjacent organs, making it possible for skin to slide over them.

The hypodermis contains fat cells that vary in number according to the area of the body, and in size according to the nutritional status of the individual.

Sources of development of the structural components of the skin
Epidermis derived from the skin ectoderm.
Dermis derived from dermatomes of the somites of the paraxial mesoderm.
Hypodermis derived from mesenchyme.

13 Derivatives of the skin **Hairs**

The ***hairs*** are elongated keratinized structures. Their colour, size, and disposition vary according to race, age, sex, and region of the body. The hair consists of 2 parts:

> ***shaft*** projects above the skin;

> ***root*** is embedded within the skin epidermal invagination termed the ***hair follicle.***

The ***hair follicle*** is located in the dermis (fig. 17.3).

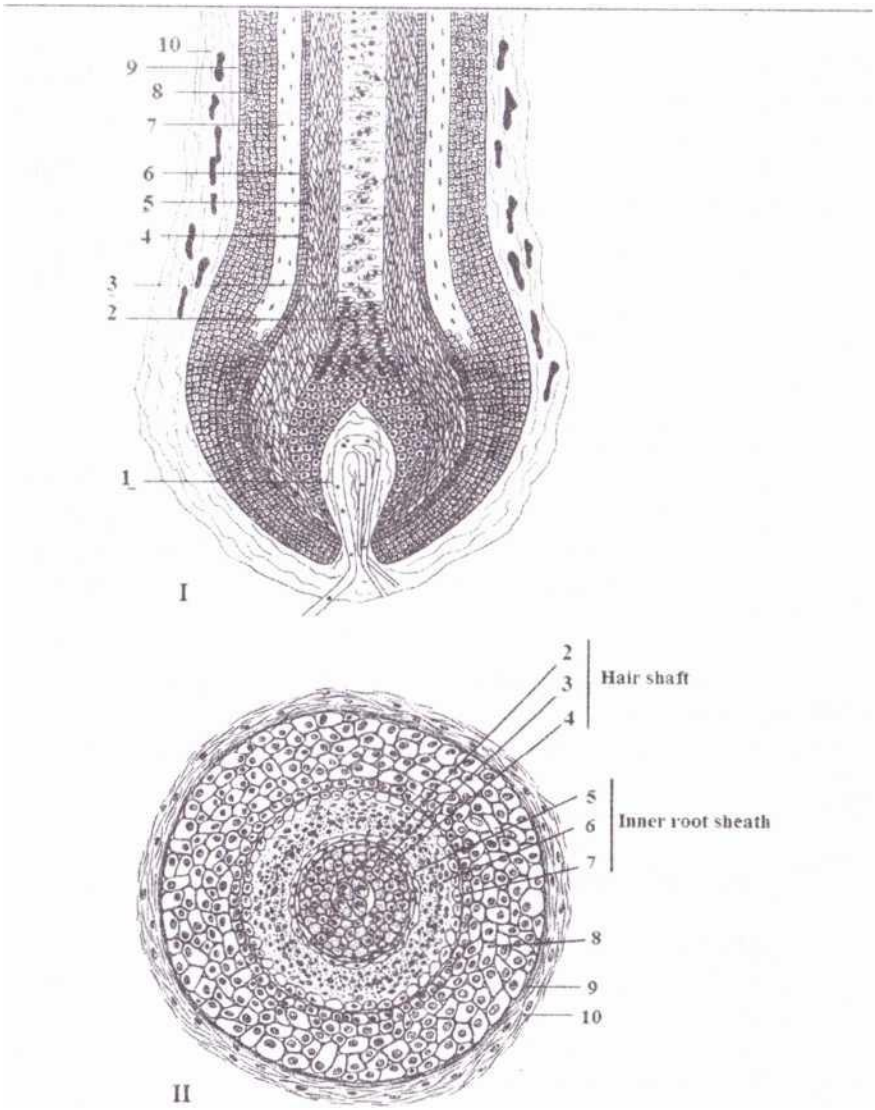


Figure 17.3. Schematic diagram of the hair follicle and hair. I - longitudinal section, II - cross section; 1 - papilla, 2 - medulla, 3 - cortex. 4 - hair cuticle, 5 - inner root sheath cuticle, 6 - Huxley's layer, 7 - Henle's layer, 8 - external root sheath, 9 — glassy membrane, 10 - dermal connective tissue

The ***dermal papilla*** is at the base of the hair follicle. The dermal papilla contains a capillary network. The sebaceous gland is situated in the upper follicle, as is the erector muscle of the hair.

The hair follicle consists of:

> hair bulb,
> inner root sheath,
> hair shaft.

New hair is made inside the onion-shaped ***hair bulb*** that lies within the hair follicle. It has a cavity in which the ***dermal papilla*** is embedded. Special cells in the hair bulb produce the pigment that colours hair. The pigment is called melanin.

The ***bulb*** contains the hair matrix, the germ layer that forms the inner root sheath, and the ***hair shaft*** that is composed of three layers:

> ***medulla,***
> ***cortex*** and
> ***hair cuticle.***

Medulla is the innermost layer. The middle layer - ***cortex*** - contains fibers which are important for hair‘s strength and elasticity. The outermost layer is known as the ***hair cuticle.*** The cuticle is thin and colourless and serves to protect the cortex.

Inner root sheath is derived from the stratum corneum of the epidermis and is composed of three layers:

> ***internal root sheath cuticle*** (keratinized cells),
> ***granular epithelial (Huxley’s) layer*** (1-3 layers of homy, flattened, nucleated cells rich in trichohyalin granules) and
> ***pale epithelial (Henle’s) layer*** (a single layer of cuboidal epithelium forming the outer boundary of the inner stratum of a hair follicle).

Outer root sheath surrounds the hair follicle and secures the hair shaft within the follicle. ***Outer root sheath*** is derived from the stratum germinativum of the epidermis and is composed of several layers of cells similar to the epidermis.

External to this layer is a homogeneous ***glassy membrane*** corresponding to the basal lamina of the epidermis.

Entire root sheath (inner and outer) is enclosed by ***connective tissue sheath*** derived from the dermis.

Nails

The ***nail*** is plate of keratinised epithelial cells on the dorsal surface of each distal phalanx (fig. 17.4).

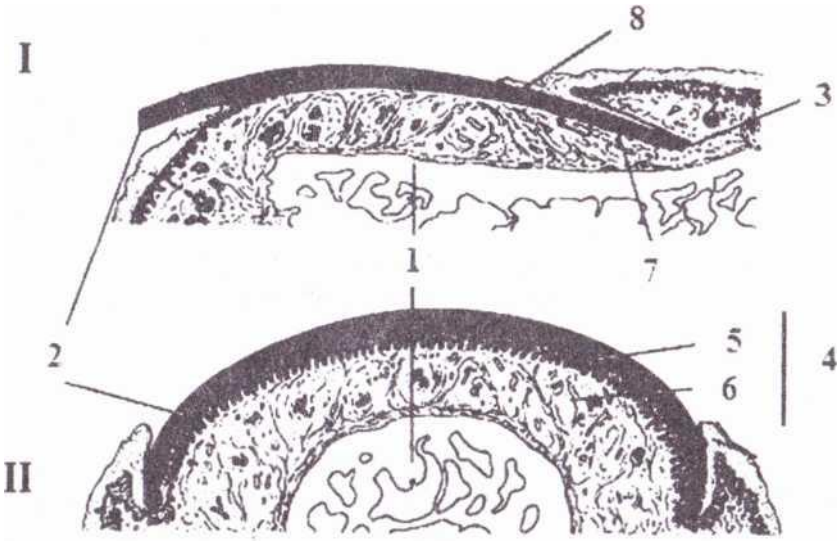


Figure 17.4. Nail and its components. I — longitudinal section, **II** — cross section; 1 - distal phalanx, 2 - nail plate, 3 - nail root. 4 - nail bed: 5 - epithelium, 6 - connective tissue, 7 - nail matrix, 8 - eponychium

The proximal part of the nail is the ***nail root.*** The epithelium covering the nail root consists of usual layers of cells. The stratum corneum of this epithelium forms the ***eponychium***, or ***cuticle.***

The ***nail plate*** rests on the bed of epithelium called ***nail bed.*** Only the stratum basale and stratum spinosum of epidermis and connective tissue are present in the nail bed. The part of the nail bed supporting the root ol the nail is called ***nail matrix,*** from which new formation of nail takes place.

Glands of the skin

Sweat glands

The ***sweat glands*** produce sweat or perspiration. Besides excretion these glands help in temperature regulation by sweating.

There are 2 types of sweat glands - ***merocrine*** and ***apocrine.***

The ***merocrine sweat glands*** are present in the skin of all parts of the body. They are simple, coiled tubular glands whose ducts open at the skin surface.

The swear gland consists of 2 parts (fig. 17.5):

Figure 17.5. Sweat gland. 1 - secretory portion, 2 - secretory cells, 3 - myoepithelial cells, 4 -duct (from ***K).H.A(panacbee, H.A.IOpumi u dp***., 1999)

> ***secretory portion*** lies deep in the dermis, lined by a single cuboidal epithelium. Myoepithelial cells surround secretory cells;
> ***ducts*** are lined by 2 layers of dark cuboidal cells.

The ***apocrine sweat glands*** are present in the subcutaneous tissue ol the axillary, areolar, and anal regions. Their ducts open into hair follicles. These glands become fully developed only after puberty. They are large and branched tubular glands. The lumen of secretory part is large. The lining of epithelium may be squamous, cuboidal or columnar. The secretions of apocrine sweat glands are viscous.

Sebaceous glands

The ***sebaceous glands*** are branched alveolar glands of the holocrine type.

The ***secretory portion*** of the gland (the acini) consists of 2 types of epithelial cells (fig. 17.6):

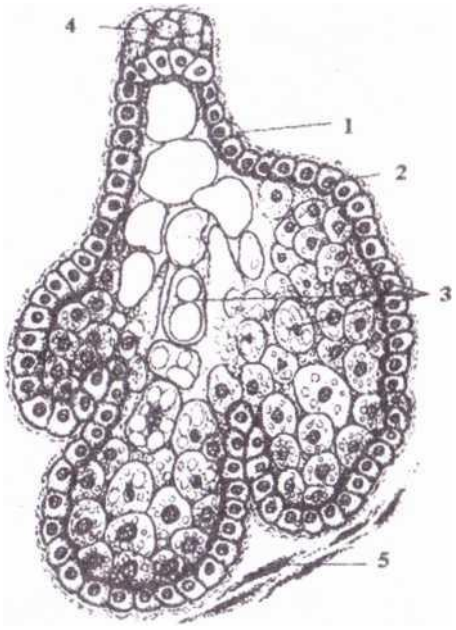


Figure 17.6. Sebaceous gland. 1 - basal lamina, 2 - basal cells, 3 - inner cells, 4 - duct, 5 - arrector pili

> small outmost ***basal cells*** rest on the basal lamina.
> ***inner cells*** are larger, more rounded and filled with lipid.

The ***ducts*** usually end in the upper portion of the hair follicle. They are very short and lined by stratified epithelium.

The secretion of the sebaceous glands is called ***sebum.*** Its oily nature helps to keep the skin and hair soft. It helps to prevent dryness of the skin and also makes it resistant to moisture.

0 Clinical correlations

Albinism, an inherited disorder, is caused by the absence of the pigment melanin and results in no pigmentation in skin, hair, or eyes. Albinos have an abnormal gene, which restricts the body from producing melanin. There is no cure for albinism, and individuals should use a sunscreen at all times because they are much more likely to get sun damage and skin cancer. This disorder can occur in any race. ***Vitiligo*** is a pigmentation disorder in which melanocytes (the cells that make pigment) are destroyed. As a result, white patches of skin appear on different parts of the body. The cause of vitiligo is not known, but some possible causes include physical trauma or certain diseases such as diabetes. There is no cure for vitiligo, but there are several treatments, including light-sensitive drugs used in combination with ultraviolet light treatment. _____

RESPIRATORY SYSTEM

0 Overview of the respiratory system

The respiratory system includes the lungs, series of air passages that link the sites of gas exchange w ith the external environment and the respiratory' muscles.

Functions of the respiratory system are:

1) respiration (gas exchange);
2) conditioning of the air (warming, moistening, removal of particulate materials);
3) vocalization (when the air passes through the pharynx and larynx, it makes the vocal cords in larynx to vibrate which helps in production of sound and speech in humans);
4) sense of smell (olfactory mucosa of the nasal cavity);
5) endocrine functions (hormone production and secretion of prostaglandins, angiotensin I);
6) coughing and sneezing (when any foreign particles enter the nasal passages, it can result into irritation; these irritants are forced out of the respiratory tract through cough or even sneeze);
7) protective (airway epithelial cells can secrete a variety of molecules that aid in lung defense: secretory immunoglobulins (IgA), collectins (including surfactant), and other peptides; these secretions can act directly as antimicrobials to help keep the airway free of infection);
8) fibrinolysis (lungs contain a fibrinolytic system that lyses clots in the pulmonary vessels).

The respiratory system is divided into two ***principal regions:***

> ***conducting portion***, consisting of
  - nasal cavity,
  - nasopharynx,
  ® larynx,

- trachea,
- bronchi,
- bronchioles, and
- terminal bronchioles.

The conducting portion serves two main functions:

- to provide a conduit through which air can travel to and from the lungs;
- to conditioning the inspired air;

and

> ***respiratory portion,*** consisting of

- respiratory bronchioles,
- alveolar ducts,
- alveolar sacs, and
- alveoli.

The ***function*** of respiratory portion is the exchange of oxygen and carbon dioxide between inspired air and blood.

0 Conducting portion

The wall of the conducting portion of the respiratory system consists of:

I. ***mucosa.***

1) respiratory ***epithelium*** - pseudostratified columnar ciliated (simple cuboidal in the smallest airways);

2) ***lamina propria*** consists of loose connective tissue, contains lymphoid aggregations; these form part of the mucosa-associated lymphoid tissue, which secrete Ig A as a defense against invading microorganisms;

3) ***muscularis*** mucosa consists of smooth muscle tissue, becomes increasingly prominent as the airway diameter decreases;

II. ***submucosa*** consists of loose connective tissue, contains serous and mucous glands which become less numerous in the narrow airways and are not present beyond the tertiary bronchi;

III.***fibro-cartilage layer*** diminishes as the diameter of the airway decreases to be absent beyond the tertiary bronchi;

IV. ***adventitia*** consists of loose connective tissue.

Respiratory epithelium consists of' five cell types (fig, 18.1):

1. ***ciliated columnar cells*** constitute the most abundant type; they have about 300 cilia on its apical surface;
2. ***mucous goblet cells*** have mucous droplets on their apical portion;
3. ***brush cells*** have numerous microvilli on their apical surface. The basal surface of these cells is in contact with afferent nerve endings. Thus, the brush cells are regarded as a receptor cells;
4. ***basal (short) cells*** are small rounded cells that lie on the basal lamina; they differentiate into the other cell types;
5. ***small granule cells*** have numerous granules; these cells constitute a population of cells of the diffuse neuroendocrine system.

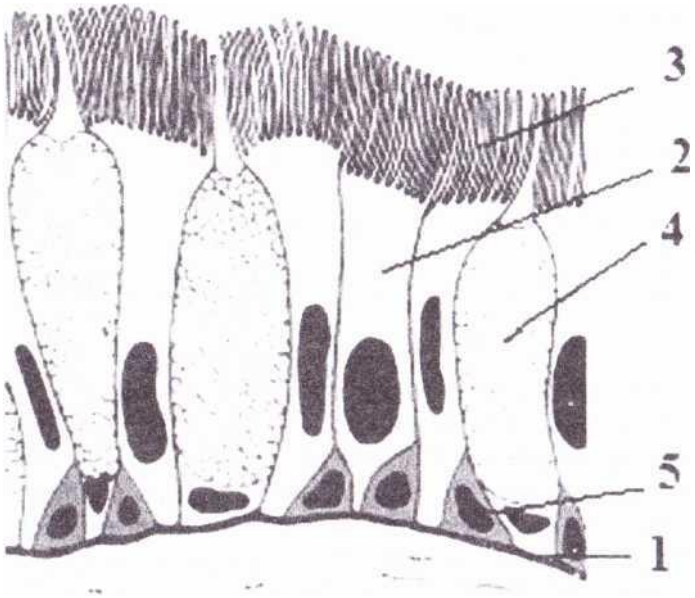


Figure 18.1. Schematic diagram **of the respiratory epithelium. 1** - basal lamina, 2 - ciliated columnar cell, 3 - cilia, 4 - goblet cell, 5 - basal cell

Nasal cavity

The ***nasal cavity*** consists of vestibule, respiratory region, and olfactory region.

Vestibule is lined by stratified squamous epithelium, contains numerous hairs, sebaceous and sweat glands

Respiratory region is lined by pseudostratified columnar ciliated epithelium with numerous goblet cells; the lamina propria is very vascular, which serves to warm the inspired air; it contains serous and mucous glands.

Paranasal sinuses are lined by pseudostratified columnar ciliated epithelium with few goblet cells.

Trachea

The ***trachea*** has 4 layers (fig. 18.2):

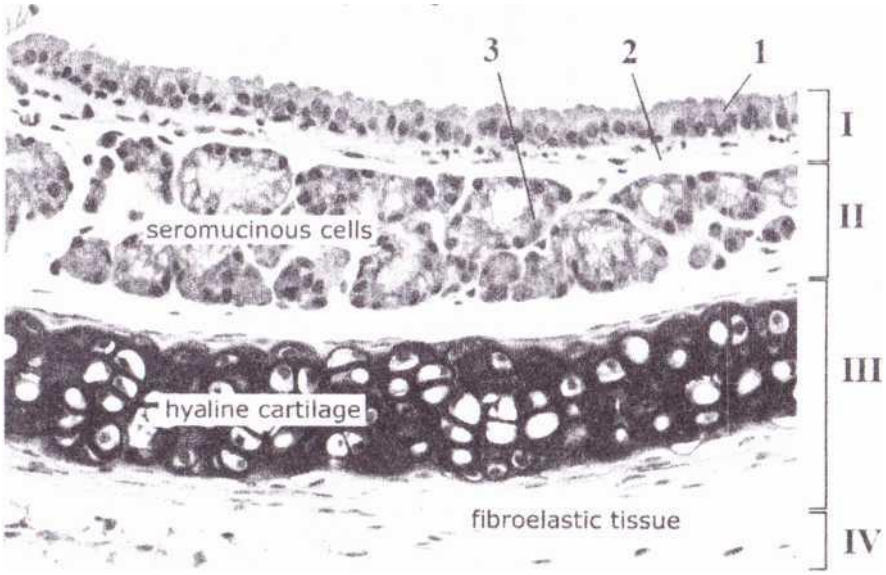


Figure 18.2. Photomicrograph of trachea. I - mucosa: 1 - respiratory epithelium, 2 - lamina propria; **II** - submucosa: 3 - secretory portions of gland; **III** - fibro-cartilage layer; **IV** - adventitia

I. *mucosa*

1) ***respiratory epithelium*** is pseudostratified columnar ciliated;

2) ***lamina propria*** consists of loose connective tissue with elastic fibers, contains mucous, serous and mixed glands;

II. ***submucosa*** consists of loose connective tissue, contains serous and mucous glands;
III. ***fibro-cartilage layer*** contains 16-20 hyaline C-shaped rings; the posterior ends of the cartilages are connected by connective tissue and smooth muscle;
IV. ***adventitia*** consists of loose connective tissue.

Bronchial tree (fig. 18.3)

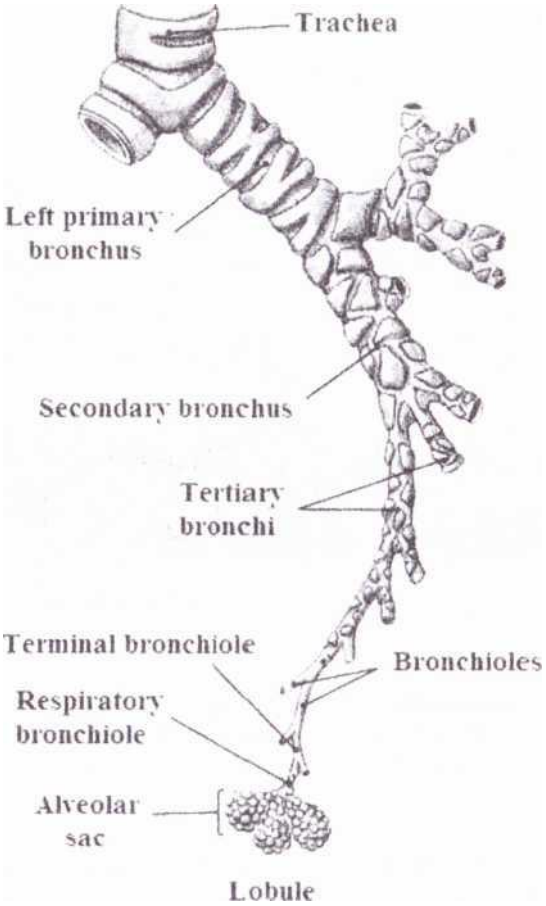


Figure 18.3. Schematic diagram of the bronchial tree.

The trachea divides into 2 primary bronchi that enter the lungs at the hilum. After entering the lungs, the ***primary bronchi*** give rise to three bronchi in the right lung and two in the left lung, each of which supplies a pulmonary lobe. These ***lobar bronchi*** divide repeatedly, giving rise to smaller bronchi, whose terminal branches are called ***bronchioles.*** Each bronchiole enters a pulmonary lobule, where it branches to form 5-7 ***terminal bronchioles.***

Histologically bronchi are divided into ***large***, ***middle*** and ***small.*** The wall of bronchi has features in each part of a bronchial tree.

Main (primary) bronchi (diameter 15 mm) have the same structure as a trachea.

Large bronchi (diameter 10-15 mm) (lobar or secondary, segmental or tertiary) (fig. 18.4) are lined by pseudostratified columnar ciliated epithelium with numerous goblet cells; muscularis mucosa forms closed rings, glands are numerous, the cartilage rings are replaced by isolated plates.

Middle bronchi (diameter 5-2 mm) (subsegmental) are covered by pseudostratified columnar epithelium which is lower, than in large, with the smaller content of goblet cells; a smooth muscle cells form crisscrossing bundles; glands are few, fibrocartilage layer contains the islands of an elastic cartilage.

Small bronchi (diameter 2 mm or less) (intralobular) (fig. 18.5) are covered by lower epithelium, than middle, goblet cells are individual; glands and cartilage are absent, a smooth muscle cells form circular bundles. Smooth muscle tone controls the diameter of the conducting passages.

Terminal bronchioles are more distal part of the conducting passages with diameter 1mm or less. They are lined by simple cuboidal epithelium containing ***Clara cells.*** Cartilage, glands and goblet cells are absent; lamina propria contains the elastic fibers and smooth muscle cells which are spirally arranged.

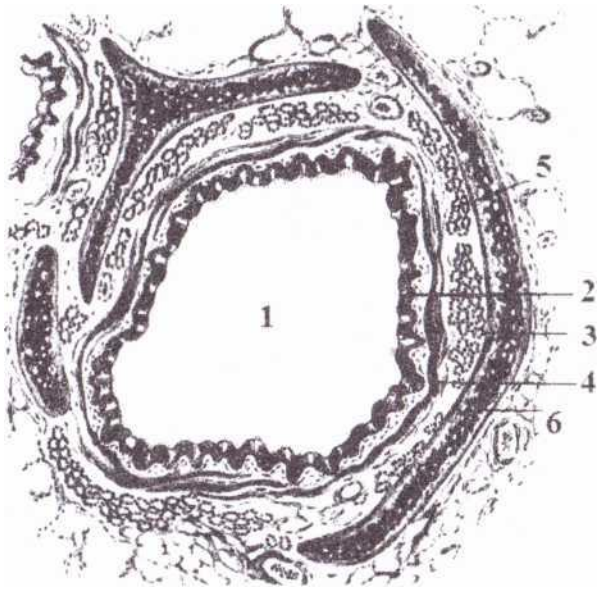


Figure 18.4. Large bronchus. 1 - lumen 2 - pseudostratified columnar ciliated epithelium, 3 - lamina propria, 4 - muscularis mucosa, 5 - glands, 6 - hyaline cartilage

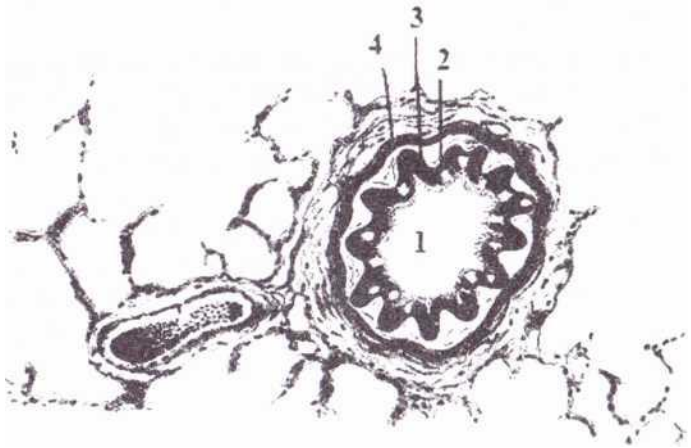


Figure 18.5. Small bronchus. 1 - lumen, 2 - pseudostratified ciliated epithelium, 3 — lamina propria, 4 — muscularis mucosa

Clara cells (nonciliated bronchiolar secretory cells) are domeshaped cells with short microvilli found in the small airways (bronchioles) of the lungs. These cells may secrete glycosaminoglycans to protect the bronchiole lining. One of the main functions of Clara cells is to protect the bronchiolar epithelium. They do this by secreting a small variety of products, including Clara cell secretory protein (CCSP) and a solution similar to the component of the lung surfactant. They are also responsible for detoxifying harmful substances inhaled into the lungs.

0 Respiratory portion of the respiratory system

The ***respiratory portion*** of the respiratory' system consists of structural and functional units - ***acini,*** - each includes ***respiratory bronchioles***, ***alveolar ducts*** and ***alveolar sacs*** (fig. 18.6).

Acini separate by thin layers of loose connecting tissue; 12-18 acini form pulmonary lobule.

Respiratory' bronchioles

Each terminal bronchiole subdivides into 2 ***respiratory bronchioles.*** The respiratory bronchiolar structure is identical to that of the terminal bronchioles. But the wall of respiratory bronchiole is beset with a number of alveoli, where gas exchange occurs.

Alveolar ducts

Each respiratory bronchiole divides into ***alveolar ducts.*** They are lined by squamous epithelium. In the lamina propria surrounding the rim of the alveoli is a network of smooth muscle cells. The smooth muscle of the respiratory bronchioles and alveolar ducts regulates alveolar air movements. Smooth muscle disappears at the distal ends of alveolar ducts. Alveolar ducts open into atria that communicate with alveolar sacs. Each of alveolar ducts gives rise to several alveoli.

Alveoli

Alveoli are saclike evaginations of the respiratory bronchioles, alveolar ducts, and alveolar sacs.

Alveoli are densely packed together; inter-alveolar septa form a common wall between adjacent alveoli. These septa contain network of elastic fibers and blood vessels. Neighbouring alveoli may be connected to each other by small ***alveolar (Kohn')pores*** (fig. 18.7).

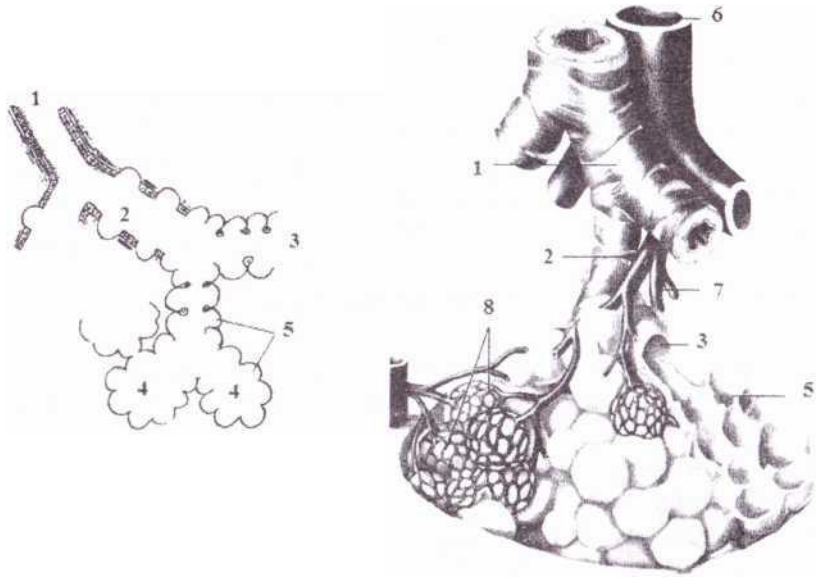


Figure 18.6. Schematic diagrams of the terminal bronchiole and acinus of the lung. 1 — terminal bronchiole, 2 — respiratory bronchiole, 3 — alveolar duct, 4 — alveolar sacs, 5 - alveoli, 6 - branch of pulmonary artery, 7 - arteriole, 8 - capillaries

Alveoli are lined by simple squamous epithelium. Alveolar epithelium consists of cells of two types:

> ***type I cell*** (squamous alveolar cell) are flattened, irregularshaped, make up 97% of the alveolar surface. They are the component of air- blood barrier;

> ***type II cells*** (great alveolar cells) are rounded in shape, occupy 3% of the alveolar surface area. These cells are typical secretory cells; they secrete a surface-active lipoprotein complex (phospholipoprotein) called ***surfactant.*** Surfactant reduces surface tension and prevents alveoli from collapsing during expiration.

Brush cells are also present in the alveolar wall, but they are few in number. They may serve as receptors that monitor air quality in the lung.

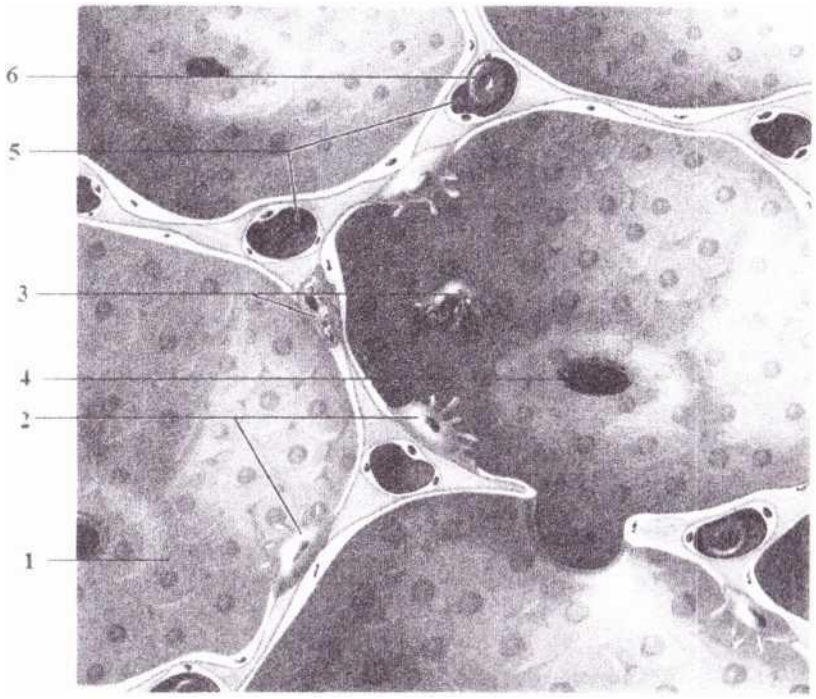


Figure 18.7. Schematic diagram of pulmonary alveoii. 1 - type I cell, 2 - type II cell, 3 - alveolar macrophage, 4 - alveolar pore, 5 - capillaries, 6 - erythrocyte

Alveolar macrophages or dust cells are found in the alveolar wall or free in the alveolar space. They are derived from blood monocytes.

0 Air-blood barrier

Air in the alveoli is separated from capillary blood by components, which form the ***air-blood harrier*** (fig. 18.8).

The air-blood barrier exists in the gas exchanging region of the lungs. It exists to prevent air bubbles from forming in the blood, and from blood entering the alveoli.

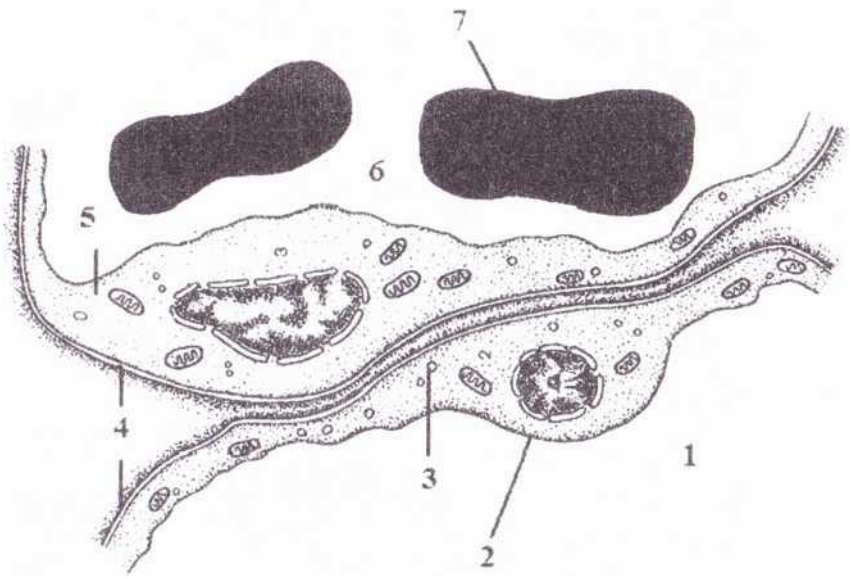


Figure **18.8.** Schematic diagram of the air-blood barrier. 1 - alveole, 2 - surfactant, 3 - type I cell, 4 - fused basal laminae, 5 - endothelial cell, 6 - capillary, 7 - erythrocytes

The ***air-blood barrier*** is formed by:

1) cytoplasm of type 1 cells;
2) fused basal laminae of the alveolar and endothelial cells;
3) cytoplasm of endothelial cells.

The barrier is permeable to molecular oxygen, carbon dioxide, carbon monoxide and many other gases.

0 Pleura

The ***pleura*** is a serous membrane which folds back onto itself to form a two-layered, membrane structure. The thin space between the two pleura! layers is known as the pleural cavity; it normally contains a small amount of pleural fluid. The outer pleura (parietal pleura) is

attached to the chest wall. The inner pleura (visceral pleura) covers the lungs and adjoining structures.

Pleura is formed by mesothelial cells overlying vascularised loose connective tissue.

The parietal pleura is highly sensitive to pain while the visceral pleura is not, due to its lack of sensory innervation.

0 Development of the respiratory system

Upper part of respiratory system (from nose to larynx) develops from the pharyngeal apparatus which is a part of head and neck.

Lower part of respiratory system (below the larynx up to lung alveoli) develops from a ventral evagination of the foregut (laryngotracheal diverticulum) (fig. 18.9).

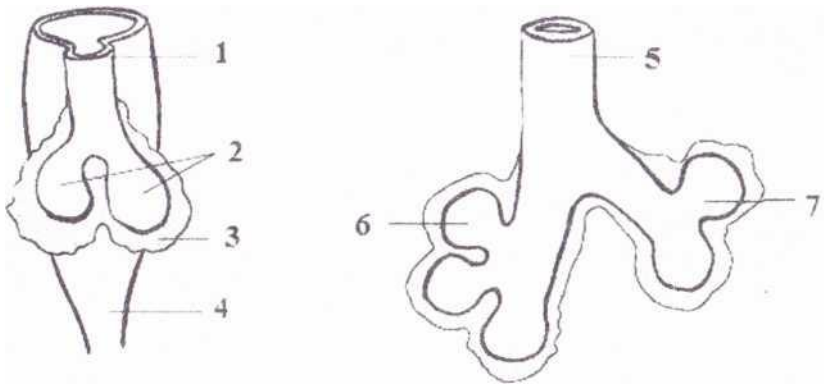


Figure 18.9. Stages in the development of the bronchi and lungs. 1 - laryngotracheal fold and groove, 2 - lung buds, 3 — mesenchyme, 4 - esophagus, 5 - trachea, 6 — right lobar bronchi, 7 - left lobar bronchi

The laryngotracheal diverticulum arises from endoderm on the ventral wall of the foregut. Tracheoesophageal folds develop on either side and join to form a tracheoesophageal septum that separates it from the rest of the foregut. This divides the foregut into the laryngotracheal tube (ventral) and the esophagus (dorsal). The caudal end of the

laryngotracheal diverticulum enlarges to form the lung bud, which is surrounded by mesenchyme.

After that the lung bud divides into two bronchial buds, which enlarge to form the bronchi.

The bronchial buds give rise to the epithelium lining all the respiratory passages, the alveoli and the associated glands.

The surrounding mesenchyme gives rise to the connective tissue, cartilage, muscle and blood vessels.

0 Clinical correlations

Respiratory distress syndrome is common in premature infants and is due to a deficiency of surfactant.

Asthma is chronic disease of the airways characterized by variable and recurring symptoms, reversible airflow obstruction, and bronchospasm. Patients with asthma have two different pathologic processes that make breathing difficult. First, there is inappropriate constriction of airway smooth muscle. This affects primarily the bronchioles, which have no cartilage to keep them open. Second, there is excessive mucus secretion.

Emphysema is chronic obstructive pulmonary disease characterized by is an abnormal permanent enlargement of air spaces distal to the terminal bronchioles. Emphysema is called an obstructive lung disease because the destruction of lung tissue around alveoli makes them unable to hold their functional shape upon exhalation.

This causes the small airways to collapse during forced exhalation, as alveolar collapsibility has decreased. As a result, airflow is impeded and air becomes trapped in the lungs, in the same way as other obstructive lung diseases. Symptoms include shortness of breath on exertion, and an expanded chest. Emphysema is often caused by smoking.

CARDIOVASCULAR SYSTEM

13 Overview of the cardiovascular system

The **cardiovascular** ***system*** consists of the ***blood*** and ***lymphatic vascular systems.***

The ***blood vascular system*** is composed of the following structures:

> the ***heart***, whose function is to pump the blood,

> the ***arteries,*** whose function is to carry the blood with nutrients and oxygen to the tissues,

> the ***capillaries***, a diffuse network of thin tubules through whose walls the interchange between blood and tissues takes place,

> the ***veins,*** whose function is to convey products of metabolism toward the heart.

The ***lymphatic vascular system*** begins in the ***lymphatic capillaries,*** blind-ended tubules that terminate in the ***blood vascular system*** emptying into the large veins near the heart. The function of the lymphatic system is to return to the blood the fluid of the tissue spaces.

0 General structure of blood vessels

The ***blood vessels*** have a common basic structure.

Blood vessels are usually composed of the following layers, or tunics (fig. 19.1):

I. ***tunica intima*** consists of:

1) layer of ***endothelial cells*** lining the vessels interior surface; these cells rest on a basal lamina;

2) ***subendothelial layer***, consisting of loose connective tissue;

3) in arteries the intima is separated from the media by an ***internal elastic lamina***, composed of elastin;

II. ***tunica media*** consists of smooth muscle cells; interposed among the smooth muscle cells are variable amounts of elastic and reticular fibers.

In larger arteries, a thinner ***external elastic lamina*** separates the media from the outer tunica adventitia;

III. ***tunica adventitia*** consists of loose connective tissue with longitudinally oriented collagen and elastic fibers; it contains nerves and vasa vasorum.

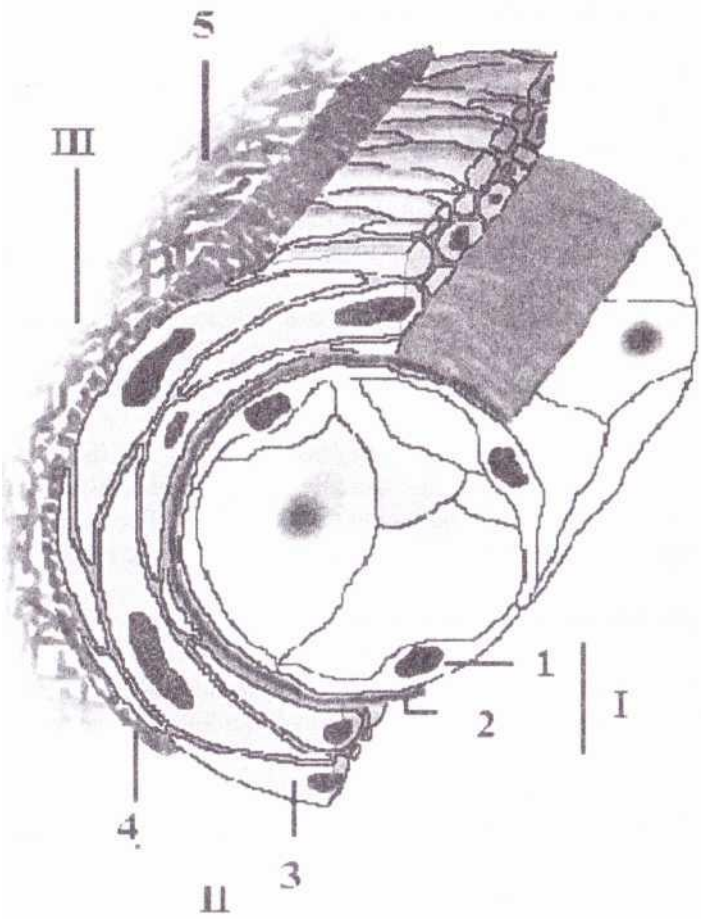


Figure 19.1. Schematic diagram of blood vessel wall. I- tunica intima: **1** — endothelial cells, 2 - internal clastic lamina, II - tunica media: 3 - smooth muscle cells, 4 - external elastic lamina, III - tunica adventitia: 5 - loose connective tissue

Blood vessels are structurally adapted according to hemodynamic factors.

0 Arteries

Arteries transport blood to tissues. They resist changes in blood pressure in their initial portions and regulate blood flow in their terminal portions.

There are 3 main types of arteries:

> Elastic (large) arteries
> Muscular (medium) arteries
> Small arteries and arterioles

Elastic arteries

The blood is pumped from the heart into large, ***elastic*** (conduction) arteries. The aorta and its large branches are the typical elastic arteries.

Elastic arteries have the following characteristic (fig. 19.2):

I. ***tunica intima:***

1) ***endothelium*** is smooth without of folds;
2) ***subendothelial layer*** is thick and contains collagen and elastic fibers;
3) ***internal lamina*** is present;

II. ***tunica media*** consists of concentrically arranged perforated elastic laminae (fig. 19.3);

III. ***tunica adventitia*** consists of loose connective tissue, contains elastic and collagen fibers, blood vessels and nerves.

Muscular (medium) arteries

Blood passes from the elastic arteries via arteries of intermediate type into the ***muscular*** (distribution) arteries.

Most of the arteries in the human body are ***muscular arteries.***

In muscular arteries (fig. 19.3): the blood passes at a reduced pressure and speed. The size of their lumen is controlled by contraction or relaxation of smooth muscle on their wall.

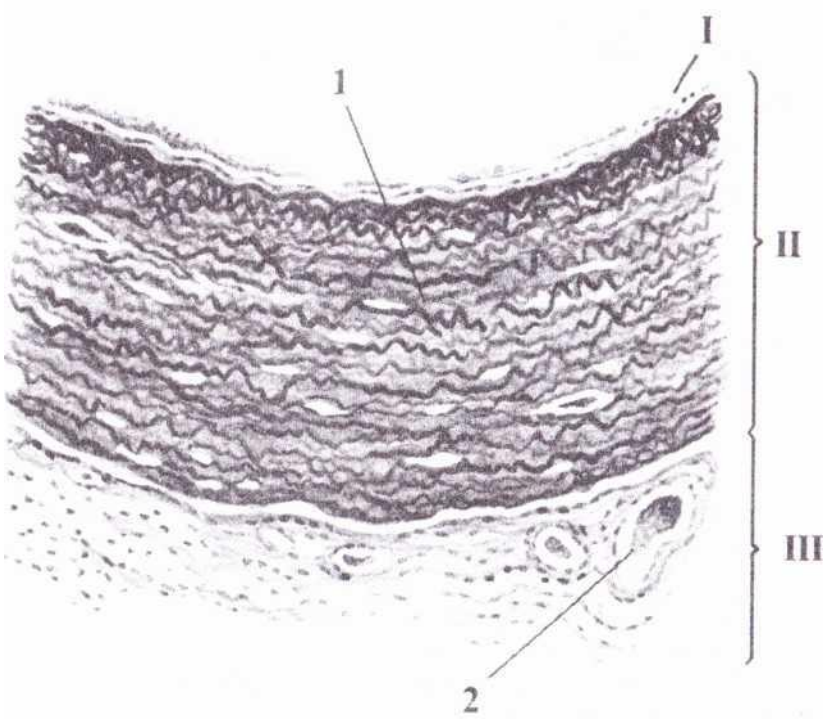


Figure 19.2. Schematic diagram of the aorta. I - tunica intima, II - tunica media, III — tunica adventitia, 1 - perforated elastic laminae, 2 - vasa vasorum

Muscular arteries have the following characteristic

I. ***tunica intima*** forms numerous small folds, and contains:

1) ***endothelium*** is simple squamous epithelium,

2) ***subendothelial layer*** contains a few smooth muscle cells,

3) ***internal elastic lamina*** is prominent and forms small wavy folds;

II. ***tunica media*** comprises a thick layer of circumferentially arranged smooth muscle; ***external elastic lamina*** is present in large muscular arteries;

III.***tunica adventitia*** consists of loose connective tissue, contains elastic and collagen fibers.

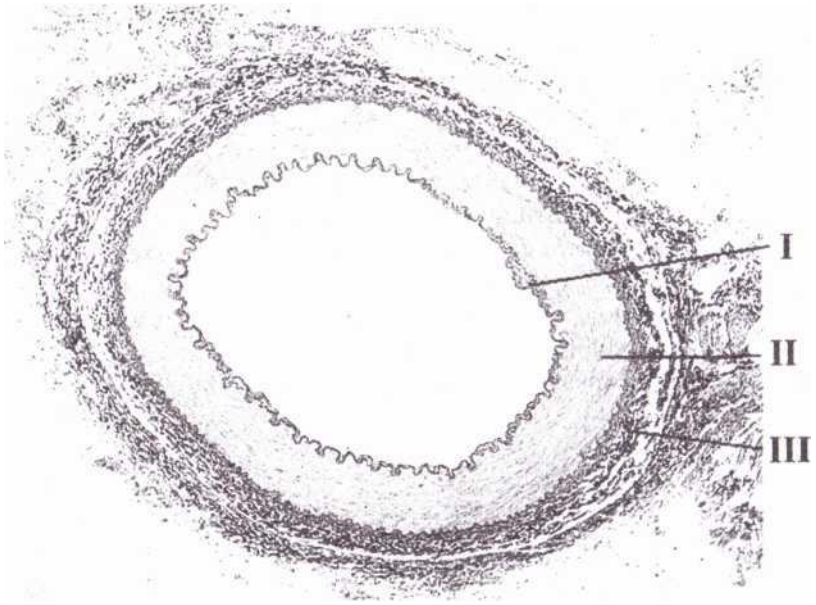


Figure 19.3. Photomicrograph of the muscular artery. I — tunica intima, II - tunica media, III - tunica adventitia

Arterioles

These are generally less than 0,5 mm in diameter and have relatively narrow lumens. The wall of the arterioles contains:

I. ***tunica intima*** forms numerous small folds, consists of:

1) ***endothelium*** is simple squamous epithelium,

2) ***subendothelial layer*** is very thin.

3) ***internal elastic lamina*** is prominent and forms small wavy folds;

II. ***tunica media*** composed of one or two circularly arranged layers of smooth muscle cells; external elastic lamina is absent;

III. ***tunica adventitia*** is thin.

Specialized sensory structures in arteries

Specialized sensory structures in arteries participate in reflex regulation of a circulation

I. ***The carotid sinus*** is near the bifurcation of the common carotid artery , this is dilating of a lumen of an internal carotid artery immediately near of its ramification from the common carotid artery (fig. 19.4).

There are numerous ***baroreceptors*** in the tunic adventitia of carotid sinus. From the baroreceptors information enters in the centers regulating activity of cardiovascular system.

II. ***Carotid body*** is small structure encountered near the bifurcation of the common carotid artery (fig. 19.4, 19.5) acts as chemoreceptors sensitive to low oxygen tension, high carbon dioxide concentration, and low arterial blood pH.

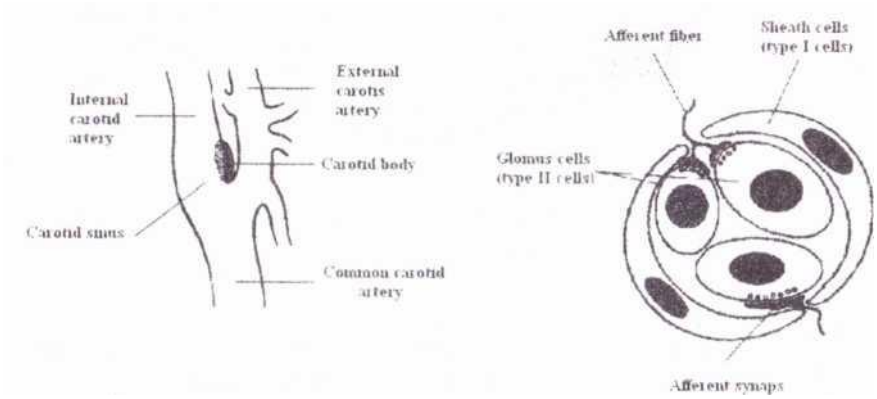


Figure 19.4. Localization of the carotid sinus Figure 19.5. Cells of carotid body and carotid body

The carotid body consists of glomus cells (type I cells) and sheath cells (type II cells) surrounded by a rich vascular supply whose capillaries are of the fenestrated type. Most of the nerves of the carotid body are afferent fibers.

III. ***Aortic bodies*** and ***jugular glomera*** are similar in structure to the carotid body and are thought to have a similar function.

0 Veins

The ***veins*** return blood to the heart, aided by the action of smooth muscle and specialized valves.

Classification of the veins

> Unmuscular (atypical)
> Muscular
1) with weak development of muscular elements;
2) with middle development of muscular elements;
3) with strong development of muscular elements
> Venules

Unmuscular veins

The ***unmuscular veins*** are in organs with dense walls (meninges, bones, spleen, etc.) with which they strongly fuse external tunic.

The wall of these veins consists of endothelium, which is surrounded by layer of a connective tissue. Smooth muscle cells are absent.

Muscular veins with weak development of muscular elements The ***muscular veins with weak development of muscular elements*** (fig. 19.6) are above the level of the heart on which blood goes passively owing to weight. The structure of the wall of these vessels has the following characteristics:

I. ***tunica intima:***
1) ***endothelium.***
2) ***subendothelial layer*** is weak-developed ,
3) internal lamina is absent;
II. ***tunica media*** is thin with small amount of smooth muscle cells; external elastic lamina is absent;
III. ***tunica adventitia*** contains loose connective tissue.

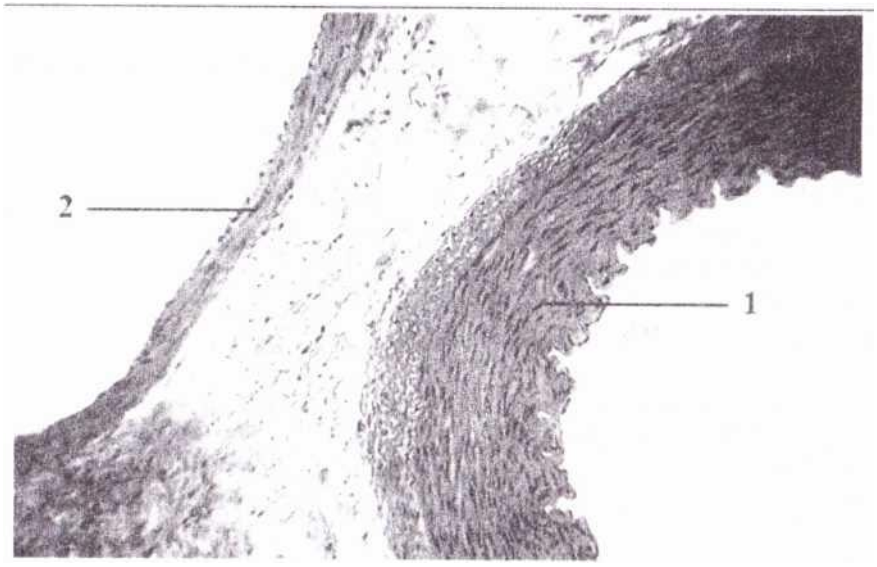


Figure 19.6 Photomicrograph of a muscular artery (1) a muscular vein (2).

Muscular veins with middle development of muscular elements

The ***muscular veins with middle development of muscular elements*** are on the level of the heart. The structure of the wall of these vessels has the following characteristics:

I. ***tunica intima*** forms the ***valves*** and consists of:

1) ***endothelium.***

2) ***suhendothelial layer*** is weak-developed ,

3) internal lamina is absent:

II. ***tunica media*** consists of few layers of smooth muscle cells; external elastic lamina is absent;

III. ***tunica adventitia*** contains loose connective tissue.

Muscular veins with strong development of muscular elements

The ***muscular veins with strong development of muscular elements*** are below the level of the heart.

These veins contain well developed bundles of smooth muscle cells in all three tunics: in intima and adventitia bundles have a longitudinal direction, and on the media - circular.

There are numerous valves.

Valves consist of two semilunar folds of the tunica intima that project into the lumen. They are composed of elastic connective tissue and are lined on both sides by endothelium.

Venules

The ***venules*** have very thin walls:

I. ***tunica intima*** consists of endothelial cells;

II. ***tunica media*** may contain only contractile pericytes, but a few smooth muscle cells are usually present;

III. ***tunica adventitia*** consists of loose connective tissue.

0 Capillaries

The ***capillaries*** are microscopic vessels with diameter of about 8 pm. They branch and anastomose to form a diffuse network. Capillaries have structure to permit metabolic exchange between blood and surrounding tissues.

General structure of capillaries

Capillaries are composed of (fig. 19.7):

I. single layer of polygonal ***endothelial cells***; external surface of endothelial cells rest on the ***basal lamina***;

II. ***pericytes*** are cells with long cytoplasmic processes that partly surround the endothelial cells; pericytes have contractile function.

There are 3 main types of capillaries (fig. 19.8):

> ***Continuous,*** or ***somatic,*** capillaries have uninterrupted lining of endothelial cells and basal lamina (fig. 19.8-1);

Distribution-, all kinds of muscle tissue, connective tissue, exocrine glands, nervous tissue.

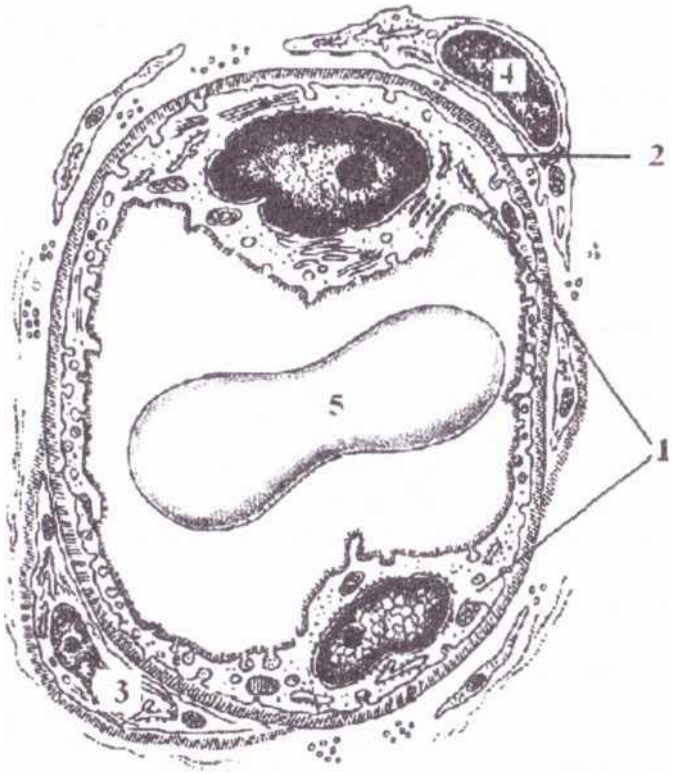


Figure 19.7 Structure of capillary. 1 - endothelial cell, 2 - basal lamina, 3 - pericytes, 4 - adventitial cell, 5 - erythrocyte

> ***Fenestrated***, or ***visceral***, capillaries have large fenestrae that are closed by a diaphragm; a continuous basal lamina is present (fig. 19.8-11).

