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HUMAN ANATOMY, HISTOLOGY AND DEVELOPMENT

Handout for Pharmacy Students at Albert Szent–Györgyi Medical University

SZEGED
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INTRODUCTION

Anatomy is the science of dissection, i.e. the cutting apart and separation of the cells, tissues and organs of the body. During the dissection of the human body, we have to be familiar with the directions and planes of the body in space. Therefore, we must determine and name the directions and planes precisely: the terminology of directions and planes is the basis of descriptive anatomy (Fig. 1). Dissection is always followed by a systematic morphological study of the separated pieces. The methods of morphology are manifold and constantly developing; they allow new insights into the structures of living organisms. Organs and organ systems are studied by means of dissection with simple instruments such as scissors, a scalpel and forceps. However, postmortem dissection is only one of the methods used; human anatomy research often involves the usage of different radiological methods in the examination of the living body. These methods provide much useful information on normal and pathological structures.

Due to the limited resolving power of the human eye, tissues and cells are studied more usually with the light microscope. Electron microscopes are the ultimate tools in research on cell morphology. The present knowledge and concepts on cellular ultrastructure are based on the information provided by the electron microscope in the past forty years. Electron microscopes are not only tools of scientific research, but are also used in the diagnostics of certain human diseases. These methods of morphological investigation embrace a broad scale of spatial dimensions, and allow the study of different levels of organization ranging from body parts to molecules (Table 1).

This handout summarizes the knowledge on human anatomy required by the Pharmacy Student. The handout contains only a few illustrations; the other, frequently necessary ones will be presented during the lectures. Anatomical and medical terms are explained in the "Vocabulary" section.
Fig. 1: Principal planes and directions in human anatomy. Terms are explained in the "Vocabulary".
Table 1
Dimensions in anatomy on a logarithmic scale: the metric values differ by a factor of 10. The resolving power of the naked eye is 100 μm, that of the light microscope is 100 nm, and that of an average transmission electron microscope is between 1 and 10 nm.

<table>
<thead>
<tr>
<th>METRIC UNITS</th>
<th>LIVING STRUCTURES AND MOLECULES IN THE RANGE INDICATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>meter (m)</td>
<td>man</td>
</tr>
<tr>
<td>decimeter (dm)</td>
<td>limbs</td>
</tr>
<tr>
<td>centimeter (cm)</td>
<td>organs</td>
</tr>
<tr>
<td>millimeter (mm)</td>
<td>tissues</td>
</tr>
<tr>
<td>100 micrometers (μm)</td>
<td>oocytes (egg cells)</td>
</tr>
<tr>
<td>10 micrometers (μm)</td>
<td>other cells</td>
</tr>
<tr>
<td>1 micrometer (μm)</td>
<td>bacteria</td>
</tr>
<tr>
<td>100 nanometers (nm)</td>
<td>viruses</td>
</tr>
<tr>
<td>10 nanometers (nm)</td>
<td>proteins</td>
</tr>
<tr>
<td>1 nanometer (nm)</td>
<td>amino acids</td>
</tr>
<tr>
<td>below 1 nm</td>
<td>atoms</td>
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</tbody>
</table>
I. THE STRUCTURE OF THE CELL

The cell is the living morphological unit of human tissues. Cells are manifold, but all of them have certain common structural characteristics. Every cell is bounded by the cell membrane or plasmalemma. Inside this we find the cytoplasm, which contains a regimen of cytoplasmic organelles, inclusions and structural proteins. Every cell has a nucleus, containing the genetic material in the form of chromatin. The cell nucleus is separated from the cytoplasm by the nuclear membrane, which is similar to the cell membrane in structure and chemical composition.

I. 1. The cell membrane (plasmalemma)

All cellular membranes (internal or external) consist of a bimolecular layer of phospholipids, with their hydrophilic ends at the outer surface and their hydrophobic chains projecting toward the middle of the bilayer. This concept of the uniformity of external and internal cellular membranes is the unit membrane concept or hypothesis. The concept was originally based on the electron microscopic appearance of the membranes. The plasmalemma is invisible in the light microscope, whereas in the electron microscope it appears as a 8-10-nm-wide, dense line. The proteins of the cell membrane are of two kinds. Some of them do not interact directly with the hydrophobic core of the phospholipids. These peripheral or extrinsic proteins are usually bound to other (integral) proteins or to the hydrophilic heads of the phospholipid layer. Some peripheral proteins are located on the inner surface, and some on the outer surface of the cell membrane. Most of the proteins of the cell membrane are inserted into the lipid bilayer; some of them can move or float in it tangentially. The integral proteins are globular particles of varying size that occupy the cytoplasmic and the extracellular surfaces of the lipid bilayer. Their hydrophilic region projects outward, and their hydrophobic region is located between the hydrophobic regions of the phospholipid chains. The transmembrane proteins extend throughout the entire thickness of the membrane, with their hydrophilic ends outside, and their middle hydrophobic region inside the lipid bilayer. The transmembrane proteins are membrane receptors and ion channels which regulate the communication between the cell and its surroundings. Some of the membrane proteins (glycoproteins) and some lipids (glycolipids) have polysaccharide components on their extracellular portions. The polysaccharide chains project from the outer surface of the membrane into the extracellular space and contribute to the formation of a carbohydrate-rich surface coat or glycocalyx. Many tissue antigens are located in the coat, including the major histocompatibility antigen systems and, in the case of erythrocytes, the
blood group antigens. The ectoenzymes of the epithelial cells of the gut are similarly located in the glycocalyx. Special adhesive molecules enabling the cells to attach selectively to other living surfaces (cell membranes or extracellular matrix) are also present in the glycocalyx. The cell membrane may form specialized **intercellular junctions**, which mechanically link cells together and facilitate direct communication and the transport of material from one cell to another. The surface coat and complexes of large transmembrane proteins play important roles in the functional structure of these junctions.

**I. 2. The endoplasmic reticulum**

Several membrane systems are found in the cytoplasm; most of these form flattened sacs (or cisternae) and membrane-bound tubules, all of them having a narrow cavity inside. The tubules and flattened cisternae of the endoplasmic reticulum (ER) build up a continuously interconnected, extensive network in the cytoplasm. The ER occurs in two forms: the **rough ER (rER)** and the **smooth ER (sER)**. The surface of the rER is studded with uniform, small particles of ribonucleoprotein: the **ribosomes**. The rER is therefore involved in protein synthesis.