Distribution, endocrine glands, glomerulus of kidney.

> ***Discontinuous sinusoidal*** capillaries have wide diameter (30-40 jim). The endothelial wall is discontinuous, and endothelial cells show multiple fenestrations (fig. 19.8-lII).without diaphragms; the basal lamina is discontinuous.

Distribution, the liver, hematopoietic organs such as bone marrow and spleen.

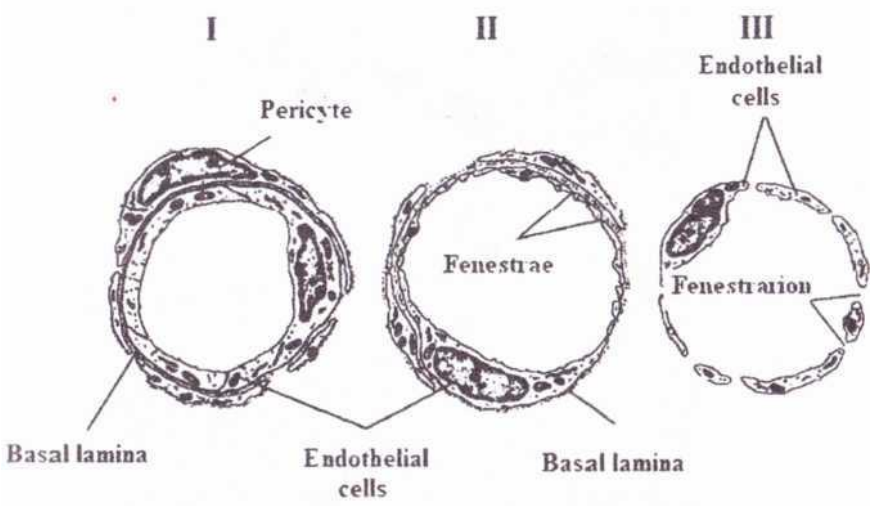


Figure 19.8 Types of capillaries. I - continuous (somatic) capillary, **II** - fenestrated (visceral) capillary, III - discontinuous sinusoidal capillary

0 Lymphatic vascular system

Lymphatic vascular system consists of endothelium-lined thin- walled channels that collect fluid from the tissue spaces and return it to the blood. This fluid is called lymph, it circulate in only one direction - toward the heart.

Three types of lymph vessels can be distinguished based on their size and morphology.

Lymphatic capillaries begin as blind-ending tubes in connective tissue (fig. 19.9).

The basal lamina is absent and the endothelial cells do not form tight junctions, which facilitates the entry of liquids into the lymph capillary. Temporary openings in the endothelial lining of the lymph capillaries also allow the entry of larger particles into the lymph capillaries. Collagen filaments ***(anchoring filaments***) link the endothelium to the surrounding tissue preventing collapse of the lymphatic lumen.

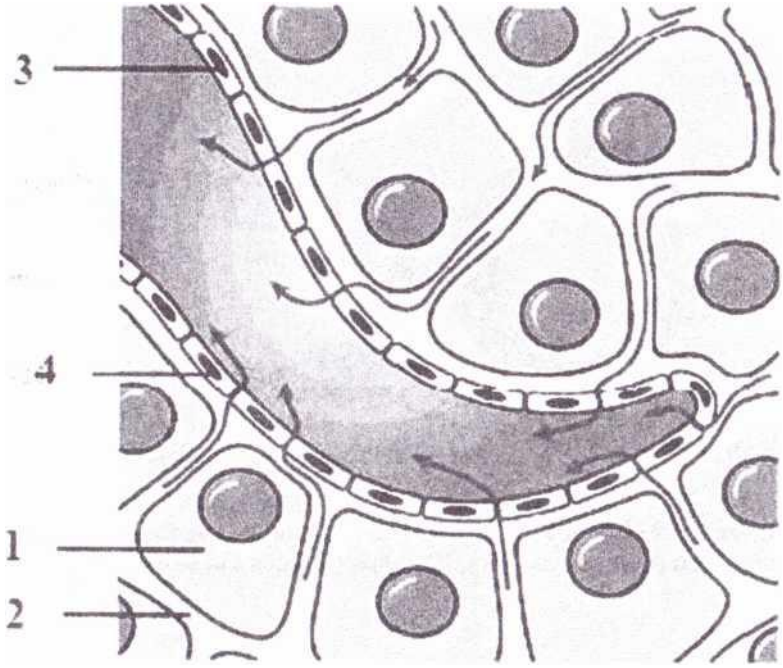


Figure 19.9. Schematic diagram of a lymphatic capillary. 1 - tissue cell, 2 - tissue fluid, 3 - wall of lymphatic capillary, 4 - opening into lymph vessel

Lymphatic collecting vessels (fig. 19.10) are formed in the result of the fusion of some lymphatic capillaries. The lymphatic vessels form valves. The lymph is moved by the compression of the lymph vessels by surrounding tissues. The direction of lymph flow is determined by the valves. Lymph vessels empty intermittently into lymph nodes from which the lymph continues in efferent lymph vessels.

Lymphatic ducts contain one or two layers of smooth muscle cells in their wall. They also form valves. Peristaltic contractions of the smooth muscle contribute to the movement of lymph towards the heart in addition to the compression of the ducts by surrounding tissues.

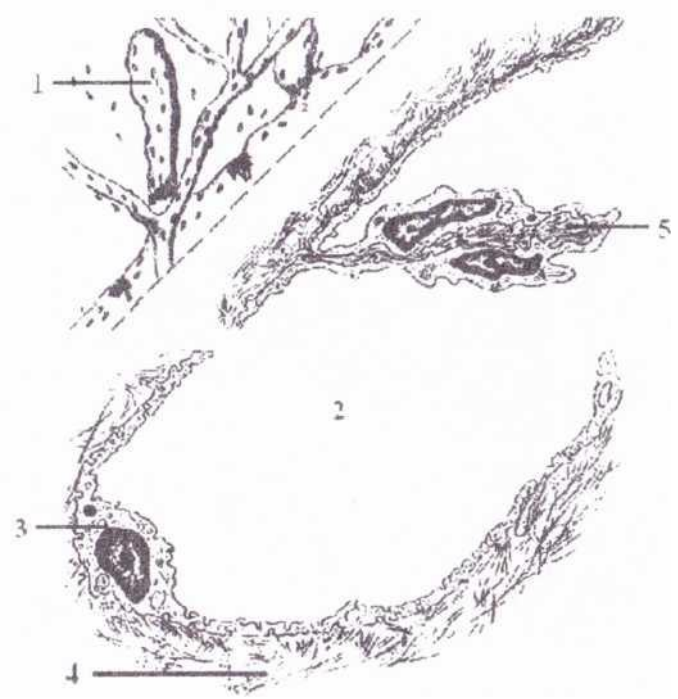


Figure 19.10. Lymphatic vessels. 1 - lymphatic capillary, 2 - lymphatic vessel, 3 - endothelial cell, 4 - anchoring filaments, 5 - valve

0 Heart

The ***heart*** is a muscular organ that contracts rhythmically, pumping the blood through the circulatory system. It is also responsible for producing a hormone called ***atrial natriuretic factor.***

The heart wall consists of 3 tunics (fig. 19.11):

I. ***Endocardium*** consists of:

1) endothelial cells,
2) subendothelial layer of loose connective tissue,
3) muscular-elastic layer,
4) external connective tissue layer.

Between the endocardium and the myocardium is a connective tissue subendocardial layer, which consists of veins, nerves, and branches of Purkinje cells.

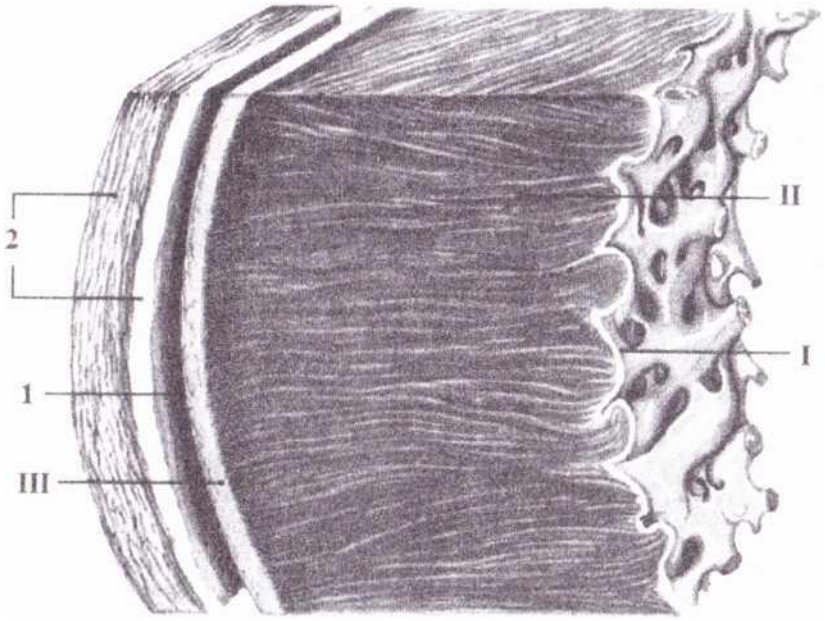


Figure 19.11. Wall of the heart. I - endocardium, **II** - myocardium, **III** - epicardium, 1 - space, 2 - pericardium

I. ***Myocardium*** is the thickest and consists of cardiac muscle cells (fig. 19.12).
II. ***Epicardium*** is the serous covering of the heart, forming visceral layer of the pericardium.

It is covered by simple squamous epithelium (mesothelium) supported by a thin layer of connective tissue.

Types of the cardiac muscle cells

There are 3 types of the cardiac muscle cells:
1) ***contractile (ordinary, working);***
2) ***conductive;***
3) ***secretory (endocrine).***

Contractile cardiac cells form the basic part of a myocardium and are characterized highly developed contractile system (fig. 19.13);

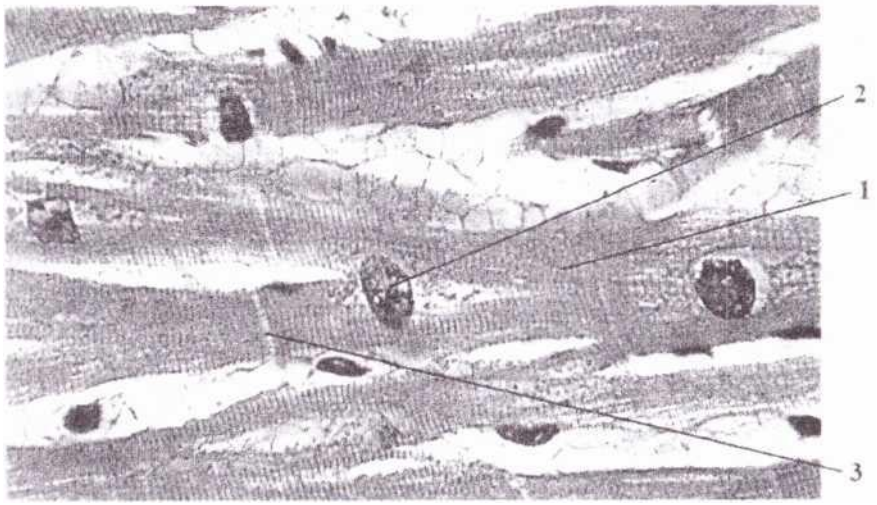


Figure 19.12. Photomicrograph of the myocardium. 1 - cardiac muscle cells, 2 - nucleus of cardiac muscle cell, 3 - intercalated disk

Conductive cardiac ceils (fig. 19.14) have ability to generation and conduction of electrical impulses through an ***impulse-generating and impulse-conducting system of heart.***

There are 2 types of conductive cardiac cells:

> ***pacemaker (nodal) cells*** or ***P-cells*** are the modified cardiac muscle cells with pale cytoplasm and fewer myofilaments; these cells are situated in the sinoatrial, atrioventricular nodes and internodal tracts.

> ***Purkinje fibers*** form atrioventricular bundle of His. Purkinje fibers are modified cardiac muscle cells found in the ***subendocardium*** of the ventricles. They constitute part of the specialized impulse conducting system, which connects to the right and left bundle branches and regulates the heartbeat. These are large muscular cells with a vacuolated cytoplasm due to the high glycogen content. Other characteristics that help distinguish Purkinje fibers from typical cardiac muscle cells are that they contain fewer myofibrils, and more sarcoplasm.

The bundles of Purkinje cells travel in the subendocardial layer to the apex of the heart, where they being giving off side branches that make contact with working cells.

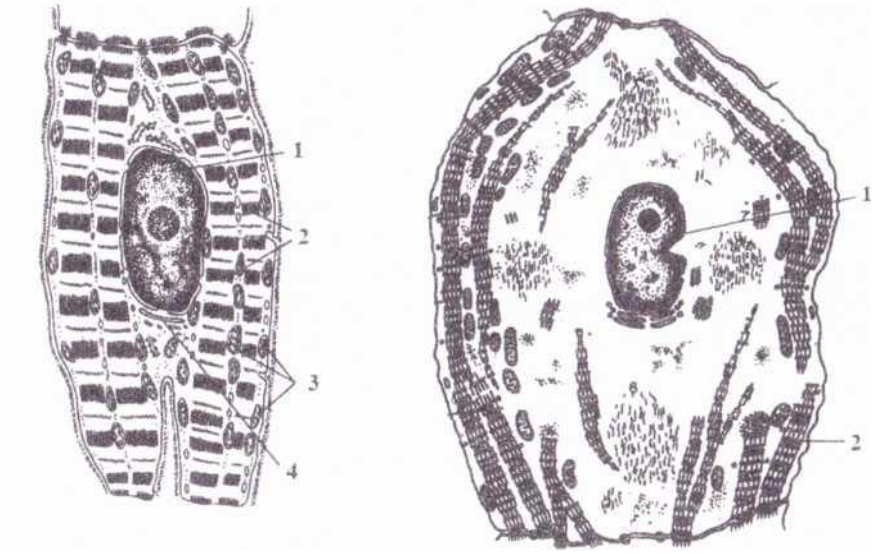


Figure 19.13. Schematic diagram of contractile cardiac cell. 1 - nucleus, 2 - contractile system, 5 - mitochondria, (from ***KJ. HAcfianacbee, H.A.fOpmaudp.,*** 1999) 4 - Golgi complex

Figure 19.14. Schematic diagram of condı cardiac ceil 1 - nucleus, 2 - contractile syste 2 - conlractile system, 5 - mitochondria, (from ***KJ. HAcfianacbee, H.A.fOpmaudp.,*** 1999) 4 - Golgi complex

Secretory (endocrine) cardiac cells are found in atrial cells and are characterized by weak development of contractile system. In their sarcoplasm near to poles of a nucleus there are granules containing hormone (***atrial natriuretic factor, auriculin,*** or ***atriopeptin).***

Cardiac skeleton

The ***cardiac skeleton*** is comprised of dense connective tissue that encircles the base of the two arteries leaving the heart and the openings between the chambers. It serves as an attachment for cardiac muscle and the cuspid valves of the atria and ventricles. It also serves as an attachment site for the semi lunar valves of the aorta and the pulmonary artery. The atrioventricular (A-V) bundle passes from the right atrium to the ventricular septum via the fibrous skeleton.

The cardiac skeleton consists of dense connective tissue arranged into:

1) 4 fibrous rings which surround the valve orifices;
2) 2 fibrous trigones connecting the fibrous rings;
3) membranous part of interventricular and interatrial septa.

Heart valves

The ***heart valves*** are composed of three layers:

> ***fibrosa*** forms the core of the valve and consists of dense irregular connective tissue of skeletal rings of the heart;

> ***spongiosa*** is formed by loose connective tissue located on the atrial and/or blood vessel side of each valve; it serves as the shock absorber.

> ***ventricularis*** is the part adjacent to the ventricular and/or atrial surface of each valve, is covered with endothelium; the outside extends into the fibrous cap on the tips of the papillary muscles.

0 Development of the heart and blood vessels

Distinguish 5 stages to heart development.

> Specification of cardiac precursor cells
> Migration of cardiac precursor cells and fusion of the primodia
> Heart looping
> Heart chamber formation
> Septation and valve formation

The primordium of the heart forms in the ***cardiogenic plate*** (the part of the ***splanchnopleuric mesoderm)*** located at the cranial end of the embryo. Angiogenic cell clusters which lie in a horse-shoe shape configuration in the plate coalesce to form two endocardial tubes. These tubes are then forced into the thoracic region due to cephalic and lateral foldings where they fuse together forming a single endocardial tube.

The tube can be subdivided into primordial heart chambers starting caudally at the inflow end: the sinus venosus, primitive atria, ventricle, and bulbus cordis.

The heart tube begins to grow rapidly forcing it to bend upon itself. The result is the bulboventricular loop. Septa begin to grow in the atria, ventricle and bulbus cordis to form right and left atria, right and left ventricles and two great vessels-the pulmonary artery and the aorta. By the end of the eighth week partitioning is completed and the fetal heart has formed.

0 Clinical correlations

Ischemic heart disease is the imbalance between the supply and demand of the heart for oxygenated blood. The most cause of ischemic heart disease is atherosclerosis. In atherosclerosis, the lumen of coronary arteries progressively narrows.

Most problems associated with ***valve damage*** are associated with the opening and closing of the valve. If a valve doesn't open all the w'ay, less blood moves through to the next chamber. If a valve doesn't close tightly, blood may leak backward.

Problems opening - stenosis. Valve stenosis occurs when a valve fails to open fiilly. The valve may have become hardened or stiff with calcium deposits or scarring. This is problematic because blood has to flow through a smaller opening, so less blood gets through the valve into the next chamber.

Problems closing - regurgitation. Insufficient blood flow (also called regurgitation) results when the valve fails to close tightly. The valve's supportive structures may be loose or torn. Or, the valve itself may have stretched or thinned. This is problematic because blood will leak back through the valve into the heart. As a result, the heart must work harder to re-pump the blood through the heart.

Varicose veins are veins that have become enlarged and tortuous.

Veins have leaflet valves to prevent blood from flowing backwards (retrograde). Leg muscles pump the veins to return blood to the heart, against the effects of gravity. When veins become varicose, the leaflets of the valves no longer meet properly, and the valves do not work. This allows blood to flow backwards and they enlarge even more. Varicose veins are most common in the superficial veins of the legs, which are subject to high pressure when standing.

Pacemaker dysfunction Dysfunction of the heart's pacemaker (sinus or sinoatrial node) may result in a persistently slow heartbeat (sinus bradycardia) or complete cessation of normal pacemaker activity (sinus arrest). When activity ceases, another area of the heart usually takes over the function of the pacemaker. This area, called an escape pacemaker, may be located lower in the atrium, in the atrioventricular node, in the conduction system, or even in the ventricle.

ENDOCRINE SYSTEM I. CENTRAL ENDOCRINE ORGANS

0 Overview of the endocrine system

The ***endocrine system*** is a system of glands, each of which is ductless and secretes the ***hormones*** into the bloodstream to regulate many functions of an organism, including growth, development, and metabolism. The blood and lymph carry hormones to the ***target organs.***

Hormones are substances (chemical mediators) released from endocrine tissue into the blood that attach to ***target cells*** and allow communication among cells.

The ability of a target cell to respond to a hormone depends on the presence of receptors, within the cell or on its plasma membrane, to which the hormone can bind.

Classification of the endocrine structural components

I. Central regulatory formations of the endocrine system:
   - > hypothalamus,
   - > hypophysis cerebri (pituitary gland),
   - > pineal gland (epiphysis)

II. Peripheral endocrine organs:
   - > thyroid gland,
   - > parathyroid glands,
   - > adrenal (suprarenal) glands

III. Organs having endocrine and nonendocrine functions:
   - > gonads (testes, ovaries),
   - > pancreas,
   - > placenta

IV. ***Isolated endocrine cells*** in the epithelium of the organs of the respiratory passages, gastro-intestinal tract, urinary system
   - > **APUD cells,**
   - > isolated endocrine cells which secrete steroid and other hormones.

APUD cells constitute a group of the endocrine cells which have the common function of secreting low molecular weight polypeptide hormones. The name is derived from an abbreviation, referring to the following:
Amine - for high amine content,
Precursor Uptake - for high uptake of (amine) precursors,
Decarboxylase - for high content of the enzyme amino acid decarboxylase (for conversion of precursors to amines).

El Hypothalamus

The ***hypothalamus*** is a portion of the brain which is responsible for certain metabolic processes and other activities of the autonomic nervous system. It synthesizes and secretes certain neurohormones, often called hypothalamic-releasing hormones, and these in turn stimulate or inhibit the secretion of pituitary hormones. The hypothalamus controls body temperature, hunger, thirst, fatigue, sleep, and circadian cycles.

The ***hypothalamus*** contains ***neurosecretory (magnocellular*** and ***parvocellular) nuclei***

The secretory neurons (fig.20.1) of these nuclei have all characteristics of typical neurons, including the ability to product the ***neurohormones.***

Neurosecretory nuclei of hypothalamus depending on their sizes and functions are subdivided into ***magnocellular*** and ***parvocellular.***

I. ***Magnocellular nuclei (supraoptic and paraventricular).***

The axons of neurosecretory cells of these nuclei forming hypothalamo-hypophyseal tract pass along the infundibular stalk and terminate in neurohypophysis as accumulations in relations to blood capillaries (flg.20.2). These accumulations are called ***Herring bodies.***

The neurosecretory cells of ***supraoptic nucleus*** secrete ***vasopressin*** also called ***antidiuretic hormone (ADH).***

The main effect of ***vasopressin*** is:
> to increase the permeability to water of the distal convoluted tubules and the collecting tubules of the kidney; as a result, water is absorbed by these tubules and urine becomes hypertonic;
> to contract smooth muscle tissue of small arteries and raises the blood pressure.

The neurosecretory cells of***paraventricular nuclei*** secrete ***oxytocin.***

Oxytocin stimulates contraction of:

> the smooth muscle tissue of the uterine wall during childbirth and
> the myoepithelial cells of alveoli of the mammary glands during the nursing.

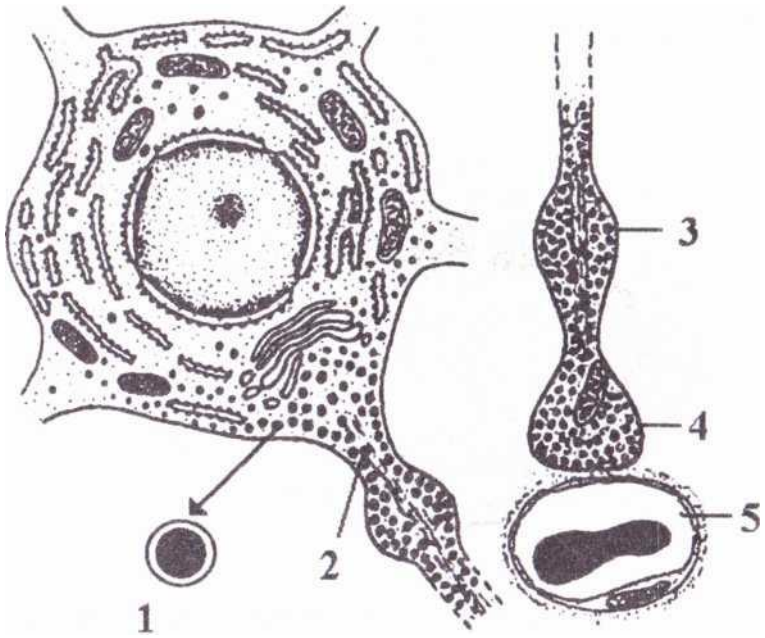


Figure 20.1. Schematic representation of the secretory neuron. 1 — neurosecretory granules, 2 - axon, 3 - accumulation (Herring body), 4 - axovasal synapse, 5 - blood capillary (from ***EuKoe B.JI.,*** 1999)

II. Neurosecretory cells of the ***parvocellular nuclei*** synthesize and secrete certain neurohormones, often called ***hypothalamic-releasing hormones***, and these in turn stimulate or inhibit the secretion of pituitary hormones:

> ***Thyrotropin-releasing hormone (TRH)*** or ***thyroliberin*** stimulates the release of ***thyroid-stimulating hormone (TSH)*** and ***prolactin*** by the pars distalis of adenohypophysis; TRH is produced by the medial neurons of the ***paraventricular nucleus***;

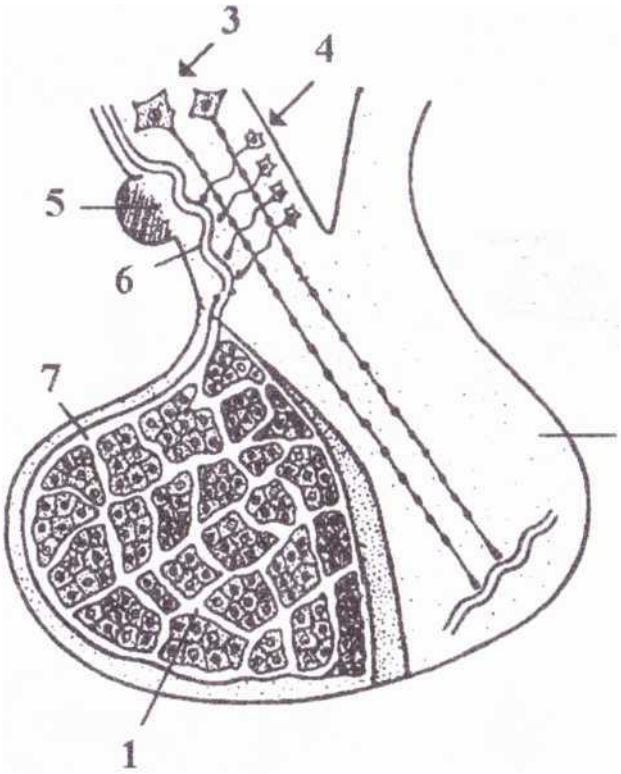


Figure 20.2. Hypothalamo-hypophyseal neurosecretory system. 1 - pars distalis of adenohypophysis, 2 - neurohypophysis, 3 - magnocellular nuclei, 4 - parvocellular nuclei, 5 - optic chiasm, 6 - primary capillary network, 7 - secondary capillary network (from ***Ebixoa B.U.,*** 1999)

> ***Gonadotropin-releasing hormone (GnRH)*** or ***luliberin*** is responsible for the release of ***follicle-stimulating hormone (FSH)*** and ***luteinizing hormone (LH)*** from the pars distalis of adenohypophysis; is secreted by the neurons of the ***arcuate nucleus*** in the mediobasal hypothalamus;

> ***Growth hormone-releasing hormone (GHRH)*** or ***somatocrinin*** stimulates cells in the pars distalis of adenohypophysis to secrete ***growth hormone (GH),*** GHRH is secreted by the neurons of the ***arcuate nucleus*** in the mediobasal hypothalamus;

> ***Corticotropin-releasing hormone (CRH)*** acts on cells in the pars distalis of adenohypophysis to release ***adrenocorticotropic hormone (ACTH);*** CRH is produced by parvocellular neuroendocrine cells (which are contained within the paraventricular nucleus) of the hypothalamus;

> ***Somatostatin*** acts on the pars distalis of adenohypophysis to ***inhibit*** the release of ***growth hormone (GH)*** and ***thyroid-stimulating hormone (TSH):*** somatostatin is produced by neuroendocrine neurons of the ***periventricular nucleus*** of the hypothalamus;

> ***Dopamine*** acts on the pars distalis of adenohypophysis to ***inhibit*** the release of ***prolactin (PRL)*** from the pars distalis of adenohypophysis; is secreted by the neurons of the ***arcuate nucleus*** in the mediobasal hypothalamus;

Hormones of ***parvocellular nuclei*** are released at the median eminence from neurosecretory terminals of these neurons into the ***primary capillary plexus*** of the hypothalamo-hypophyseal portal system.

I he portal system carries these hormones to the ***secondary plexus*** in the pars distalis of the pituitary, where they regulate hypophyseal functions.

0 Hypophysis (pituitary gland)

The ***hypophysis (pituitary)*** is a pea-sized gland at the base of the brain which is located in the sella turcica of sphenoid bone (fig.20.3).

The ***hypophysis*** consists of two parts (fig.20.4):

I. ***Adenohypophysis*** (anterior pituitary) which has three subdivisions:
   1. pars distalis (anterior lobe);
   2. pars tuberalis (intermediate lobe);
   3. pars intermedia (tuberal lobe);

II. ***Neurohypophysis*** (posterior pituitary).

!. Adenohypophysis

1. **Pars distalis** (75% of the mass of the hypophysis) coasists of branching cords of epithelial cells with capillaries between them (fig.20.5).

Cells types of pars distalis have been described as

- ***chromophobic cells*** (***chromophobes***) and
- ***chromophilic cells (chromophils).***

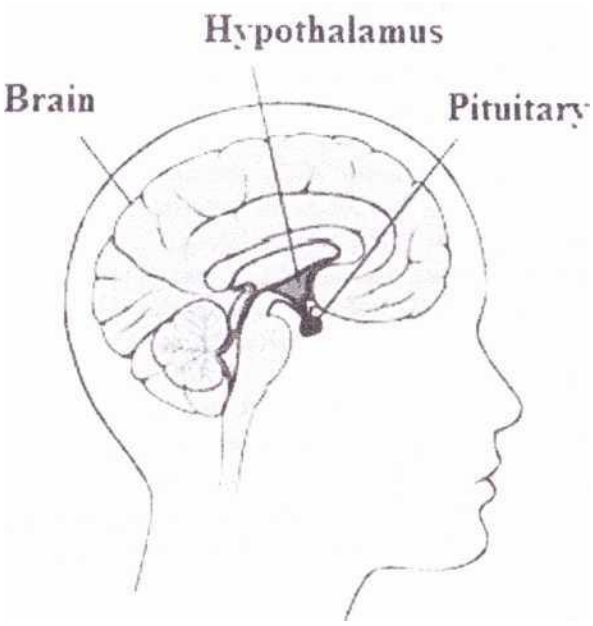


Figure 20.3. Position of the

Chromophobes are:

- degranulated inactive resting cells capable of differentiation into a particular type of chromophils;
- undifferentiated cells;
- follicular cells which form a supporting network for the other cells.

Chromophils are called ***acidophilic*** (acidophils) or ***basophilic*** (basophils) according to their staining.

Acidophils contain eosinophilic granules in their cytoplasm. ***Subtypes of acidophils:***

1) ***somatotropic cells (somatotrophs)*** produce ***somatotropin (growth hormone),*** which acts on growth of long bones;

2) ***mammotropic cells (lactotropic cells, lac totrop Its)*** produce ***prolactin (mammotropic hormone),*** which promotes milk secretion.

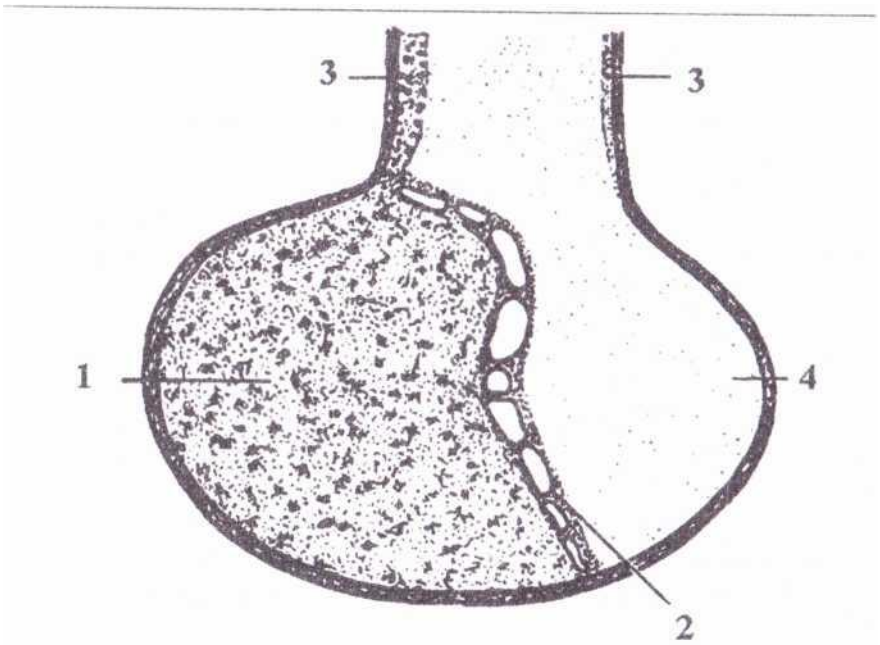


Figure 20.4. Schematic diagram of the hypophysis. 1 - pars distalis, 2 - pars intermedia, 3 - pars tuberalis, 4 - neurohypophysis (from *Bmkob* ***B.J7,*** 1999)

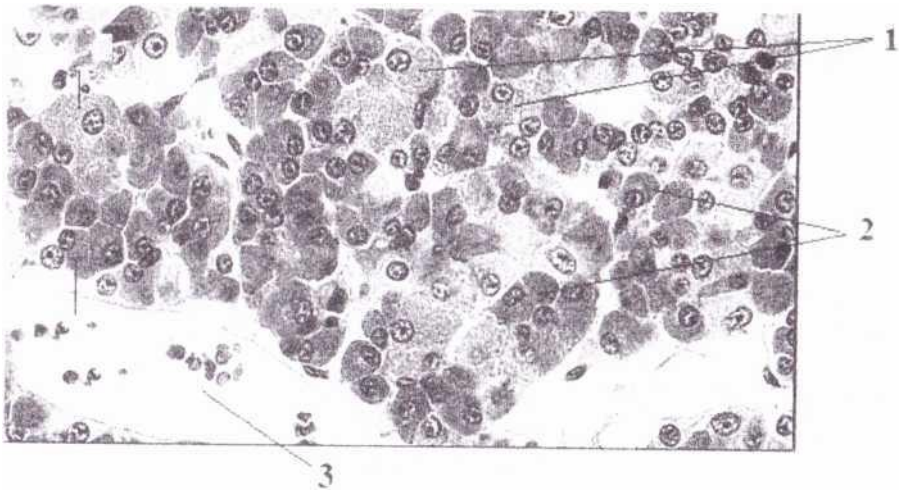


Figure 20.5. Photomicrograph of pars distalis of adenohypophysis. 1 - acidophils, 2 — basophils, 3 — blood capillary

Basophils contain small basophilic granules in their cytoplasm. *Subtypes of basophils:*

1) *thyrotropic cells (thyrotrophs)* produce *thyrotropic hormone (thyrotropin),* which stimulates thyroid hormone synthesis;

2) *gonadotropic cells (gonadotrophs)* produce:

> *follicle-stimulating hormone (FSH),* which promotes ovarian follicle development and estrogen secretion in female and stimulates spermatogenesis in male;

> *luteinizing hormone (LH),* which promotes ovarian follicle maturation, ovulation and progesterone secretion in female, androgen secretion in male,

3) *corticotropic cells (corticotrophs)* produce *adrenocorticotropic hormone (ACTH),* which stimulates secretion of adrenal cortex hormones.

2. Pars tuberalis surrounds the infundibulum of the neurohypophysis. Most of the cells of the pars tuberalis produce *gonadotropins (FSH* and *LH).*

3. Pars intermedia forms a thin layer between the pars distalis and the neurohypophysis. It contains small ceils, which produce:

> *melanocyte-stimulating hormone (MSH),* which stimulates production of melanin by melanocytes;

> *lipotropin* or *lipotropic hormone (LPH),* which stimulates metabolism of fats.

II. Neurohypophysis *Neurohypophysis*

(fig.20.6) consists of:

> *unmyelinated axons* and *dilated axon endings* of secretory neurons from supraoptic and paraventricular nuclei of the hypothalamus; these axons form hypothalamo-hypophyseal tract, pass along the in infundibular stalk and terminate in the neurohypophysis as dilated terminal parts *(Herring bodies)* in relation to fenestrated blood capillaries; hormones vasopressin and oxytocin produced by these nuclei migrate along the axons in the neurohypophysis;

> ***fenestrated blood capillaries***;
> ***pituicytes*** are specific type of highly branched glial cells; their main function is supporting.

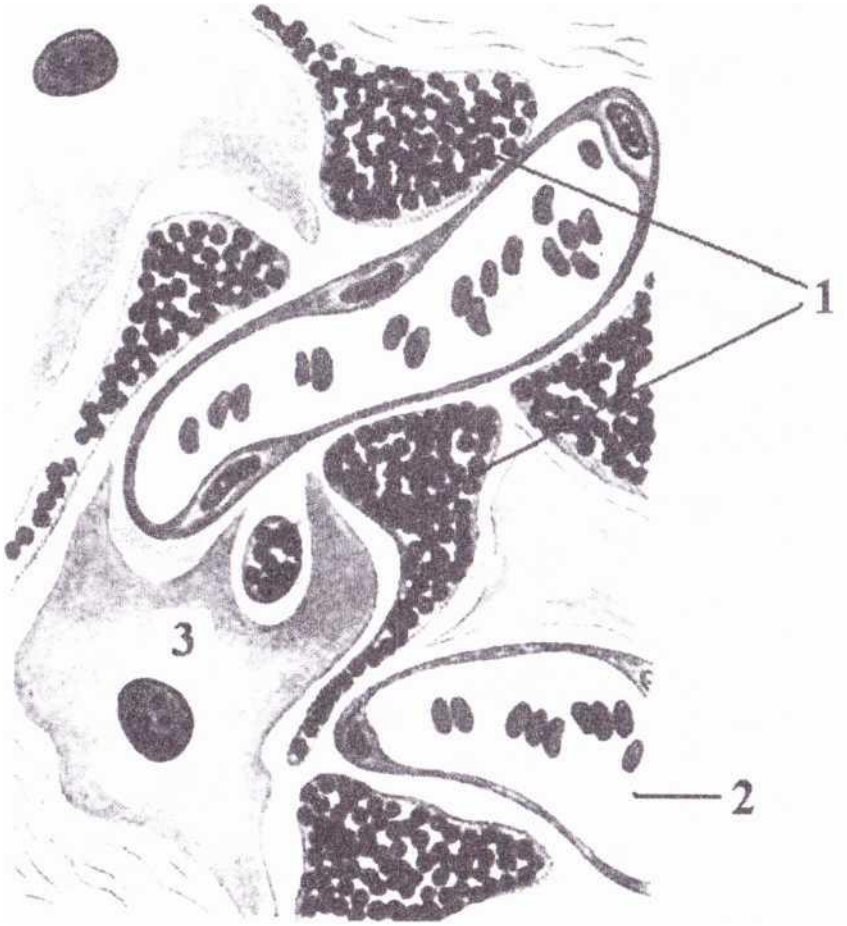


Figure 20.6. Schematic diagram of structure of neurohypophysis. 1 - Herring bodies, 2 - fenestrated blood capillary, 3 -pituicyte

0 Development of the hypophysis (fig.20.7)

Adenohypophysis arises from an invagination from the ectodermal roof of primitive mouth cavity and forms ***Rath he's pouch.***

Neurohypophysis is neuro-ectodermal in origin and arises as an evagination from the floor of the diencephalon.

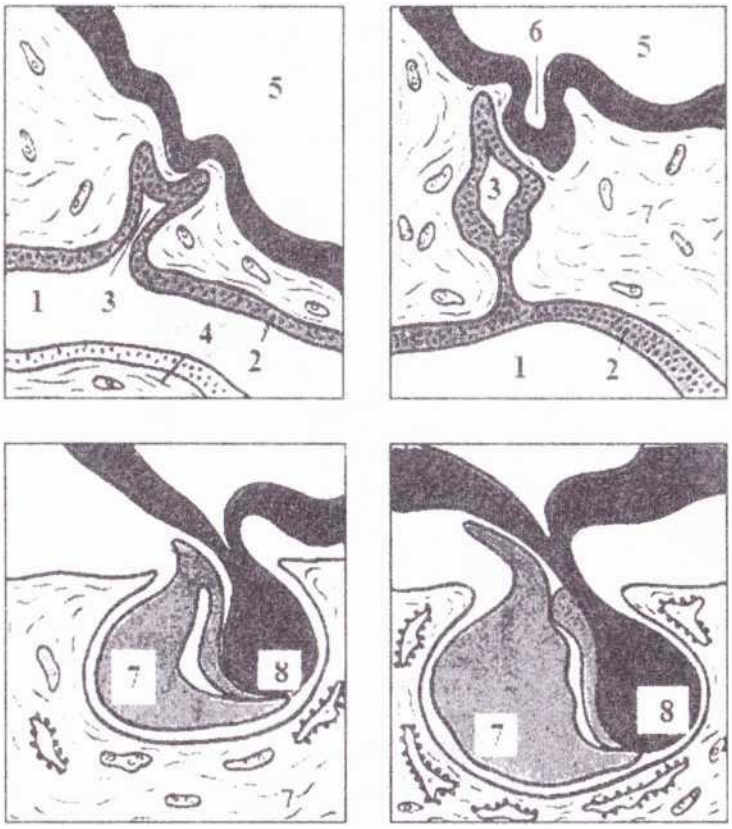


Figure 20.7. Development of the hypophysis. 1 — oral cavity, 2 — ectodermal epithelium of the oral cavity, 3 — Rathke's pouch, 4 — tongue, 5 — cavity of third ventricle, 6 - evagination of the diencephalon 7 - adenohypophysis, 8 — neurohypophysis (from *K). KAfpanacba-i, H.A.fOpwiu u dp.*, 1999)

0 Pinea! gland (epiphysis cerebri or pineal body)

The ***pineal gland*** is a small conical body, is evagination from the posterior part of the roof of the third ventricle of the brain.

Connective tissue septa penetrate the pineal tissue and divide the organ into the irregular lobules.

The parenchyma of the pineal lobule consists of 2 types of cells:

> ***Pinealocytes*** (90% of pineal cells), which have basophilic cytoplasm with large irregular or lobate nuclei; long highly-branched processes with terminal buds that end in relation to the wall of capillaries or in relation to the ependyma of the third ventricle. These cells produce ***melatonin*** and its precursor, ***serotonin.***

> ***Interstitial (pineal astrocytes)*** (5% of pineal cells) are a specific type of neuroglial cells with elongated nuclei. These cells separate the pinealocytes from one another.

Pineal gland may contain basophilic bodies (pineal sand, pineal concretions) consisting of concentric layers of calcium and magnesium phosphate within an organic matrix.

Appearance of concretions is the normal phenomenon which first registers in childhood; with age their amount and sizes is increased.

Histophysiology of the pineal gland

The pineal gland is photosensitive organ and is an important regulator of day/night cycle (circadian rhythms) and seasonal biorhythms. It obtains information about light and dark cycles from retina via retinothalamic tract, which connects in the suprachiasmatic nucleus with sympathetic neural tract travelling into pineal gland.

During the day, light impulses inhibit the production of the major pineal gland hormone, ***melatonin.*** Plasma level of melatonin increases during darkness and decreases during light. In humans, these circadian changes of melatonin play an important role in regulation of daily body rhythms.

The pineal gland plays a role in altering emotional responses to reduced day length during winter in temperate and subarctic zones (seasonal affective disorders).

The pineal secretion promotes rhythmic changes in the secretary activity of the gonads and other organs.

Melatonin suppresses production of ***gonadotrophin releasing hormone*** by the hypothalamus, thus suppressing pituitary ***gonadotrophin*** secretion and activation of gonadal growth and hormonal secretion. At children with tumours, destroying an epiphysis, premature pubescence develops often.

0 Clinical correlations

Central diabetes insipidus is caused by a lack of ADH. Central diabetes insipidus can be caused by damage to the hypothalamus or pituitary gland as a result of:

> head injury,
> infection,
> surgery,
> tumor.

Central diabetes insipidus is a disorder in which there is an abnormal increase in urine output, fluid intake and often thirst. It causes symptoms such as urinary frequency, nocturia (frequent awakening at night to urinate) or enuresis (involuntary urination during sleep or "bedwetting")- Urine output is increased because it is not concentrated normally. Consequently, instead of being a yellow colour, the urine is pale, colourless or watery in appearance and the measured concentration (osmolality or specific gravity) is low.

Hypothalamic disease concerns to a category of diseases of endocrine system. At hypothalamic disease functioning of hypophysis and produce of gonadotrophic hormones is broken; there is a dysfunction of nervous and reproductive systems, the consequence of which male infertility becomes. Most frequently the reasons of hypothalamic disease are cranio-cereberal trauma, an infection, strong stress, tumoral process, an intellectual overstrain. Hypothalamic disease can arise at sharp weight reduction or owing to carrying out of hormonal therapy. The additional factor, provoking the occurrence of hypothalamic disease is the alcoholic intoxication of an organism.

Acromegaly is a syndrome that results when the pituitary gland produces excess growth hormone (hGH) after epiphyseal plate closure at puberty. A number of disorders may increase the pituitary's GH output, although most commonly it involves a GH producing tumor called pituitary adenoma, derived from a distinct type of cell (somatotrophs). Acromegaly most commonly affects adults in middle age, and can result in severe disfigurement, serious complicating conditions, and premature death if unchecked.

Pituitary gigantism is a syndrome in children when the excessive growth hormone produces excessive growth of bones and the child can achieve excessive height; from 2.1 to 2.7 m in stature by adulthood if left untreated.

ENDOCRINE SYSTEM II. PERIPHERAL ENDOCRINE ORGANS

0 Thyroid gland

The ***thyroid gland*** is one of the largest endocrine glands in the body.

The thyroid gland is derived from the cephalic portion of the alimentary canal (***endoderm***).

Function of the thyroid gland is to produce the hormones:

> thyroid hormones which stimulate the rate of metabolism and are necessary for normal growth and development (cells of the brain are a major target for the thyroid hormones T_3 and T_4; thyroid hormones play a particularly crucial role in brain maturation during fetal development):

- ***tetraiodothyronine*** or ***thyroxin (T_4),*** which contains four atoms of iodine;
- ***triiodothyronine (T_3),*** which contains three atoms of iodine;

> ***calcitonin***, which main effect is to lower blood calcium levels by inhibiting bone resorption.

Structure of the thyroid gland

The thyroid gland, located in the cervical region in front of the larynx, consists of two lobes united by an isthmus (fig.21.1).

The thyroid gland is covered by connective tissue capsule. Septa extending into the gland from the capsule divide organ into lobules. The thyroid is an extremely vascularised organ, with an extensive blood capillary network.

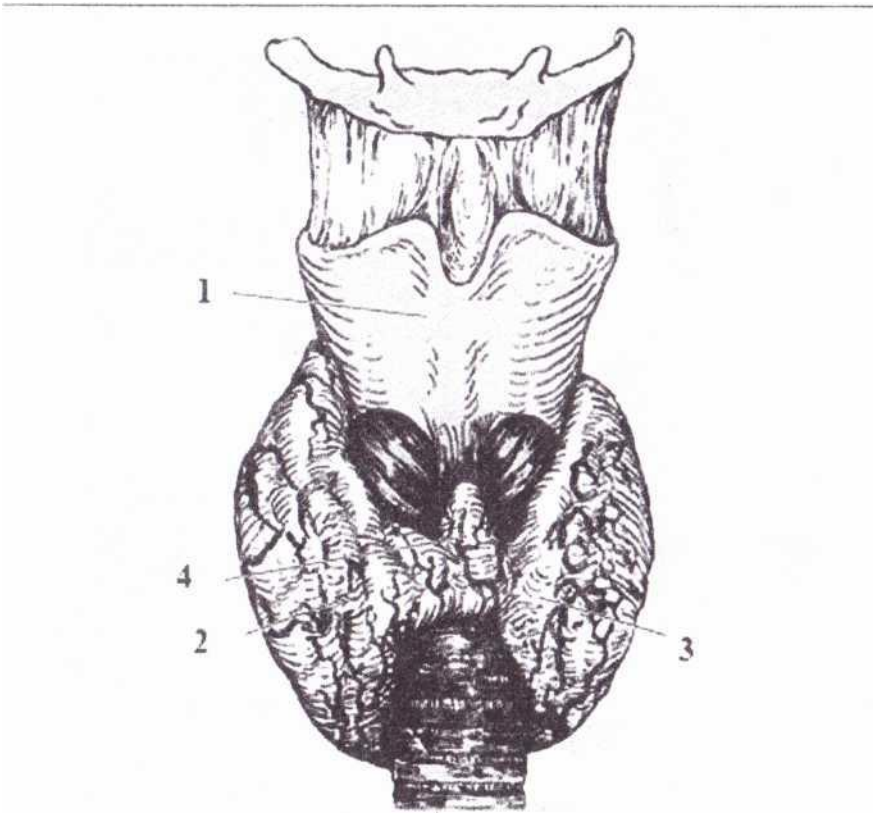


Figure 21.1. Position of the thyroid gland. 1 - larynx, 2 - right lobe, 3 - left lobe, 4 - isthmus

Thyroid tissue is composed of ***follicles,*** which are ***structural units*** of the gland (fig.21.2).

Each follicle consists of a simple epithelium resting on a basal lamina. The follicle has a cavity, which is filled by a gelatinous substance called ***colloid.***

Follicular epithelium consists of two types of cells:

> follicular cells,

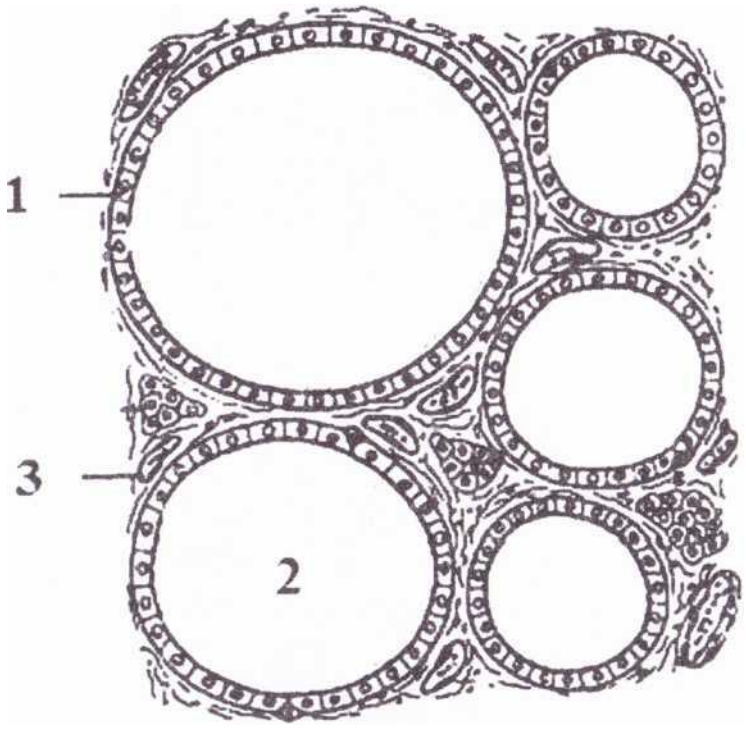


Figure 21.2. Schematic diagram of structure of the follicles of thyroid gland.
1 - follicular cells, 2 - colloid, 3 - blood capillary

Ultrastructure of follicular cells

Round nucleus of the follicular cell is in the center of the cell. The basal part of the cell is rich in rough endoplasmic reticulum. The apical pole contains Golgi complex, abundant small secretory granules. The cell membrane of the apical pole has number of ***microvilli.*** Numerous lysosomes and some large phagosomes are found in this region. Mitochondria, ribosomes are distributed throughout in the cytoplasm.

The follicular cells vary in shape depending on the level of their activity.

Normally (at an average level of activity) the follicular cells are ***cuboidal,*** and colloid in the follicles is of moderate amount.

When the cells are inactive, they have ***squamous*** shape.

When the cells are highly active they become ***columnar*** and colloid is scanty.

Secretory cycle of the follicular cells

The secretory cycle (fig.21.3) of the follicular cells consists of:

> phase of production of hormones
> phase of liberation of hormones.

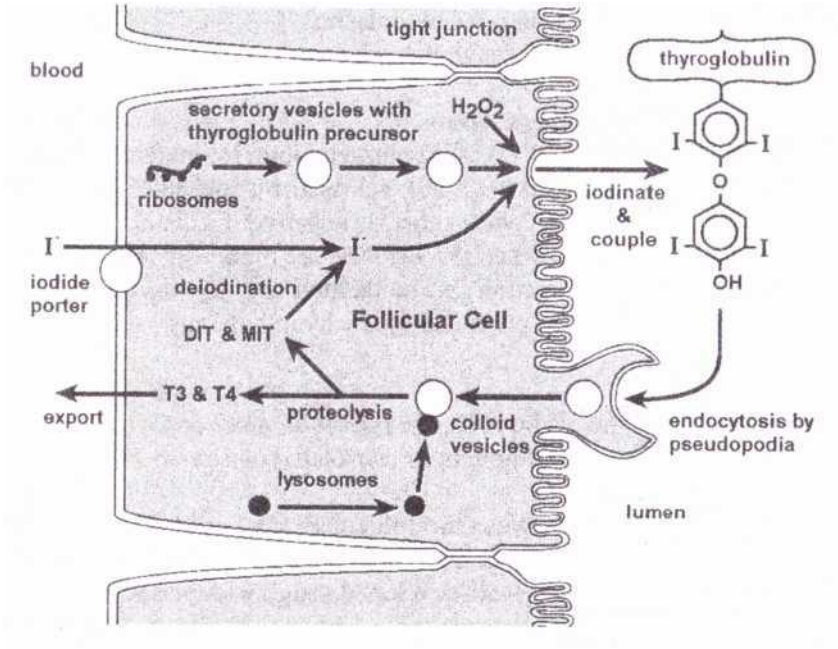


Figure 21.3. Schematic diagram of the secretory cycle of the follicular cells.

The phase of production of hormones includes:

1) absorption of initial products (aminoacid tyrosine, carbohydrates, water, iodide) from blood capillaries;
2) synthesis of thyroglobulin in the rough endoplasmic reticulum;
3) non-enzymic iodination and coupling together of tyrosine residues with the protein thyroglobulin; elemental iodine required for this reaction is produced by action of peroxidase on iodide ions and the reaction takes place on the apical surfaces of follicular cells;
4) release of thyroglobulin into the lumen of the follicle and formation of colloid.

The ***phase of liberation*** includes:

1) resorption of thyroglobulin from colloid by pinoeytosis;
2) hydrolysis of the thyroglobulin molecules by proteases in the lysosomes;
3) liberation of T_3 and T_4 into the cytoplasm;
4) liberation of T_3 and T_4 through the cell membrane into capillaries.

Thyroid gland regulation

The production of thyroxin and triiodothyronine is regulated by thyroid-stimulating hormone (TSH), released by the anterior pituitary. The thyroid and thyrotrophes form a negative feedback loop: TSH production is suppressed when the T_4 levels are high.

The TSH production is modulated by thyrotropin-releasing hormone (TRH). which is produced by the hypothalamus.

C cells

Another type of the cells, the ***parafollicular***, or ***C, cells*** is found as part of the follicular epithelium or as isolated clusters between thyroid follicles

These cells lie between the follicular cells and their basal lamina (fig.21.4). Parafollicular cells are larger and stain less intensely than follicular cells. They have well-developed rough endoplasmic reticulum, large Golgi complex, numerous mitochondria.

Parafollicular cells produce the hormone ***calcitonin***, whose main effect is to ***lower blood calcium levels*** by inhibiting bone resorption.

Secretion of calcitonin is triggered by an elevation in blood calcium concentration.

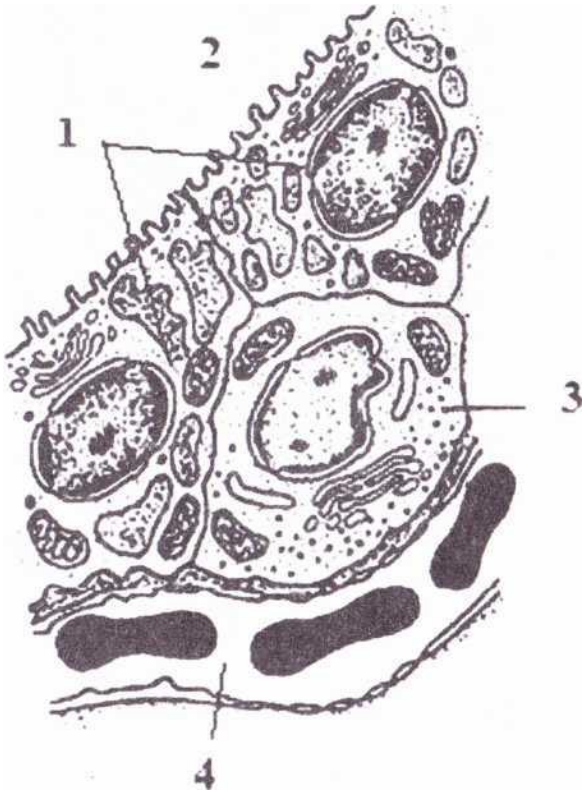


Figure 21.4. Schematic diagram of the thyroid gland cells. I - follicular cells, 2 - colloid, 3 — parafollicular cell, 4 - blood capillary

0 Parathyroid glands

The ***parathyroid glands*** are 4 small glands (fig.21.5). They are behind the thyroid gland, one at each end of the upper and lower poles.

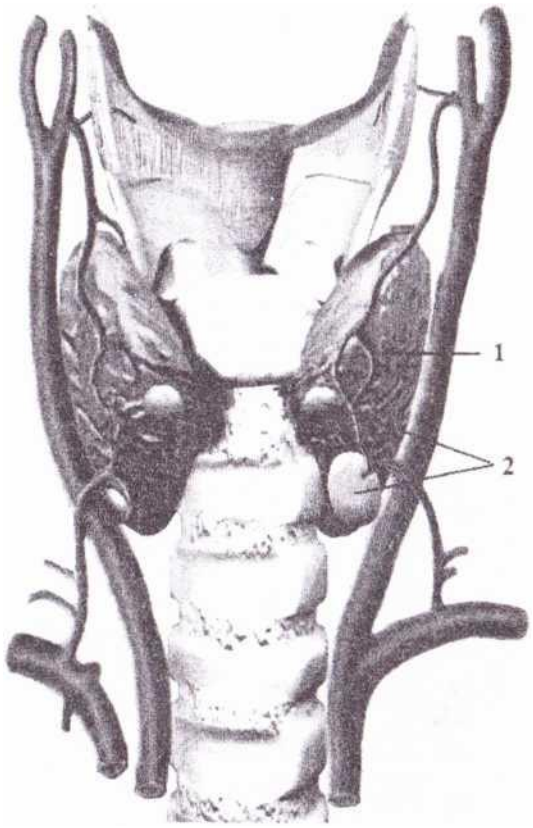


Figure 21.5. Position of the parathyroid glands. Back view. 1 - thyroid gland, 2 - parathyroid glands

These glands are situated under the capsule that covered the thyroid gland.

Each parathyroid gland is covered by connective tissue capsule. The capsule sends septa into the gland.

The parenchyma of the parathyroid gland consists of two types of cells: 1) ***Chief cells*** are most numerous. They have a pale-staining cytoplasm with vesicular nucleus. These cells produce ***parathyroid hormone***

(PTH) or ***parathormone.*** This hormone acts on the osteoclasts of bone (issue, increasing their number and activity, and thus promoting the absorption of the bone matrix and release of calcium into the blood.

2) ***Oxyphil cells*** are polygonal in shape and larger than chief cells. The function of these cells is unknown.

Both the release of calcitonin by C cells in the thyroid gland and (lie release of parathyroid hormone are regulated by negative feedback from blood calcium concentrations.

0 Adrenal (suprarenal) glands

The ***adrenal glands*** are paired organs located near the upper pole of the kidneys.

Each gland is covered by connective tissue capsule and has 2 parts (fig.21.6, 21.7);

V an outer ***cortex*** and

> an inner ***medulla.***

Cortex and medulla differ in origin, structure, and functions.

Adrenal cortex

Adrenal cortex is subdivided into 3 zones:

1. **outer** *zona glomerulosa;*
2. **middle** *zona fasciculata*
3. **inner** *zona reticularis.*

1) . ***Zona glomerulosa*** consists of columnar cells arranged in rounded groups. The cells have light basophilic cytoplasm.

Cells of zona glomerulosa secrete ***mineralcorticoid hormones***, which function is regulation of sodium and potassium homeostasis and water balance. Principal hormone, ***aldosterone,*** acts on the distal tubules of the nephrons in the kidney, gastric mucosa, salivary and sweat glands to stimulate resorption of sodium, as well as to stimulate excretion of potassium by the kidneys.

Aldosterone also participates in blood pressure regulation.

Zona glomerulosa is under feedback control of the renin-angiotensin- aldosteron system.

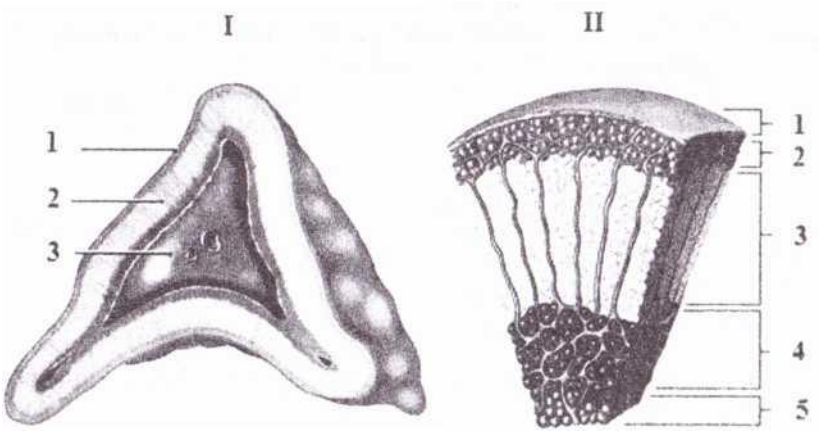


Figure 21.6. Schematic diagram of the adrenal gland. Transverse section:] - capsule, 2 — cortex, 3 - medulla. Microscopic section: 1 - cortex, 2 - zona glomerulosa, 3 - zona fasciculata, 4 - zona reticularis, 5 - medulla

2) . ***Zona fasciculata*** is the thickest zone. It consists of narrow cords of polyhedral cells (one or two cells thick). The cytoplasm of the cells is rich in smooth endoplasmic reticulum and lipid droplets.

Zona fasciculate produces ***glucocorticoids,*** mainly ***cortisol*** and ***corticosteron.*** These hormones regulate the carbohydrate, protein and lipid metabolism, and also suppress the immune response by decreasing of number of circulating lymphocytes.

Secretion of glucocorticoids is under control of ***ACTH*** of adenohypophysis.

3) . ***Zona reticularis*** consists of cells disposed in irregular cords that form an anastomosing network. These cells are smaller than those of the other two layers. Lipofuscin pigment granules in the cells are large and numerous.

Zona reticularis is responsible for secretion of small quantities of ***androgens*** and ***glucocorticoids.***

Zona reticularis is under control ***of ACTH*** of adenohypophysis.

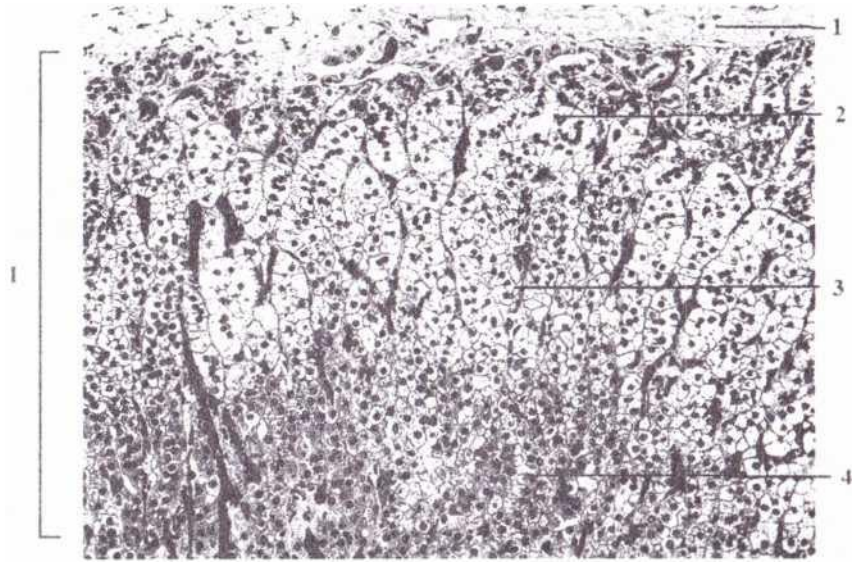


Figure 21.7. Photomicrograph of adrenal gland. I - cortex, **1** — capsule, 2 - zona glomerulosa, 3 - zona fasciculata, 4 - zona reticularis

Adrenal medulla

The ***adrenal medulla*** is composed of polyhedral ***chromaffin*** cells arranged in cords or clumps and supported by reticular fiber network.

The adrenal medulla consists of two types of cells:

> ***epinephrin-secreting cells,*** which have smaller, less-electron-dense granules;

> ***norepinephrin-secreting cells,*** which have larger, more electron- dense granules.

Acute physical and psychological stresses initiate release of adrenal medullary hormones (catecholamines adrenaline, or epinephrine and noradrenaline or norepinephrine); they act on adrenergic receptors throughout the body particularly in the heart and blood vessels, bronchioles, visceral and skeletal muscle.

Major effects of nonepinephrine and epinephrine:
increase heart rate, increase blood pressure, reduce blood flow to viscera and skin, stimulate conversion of glycogen to glucose, increase sweating, induce dilation of bronchioles, increase rate of respiration, decrease digestion, decrease urine production.

The adrenal medulla is also responsible for the secretion of ***enkephalins***, ***opioid peptides,*** which may be involved in control of pain.

0 Histogenesis of the adrenal glands

The adrenal glands are derived from 2 embryonic sources:
> adrenal cortex is ***mesodermal***, derived from coelomic epithelium;
> adrenal medulla is ***ectodermal***, derived from neural crests.

0 Clinical correlations

Imbalance in production of thyroid hormones arises from disfunction of the thyroid gland itself, the pituitary gland, which produces thyroid-stimulating hormone (TSH), or the hypothalamus, which regulates the pituitary gland via thyrotropin-releasing hormone (TRH).

Hyperthyroidism, or overactive thyroid, is an autoimmune disease the overproduction of T_3 and T_4. Hyperthyroidism is thus a cause of ***thyrotoxicosis.***

The disease can result in the formation of a ***toxic goiter*** as a result of thyroid growth in response to a lack of negative feedback mechanisms. It presents with symptoms such as a thyroid goiter, protruding eyes (exopthalmos), palpitations, excess sweating, diarrhea, weight loss, muscle weakness and unusual sensitivity to heat.

Hypothyroidism is the underproduction of T_3 and T_4. Hypothyroid disorders may occur as a result of congenital thyroid abnormalities, autoimmune disorders such as ***Hashimoto's thyroiditis***, iodine insufficiency, or the removal of the thyroid following surgery to treat severe hyperthyroidism. Typical symptoms are abnormal weight gain, tiredness, baldness, temperature intolerance (both heat and cold), and palpitation.

In areas of the world where iodine is lacking in the diet the thyroid gland can become considerably enlarged, a condition called ***endemic goiter.*** Pregnant women on a diet that is severely deficient of iodine can give birth to infants who can present with thyroid hormone deficiency, manifesting in problems of physical growth and development as well as brain development (***endemic cretinism).*** In many developed countries, newborns are routinely tested for congenital hypothyroidism as part of newborn screening. Children with congenital hypothyroidism are treated supplementally with levothyroxine, which facilitates normal growth and development.

Pheochromocytoma is a tumor of chromaffin cells. The most common symptoms of pheochromocytoma are hypertension or high blood pressure.

Cushing's syndrome is the result of the excessive production of corticosteroids by the adrenal glands. An overproduction of corticotrophin of the pituitary gland, which stimulates the adrenal glands to produce the corticosteroids, could be of one cause. It also can be in excessive cortisol levels in the blood which may be the result of a tumour of the pituitary glands, adrenal glands. The symptoms of Cushing's syndrome are: change in body habitus; weight gain in the face, on the back of the neck, excess hair growth on the face, neck, chest, abdomen, and thigh, generalized weakness and fatigue, loss of muscles, menstrual disorders in women, high blood pressure, and high blood sugar.

Addison's disease (also ***chronic adrenal insufficiency)*** is a chronic endocrine disorder wherein the adrenal glands produce insufficient steroid hormones (glucocorticoids and often mineralocorticoids). Treatment involves replacing the absent hormones (oral hydrocortisone).

DIGESTIVE SYSTEM I.

ORAL CAVITY AND ASSOCIATED STRUCTURES 0

Overview of the digestive system

Digestive system consists of:

> long muscular alimentary tract (tube) and
> associated glands - salivary glands, pancreas, and liver.

Functions of the digestive system:

1) digestive:
   a) mechanical and chemical processing of food;
   b) absorption of nutrients;
   c) removal of the undigested substances;
2) excretive - removal through a wall of a digestive canal of the harmful substances (at renal insufficiency);
3) immune defence;
4) endocrine - secretion of the hormones having local and system effects.

General plan of structure of the digestive tube

The alimentary tract from the proximal part of the esophagus to the distal part of the anal canal is a hollow tube of varying diameter. This tube has the same basic structural organization throughout its length.

The wall of the digestive tube is made up of 4 principal layers:

1. ***tunica mucosa (mucosa)*** consists of:
   1) ***lamina epithelialis mucosae*** consists of only of epithelium;
   2) ***lamina propria mucosae*** consists of loose connective tissue, rich in blood and lymph vessels, sometimes also contains glands and lymphoid tissue;

3) ***lamina muscularis mucosae*** consists of some layers of smooth muscle tissue;

II. ***tunica submucosa*** (submucosa) consists of loose connective tissue, contains nerves, blood vessels, and glands in some organs;

III. ***tunica muscularis (muscularis)*** consists of some layers of smooth muscle tissue (sometimes of skeletal muscle tissue).

IV. outer layer:

tunica adventitia consists of loose connective tissue, or

tunica serosa consists of simple squamous epithelium called mesothelium and small amount of loose connective tissue.

0 Oral cavity

The ***oral cavity*** is divided into a vestibule and the oral cavity proper.

Features of a structure of a mucosa of an oral cavity

1. epithelium is stratified squamous nonkeratinized or parakeratinized;
2. lamina propria has papillae;
3. muscularis mucosae is absent;
4. submucosa consists of loose connective tissue, contains diffuse small salivary glands.

The oral cavity is lined by a ***masticatory*** mucosa, a ***lining*** mucosa, and ***specialized*** mucosa.

The ***masticatory*** mucosa is found on the gingival (gums) and the hard palate. It contains stratified squamous keratinized epithelium.

The ***lining*** mucosa is found on the lips, cheeks, alveolar mucosal surface, floor of the mouth, inferior surfaces of the tongue, and soft palate. The epithelium of the lining mucosa is nonkeratinized stratified squamous.

The specialized mucosa is restricted to the dorsal surface of the tongue, where it contains papillae and taste buds.

0 Tongue

The ***tongue*** is a muscular organ. It consists of striated muscles covered by mucosa whose structure varies according to the region. The muscle fibers cross one another in 3 planes (fig.22.1).

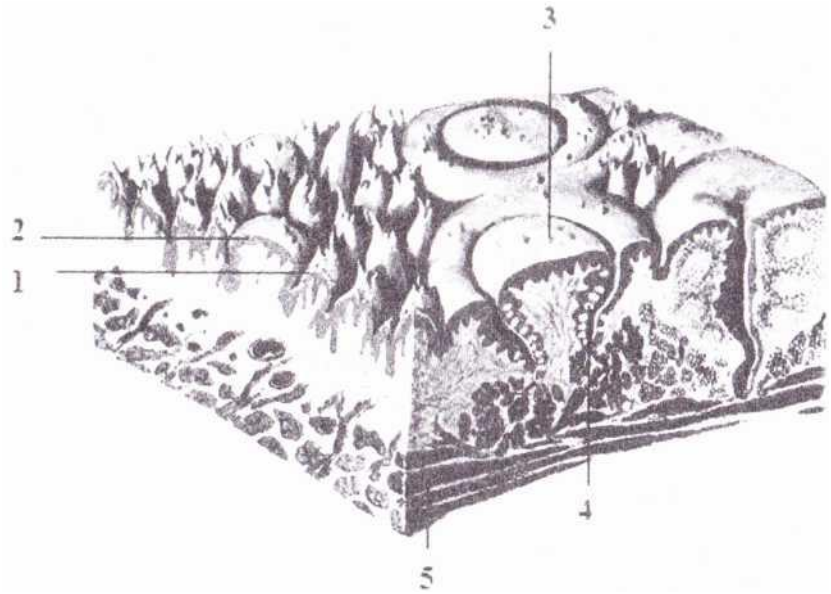


Figure 22.1. Schematic diagram of a tongue. 1 - filiform papillae, 2 - fungiform papillae, 3 - circumvallate papillae, 4 - taste buds. 5 - striated muscles

Functions of the tongue

1) . The tongue plays an important part in the process of ***digestion.*** Due to its muscular nature, tongue can manipulate in any direction, this facilitates the food to be properly mixed with saliva. Tongue can now turn the chewed food into a bolus and push it into the esophagus, from where the food will proceed further into the stomach through the peristaltic movement.

2) . The tongue carries on its surface the ***taste*** buds which send information to the brain about the nature of the food being eaten. It seems likely that the sensation of taste is not merely to make eating a pleasure, but also to act as a protective mechanism' designed to cause the rejection of noxious (harmful) foods.

3) .The tongue is responsible for ***speech.***

The ***dorsal surface*** of the tongue is lined by specialized mucosa, is irregular, because contains a great number of small eminences called ***papillae.*** Mucosa of the dorsal surface consists of 2 layers:

1) stratified squamous parakeratinized epithelium;

2) lamina propria consisting of loose connective tissue, which is strongly adherent to the muscles.

Papillae of the tongue are projections of the epithelium and lamina propria.

Distinguish 4 types of the papillae.

1. ***Filiform papillae*** have elongated conical shape, are most numerous, covered with the stratified squamous highly keratinized epithelium, do not contain taste buds (fig.22.2).

Figure 22.2. Photomicrograph of the filiform papillae of the tongue.

2. ***Fungiform papillae*** have broad rounded top and a narrow base, are present among the filiform papillae. These papillae have stratified squamous nonkeratinized epithelium and contain taste buds (fig.22.3).

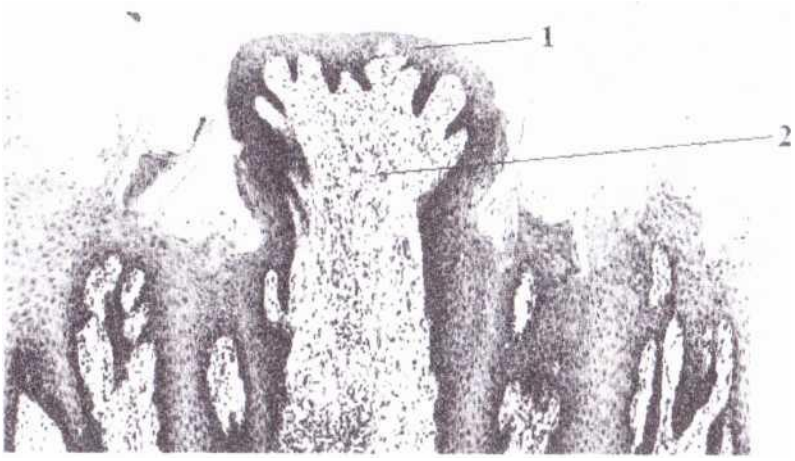


Figure 22.3. Photomicrograph of the fungform papilla of the tongue.
1 - stratified squamous nonkeratinized epithelium, 2 - connective tissue

3. ***Foliate papillae*** are poorly developed in humans. They consist of two or more parallel ridges and furrows on the dorsolateral surface of the tongue contain some taste buds (fig.22.4).

4. ***Circumvallatepapillae*** are 6-15 largest papillae, which situated in the V region in the posterior portion of the tongue. Each papilla has a broad rounded top, a narrow base and is surrounded by a circular groove, whose outer wall is called vallum. Taste buds are numerous (fig.22.5).

The ***lower surface*** of the tongue (fig.22.6) is lined by lining mucosa. Mucosa is smooth, and consists of 3 Sayers:

1) stratified squamous nonkeratinized epithelium;
2) lamina propria;
3) submucosa.

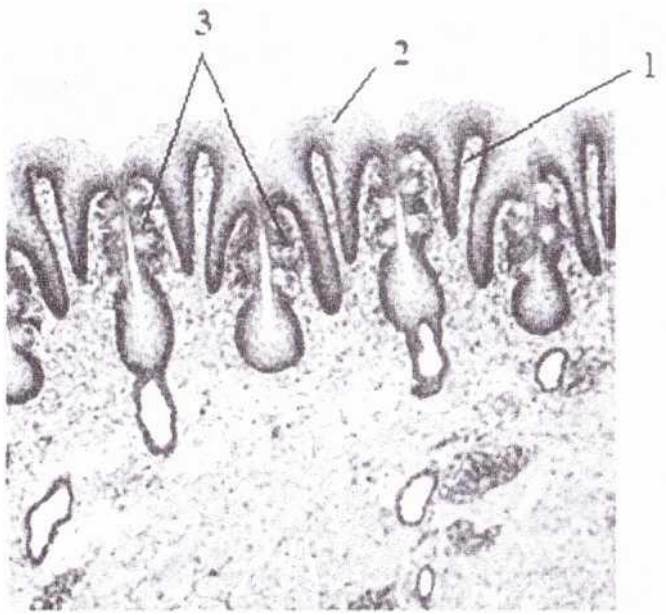


Figure 22.4. Photomicrograph of the foliate papillae of the tongue.
1 — papilla, 2 - stratified squamous nonkeratinized epithelium, 3 - taste

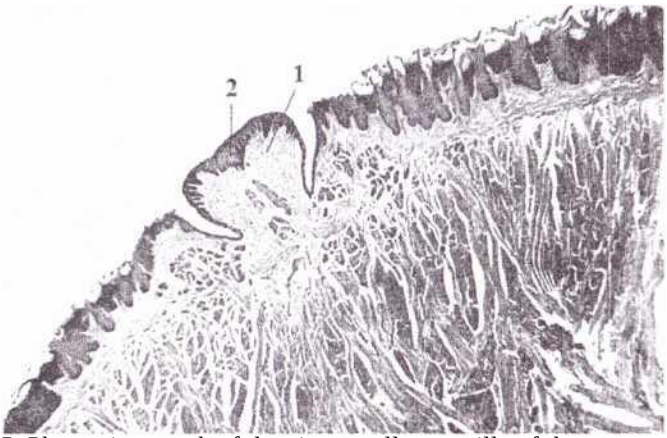


Figure 22.5. Photomicrograph of the circumvallate papilla of the tongue.
I - papilla, 2 - stratified squamous nonkeratinized epithelium

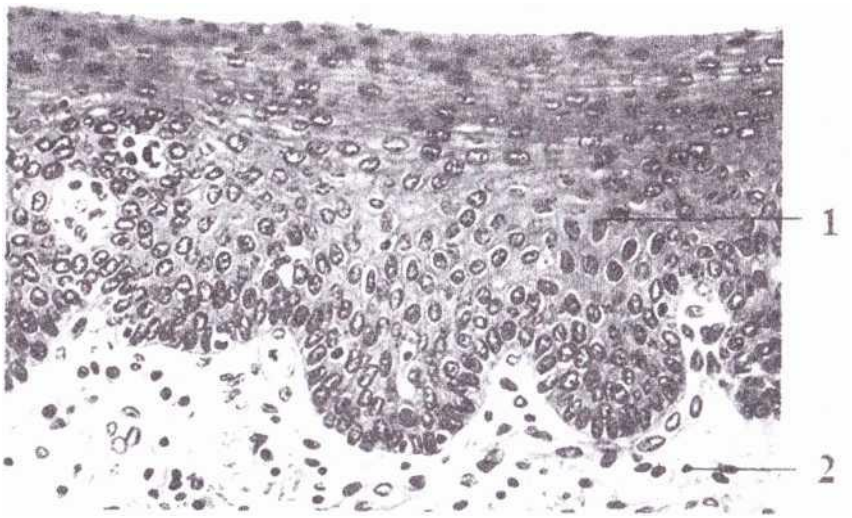


Figure 22.6. Photomicrograph of the lower surface of the tongue. 1 - stratified squamous nonkeratinized epithelium, 2 - lamina propria

0 Tonsils

The ***tonsils*** are organs composed of aggregates of incompletely encapsulated lymphoid tissues that lie in of the initial portion of the digestive tract.

The palatine, lingual, pharyngeal and tubal tonsils (adenoids) form ***Waldeyer's ring.***

Palatine tonsil

Two ***palatine tonsils*** (fig.22.7) are located in the lateral walls of the oral part of the pharynx. Their surface is covered by stratified squamous nonkeratinized epithelium which forms deep ***crypts***, and the resulting increase of the surface area is one way to facilitate the contact

of antigens with the immune cells. The tonsil contains numerous lymphoid follicles (nodules) with germinal centers.

The base of the tonsil is separated from underlying muscle by a connective tissue hemicapsule. This capsule acts as a barrier against spreading tonsillar infections.

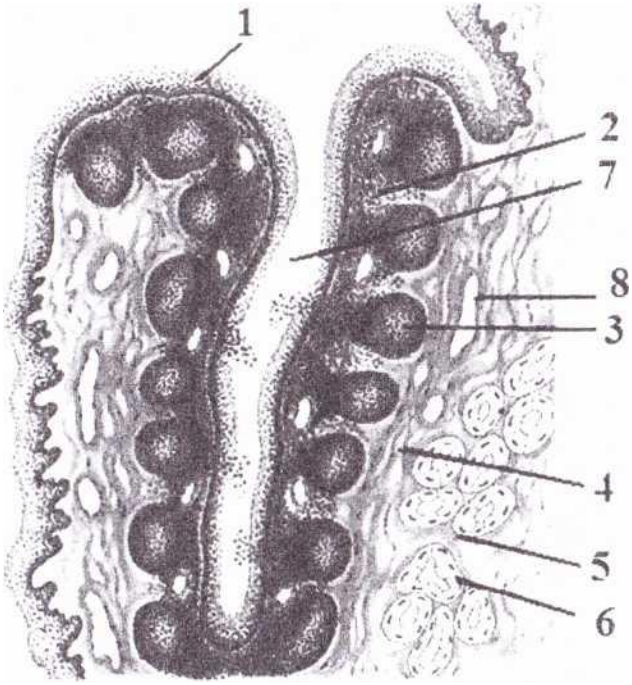


Figure 22.7. **Schematic diagram of the tonsil.** 1 - epithelium, 2 - lamina propria, 3 - lymphoid follicle, 4 — smooth muscle cells, 5 — submucosa, 6 — salivary glands, 7 - crypt, 8 - blood vessel

0 Teeth & Associated structures

Each ***tooth*** is composed of 3 parts (fig.22.8):

1) ***crown*** is the portion of the tooth that projects above the gingiva (gum);
2) one or more ***roots*** are situated below the gingival that hold the teeth in bony sockets called ***alveoli,*** one for each tooth;
3) ***neck*** is constricted part between crown and root.

Teeth are made up of 3 specialized tissues: ***dentin, enamel*** and ***cementum.*** Within a tooth there is ***centra! pulp cavity*** occupied by ***dental pulp.***

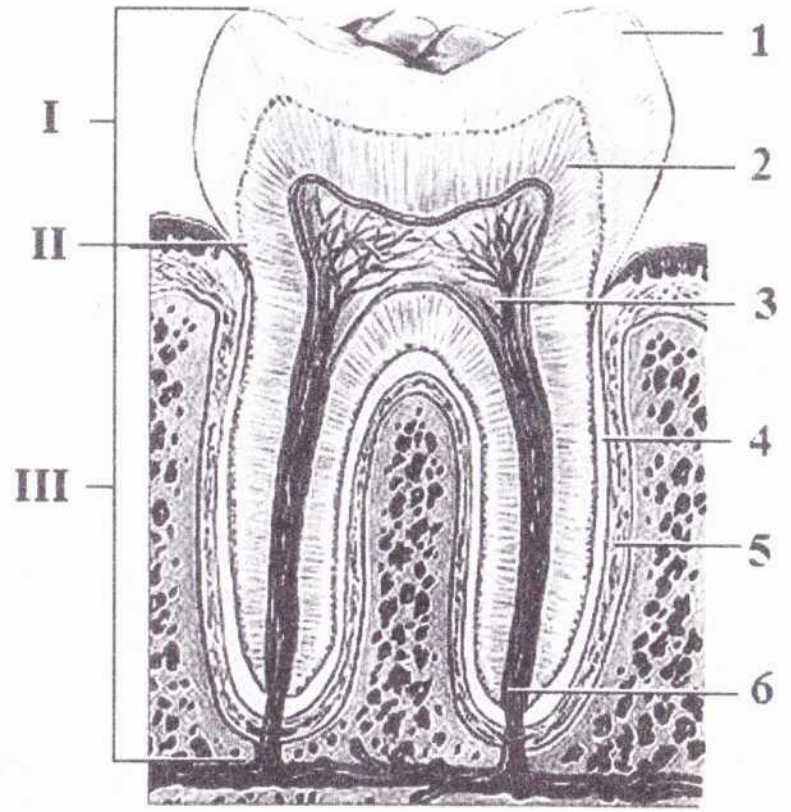


Figure 22.8. Schematic diagram of tooth. I - crown, II - neck, III - root,] - enamel, 2 - dentin, 3 - pulp, 4 - cementum, 5 - periodontal ligament, 6 - nerve and blood vessels

Dentin

The ***dentin*** is a calcified tissue of the tooth; it is covered by enamel on the crown and cementum on the root and surrounds the entire pulp.

Dentin is made up of:

> 70% inorganic materials (hydroxyapatite, which is a crystalline calcium phosphate - $Ca_{10}(PO_4)_6(OH)_2$),

> 20% organic materials (collagen proteins),

> 10% water.

The organic matrix of dentin is secreted by ***odontoblasts,*** cells that line the internal surface of the tooth, separating it from the pulp cavity. Odontoblasts have the structure of protein-secreting cells. These cells have slender, branched cytoplasmic extensions (***odontoblast processes***) that penetrate perpendicularly through the dentin.

Dentin consists of microscopic channels, called ***dentinal tubules*** (fig.22.9), w'hich radiate outw'ard through the dentin from the pulp to the exterior cementum or enamel border. These tubules contain fluid and odontoblast processes.

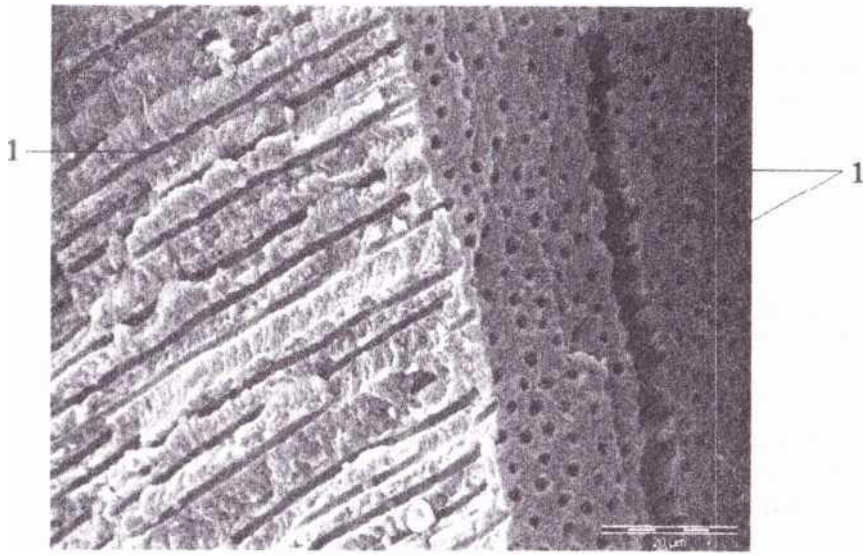


Figure 22.9. Electron micrograph of dentin. 1 - dentinal tubules

There are three types of dentin.

> ***Primary dentin*** is the outermost layer of dentin, it borders the enamel. The outer layer closest to enamel is known as ***mantle dentin.*** This layer

is unique to the rest of primary dentin. Mantle dentin is formed by newly differentiated odontoblasts. Below it the ***circumpulpal dentin*** is situated. This is a more mineralized dentin which makes up most of the dentin layer; it is secreted after the mantle dentin by the odontoblasts.

> ***Secondary dentin (regular secondary dentin)*** is a layer of dentin produced after the root of the tooth is completely formed. It grows much more slowly than primary dentin. It has a similar structure to primary dentin, although its deposition is not always even around the pulp chamber.

> ***Tertiary dentin (irregular secondary dentin or reparative dentin)*** is created in response to a stimulus, such as a carious attack. Tertiary dentin is deposited rapidly, with a sparse and irregular tubular pattern and some cellular inclusions known as osteodentin.

Enamel

The ***enamel*** along with dentin, cementum, and dental pulp is the hardest substance of the human body, the richest in calcium and avascular. It consists of about

> 95% calcium salts (mainly hydroxyapatite),
> 1% organic material (collagen proteins),
> 4% water.

The ***enamel*** contains (fig.22.10):

1) elongated ***enamel rods*** that are bound together by
2) ***interrod enamel.***

Enamel rod is a tightly packed mass of hydroxyapatite crystals in an organized pattern. Enamel rods are found in rows along the tooth, and within each row, the long axis of the enamel rod is generally perpendicular to the underlying dentin. Both ***interrod enamel*** and enamel rods are formed of hydroxyapatite crystals; they differ only in the orientation of the crystals.

Cementum

The ***cementum*** is a specialized calcified substance covering the dentin of the neck and root of a tooth, Cementum is similar in composition to bone, although Haversian systems and blood vessels are 370

absent. It is thicker in the apical region of the root, where are cementocytes, cells with appearance of osteocytes. Like osteocytes, cementocytes are encased in lacunae that communicate through canaliculi. Cementum is secreted by cells called cementoblasts.

Figure 22.10. Electron micrograph of enamel. 1 - enamel rods, 2 - interrod enamel

The chemical composition of cementum:

> 65% inorganic material (mainly hydroxyapatite),
> 23% organic material (mainly collagen typel) and
> 12% water.

Distinguish two types of cementum:

> ***acellular*** cementum has no cellular components, covers all surface of the root of the tooth as a thin layer of calcified matrix;

> ***cellular*** cementum covers 1/3-1/2 of the root apex, contaias cementocytes and calcified matrix.

The main role of cementum is to anchor the tooth by attaching it via the periodontal ligaments. It also plays an important role in forming of new teeth. Its bottom surface is tangent to the periodontal ligaments running through the jaw' (via collagen fibers), and the upper portion of the surface is firmly cemented to the dentin of the tooth.

Dental pulp

The ***dental pulp*** is the central part of the tooth filled with soft connective tissue. The central region of the coronal and radicular pulp contains large nerve trunks and blood vessels.

Dental pulp has three layers (from innermost to outermost):

1) ***cell rich zone*** contains fibroblasts and undifferentiated mesenchvmal cells;
2) ***cell free zone*** (zone of Weil) is rich in both capillaries and nerve networks;
3) ***odontoblastic layer*** contains cell bodies of the ***odontoblasts.***

Cells found in the dental pulp include fibroblasts (the principal cells), odontoblasts, macrophages, granulocytes, mast cells and plasma cells.

Associated structures

The ***associated structures*** of the tooth responsible for to attach the tooth to surrounding tissues and to allow sensations of touch and pressure:

> cementum;
> periodontal ligament;
> alveolar bone;
> gingiva.

Periodontal ligament is composed of a special type of dense connective tissues whose fibers penetrate the cementum of the root and

bind it to the bony wall of its socket. Its fibers are organized so as to support the pressures exerted during mastication.

Alveolar bone forms the sockets and is in immediate contact with the periodontal ligament. It is primary bone in which the collagen fibers are not arranged in lamellar pattern. These fibers are arranged in bundles that penetrate this bone and the cementum.

Gingiva is a mucous membrane bound to the periosteum of the maxillary and mandibular bones. It is lined by stratified squamous keratinized epithelium. This epithelium is bound to the tooth enamel. Between the enamel and the epithelium is the gingival crevice - a small deepening surrounding the crown.

0 Tooth development

At about 6 weeks of gestation the oral epithelium proliferates, bulges into the underlying mesenchyme and forms a ***dental lamina*** (fig.22.11). The dental lamina connects the developing tooth bud to the epithelial layer of the mouth for a significant time.

Tooth development is divided into the following stages:

> ***bud stage,***
> ***cap stage,***
> ***bell stage,*** and finally
> ***maturation (crown stage).***

1) ***Bud stage***

In each quadrant of the mouth, the dental lamina then develops globular swellings ***(tooth buds).*** The tooth bud is the group of cells at the end of the dental lamina.

2) ***Cap stage***

Mesenchymal cells aggregate near the pole of tooth bud. These cells are called the ***dental papilla.*** At this point, the tooth bud grows around the mesenchymal aggregation, taking on the appearance of a cap, and becomes the ***enamel (or dental) organ.*** A condensation of mesenchymal cells called the ***dental follicle*** surrounds the enamel organ and limits the dental papilla. Eventually, the enamel organ will produce enamel, the dental papilla will produce dentin and pulp, and the dental follicle will produce all the supporting structures of a tooth.

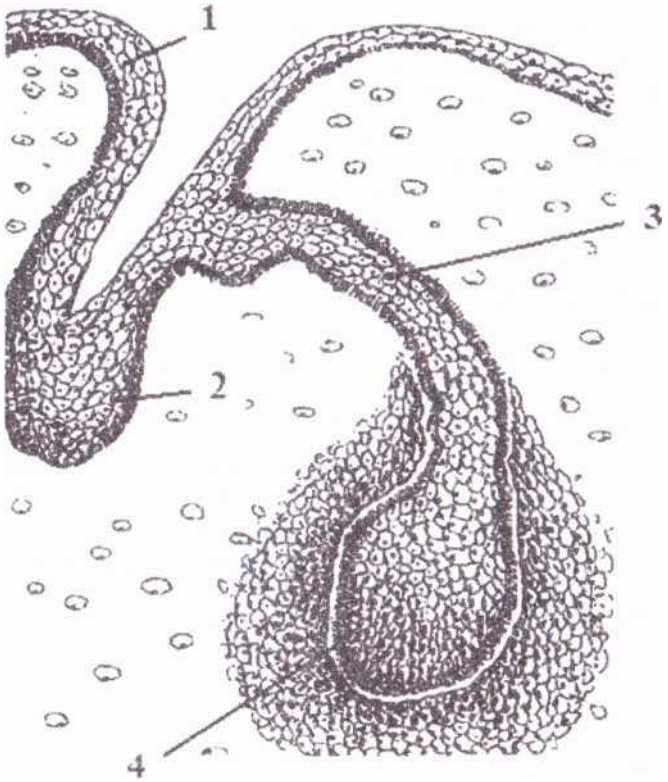


Figure 22.11. Schematic diagram of developing tooth. 1 - oral epithelium, 2 - vestibular lamina, 3 - dental lamina, **4** - enamel organ

3) ***Bell stage***

The dental organ is bell-shaped during this stage (fig.22.12). Cells of the enamel organ are divided into three layers. Cuboidal cells on the periphery of the dental organ are known as ***outer enamel epithelium.*** The columnar cells of the enamel organ adjacent to the dental papilla are known as ***inner enamel epithelium.*** The ***stellate reticulum*** is a group of cells located in the center of the enamel organ of a developing tooth. These cells are star shaped and synthesize glycosaminoglycans. The cells between the inner enamel epithelium and the ***stellate reticulum*** form a layer known as the ***stratum intermedium.***

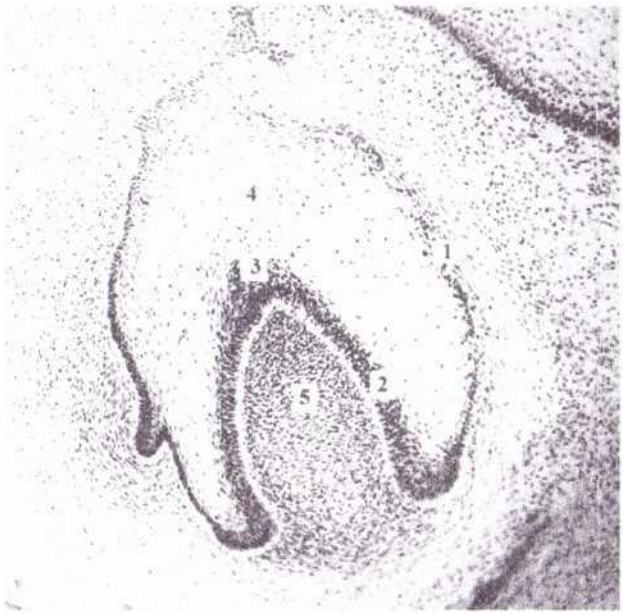


Figure 22.12. Photomicrograph of developing tooth. 1 - outer enamel epithelium, 2 - inner enamel epithelium. 3 - stratum intermedium, 4 -stellate reticulum, 5 - dental papilla

The cells of ***inner enamel epithelium*** give rise to ***ameloblasts,*** which produce enamel.

The ***dental papilla*** contains cells that develop into ***odontoblasts***, which are dentin-forming cells. Mesenchymal cells within the dental papilla are responsible for formation of tooth ***pulp*** (fig.22.13).

The ***dental follicle*** gives rise to eementoblasts, osteoblasts, and fibroblasts. Cementoblasts form the cementum of a tooth. Osteoblasts give rise to the alveolar bone around the roots of teeth. Fibroblasts develop the periodontal ligaments which connect teeth to the alveolar bone through cementum.

4) ***Maturation (crown stage)***

Hard tissues, including enamel and dentin, develop during this stage of tooth development.

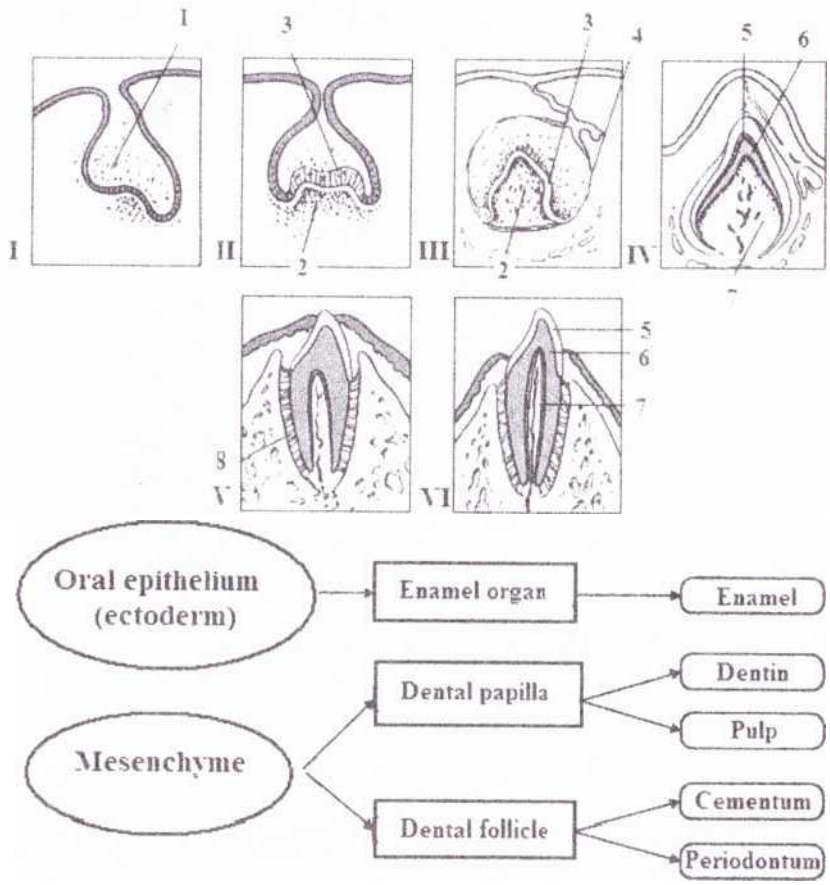


Figure 22.13. **Schematic diagram of tooth development.** I - bud stage, II - cap stage, III - early bell stage, IV - late bell stage, Y, VI - maturation; 1 - tooth bud, 2 - dental papilla, 3 - inner enamel epithelium, 4 - outer enamel epithelium, 5 — enamel, 6 - dentin, 7 — dental pulp, 8 - periodontal ligament

Dentinogenesis

Dentin formation is the first identifiable feature in the crown stage of tooth development.

Odontoblasts, the dentin-forming cells, differentiate from cells of the dental papilla. They begin secreting an organic matrix, which contains collagen fibers, around the area directly adjacent to the inner 376

enamel epithelium. Further odontoblasts begin to move toward the center of the tooth, forming an extension called the ***odontoblast processes.***

Amelogenesis is the formation of enamel on teeth and occurs during the crown stage of tooth development after dentinogenesis.

Cementogenesis occurs late in the development of teeth.

The cementoblasts differentiate from cells of ***dental follicle.*** The cementoblasts secrete matrix of proteins and collagen fibers. Then mineralization takes place.

0 Salivary glands

The major ***salivary glands*** are paired organs with long ducts that empty into the oral cavity.

These are three pairs of major salivary glands, the ***parotid***, ***submandibular*** and ***sublingual***, and numerous small glands situated in the mucosa of the lips, cheeks, tongue and palate.

The functions of the salivary glands

> ***digestive*** (to wet and lubricate the oral cavity and its contents, to initiate the digestion of carbohydrates);
> ***immunologic*** (to secrete IgA, lysozyme, lactoferrin);
> ***excretive*** (to excrete products of a metabolism, medicine, heavy metals);
> ***regulation of a water-salt homeostasis*** (to excrete of the liquid containing ions Na, K, Ca, Cl);
> ***endocrine*** (to secrete of an active substances: parotin, the factor of growth of nerves, the epidermal factor of growth, etc).

General plan of the structure of the large salivary glands

The large salivary glands are compound tubulo-alveolar glands. The large salivary gland is covered by connective tissue capsule; septa divide the gland into lobules.

Major salivary gland consists of:

> secretory portion,
> duct system.

The ***secretory portion*** consists of two general types of cells:
1) ***secretory*** (serous and mucous) and
2) ***myoepithelial cells.***

Serous cells (fig.22.14) are pyramidal in shape, with a broad base resting on the basal lamina and a narrow apical surface facing the lumen.

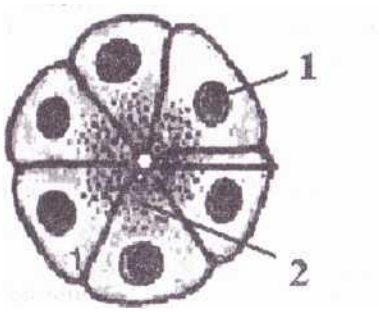


Fig.22.14. Serous cells of the salivary gland gland. 1 — nucleus, 2 - granules of mucinogen

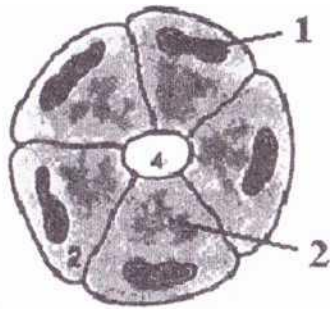


Fig.22.15. Mucous cells of the salivary
1 -nucleus,

They have characteristics of polarized protein-secreting cells. Nuclei are spherical and placed near the centre of the cell. The basal part of cytoplasm takes a deep basic stain due to rough endoplasmic reticulum. The supranuclear part contains large serous granules.

Mucous cells (fig.22.15) are cells are large, pale with oval nuclei in the basal parts. The cytoplasm contains large mucinogen granules.

Myoepithelial (basket) cells (fig.22.16) have many long cytoplasmic processes and surround serous acini, mucous tubules, and intercalated ducts. These cells are of epithelial origin but contain myofibrils in their cytoplasm and help in the expulsion of secretion.

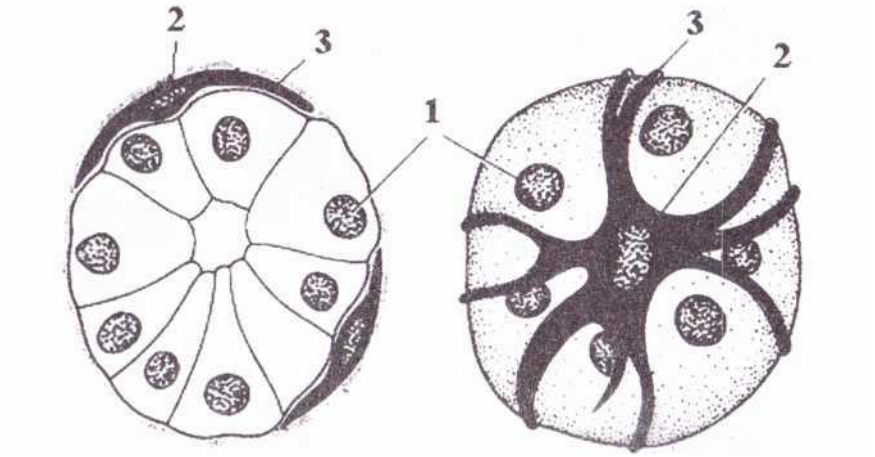


Fig.22.16. Myoepithelial (basket) cells. 1 — nuclei of the secretory cells, 2 — nuclei of the myoepithelial cells, 3 — processes of the myoepithelial cells (from ***K). H.Afpanacbee, H.A.IOpwta u dp.,*** 1999)

3 types of the secretory portion are described (fig.22.17):

1) ***serous acini*** (alveoli) which consist of only serous cells;
2) ***mucous tubules*** consisting of only of mucous cells and are tubular;
3) ***mixed acini*** which consist of both types of secretory cell: serous cells form caps (demilunes of Gianuzzi) surrounding the terminal part of the mucous cells.

The ***duct system*** consists of:

1) ***intercalated ducts*** lead from acini; are lined by simple cuboidal epithelium;
2) ***intralobular,*** or ***striated, ducts*** are lined by simple columnar epithelium and characterized by ***radial striations*** that extend from the bases of the cells to the level of the nuclei; the "striations" consist of infolding of the basal plasma membrane with numerous elongated mitochondria aligned parallel to the infolded membranes;
3) ***interlobular,*** or ***excretory, ducts*** are lined by stratified cuboidal or columnar epithelium;
4) ***main duct*** of each major salivary gland empties into the oral cavity and is lined by stratified squamous nonkeratinized epithelium.

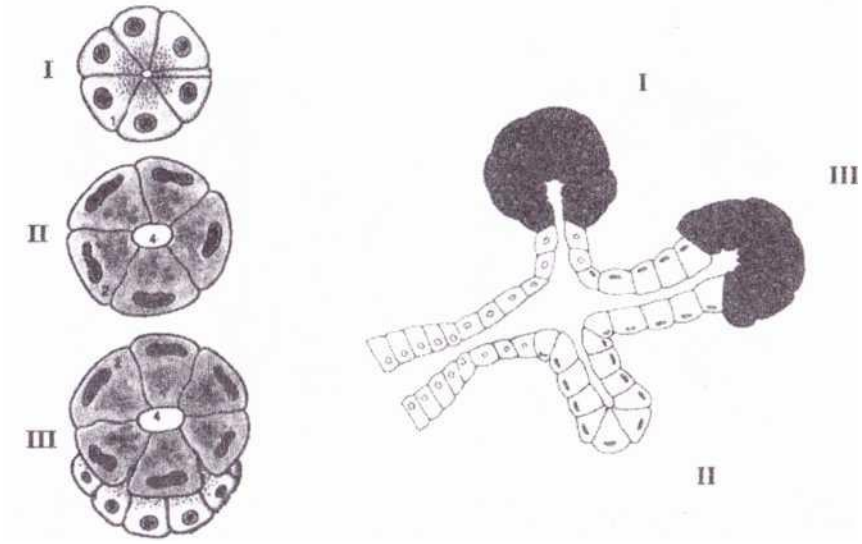


Fig.22.17. Secretory portions of the large salivary glands. I — serous, **II-** mucous, **III -** mixed

The features of structure of major parotid glands

Parotid gland is a branched acinar gland and contains exclusively serous secretory portions (***serous acini).*** The secretion of this gland is rich in proteins and has a high amylase activity.

Submandibular (submaxillary) gland is a branched tubuloacinar gland and contains serous (predominant) and mixed secretory portions.

Sublingual gland is a branched tubuloacinar and contains mixed (predominant), mucous, and serous (not numerous) secretory portions.

Saliva

The ***saliva*** is mixed secretion from major and small salivary glands. The salivary glands produce about 1200 mL of saliva a day. Human saliva is composed of

> 98% water,

> 2%:

- electrolytes (Na^+, K^+, Ca^H, Mg"\ Cl , $HC0_3$,$P04_3$,1);
- mucus;
- antibacterial compounds (lysozyme, salivary lactoperoxidase, lactoferrin, immunoglobulin A);
- Epidermal growth factor or EGF;
- various enzymes (a-amylase, lingual lipase);
- cells (possibly as much as 8 million human and 500 million bacterial cells per mL);
- opiorphin, a newly researched pain-killing substance.

Functions of the saliva

> Moistening dry foods to aid swallowing.

> Providing a medium for dissolved and suspended food materials that chemically stimulate taste buds.

> Buffering of the contents of the oral cavity through its high concentration of bicarbonate ion.

> Digestion of carbohydrates by the digestive enzyme a-amylase.

> Controlling the bacterial flora because of the presence of the antibacterial enzyme lysozyme.

> Source of calcium and phosphate ions essential for normal tooth maintenance.

0 Clinical correlations

Dental caries is a disease where bacterial processes damage hard tooth structure (enamel, dentin, and cementum). These tissues progressively break down, producing dental caries (cavities in the teeth). Two groups of bacteria are responsible for initiating caries: ***Streptococcus mutans*** and ***Lactobacillus***. If left untreated, the disease can lead to pain, tooth loss, infection, and, in severe cases, death. Today, caries remains one of the most common diseases throughout the world.

Salivary gland diseases

Sialolithiasis is a condition where tiny salivary ***stones*** form in the glands. The stones, called sialoliths, are made of calcium. Some

stones do not cause any symptoms, but some stones block the ducts. The saliva flow is partially or completely stopped. The gland might enlarge and an infection can develop.