The surface of the sER is smooth. The sER occurs mostly in cells which synthesize triglycerides, cholesterol or steroid hormones. The sER membranes contain the arrays of enzymes necessary for the synthesis of triglycerides, cholesterol and steroid hormones. A special form of sER is found in the striated muscle cells: this is called the sarcoplasmic reticulum. The sarcoplasmic reticulum is involved in the release and sequestration of intracellular calcium ions.

**I. 3. The Golgi apparatus (dictyosome)**

The Golgi apparatus is the site of the concentration, chemical modification and packaging of secretory proteins synthesized on the rER. It consists of a parallel array of flattened membrane cisternae. There is no continuity between the cavities of the cisternae. The membrane assemblages are often curved around one pole of the cell nucleus, resulting in arciform structures visible in the light microscope after silver impregnation. This structure was called the dictyosome by classical cytologists.

**I. 4. Mitochondria**

The mitochondria are membranous organelles; they are the sites of chemical energy production. In living cells, mitochondria appear as thread-like cytoplasmic structures (0.1-0.3 μm thick and 2-6 μm long). Mitochondria are bounded by a double unit membrane: an outer
and an inner one. The inner membrane forms crest-like elevations (cristae), which occupy most of the inner mitochondrial space. The rest of the cavity is filled with a homogenous substance called the matrix. The outer membrane is smooth and covers the mitochondria. In some endocrine cells which produce steroid hormones, the cristae are replaced by membranous tubules formed by the inner membrane.

I. 5. Lysosomes

Lysosomes are rounded, but often irregular membrane-bound organelles, 0.2-0.5 μm in diameter. They contain hydrolytic enzymes (e.g. acid phosphatases, proteases, phospholipases and nucleases), which are important intracellular digestion enzymes. Lysosomes play important roles during phagocytosis, when the cell ingests extracellular particles (e.g. bacteria). Phagocytosis results in an intracellular vacuole (the phagocytotic vacuole) containing the engulfed bacteria. Lysosomes fuse with the endocytotic vacuole to form a phagosome, inside which the lysosomal enzymes kill and digest the bacteria. At the end of the process, the phagosome is transformed into the residual body containing the debris of the bacteria.

I. 6. Centrioles (centrosomes or cell centers)

Centrioles are visible with the light microscope: after special staining they appear as a pair of short rods (0.2 μm thick and 0.5 μm long), lying close to the cell nucleus. In the electron microscope, the centrioles are seen consist of triplets of microtubules which are oriented obliquely at an angle of 40°. The triplets are embedded in an electron-dense wall. Centrioles are essential for the formation of cilia and flagella, and they play an important role during mitotic cell division.

Apart from these organelles, the cytoplasm of the cell contains numerous small, amorphous particles, the cytoplasmic inclusions. These are the assemblages of organic substances which are the raw materials for the synthesis of various molecules. Glycogen inclusions form dense 20-30-nm particles in the cytoplasm. Lipids are stored as spherical droplets of different sizes; in adipocytes (fat cells), a single large droplet fills the cytoplasm completely. Pigment is stored in membrane-bound vesicles, the melanosomes, which contain not only the pigment melanin but also the enzyme tyrosinase, which participates in pigment synthesis. Melanosomes bud off from the Golgi apparatus. Other inclusions in the cytoplasm, the lipofuscin and hemosiderin granules, are metabolically inactive. Both of them contain the end-products of various degradation processes.

I. 7. Cytoskeleton
The cytoskeleton consists of a regimen of filamentous proteins forming a cobweb-like network in the cytoplasm. This is not only the backbone of the cytoplasm, maintaining the shape of the cell, but also the molecular network providing it with the ability to move and change in size and shape. The cytoskeleton is hardly visible in the light microscope, unless it is stained by means of immunohistochemical or silver impregnation methods. The main cytoskeletal structures are the microtubules, microfilaments, intermediate filaments and myosin filaments. Microtubules are long cylinders about 24 nm in diameter. They are essential in cilia, flagella, centrioles and mitotic spindles. The microtubules are built up by the spirally directed polymerization of small globular tubulin protein subunits. Microfilaments are about 6-8 nm thick, composed of the protein actin. Actin binds to the protein myosin in the presence of an energy source (ATP) and this binding leads to various kinds of cellular movement, including muscular contraction. Intermediate filaments are about 10 nm thick, composed of filamentous, elongated protein subunits. The keratin filaments in epithelial cells, vimentin in connective tissues, desmin in muscle cells, neurofilaments in neurons and glial fibrillary acidic protein (GFAP) in neuroglia are all intermediate filaments. Their chemical compositions are similar though not identical.

I. 8. Cell structures extending from the plasmalemmal surface

I. 8. 1. Microvilli

Microvilli are finger-like cytoplasmic extensions 0.1 μm wide and 0.5-5 μm long. They contain actin filaments inside and their function is mainly to increase the surface of the cell: they form the brush border on the apical surface of epithelial cells. Several ectoenzymes are found in the glycocalyx of the brush border.

I. 8. 2. Cilia and flagella

These are motile, membrane-covered hair-like extensions containing 10 pairs of microtubular structures, which are decorated by filaments and arm-like projections with ATPase activity. Their width is 0.2-0.3 μm and they are variable in length (up to 70 μm). Certain epithelia of the body are equipped with cilia in order for them to perform their functions (e.g. the epithelium of the airways or some epithelia in the internal genital organs). The spermatozoon is the only mobile cell in the human body which moves with the help of its long flagellum.

I. 9. The cell nucleus

The cell nucleus is the most conspicuous structure in the cell; it is well-observable in unstained living cells too. It is usually rounded or elliptical, and sometimes lobulated (e.g. mature neutrophilic granulocytes). The nucleus is stained with basic dyes (hematoxylin or
toluidine blue) in light microscopy. The **nucleoplasm** is separated from the cytoplasm by the **nuclear envelope**, which is a double unit membrane, studded with ribosomes on its cytoplasmic surface. The double membrane is called the **perinuclear cistern**. The perinuclear cistern contains the **nuclear pore channels** which allow communication between the cytoplasm and the nucleoplasm. The nucleoplasm contains chromatin granules, which are the aggregated parts of the interphase chromosomes, stained deeply with basic dyes, and rich in deoxyribonucleic acid (DNA). The **nucleolus** is a prominent organelle in the nucleoplasm containing mainly ribonucleic acid (RNA). The nucleus is the repository of the genetic material of the cell, *i.e.* all the information necessary for the synthesis of cellular proteins is encoded in the DNA. The RNA molecules are informational transfer systems which regulate the intensity and timing of the different synthetic activities in the cell during the cell cycle.