Sialadenitis is a painful infection of a salivary gland. Staphylococcus, streptococcus, Haemophilus influenzae or anaerobic bacteria are usually the cause. The condition is common with elderly adults who have salivary gland stones, but infants can also develop sialadenitis during the first few weeks of life.

Cysts can develop in the salivary glands after injuries, infections, stones or tumors. Sometimes babies are born with cysts in the parotid gland because of a problem with early development of the ears.

Pleomorphic adenomas are the most common parotid tumor. It grows slowly and is benign. A pleomorphic adenoma begins as a painless lump at the back of the jaw, just below the earlobe. These are more common in women.

Cancerous (malignant) tumors are rare in the salivary glands and usually occur between ages 50 to 60. Some types grow fast and some are slow-growing.

DIGESTIVE SYSTEM II. PHARYNX. ESOPHAGUS. GASTROINTESTINAL TRACT 0 Pharynx

The ***pharynx*** is a common passage for food and air.

Pharynx is divided into 3 parts: nasopharynx, oropharynx and laryngopharynx.

The wall of the pharynx has 4 layers:

I. ***Mucosa*** consists of:

1) ***epithelium*** is pseudostratified columnar ciliated in nasopharynx and stratified squamous nonkeratinised in oropharynx and laryngopharynx;

2) ***lamina propria*** consists of loose connective tissue, contains serous and mucous glands and aggregations of lymphoid tissue.

II. ***Submucosa*** consists of loose connective tissue, contains the lymphoid tissue of pharyngeal tonsil in the posterior wall and tubal tonsils in the lateral wall of nasopharynx, and palatine tonsil in the lateral wall of oropharynx.

III. ***Muscularis*** consists of two layers of skeletal muscle tissue.

IV. ***Adventitia*** consists of a loose connective tissue.

0 Esophagus

The ***esophagus*** is muscular tube 25cm long that carries food from phamx to stomach.

The wall of the esophagus has 4 layers (fig.23.1):

I. ***Mucosae*** consists of

1) ***epithelium*** is stratified squamous nonkeratinized;

2) ***lamina propria*** consists of loose connective tissue, contains the branched tubular esophageal cardiac glands in the region near the stomach;

3) ***muscularis mucosae*** contains longitudinal layer of smooth muscle tissue;

II. ***Submucosae*** consists of loose connective tissue, contains the secretory parts of the mucous esophageal glands proper;

III. ***Muscularis*** has an outer longitudinal and an inner circular layers;

in the upper 1/3 of the esophagus the muscular layer consists of only striated muscle fibers;

in the middle 1/3 - a mixture of striated and smooth muscle tissue; and in the lower 1/3 - only smooth muscle tissue.

IV. ***External tunic'.***

in the peritoneal cavity esophagus is covered by ***serosa*** which consists of loose connective tissue and a simple squamous epithelium (mesothelium);

in the thoracic cavity esophagus is covered by ***adventitia*** which consist of loose connective tissue.

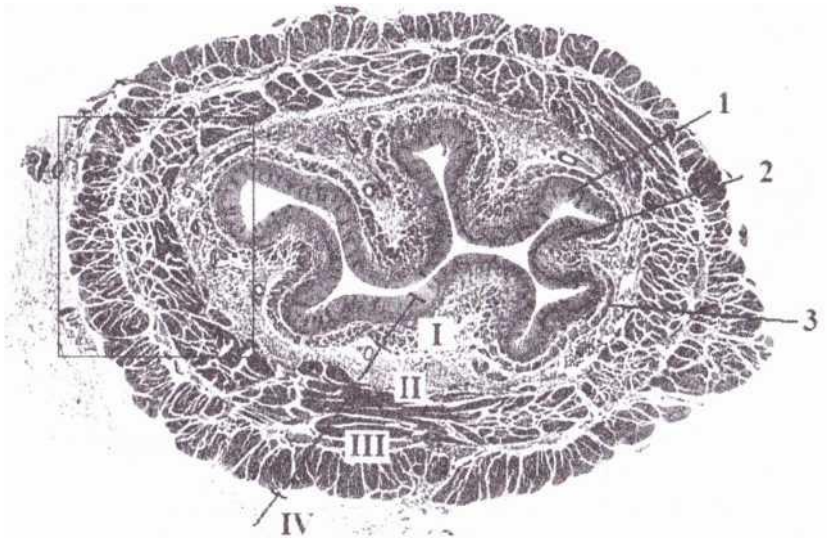


Fig.23.1. Photomicrograph of the esophagus (cross section). I - mucosa: 1 - epithelium, 2 — lamina propria, 3 - muscularis mucosa; **II** — submucosa, III — muscularis, IV - adventitia

0 Stomach

T he ***stomach*** is the dilated segment of the digestive tract which receives food from the esophagus, undergoes mechanical and chemical breakdown to form chyme.

The functions of the stomach

> to transform the ingested food by muscular activity into a viscous mass (chyme) and progress it to the distal part of gastro-intestinal tract;

> to continue the digestion of carbohydrates initiated in the mouth, promote the initial digestion of protein and lipids with the enzymes pepsin and gastric lipase;

> to product of intrinsic factor, which is essential for vitamin B_{12} absorption;

> absorption of some substances such as water, salt sugar and other; ***y***

endocrine secretion.

Stomach has 4 regions: cardia, fundus, body and pylorus (fig-23.2).

Because the fundus and body are identical in microscopic structure the stomach has such histological parts:

> cardiac;

> fundic;

> pyloric.

The wall of the stomach consists of the 4 layers (fig.23.3):

I. Mucosa; ‘
II. Submucosa;
III. Muscularis;
IV. Serosa.

Gastric mucosa has a complex relief:

> ***longitudinal folds*** or ridges termed rugae composed of the mucosa and submucosa;

> ***gastric pits*** (foveolae) are the invaginations of the epithelium into the lamina propria which serve as the ducts of gastric glands;

> ***mamillated areas*** - bulging irregular areas formed by grooves or shallow trenches.

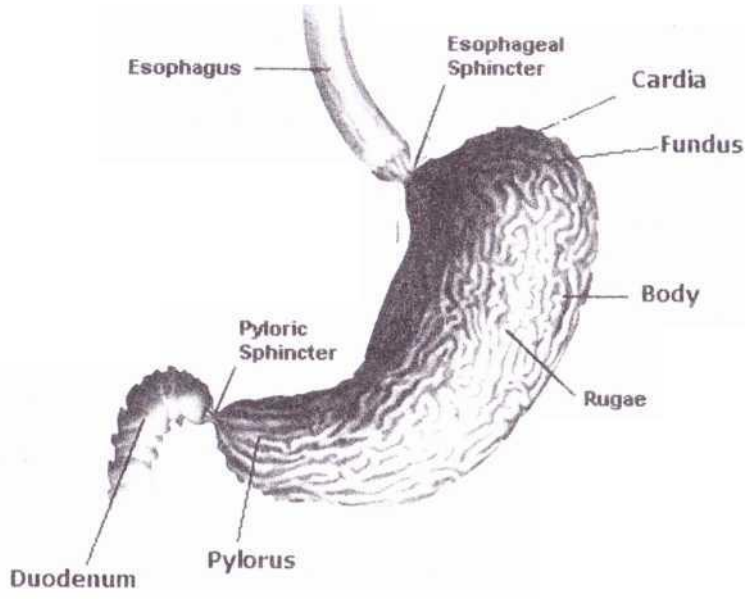


Figure 23.2. Regions of the stomach.

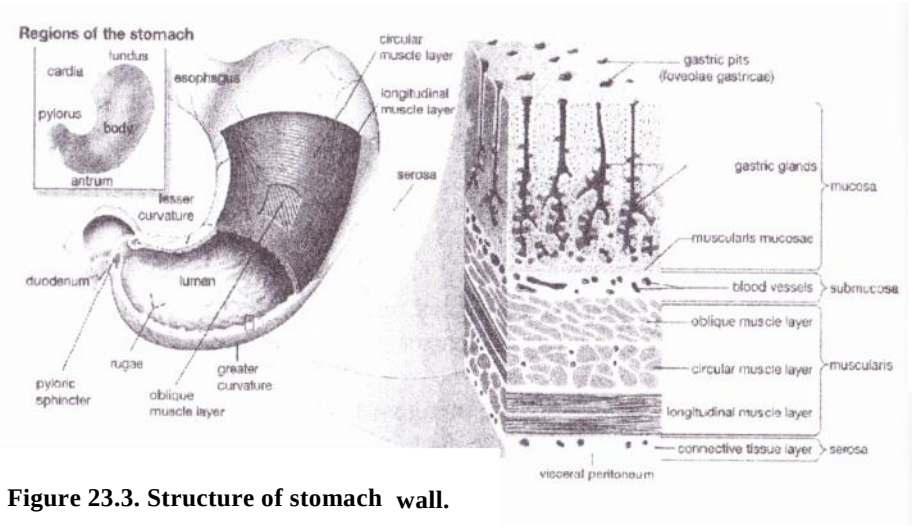


Figure 23.3. Structure of stomach wall.

I ***Gastric mucosa*** consists of:

1) surface ***epithelium*** is simple columnar and mucous secreting;

2) ***lamina propria*** is composed of loose connective tissue; it is packed gastric glands;

3) ***muscularis mucosae*** is well developed, consists of three layers of smooth muscle cells.

II ***Submucosa*** consists of loose connective tissue, blood vessels and submuscular nerve plexus.

III. ***Muscularis*** is composed of smooth muscle cells oriented in three layers, an inner oblique, middle circular and outer longitudinal layer.

At the pylorus, the middle layer is greatly thickened to form the pyloric sphincter.

IV. ***Serosa*** consists of a layer of squamous cells (mesothelium) with a small amount of underlying connective tissue.

Glands in the lamina propria empty into the bases of the gastric pits. The stomach is divided into three histological regions based on the nature of the glands.

1) . The ***cardiac region*** is a narrow band near the opening of the esophagus, which contains ***cardiac glands.*** Cardiac glands are composed almost entirely of mucus-secreting cells, with the odd enteroendocrine cell present. These glands may branch and frequently coil at their terminal part. Their secretion protects the esophagus against gastric reflux. Gastric pits in the cardiac region are fairly shallow.

2) . The ***fundic region*** constitutes the majority of the stomach. The glands in this region are known as ***gastric*** or ***fundic glands*** and extend all the way to the muscularis mucosae. 3-7 glands open into the base of each gastric pit.

Each gland has long, narrow neck and a short, wider base (fig.23.4). At their base, the glands may divide into two or three branches which become slightly coiled.

The following cells types can be seen in the glands of the fundic region:

> ***Mucous neck cells*** are located in the neck region and secrete a ***mucous.***

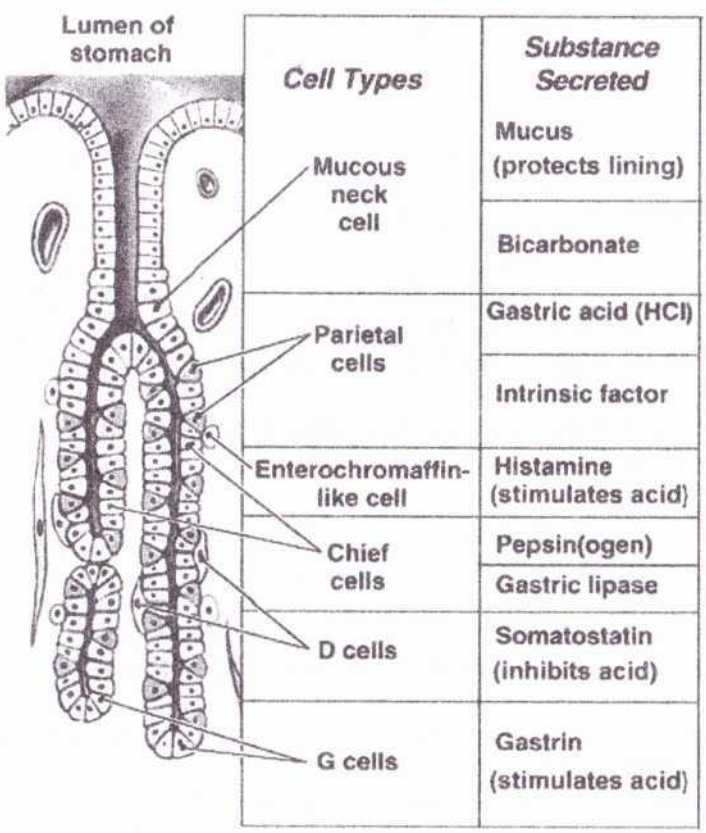


Figure 23.4. Schematic diagram **of** the gastric gland. 1 - gastric pit, 2 - mucus cells, 3 - parietal cells, 4 - chief cells, 5 - enteroendocrine cells

> ***Parietal (or oxyntic) cells*** (fig.23.5) are found predominantly in the upper part of the gland. They secrete ***HCl*** and ***intrinsic factor.*** They are intensely eosinophilic due to the amount of membrane comprising an extensive intracellular canalicular system and numerous mitochondria. HCl secretion is stimulated mainly by gastrin. Intrinsic factor is a glycoprotein that binds vitamin $B|_2$, essential for maturation of red blood cells.

> ***Chief cells*** are located mainly near the base of the glands and are typical protein-secreting cells. Their basophilia stems from their

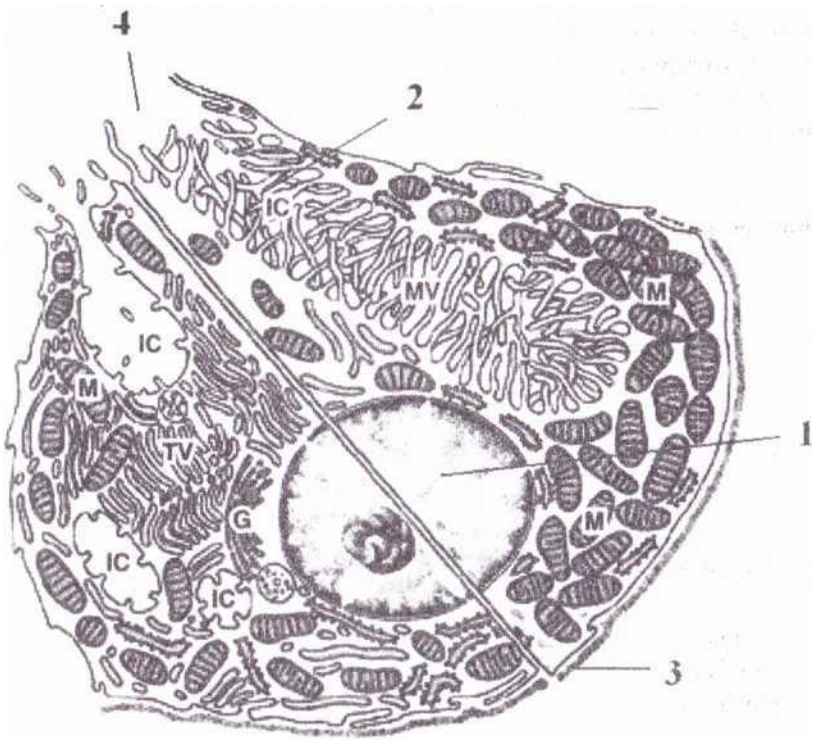


Figure 23.5. Schematic diagram of the parietal (oxyntic) cell. 1 - nucleus, 2 intracellular canaliculus, 3 - basal lamina, 4 - lumen (from *Junqueira L.C.*, (*'arneiro*2005)

abundant rER. They secrete ***pepsinogen*** and ***lipase.*** Pepsinogen is converted to the proteolytic enzyme pepsin upon contact with the acidic gastric juice.

> ***Enteroendocrine cells*** (fig.23.4, 23.9, tab. 23.1) are more prevalent near the base of gland. Enteroendocrine cells secrete their product into the lamina propria whence it is taken up by blood vessels. The major secretory product of the enteroendocrine cells of the stomach is ***gastrin,*** which stimulates the production of HC1. Other products are ***glucagon***, ***serotonin, substance P*** and ***VIP.***

> ***Undifferentiated cells*** are found in the neck region and give rise to all the other cell types. They are low columnar cells. They travel upwards to replace surface mucous cells whose lifespan is 3-5 days, and downward to replace parietal, chief and enteroendocrine cells, whose lifespan is about a year.

3) . The ***pyloric region*** is the part of the stomach proximal to the pyloric sphincter, and contains ***pyloric glands.*** These are short, coiled, branched tubular glands with a wide lumen. Their cells secrete mucous and are similar in appearance to the surface mucous cells. The gastric pits in this region are very deep, going about halfway down to the muscularis mucosae.

Gastric glands secrete ***gastric juice.*** Gastric juice is a watery secretion w'ith Ph 0,9-1,5.

The components of ***gastric juice*** are:
^ hydrochloric acid (HC1) is produced by parietal cells; it converts inactive pepsinogen into the active enzyme pepsin;
> pepsin is proteolytic enzyme;
> mucus is acid-protective coating for the gastric mucosa;
> intrinsic factor binds to vitamin B_{i2}; it is essential for absorption of vitamin $B_{[2}$ which occurs in the distal part of the ileum.

0 Small intestine

The ***small intestine*** is the longest component of the digestive tract (over 6 m), is divided into three portions: duodenum, jejunum, ileum.

The functions of the small intestine:
> terminal food digestion;
> nutrient absorption;
>mechanical (to progress of the contents to the distal part of the large intestine);
> endocrine secretion;
> immune defence.

The wall of the small intestine consists of 4 layers:

I. mucosa;
II. submucosa;
III. muscularis;
IV. serosa or adventitia.

The ***relief*** of mucosa of the small intestine:

> ***folds (plicae circularis),*** consisting of mucosa and submucosa;
> ***intestinal villi*** are fingerlike surface projections of the mucosa into the lumen of the small intestine;
> ***intestinal glands (crypts of Lieberkuhn)*** are invaginations of the epithelium into lamina propria (the simple tubular glands).

I. ***Mucosa*** consists of:

1) simple columnar ***epithelium***;

2) ***lamina propria*** is composed of loose connective containing tissue with blood vessels, nerves and smooth muscle cells; these cells are responsible for the rhythmic movements of the villi, which are important for absorption; lamina propria contains aggregates of lymphoid tissue which is termed as ***gut-associated lymphoid tissue (GALT);***

3) ***muscularis mucosae*** consists of smooth muscle cells.

The intestinal epithelium consists of some types of cells:

> enterocytes (absorptive cells),
> goblet cells,
> Paneth's cells,
V enteroendocrine cells,
> M (microfold) cells,
> stem (undifferentiated) cells.

Enterocytes (fig.23.6) are tall columnar cells, with oval nuclei in the basal half of the cell, specialized for the transport of substances. In the apex of each cell there is the ***striated (brush) border*** of closely packed microvilli, which greatly increase the surface area for absorption.

Amino acids and monosaccharides are absorbed by active transport, monoglycerides and fatty acids cross the microvilli membranes passively. Absorbed substances enter either the fenestrated

capillaries in the lamina propria just below the epithelium, or the lymphatic lacteal (most lipids and lipoprotein particles).

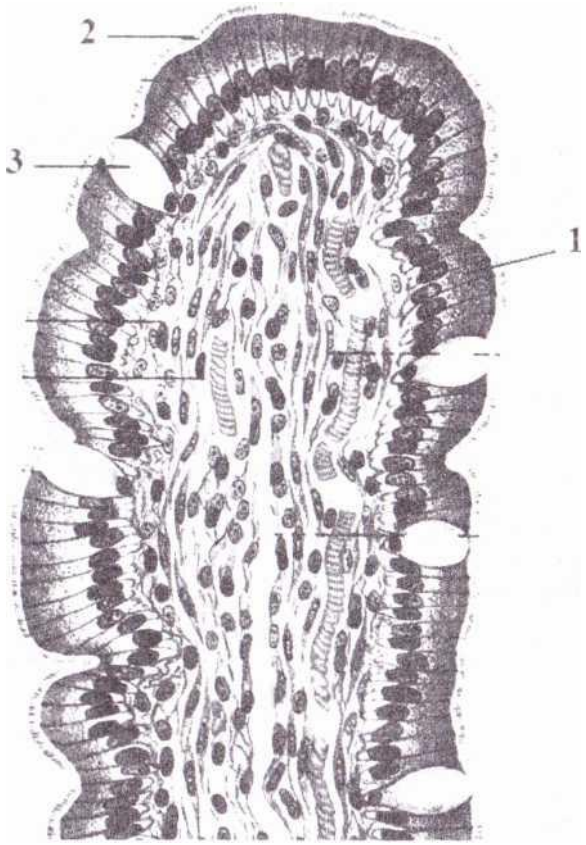


Figure 23.6. Schematic diagram of the villus. ' 1 — enterocytes, 2 - striated border, 3 - goblet cells

Goblet cells are found interspersed among the absorptive cells. They are unicellular mucus secreting glands. The slender base of the cell contains the nucleus and organelles. Goblet cells usually appear pale or empty due to the loss of their contents upon preparation. They progressively increase in number from the proximal to distal part of

intestine. The main function of the gobiet mucus is to protect and lubricate the lining of the intestine.

Paneth's celts are pyramidal cells that present only at the bases of intestinal glands. These exocrine cells contain large acidophilic granules in the apical cytoplasm; the basal cytoplasm is basophilic. The granules contain the antibacterial enzyme ***lysozyme.*** Lysozyme is the enzyme that digests the cell wall of some bacteria. Paneth's cells also phagocytise some bacteria and protozoa. They may have a role in regulating intestinal flora.

Enteroendocrine cells (table 23.1, fig.23.9) are most often found in the lower part of the crypts but can occur at all levels of the epithelium. Their most abundant products are ***cholecystokinin*** (***CCK***), which stimulates pancreatic enzyme secretion and gall bladder contraction, ***secretin,*** which stimulates pancreatic and biliary bicarbonate secretion, and ***gastric inhibitory peptide (GfP),*** which inhibits gastric acid secretion.

M or microfold cells overlie Peyer's patches and other large lymphatic aggregations. They endocytize antigens and transport them to the underlying lymphoid cells where immune responses to foreign antigens can be initiated. M cells represent an important link in the intestinal immune system.

Stem (undifferentiated) cells are situated in depth of the intestinal crypts, they are similar to absorptive cells, but their microvilli are not so well developed. Stem cells proliferate actively by mitosis. The new-formed cells migrate upwards from the crypt to reach the walls of villi and differentiate into absorptive or goblet cells.

II. ***Submucosa*** consists of a loose connective tissue, contains aggregates of lymphoid tissue known as Peyer's patches. In the submucosa of the duodenum there are duodenal ***glands of Brunner*** (fig.23.7); these are compound tubular mucous glands.

III. ***Muscularis*** is composed of 2 layers of smooth muscle tissue.

I V. Either a ***serosa*** or an ***adventitia*** may be present.

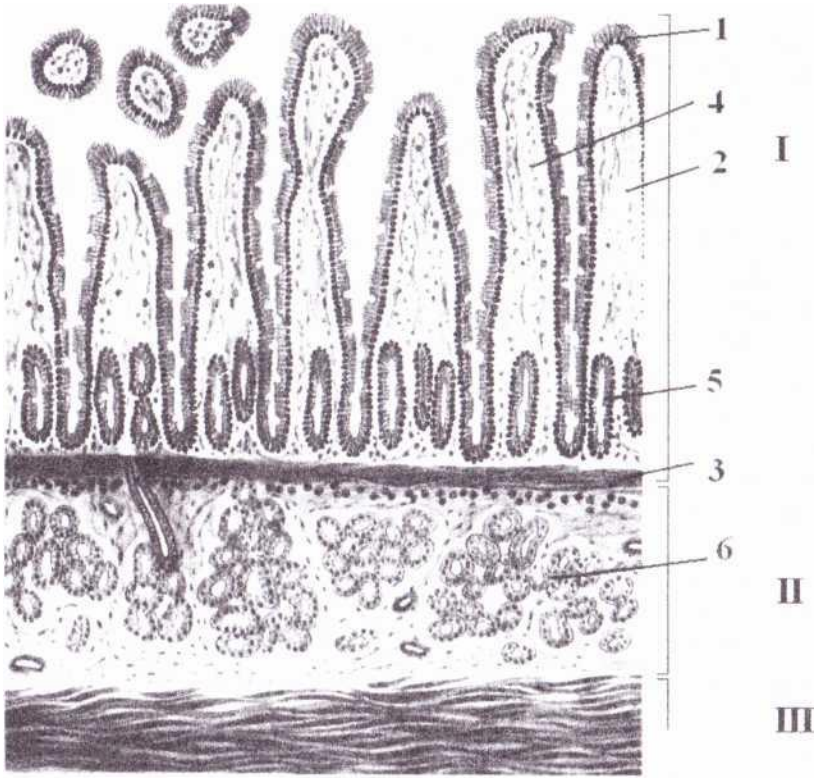


Figure 23.7. Diagram of structure of duodenum. I - mucosa: **1** - epithelium, 2 - lamina propria, 3 - muscularis mucosae, 4 - villus, 5 - crypt, II - submucosa: 6 - duodenal glands of Brunner, III - muscularis

0 Large intestine

The ***large intestine*** consists of the colon, cecum, appendix, rectum and anal canal.

The functions of the large intestine

y Absorption of water and electrolytes.

> Elimination of undigested food and waste.

> Mechanical (to progress of the contents to the distal part of the large intestine).
> Absorption of vitamins K and B.
> Endocrine secretion.
> Immune defence.

The wall of the large intestine consists of 4 layers (fig.23.8):

I. mucosa;
II. submucosa;
III. muscularis;
IV. serosa or adventitia.

The ***relief*** of mucosa of the large intestine:

> ***semilunaris folds*** consisting of mucosa and submucosa;
> ***intestinal glands (crypts)*** are straight, tubular, contain a great abundance of goblet and absorptive cells and small number of cnteroendocrine cells.

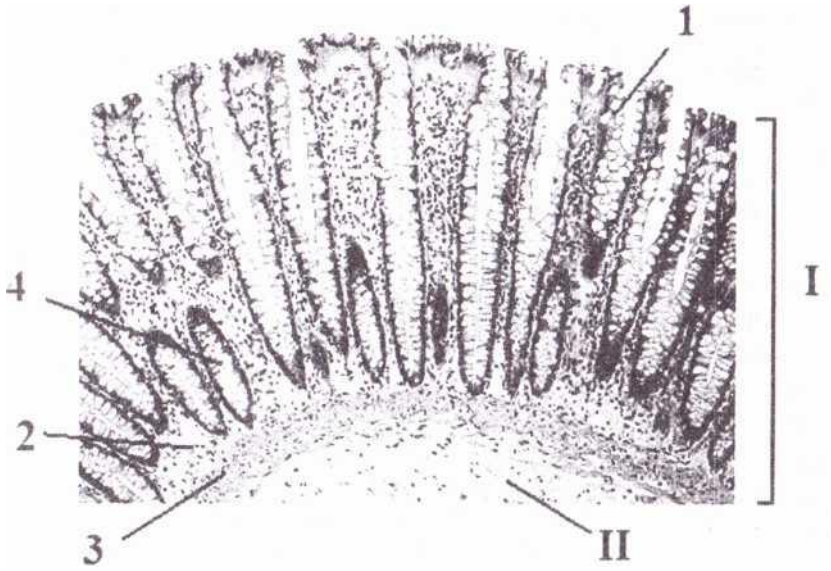


Figure 23.8. Photomicrograph of the large intestine. I - mucosa: 1 — epithelium, 2 - lamina propria, 3 - lamina muscularis, 4 - crypts; **II** - submucosa

I. ***Mucosa*** consists of:

1) simple columnar ***epithelium***;

2) ***lamina propria*** is composed of loose connective tissue, it is rich in lymphoid cells and lymph nodules; extensive development of GALT reflects the abundance and variety of microorganisms and noxious end products of metabolism;

3) ***muscularis mucosae*** consists of smooth muscle tissue, has a circular and longitudinal layer.

Epithelium consists of some types of cells:

> absorptive cells,
> goblet cells,
> stem (undifferentiated) cells,
> enteroendocrine cells,

Absorptive cells are tall columnar and have short, irregular microvilli. The absorptive cells actively transport electrolytes. Water is also absorbed as it passively follows the electrolytes.

Goblet cells are more prevalent in the crypts than along the surface, and their number increases distally toward the rectum. The mucus facilitates the passage of the colonic contents, and covers bacteria and particulate matter.

Stem (undifferentiated) cells are located at the bases of the crypts. Epithelium of the large intestine is replaced about every 6 days by the proliferation and differentiation of these cells. ***Enteroendocrine cells*** are rare.

II. ***Submucosa*** consists of a loose connective tissue. It is rich in lymphoid follicles (nodules).

III. ***Muscularis*** consists of an inner circular and outer longitudinal layer of smooth muscle tissue. The inner circular layer is typical, but the outer longitudinal layer of the colon is very thin, except for three extremely thick longitudinal bands, called ***teniae coli.***

IV. ***Serosa*** consists of mesothelium with and thin layer of underlying connective tissue, is characterized by small protuberances composed of adipose tissue - the ***appendices epiploicae.***

Table 23.1. Principal enteroendocrine cells of the gastrointestinal tract.

Cell type	Location	Hormone produced	Major action
A	stomach	glucagon	hepatic glycogenolysis
G	stomach	gastrin	stimulation of gastric acid and pepsinogen secretion
S	duodenum	secretin	pancreatic enzyme secretion, pancreatic bicarbonate ion secretion, inhibition of gastric acid secretion
K	small intestine	gastric inhibitory polypeptide	inhibition of gastric acid secretion
1	small intestine	cholecystokinin	pancreatic enzyme secretion, pancreatic bicarbonate ion secretion, gallbladder contraction
D	pylorus, duodenum	somatostatin	inhibition of other endocrine cells
D1	digestive tract	vasoactive intestinal polypeptide (VIP)	ion and water secretion, increased gut motility
EC	digestive tract	motilin, serotonin, substance P	increased gut motility
ECL	stomach, large intestine	histamine	stimulation of gastric acid secretion
L	small intestine	enteroglucagon	hepatic glycogenolysis

Appendix

The appendix is an evagination of the cecum; it is characterized by small, narrow lumen that is caused by the presence of abundant lymphoid follicles in its w[r]all. The general structure of the appendix is similar to that of the large intestine.

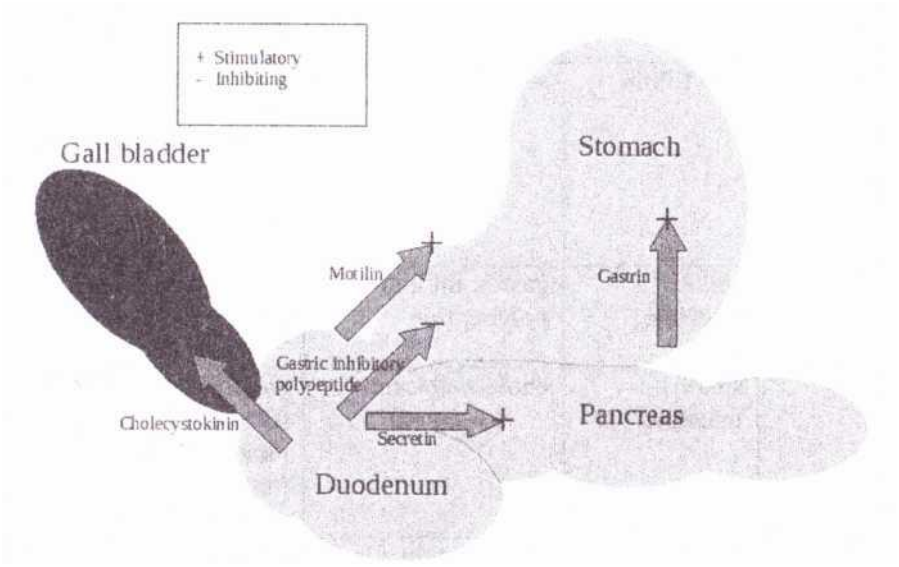


Figure 23.9. Actions of the major digestive hormones secreted by enteroendocrine cells

0 Clinical correlations

Gastroesophageal reflux disease (GERD) happens when a band of muscle at the end of your esophagus does not close properly. This allows stomach contents to leak back, or reflux into, into the esophagus and irritate it.

Barrett's esophagus is most often diagnosed in people w[r]ho have long-term gastroesophageal reflux disease (GERD) - a chronic regurgitation of acid from the stomach into the low er esophagus. It

increases the risk of developing esophageal cancer.

Esophageal cancer is malignancy of the esophagus. Squamous cell cancer arises from the cells that line the upper part of the esophagus. Adenocarcinoma arises from glandular cells that are present at the junction of the esophagus and stomach.

Peptic ulcer disease is an ulcer (mucosal erosions) of an area of the gastrointestinal tract that is usually acidic and thus extremely painful. As many as 70-90% of ulcers are associated with ***Helicobacter pylori,*** a spiral-shaped bacterium that lives in the acidic environment of the stomach.

Pernicious anemia. Atrophic gastritis will cause an inability to absorb vitamin Bj_2 and can lead to deficiencies such as decreased DNA synthesis and nucleotide metabolism in the bone marrow. A long-term deficiency in vitamin $B_{)2}$ can lead to pernicious anaemia, characterized by large fragile erythrocytes. It can be treated with injections of replacement vitamin B_{12} (hydroxocobalamin or cyanocobalamin). ***Achlorhydria*** is autoimmune disease of the parietal cells. The damaged parietal cells are unable to produce the required amount of gastric acid. This leads to an increase in gastric pH, impaired digestion of food and increased risk of gastroenteritis.

DIGESTIVE SYSTEM III. PANCREAS.
LIVER. GALLBLADDER 0 Pancreas

The ***pancreas*** is both an exocrine and endocrine gland. The exocrine part produces about 1.5 L of pancreatic juice every day. The endocrine part, which accounts for -1-2% of the pancreas, consists of the clusters of cells of the endocrine tissue known as ***islets of Langerhuns.*** These cells produce insulin, glucagon and a number of other hormones.

The pancreas is covered by a thin capsule of connective tissue that sends septa into it, dividing the pancreatic lobules.

Exocrine pancreas

The ***exocrine pancreas*** secretes digestive enzymes that can digest most food substances:

> proteolytic endopeptidases (trypsinogen, chymotrypsinogen) and proteolytic exopeptidases (procarboxypeptidase, proaminopeptidase) digest proteins into smaller peptides or amino acids;

> amylolytic enzymes (a-amylase) digest carbohydrates into to glucose and small saccharides;

> lipases (triacylglycerol lipase, phospholipase) hydrolyses triglycerides into fatty acids and monoglycerides;

> nucleolytic enzymes (deoxyribonuclease, ribonuclease) digest nucleic acids producing mononucleotids.

The ***exocrine pancreas*** constitutes main part of gland (97%). It is compound serous tubuloacinar gland, which consists of:

> secretory portion (acini),

> duct system.

Acini have elongated shape (fig.24.1), narrow lumen, are composed of 2 types of cells:

> acinar and
> centroacinar cells.

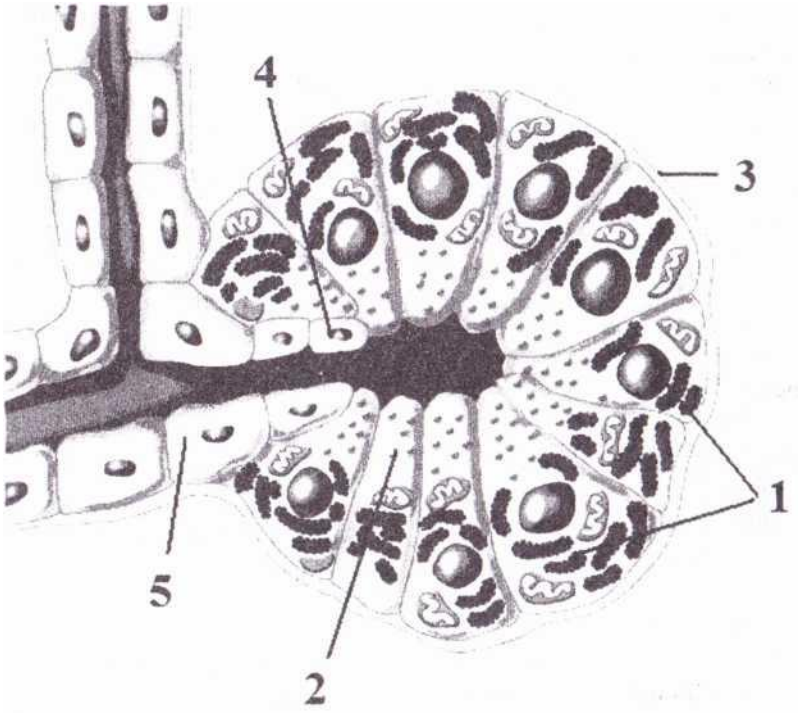


Figure 24.1. Schematic diagram of the structure of pancreatic acinus. 1 - acinar cells, 2 - zymogen granules, 3 - basal lamina, 4 - centroacinar cells, 5 - intercalated duct

Acinar cells are highly polarized, with spherical basally located nuclei, the basal cytoplasm is basophilic, consists of rough endoplasmic reticulum, the apical part contains acidophilic ***zymogen granules.*** Zymogen granules are secretory vesicles containing the inactive precursors of digestive enzymes. They are activated in the lumen of the digestive canal.

Centroacinar cells are small, flattened with pale cytoplasm, are situated in the centre of acinus. They represent the terminal lining cells of intercalated ducts.

Duct system consists of:

> ***intercalated duct*** begins within the acinus, is lined by simple squamous epithelium; these cells secrete fluid and bicarbonate ions of the pancreatic juice; intercalated ducts are short and drain into intralobular ducts;

> ***intralobular duct*** is lined by simple cuboidal epithelium; intralobular ducts drain into larger intralobular ducts;

> ***interlobular ducts*** are in the septa of the gland; are lined by simple columnar epithelium; intralobular ducts drain directly into main pancreatic duct;

> ***main pancreatic duct*** of the gland is lined by tall columnar epithelium.

The main pancreatic duct opens into the summit of the major duodenal papilla, usually in common with the bile duct. A duct draining the lower parts of the head of the pancreas, the accessory pancreatic duct (of Santorini), is very variable. If present, it may open into the minor duodenal papilla ~2 cm above the major papilla in the duodenum.

Endocrine pancreas

The ***endocrine pancreas*** is the ***islets of Langerhans*** are distributed throughout the organ in cell groupings of varying size. The islets constitute about 1 to 2% of the volume of the pancreas.

Polygonal cells of the islets are arranged in short, irregular cords that are profusely invested with a network of fenestrated capillaries.

Each cell type of the islet can be correlated with a specific hormone, and each has specific location in the islet (fig.24.2).

> 75% ***B (beta)-cells*** are most numerous, blue-stained, form the central part of the islets, secrete hormone ***insulin.*** Insulin decreases blood glucose levels. Its principal effects are on the liver, skeletal muscles, and adipose tissue. Insulin stimulates:

- uptake of glucose from the circulation into cells and activates glucokinase in liver cells;
- storage of glucose by activation of glycogen syntheses;

- phosphorylation and use of glucose by promoting its glycolysis within cells.

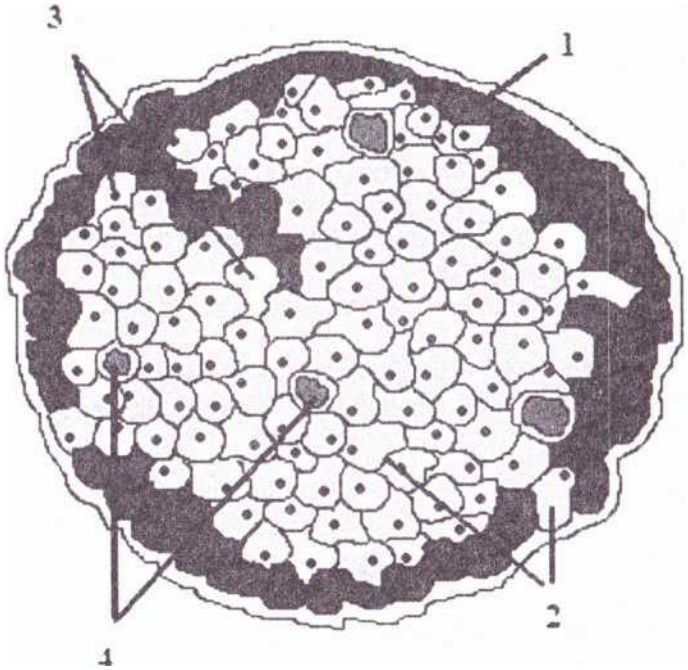


Figure 24.2. **Schematic diagram of the islet of Langerhans.** 1 - A (alpha)-cells, 2 - B (beta)-cells, 3-D (delta)-cells, 4 - blood capillaries

> 20% ***A (alpha)-cells*** constitute of the islet, are stained pink, are distributed on the periphery of the islets, secrete hormone ***glucagon.*** The effects of glucagon are generally opposite to those of insulin. It stimulates release of glucose into the bloodstream, and stimulates gluconeogenesis (synthesis of glucose from metabolites of amino acids) and glycogenolysis (breakdown of glycogen) in the liver.

> 5-10% ***D (delta)-cells*** secrete ***somatostatin,*** a locally acting hormone which inhibits insulin and glucagon secretion.

> ***Dl-cells*** secrete hormone ***vasoactive intestinal peptide (VIP),*** which has effects similar to glucagon, but also stimulates the exocrine function of the pancreas.

> ***PP-cells*** secrete hormone ***pancreatic polypeptide (PP),*** which stimulates chief cell in gastric glands and inhibits bile and bicarbonate secretion.

y EC-(enterochromaffin) cells secrete several peptides including:
O ***motilin,*** which increases gastric and intestinal motility,
O ***secretin,*** which stimulates I ICO ;' secretion in pancreatic juice and pancreatic enzyme secretion;
O ***substance P.*** which has neurotransmitter properties.

D-, D1-, PP- and EC-celis are present in the islets or else distributed singly or in small groups between the exocrine acini and along the ducts.

0 Liver

The ***liver*** is the largest gland in the body.

The functions of the liver:

> synthesis and endocrine secretion of many plasma proteins (albumins, lipoproteins, glycoproteins, prothrombin and fibrinogen);
> storage of vitamins (A, D, K) and iron;
> detoxification of many drugs and toxins;
y metabolic functions (synthesis of urea, metabolism of cholesterol and fat, glycogen synthesis, storage of glycogen, glucogenolysis, gluconeogenesis);
> protective (destruction of microorganisms, toxins brought by the blood);
> production of bile required for emulsifying fats;
> catabolism of hemoglobin from worn-out red blood cells;
> volume reservoir for blood;
> embryonic hematopoiesis (in the first trimester fetus, the liver is the main site of red blood cell production);

The ***liver*** is enclosed in a thin connective tissue capsule (Glisson's capsule).

The liver receives a dual vascular supply.

> All of the blood which passes through the intestine and spleen is delivered to the liver by the ***hepatic portal vein.*** This ***portal blood*** carries not only nutrients but also various contaminants (drugs, toxins from food, bacteria, by products of blood-cell recycling) which have been absorbed through the intestinal mucosa or produced in the spleen.

> The ***hepatic artery*** brings fresh, oxygenated blood from the aorta.

Portal venous blood from the intestine and spleen and arterial blood from the aorta mix together in hepatic sinusoids before leaving the liver in the hepatic vein.

The basic structural component of the liver is the ***liver cells***, or ***hepatocytes.***

Structural units of the liver are the ***liver lobules.*** Liver lobule is hexagonal prisms in a cross section about 1mm x 2mm (fig.24.3).

Within each lobule, hepatocytes are arranged into ***hepatic cords*** one or two cells thick. Hepatic cords are radially disposed in the liver lobule. The cords of hepatocytes represent the parenchyma of the liver. The spaces between the cords contain sinusoidal capillaries (***liver sinusoids)*** lined by a fenestrated endothelium.

At the corners of the lobules there are the ***portal spaces,*** which are occupied by the ***portal triads.***

The portal triad contains:

1) interlobular vein (a branch of the portal vein):
2) interlobular artery (a branch of the hepatic artery);
3) interlobular bile duct (part of the bile duct system).

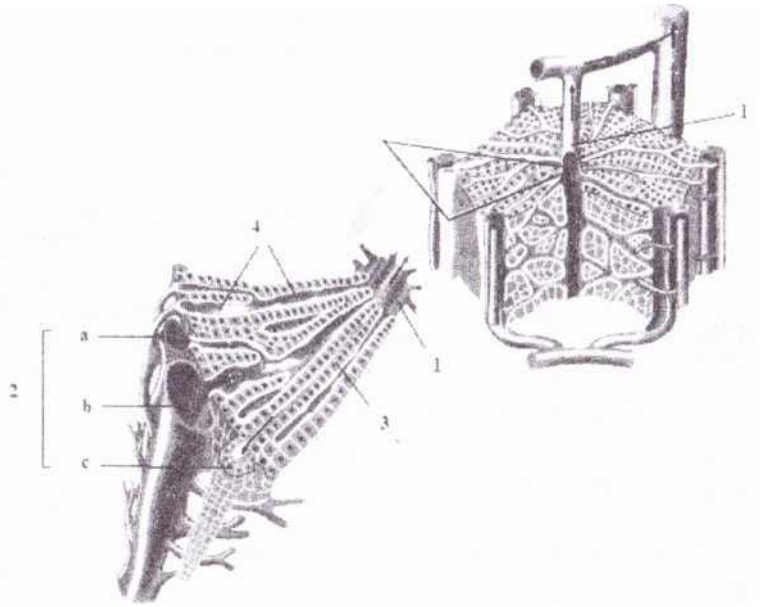


Figure.24.3, Diagram of a "classic" liver lobule. 1 - central vein, 2 - portal triad: a - interlobular artery, b - interlobular vein, c - interlobular bile duct, 3 - hepatic cords, 4 - hepatic sinusoids

The concepts of the liver lobules

I. The ***classic liver lobule*** is hexagonal in section. In the centre of the liver lobule there is a central vein. At the corners of the lobules there are the portal triads. The blood flow is directed from periphery to the center, and bile - from the center to periphery (fig.24.4).

II. The ***portal lobule*** comprises of the adjoining parts of 3 classic lobules. It is triangular in shape and has at the center the portal triad and a central vein at the tip of each of its angles. The blood flow is directed from the center to periphery, and bile - from periphery to the center.

III. The ***hepatic acinus*** is situated in adjacent areas of two hepatic lobules. The terminal branches of the portal vein, an arterial branch and a bile ductule are in the center of the hepatic acinus. The

blood flow is directed from the center to periphery, and bile - from periphery to the center.

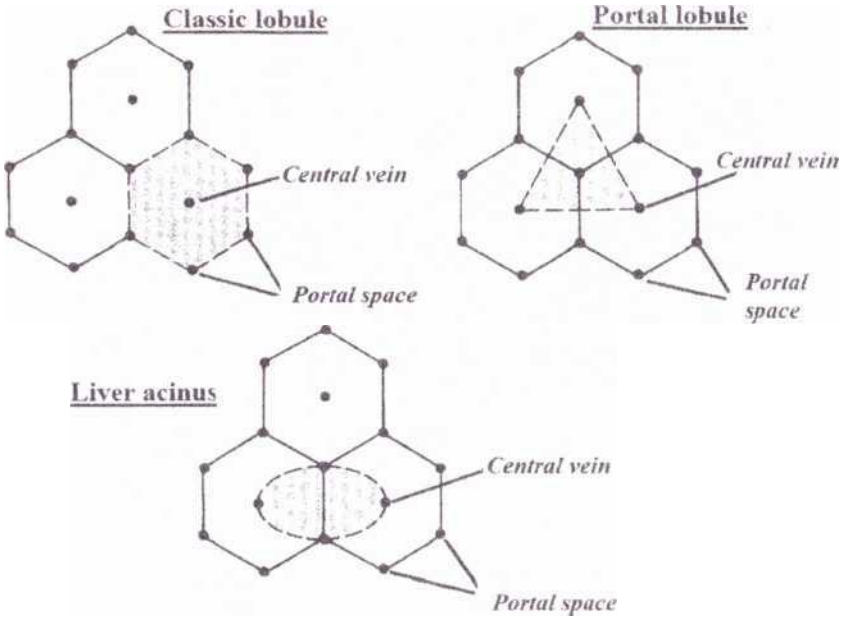


Figure 24.4. Schematic diagram of the liver lobules.

The endothelial cells of the wall of sinusoids are separated from the underlying hepatocytes by a narrow subendothelial space known as the ***perisinusoidal space (space ofDisse)*** (fig.24.5).

It contains the blood plasma. Microvilli of hepatocytes extend into this space, allowing proteins and other plasma components from the sinusoids to be taken up by the hepatocytes. Blood fluids percolate through the endothelial wall and make intimate contact with the hepatocyte surface, permitting an exchange of macromolecules from the sinusoidal lumen to the liver cell and vice versa.

Sinusoid lining cells:

1) ***endothelial cells***;

2) ***Kupffer cells*** (macrophages) are found on the luminal surface of the endothelial cells. Kupffcr cells are typical macrophages;

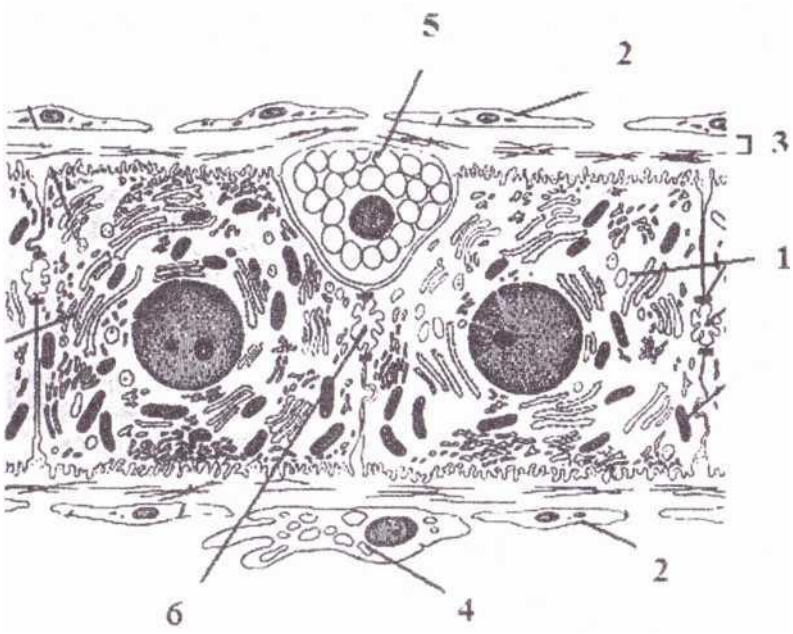


Figure 24.5. Schematic diagram of space of Disse. 1 - hepatocyte, 2 - endothelium of sinusoids, 3 - space of Disse, 4 - Kupffer cell, 5 - Ito cell, 6 - bile canaliculus

3) ***hepatic stellate cells (Ito cells)*** are located in the spaces of Disse; they have the capacity to accumulate exogenously administered vitamin A; the stellate cell is the major cell type involved in liver fibrosis, which is the formation of scar tissue in response to liver damage;

4) ***pit cells*** are hepatic natural killer cells that are located in the liver sinusoids where they adhere to endothelial cells; pit cells are involved in killing metastasizing tumor cells,

Hepatocytes

The hepatocytes are large polygonal cells (fig.24.6). The liver cell has one or two rounded nuclei with dispersed chromatin and prominent nucleoli. Some of the nuclei are polyploid; most cells in the adult are tetraploid (4n amount of DNA).

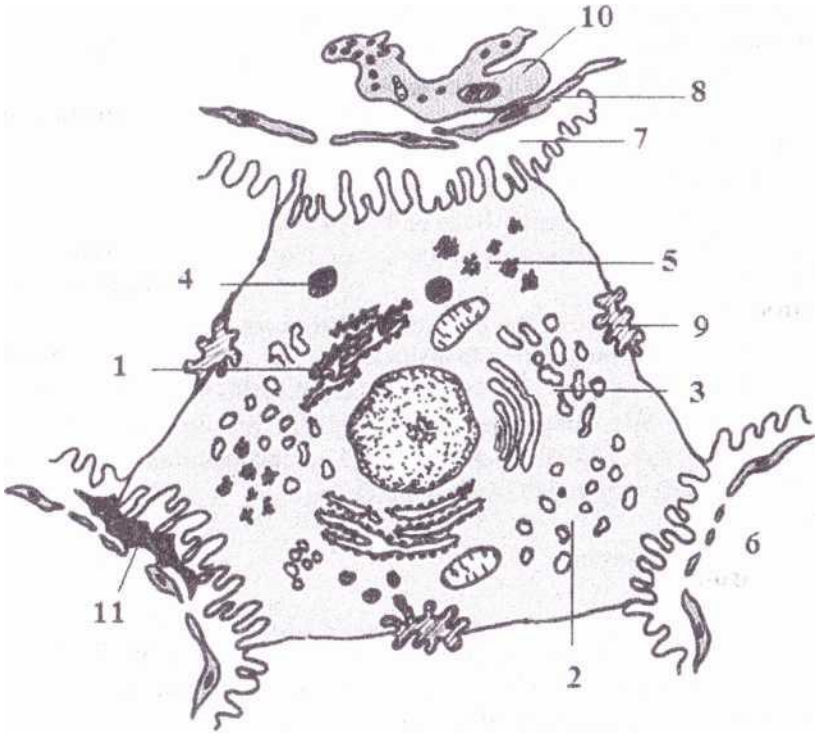


Figure 24.6. Schematic diagram of hepatocyte. 1 - rough endoplasmic reticulum, 2 - smooth endoplasmic reticulum, 3 - Golgi complex, 4 — lysosome, 5 - glycogen, 6 — hepatic sinusoid, 7 — space of Disse, 8 - sinusoidal endothelium, 9 - bile canaliculus, 10 - Kupffer cell, 11 - Ito cell

The hepatocytes have abundant endoplasmic reticulum - both smooth and rough. The ***rough endoplasmic reticulum*** forms aggregates in the cytoplasm. Several proteins are synthesized on polyribosomes in these structures. The ***smooth endoplasmic reticulum*** is responsible for the processes of oxidation, methylation. and conjugation required for inactivation or detoxification of various substances.

Each liver cell has approximately 2000 ***mitochondria.***

Hepatocyte ***lysosomes*** are responsible for degradation of intracellular organelles and endocytosis of many macromolecules. ***Peroxisomes*** are abundant in hepatocytes.

The functions of ***Golgi complexes*** include the formation of lysosomes and secretion of plasma proteins.

Zonal features of the hepatocytes

The surface of each liver cell is in contact with the wall of the sinusoids, through the space of Disse, and with the surfaces of other hepatocytes.

1) The surface of the hepatocyte that feces the space of Disse has many microvilli protruding in that space.

2) Wherever two hepatocytes abut, they delimit a tubular space between - the bile canaliculus. The canaliculi are limited only by the plasma membranes of two hepatocytes. The cell membranes near these canaliculi are firmly joined by tight junctions.

Biliary system

The ***biliary system*** is the system of canals on which bile from a liver flows to the gallbladder and than to the duodenum. Biliary tract includes ***intrahepatic*** and ***extrahepatic passages.***

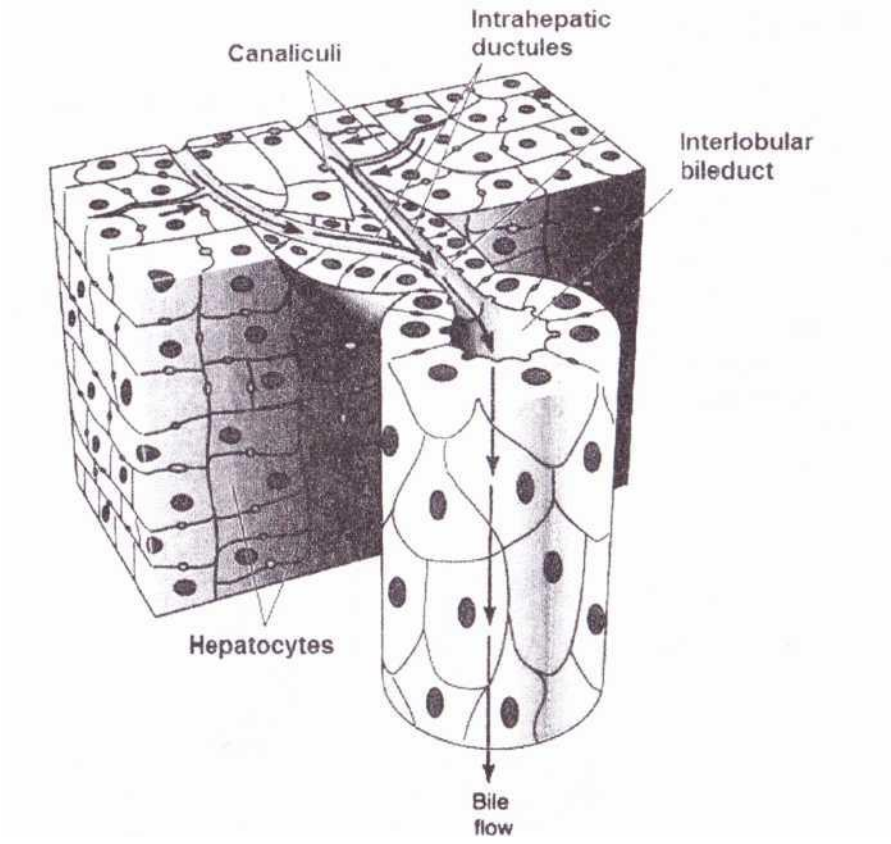
Intrahepatic passages consist of:

> intralobular (the bile canaliculi and the bile ductules) and
> interlobular are situated in the interlobular connective tissue (the bile ducts).

Extrahepatic passages consist of:

> right and left hepatic ducts,
> hepatic duct,
> common bile duct (ductus choledochus).

The ***bile canaliculi*** (fig.24.7) are thin tubes that collect bile secreted by hepatocytes. The bile canaliculi are formed by grooves on the lateral faces of the hepatocytes. The bile canaliculi form a complex anastomosing network progressing along the cords of the liver lobule and terminating in the region of the portal spaces.



The bile flows from the center of the classic lobule to its periphery. At the periphery, bile enters the ***intrahepatic bile ductules,*** or ***Herings canals.***

After a short distance, the ductules cross the limiting hepatocytes of the lobule and end in the ***interlobular bile ducts*** in the portal triads. They gradually enlarge and fuse, forming right and left hepatic ducts, which leave the liver.

Intrahepatic bile ductules are lined by a cuboidal epithelium. All other parts of the bilary system are lined by a tall columnar epithelium.

0 Gallbladder

The ***gall bladder*** is a pear-shaped sac that stores and concentrates bile (30-70 mL).

The wall of the gall bladder consists of 3 layers (fig.24.8, 24.9):

I. ***Mucosa*** has numerous branching and anastomosing folds and consists of:

1) ***epithelium*** is simple columnar specialized for absorption, with an apical brush border of microvilli; gall bladder epithelium includes only this single cell type; it has no goblet cells;

2) ***lamina propria*** is formed by loose connective tissue.

II. ***Fibro-muscular layer*** contains smooth muscle tissue and loose connective tissue.

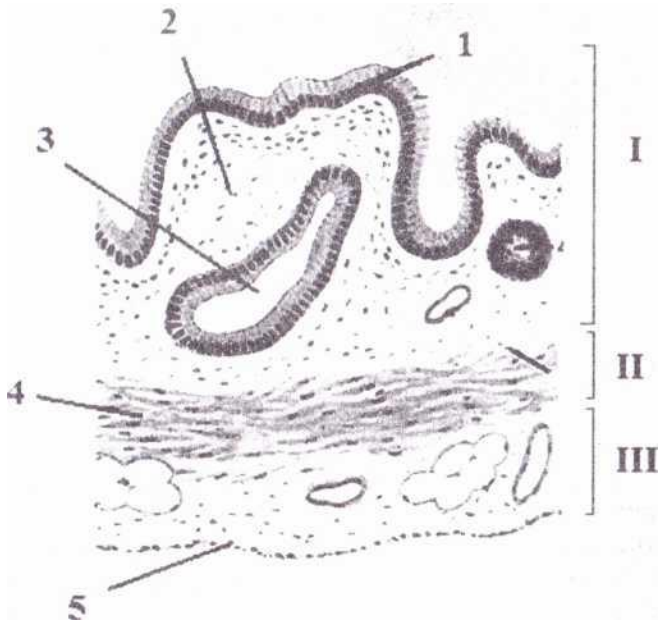


Figure 24.8. Diagram of gallbladder structure. I- mucosa, 1 - epithelium. 2 - lamina propria, 3 - Rokitansky-Ashoff sinus, II - fibro-muscular layer, III - serous layer

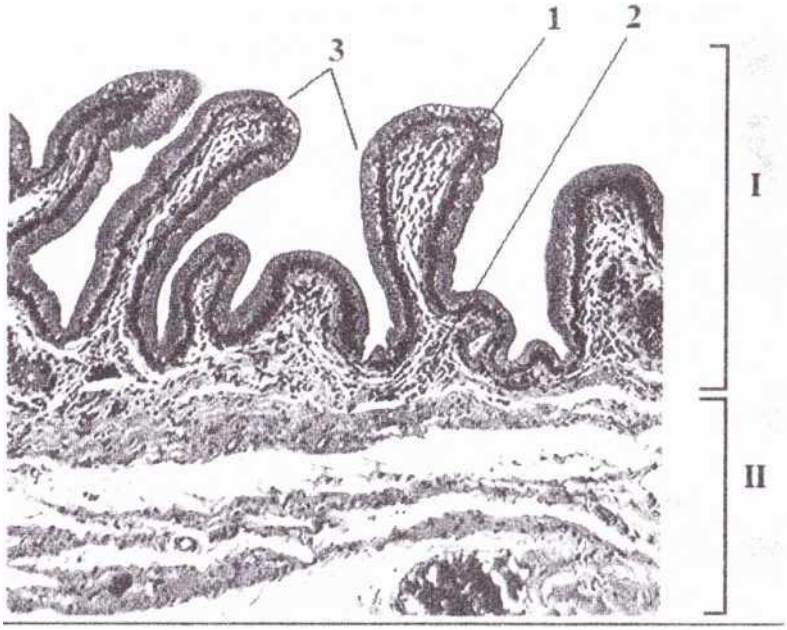


Figure 24.9. <u>Photomicrograph</u> of gallbladder structure. I- mucosa, **1** - epithelium, 2 - lamina propria, 3 - mucosal folds, **II -** fibro-muscular layer

I. ***Adventitia*** covers the upper surfaces of the body and neck; the fundus and lower surface of the body have a serous layer.

Mucosa forms deep diverticula, called ***Rokitansky-Ashoff sinuses*** (fig.24.10). Bacteria may accumulate in these sinuses, causing chronic inflammation.

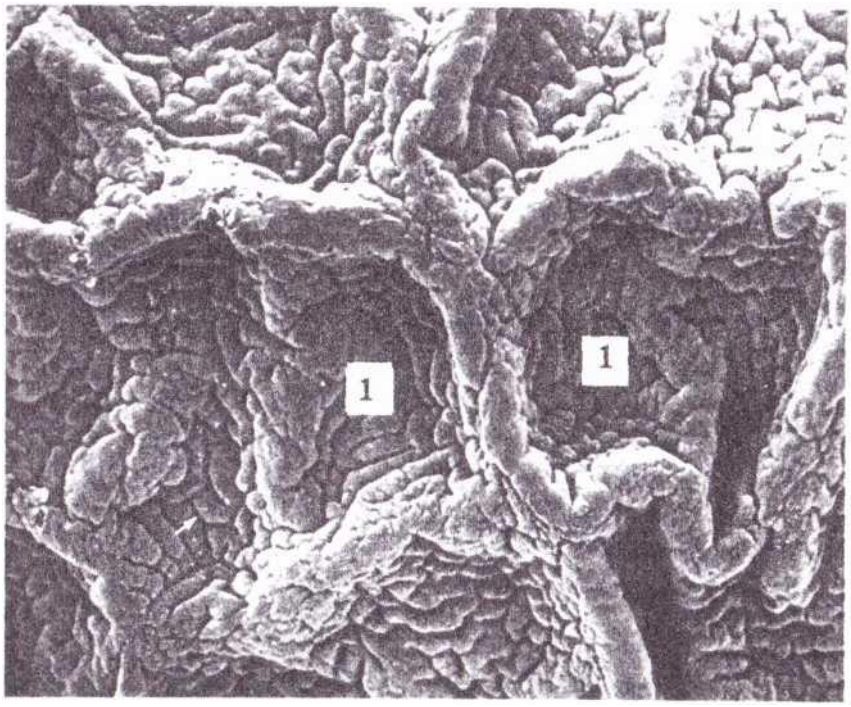


Figure 24.10. **Electron micrograph of gallbladder mucosa.** 1 - Rokitansky-Ashoff sinuses

Clinical correlations

Liver fibrosis results from chronic damage to the liver. The main causes of liver fibrosis in industrialized countries include chronic hepatitis C virus (HCV) infection, alcohol abuse, and nonalcoholic hepatitis.

Liver fibrosis is the excessive accumulation of extracellular matrix proteins including collagen that occurs in most types of chronic liver diseases. Advanced liver fibrosis results in cirrhosis, liver failure,

and portal hypertension and often requires liver transplantation. Activated hepatic stellate cells have been identified as major collagen- producing cells in the injured liver.

Diabetes mellitus type 1 is caused by the destruction or dysfunction of insulin-producing beta cells by the cells of the immune system. The subsequent lack of insulin leads to increased blood and urine glucose.

Gallstones (biliary calculi) are small stones made from cholesterol, bile pigment and calcium salts, usually as a mixture that forms in the gall bladder. Gallstones are a common disorder of the digestive system, and affect around 15 per cent of people aged 50 years and over. Some things which may lead to the formation of gallstones include the crystallisation of excess cholesterol in bile and the failure of the gall bladder to fully empty.

Presence of gallstones in the gallbladder may lead to acute cholecystitis, an inflammatory condition characterized by retention of bile in the gallbladder and often secondary infection by intestinal microorganisms.

IMMUNE SYSTEM. CELLULAR INTERACTION AT IMMUNE RESPONSES 0 Overview of the immune system

The ***immune system*** consists of groups of cells, diffuse lymphoid tissue, and organs that monitor body surfaces and internal fluid compartments and react to the presence of potentially harmful substances and microorganisms.

The organs of immune system: ***y central*** or
primary (red bone marrow, thymus) and
> ***peripheral*** or ***secondary*** (spleen, lymphoid nodes, tonsils, appendix, solitary nodules, and Peyer's patches of the ileum).

The cells of immune system have the ability to distinguish ***"self'*** (molecules normally present within an organism) from "***nonself*** (foreign substances, i.e., those not normally present) and to coordinate the destruction or inactivation of foreign substances.

The cells of immune system include ***lymphocytes*** and various ***supporting cells.***

Three types of lymphocytes are recognized:
> ***T cells,*** *У* ***B cells***,
y natural killers (NK) cells.

Supporting cells include ***reticular cells, macrophages, follicular dendritic cells, Langerhans ' cells*** and ***epith elioreticular cells.***
Supporting cells are organized into meshwork.

Antigens

Antigens are the foreign (nonself) to the organism substances that can induce a specific immune response. Antigens can be infection organism (bacteria, viruses, fungi, parasites), foreign cells and tissues, transformed cells (cancerous cells), or soluble substances (e.g., foreign proteins, polysaccharides, nucleoproteins, or toxins).

0 Characteristic of T lymphocytes (T **cells)**

T cells represent 60-80% of blood lymphocytes. They have a long lifespan and are involved in ***cell-mediated immunity.***

The abbreviation ***T,*** in ***T cell,*** stands for thymus, since this is the principal organ responsible for the T cell's maturation.

T cells originate in the bone marrow and migrate to the thymus, where they differentiate into immunocompetent cells. Initially, lymphocytes are genetically programmed to recognize a single antigen out of virtually an infinite number of possible antigens. This process is termed ***antigen-independent proliferation and differentiation*** Then immunocompetent cells migrate to the blood, lymph, and special T- regions of peripheral (secondary) lymphoid organs where they undergo ***antigen-dependent activation and differentiation*** into ***effector lymphocytes*** (cytotoxic cells, helpers, and suppressors) and ***memory cells.*** T memory cells react rapidly to the reintroduction of the same antigens.

0 Characteristic of B lymphocytes (B cells)

B- cells are named so because they were first recognized in the ***bursa of Fabricius*** in birds. They have variable lifespan and are involved in ***humoral immunity*** by production and secretion of circulating antibodies (immunoglobulins).

B- cells represent 20-30 % of blood lymphocytes, derive from ***bursa-equivalent organs*** (red bone marrow and GALT in mammals) where they undergo ***antigen-independent proliferation and differentiation.*** Then these cells migrate to the blood, lymph, and special B-regions of peripheral (secondary) lymphoid structures where they proliferate and differentiate into the ***effector lymphocytes*** (antibody- secreting plasma cells) and ***memory cells*** which react very rapidly to reintroduction of the same antigen. This process is called ***antigen- dependent activation and differentiation.***

0 Characteristic of natural killer (NK) cells

NK cells constitute about 5-10% of circulating lymphocytes. NK cells develop from the same precursor cells as T and B cells. These cells genetically are programmed to recognize transformed cells (tumor cells or infected with a virus). Following recognition of antigens, NK cells

release proteins (***perforins*** and ***fragmentins***) that open holes in foreign cell membranes, with consequent self-destruction (a process known as apoptosis) or cell lysis.

0 Characteristics of human immunoglobulins

Antibodies (immunoglobulins) are circulating plasma glycoproteins that interact specifically with the antigens that elicited their formation.

Antibodies are secreted by plasma cells that arise by proliferation and differentiation of B-lymphocytes.

Five classes of immunoglobulins are recognized in humans: IgG, IgA, IgM, FgE and IgD,

IgG, the most abundant class, constitutes 85% of serum immunoglobulins. IgG is principal ig in secondary immune response; stimulates chemotaxis; activates complement; crosses the placental barrier, protects the newborn against infection (passive immunity).

IgA (5-15% in the blood), presents in body secretions (tears, colostrum, saliva, nasal, bronchial, intestinal and prostatic secretions, and the vaginal fluid); is resistant to several enzymes, and protects against the proliferation of microorganisms in body secretions.

IgM (5-10% of serum immunoglobulins) is produced during primary immune response; activates macrophages; is found on the surfaces of B-lymphocytes as antigen receptor.

IgE (< 1%) stimulates mast cells to release histamine, heparin; is responsible for anaphylactic hypersensitivity reactions; levels increase in parasitic infections.

IgD (< 1%) is found on the plasma membranes of B- lymphocytes and is involved in the differentiation of these cells.

0 Characteristic of the plasma ceiis

The ***plasma cells*** are large lymphocytes. They have basophilic cytoplasm and an eccentric nucleus with heterochromatin in a characteristic cartwheel or clock face arrangement. Rough endoplasmic reticulum is concentrically located around of a nucleus. Well developed Golgi complex displaces the nucleus to one side of the cell (perinuclear halo) (fig.25.1).

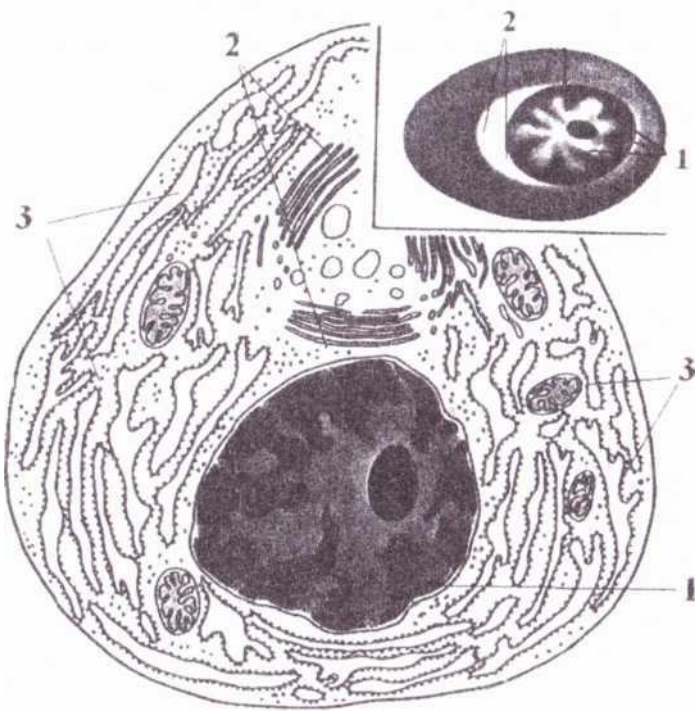


Figure 25.1. Schcmatic diagram of plasma cell. 1 - chromatin, 2 - Golgi complex (perinuclear halo), 3 - rER

0 immune responses to antigens

The initial reaction of the organism to invasion by the antigen is the ***nonspecific defence (inflammatory response).*** The inflammatory response may either sequester the antigen with enzymes secreted by neutrophils, or phagocytise the antigen by macrophages. Degradation of the antigen may lead to presentation of portion of the antigen to immunocompetent lymphocytes to elicit the ***specific immune response.***

The specific immune response is generated when immunocompetent lymphocytes encounter the antigen.

Primary immune response is observed at the first encounter with the antigen. In this case antibodies or specific lymphocytes directed

against this antigen can be detected in the blood in several days. Then a few antigen-specific B cells remain as ***memory cells***, which react very rapidly to reintroduction of the same antigen ***(secondary immune response).***

Basic types of specific immune responses

1. ***Cell-mediated immunity*** is mediated by specific cytotoxic T lymphocytes that destroy microorganisms (fungal, mycobacterial), foreign cells (from tumors and transplants), and virus-infected ceils.

2. ***Humoral immunity*** is related to the presence of circulating antibodies that inactivate or destroy foreign substances. The antibodies are produced by plasma cells derived from B-lymphocytes.

Major histocompatibility complex

The ***major histocompatibility complex (MHC)*** is a large genomic region found on the cel! surface in most vertebrates that encodes MHC molecules.

There are two general classes of MHC molecules: class I and class II.

Class I MHC molecules are found on almost all cells and present proteins to cytotoxic T cells.

Class **II** MHC molecules are found on certain immune cells themselves, chiefly macrophages and B cells, also known as antigen- presenting cells (APC). These APC ingest microbes, destroy them, and digest them into fragments. The Class II MHC molecules on the APC present the fragments to helper T cells, which stimulate an immune reaction from other cells.

Cellular (cell-mediated) immune response

Activation phase

The ***cellular immune response*** begins when antigen, such as virus, enters a body cell. The viral proteins, which are antigens, are broken down by the cell and attached to class 1 MHC proteins (fig.25.2). These complexes are presented on the cell's surface.

Cytotoxic T (Tc) cell has T-cell receptors that are specific for the displayed antigen. T-cell receptors bind to the complexes of antigen and class I MHC proteins. This binding activates the T_c cell. They proliferate to form a clone of T_c cell with specific receptors for the same antigen.

Effector phase

Upon binding, a T_c cell is stimulated to release proteins called ***perforins.*** Perforins kill the target cel! by poking holes in its plasma membrane and causing the cell to lyse.

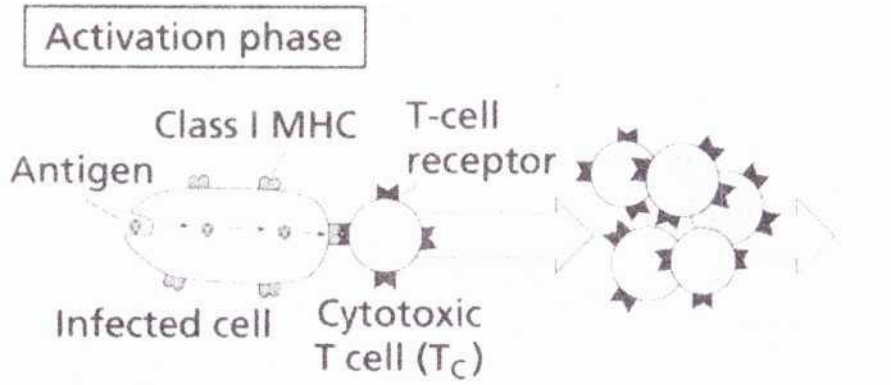


Figure 25.2. Schematic diagram of the activation phase of cellular immune response.

Humoral immune response

The humoral immune response is also called the ***antibody- mediated response*** because of its use of specific immune-system structures called ***antibodies.***

During ***activation phase*** macrophage engulfs an antigen by phagocytosis (fig.25.3). Enzymes of lysosomes of macrophage break down the antigen into fragments (this phenomenon called ***antigen processing).*** Within the cell, the processed antigens combine with class II MHC proteins. This complex is displayed on the macrophage's plasma membrane. This display is known as ***antigen presentation***, and macrophage are considered ***antigen-presenting cell.***

Helper **T** cell **(TH** cell) has T-cell receptors that can bind to both class II MHC protein and this particular presented antigen. This binding

triggers the macrophage to release the cytokine interleukin-**1 (IL-1),** which activates the $T_H$cell

The activated $T_H$cell now releases its own cytokine interleukin-2 (IL-2), which stimulate the TH cell to proliferate. The cell proliferates to form a clone of T_H cells, all with the same T-cell receptors.

Next phase, called the ***effector phase,*** involves a communication between helper-T cells and B-cells (fig.25.4). Activated helper-T cell releases cytokines ("helping signals") that stimulate the B cell to divide. The resulting B-cell develops into either ***plasma cells*** or ***B memory cells.***

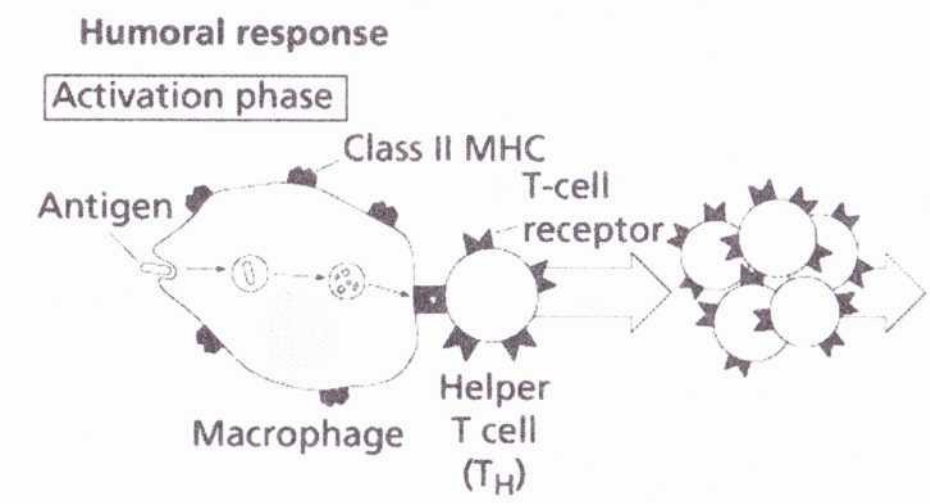


Figure 25.3. Schematic diagram of the cellular interaction. Activation phase of humoral immune response.

The plasma cells begin to produce huge quantities of antibodies that can bind and inactivate the antigen (fig.25.5). B memory cells retain a "memory" of the specific antigen that can be used to mobilize the immune system faster if the body encounters the antigen later in life. These cells generally persist for years.

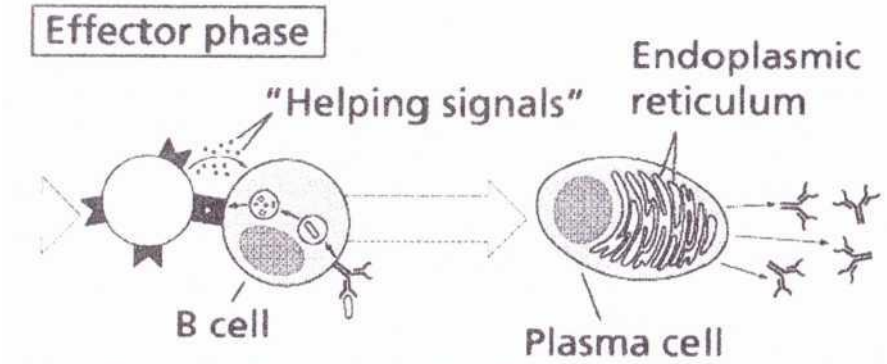


Figure 25.4. Schematic diagram of the cellular interaction. Effector phase of humoral immune response.

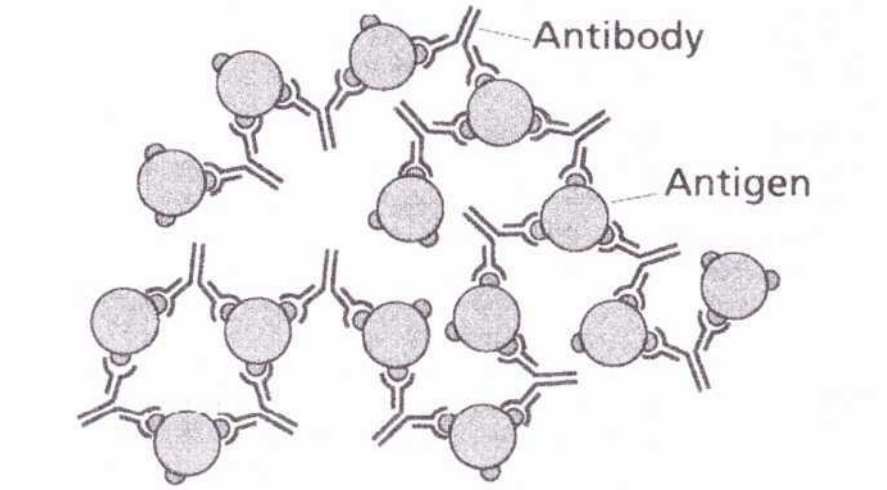


Figure 25.5. Schematic diagram of the formation of an antigen-antibody complex.

Clinical correlations

Autoimmune disorders

An autoimmune disorder is a malfunction of the body's immune system that causes the body to attack its own tissues.

Some of the more common autoimmune disorders include rheumatoid arthritis, systemic lupus erythematosus (lupus), and vasculitis, among others. Additional diseases that are believed to be due to autoimmunity include glomerulonephritis, Addison's disease, mixed connective tissue disease, polymyositis, Sjogren's syndrome, progressive systemic sclerosis, and some cases of infertility.

Autoimmune reactions can be triggered in several ways:

> A substance in the body that is normally confined to a specific area (and thus is hidden from the immune system) is released into the bloodstream. For example, a blow to the eye can cause the fluid in the eyeball to be released into the bloodstream. The fluid stimulates the immune system to recognize the eye as foreign and attack it.

> A normal body substance is altered, for example, by a virus, a drug, sunlight, or radiation. The altered substance may appear foreign to the immune system. For example, a virus can infect and thus alter cells in the body. The virus-infected cells stimulate the immune system to attack.

> A foreign substance that resembles a natural body substance may enter the body. The immune system may inadvertently target the similar body substance as well as the foreign substance. For example, the bacteria that cause strep throat have some antigens that are similar to those in human heart cells. Rarely, the immune system may attack a person's heart after strep throat (this reaction is part of rheumatic fever).

> The cells that control antibody production - for example, B lymphocytes (a type of white blood cell) - may malfunction and produce abnormal antibodies that attack some of the body's cells. Symptoms of the autoimmune disorders vary depending on the disorder and the part of the body affected. Some autoimmune disorders affect certain types of tissue throughout the body - for example, blood vessels, cartilage, or skin. Other autoimmune disorders affect a particular organ. Virtually any organ, including the kidneys, lungs, heart, and brain, can be affected. The resulting inflammation and tissue damage can cause pain, deformed joints, weakness, jaundice, itching, difficulty breathing, accumulation of fluid (edema), delirium, and even death.

CENTRAL (PRIMARY) LYMPHOID ORGANS

The ***central*** or ***primary lymphoid organs*** generate lymphocytes from immature progenitor cells.

The ***thymus*** and the ***bone marrow*** constitute the primary lymphoid tissues involved in the production and early selection of lymphocytes.

The ***secondary lymphoid organs*** include the lymph nodes, spleen, and small masses of lymph tissue such as Peyer's patches, the appendix, tonsils, and the mucosa-associated lymphoid tissue (MALT). The secondary lymphoid organs serve two basic functions: they are a site of further lymphocyte maturation, and they efficiently trap antigens for exposure to T and B cells.

0 Red bone marrow

The ***red bone marrow*** is found mainly in the flat bones, such as the hip bone, breast bone, skull, ribs, vertebrae and shoulder blades, and in the cancellous material at the epiphyseal ends of the long bones such as the femur and humerus.

Functions of red bone marrow

1. Production of myeloid and lymphoid blood cells.
2. Proliferation and antigen-independent differentiation of B- lymphocyte (red bone marrow is the mammalian equivalent of the bursa of Fabricius of birds).
3. Storage in macrophages of iron derived from the breakdown of hemoglobin.
4. Destruction of aged and defective blood cells.

Structure of red bone marrow

Red bone marrow (fig.26.1) is composed of 3 main components:

> stroma,
> hematopoietic cords,
> sinusoidal capillaries (sinusoids).

Stroma consists of a three-dimensional meshwork of reticular tissue, which contains reticular cells and reticular fibers, macrophages, adipose cells, cells of endosteum, osteoblasts, osteoclasts, endothelial cells forming the wall of sinusoids.

Hematopoietic component (hematopoietic cords) is formed by the myeloid tissue and contains the myeloid and lymphoid cells at different stages of their development, cooperating with stromal elements. Stroma provides the ***hematopoietic microenvironment*** that facilitates hematopoiesis by the generation of colony stimulating factors, affecting hematopoiesis.

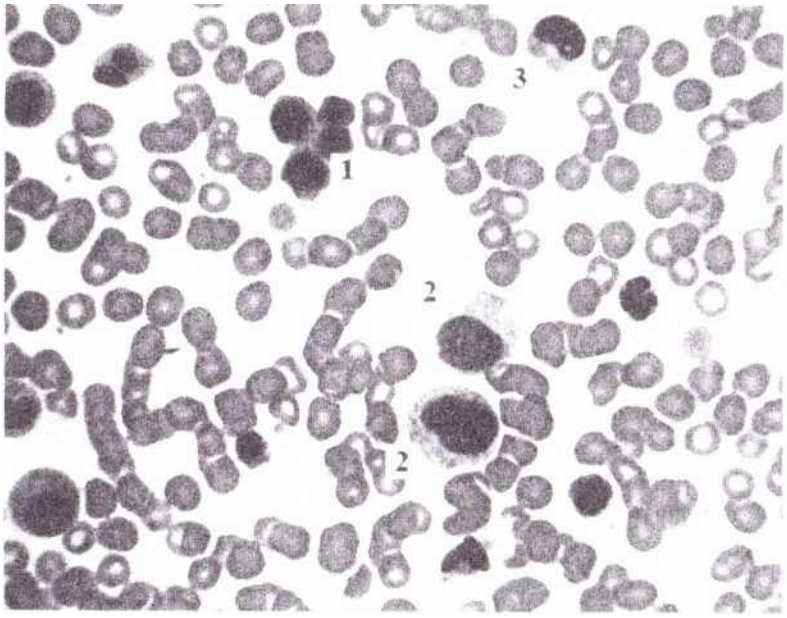


Figure 26.1. Red bone marrow smear. 1 — erythroid cells, 2 — neutrophilic myelocytes, 3 - early neutrophilic metamyelocyte

There is ***compartmentalization*** in the bone marrow, in that certain cell types tend to aggregate in specific areas in nests or clusters.

For instance, ***erythropoietic cells*** develop in erythroblastic islets, in contact with the macrophages which accumulate and transfer them the

iron necessary for synthesis of hemoglobin. The erythroblastic island consists of macrophage surrounded by erythrocyte progenitor cells (fig.26.2).

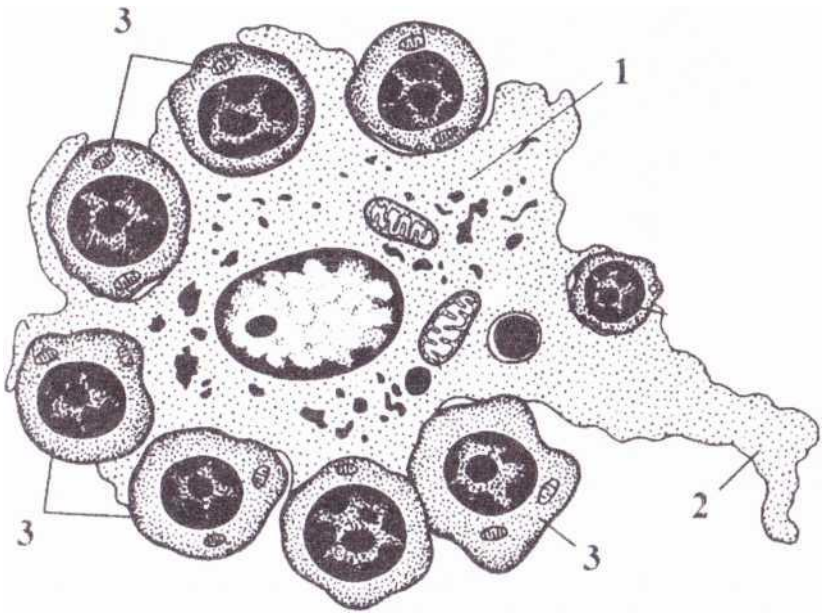


Figure 26.2. Schematic diagram of erythroblastic islet. 1 - macrophage, 2 — processes of macrophage, 3 - erythropoietic cells (from ***lO.E.Acfccmacbee, H.A JOpuna u dp.,*** 1999)

Megakaryocytes (fig.26.3) unlike other blood cells, remain in the bone marrow when mature, being extraordinarily large (diameter up to 60 pm), with a highly polyploid nucleus. They normally lie close beside blood sinuses, and they extend processes through holes in the endothelial lining of these vessels; liberating the platelets.

Granulocytes mature near the cells of endosteum and contact with reticular and adipose cells.

Sinusoidal capillaries are a system of interconnected blood vessels. They are formed by a continuous layer of endothelial cells.

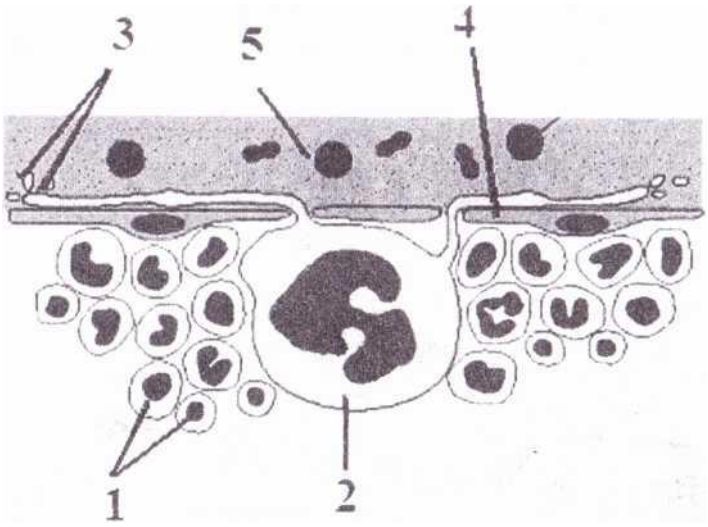


Figure 26.3. Schematic diagram of megakaryocyte among other cells in the bone marrow. 1 - developing blood cells, 2 - megakaryocyte, 3 - processus of megakaryocyte. 4 - endothelial cells of sinusoid, 5 - lumen of sinusoid

Some regions of the endothelium are thin and may be sites for migration of mature cells from the stroma into the sinusoids. The release of mature blood cells from the bone marrow is controlled by releasing factors produced in response to the needs of the organism.

Bone marrow barrier

The biood vessels constitute a barrier, inhibiting immature blood cells from leaving the bone marrow. Only mature blood cells contain the membrane proteins required to attach to and pass the blood vessel endothelium. Hematopoietic stem cells may also cross the bone marrow barrier, and may thus be harvested from blood.

Yellow bone marrow

The ***yellow bone marrow*** is located in the hollow centers of the long bones such as in the legs and in the arms, largely consists of ***fat cells.*** The yellow bone marrow turns into red marrow in emergencies

such as blood loss or anaemia. It would be able to convert itself within 1 - 2 hours to take over the role of a red marrow and this is one of the natural reserves to sustain life in extreme events.

0 Thymus

The ***thymus*** is bilobed organ situated above the heart and below the thyroid gland (fig.26.4).

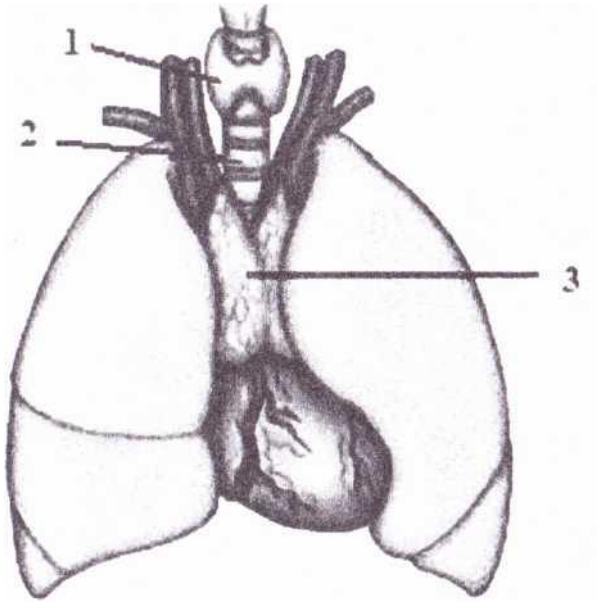


Figure 26.4. Position of the thymus. 1 - thyroid gland, 2 — trachea, 3 **-** thymus

Functions of the thymus

1. Development of T-lymphocytes derived from bone marrow (proliferation and antigen-independent differentiation of T-lymphocyte).
2. Secretion of hormones which regulate T-cell maturation and proliferation (thymulin, thymopoietin and thymosin alpha 1).
3. Haematopoiesis during fetal development.

Structure of the thymus

The ***thymus*** has a connective tissue capsule that penetrates into the parenchyma and divides organ into ***lobules*** (fig.26.5).

The thymus has two tissue components: ***parenchyma*** and ***stroma.***

The ***parenchyma*** is composed mostly of T lymphocytes in various stages of development into mature T cells.

The ***stroma*** is composed of special ***epithelioreticular supporting cells, macrophages*** and ***thymic interdigitating cells.***

The epithelial reticular cells are stellate cells with pale oval nuclei (fig.26.6); cytoplasm contains secretory granules which contain the thymic hormones. These cells are bound together by desmosomes and form extensive network.

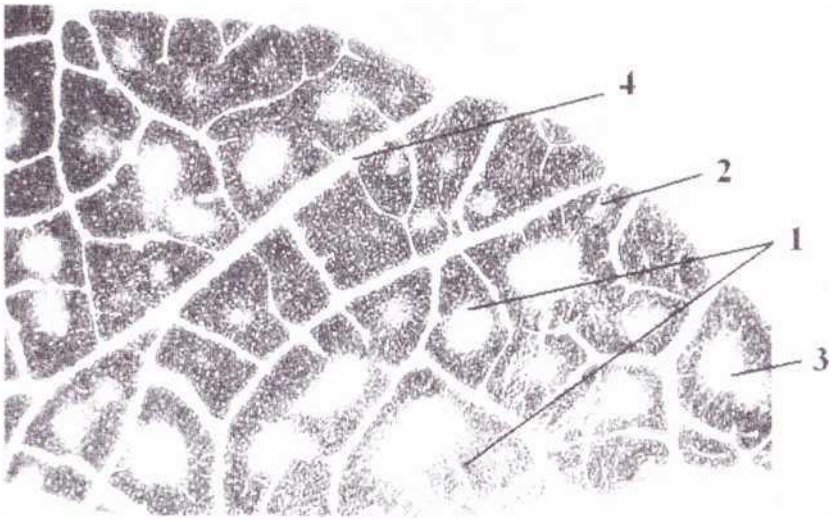


Figure 26.5. Photomicrograph of human thymus. 1 - lobule, 2 - cortex, 3 - medulla, 4 - septa

Each lobule of the thymus has a peripheral dark zone (the ***cortex)*** and a central light zone (the ***medulla).*** High concentration of T lymphocytes in the cortex is the basis for the intense basophilia of this

region and this is the site of precursor cell proliferation and maturation. Mature immunocompetent T cells then move from the cortex toward the medulla where they enter the bloodstream to be taken out of the thymus.

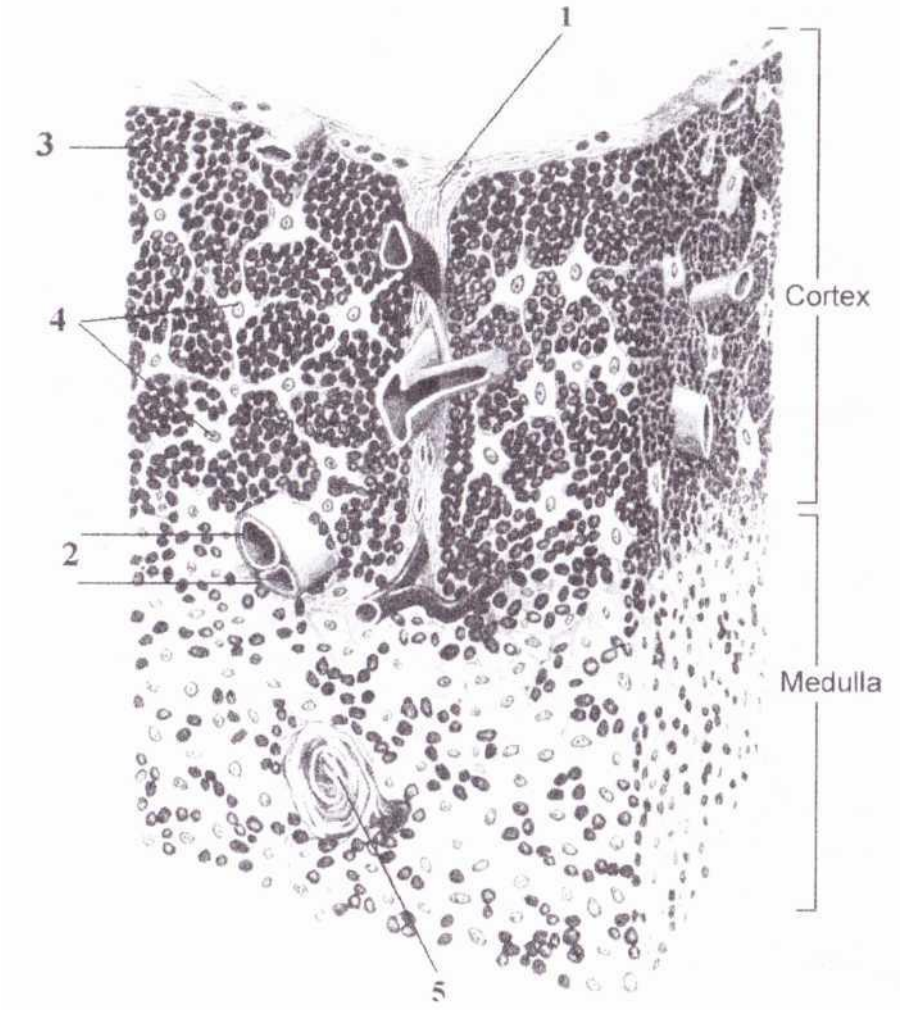


Figure 26.6. Schematic diagram of thymic lobule. 1 - septum, 2 - blood vessels, 3 — thymocytes, 4 — epithelioreticular cells, 5 — Hassall's corpuscle

The ***cortex*** is composed of densely packed lymphocytes (immature T-lymphocytes or ***thymocytes***), epithelioreticular cells, and few macrophages. Large, dividing thymocytes are present in the most peripheral zone of the cortex. Smaller cells are evident toward the center of cortex.

In the ***medulla,*** the stroma consists of prominent ***epithelioreticular cells*** that have large, pale-staining nuclei and substantial amounts of eosinophilic cytoplasm. There are fewer T cells because most of them have entered the blood stream via vessels at the corticomedullary junction.

Antigen presenting cells (APC) are also found in the medulla where they are called ***thymic interdigitating cells.*** These cells are thought to present self-antigens to the matured T cells. T cells that recognize these sell-antigens are removed by a process called apoptosis. This process helps to prevent autoimmune diseases.

The medulla also contains ***Hassall's corpuscles*** (fig.26.6). These structures are concentrically arranged, flattened epithelioreticular cells that degenerate. Their function is unknown.

Blood-thymus barrier

The ***blood-thymus barrier*** regulates exchange of substances between the circulatory system and thymus, providing a sequestered environment for immature T cells to develop. The barrier also prevents the immature T cells from contacting foreign antigens (since contact with antigens at this stage will cause the T cells to die by apoptosis).

Blood-thymus barrier components:

1) endothelium of a capillary;
2) basal lamina of a capillary endothelium;
3) basal lamina of epithelioreticular cells;
4) epithelioreticular cells.

0 **Development of the thymus**

The two main components of the thymus, the thymocytes and the epithelioreticular cells, have distinct developmental origins. The

thymic epithelium is the first to develop, and appears in the form of two flask-shape ***endodermal diverticula***, which arise, one on either side, from the third branchial pouch (pharyngeal pouch), and extend lateral and backward into the surrounding ***mesoderm*** and ***neural crest-derived mesenchyme*** in front of the ventral aorta.

Here they meet and become joined to one another by connective tissue, but there is never any fusion of the thymus tissue proper. The pharyngeal opening of each diverticulum is soon obliterated, but the neck of the flask persists for some time as a cellular cord. By further proliferation of the cells lining the flask, buds of cells are formed, w'hich become surrounded and isolated by the invading mesoderm.

During the late stages of the development of the thymic epithelium, hematopoietic bone-marrow precursors migrate into the thymus. Normal thymic development thereafter is dependent on the interaction between the thymic epithelium and the hematopoietic thymocytes.

0 Involution of the thymus

> ***Changes with age.*** The thymus is relatively large at birth. There is rapid growth until the end of the second year, and then it slows. The maximum size is achieved at puberty (about 35 grams), and then there is a decrease in size through a process known as ***age involution*** (tab.26.1). There is a replacement of cortical thymocytes with fat, an increase in the number and size of Hassall's corpuscles. The atrophy is due to the increased circulating level of sex hormones. Despite involution, the thymus remains functional throughout life.

Table 26.1. Changes of thymus with age

Age	**Mass**
birth	about 15 grams
puberty	about 35 grams
twenty-five years	25 grams
sixty years	less than 15 grams
seventy years	as low as 5 grams

> ***Acute (stress) involution*** may occur in response to severe disease and metabolic stress associated with pregnancy, lactation, infection, surgery, malnutrition, malignancy and other systemic insults. Stress involution is characterized by greatly increased lymphocyte death and is probably mediated by high levels of corticosteroids.

El Clinical correlations

Immunodeficiencies occur when one or more of the components of the immune system are inactive. In developed countries, obesity, alcoholism, and drug use are common causes of poor immune function. In developing countries malnutrition is the most common cause of immunodeficiency. Diets lacking sufficient protein are associated with impaired cell-mediated immunity, complement activity, phagocyte function, IgA antibody concentrations, and cytokine production. Deficiency of single nutrients such as iron; copper; zinc; selenium; vitamins A, C, E, and B_6; and folic acid (vitamin B_9) also reduces immune responses.

Additionally, the loss of the thymus at an early age through genetic mutation or surgical removal results in severe immunodeficiency and a high susceptibility to infection.

Immunodeficiencies can also be inherited or acquired.

Chronic granulomatous disease, where phagocytes have a reduced ability to destroy pathogens, is an example of an inherited, or congenital, immunodeficiency. ***AIDS*** and some types of cancer cause acquired immunodeficiency.

Hypersensitivity is an immune response that damages the body's own tissues. ***Allergy*** is a hypersensitive disorder of the immune system. Allergic reactions occur to normally harmless environmental substances known as allergens; these reactions are acquired, predictable, and rapid. Symptoms can range from mild discomfort to death.

PERIPHERAL (SECONDARY) LYMPHOID ORGANS 0 Lymph nodes

The ***lymph nodes*** are small encapsulated bean-shaped organs composed of lymphoid tissue lying in the path of lymph vessels. They range in size from 1 mm to about 1 to 2 cm in their longest dimension.

Functions of lymph nodes

1. Non-specific filtration of particulate matter and microorganisms from lymph by the phagocytic activity of macrophages, thus preventing exogenous material from reaching the general circulation.
2. Interaction of circulating lymphocytes with antigen-containing lymph.
3. Aggregation, activation and antigen-dependent proliferation of B-lymphocytes in response to antigenic stimulation, plasma cell formation and antibody production.
4. Aggregation, activation and antigen-dependent proliferation of T-lytnphocytes with induction of cytotoxic immune responses after antigenic stimulation.

Structure of the lymph node

The ***lymph node*** (fig.27.1) has a convex side, through which multiple ***afferent lymphatic vessels*** enter, and a concave depression, the ***hilum,*** through which arteries and nerves enter and veins and ***efferent lymphatic vessel*** leave the organ.

The lymph node is surrounded by a connective tissue capsule, and inside the organ the capsule extends to form trabeculae. Reticular tissue composed of reticular cells and reticular fibers form a supporting reticular meshwork inside the node. This meshwork contains two populations of cells:

> ***reticular cells*** which synthesize and secrete reticular fibers and ground substance;

> ***follicular dendritic cells*** with filiform processes which are cells of the immune system. They assist in B cell maturation by the presentation of intact antigen to the B cells.

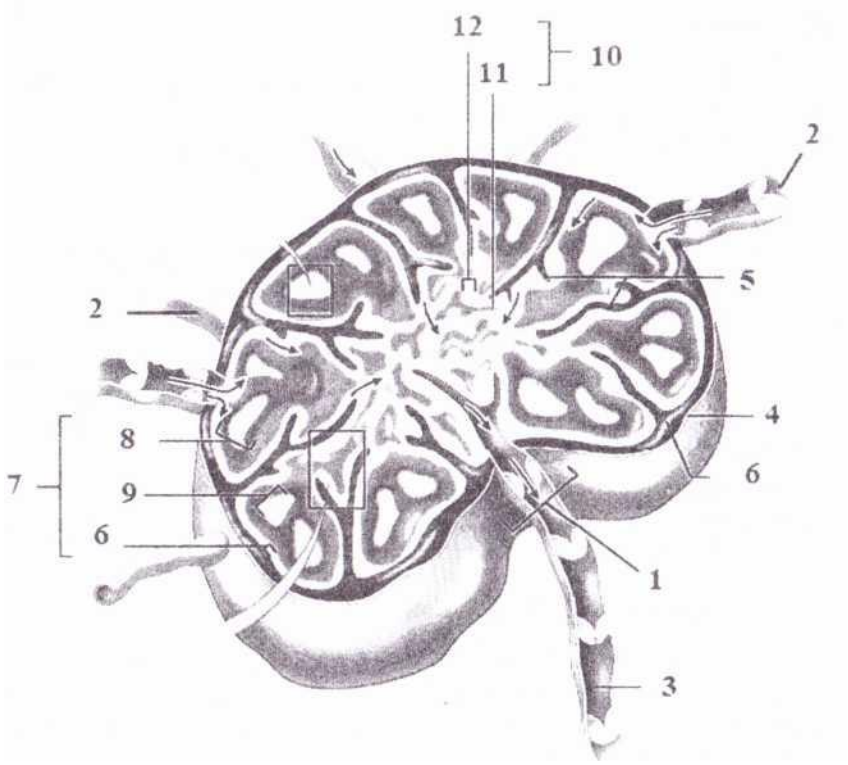


Figure 27.1. Schematic diagram of lymph node. 1 —hilrnri, 2 - afferent lymphatic vessels, 3 - efferent lymphatic vessel, 4 - capsule, 5 — trabeculae, 6 - subcapsular sinus, 7 - cortex, 8 - lymphatic nodule, 9 — germinal center, 10 — medulla, 11 - medullary cord, 12 - medullary sinus

The lymph node contains:

> ***outer cortex,***
> ***deep {inner) cortex*** (***paracortex***), and
> ***medulla.***

Outer cortex is formed by lymphoid tissue whose meshwork is populated by B-cells and macrophages. Within the cortical lymphoid tissue are spherical structures called ***lymphatic nodules (follicles).***

Nodules are temporary structures, which may appear and disappear in the same site. Nodules are spherical structures (0,2-1 mm diameter) lacking a connective tissue capsule. They are mainly composed of dense aggregates of B-lymphocytes.

When a nodule is unstimulated, it is termed a ***primary nodule,*** when active immune responses are underway, it becomes a ***secondary nodule.***

Secondary lymphatic nodule (fig.27.2) consists of:

> ***germinal centre*** is central less-stained area, the site of B-lymphocyte proliferation under the antigen influence; contains large proliferating B-lymphocytes and plasma cells interspersed with macrophages and dendritic cells.

> ***corona (mantle zone)*** is more intensely stained peripheral area, which contains small resting B cells and dendritic cells.

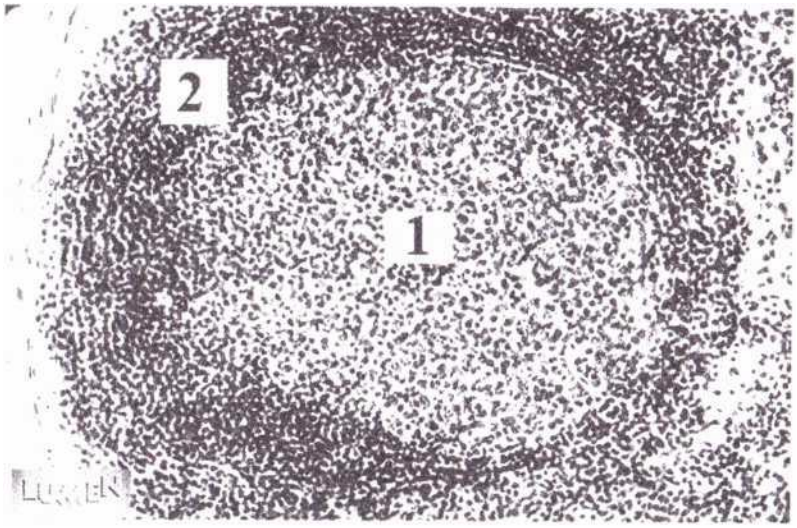


Figure 27.2. Photomicrograph of lymphatic nodule of lymph node. 1 - germinal center, 2 - corona

Paracortex (situated between the cortex and the medulla) lacks distinct morphological boundaries, is a region occupied by T- lymphocytes. This region has been shown to be thymus-dependent and if the thymus is removed experimentally, the paracortical zone disappears.

Medulla is formed from branching ***medullary cords*** of B- lymphocytes, between which the ***medullary sinuses*** are found.

Lymph circulation

The ***sinuses*** (fig.27.3) of the node are irregular spaces formed by reticular tissue containing various lymphocytes, antigen-presenting cells, macrophages. The sinuses act as mechanical filters in which lymph flow is extremely slow and are the sites where many cells are trapped.