**I. 10. Types of cell divisions**

**I. 10. 1. Mitosis**

Most adult human tissue cells (either normal or pathological) undergo division. The new cells which arise during mitotic cell division replace the old ones. Mitosis is the basic process underlying any kind of tissue regeneration and repair (*e.g.* wound healing). During mitosis, one cell generates two new daughter cells, which are identical to their parent cell, containing the same number of chromosomes and the same genetic information.

**I. 10. 2. Meiosis**

Meiosis is longer than mitosis because it consists of two sequential cell divisions which reduce the number of chromosomes to half of the original (four haploid daughter cells are formed, each containing 23 chromosomes). On the other hand, the daughter cells are not identical to the parent with respect to genetic information, since a special change takes place in the chromosome structure during meiosis.

**II. BASIC HISTOLOGY**

The **tissues** are groups of cells of similar origin and function. Between the cells there is an **extracellular space**, the size of which differs from tissue to tissue. The extracellular substances filling the space are specific to the tissue because they are synthesized by the tissue cells. Tissues differentiate from the embryonic germ layers.

**II. 1. Epithelial tissues**
These tissues cover organ surfaces and secrete different substances. They are separated from the connective tissue by means of the basal lamina, a complex, 20-120-nm-thick macromolecular, extracellular sheet. We distinguish covering epithelia, glandular epithelia and sensory epithelia, depending on their functional specializations.

II. 1. 1. Covering epithelia

The cells are linked to each other tightly and are regularly coupled with intercellular junctions (such as gap junctions, tight junctions and desmosomes). We distinguish simple and stratified covering epithelia. Simple epithelia contain one row of cells, and some surface specializations such as cilia or brush border, and regularly cover the mucous membranes. Those simple epithelia which contain two rows of cell nuclei are called pseudostratified epithelia. The second row of nuclei originates from the presence of young, small, undifferentiated cells located close to the basal lamina. These cells divide and replace the injured, mature cells on the surface. Simple epithelia perform important transport functions, allowing substances to pass through. Absorption of external material (such as chemicals, food or drugs) and excretion (eliminating certain cellular products) are the main transport functions performed by simple covering epithelia. The simple, flat (squamous) covering epithelium inside the blood and lymph vessels is called endothelium. The serous membranes of the body cavities are also covered with flat epithelial cells which are termed mesothelium, because they develop from the mesoderm of the body cavities. Stratified epithelia contain more than two cell layers, provide greater mechanical stability and protection (e.g. stratified epithelium of the skin).

II. 1. 2. Glandular epithelia

These are specialized for secretion. They may secrete proteins and mucins. We distinguish serous and mucous glandular cells, depending on the protein and mucin contents of the secreted material. Both types have well-developed rER and Golgi apparatus and numerous secretory granules. Glandular epithelia may represent single glandular cells, the unicellular glands (e.g. goblet cells), and the multicellular complex glands, which sometimes form large organs (e.g. the salivary glands and the pancreas). Exocrine glands secrete onto the epithelial surface; they produce enzymes or mucins which exert their functions locally (the enzymes digest food, while the mucins cover and protect the surface from the action of the enzymes). Exocrine glands have excretory ducts which are connected to the surface. Endocrine glands secrete hormones which they release directly into the bloodstream and
affect distant tissues (e.g. the parathyroid hormone of the parathyroid glands influences the bone tissue, promoting the release of calcium from the bone matrix).

**II. 1. 3. Sensory epithelia**

The sensory epithelia are specialized for the detection of chemical or mechanical signals and transform them into action potentials. Sensory epithelial cells regularly have cilia, which are the sensors of the cells. The **primary sensory epithelial cell** has a long axonal process which conducts the electric impulses to the nervous system (e.g. the olfactory epithelium in the nasal cavity). The **secondary sensory epithelial cell** is in contact with the peripheral processes of primary sensory neurons, which conduct the electric impulses generated by the sensory cell. The taste buds of the tongue contain secondary sensory epithelia.

**II. 2. Connective tissues**

The connective tissues form loose layers beneath the epithelia, cover muscles, bones and blood vessels and fill the space between different tissue elements in parenchymatous organs. The connective tissue is the “battlefield” of the immune system, i.e. the site of most inflammatory reactions. Connective tissues contain a large extracellular space filled with extracellular matrix, which consists of an **amorphous ground substance** (Table 2), **tissue fluid** and **protein fibers** (Table 3). The amorphous substance and the protein fibers are synthesized by the **cells of the connective tissue** (Table 4).

The tissue fluid contains water, ions and medium- and small-sized molecules, which are nutrients originating from the blood and waste products released from the tissue cells. The tissue fluid of the extracellular space comes from the blood; it passes through the capillary wall in consequence of the hydrostatic pressure. The pathological accumulation of tissue fluid in the extracellular space is called **edema**, which is manifested as the swelling of the tissue or body part. Edema builds up in the tissues in diseases of the circulation (e.g. heart failure), inflammation, diseases of the kidney (e.g. glomerulonephritis) and some diseases of the endocrine system.

| Table 2 |
The molecular composition of the amorphous substance in extracellular spaces.
<table>
<thead>
<tr>
<th>MOLECULES OF THE AMORPHOUS SUBSTANCE</th>
<th>DISTRIBUTION IN THE HUMAN BODY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyaluronic acid</td>
<td>All connective tissues, synovial fluid, cartilage, vitreous body of the eye</td>
</tr>
<tr>
<td>Chondroitin sulfate</td>
<td>Cartilage, bone, skin, cornea</td>
</tr>
<tr>
<td>Dermatan sulfate</td>
<td>Skin, tendon, aorta</td>
</tr>
<tr>
<td>Heparan sulfate</td>
<td>Aorta, lung, liver, basal laminae</td>
</tr>
<tr>
<td>Keratan sulfate</td>
<td>Cartilage, cornea, skin</td>
</tr>
<tr>
<td>Laminin</td>
<td>Basal laminae</td>
</tr>
<tr>
<td>Fibronectin</td>
<td>Loose connective tissue</td>
</tr>
<tr>
<td>Chondronectin</td>
<td>Cartilage</td>
</tr>
</tbody>
</table>
Table 3

The types of protein fibers in connective tissue.

<table>
<thead>
<tr>
<th>FIBER TYPE</th>
<th>MOLECULAR COMPOSITION</th>
<th>TISSUE DISTRIBUTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>COLLAGEN FIBERS</td>
<td>Hydroxyproline, hydroxylysine in helical polypeptide chains</td>
<td>Loose connective tissue, tendons, cartilage, bone, basal laminae</td>
</tr>
<tr>
<td>RETICULAR FIBERS</td>
<td>Collagen and glycoproteins</td>
<td>Abundant in hemopoietic organs (spleen, lymph nodes, red bone marrow), some parenchymatous organs (liver, endocrine glands)</td>
</tr>
<tr>
<td>ELASTIC FIBER SYSTEM</td>
<td>Oxytalan, elaunin and elastic fibers containing elastin</td>
<td>Abundant in embryonic tissues, eye, skin, blood vessel wall</td>
</tr>
</tbody>
</table>

Table 4

Cell types of connective tissue.

<table>
<thead>
<tr>
<th>CELL TYPE</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIBROBLASTS</td>
<td>Synthesis and production of fibers and amorphous substance</td>
</tr>
<tr>
<td>PLASMA CELLS</td>
<td>Synthesis of antibodies in immunologic reactions</td>
</tr>
<tr>
<td>LYMPHOCYTES</td>
<td>Production of substances which control the activities of other leukocytes (interleukins)</td>
</tr>
<tr>
<td>NEUTROPHILIC LEUKOCYTES</td>
<td>Phagocytosis of bacteria</td>
</tr>
<tr>
<td>MAST CELLS</td>
<td>Production of histamine, proteases and leukotrienes</td>
</tr>
<tr>
<td>MACROPHAGES</td>
<td>Phagocytosis and ingestion of tissue debris, bacteria, foreign particles</td>
</tr>
<tr>
<td>ADIPOSE CELLS (ADIPOCYTES)</td>
<td>Storage of fat - energy reservoir</td>
</tr>
</tbody>
</table>

Connective tissues are manifold. The most common type is called loose connective tissue. Loose connective tissue is found in the skin, the wall of the gut, the airways and the excretory ducts, where it forms layers and supports the covering epithelia (e.g. the lamina propria of mucous membranes). The thin layer of loose connective tissue in the serous membranes
contains numerous blood and lymph vessels. In parenchymatous organs, it fills the tiny
spaces between groups of cells (liver, salivary glands and pancreas). Dense connective tissue
has mainly a mechanical function in the transmission of forces (tendons and fasciae).
Supporting tissues such as cartilage and bone are related to connective tissues, but their cells
and extracellular substances are more specialized. There are some skin areas where the
adipose cells are abundant and form adipose tissue. Two types of adipose tissue are found in
the human body: common or yellow adipose tissue and brown adipose tissue. The former
contains rounded adipocytes which are filled with one large lipid droplet; due to the presence
of carotenoids, the lipid is yellowish. This adipose tissue accumulates in a cushion-like
manner and contributes considerably to the shape and weight of the body. The adipocytes of
brown adipose tissue contain several small lipid droplets and numerous mitochondria (the
presence of mitochondria gives the brown color). This tissue is present in fetuses and
newborn babies, providing them with an energy source which protects the body against cold.

II. 3. Mucous membranes (wet membranes)

The surface of the cavities of the respiratory, alimentary and uropoietic organs is covered by
mucous membranes. Mucous membranes are lined with epithelia and contain glands which
discharge onto the epithelial surface. Mucous membranes are supported by layers of loose
connective tissue. The epithelium is separated from the loose connective tissue by the basal
lamina. The mucous membrane regularly has three layers:

1. the covering epithelium;
2. the lamina propria;
3. the muscularis mucosae.

The covering epithelium is generally simple or pseudostratified (except for the urinary
organs, where we find stratified epithelium). The epithelial cells have certain surface
specializations (cilia or a brush border), and they are coupled by intercellular junctions, such
as desmosomes and tight junctions. The epithelia not only act as barriers, but also fulfill
transport functions: since the lamina propria is well vascularized, drugs may be deposited
onto the surface in the hope of fast and effective penetration. Most of these epithelial cells
transport the substances actively in both directions. The epithelia regenerate quickly because
they have young, undifferentiated cells with mitotic activity, close to the basal lamina. Some
epithelia contain unicellular glands: the goblet cells. Since most of these epithelia are
subjected to various, long–lasting chemical and mechanical stimuli, their undifferentiated
cells may be transformed into a different type of epithelium; this process is called **metaplasia** (e.g. the simple columnar epithelium in the airways in chronic smokers may be replaced by stratified squamous epithelium). Metaplasia may be a warning sign of an epithelial cancer. The **lamina propria** is a specialized loose connective tissue. It contains immune cells which often form lymphoid follicles. This certainly reflects the importance of the lamina propria in local immunity: foreign particles and infectious agents which penetrate the epithelium are captured by the phagocytes and destroyed by the lymphocytes in this layer. The lamina propria contains a capillary plexus, abundant lymphatic vessels and autonomic nerves. The glands too (if they exist) are located in this layer. The **muscularis mucosae** is a thin sheet of smooth muscle cells, which supports the mucous membrane and adjusts the surface to the requirements; the muscularis mucosae may produce folds and slight movements which may help transport or glandular secretion.

**III. THE BASIC ARCHITECTURE AND PARTS OF THE HUMAN BODY**

The anatomical names referring to the body parts are widely used in the terminology. Therefore we shall briefly summarize the gross structure of the human body, indicating some of the Latin and Greek names which describe the structures. The head is named the **caput**, and the bony structure maintaining its size and shape is the skull or **cranium**. The skull has a cavity inside, the **skull cavity**, which contains the brain. The neck (**cervix**) connects the head to the trunk (**truncus**). The upper and lower limbs (**extremities**) are attached to the trunk. The neck and the trunk are supported mainly by the backbone or spine (**vertebral column**). The inner cavity of the spine (the **vertebral canal**) contains the spinal cord. The trunk is subdivided into two large cavities:

1. The **thoracic cavity** (or **cavum thoracis**) contains the lungs, the heart and the **mediastinum**, which is the space between the two lungs. The lungs and the heart reside in their own cavities; the **pleural cavity** is for the lungs, while the **pericardiac cavity** contains the heart. Although both of them are parts of the thoracic cavity, their developmental origins are completely different and they are also separated anatomically.

2. The **abdominal cavity** (or **cavum abdominis**) is further subdivided into a large upper part (the **abdomen proper**) and a smaller lower part, the **pelvis**. The pelvic cavity is subdivided again into an upper part, the **greater pelvis**, and a lower part, the **lesser pelvis**. The abdomen
proper contains the organs of the digestive system which extend into the greater pelvis. The lesser pelvis contains the urinary bladder, internal genital organs and the rectum.