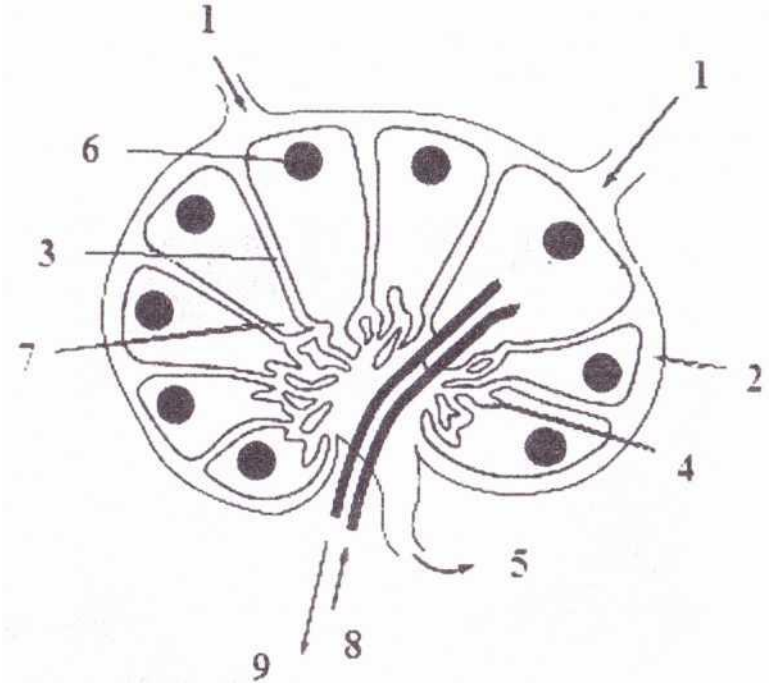


Figure 27.3. Schematic diagram of lymph node sinuses. 1 - afferent lymphatic vessels, 2 - subcapsular sinus, 3 - intermediate sinus, 4 - medullary sinuses, 5 - efferent lymph vessel. 6 - lymphatic nodule, 7 - medulla, 8 - artery, 9 — vein

Lymph enters the ***subcapsular sinus*** from multiple afferent lymph vessels. The subcapsular sinus communicates through ***intermediate (peritrabecular) sinuses*** (run parallel to the trabeculae of the capsule into the inferior of the node) with the ***medullary sinuses.*** l.yniph passes through the medullary sinuses and leaves the lymph node at the hilus via a single efferent lymph vessel. Valves in the vessels control the flow.

E3 Spleen

The ***spleen*** is a large lymphoid organ situated in the left upper part of the abdomen.

Functions of the spleen

The ***spleen*** functions in both the immune and hematopoietic systems.

The ***functions*** of the spleen ***as organ of immune system.***

1. Removal of macromolecular antigens from the blood.
2. Antigen presentation by antigen presenting cells and initiation of immune response.
3. Antigen-dependent proliferation and differentiation of T- and B-lymphocytes, which ensure the immunological responses.

The ***functions*** of the spleen ***as hematopoietic organ.***

1. Removal and destruction of aged, damaged and abnormal erythrocytes and platelets.
2. Retrieval ofiron from erythrocyte hemoglobin.
3. Storage of blood.
4. Formation of the erythrocytes during the fetal life.

Structure of the spleen

The ***spleen*** (fig.27.4) is surrounded by a capsule of dense connective tissue that sends trabeculae, which divide the parenchyma, or ***splenic pulp,*** into incomplete compartments. The medial surface of

the spleen has a hilura, which is the site for entry and exit of the blood vessels and nerves.

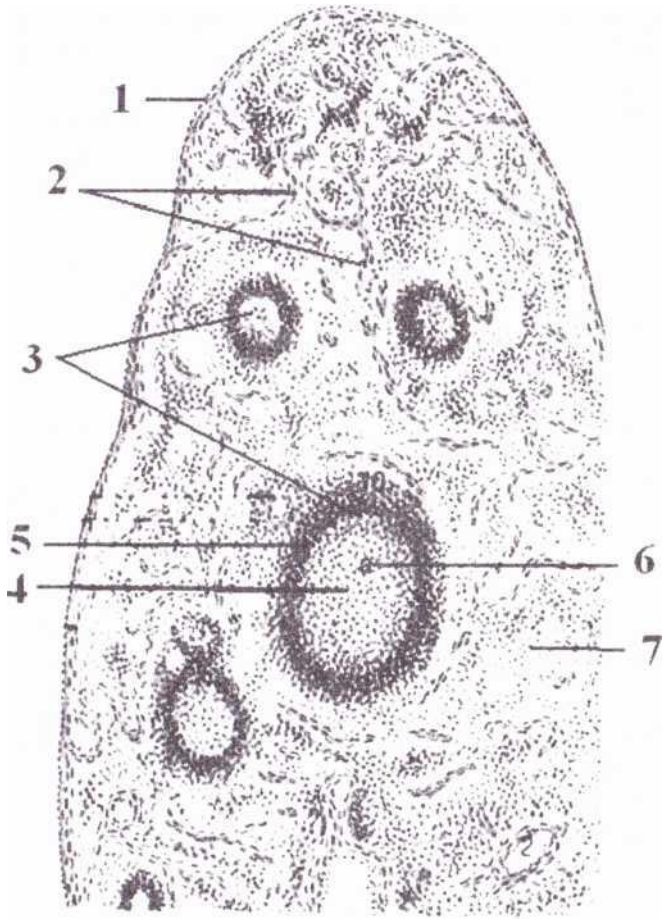


Figure 27.4. Schematic diagram of the spleen. 1 - capsule, 2 - trabeculae, 3 — white pulp (splenic nodules), 4 - germinal center, 5 - germinal center, 6 - central artery, 7 — red pulp

Stroma of the spleen is formed by reticular tissue consisting of reticular cells and reticular fibers.

The splenic pulp is divided into two functionally and morphologically different regions: ***white pulp*** and ***red pulp.*** Between white pulp and red pulp there is the ***marginal zone.***

White pulp

The ***white pulp*** (20% of the total mass of the spleen) is composed of lymphoid tissue surrounding an artery.

White pulp consists of:

> ***periarterial lymphatic sheaths*** (PALS);
> ***lymphatic*** nodules.

Branches of the splenic artery course through the capsule and trabeculae of the spleen and enter the white pulp. Within the white pulp, these vessels are called the ***central arteries*** (fig.27.5).

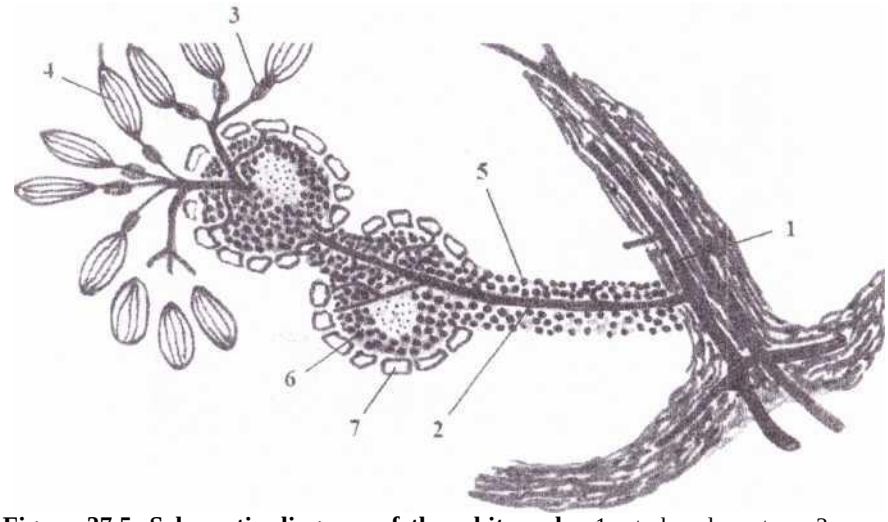


Figure 27.5. Schematic diagram of the white pulp. 1 - trabecular artery, 2 — central artery, 3 - sheathed capillaries, 4 - splenic sinus, 5 - periarterial lymphoid sheathe (PALS), 6 - splenic nodule,
7 - marginal zone

Lymphoid tissue that surrounds the central artery constitutes the ***periarterial lymphatic sheaths*** (PALS). The PALS has a cylindrical configuration that conforms to the course of the central artery. Within

PALS, there are circumferential layers of reticular cells and reticular fibers that support lymphocytes which are predominantly ***T-cells.***

Lymphatic nodules are on periphery of periarterial lymphoid sheaths, are circular masses of lymphoid tissue, and are populated by mainly ***E-lymphocytes.*** Lymphatic nodules displace the central artery, so that is occupies an eccentric rather than a central position.

The nodule (fig.27.6) consists of:

> ***germinal center***, which is central less-stained area, the site of B- lymphocyte proliferation under the antigen influence;

> ***mantle zone (corona)*** is a narrow zone of small lymphocytes.

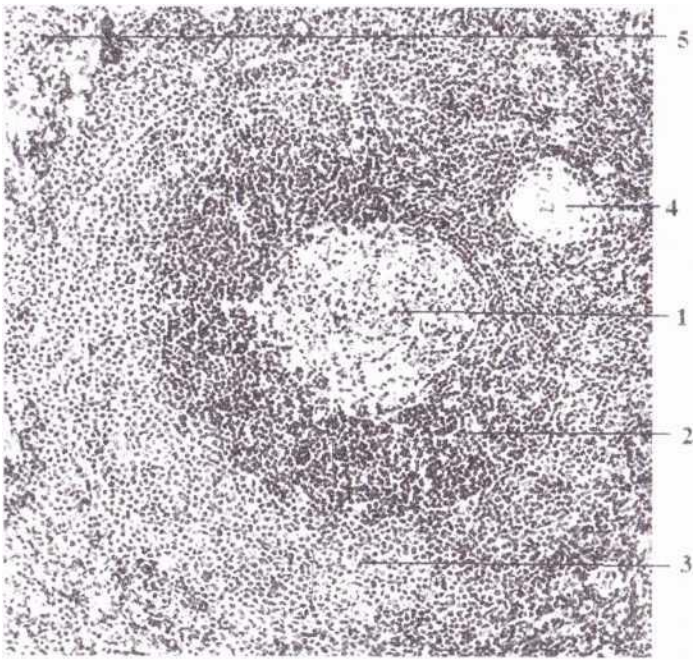


Figure 27.6. Photomicrograph of splenic nodule. 1 - germinal center, 2 — mantle zone 3 - marginal zone, 4 - central artery, 5 - red pulp

Germinal centers develop within 24 hours after antigen influence and may become very large and visible with the naked eye. These enlarge4d nodules are called ***splenic nodules*** or ***Malpighian corpuscles.***

The ***marginal zone*** is the transition between the white and red pulp. It consists of many sinuses and loose lymphoid tissue. The marginal zone contains few lymphocytes but many active macrophages. It removes antibodies and T- and B-lymphocytes from the blood and plays a major role in the immunological activity of the spleen.

Red pulp

The ***red pulp*** (fig.27.7) is reticular tissue of diffuse type, which consists of:

> ***splenic (venous) sinuses*** separated by
> ***splenic cords*** (cords of Billroth).

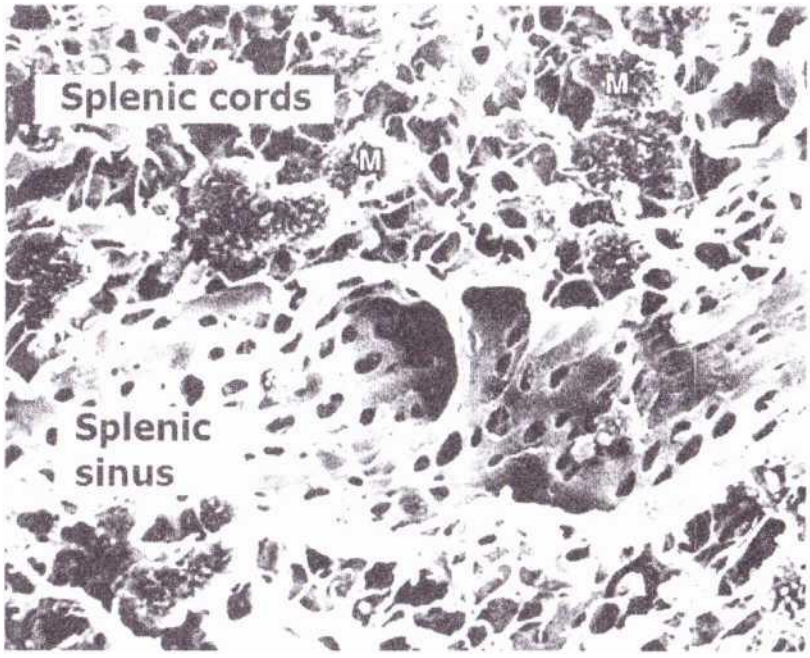


Figure 27.7. Electron micrograph of red pulp oi the spleen.

Splenic cords consist of loose meshwork of reticular cells and reticular fibers that contains formed elements of the blood (erythrocytes, platelets, and granulocytes), macrophages, lymphocytes, plasma ceils.

Splenic (venous) sinuses (fig.27.8) are long vascular channels with an unusual endothelium and basal lamina. The endothelial cells are elongated with tapered ends. They lie parallel to the long axis of vessel and have nuclei that bulge into the lumen. The blood cells passing into these vessels from the cords must cross the sinus walls through thin slits between endothelial cells. The basal lamina of the splenic sinuses is fenestrated. Strands of basal lamina loop around the staves of a barrel. These strands are at right angles to the long axes of the endothelial cells. Reticular fibers appear to merge with the perisinusoidal loops of basal lamina.

From the sinuses, the blood passes to pulp veins, and finally to trabecular veins.

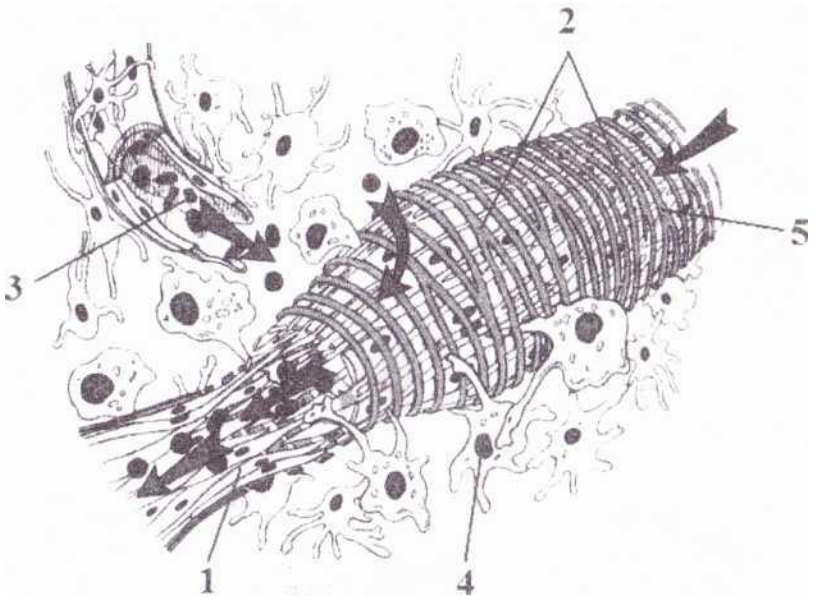


Figure 27.8. Schematic diagram of splenic sinus. 1 - endothelial cells of splenic sinus, 2 - reticular fibers, 3 - terminal arterial capillaries (open circulation), 4 - phagocytic cells, 5 - closed circulation

Spleen blood supply (fig.27.9)

The ***splenic artery*** enters the hilus and branch into ***trabecular arteries.*** They enter the parenchyma, are enveloped by lymphatic sheath and are called ***centra*/ *arteries.*** These arteries are surrounded by a sheath of T-lymphocytes (periarterial lymphatic sheath). The central arteries penetrate the lymphatic nodules, usually in the periphery.

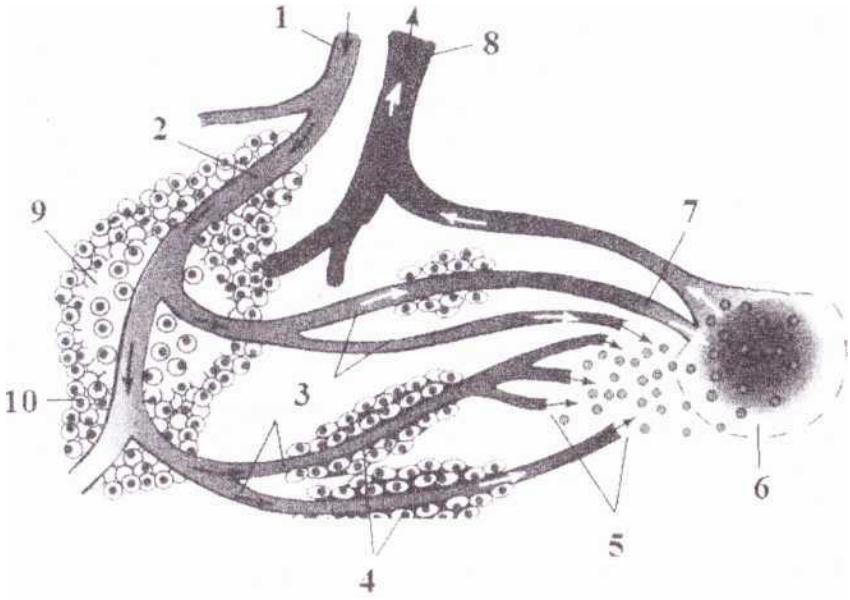


Figure 27.9. Schematic diagram of spleen blood supply. 1 - trabecular artery, 2 - central artery, 3 - penicillar arteries, 4 - sheathed capillaries, 5 — terminal arterial capillaries (open circulation), 6 — splenic sinus, 7 - closed circulation, 8 - trabecular vein, 9 - splenic nodule, 10 - PALS

After leaving the white pulp, the central arteries continue into the red pulp and subdivide to form the ***penicillar arterioles.*** The ***penicillar arterioles*** than continue as arterial capillaries.

Some arterial capillaries are surrounded by ellipsoids of reticular cells, lymphocytes and macrophages and are thus called ***sheathed capillaries.***

From these vessels blood flows:

> into the splenic sinuses ***(closed circulation),***

> into the splenic cords ***(open circulation***), from where blood filters into sinuses.

Sinuses empty into the pulp veins.

69 Clinical correlations

Splenomegaly is the enlargement of the spleen. Splenomegaly can result from antigenic stimulation (e.g., infection), obstruction of blood flow (e.g., portal vein obstruction), underlying functional abnormality (e.g., hemolytic anemia), or infiltration (e.g., leukemia).

Asplenia is the absence of normal spleen function.

> Some people congenitally completely lack a spleen, although this is rare.

> Sickle-cell disease can cause a functional asplenia (or autosplenectomy) by causing infarctions of the spleen during repeated sickle-cell crises.

> It may be removed surgically (known as a splenectomy). Indications for splenectomy include following abdominal injuries with rupture and hemorrhage of the spleen, or in the treatment of certain blood diseases (idiopathic thrombocytopenic purpura).

People can live without a spleen. Sometimes the spleen must be removed surgically (splenectomy) because of irreparable damage (for example, due to an injury sustained in a car crash). When the spleen is removed, the body loses some of its ability to produce protective antibodies and to remove unwanted microorganisms from the blood. As a result, the body's ability to fight infections is impaired. People who do not have a spleen are at particularly high risk of infections because of the spleen’s role in fighting certain kinds of bacteria, such as Streptococcus pneumoniae. Neisseria meningitidis, and Haemophilus influenzae. Because of this risk, people receive vaccinations to help protect them from infection with these organisms.

URINARY SYSTEM

0 Overview of the urinary system

The urinary system consists of the paired kidneys and ureters, and unpaired bladder and urethra-

Functions of the urinary system

> Regulation of water, inorganic ion balance, and acid-base balance
> Removal of metabolic waste products from the blood and their excretion in the urine
> Removal of foreign chemicals from the blood and their excretion in urine
> Production of hormones/enzymes:
  9 erythropoietin, which controls erythrocyte production;
  ® renin, an enzyme that controls blood pressure and blood volume; renin cleaves circulating angiotensinogen to release angiotensin I.

0 Kidneys

The ***kidney*** (fig.28.1) is covered by a capsule of connective tissue consisting of collagen, elastic fibers and smooth muscle cells.

The kidney is divided into:

> an inner ***medulla*** and
> an outer ***cortex***

The ***medulla*** consists of 10-18 medullary pyramids. From the base of each medullary pyramid the medullary rays penetrate the cortex.

The ***cortex*** is the peripheral part lying between the capsule and the bases of renal pyramids.

The cortical tissue surrounding each medullary pyramid is a ***renal lobe,*** and each medullary ray forms the center of a conical ***renal lobule.***

A part of cortex projects inwards between the renal pyramids and forms the ***renal columns of Berlin.***

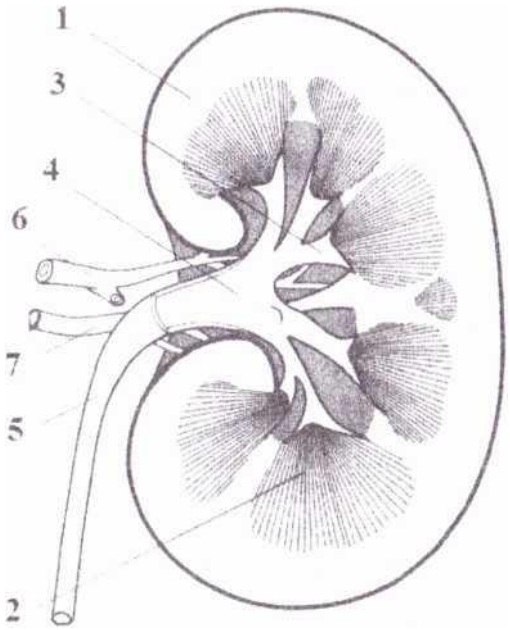


Figure 28.1. Schematic diagram of the kidney structure. 1 - cortex, 2 - medulla, 3 - calyx, 4 - renal pelvis, 5 - ureter, 6 - renal artery, 7 - renal vein

Nephron

Each kidney is composed of 1-4 millions ***nephrons*** - the structural and functional units (fig.28.2).

Each nephron consists of:

1) dilated portion, the capsule of the renal corpuscle,
2) proximal convoluted tubule,
3) proximal straight tubule (thick descending limb of Henle's loop),
4) thin descending limb of Henle's loop,
5) thin ascending limb of Henle's loop,
6) distal straight tubule (thick ascending limbs of Henle's loop),
7) distal convoluted tubule.

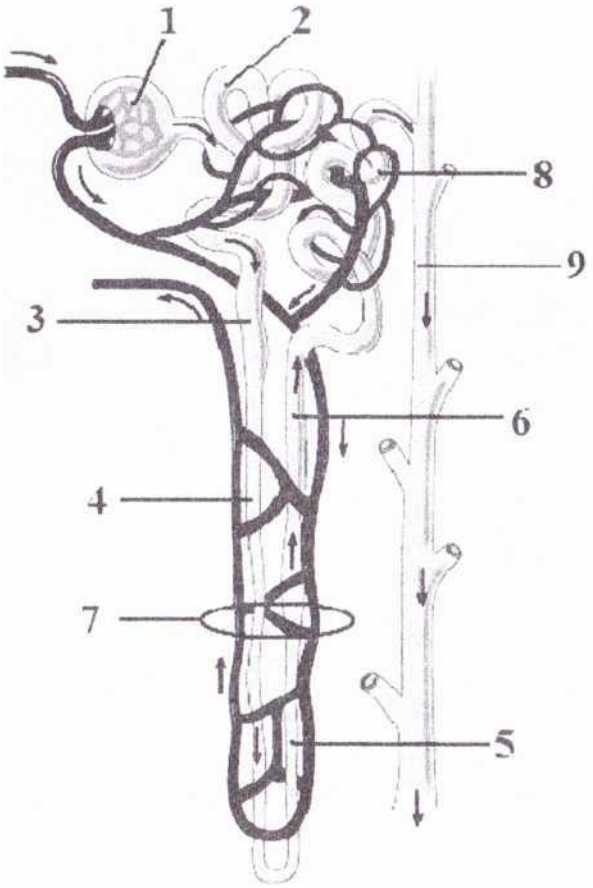


Figure 28.2. Diagram of the nephron structure. 1 — renal corpuscle, 2 - proximal convoluted tubule, 3 - proximal straight tubule (thick descending limb), 4 - thin descending limb of the loop of Henle, 5 - thin ascending limb of the loop of Henle, 6 - distal straight tubule (thick ascending limbs of the loop of Henle), 7 - Henle's loop, 8 - distal convoluted tubule, 9 — collecting tubule

Renal corpuscle

Each ***renal corpuscle*** consists of (fig.28.3):

> a tuff of***fenestrated*** capillaries, the ***glomerulus,*** surrounded by

> a double-walled epithelial ***Bowman's capsule***

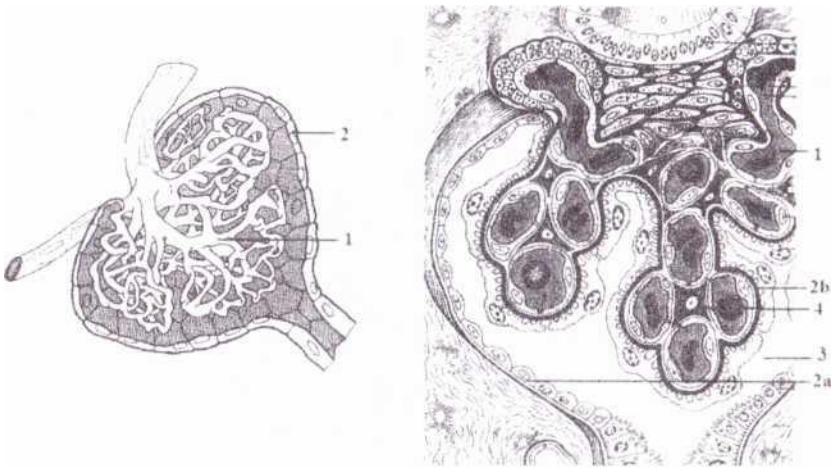


Figure 28.3. Diagram of the renal corpuscle structure. 1 — glomerulus, 2 - Bowman's capsule: a - parietal layer, b - visceral layer (podocytes), 3 - urinary space, 4 - intraglomerular mesangial cell

The ***parietal layer*** of the capsule consists of a simple squamous epithelium surrounded by basal lamina.

The ***visceral layer*** of the capsule envelops the capillaries of the glomerulus.

Between two layers of Bowman's capsule there is the ***urinary space***, which receives the fluid filtered through the capillary wall and the visceral layer.

The visceral layer lined by modified celts termed the ***podocytes*** (fig.28.4, 28.5). The podocytes have a cell body from which several primary processes arise. Each primary process gives secondary processes, called ***pedicels*** that embrace the capillaries of the glomerulus. Between the pedicles there are little spaces termed ***filtration slits.*** Between the fenestrated endothelial cells of glomerular capillaries and the podocytes is a thick basement membrane.

The basement membrane is derived from the fusion of capillary- and podocyte-produced basal laminae. Under electron microscope, one can distinguish a central electron-dense layer (lamina densa) and, on each side, a more electron-lucent layer (lamina rara).

The glomerular basal lamina is a selective macromolecular filter between the blood and the glomerular filtrate.

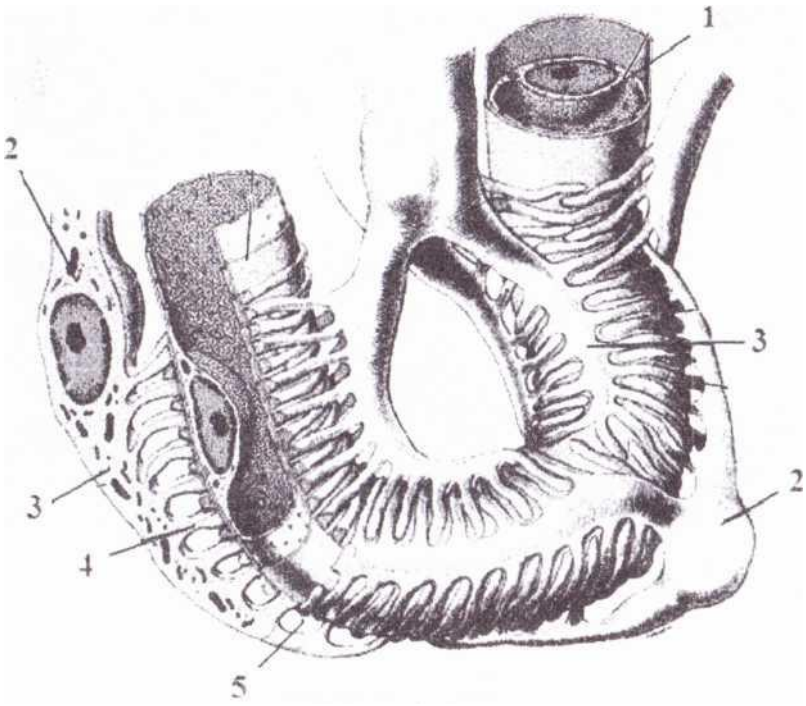


Figure 28.4. Visceral layer of Bowman's capsule. 1 - blood capillary' of glomerulus, 2 — podocyte cell body, 3 - primary processes, 4 - secondary processes, 5 - filtration slits (from ***Jimqueira L.C., Carneiro J.,*** 2005)

Thus, the ***filtration barrier*** of the renal corpuscle (fig.28.6) consists of:

1. cytoplasm of the fenestrated endothelial cells of glomerular capillaries;
2. thick basement membrane.
3. filtration slits between the pedicles of the podocytes.

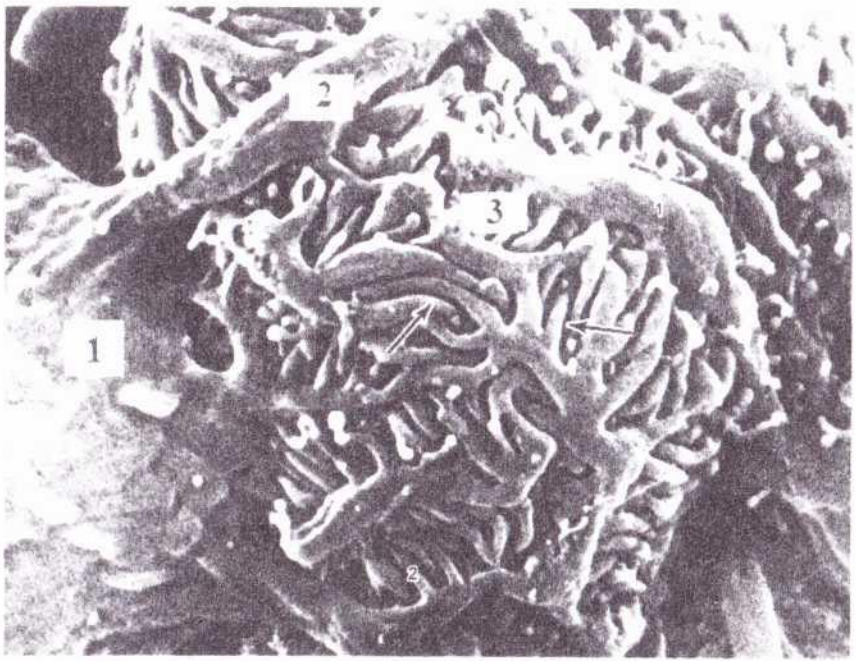


Figure 28.5. Scanning electron micrograph of a glomerulus. 1 - podocyte cell body, 2 - primary processes, 3 - secondary processes

Mesangium

Between capillaries there is a special tissue which consists of ***intraglomerular mesangial cells*** (fig.28.3). These ceils are specialized pericytes which contain contractile proteins and may act as macrophages. They are an unusual example of phagocytic cells derived from smooth muscle and not monocytes.

Tubes of the nephron (fig.28.7)

Proximal thick segment consists of proximal convoluted tubule and proximal straight tubule (thick descending limb), and is formed by simple cuboidal or columnar epithelium. The apexes of epithelial cell have numerous microvilli, which form a ***brush border*** The basal portions of these cells have membrane invaginations; mitochondria are

concentrated between them and arranged parallel to the long axis of the cell ***(basal striations).***

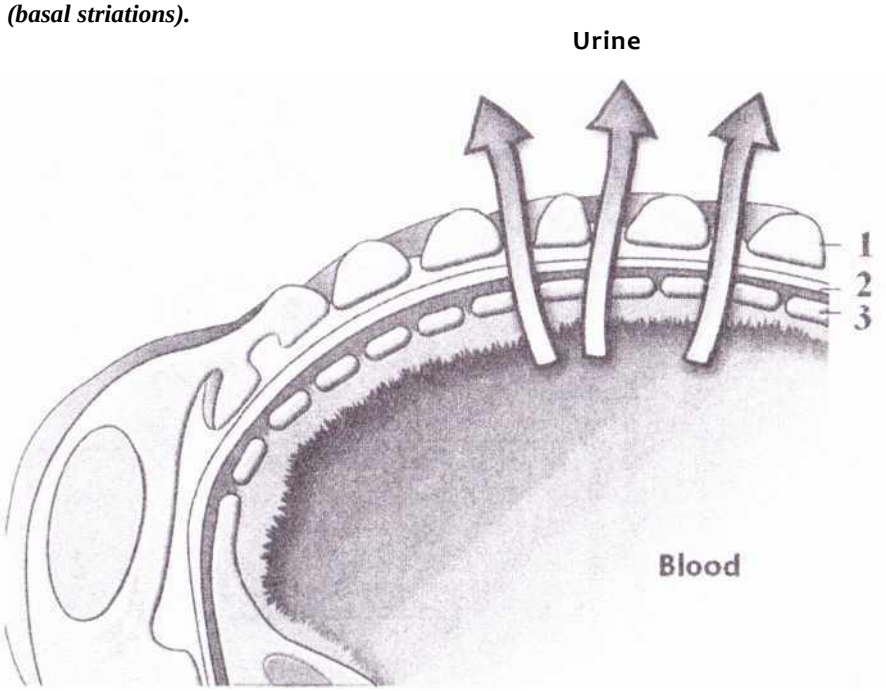


Figure 28.6. Schematic diagram of filtration barrier of the renal corpuscle.
1- podocyte, 2 - basement membrane, 3- endothelial cell of glomerular capillary

The proximal segment is the initial and major site of ***reabsorption.*** The proximal convoluted tubules reabsorb about 150 L of fluid per day or about 80% of ultrafiltrate into the vessels of the peritubular capillary network. The proximal convoluted tubules also reabsorb amino acids, sugars, and polypeptides.

Thin segment constitutes the thin part of the loop of Henle, is formed by simple squamous epithelium. Thin segment is part of the countercurrent exchange system that functions in concentrating urine.

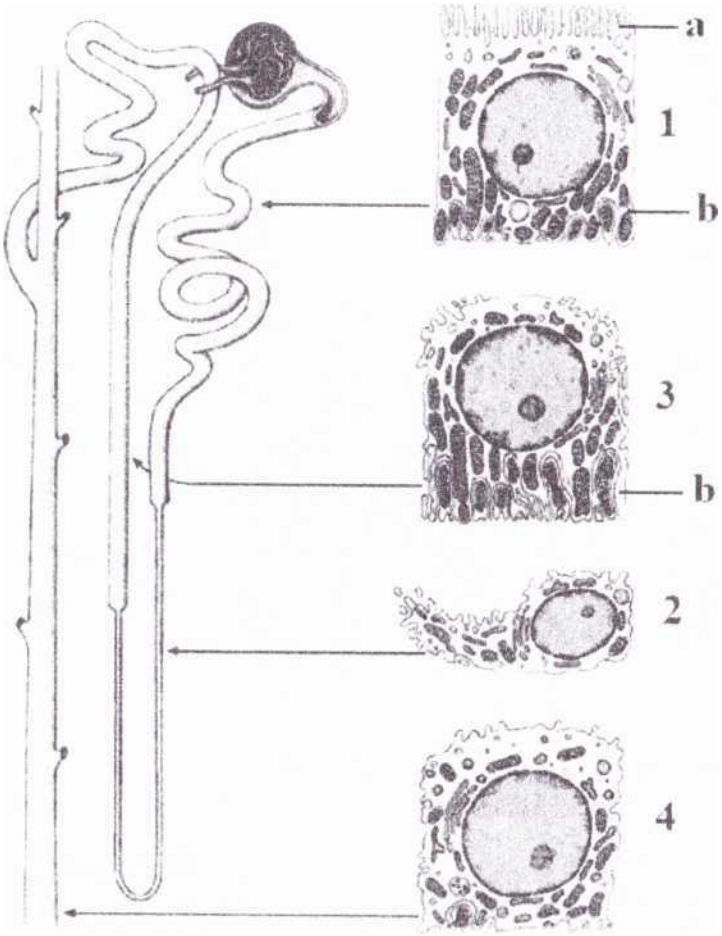


Figure 28.7. **Diagram ot structure of the tubes of the nephron.** 1 - proximal thick segment: a - brush border, b -basal striations; 2 - thin segment, 3 - distal thick segment, 4 - collecting tubule (from *Junqueira L.C., CarneiroJ.,* 2005)

Distal thick segment consists of distal straight tubule (thick ascending limbs of Henle's loop) and distal convoluted tubule, is lined by simple cuboidal epithelium. There is ***no brush border.*** The basal portion of these cells has ***basal striations***

Distal straight tubule transports ions (Na^+, K^+, Cl') from tubular lumen to the interstitial connective tissue. Distal convoluted tubule is responsible for reabsorption of Na^+ and secretion of K^+ into ultrafiltrate, reabsorption of bicarbonate ions.

Collecting duct system

The ***collecting duct system*** of the kidney consists of a series of tubules and ducts that connect the nephrons to the ureter. It participates in electrolyte and fluid balance through reabsorption and excretion, processes regulated by the hormones aldosterone and antidiuretic hormone.

The collecting duct system includes the collecting tubules, cortical collecting ducts, and medullary collecting ducts.

Urine passes from the distal convoluted tubules to collecting tubules that join each other to form larger, collecting ducts, finally the ***papillary ducts of Bellini,*** which open at the apex of each renal papilla.

Collecting tubules and ***collecting ducts*** are lined by simple cuboidal or columnar epithelium which consists of two types of cells:

> ***light cells*** are principal cells of this system with electron-lucent cytoplasm and few organelles; function of these cells is passive reabsorption of water;

> ***dark intercalated (IC) cells*** with microvillous surface and mitochondria in the cytoplasm; function of these cells is secretion of hydrochloric acid.

Types of the nephrons (fig.28.8)

1) ***Cortical (subcapsular) nephrons*** constitute 80%; their glomeruli are located high in the cortex, these nephrons have short loops. Glomeruli function under the high pressure and actively participate in formation of glomerular ultrafiltrate.

2) ***Juxtamedullary nephrons*** constitute 20%; their glomeruli are located near the corticomedullary junction, they have very long Henle's loops, extending deep into the medulla. Glomeruli function under small pressure and don't play the important role in a process of a filtration. Their structural features are essential to the urine-concentrating mechanism.

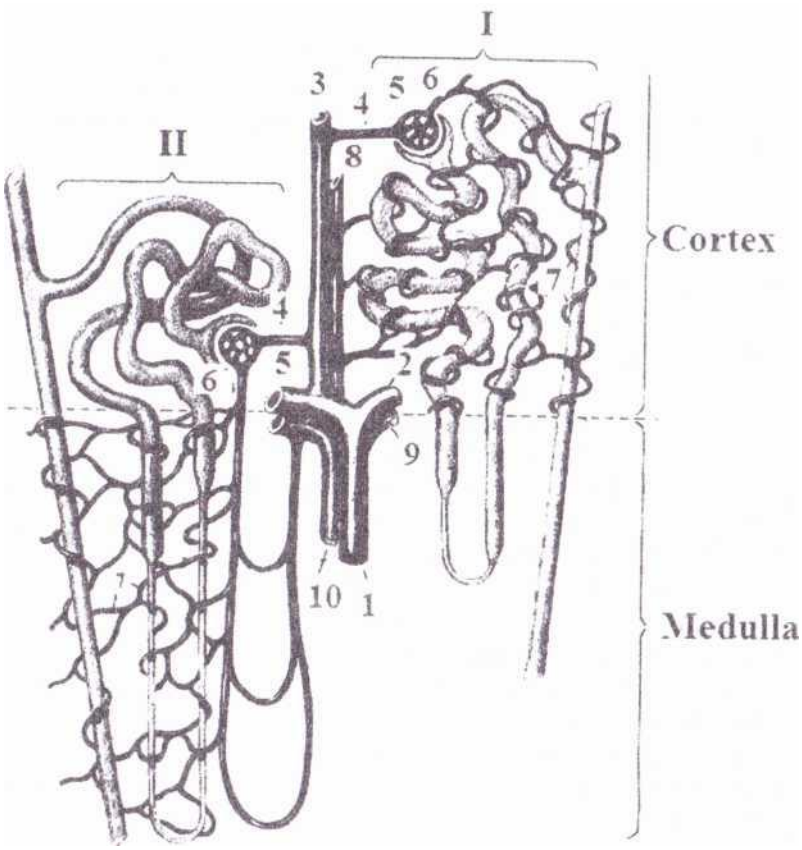


Figure 28.8. **Kidney blood supply.** I - cortical nephron, II - juxtamedullary nephrons; 1 - interlobar artery, 2 - arcuate artery, 3 - interlobular artery, 4 - afferent arteriole, 5 - capillaries of the glomerulus, 6 — efferent arteriole, 7 - peritubular capillary network, 8 - interlobular vein, 9 - arcuate vein, 10 - interlobar vein (from ***K). H./Ufumacbea, H.A. lOpwia u dp.,*** 1999)

Kidney blood supply

The kidney has a rich blood supply. 1200-1300 ml of blood passes through both kidneys each minute.

Arteries

Kidney receives blood from ***renal artery,*** which near the hilum of the kidney gives rise to 5 ***segmental arteries.*** Each segmental artery gives off ***interlobar arteries*** (flg.28.8), located between the renal pyramids. At the level of the corticomedullary junction, the interlobar arteries form the ***arcuate arteries.*** Arcuate arteries give off ***interlobular arteries,*** which follow in the cortex vertically towards to the renal surface. Interlobular arteries give arise the ***afferent arterioles***, which supply blood to the ***capillaries*** of the glomeruli ***(primary capillary network).*** Blood passes from these capillaries into the ***efferent arterioles,*** which form a ***peritubular capillary (secondary) network*** that will nourish the proximal and distal tubules and carry away absorbed ions and low-molecular-weight materials.

In ***cortical nephrons*** the efferent arteriole has a smaller lumen than the afferent arteriole. This inequality serves to promote the filtration pressure in the glomerulus.

In ***juxtamedullary nephrons*** the efferent arteriole is of the same calibre as the afferent.

Veins

The ***interlobular veins*** receive peritubular capillaries and the ***stellate veins.***

These veins end in ***arcuate veins,*** which also receive the ***venule rectae.*** The ***arcuate veins*** join to form ***interlobar veins,*** which form the ***renal vein.***

0 Endocrine system of kidney

Juxtaglomerular apparatus

The ***juxtaglomerular apparatus*** regulates the systemic blood pressure by activation of the renin-angiotensin-aldosterone system.

Juxtaglomerular apparatus is the modification of the distal convoluted tubule and the afferent arteriole at the region of their contact (fig. 2 8.9).

The juxtaglomerular apparatus consists of 3 components:

1. ***Macula densa*** is an area of closely packed specialised columnar cells in the wall of the distal convoluted tubule. The cells of macula densa are

sensitive to the ionic content and water volume of the fluid in the tubule ***(osmoreceptors).*** If low water volume is detected by these cells, they will produce molecular signals that promote renin secretion by other ceils of the juxtaglomerular apparatus, called the juxtaglomerular cells.

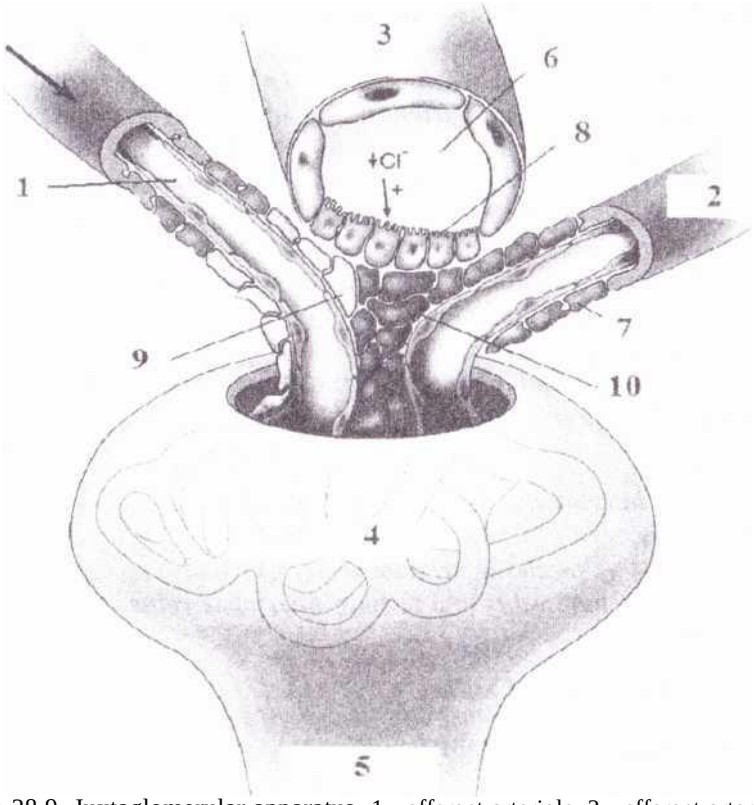


Figure 28.9. Juxtaglomerular apparatus. 1 - afferent arteriole, 2 - efferent arteriole, 3 - distal convoluted tubule, 4 - glomerulus, 5 - proximal convoluted tubule, 6 - urine, 7 - smooth muscle cells, 8 - macula densa, 9 - juxtaglomerular cells, 10 - extraglomerular mesangial cells

2. ***Juxtaglomerular cells*** are specialised smooth muscle cells in the tunica media of the afferent (and, sometimes, efferent) arteriole. The cytoplasm of these cells contains granules of the enzyme ***renin.*** These

cells play a critical role in the renin-angiotensin system and thus in renal autoregulation, the self-governance of the kidney.

3. ***Extraglomerular mesangial cells*** (also known as ***Goormaghtigh cells)*** form a conical mass: laterally it is bounded by the afferent and efferent arterioles. These cells are flat and elongated with cytoplasmic processes. Exact function of these cells is not established. It is supposed, that they transfer a signal from the cells of the macula densa to the arterioles and secrete hormone erythropoietin and renin.

Renal interstitium

Both the cortex and the medulla contain specialized cells in the spaces between the nephrons, collecting tubules, and blood and lymph vessels. These ***interstitial cells*** are more frequent in the medulla. Interstitial cells secrete ***prostaglandin,*** which participate in regulation of the systemic and renal bloodstream, and vasodilator ***bradykinin.***

0 Histophysiology of the kidney (urine formation)

The kidneys regulate the chemical composition of the internal environment of the organism by a complex process that involves (fig.28.10):

> glomerular filtration;
> reabsorption;
> secretion.

Filtration takes place in the glomerulus. The glomeruli are composed of blood capillaries in which the hydrostatic pressure - about 45 mm Hg - is higher than in other capillaries.

Endothelial cells of glomerular capillaries are fenestrated with numerous openings.

The glomerular filtrate has a chemical composition similar to that of blood plasma but contains almost no protein, since macromolecules do not cross the glomerular wall.

Selective reabsorption takes place mainly in the proximal convoluted tubules. The substances reabsorbed include water, glucose, aminoacids, proteins of small molecular size, and various ions including sodium, chloride, phosphate, bicarbonate and calcium.

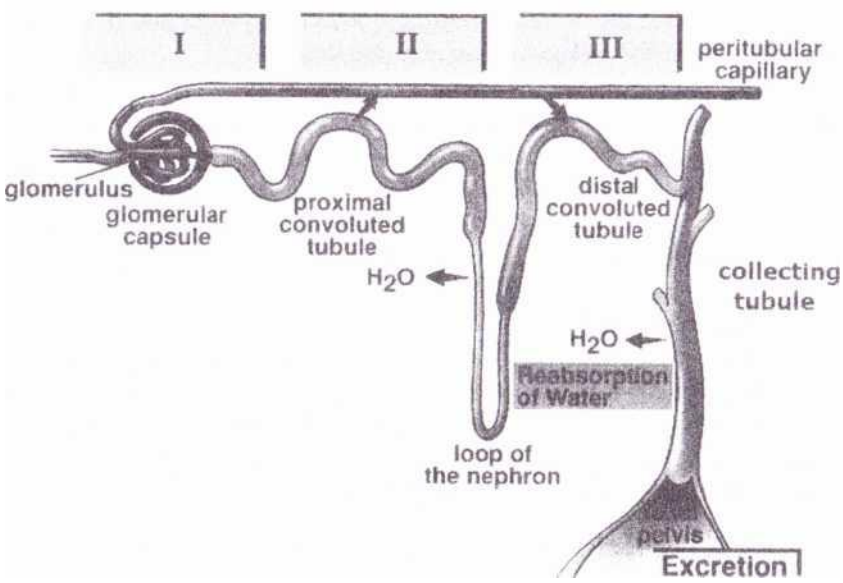


Figure 28.10. Schematic diagram of urine formation. I - glomerular filtration, IT - selective reabsorption, III - secretion

Very large proportion of the water in the glomerular filtrate is reabsorbed through the loops of Henle. Water diffuses passively, following the osmotic gradient.

The tlltrate is reduced from an original volume of about 200 litres per day to an average urine output of 1,5 litres per day.

Secretion is the opposite of reabsorption. This mechanism also changes the composition of urine. Some substances are actively secreted into the tubules. Substances secreted into the urine include ammonia, hydrogen ions, and potassium.

0 Urinary passages

The calyces, renal pelvis, ureter, and bladder have the same basic histological structure (fig.28.11).

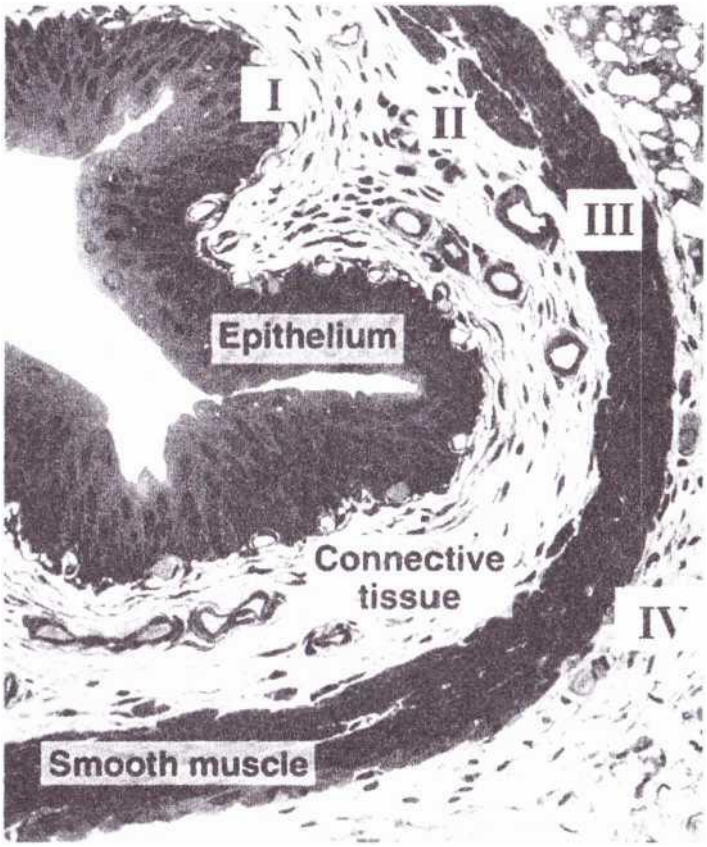


Figure 28.11. Photomicrograph of cross section of the ureter. I — mucosa, II - submucosa, III — muscularis, IV - outer layer

The wall of these organs consists of 4 layers:

I. Mucosa
II. Submucosa
III. Muscularis
IV. Adventitia

Mucosa consists of:

1) ***transitional epithelium*** having 4 or 5 layers of cells;

1) ***lamina propria*** which consists of loose connective tissue.

Submucosa consists of loose connective tissue.

Muscularis consists of bundles of smooth muscle cells with intervening connective tissue.

Adventitia consists of loose connective tissue with collagen and elastic fibers. The upper part of the bladder is covered by serous peritoneum.

Transitional epithelium having 6 or 8 layers of cells; the superficial cells are rounded and bulge into the lumen in the empty bladder. These cells are frequently polyploid or binucleate. When the epithelium is stretched, as when the bladder is full of urine, the epithelium is only three or four cells in thickness, and the superficial cells become squamous (fig.28.12).

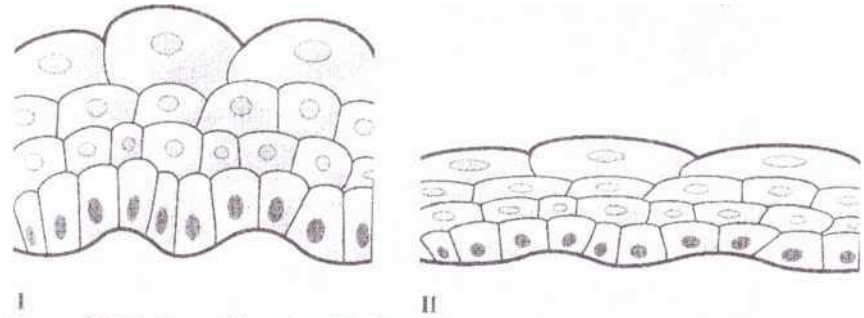


Figure 28.12. Transitional epithelium. I -relaxed, II - stretched

12 Development of the kidney

The human kidney has passed through three stages of evolution:

> pronephros,

> mesonephros,

y metanephros.

Pronephros is formed from the nephrogenic cord of the cervical region (fig.28.13-1). The human pronephros has not connection with blood system, is non-functional, and disappears soon after its formation. Nephric duct formed in relation to the pronephros and ending in the cloaca, however, persists.

Mesonephros (flg.28.13-2) consists of a series of excretory tubules that develop in the thoracolumbar region. These tubules drain into the ***nephric duct*** which may now be called the ***mesonephric duct.*** Most of the mesonephric tubules disappear, but some of them are modified and take part in forming the duct system of the testis.

Definitive kidney (fig.28.13-3) arises from two distinct sources. The ureters, the pelvis, calyces, papillary ducts and collecting tubules of the kidney are derived from the ***mesonephric duct.*** The nephrons are derived from the lowest part of the nephrogenic cord the cells of which form the ***metanephric blastema.*** The ends of the nephrons dilate and become invaginated by a mass of mesodermal tissue. This tissue differentiates to form the glomerulus.