The two body cavities are separated from each other by a large, flat cross–striated muscle, the **diaphragm**. The diaphragm is not only a partition, but also an important respiratory muscle. Several important structures traverse the diaphragm, including the aorta, the esophagus, the inferior vena cava, the thoracic duct, other veins and arteries, the vagus nerves and the sympathetic chain. The body cavities are lined with **serous membranes**, which develop from the mesoderm. The **pleura** forms the pleural cavity and covers the lungs and the inner surface of the thorax and the upper (thoracic) surface of the diaphragm, whilst the **peritoneum** covers most of the organs of the digestive system, the wall of the abdominal cavity and the lower (abdominal) surface of the diaphragm. The peritoneum also extends into the pelvis. The **pericardium** is the serous membrane which forms the pericardiac cavity and covers the heart.

### IV. BONES AND JOINTS OF THE HUMAN BODY

#### IV. 1. The basic anatomical structure of bones

Adult bones have an outer compact shell and an inner spongy part which is cavitated. The cavities are surrounded by trabecular, mesh–like bone tissue. The **red bone marrow** resides in the cavities. Long bones contain a large medullary cavity in the elongated part, whilst their end pieces are spongy inside. Pneumatic bones contain air-filled cavities which are empty. Bones are covered by a fine connective tissue layer; this is the **periosteum** which conveys the blood vessels and the nerves. The medullary cavities are lined by the **endosteum**, another fine layer of connective tissue. The periosteum and the endosteum contain osteoblastic cells from which new bone can be made. The preservation of the periosteum and endosteum during bone surgery is very important for the healing of bone.

#### IV. 2. Histology of bone

Bone tissue contains various **cells** and a substantial amount of intercellular substance, called **bone matrix**. Bone matrix consists of inorganic matter, which is partly calcium and phosphorus salts, forming hydroxyapatite crystals, and partly amorphous calcium phosphate. The organic matter of the matrix is mainly collagen and several glycoproteins. The association of hydroxyapatite with the organic molecules is responsible for the hardness and resistance of bones.

There are three different cell types in bone:
1. **Osteoblasts** are responsible for the synthesis of the organic materials of the matrix. Their presence is necessary for the deposition of inorganic matter, too. As soon as they deposit matrix around themselves, they differentiate into **osteocytes**.

2. **Osteocytes** are responsible for the maintenance of healthy bone tissue and the composition of the matrix itself. The osteocytes occupy the microscopic cavities called the **lacunae** of the bone. The cytoplasmic processes of the osteocytes extend into the **canaliculi**, which connect the lacunae to the capillaries. The cytoplasmic processes are in contact with the capillaries; this cell–to–cell contact is the site of every transport process between the blood and the bone. The neighboring osteocytes are connected by means of their processes, so the transported substances proceed from cell to cell and quickly reach the osteocytes surrounding a single capillary.

3. **Osteoclasts** are large, multinucleated cells derived from blood–borne monocytes. They are involved in the resorption of the matrix: they digest the organic molecules and liberate inorganic salts from the extracellular substance.
IV. 3. The main types of bones in the human body

The adult human skeleton consists of more than 200 bones. They differ in shape and size but they have common features as concerns the shape and internal structure. The main types are as follows:

1. long bones (humerus and metacarpals);
2. flat bones (hip bone and parietal bone);
3. irregular bones (vertebrae and carpal bones);
4. pneumatic bones, containing cavities which are filled with air (maxilla).

IV. 4. The human skeleton

The human skeleton consists of the axial skeleton, the extremities and the skull. The axial skeleton is formed by the vertebrae, which together constitute the spine, the ribs and the sternum (breast–bone). The extremities have two parts; the free extremity and the girdle, which connects the limb to the axial structures. The upper extremity has the shoulder girdle, which consists of the clavicle and the scapula. The free extremity includes the humerus (arm–bone), the radius and the ulna (forearm–bones), the bones of the wrist (carpal bones) and the bones of the hand (metacarpal bones and the phalanges of the fingers). The lower extremity has the pelvic girdle (or pelvis), which consists of the hip bones, the sacrum and the coccyx (tail–bone). The bones of the free limb are the femur (in the thigh), the patella (or knee-cap), the tibia and the fibula (in the leg), the tarsal bones, the metatarsal bones and the phalanges of the fingers (in the foot). The skull (cranium) has two parts: the one sheltering the brain is the neurocranium, the other which belongs to the face is the viscerocranium. The top of the neurocranium (the calvaria) is built up from flat bones; the base is formed by complicated, often cavitated bones, such as the temporal, occipital and sphenoidal bones. The inner surface of the base of the skull supports the brain and forms several openings, holes and canals for the cranial nerves. The outer surface is closely associated with the bones of the viscerocranium and has articular facets for the first cervical vertebra (which is called the atlas). This atlantooccipital joint is the site of the movements of the head.

The viscerocranium has several (often hidden) bones which form the oral cavity, the nasal cavity and the orbit. The most prominent bones are the mandible (lower jaw), the maxilla (upper jaw) and the zygomatic bone (cheek bone). Some of these bones are pneumatic bones containing closed, air–filled cavities, which ultimately open into the nasal cavity with narrow canals. These cavities are the paranasal sinuses: the frontal sinus (in the frontal bone), the
ethmoidal sinuses (in the ethmoid bone), the sphenoid sinus (in the sphenoid bone) and the maxillary sinus (in the maxilla). Their inflammation is called sinusitis.

IV. 5. Joints of the human body

Joints are unions between bones. Depending on the type of tissue situated between the bones we distinguish bony, fibrous, cartilaginous and synovial joints. Bony unions are developmentally related to cartilaginous ones; in the hip bone, for instance, the different parts are connected by cartilaginous segments which, during postnatal development undergo gradual ossification and the bony parts grow together, forming a single hip bone by the end of puberty. In fibrous joints, the bones are connected by fibrous tissue. The sutures between the bones of the skull are typical fibrous connections. In cartilaginous joints, the bony surfaces are united by fibrocartilaginous discs. The pubic symphysis connecting the hip bones is a typical cartilaginous joint. The bodies of the vertebrae are separated by intervertebral discs, which are cartilaginous joints too. Fibrous and cartilaginous joints allow very limited, sometimes undetectable movements. Synovial joints, on the other hand, permit a large variation of movements. Synovial joints have bony surfaces covered by cartilage and separated by a gap, the articular cavity. The joint is covered with a dense connective tissue forming the articular capsule, which isolates the joint from the surroundings. The capsule is attached to the bones. The dense connective tissue sometimes forms articular ligaments, which strengthen the joint and limit the movements. The articular cavity is lined from inside by a delicate vascular membrane, the synovial membrane. The synovial membrane secretes a watery, viscous fluid, the synovial fluid, which lubricates the articular surfaces. The inflammation of the synovial joint is called arthritis.
V. MUSCLES OF THE HUMAN BODY

V.1. The main histological types of muscle tissue

V.1.1. Smooth muscle

These are long, fusiform cells, which form thick layers in tubular organs (stomach, intestines, etc.). Smooth muscle forms organs too, such as the uterus or the prostate. Smooth muscle layers may form thick, ring-like structures (the sphincters) in the wall of certain tubular organs (e.g. the pyloric sphincter of the stomach). Smooth muscle is innervated by autonomic nerves.

V.1.2. Cross-striated muscle

Cross-striated muscle is of two kinds histologically, depending on the differences in the cellular organization.

Cardiac muscle is built up from single muscle cells, which often branch and are connected by highly specialized intercellular junctions. Cardiac muscle is highly vascularized and the capillaries run between the muscle cells, ensuring a fast and effective oxygen supply. Cardiac muscle forms one large organ, the heart. Heart muscle does not require innervation because the muscle cells generate rhythmic action potentials. However, the heart is richly innervated by autonomic and sensory nerves which are able to modulate its functions. The cardiac muscle forms characteristic surface elevations inside the heart: these are the papillary muscles in the ventricles and the pectinate muscles in the atria.

Skeletal muscle is highly specialized cross-striated muscle which forms definite organs, the skeletal muscles. Skeletal muscles are composed of cross-striated muscle fibers which are large, elongated multinucleated muscle cells. The main components of the muscle fiber are the myofibrils, which are the contractile elements, occupying 85-90% of the total cell volume. Each myofibril is composed of serially repeating segments of identical ultrastructure, the sarcomeres. An individual sarcomere is 2.5-3 μm long and bordered by electron-dense plates, the Z lines or discs. Between two Z lines, we encounter several other lines and bands, all of which reflect the orderly arrays of the contractile proteins actin, troponin and tropomyosin. The contraction of the myofiber is brought about by the shortening of the sarcomeres by means of a sliding movement of the actin filaments towards the center of the sarcomere. During relaxation, this sliding movement is reversed and the normal resting length of the sarcomere (2.5-3 μm) is restored. The cytoplasm of the myofiber is called the sarcoplasm. It contains free ribosomes, mitochondria, coated vesicles and lysosomes. The endoplasmic reticulum forms the sarcoplasmic reticulum, which is an orderly array of
flattened, fenestrated sacs around the myofibrils. The sarcoplasmic reticulum contains membrane-associated Ca,Mg ATPase and a water-soluble calcium-binding protein, calsequestrin. Depolarization of the muscle membrane (initiated at the neuromuscular junction) stimulates the rapid release of Ca\(^{++}\) from the sarcoplasmic reticulum and this in turn activates the contractile mechanism of the sarcomere. Relaxation requires a longer time and is achieved by the active Ca, Mg ATPase–mediated return of Ca\(^{++}\) into the sarcoplasmic reticulum.

The muscle fibers are innervated by sensory and motor nerves, which establish receptors (e.g. muscle spindles) and effectors (neuromuscular junctions) on the surface of the fibers. The skeletal muscles are innervated by cranial and spinal nerves. There are more than 300 skeletal muscles in the human body.

**V.2. The anatomy of the skeletal muscles**

**V. 2. 1. Muscles as organs**

Muscle fibers form groups called muscle fascicles. These fascicles are separated by connective tissue, the perimysium. The fascicles and the perimysium together form the muscle, which is again covered by loose connective tissue. The connective tissue systems contain the nerves and blood vessels supplying the muscle. The “fleshy” part of the muscle is called the “belly” or “head”, which moves during contraction and relaxation. This part of the muscle (the head or belly) determines muscle shape and size.

The belly of the muscle regularly tapers into a tendon. The tendon is dense connective tissue and connects the muscle to other structures (e.g. bones). The tendons may have different shapes, thicknesses and lengths. Mainly tendons form the origin and the insertion of the muscles. The points of origin and insertion explain the functions of a particular muscle. In the case of the limbs, the upper (proximal) location is regularly termed the origin, and the lower (distal) one the insertion. In muscles connecting the limbs to the trunk, the origin is regularly closer to the midsagittal plane. Tendons are often surrounded by tendon sheaths. Tendon sheaths are delicate tubes with an outer thick and strong fibrous layer and an inner, thin, shiny synovial coat. Inflammation of the tendon sheath is quite frequent; it is called tenosynovitis.

Muscles have been named according to (1) their location (brachialis, pectoralis); (2) their direction (rectus, obliquus); (3) their action (supinator, flexor); (4) their shape (deltoid, trapezius); (5) the number of divisions or heads (quadriceps); or (6) their points of attachment (sterno - cleido - mastoid).
Muscles form muscle groups which are named according to their location in the body (facial muscles, thoraco-humeral muscles, perineal muscles, etc.) or according to their functions (muscles of mastication, muscles of respiration, flexors, extensors, abductors, adductors, etc.). Skeletal muscles have the capacity of healing and regeneration. Severed or destroyed muscle fibers may be replaced by newly-formed ones. Regeneration of skeletal muscle fibers is complete following segmental necrosis, but it is incomplete in response to necrosis of large areas. In these cases healing is completed by fibrosis (scarring). Careful surgical treatment promotes the process of regeneration of injured skeletal muscles.

V. 2. 2. Innervation of the skeletal muscles

The skeletal muscles are innervated by spinal and cranial nerve α– and γ–motor neurons, which establish neuromuscular junctions on the surface of the muscle fibers. However, for muscles to work effectively, the motor neurons have to adjust their activity from time to time. These adjustments are made with the help of sensory nerve endings, which provide the information on the state of contraction. The sensory nerve endings form receptors in the muscle: these are the muscle spindle and the Golgi tendon organ.

The neuromuscular junction is a highly-specialized synapse in which the axon terminal of the α–motor nerve cell releases acetylcholine upon nerve excitation, to bring about the transmission of the nerve impulse to the muscle. The transmitter acetylcholine acts on postsynaptic acetylcholine receptors, which are large protein molecules in the plasma membrane of the muscle. Surplus acetylcholine is destroyed by acetylcholine esterase, which is located in the synaptic cleft of the neuromuscular junction.

The sensory nerve endings terminate in the muscle spindles, which are encapsulated receptors between the muscle fibers. The spindle is 80–250 μm thick and up to 10 mm long. The number of spindles in the muscle varies; the small muscles of the hand have the richest supply, and the large limb muscles are the least well-supplied. The spindle has its own intrafusal muscle fibers which are wrapped up by the sensory nerve endings. The intrafusal fibers are supplied by the γ–motor neurons, which establish neuromuscular junctions in the muscle spindle. These motor end–plates are smaller and slightly different in shape as compared to the ordinary ones. The Golgi tendon organs are found at the musculotendinous junctions. These are encapsulated receptors where a single sensory axon ramifies between the bundles of collagen fibers.