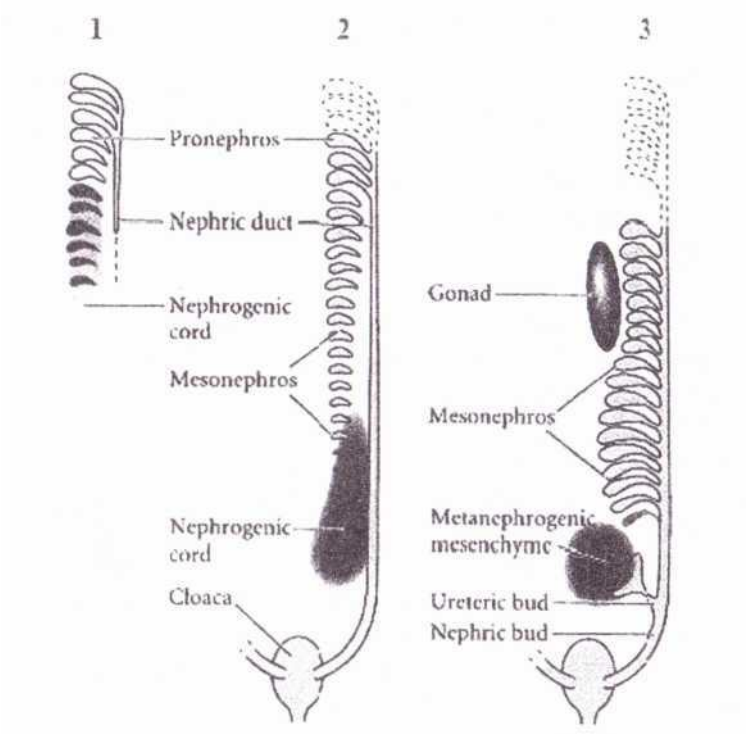


Figure 28.13. General scheme of development of the kidney.

0 Clinical correlations

Acute kidney injury (AKI) is a rapidly progressive loss of renal function, generally characterized by oliguria (decreased urine production); body water and body fluids disturbances; and electrolyte derangement. AKI can result from a variety of causes, generally classified as ***prerenal, intrinsic,*** and ***postrenal.*** An underlying cause must be identified and treated to arrest the progress, and dialysis may be necessary to bridge the time gap required for treating these fundamental causes.

Prerenal causes of AKI are those that decrease ***effective blood flow to the kidney*** (low blood volume, low blood pressure, heart failure, renal artery stenosis, renal vein thrombosis, which is the formation of a blood clot in the renal vein).

Intrinsic AKI can be due to damage to the glomeruli, renal tubules, or interstitium (glomerulonephritis, acute tubular necrosis, and acute interstitial nephritis).

Postrenal AKI is a consequence of ***urinary tract obstruction*** (prostatic hyperplasia, kidney or bladder stones, bladder, ureteral or renal malignancy).

Chronic kidney disease (insufficiency) is a slowly progressive (months to years) decline in the kidneys' ability to filter metabolic waste from the blood.

Chronic kidney disease leads to a build-up of fluid and waste products in the body. This condition affects most body systems and functions, including red blood cell production, blood pressure control, and vitamin D and bone health.

Diabetes and high blood pressure are the two most common causes of the ***chronic kidney insufficiency*** and account for most cases. Many other diseases and conditions can damage the kidneys, including:

> Problems with the arteries leading to or inside the kidneys
> Birth defects of the kidneys (such as polycystic kidney disease)
> Some medications

> Certain toxic chemicals
> Autoimmune disorders (such as systemic lupus erythematosus and scleroderma)
> Injury or trauma
> Glomerulonephritis
> Kidney stones and infection
> Reflux nephropathy (in which the kidneys are damaged by the backward flow of urine into the kidneys)

The final stage of chronic kidney disease is called end-stage renal disease (ESRD). The kidneys no longer function and the patient needs dialysis or a kidney transplant.

Bladder or kidney stones form from the salts of calcium oxalate and uric acid. These stones form by precipitation around some sort of nucleus composed of bacteria, blood clumps, or similar foreign substances. The diet has also been known to cause these bladder or kidney stones. These stones can form in or near the kidney or the ureter and are not necessarily formed just in the bladder. As they pass down the ureter, oftentimes there is severe pain accompanying this passage of stones. In some cases, these bladder or kidney stones are too large to pass through the ureter and have to be surgically removed. In most cases, the stones pass through on their own without surgery. If your doctor suspects you have a bladder or kidney stone, you may be asked to fast for several days and severely limit your intake of water.

MALE REPRODUCTIVE SYSTEM

E3 Overview of the male reproductive system

The human male reproductive system consists of a number of sex organs that are a part of the human reproductive process.

The ***male reproductive system*** is composed of:

> testes,
> genital excurrent ducts,
> accessory glands (prostate gland, seminal vesicles, bulbo-urethral glands),
> copulatory organ (penis).

Functions of the male reproductive system

> reproductive (production of the male gametes- spermatozoa),
> endocrine (production of the ***androgen*** (male sex hormone) - ***testosterone).***

0 Testis

The ***testis*** is surrounded by a thick connective tissue capsule called tunica albuginea. On the posterior surface of the testis the tunica albuginea forms the mediastinum (fig.29.1).

Connective tissue septa penetrate the giand and divide it into 250 pyramidal lobules. Each lobule is occupied by 1- 4 ***convoluted seminiferous tubules***, which form a network. These are sperm producing tubules.

Convoluted seminiferous tubules The ***convoluted seminiferous tubules*** (fig.29.2) consist of: ***y*** fibrous ***tunica propria*** and

> complex stratified ***seminiferous,*** germinal, or spermatogenic, ***epithelium.***

Tunica propria consists of several layers.

1) . ***Basal layer*** consists of thin collagen fibers and is located between the basal membranes of germinal epithelium and myoid cells.

2) . ***Myoid layer*** consists of spindle-shaped myofibroblastes (myoid ceiis) which exhibit smooth muscle characteristic; the contractile activity of these cells aids movement of spermatozoa along the tubules.
2). ***External Jibrous*** layer consists of collagen fiber and fibroblasts.

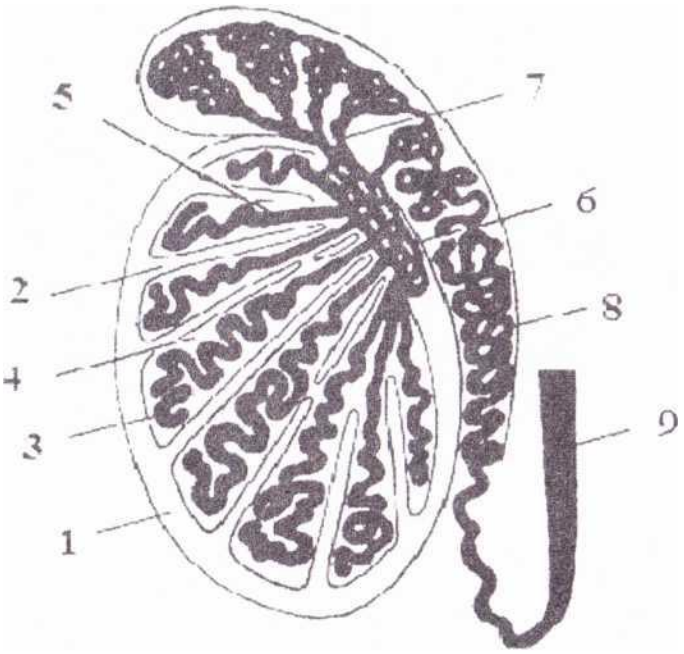


Figure 29.1. Schematic diagram of a testis. 1 - tunica albuginea, 2 - septum. 3 - seminiferous tubules. 4 - interstitium, 5 - straight tubules, 6 - rete testis, 7 - efferent ductules, 8 - duct of epididymis, 9 - ductus deferens

Seminiferous epithelium

Seminiferous epithelium consists of 2 basic cell populations:
1) ***spermatogenic cells*** in different stages of their development and
2) ***Sertoli (supporting) cells.***

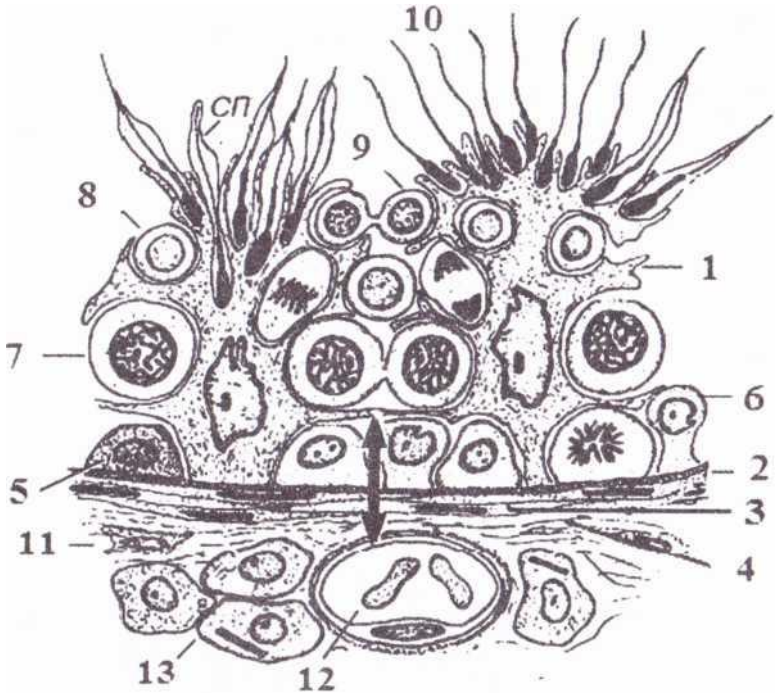


Figure 29.2. Seminiferous tubule wall. 1 - Sertoli cell, 2 - basal layer, 3 - mvoid cells. 4 - external fibrous layer, 5 - type A spermatogonium, 6 - type B spermatogonium, 7 - primary spermatocyte, 8 - secondary spermatocyte, 9 - spermatids, 10 - spermatozoa, 11 - interstitium, 12 - blood capillary, 13 - Leydig cells, 14 - tight junctions between Sertoli cells, arrow shows blood testis barrier

Spermatogenic cells

Spermatogenie cells (fig.29.3) are arranged in concentric layers (5 or 6) and differentiate progressively from the periphery to the lumen of the tubule:
> ***spermatogonia*** (types A and B) are the undifferentiated germ cells, are located at the periphery of the tubule;
spermatogonia type A are stem cells for spermatogenic lineage that are classed as type A dark (Ad) or A pale (Ap); type Ad are true stem cells;

spermatogonia type B are progenitor ceil for primary spermatocyte;

> ***primary spermatocytes*** (46 chromosomes, 4N DNA) are found in the middle of the seminiferous tubule; primary spermatocyte results from the growth and differentiation of one type B spermatogonium;

> ***secondary spermatocytes*** (23 chromosomes, 2N DNA) arise from the division of primary spermatocytes; they are located near the lumen of the seminiferous tubule;

> ***spermatids*** (23 chromosomes, IN DNA) are small cells with condensed chromatin;

> ***spermatozoa.***

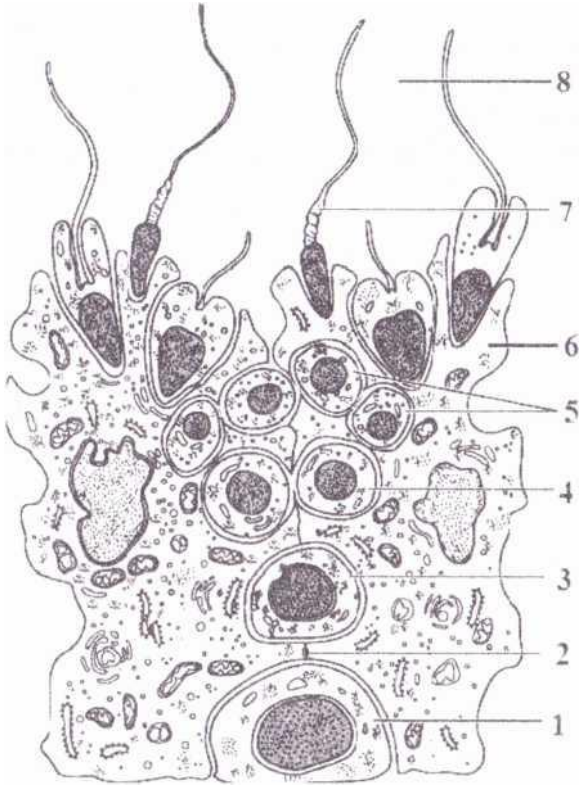


Figure 29.3. Seminiferous epithelium. 1 - spermatogonium, 2 - tight junction, 3 — primary spermatocyte, 4 — secondary spermatocyte, 5 - spermatid, 6 - Sertoli cell, 7 — spermatozoon, 8 — lumen of seminiferous tubule

Sertoli (supporting) cells

Sertoli (supporting) cells (fig.29.3) are tall pyramidal cells. The bases of the Sertoli cells rest on the basal lamina, apical ends extend into the lumen of the seminiferous tubule.

Functions of Sertoli celts.

1) support, protection, and nutrition of the developing spermatozoa;
2) phagocytosis of cytoplasmic fragments, which form during spermatogenes is;
3) secretion of:

> into the seminiferous tubules a ***fluid*** that Hows in the direction of the genital ducts and is used for sperm transport;

> ***androgen binding protein*** that serves to concentrate testosterone in the seminiferous tubule; it is necessary for spermatogenesis;

> ***sexual steroids*** - estrogens and testosterone;

> peptides ***inhibin*** and ***activin,*** which suppress and activate FSH synthesis and release in the anterior pituitary gland:

> ***Antimullerian hormone*** that promotes the normal development of the male reproductive system.

Sertoli cells are bound together by tight junctions between their lateral processes at the level of spermatogonia.

Lateral processes of Sertoli cells divide the seminiferous epithelium into 2 compartments:

> ***basal (abluminal)*** compartment and

> ***adluminal*** compartment.

The ***basal compartment*** contains spermatogonia and has free access to materials found in the blood.

The ***adluminal compartment*** contains spermatocytes, spermatids and spermatozoa.

B Blood-testis barrier

The ***blood-testis barrier*** (fig.29.2) is a barrier between the blood vessels and the seminiferous tubules. The barrier prevents passage of cytotoxic agents (substances that are toxic to cells) into the seminiferous tubules. This barrier protects also the developing sperm cells from immunologic attack and consists of:

> endothelial cells of blood capillary of interstitial connective tissue;
> basal lamina of endothelial cells;
> interstitial connective tissue;
> tunica propria of seminiferous tubule;
> tight junctions between lateral processes of Sertoli cells.

0 Endocrine function of the testis

The spaces between the seminiferous tubules are filled with interstitial connective tissue, nerves, blood and lymphatic vessels. The principal cells of interstitial tissue are the ***interstitial,*** or ***Leydig, cells,*** which have the characteristic of steroid-secreting ceils (fig.29.2).

Leydig cells are rounded in shape, have a central located nuclei and an eosinophilic cytoplasm. These cells produce the male steroid hormone ***testosterone,*** which is responsible for the development of male reproductive tissues such as the testis and prostate as well as promoting secondary sexual characteristics such as increased muscle and bone mass and hair growth.

0 Spermatogenesis

Spermatogenesis is the process of differentiation of the male germ cells. The mature male functional sperm cells are produced within the seminiferous tubules of the testes.

Spermatogenesis can be divided into 3 phases (fig.29.4):

I, ***Spermatogonia! phase (mitosis)*** begins with the spermatogonia, situated in the basal compartment of seminiferous epithelium. These cells undergo serious mitoses, and newly formed cells can follow' one or two paths:
they can continue, after one or more mitotic divisions, as stem cells, or type A spermatogonia or
they can differentiate during progressive mitotic cycles to become type B spermatogonia.

Type A spermatogonia are the stem cells, type B spermatogonia are the progenitor cells that differentiate into primary spermatocytes (46 chromosomes, 4N DNA).

Incomplete cytokinesis of cells results in the cells being linked by cytoplasmic bridges until spermatozoa. This linkage results in a synchronous development of the cells within a given region of the tubule.

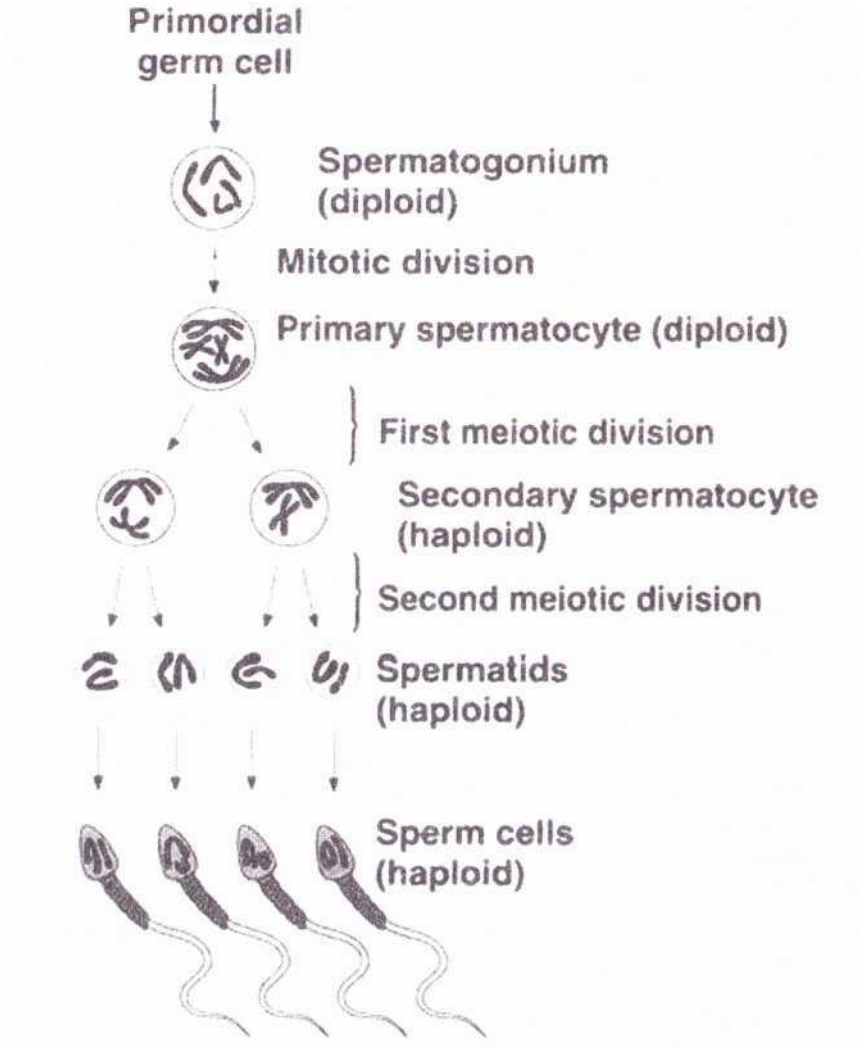


Figure 29.4. Schematic diagram illustrating spermatogenesis.

II. ***Spermatocyte phase (meiosis),*** during which primary spermatocytes undergo two successive divisions, to reduce both half of chromosome number and the amount of DNA, producing spermatids.

Meiotic division (I) of a primary spermatocyte gives rise to a pair of secondary spermatocytes (23 chromosomes, 2N DNA); meiotic division (II) of a secondary spermatocyte gives rise to a pair of spermatids (23 chromosomes, IN DNA).

Because there is no S phase (DNA synthesis) between the first and second meiotic divisions of the spermatocytes, the amount of DNA per cell is reduced by half in this second division, forming haploid (IN) cells.

This process occurs in the adluminal compartment of seminiferous epithelium.

III. ***Spermatid phase (spermiogenesis),*** during which the spermatids go through process of cytodifferentiation, producing spermatozoa.

Spermatids undergo spermiogenesis, a complex of differentiation that includes (fig.29.5):

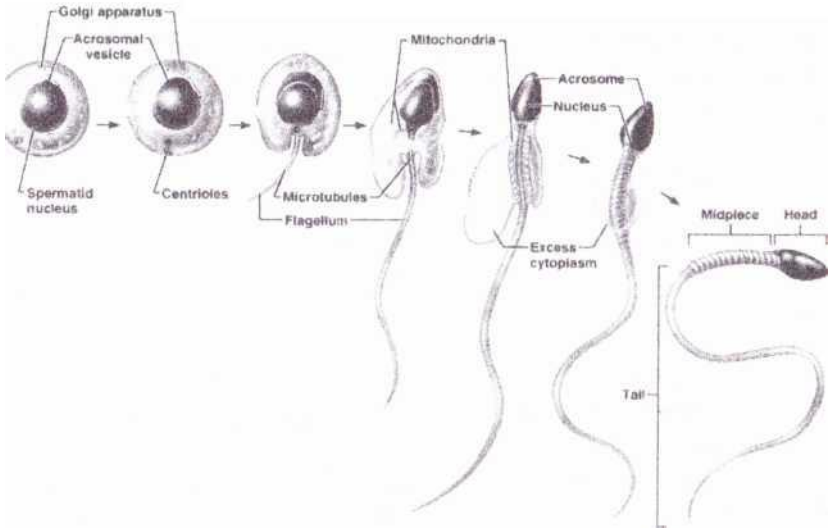


Figure 29.5. Schematic diagram illustrating spermiogeDesis.

> formation of the acrosome,
> condensation and elongation of the nucleus,
> formation of the flagellum,
> loss of much of the cytoplasm.

The end result is the mature spermatozoa, which are then released into the lumen of the seminiferous tubule. Complete cycle (gonia to zoa) takes 60 to 70 days.

Influencing factors

The process of spermatogenesis is highly sensitive to fluctuations in the environment, particularly ***hormones*** and ***temperature.*** Testosterone is required in large local concentrations to maintain the process, which is achieved via the binding of testosterone by androgen binding protein present in the seminiferous tubules. Testosterone is produced by interstitial cells (Leydig cells).

Seminiferous epithelium is sensitive to elevated temperature, and will be adversely affected by temperatures as high as normal body temperature. Consequently, the testes are located outside the body in a sack of skin called the scrotum. ***Dietary deficiencies*** (such as vitamins B, E and A), ***anabolic steroids***, ***metals*** (cadmium and lead). ***X-ray*** exposure, ***dioxin***. ***alcohol,*** and ***infectious diseases*** will also adversely affect the rate of spermatogenesis.

0 Male genital ducts

The ***male genital ducts*** are subdivided into:
> intratesticular and
> excurrent ducts.

Intratesticular ducts

Intratesticular ducts are the tubuli recti, the rete testis, and the efferent ductules.

At the termination of each convoluted seminiferous tubule, the lumen narrows and continues in short segments, called tubuli recti (straight tubules). Tubuli recti connect the convoluted tubules to a labyrinth of the mediastinum, the rete testis. The rete is connected to the

portion of the epididymis by ductuli efferentes. The ductuli efferentes fuse to form the ductus epididymis.

Tubuli recti are lined with Sertoli cells in an initial part, in the distal part - simple cuboidal epithelium.

Rete testis is a highly anastomotic network of channels lined with simple cuboidal epithelium.

From the rete testis 10-20 efferent ductules extend that form the head of the epididymis.

Efferent ductules consist of (fig.29.6, 29.7):

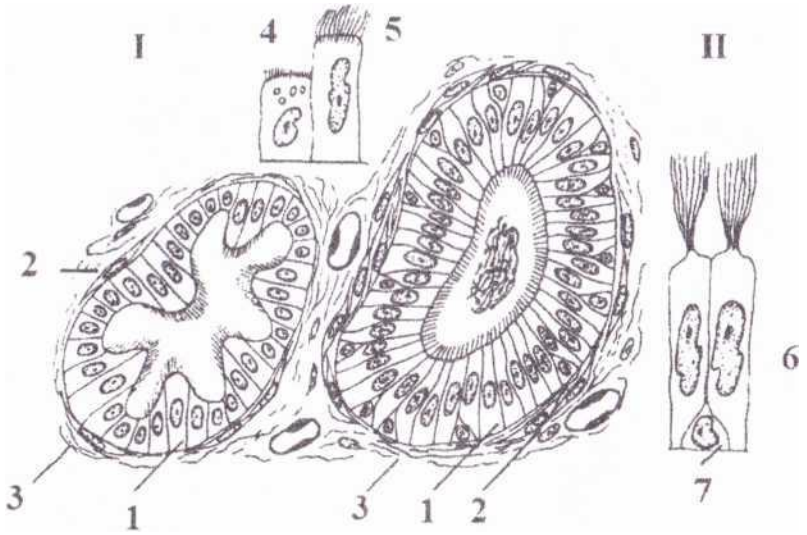


Figure 29.6. Schematic diagram of efferent ductule of epididymis (I) and duct of epididymis (II). 1 - mucosa, 2 - muscularis, 3 - adventitia, 4 - nonciliated cuboidal cell, 5 - columnar ciliated cell, 6 — principal cell, 7 - basal cell (from *Bukos B.JI.*, 1999)

I. ***mucosa*** which contains:

1) pseudostratified columnar ***epithelium*** composed of:

> columnar ciliated cells that promote the transport of spermatozoa toward the ductus epididymis;

> nonciliated cuboidal cells that absorb much of the fluid secreted by the seminiferous tubules;

2) ***lamina propria*** is composed of loose connective tissue;

II. ***muscularis*** is composed of circularly oriented smooth muscle cells;

III. ***adventitia*** consists of loose connective tissue.

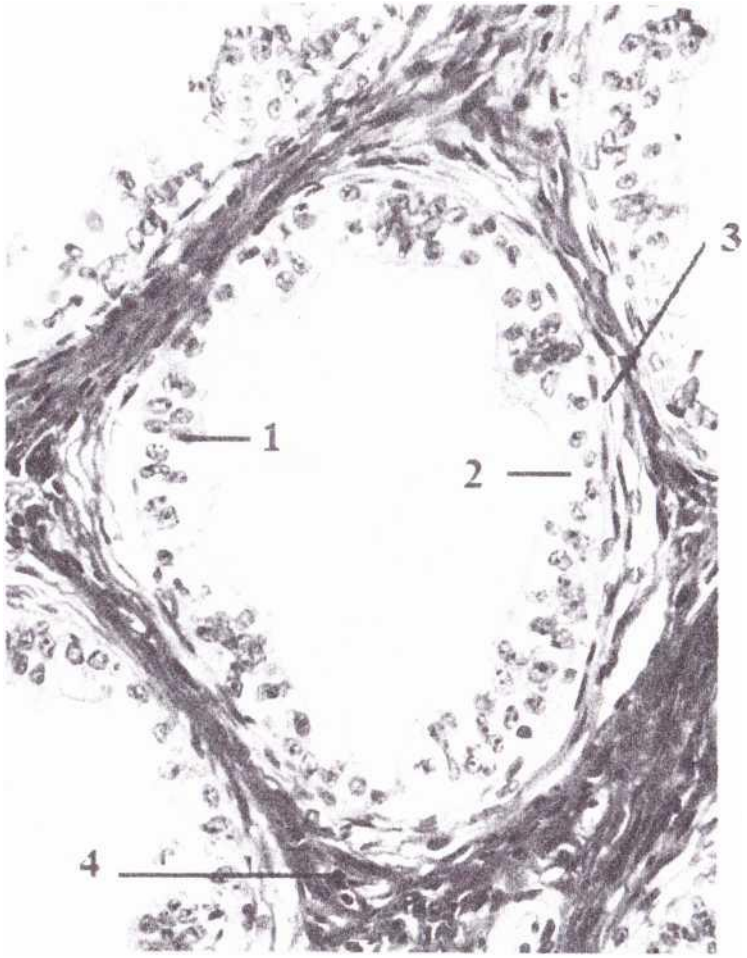


Figure 29.7. Photomicrograph of efferent ductule of epididymis. 1 - pseudostratified columnar epithelium, 2 — lamina propria

Excurrent ducts

Excurrent ducts are the duct of epididymis, which forms the epididymis, the ductus (vas) deferens and the ejaculatory duct.

Duct of epididymis consists of (fig.29.6, 29.8):

I. ***Mucosa*** which contains:

1) pseudostratified columnar ***epithelium*** that composed of:

> tall columnar (principal) cells with long microvilli (stereocilia); ***y*** basal cells that are the stem cells;

2) ***lamina propria*** is composed of loose connective tissue;

II. ***Muscularis*** is composed of smooth muscle cells whose peristaltic contractions help to move the sperm along the duct;

III. ***Adventitia*** consists of loose connective tissue.

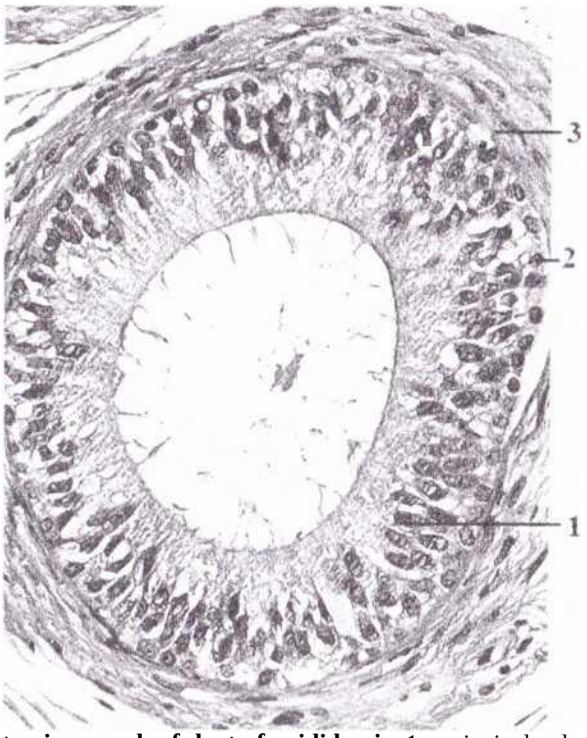


Figure 29.8. Photomicrograph of duct of epididymis. 1 - principal columnar cells, 2 - basal cells, 3 - smooth muscle cells

Ductus (vas) deferens is the continuation of the ductus epididymis; it empties into the prostatic urethra. The ductus deferens has a thick wall but a small lumen. The wall of the ductus deferens consists of 3 layers (fxg.29.9):

I. ***Mucosa*** forms longitudinal folds and comprises:

1) pseudostratified columnar ***epithelium*** that composed of:

> columnar cells with stereocilia;

> basal cells that are the stem cells;

2) ***lamina propria*** is composed of loose connective tissue rich in elastic fibers;

II. ***Muscularis*** consists of longitudinal inner and outer layers separated by a circular layer;

III. ***Adventitia*** consists of loose connective tissue.

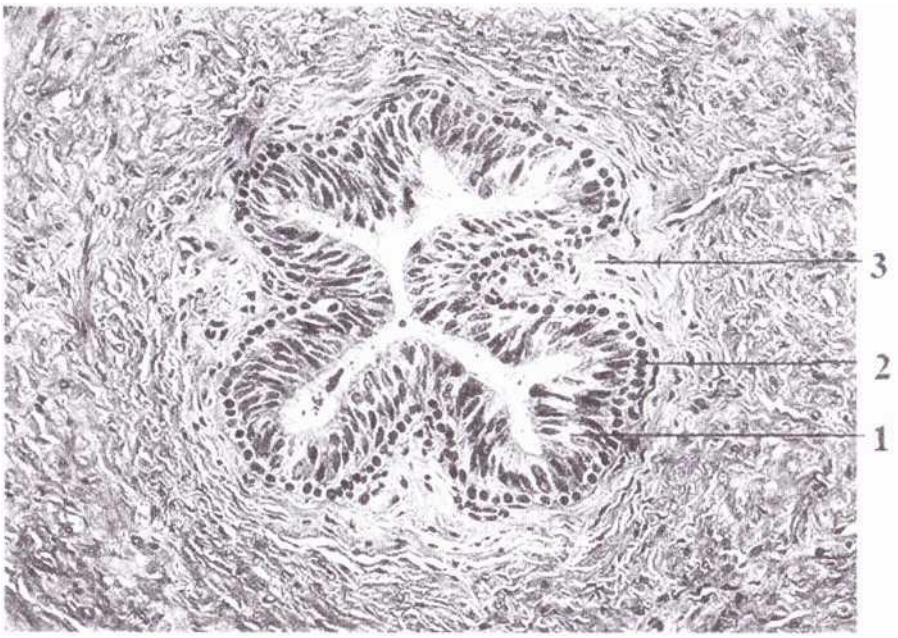


Figure 29.9. **Photomicrograph of ductus deferens.** 1 - pseudostratified columnar epithelium. 2 — basal cells, 3 — lamina propria

Ejaculatory duct connects the ductus deferens to prostatic urethra.

I. ***Mucosa*** has many folds and is lined by

1) pseudostratified columnar ***epithelium***, containing tall secretory cells;

2) ***lamina propria*** is composed of loose connective tissue with elastic fibers.

II. ***Muscularis*** is absent; the fibromuscular tissue of the prostate substitutes it.

The ejaculatory duct is supported by fibrous tissue of the prostate.

13 Accessory' genital glands

The ***accessory genital glands*** are

> prostate gland,
> seminal vesicles,
> bulbourethral glands.

Prostate gland

The ***prostate gland*** is the largest accessory sex gland which surrounds the bladder neck and the first part of the urethra.

The prostate gland is covered by connective tissue capsule rich in smooth muscle cells. From capsule incomplete septa extend and divide the gland into 50 or so lobules. The fibromuscular stroma surrounds the glands.

The gland is composed of about 30 to 50 compound tubulo- alveolar prostatic glands which are divided on 3 groups (fig.29.10):

> ***mucosal*** (central zone),
> ***submucosal*** (transitional zone),
> ***main*** (peripheral zone).

The ***prostatic glands*** (llg.29.11) consist of:

1. secretory portions,
2. duct system.

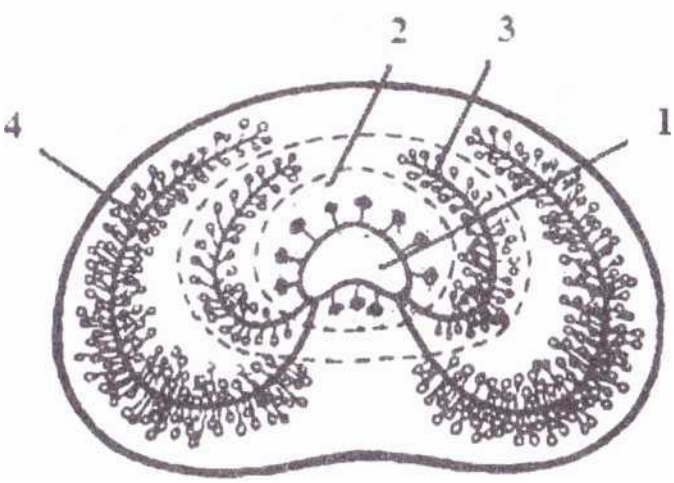


Figure 29.10. Schematic diagram of prostatic glands. 1 - urethra, 2 - mucosal (central zone), 3 - submucosal (transitional zone), 4 - main (peripheral zone)

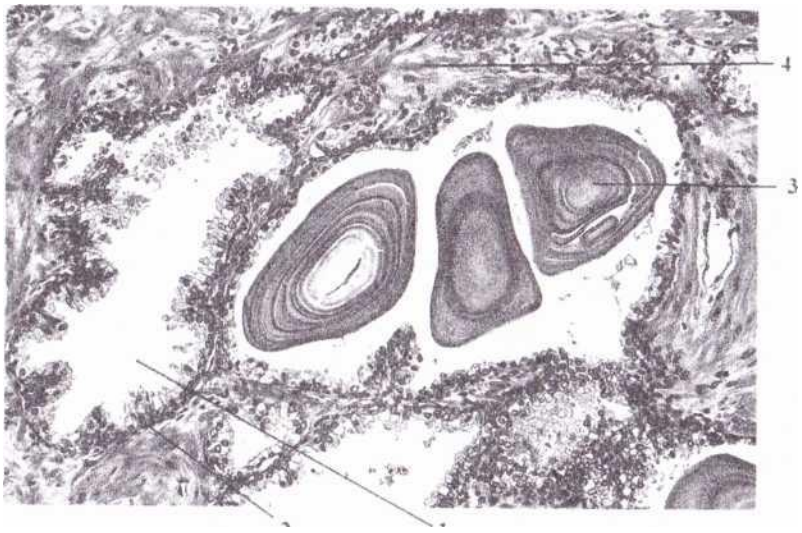


Figure 29.11. Photomicrograph of a prostate gland. 1 - mucosal glands, 2 - prostatic epithelium. 3 - prostatic concretions, 4 - fibromuscular stroma

The secretory portions of prostatic gland are lined by a pseudostratified columnar epithelium which consists of 3 types of cells:

> ***columnar*** with basally located nuclei;

> ***basal*** which are located along the basement membrane;

> ***endocrine*** which secrete serotonin, somatostatin, and other peptides influencing on secretory activity of epithelium and contractility of smooth muscle cells of stroma.

Small spherical bodies of glycoproteins composition are frequently observed in the lumen of prostatic glands. These bodies

are often calcified. They are called ***prostatic concretions.*** Their significance is not understood. Their number increases with age.

The secretion of the prostate is fluid with a slight acidic reaction and is rich in an enzyme called acid phosphatase. The secretion nourishes the spermatozoa.

The ducts of the glands of mucosal layer secrete directly into urethra; the other two layers have ducts that open into the prostatic sinuses located on the utethral crest.

Seminal vesicles

The ***seminal vesicles*** (fig.29.12) are paired sacculated glands consisting of:

I. ***mucosa*** which has many branched folds and comprises:

1) pseudostratified columnar ***epithelium***;

2) ***lamina propria*** which is composed of loose connective tissue with elastic fibers;

II. ***muscularis*** which consists of outer longitudinal and inner circular layer of smooth muscle tissue.

III. ***adventitia*** merges with the surrounding connective tissue.

The viscid secretion of the seminal vesicles contains spermatozoa-activating substances such as fructose, citrate, prostaglandins, and several proteins.

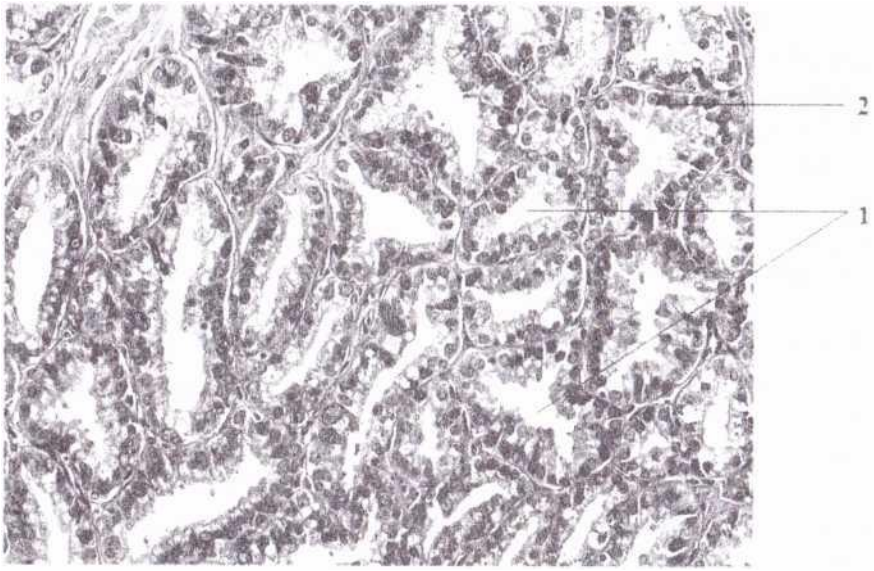


Figure 29.12. Photomicrograph of human seminal vesicle. 1 - lumens of glands, 2 - pseudostratified columnar epithelium of the glands

Bulbourethral glands (Cowper's glands)

The ***bulbourethral glands*** are located proximal to the membranous portion of the urethra and empty into it. They are compound tubulo-alveolar glands lined with mucus-secreting simple euboidal epithelium. Skeletal and smooth muscle cells are present in the septa that divide each gland into lobes. The secretion is clear mucus, contains galactose, galactosamine, galacturonic acid, sialic acid and acts as a lubricant.

0 Penis

The ***penis*** is the male copulatory organ. When the male becomes sexually aroused, the penis becomes erect and ready for sexual activity.

The ***erectile tissue*** of the penis contains a specialized arrangement of arteries, shunts, and venous sinusoids within a matrix of connective tissue and smooth muscle. The erectile tissue is organized

into paired dorsal corpora cavernosa and one ventral ***corpus spongiosum.*** The corpora cavernosa are surrounded by tough fibrous connective tissue, the tunica albuginea. Between this sheath and the overlying skin is a layer of very loose elastic connective tissue (Buck's fascia) that permits the skin of the penis to move freely along the shaft. The skin includes a smooth muscle layer (the dartos). The penile urethra passes through the corpus spongiosum, where it is associated with small mucous ***glands of Littre.***

0 Development of the reproductive systems

The genetic sex of a child is determined at fertilization by presence or absence of the Y chromosome.

The reproductive organs are developed from the ***intermediate mesoderm.*** The permanent organs of the adult are preceded by the structures which disappear before the end of fetal life. These embryonic structures are two primitive ducts that adjacent to each developing gonad and can give rise to either the male or the female reproductive tracts. The ***Wolffian (mesonephric) ducts*** are more medial. The ***Mullerian (paramesonephric) ducts*** are more lateral, but then fuse in the midline more caudally (fig.29.13). The Wolffian duct remains as the duct in males, and the Mullerian as that of the female.

During embryonic development there is a ***sexually indifferent stage*** in which the embryo has the potential to develop either male or female structures.

Sexual differentiation begins with ***sexual determination***, which depends upon the sex chromosomes, X and Y. Sexual determination involves the specification of the gonads as either testes or ovaries. If the

embryo is XY, the presence of the ***SRY gene*** (sex-determining region of the **Y** chromosome) will direct the gonads to develop as testes. In the absence of a Y chromosome and SRY gene, the gonads develop as ovaries.

Once the gonad begins to develop as a testis, the two types of cells in the testis differentiate and begin to generate important regulatory molecules that direct sexual differentiation. The ***Leydig cells*** produce

testosterone, which promotes development of the Wolffian ducts. The Wolffian ducts then differentiate to form the epididymis, vas deferens, seminal vesicles, and ejaculatory' ducts. The ***Sertoli cells*** produce ***Mullerian inhibiting substance (MIS),*** a peptide hormone which causes the Mullerian ducts to regress.

Female development proceeds when there is an absence of the SRY gene. No testosterone or MIS is made. The Wolffian ducts regress, and the Mullerian ducts persist, developing into the fallopian tubes, the uterus and the upper part of the vagina.

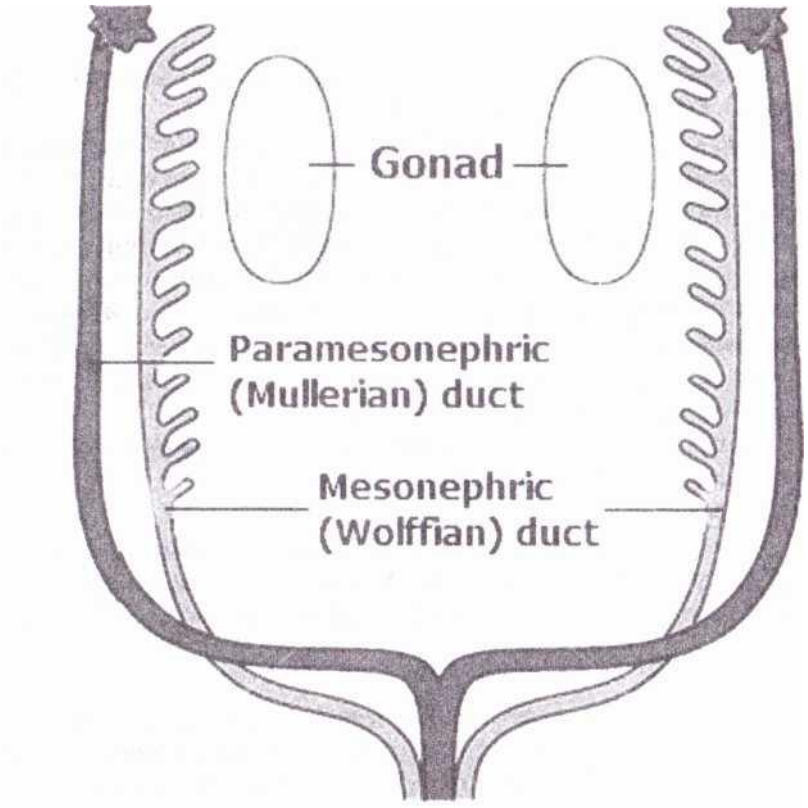


Figure 29.13. Schematic diagram of the sexually indifferent stage.

The gonads develop in close association with the urinary system. The testes (like ovaries) are derived from three sources:

> ***intermediate mesoderm*** forms longitudinal elevation along dorsal body wall ***- urogenital ridge;***

> mesodermal epithelium that lines the urogenital ridges form ***gonadal ridge,***

> formation of ***primary sex cords*** from gonadal ridge, migration of primordial germ cell from the yolk sac; later sex cords differentiate into gonads.

o Clinical correlations

In men over 50 enlargement of the prostate ***(benign prostatic hypertrophy)*** is common. Sometimes the result is pressure on the urethra and bladder, which interferes with urination, precipitating urinary retention and kidney disease.

Prostate cancer is the leading malignancy in men and is second only to lung cancer as a cause of cancer death in men. It occurs predominantly in older men. Many factors, including genetics and diet, have been implicated in the development of prostate cancer. ***Prostate-specific antigen (PSA)*** is a protein produced by the cells of the prostate gland. PSA is present in small quantities in the serum of men with healthy prostates, but is often elevated in the presence of prostate cancer. A blood test to measure PSA is considered the most effective test currently available for the early detection of prostate cancer.

FEMALE REPRODUCTIVE SYSTEM

o Overview of the female reproductive system

The ***female reproductive system*** is composed of:
> internal organs (ovaries, uterine tubes, uterus, and vagina) (fig.30.1),
> externa! genitalia (mons pubis, labia majora and minora, clitoris, vestibule and opening of the vagina, and external urethral orifis).

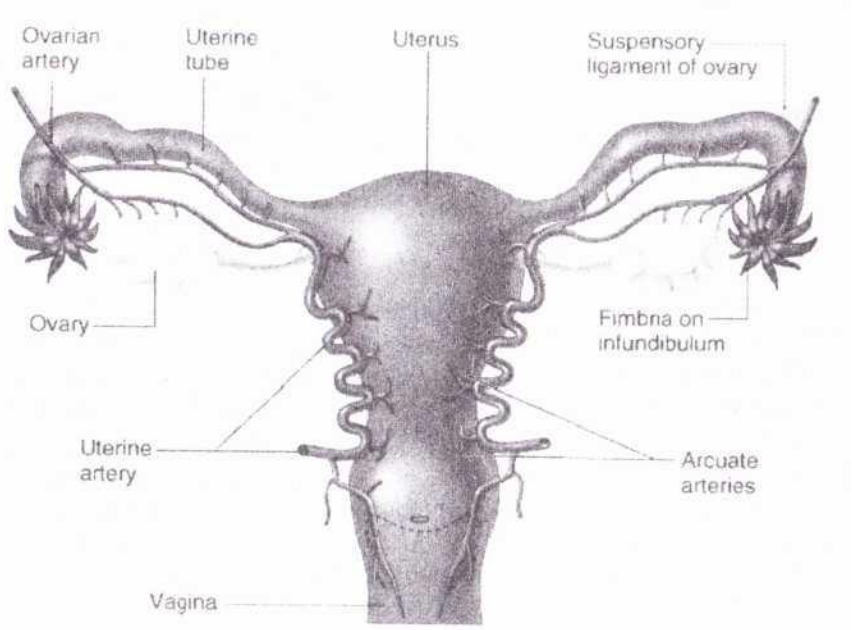


Figure 30.1. Schematic diagram of female sex organs.

Functions of the female reproductive system
> reproductive (production of gametes - ova);

> endocrine (production and secretion of female sex hormones: estrogens and progesterone).

0 Ovary

1 he surface of the ***ovary*** is covered by a single layer of cuboidal epithelium (germinal epithelium). Connective tissue forms a thin capsule called tunica albuginea.

Ovary is divided into an outer cortex and an inner medulla (fig.30.2).

The medulla is composed of loose connective tissue, which contains blood vessels and nerves.

The cortex consists of connective tissue stroma in which the ***ovarian follicles*** are embedded.

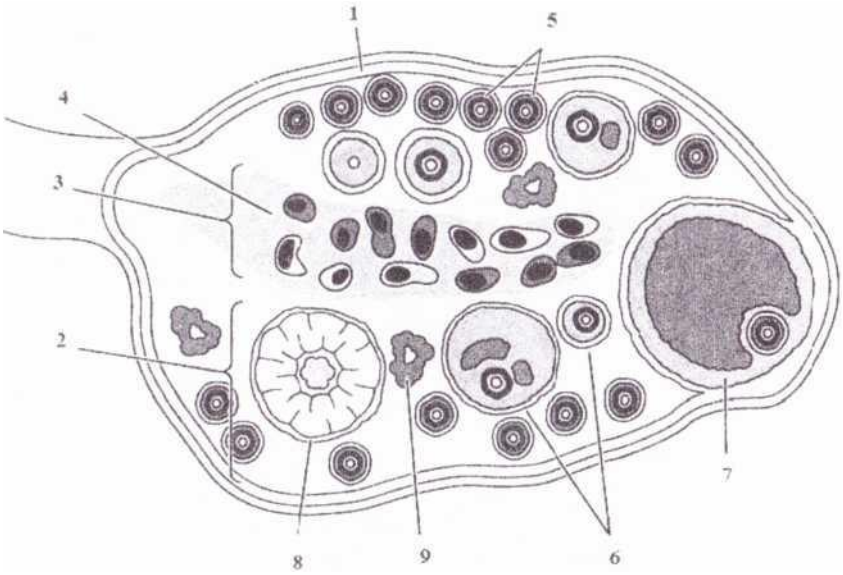


Figure 30.2. Schematic diagram of the ovary. 1 - tunica albuginea, 2 - cortex, 3 - medulla, 4 - blood vessels, 5 - primordial follicles, 6 - growing follicles, 7 — preovulatory follicle. 8 — corpus luteum, 9 - corpus albicans

Ovarian follicles

The ***ovarian follicles*** consist of one oocyte surrounding by follicular cells.

Types of ovarian follicles:

> primordial follicles;
> growing follicles:
  » primary,
  • secondary;
> mature (tertiary, preovulatory, Graafian) follicles.

The ***primordial follicles*** (fig.30.3) are found in the peripheral part of cortex.

Primordial follicle consists of the oocyte in prophase of the first meiotic division surrounding by a single layer of squamous follicle cells. The outer surface of the follicle cells is bounded by a basal lamina.

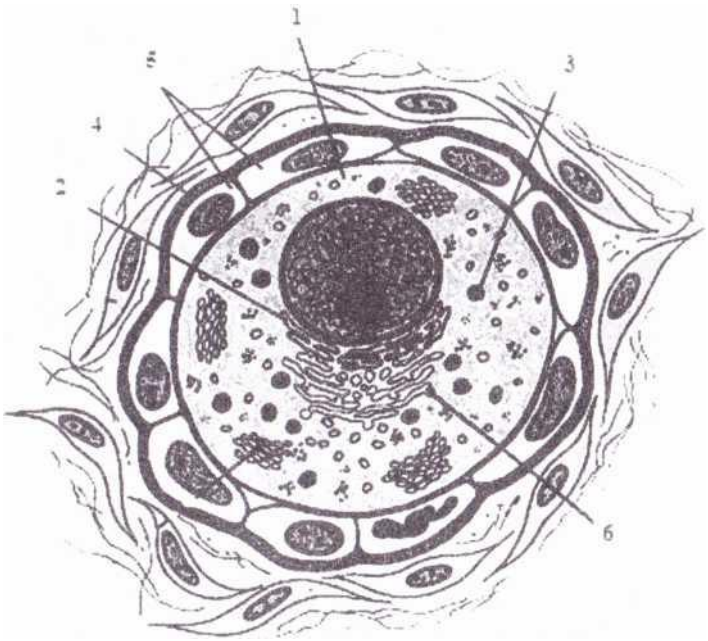


Figure 30.3. Primordial follicle. 1 - oocyte, 2 - rER, 3 -• mitochondrion, 4 - basal lamina, 5 - follicle cells, 6 - Golgi complex (from ***Ross M.H.,*** 2003)

The ***primary follicle*** consists of the oocyte surrounding by a single layer of cuboidal or columnar follicular (granulosa) cells (fig.30.4). A homogeneous, deeply staining, acidophilic refractive layer called ***zona pellucida*** (glycoproteins between the oocyte and granulosa cells) becomes visible. Zona pellucida is secreted by growing oocyte and follicular cells.

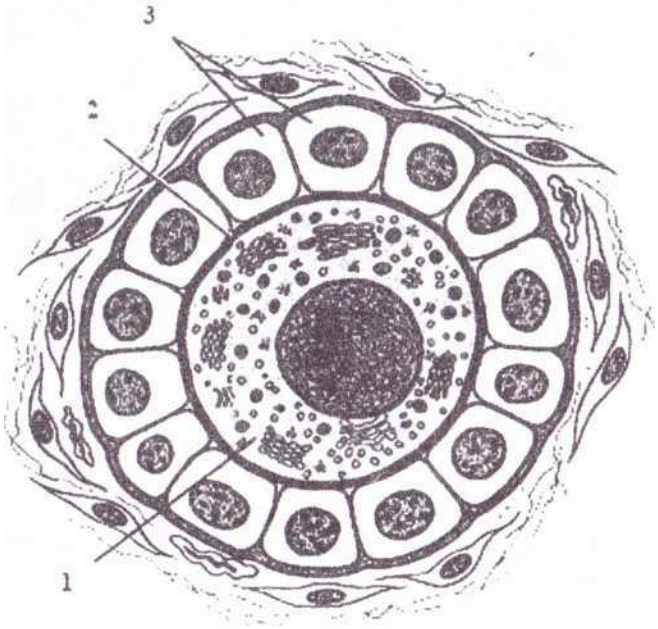


Figure 30.4. Primary follicle. 1 — oocyte, 2 - forming zona pellucida, 3 - follicle cells (from ***Ross M.H***., 2003)

Late primary follicles

The continued proliferation of granulosa cells will result in the formation of the stratified epithelium surrounding the oocyte (fig.30.5). Connective tissue cells surrounding the follicle form concentric sheaths, the ***thecafolliculi.***

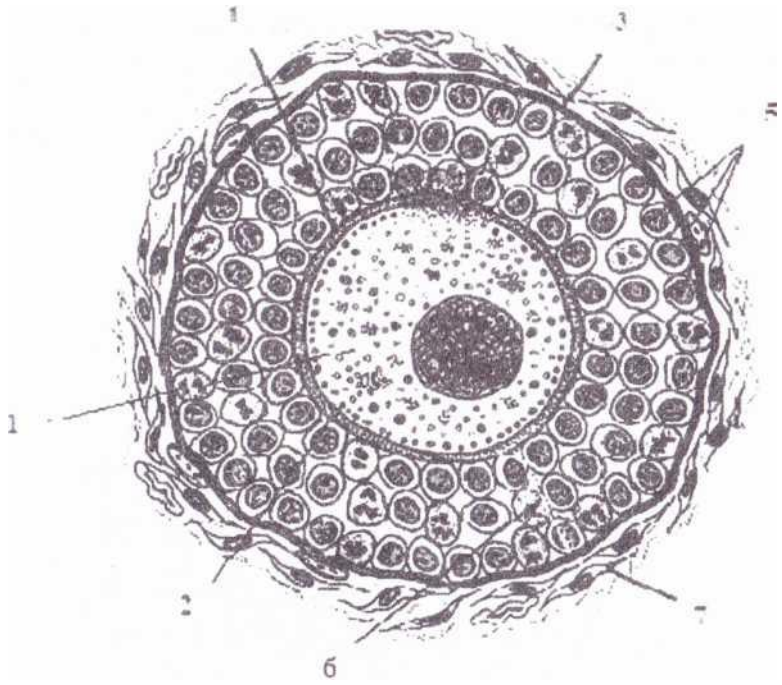


Figure 30.5. Late primary follicle. 1 - oocyte, 2 - cortical granules, 3 - basal lamina, 4 - zona pellucida, 5 - granulosa cells, 6 - stratum granulosum, 7 - theca folliculi (from ***Ross M.H.,*** 2003)

Secondary follicles

Small fluid-filled spaces become visible between the granulosa cells (fig.30.6). These spaces enlarge and fuse to form the follicular antrum. The oocyte is now located eccentric in the follicle, and is surrounded by granulosa cells.