The normal function, size and shape of the muscles largely depend on the presence of functioning neuromuscular junctions, that is the presence of normal innervation. Damage to
the motor end-plates (e.g. in consequence of poisoning with the snake venom \(\alpha\)-bungarotoxin, or the illness myasthenia gravis), an injury to the motor nerve fibers running in the peripheral nerve, or the destruction of motor nerve cells by spinal cord injury or illness such as motor neuron disease, can impair or even destroy the whole motor unit. As a consequence, the muscle will be unable to perform the voluntary movements. This situation is called paralysis or palsy. The muscle becomes weak and thin; this is muscle atrophy. The signs of atrophy are often visible on the body surface, and frequently used in the setting-up of a neurological diagnosis.

V. 3. The main muscle groups of the human body

The skeletal muscles are arranged regularly in groups, which act on a particular joint or on several joints simultaneously. Some members of the group act together, performing the same or very similar movements; these muscles are called synergists. Other members of the group may perform the opposite movement at the same joint; these muscles are the antagonists. Muscle groups are often named on the basis of their functions (i.e. the kind of movement produced). Thus, we distinguish flexors, extensors, abductors, adductors, rotators, pronators, supinators, evertors, invertors, levators, depressors, protractors and retractors. There are special groups performing complex movements, which we can not describe with these terms. These are the muscles of respiration, the muscles of mastication, the muscles of facial expression and the cross-striated muscles of the perineum (these muscles act on the urethra, vagina, penis, clitoris and anus). Other special groups of cross-striated muscles, which do not belong to the skeletal system, are the muscles of the tongue, pharynx and larynx (although some of them are attached to skeletal structures).

VI. ANATOMY AND HISTOLOGY OF THE CIRCULATORY SYSTEM AND HISTOLOGY OF THE BLOOD

The circulation of blood fulfils several important functions, such as the oxygenation of the tissues and the transport of metabolic products, hormones, drugs, immunoglobulins, inflammatory cells and infectious agents. Blood reaches the individual cells of the human body, and maintains their communication with other cells and their constant environment.
Anatomically, the circulatory system is composed of a huge system of blood vessels and a central pump, the heart, which maintains the movement and pressure of the fluid. The blood vessels are arteries, which divide into smaller branches and then into arterioles, which give rise to capillaries. Capillaries are the smallest vessels and communicate directly with the cells. Capillaries are collected into venules, and then into smaller and larger veins.

VI. 1. The heart (cor)

The heart is a muscular organ containing four cavities, two atria and two ventricles. The muscle layer of the heart is the myocardium. The atria and the ventricles are separated by valves, which regulate the direction of blood flow. The heart is covered with a double-layered serous membrane, the pericardium. Some drops of fluid are present between the two layers, facilitating the contraction movements. The heart cavities and the valves are lined with another smooth, shiny, thin layer, the endocardium. Inflammations may affect the various layers separately, so we distinguish myocarditis, pericarditis and endocarditis.

VI. 1. 1. The right atrium

The right atrium is on the right side of the heart. It receives three veins, which bring venous blood from the body and from the heart itself; the superior vena cava comes from the direction of the head, neck and upper limbs, the inferior vena cava comes from the abdominal cavity and lower limbs, and the much smaller coronary sinus conveys the venous blood from the heart musculature. The right atrium opens into the right ventricle by means of the tricuspidal valve.

VI. 1. 2. The left atrium

The left atrium occupies mainly the posterior aspect of the heart as it lies in the thoracic cavity. The left atrium receives the pulmonary veins (regularly four), which bring fresh, oxygenated blood from the lungs. The left atrium is separated from the left ventricle by the bicuspidal (or mitral) valve. The two atria are separated by an interatrial septum, which has a thin, transparent segment called the fossa ovalis. During fetal life, the foramen ovale occupies this site, maintaining a communication channel between the two atria. Immediately after birth, the foramen ovale closes and becomes the fossa ovalis. If the foramen persists after birth, severe heart and circulatory problems develop. This is a case for cardiac surgery.

VI. 1. 3. The right ventricle

The right ventricle occupies the right–anterior aspect of the in situ human heart. Venous blood enters from the right atrium and leaves through the pulmonary trunk. The pulmonary trunk has its own valve (semilunar pulmonary trunk valve), regulating the direction of the
flow. The pulmonary trunk then divides into left and right pulmonary arteries, which enter the lungs.

**VI. 1. 4. The left ventricle**

The left ventricle occupies the anterior, left and inferior aspects of the heart *in situ*. It is larger and stronger than the right ventricle. Oxygenated blood from the left atrium flows in through the mitral valve and leaves through the aorta. The aorta is the main arterial trunk which distributes the oxygenated blood to the different body parts. The aorta has its own valves (*semilunar aortic valves*). The aorta also gives rise to the **right and left coronary arteries**, which supply the heart musculature. The two ventricles are separated by a thick, muscular **interventricular septum**.

**VI. 1. 5. The innervation of the heart**

The cardiac muscle has an intrinsic electric impulse–generating system. This consists of modified cardiac muscle cells which form visible anatomical structures in the wall of the heart. The structures are as follows:

1. the **sinoatrial node** in the wall of the right atrium,
2. the **atrioventricular node** in the interatrial septum,
3. the **atrioventricular bundle of His**, penetrating the fibrous border between the atria and ventricles,
4. the **right and left bundle branches of Tawara**, running under the endocardium of the interventricular septum toward the apex of the heart.

The specialized cells of this impulse–generating system are coupled to the working muscle cells by intercellular junctions, allowing the electric impulses to spread everywhere.

Apart from this intrinsic system, the heart is richly innervated by parasympathetic and sympathetic nerves. These nerves innervate the sinoatrial and atrioventricular nodes and the coronary vessels of the heart. The parasympathetic innervation is provided by the **vagus nerve**; the sympathetic nerves originate from the **cervical sympathetic ganglia**.

**VI. 2. The blood vessels of the human body**

There are two circulation systems in the human body, both of which originate from and end in the heart. Both systems consist of arteries, veins and capillaries.

**VI. 2. 1. The pulmonary circulation** originates from the right ventricle with the pulmonary trunk. The trunk divides into **left** and **right pulmonary arteries**, which enter the lungs, and divide into smaller branches and finally into capillaries. The capillaries surround the alveoli, where the gas exchange takes place, and then unite into larger and larger pulmonary veins.
The pulmonary veins (regularly four in number) terminate in the left atrium. The function of the pulmonary circulation is gas exchange. The venous blood (rich in carbon dioxide) flows through the branches of the pulmonary arteries toward the alveoli of the lungs, where gas exchange with inhaled atmospheric oxygen takes place and the oxygen enters the alveolar capillaries. These capillaries combine into the branches of the pulmonary veins, in which the arterial blood (rich in oxygen) flows from the lungs toward the left atrium.