Theca folliculi further differentiates into two layers.

> Theca interna is layer of steroid-producing secretory cells. These cells have luteinizing hormone (LH) receptors. In response to LH stimulation, they secrete androgens that are the precursors of estrogens.

> Theca externa is the outer layer of connective tissue.

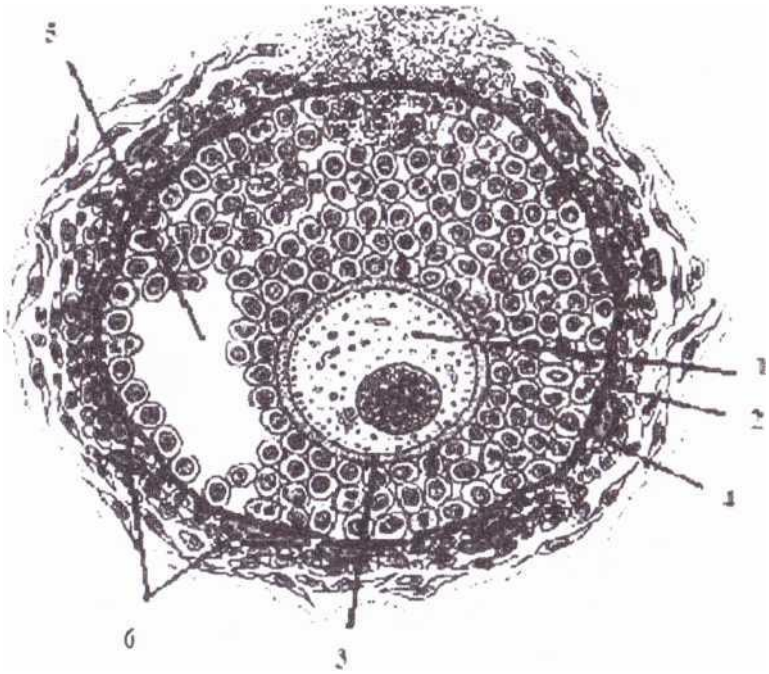


Figure 30.6. Secondary follicle. 1 - oocyte, 2 - basal lamina, 3 - zona pellucida, 4 - granulosa cells, 5 - antrum, 6 - blood vessels (from ***Ross M.H***., 2003)

Mature (tertiary, preovulatory, Graafian) follicle (fig.30.7) increases further in size (is about 2,5 cm in diameter) and bulges from the surface of the ovary. Oocyte adheres to cumulus oophorus.

0 Ovulation

Ovulation is a hormone-mediated (LH of the pituitary gland) process of liberation of the secondary oocyte by the rupture of Graafian follicle into the peritoneal cavity.

Ovulation takes place in the middle of the menstrual cycle, on the 14th day of a 28-day cycle.

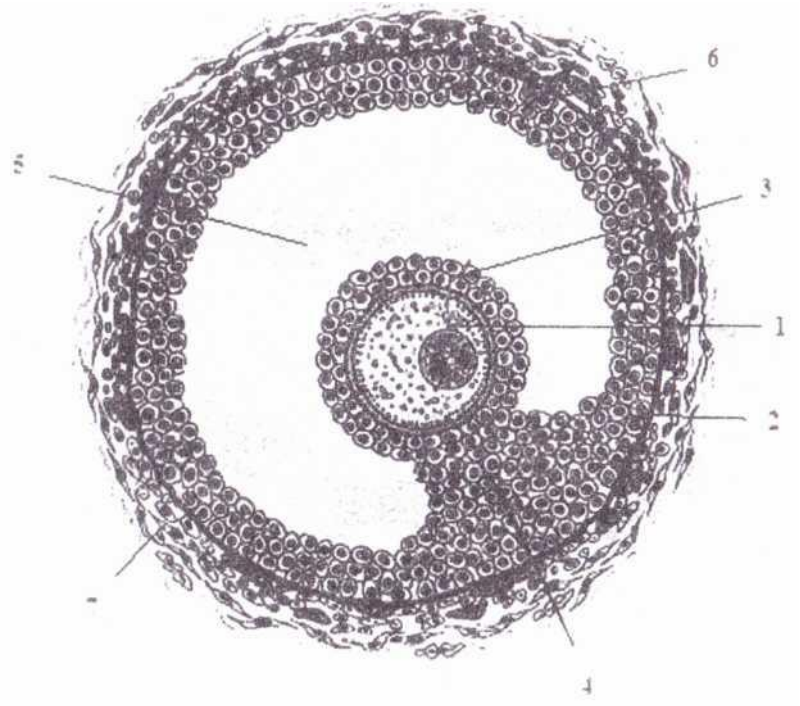


Figure 30.7. Mature follicle. 1 - oocyte, 2 - basal lamina, 3 - cells that will become corona radiata after ovulation, 4 - cumulus oophorus, 5 - antrum filled with follicular fluid, 6 - granulosa cells, 7 - theca tblliculi (from ***Ross M.H***.,

53 Corpus luteum

After ovulation, the follicular wall, composed of the granulosa and theca cells, is transformed into the temporary endocrine gland called ***corpus luteum {luteal gland).***

Development of the corpus luteum

Development of the corpus luteum includes 4 stages:

I. The cells of the granulosa and theca interna proliferate; blood vessels from theca interna rapidly grow into the granulosa layer.

U. The cells of the granulosa and theca interna (luteal cells) increase in size and become filled with yellow pigment lutein, and demonstrate features associated with steroid-secreting cells (abundant sER and mitochondria).

III. Cells of corpus luteum secrete female sexual hormones:

1) granulosa lutein cells, derived from the granulosa cells, secrete ***progesterone***;

2) theca lutein cells, derived from the cells of theca interna layer, secrete ***androgens*** and ***estrogens.***

These hormones stimulate the growth and secretory activity of the endometrium, to prepare it to the implantation of the zygote.

IV. Degeneration and involution of the corpus luteum after pregnancy or menstruation.

White scar, the ***corpus albicans***, is formed. It slowly disappears over a period of several months.

Types of the corpus luteum

1) . If the oocyte is not fertilized, the corpus luteum stops secreting progesterone and remains only for 14 days; in this case it is called the ***menstrual corpus luteum.***

2) . If the oocyte is fertilized and implantation occurs, the trophoblast cells of the blastocyst secrete the hormone human chorionic gonadotrophin (hCG). Human chorionic gonadotrophin signals the corpus luteum to continue progesterone secretion, thereby maintaining the endometrium of the uterus and providing an area rich in blood vessels in which the zygote(s) can develop. In this case the corpus luteum is called the ***corpus luteum graviditatis.*** Corpus luteum graviditatis measures 5 cm. Its function begins to decline after 8 weeks of pregnancy, although it persists throughout pregnancy.

0 Ovarian follicular atresia

Most ovarian follicles are lost by atresia mediated by apoptosis of granulosa cells on any stage of maturation. The cells of the theca interna proliferate to form the interstitial glands, also called the ***corpora atretica.*** These glands secrete estrogens.

0 Ovarian cycle

During each menstrual cycle, the ovary undergoes cyclic changes that involve two phases (fig.30.8):

> ***follicular*** phase

> ***luteal*** phase

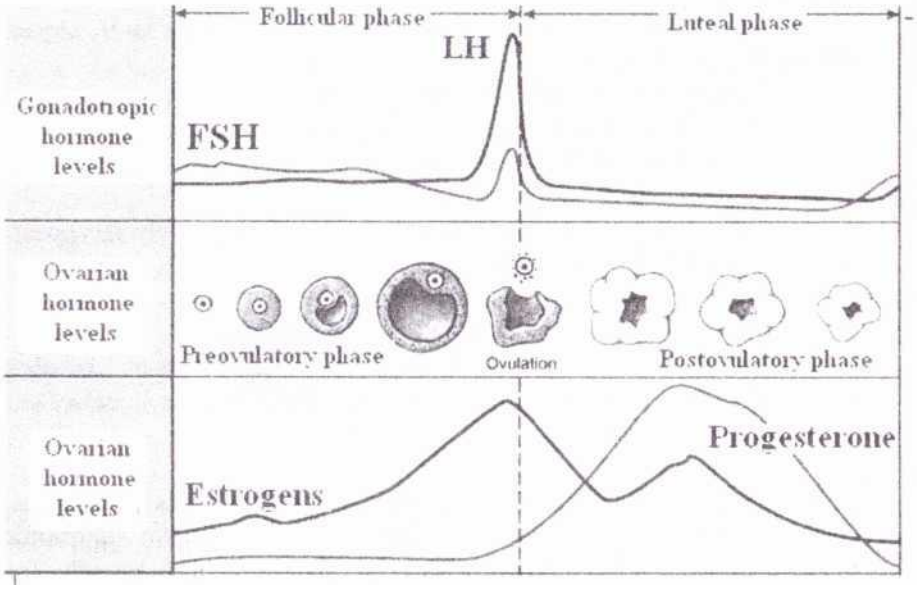


Figure 30.8. Relitionship of events that occur in ovarian cycle.

Ovulation occurs between two phases.

The follicular phase begins with the development of primary follicles under the influence of FSH and TH. FSH stimulates the granulosa and thecai cells, which begin to secrete estrogens. Late in the follicular phase, before ovulation, progesterone levels begin to rise under the influence of LH.

Ovulation is induced by a surge in the LH level, which occur with a smaller increase in the FSH level. The luteal phase begins after

ovulation, as the granulosa and thecal cells of the ruptured follicle undergo transformation to form the corpus luteum. Estrogens and large amounts of progesterone are secreted by the corpus luteum.

0 Oogenesis

Oogenesis is the process of differentiation of the oocytes (fig.30.9).

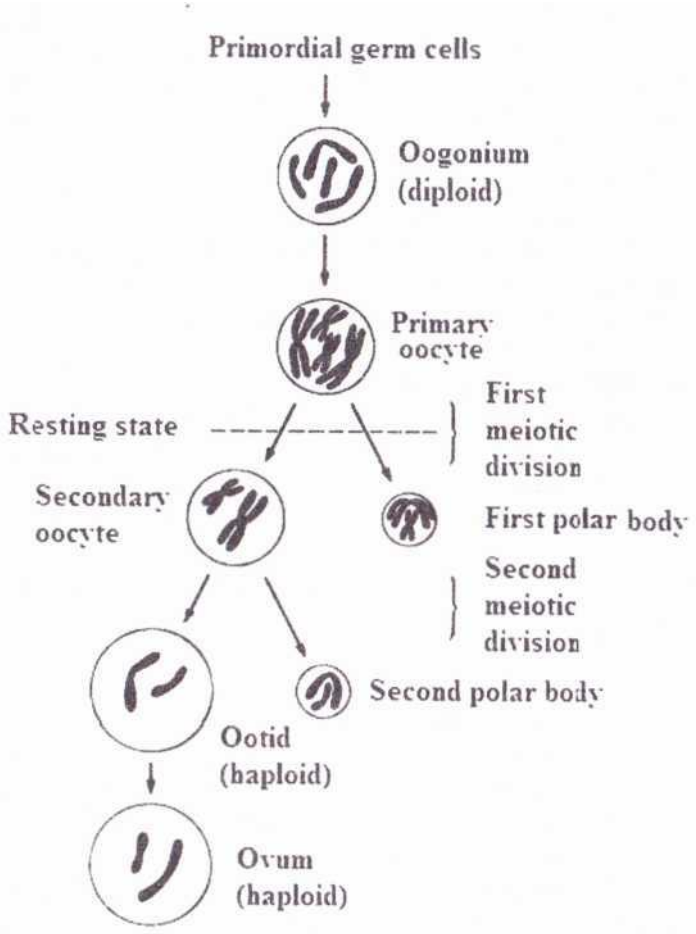


Figure 30.9. Schematic diagram of oogenesis.

The ***oogonia*** proliferate by mitosis during the fetal life in the cortex of the ovary and are used throughout the life of a woman. Each oogonium enlarges to form a ***primary> oocyte*** (46 chromosomes, 4N DNA).

Primary oocyte within the primordial follicle begins the first meiotic division in the embryo, but this process is arrested at the diplotene stage of meiotic prophase. Primary oocytes remain arrested in the first meiotic prophase for 12-50 years. The first meiotic division is completed in the mature follicle, and one daughter cell (secondary oocyte (23 chromosomes, 2N DNA)) receives most of the cytoplasm. Other daughter cell (first polar body) receives a minimal amount of cytoplasm.

The ***secondary oocyte*** begins the second meiotic division, the daughter cells being again unequal. The large daughter cell is the mature ***ovum*** (23 chromosomes, IN DNA). The smaller daughter cell is the second polar body. This second division does not occur unless fertilization of the secondary oocyte by a sperm occurs.

E3 Oviducts (uterine or Fallopian tubes)

The ***uterine tubes*** are paired muscular tubes about 12 cm long, which connect the peritoneal cavity with the cavity of uterus. They receive and transport ovum to the uterus and provide the necessary environment for fertilization and initial development of the zygote.

The wall of the oviduct is composed of three layers (fig.30.10):

> mucosa,
> muscularis,
> serosa

I. ***Mucosa*** has longitudinal folds and consists of:

1) ***epithelium*** is simple columnar and contains two types of cells:

• ciliated cells, wave of the cilia of these cells is directed toward the uterus;

« nonciliated, secretory, peg cells which produce the fluid that provides nutrition for the ovum.

2) ***lamina propria*** is composed of loose connective tissue;

II. ***Muscularis*** consists of 2 sublayers of smooth muscle tissue (outer-longitudinal and inner-circular);

III. ***Serosa*** is covered by mesothelium.

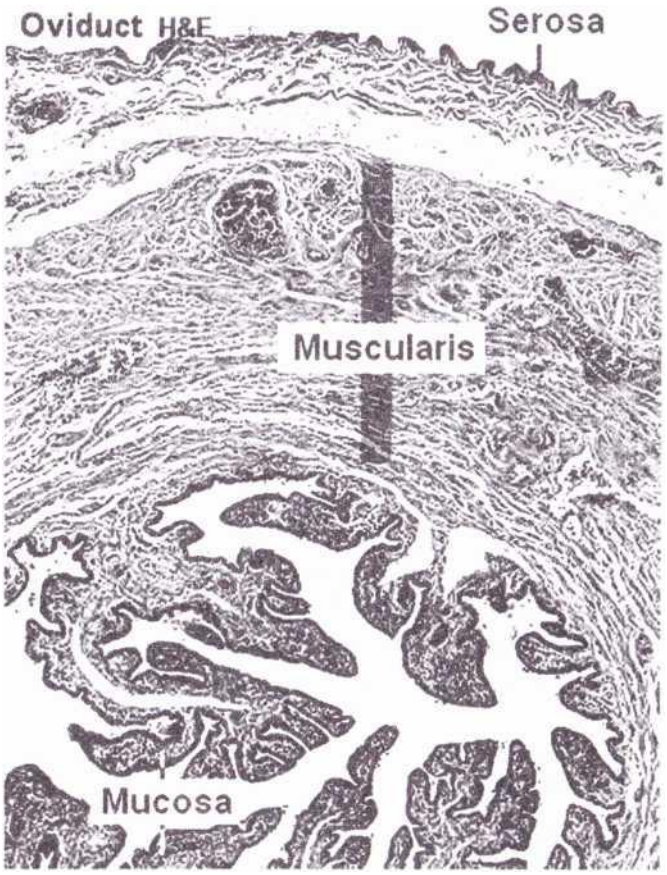


Figure 30.10. Photomicrograph of a human uterine tube.

0 Uterus

The ***uterus*** is a pear-shaped organ that receives the morula from the uterine tube.

The wall of the uterus is formed of 3 layers:

> I. mucosa ***(endometrium),***
> 11. muscularis (***myometruim***)
> III. serosa (***perimetrium***)

Endometrium consists of:

1) simple columnar ***epithelium*** that contains ciliated and secretory cells;

2) ***lamina propria*** contains simple tubular glands (the uterine glands);

Endometrium can be divided into two zones:

1) basal layer is not sloughed off during menstruation but functions as a regenerative zone for the functional layer after its rejection; is supplied by ***straight arteries.***

2) functional layer is the luminal part of the endometrium; it is sloughed off during every menstruation and it is the site of cyclic changes in the endometrium; is supplied by ***spiral arteries.***

Myometrium is composed of 3 layers of smooth muscle tissue. The middle layer contains numerous large blood vessels and is called stratum vascularis. The inner and outer layers contain smooth muscle bundles oriented parallel to the long axis of the uterus.

Outer layer is either serosa ***(perimetrium,*** the serous membrane enveloping the fundus and ventral and dorsal surfaces of the uterus) or ***adventitia*** consisting loose connective tissue.

Parametrium is the loose connective tissue around the uterus.

0 Menstrual (uterine) cycle

The ***menstrual (uterine) cycle*** is a continuum of developmental stages in the functional layer of the endometrium, normally repeats every 28 days.

Menstrual cycle has 3 successive phases (fig.30.11):

I. Menstrual

II. Proliferative

III. Secretory

Menstrual phase (1-4 days)

At the end of the secretory phase ovarian hormone levels rapidly decrease; the walls of the spiral arteries contract, closing off the blood flow and producing ischemia (local anemia), which results in death (necrosis) of their walls and of the functional layer of the endometrium. 498

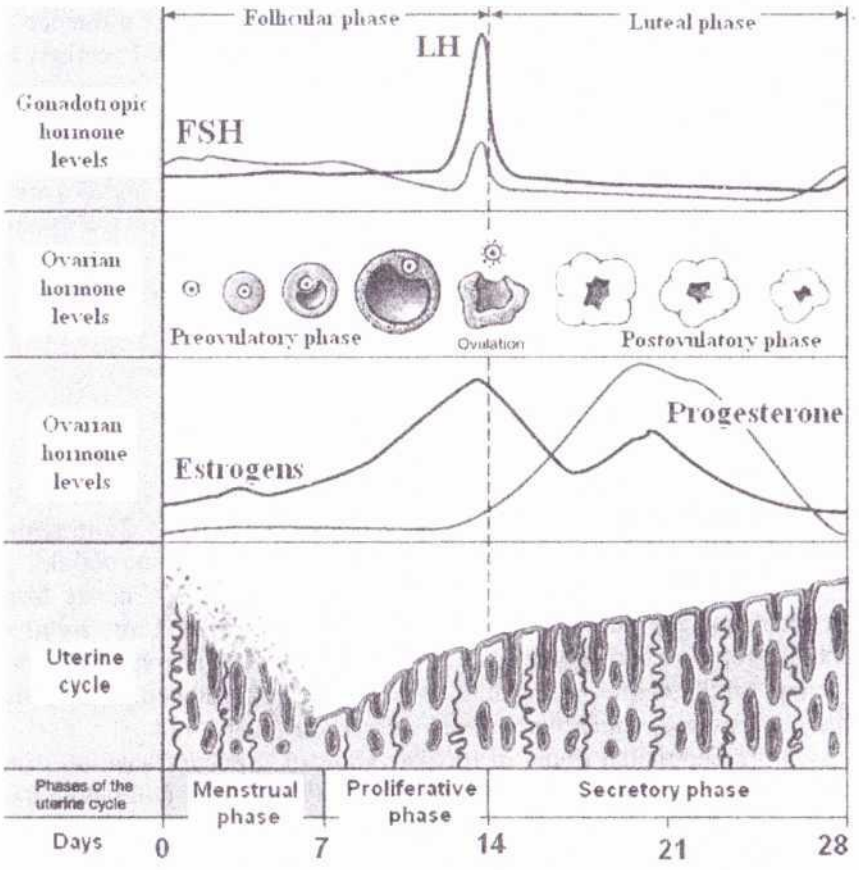


Figure 30.11. Relationship of events that occur in ovarian and menstrual cycles.

At this time, blood vessels above the constrictions rupture, and bleeding begins. The average blood loss in the menstrual phase is 35 to 50 mL. Only the basal layer containing basal parts of uterine glands are left. Proliferation of the gland cells and their migration to the surface initiate the proliferative phase.

Proliferative phase (5-14 days) is initiated under the influence of estrogens. The lost epithelium is regenerated from the basal portions of the uterine glands. At the end of the proliferative phase the endometrium is 2-3 mm thick, the glands are straight tubules with narrow lumens.

Secretory phase (15-28 days) of the menstrual cycle is regulated by progesterone of the corpus luteum. The glands become highly coiled and secrete glycoproteins that will be the major source of embryonic nutrition before implantation occurs. In this phase, the endometrium reaches its maximum thickness (5mm) as a result of the accumulation of secretions and the edema of the stroma. The last few days of this period is called ischemic phase.

0 Mammary glands (breasts) (fig.30.12)

The ***mammary glands*** are modified apocrine sweat glands of the skin. The inactive adult mammary gland is composed of 15-25 irregular lobes separated by fibrous band of' interlobar connective tissue and fat.

Each lobe contains an individual gland. The lobes radiate from the mammary papilla, or nipple. The lobes are subdivided into ***lobules.*** The excretory duct of each lobe, also called ***lactiferous duct,*** has opening on the nipple. Beneath the areola each has a dilated portion, the ***lactiferous sinus,*** which functions as a reservoir for the milk.

The epithelial lining of the duct shows a gradual transition from single layer of columnar or cuboidal cells to two layered epithelium and finally to stratified squamous nonkeratinized epithelium. Branches of the lactiferous duct are lined with a simple cuboidal epithelium. The lactiferous duct has a two layered epithelium - basal cells are cuboidal whereas the superficial cells are columnar. Lactiferous sinuses are lined by stratified squamous nonkeratinized epithelium.

The lobules contain the secretory units (alveoli), which are lined by a cuboidal or columnar epithelium (secreting cells - lactocytes) (fig.30.13). The myoepithelial cells surround the base of the alveolar secretory cells and the bases of the cells of the larger ducts, causing them to contract and eject the milk from the alveoli.

Secreting cells contain abundant granular endoplasmic reticulum, mitochondria, Golgi apparatus, lysosomes. Milk proteins are

secreted by merocrine secretion, milk lipids are secreted by apocrine secretion.

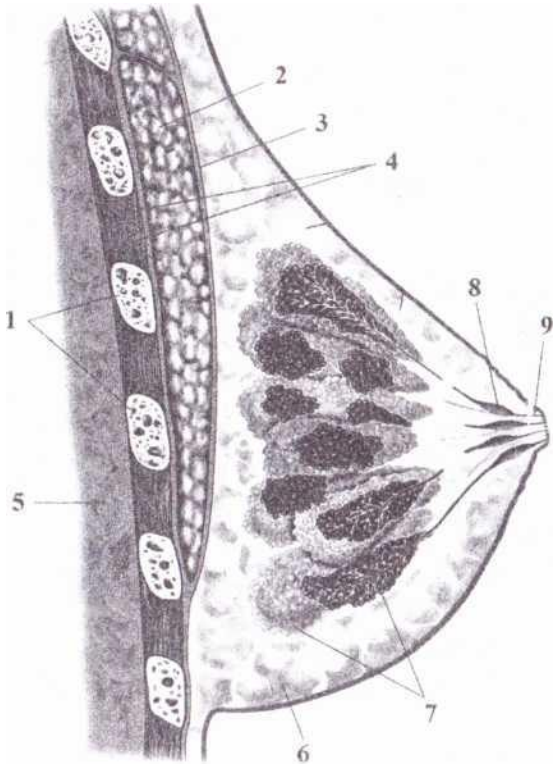


Figure 30.12. **Schematic diagram** of **the human mammary gland.** 1 - ribs, 2 - pectoralis major muscle, 3 - pectoral fascia 4 - intercostal muscles, 5 - lung, 6 - fat, 7 — gland lobules, 8 - lactiferous sinus, 9 - lactiferous duct

Hormonal regulation of the mammary gland

The initial growth of the mammary glands at puberty occurs under the influence of estrogens and progesterone produced by maturing ovary.

Lactation is under neurohormona! control of the adenohypophysis (prolactin) and hypothalamus (oxytocin). Production

of milk is stimulated by prolactin. Oxytocin stimulates the myoepithelial cells.

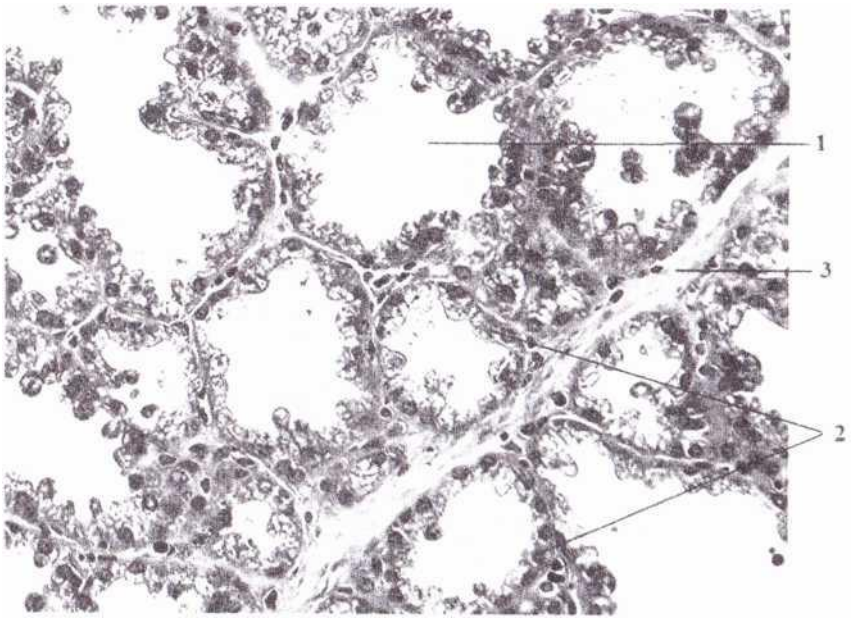


Figure 30.13. Photomicrograph of a lactating mammary gland of a young woman. 1 - secretory units (alveoli), 2 - lactocytes, 3 - interlobar connective

0 Clinical correlations

Polycystic ovary syndrome is a condition in which there is an imbalance of a woman's female sex hormones. This hormone imbalance may cause changes in the menstrual cycle, skin changes, small cysts in the ovaries, trouble getting pregnant and other problems.

Cervical cancer is most commonly caused by HPV (Human Papilloma Virus). This is a virus that is most commonly spread by sexual contact. It is thought to be the most prevalent STD (Sexually Transmitted Disease).

The Papanicolaou test (also called Pap smear, Pap test, or cervical smear) is a screening test used in gynaecology to detect premalignant and malignant (cancerous) processes in the cervix. Significant changes can be treated, thus preventing cervical cancer. The test was invented by and named after the prominent Greek doctor Georgios Papanikolaou.

In taking a Pap smear, a tool is used to gather cells from the outer opening of the cervix of the uterus and the endocervix. The cells are examined under a microscope to look for abnormalities. The test aims to detect potentially pre-cancerous changes (called cervical intraepithelial neoplasia (CIN) or cervical dysplasia). The test remains an effective, widely used method for early detection of pre-cancer and cervical cancer.

CONTROL TESTS

Cytology

1. By histochemical methods it was determined, that lysosomes and peroxisomes differ from each other in composition of the enzymes. What enzymes are in peroxisomes?

A. Oxidize, catalase
B. Acid phosphatase
C. Alkaline phosphatase
D. Lipase
E. Maltase

2. Low level of albumins and fibrinogen was detected in the patient's blood. Decreased activity of what organelle of the liver hepatocytes can cause it?

A. Granular endoplasmatic net
B. Agranular endoplasmatic net
C. Mitoehondrions
D. Golgi complex
E. Lysosomes

3. At the laboratory experiment the cell structure, which function is formation of subunits of ribosomes, was destroyed. Name the place of formation of precursors of ribosomes.

A. Polysomes
B. Mitochondria
C. Lysosomes
D. Nuclear matrix
E. Nucleolus

4. Moving of the daughter chromatids to the poles of the cell is observed in the mitotically dividing cell. On what stage of the mitotic cycle is this cell?

A. Interfase
B. Prophase
C. Metaphase
D. Anaphase
E. Telophase

5. Low level of albumins and fibrinogen was detected in the patient's blood. Decreased activity of what organelle of the liver hepatocytes can cause it?

A Granular endoplasmatic net B Agranular endoplasmatic net C Mitochondrions D Golgi complex E Lysosomes

Embryology

1. In course of a conditional experiment the development of mesenchymal cells was completely inhibited. Development of the following muscle tissue will be disturbed:

A Smooth muscle tissue B Neural muscle tissue C Epidermal muscle tissue D Cardiac muscle tissue E Skeletal muscle tissue

2. The injection of urine of pregnant woman to immature mice causes the maturation of the follicles in their ovaries. What hormone, contained in urine, does stipulate this effect?

A. Thyroxin
B. Somatostatin
C. Gonadopropin
D. Vasopressin
E. Oxytocin

3. At research of histological specimen of placenta there is a contact of chorionic villi with maternal blood. Name this type of placenta.

A. Hemochoreal
B. Endotheliochorea)
C. Desmochoreal
D. Epitheliochoreal

4. On the 7-8"' days of embryogenesis blastocyst sticks to the uterine endometrium, and then invades the endometrium, destroying tissues of endometrium. Name this process.

A. Adhesion
B. Capacitation
C. Cortical reaction
D. Invasion
E. Penetration

5. On the specimen of the human embryo taken from spontaneous abortion, in embryonic disk 2 layers of cells - ento- and ectoderm are distinguished. Name the stage of embryonic development of an embryo.

A. Gastrulation
B. Fertilization and zygote formation
C. Cleavage and blastocyst formation
D. Histogenesis and organogenesis
E. Systemogenesis

General nrincinies of organization and classification of the tissues. Epithelial tissues

1. A patient has undergone an amputation of lower extremity. Some time later painful nodules appeared in a stump. Amputatious neuromas were found out at the microscopic examination. To what pathological processes do those formations relate? A Regeneration B Dystrophy C Inflammation D Hyperemia E Metaplasia

2. A scheme presents an exocrine gland that has unbranched excretory duct with a terminal part in form of a saccule openining into ithe duct. How this gland is called according to the morphological classification of exocrine glands?

A Simple unbranched alveolar B Compound branched alveolar C Simple branched tubular D Compound unbranched alveolar E Compound unbranched alveolar tubular

3. In a histological specimen columnar secretory cells are visible. Apical parts of cells are destroyed. Name type of secretion.

A. Macroapocrine
B. Holocrine.
C. Microapocrine
D. Merocrine
E. Eccrine

4. In a histological specimen it is seen epithelium which cells have the different shape; their nuclei are located at different levels. Epithelium has columnar cells with cilia on apical surfaces. Name this epithelium.

A. Stratified squamous nonkeratinized epithelium
B. Stratified squamous keratinized epithelium
C Transitional epithelium
D. Pseudo-stratified columnar ciliated epithelium
E. Simple columnar epithelium

5. An epithelium which appears to be composed of more than one layer of

cells but which really consists of a single layer is designated as:

A. stratified
B. simple
C. columnar
D. pseudostratified
E. transitional

Blood. Lymph. Hemopoiesis

1. An electronic micropliotograph shows a macrophagic cell with erythrocytes at different stages of differentiation located along its processes. This is the cell of the following organ:

A Red bone marrow B Thymus C Spleen D Tonsil E Lymph node

2. In course of an experiment a big number of stem cells of red bone marrow was in some way destructcd. Regeneration of which cell populations in the loose connective tissue will be inhibited?

A of macrophags B of fibroblasts C of pigment cells D of lipocytes E of pericytes

3. In the red marrow' smear Ihe giant cells (35-150 jim in diameter) with irregularly lobulated nuclei and the demarcation membranes in cytoplasm have been revealed. Name these cells.

A. Adipose cells
B. Platelets
C. Megakaryocytes
D. Erythrocytes
E. Reticular cells

4. At research of blood of the of 30 y.

0. patient cells which make 0,5 % from total of leukocytes, have the S- shaped nuclei and the specific granules stain metaehromatically, are revealed. Name these cells.

A. Lymphocytes
B. Neutrophyis
C. Eosinophyls
D. Basophyls
E. Monocytes

5. Examination of a patient with the pancytopenia (low maintenance of all formed elements of the blood) demonstrates that reason of pathological changes is disorder of differentiation of multipotential stem cells and formation of unipotential progenitor cells. Suppressing of synthesis of which biologically active substances can be the reason of this condition?

A. Hormones of thyroid gland
B. Hemopoietic cytokines
C. Neurohormones
D. Immunoglobulins
E. Mediators

Connective tissues

1. Decreased blood supply to the organs causes hypoxia that activates fibroblasts function. Volume of what elements is increased in this case?

A Intercellular substance B Vessels of microcircular stream C Nerve elements D Parenchyma elements of the organ E Lymphatic vessels

2. In the connective tissue with the special properties there are cells which contain only one large fat droplet and eccentrically located

nucleus and small number of mitochondria. Name (his tissue.

A. Reticular cells
B. Fibroblasts
C. White (unilocular) adipose tissue
D. Brown (multilocular) adipose tissue
E. Melanocytes

3. In histological specimen of connective tissue there are large round cell with eccentrically placed nucleus and rough endoplasmic reticulum around of a nucleus. A well developed Golgi complex displaces the nucleus to one side of the cell (perinuclear halo). Name these cells.

A. Fibroblasts
B. Plasma cells
C. Melanocyte
D. Adipose cells
E. Macrophages

4. In histological specimen of connective tissue there are thin fibers with a diameter 0,5-2 pm, which form an extensive network. They are not visible in haematoxylin- eosin microslides but can be stained black by impregnation with silver salts. Name these fibers.

A. Elastic
B. Reticular
C. Collagen
D. Nervous
E. Muscle

5. During training at the sportsman the lower limb has been injured. The traumatologist has established the diagnosis: rupture of the tendon. What tissue the forms tendon?

A. Loose connective tissue
B. Dense regular connective tissue
C. Dense irregular connective tissue
D. Reticular tissue
E. Cartilage tissue

Skeletal tissues

1. In course of indirect histogenesis of tubular bone tissue a plate is formed between epiphyseal and diaphyseal ossification centres that provide further lengthwise growth of bones. What structure is it?

A Metaphyseal plate B Osseous collar
C Osseous plate D Osteon
E Layer of interior general plates

2. A 5 y. o. boy falls off his bike and fractures his humerus. He is taken to the emergency room, and the bone is set l»y one of the emergency room physicians. Which of the following is responsible for producing the majority of the new bone that will reunite the two fragments?

A. Cancellous bone
B. Cartilage
C. Compact bone
D. Bone marrow
E. Periosteum

3. In the histological specimen it is visible a site of tissue, which has periosteum, isogenous groups of cells, numerous elastic fibers. Name this tissue.

A. Hyaline cartilage
B. Elastic cartilage
C. Fibrocartilage
D. Primary, immature, or woven bone
E. Secondary, mature, or lamellar bone

4. At the patient it is exposed resorption of bones. With the hyperactivity of what cells of bone tissue is it connected?

A. Osteoblasts

B. Osteocytes
C. Osteoclasts
D Osteoblasts and osteocytes
E. Fibroblasts
5. Where it is possible to find primary bone tissue in the adult?
A. Suture of the flat bones of the skull
B. in the epiphyses of the long bones
C. In the diaphyses of the long bones
D. In the articular cartilages
E. In the intervertebral disks

Muscle tissues

1. Patient with injured muscles of the lower extremities was admitted to the traumatological department. Due to what cells is reparative regeneration of the muscle fibers and restoration of the muscle function possible?
A Satellite-cells B
Myoblasts C
Myofibroblasts D
Fibroblasts E
Myoepithelial cells
2. A microspecimen of the submandibular salivary gland shows some basket-shaped cells concentrated around the acini and excretory ducts. These cells surround bases of the serous cells and are called myoepitheliocytes. These cells relate to the following tissue:
A Muscle tissue B Epithelial
tissue C Nerve tissue D Special
connective tissue E Loose
connective tissue
3. At a 20 y. o. sportsman as a result of constant physical loading the functional hypertrophy of left ventricle of heart has developed. What morphofunctional process lies in its basis?
A. Increase of sizes of cells and of contractile organelles
B. increase of quantity of fibroblasts
C. Increase of quantity of conducting cardiac muscle cells
D. Increase of quantity of connective tissue
E. Increase of quantity of adipose quantity
4. In the histological specimen of the muscle tissue there are long spindle- shaped cells with single, rod-shaped, central in position nucleus. Name these cells.
A. Contractile cardiac muscle cells
B. Conductive cardiac muscle cells
C. Secretory cardiac muscle cells
D. Smooth muscle cells
E. Satellite-cells
5. At the examination of a patient with the trauma of extremity found out the damage of skeletal muscle tissue. What structural components were damaged?
A. Myoepithelial cell
B. Myosymplast
C. Smooth muscle cell
D. Cardiac muscle cell
E. Fibroblast

Nerve tissue

1. Which the following glial cells contribute to the formation of cerebrospinal fluid?
A. Microglia! cells
B. Ependymal cells
C. Astrocytes
D. Oligodendrocytes
E. Macroglial cells

2. In formation of lilood-brain barrier the glial cells, which processes surround the blood capillaries, take part. Name these cells.

A. Oligodendrocytes
B. Ependymal cells
C. Astrocytes
D. Microglia
E. Schwann cells

3. In histological specimen of skin of human finger the nerve ending, which is devoid of myelin and Schwann sheaths and connective tissue capsule, is observed. Name this ending.

A. Motor (efferent) ending
B. Neuromuscular spindle
C. Non-free encapsulated nerve ending
D. Nonfree nonencapsulated nerve ending
E. Free nerve ending

4. Which of the following cell types is responsible for the formation and maintenance of the myelin sheath around nerve fibers in the facial nerve?

A. Microglia
B. Astrocytes
C. Schwann cells
D. Oligodendrocytes
E. Ependymal cells

5. One of parts of synapse contains mitochondria, smooth endoplasmic reticulum, neurotubules, and synaptic vesicles, which contain one of the neurotransmitter substances. Name this part of synapse.

A. Presynaptic terminal
B. Synaptic cleft
C. Postsynaptic terminal
D. Axial cylinder
E. Special sheath

Nervous system

1. A sensitive neural ganglion consists of roundish neurons with one extension that divides into axon and dendrite at some distance from the perikaryon. What are these cells called?

A Pseudounipolar B Unipolar C Bipolar D Multipolar E Apolar

2. One of sections of central nervous system has layerwise arrangement of neurons. Among them there are cells of the following forms: stellate, fusiform, horizontal, pyramidal. What section of central nervous system is this structure typical for?

A Cortex of cerebrum B Spinal cord C Cerebellum D Medulla oblongata E Hypothalamus

3. In histological specimen it is visible the organ which contains grey and white matter. The grey matter is found on periphery and consists of six layers: molecular, outer granular, pyramidal cell layer, inner granular layer, ganglionic layer, multiform cell layer. Name the organ which has such morphological signs.

A. Cerebellum.
B. Medulla oblongata.
C. Cere brum.
D. Spinal ganglion.
E. Spinal cord.

4. In histological specimen it is visible layers of neurons in motor centre of cerebrum. What layers are

the most developed in this part of cerebral cortex?

A. ill, Y, Yl.

B. [.

C. II, IV.

D. 1, Vl.

E. 1, ll.

5. A 21 y. o. girl was thrown from her horse while attempting a difficult jump. After a trauma the posterior horns of spinal cord are damaged. What types of neurons will be broken?

A. Radicular neurons of spinal cord.

B. Fascicular neurons of spinal cord.

C. Internal neurons of spina! cord.

D. Associative neurons of spinal cord.

E. Pseudounipolar neurons of spinal ganglia.

Sensory system

1. A histological specimen presents a receptor zone of a sensoepitheliai sense organ. Cells of this zone are placed upon the basal membrane and include the following types: external and interna! receptor cells, external and internal phalangeal cell, stem cells, external limiting cells and external supporting cell. The described receptor zone belongs to the following sense organ:

A Acoustic organ B Visual organ C Gustatory organ D Equilibrium organ E Olfactory organ

2. The increased intraocular tension is observed in the patient with glaucoma. Secretion of aqueous humor by the ciliary' body is normal. Injury of w hat structure of the eyeball wall caused the disorder of flow-out from the anterior chamber?

A Venous sinus B Ciliary body C Choroid D Ciliary muscle E Back epithelium of cornea

3. Vitamin A deficit results in the impairment of twilight vision. Name the cells that have the above- mentioned photoreceptor function:

A Rod receptor cell B Horizontal neurons C Cone receptor cells D Bipolar neurons E Ganglion neurons

4. An infectious disease caused contractive activity of muscles that contract and dilate eye pupil (paralytic state). What functional eye system was damaged?

A Accommodative B Dioptric C Accessory D Photosensory E Lacrimal apparatus

5. Which layer of the retina contains nuclei of photoreceptor cells?

A. Photosensitive layer.

B. Outer nuclear layer.

C. Inner nuclear layer.

D. Ganglion cell layer.

E. Nerve fiber layer.

Integumentary system

1. A patient complains of dryness of head skin, itching, fragility and loss of hair. After examination he was diagnosed with seborrhea. Disturbed activity of which cells caused this condition?

A Cells of sebaceous glands

B Cells of sweat glands C
Epithelial cells D
Adipocytes E Melanocytes

2. An embryo displays disturbed process of dorsal mesoderm segmentation and somites formation. What part of skin will have developmental abnormalities?
A Derma B
Hair
C Sebaceous glands D
Epidermis E Sweat glands

3. Study of fingerprints (dactylography) is used by criminalists for persona! identification as well as for diagnostics of genetic abnormalities, particularly Dawn's disease. What layer of skin determines individuality of fingerprints?
A Papillary B
Corneum C
Reticular D
lucidum E
Basal

4. A 21 y. o. girl has skin white spots that have no a pigment. Absence of which cells of skin cause to appearance of lack of pigmentation?
A. Adipose.
B. Fibrocytes.
C. Melanocytes.
D. Plasma cells.
E. Mast cells.

5. A 45 y. o. man is involved in a road traffic accident. There was a trauma of the skin with damage of reticular layer of dermis. Name the source of regeneration of this layer.
A. Adipocytes.
B. Fibroblasts,
C. Macrophages.
D. Mast cells.
E. Plasma cells.

<u>Respiratory system</u>

1. Lung of premature infant is presented on electronic photomicrography of biopsy material. Collapse of the alveolar wall caused by the deficiency of surfactant was revealed. Disfunction of what cells of the alveolar wall caused it?
A Alveolar cells type II B
Alveolar cells type I C
Alveolar macrophages D
Secretory cells E
Fibroblasts

2. A patient was admitted to the hospital with an asphyxia attack provoked by a spasm of smooth muscles of the respiratory tracts. This attack was mainly caused by alterations in the following parts of the airways:
A Small bronchi B
Median bronchi C
Large bronchi D
Terminal
bronchioles E
Respiratory part

3. Electronic microphotography of pulmonary alveola's wall presents a big cell. Its cytoplasm has a lot of mitochondria, developed Golgi apparatus, osmiophil lamellated corpuscles. What is the main function of this cell?
A It produces surfactant
B It is a component of blood-air
barrier
C It warms the air D It
purifies the air

E It absorbs microorganisms

4. A pathological process in bronchi resulted in epithelium desquamation. What cells will regenerate bronchial epithelium?

A Basal B
Intercalary C
Ciliate D
Endocrinal E
Goblet

5. After breathinig with poisonous steams there is an increased quantity of slime in respiratory passages of a chemical production worker. What of respiratiry tract epithelial cells participate in mucouse moisening?

A. Intercalated cells
B. Goblet cells
C. Endocrine cells
D. Langergans cells
E. Fibroblasts

<u>Cardiovascular system</u>

1. A histological specimen shows a blood vessel. Its inner coat is composed by endothelium, subendothelial layer and internal elastic membrane. The middle coat is enriched with smooth muscle cells. Such morphological characteristics are typical for the following vessel:

A Muscular artery B
Elastic artery C
Capillary D
Unmuscular vein E
Muscular vein

2. Histological specimen presents a vessel the wall of which consists of endothelium, basal membrane and loose connective tissue. What type of vessel is it?

A Vein of unmuscular type
B Artery
C Vein of muscular type D Blood capillary E Lymphatic capillary

3. A histological specimen presents an artery'. One of the membranes of its wall has flat cells lying on the basal membrane. What type of cells is it?

A Endothelium B
Mesotheliuin C
Smooth muscle cells D
Fibroblasts E
Macrophages

4. In a phase, that preceded to the diastolic relaxation of myocardium, concentration of calcium ions sharply decreases in sarcoplasm of cardiac muscle cells and in the period of diastole calcium practically is absent in the free state. Define, what structures take part in accumulation of calcium?

A. Sarcoplasmic reticulum.
B. Ribosomes.
C. Lysosomes.
D. T-system,
E. Mitochondria.

5. A 40-year-old patient had nonfatal myocardial infarction. Name the mechanisms of reparation of a cardiac wall?

A. Proliferation of contractile cardiac muscle cells.
B. Proliferation of cells of connective tissue.
C. Proliferation of conducting cardiac muscle cells.
D. Proliferation of contractile and conducting cardiac muscle cells.
E. Intracellular regeneration of contractile cardiac muscle cells.

Endocrine system

1. Kidneys of a man under examination show increased resorption of calcium ions and decreased resorption of phosphate ions. What hormone causes this phenomenon?

A Parathormone B Thyrocalcitonin C Hormonal form D_3 D Aldosterone E Vasopressin

2. An endocrine gland with parenchyma consisting of epithelium and neural tissue is under morphologicalexaminati Epithelial trabeculae have two types of cells: chromophilic and chromophobic. Identify this organ:

A Hypophysis B Adrenal glands C Hypothalamus D Thyroid gland E Parathyroid gland

3. During examination of 56 y. o. man, which suffers by arterial hypertension, the high level of vasopressin in blood was diagnosed. About hyperfunction of what nucleui of hypothalamus does it testify?

A. Paraventricular.
B. Supraoptic.
C. Dorsal medial.
D. Infundibulary.
E. Ventral medial.

4. At the study of structure of epiphysis, the large polygonal cells with elaborate, elongated processes, ending of which form club-like expansions near the blood capillaries, are found. De|» .nding on the functional state they can be dark or light. Name these cells.

A. Glial cells.
B. Pinealocytes.
C. Astrocytes.
D. Pituicytes.
E. Fibrocytes.

5. During examination of a male child, reduction of growth rate was detected. By the reduced production of which hormone of hypothalamus was this phenomenon caused?

A. Somatotropic hormone.
B. Prolactin.
C. Follicle-stimulating hormone.
D. Luteinizing hormone.
E. Lipotropin.

Digestive system

1. During histological examination of the stomach it was found out that glands contain very small amount of parietal cells or they are totally absent. Mucosae membrane of what part of the stomach was studied?

A Pyloric part B Fundus of stomach C Cardiac part D Body of stomach E -

2. Examination of a 43 y.o. patient revealed that his stomach has difficulties with digestion of protein food. Gastric juice analysis revealed low acidity. Function of which gastric cells is disturbed in this case?

A Parietal exocrinocytes B Main exocrinocytes C Mucous cells (mucocytes) D Endocrine cells E Cervical mucocytes

3. A viral infection has damaged cells that form walls of bile capillaries. This stimulated conditions for inflow of bile into the blood of sinusoidal capillaries. What cells are damaged? A Hepatocytes
B Kupffer's cells C
Ito cells D Pit-cells E
Endothelial cells

4. A patient ill with chronic gastritis went for endogastric pH-metry that allowed to reveal decreased acidity of gastric juice. It is indicative of diminished function of the following cells:
A Parietal exocrine cells B
Chief exocrine cells C
Endocrine cells D Cervical
cells E Accessory cells

5. Examination of new-born demonstrates the anomaly of development of mucosa of small intestine. What embryo source was damaged?
A. Endoderm
B. Ectoderm
C. Parietal or somatopleuric mesoderm
D. Visceral, or splanchnopleuric
mesoderm
E. Mesenchyme

<u>Immune system. Lymphoid organs</u>

1. In the microspecimen of red bone marrow there were revealed multiple capillaries through the walls of which mature blood cells penetrated. What type of capillaries is it?
A Sinusoidal B
Fenestrated C
Somatic
D Visceral E
Lymphatic

2. In a histological specimen parenchyma of an organ is represented by lymphoid tissue that forms lymph nodes; the latter are arranged in a diffuse manner and enclose a central artery. What anatomic formation has such morphological structure?
A Spleen B Tonsil C
Lymph node D Thymus E
Red bone marrow

3. Histological examination of a 40 y.o. man's thymus revealed decreased share of parenchymatous gland elements, increased share of adipose and loose connective tissue, its enrichment with thymus bodies. The organ's mass was unchanged. What phenomenon is it?
A Age involution B
Accidental involution C
Hypotrophy D Dystrophy E
Atrophy

4. The specimens present sections of hemopoietic and immunogenetic organs. Organ has lymph tissue forming different structures (lymphatic nodules, lobules, cords). In what organ does antigen-independent proliferation and differentiation take place?
A Thymus B Lymphatic
nodes C Spleen
D Hemolymph nodes E
Tonsil

5. An electronic microphotograph shows a macrophagic cell with

erythrocytes at different stages of differentiation located along its processes. This is the cell of the following organ:
A Red bone marrow B Thymus C Spleen D Tonsil E Lymph node

Urinary system

1. The low specific gravity' of the secondary urine (1002) was found out in the sick person. What is the most distant part of nephron where concentration of secondary urine takes place?
A In the collecting duct B In the glomerulus Of nephron C In proximal tubule of nephron D In ascending part of loop of Henle E In distal tubule of nephron
2. A histological specimen of a kidney shows a part of the distal tubule going between the afferent and efferent arteriole. The cells building the tubule wall have dense nuclei; basal membrane is absent. Such structural formation is called:
A Macula densa B Juxtaglomerular cells C Mesangial cells D Juxtavascular cells E -
3. In the specimen of kidney under the electronic microscope the cells extending several primary processes around the capillaries and developing numerous secondary processes, called pedicels or foot processes, are found. How are these cells named?

A. Pituicytes.
B. Podocytes.
C. Endocrine cells.
D. Goblet cells.
E. Parietal cells.
4. The first phase of formation of urine takes place in the renal corpuscles. It is filtration through the wall of capillary of glomerulus, in which hydrostatic pressure is about 45-50 mm Hg. What structural components of renal corpuscle provide a high pressure in capillaries?
A. Thin wall of capillaries of renal corpuscles.
B. Plenty of capillaries.
C. Small lumen of the afferent arteriole.
D. Thickening of tunica media of arteriole.
E. Small lumen of the efferent arteriole.
5. The electronic micrograph of kidney fragment has exposed afferent glomerular arteriole, which has giant cells under its endothelium, containing secretory granules. Name the type of these cells.
A. Interstitial
B. Mesangial
C. Smooth muscle
D. Juxtovascular
E. Juxtaglomerular

Male reproductive system

1. During pubescence the cells of male sexual glands begin to produce male sex hormone testosterone that calls forth secondary sexual characters. What cells of male sexual glands produce this hormone?

A Leidig cells B
Sustentocytes C
Sertoli cells D
Supporting cells E
Spermatozoa

2. A 35 y.o. man presents to the urologist for an infertility evaluation. A biopsy of his testis is performed to check sperm production and maturation. Microscopic section reveals only a few germ cells near the basal lamina in the seminiferous tubule. Which of the following cells is the germ cell closest to the basal lamina in the seminiferous tubule?

A. Spermatogonia
B. Primary spermatocyte
C. Secondary spermatocyte
D. Spefmatid
E. Spermatozoa

3. A patient has insufficient development of the secondary sexual signs as a result of suppressing of synthesis of testosterone. Define the position of the cells, synthesizing this hormone.

A. In the connective tissue between the convoluted seminiferous tubules
B. In the tunica propria of the convoluted seminiferous tubules
C. In the ductus epididymis
D. In the rete testis
E. In the straight tubules

4. At a patient with oligospermia (diminished amount of spermatozoa in semen) abnormality of structure of spermatozoa was revealed as a result of insufficient synthesis of androgen-binding protein. What cells of the convoluted seminiferous tubules do not provide the adequate level of this protein?

A. Supporting cells
B. Interstitial endocrine cells
C. Myoid cells
D. Fibroblasts
E. Spermatogonia

5. Which of the following cells bear the primary responsibility for forming the blood-testis barrier?

A. Sertoli cells
B. Interstitial cells (of Leydig)
C. Primary spermatocytes
D. Spermatids
E. Spermatogonia

<u>Female reproductive system</u>

1. An ovary specimen stained by hematoxylin-eosin presents a follicle, where cells of follicular epithelium are placed in 1-2 layers and have cubic form, there is a bright-red membrane around the ovocyte. Name this follicle:

A Primary B
Primordial C
Secondary D
Mature E Atretic

2. The termination of a bleeding alter parturition is connected to action of hormones on structures of a uterus. What layer of uterus takes most active part in it?

A. Middle layer of myometrium.
B. Inner layer of myometrium.
C. Perimetrium.
D. Outer layer of myometrium.
E. Endometrium.

3. During the physical examination of a 26 y. o. woman who has sterility it is revealed, that the reason of sterility is the inflammation of a mucosa of uterus. What epithelium was damaged?

A. Simple squamous.
B. Simple columnar.
C. Transitional.
D. Stratified squamous nonkeratinized.
E. Stratified squamous keratinized.

4. Histologic microslide of the uterus of a 30 y. o. woman demonstrates cndometrioum which is edematous, has thickness 5 mm, the glands are corkscrew shaped, their lumens are sacculated and fill with mucoid fluid, and there are decidual cells in the stroma of endometrium. Name the phase of menstrual cycle.
A. Proliferative.
B. Secretory.
C. Regenerative.
D. Menstrual.
E. Follicular.

5. A 32-year-old woman has disorder of menstrual cycle. Examination of this patient demonstrates that the reason of this is disorder of endocrine function of corpus luteum. Absence of what hormone causes disorder of menstrual cycle?
A. Progesterone.
B. Estrogens.
C. Oxytocin.
D. Prolactin.
E. Follicle-stimulating hormone.

ANSWERS TO TESTS

Cytology
1-A, 2-A, 3-E, 4-D, 5-A
Embryology
1-A, 2-C, 3-A, 4-D, 5-A
Epithelial tissues
1 - A , 2 - A , 3 - A , 4 - D , 5 - D
Blood. Lymph. Hemopoiesis
1-A, 2 - A , 3 - C . 4 - D , 5 - B
Connective tissues
1 - A, 2 - C, 3 - B, 4 - B, 5 - B
Skeletal tissues
1 - A 2 - E , 3 - B , 4 - C , 5 - A
Muscle tissues
1 - A, 2 - A 3 - A, 4 - D, 5 - B Nerve tissue
1 - B , 2 - C , 3 - E , 4 - C , 5 - A
Nervous system 1 - A, 2 - A, 3 - C, 4 - A, 5 - E Sensory system
1-A, 2 - A, 3 - A, 4 - A, 5-B
Integumentary system 1 - A, 2-A, 3-A, 4-C, 5-B Respiratory system 1 - A, 2 - A, 3 - A, 4 - A, 5 - B
Cardiovascular system ! - A,2-A, 3 -A,4-A, 5-B Endocrine system 1 - A, 2 - A, 3 - B, 4 - B, 5 — A
Digestive system 1 - A, 2-A, 3-A, 4-A, 5-A Immune system, lymphoid organs 1 - A, 2 - A, 3 - A, 4 - A, 5 — A Urinary system I - A2-A, 3-B. 4-E, 5-E Male reproductive system i - A, 2 - A, 3 - A, 4 - A, 5 - A Female reproductive system 1 - A, 2-A3-B, 4-B, 5-A

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