VI. 2. 2. The systemic circulation is much larger and involves every part of the body. The arterial (oxygenated) blood leaves the heart through the aorta. The aorta is the largest blood vessel and distributes the blood to the main body parts. The first segment of the aorta is the ascending aorta; it gives off the coronary arteries. It then curves around the left main bronchus, forming the aortic arch. There is a small ligament connecting the aortic arch and the left pulmonary artery; Botallo’s ligament (ligamentum arteriosum). This is a developmental remnant of a real artery in fetal life; Botallo’s duct (ductus arteriosus). This duct shunts the blood from the pulmonary artery into the aorta; in fetal life, there is no respiration and no need for the blood to flow through the lungs. The aortic arch gives off the common carotid arteries for the head and neck, and the subclavian arteries for the upper limbs and thoracic wall. The common carotid arteries divide in the neck into external and internal carotid arteries. The next segment of the aorta is in the thoracic cavity, close to the vertebral column. It supplies the thoracic viscera and the thoracic wall. The aorta pierces the diaphragm and enters the abdominal cavity, where it supplies every abdominal organ and the wall. At the level of the fourth lumbar vertebra (this is the level of the umbilicus), the abdominal aorta divides into the common iliac arteries, which enter the pelvis and divide into external and internal iliac arteries. The external iliac arteries supply the lower limbs, while the internal iliac branches supply the pelvic organs (internal genital organs, urinary bladder, the lower part of the rectum) and the external genital organs. The internal iliac has one branch which functions in the fetal life only: the umbilical artery. The umbilical arteries (two in number) run to the umbilical cord and to the placenta and convey used blood. This blood is refreshed in the placenta and then returns to the fetus through the umbilical vein (a single, large vessel). The umbilical vein terminates in the liver of the fetus. The umbilical arteries and the vein obliterate after birth; their remnants are ligaments in the adult.

The veins of the systemic circulation are collected into the superior and inferior vena cava, both of which open into the right atrium. The superior vena cava collects the veins of the head
and neck, upper limbs and thoracic wall. The tributaries of the inferior vena cava come from the abdominal cavity, pelvis and lower limbs.

**VI. 2. 3. Portal venous circulation**

The abdominal viscera (except for the urinary organs) have a separate system of veins which do not join the inferior vena cava directly. They are first collected in the portal vein. The portal vein is a very large vein (2.5–3 cm in diameter) below the liver, which collects the venous blood coming from the stomach, small and large intestines, rectum, pancreas and spleen. The vein enters the liver and divides into smaller branches and finally into sinusoid capillaries. These capillaries are in contact with hepatocytes and thus the blood coming from the digestive system and containing every substance absorbed in the gut reaches the cells of the liver. The sinusoid capillaries are collected into the hepatic veins, which finally discharge into the inferior vena cava. **This is a double capillary and venous system in which arteries first give rise to capillaries; these take up different substances from the tissue, and then combine into the branches of the portal vein; this divides again in the liver into capillaries, which subsequently combine again into large veins.** This type of design of blood vessel architecture is called the **portal venous circulation**. Another (though much smaller) portal–venous-type circulation is present in the hypothalamo–hypophyseal system.

**VI. 2. 4. Histology of arteries, veins and capillaries**

The walls of arteries and veins have three layers, the tunica intima, tunica media and tunica adventitia. The thickness and composition of these layers differ considerably in arteries and veins, and depend on the size of the vessel too. However, there are similarities and structural principles, as follows. The intima is lined with a continuous layer of endothelial cells, which form a simple, squamous epithelium inside the blood vessel. The subendothelial layer contains delicate connective tissue fibers and occasional smooth muscle cells. The media consists of mainly smooth muscle and connective tissue fibers, whereas the adventitia contains connective tissue only. The vascular smooth muscle cells are richly innervated with sympathetic vasomotor nerves, whose neurotransmitter is noradrenaline. Discharge of noradrenaline from these nerves results in contraction of the smooth muscle and narrowing of the blood vessel (vasoconstriction). The arteries in the skeletal muscle also receive a cholinergic vasodilator nerve supply.

The capillaries are the smallest blood vessels maintaining the essential exchange of material between the blood and the tissues. The capillaries are lined with a single layer of flattened endothelial cells, a basal lamina and some reticular fibers. Depending on the morphology of
the endothelial cells, the intercellular junctions between them and the size of the capillary, we distinguish three different types.

1. The wall of the **continuous capillaries** consists of a layer of attenuated endothelial cells, which are coupled to each other with intercellular junctions. In cross-section, the elliptical nucleus of the endothelial cell bulges into the lumen of the capillary. The cytoplasm of the endothelial cell is approximately 0.4 μm thick and in most cases contains small (70 nm) membrane-bound transport vesicles. The intercellular junctions are mainly gap junctions, but in some continuous capillaries (in the brain and spinal cord) tight junctions are present. The tight junctions seal the interendothelial space completely; in these capillaries, therefore, only transcellular transport can take place. Continuous capillaries are present in the skeletal muscle, heart, brain, lung and skin.

2. In the next type, the cytoplasm of the endothelial cells is interrupted by microscopic holes or pores 80–100 nm in diameter. At these sites, a very thin pore diaphragm is created by the attachments of the inner and outer cell membranes. These blood vessels are called **fenestrated capillaries**. Such capillaries are present in the stomach, gut, pancreas and kidney. In the fenestrated capillaries of the kidney glomerulus, the pores are real holes without a pore diaphragm. The continuous and fenestrated capillaries have an average cross-sectional diameter of 8-12 μm.

3. **Sinusoid capillaries** are endothelium-lined, relatively large and irregular vascular channels. Unlike continuous and fenestrated capillaries which are cylindrical, the sinusoids conform in shape and size to the intercellular spaces of the organ they supply. The endothelium may be continuous (as in some lymphoid organs) or fenestrated (as in some endocrine glands), or may have large fenestrations or openings without basal lamina (as in the liver and red bone marrow).

**VI. 3. Histology of the blood**

Blood consists of the blood plasma and the cells floating in it. Plasma is an aqueous solution containing small and large molecules. Small molecules pass through the capillary wall and are in equilibrium with the extracellular fluid in different tissues. The large molecules are the plasma proteins: albumin, alfa-, beta- and gamma-globulins and fibrinogen. Gamma-globulins are antibodies, and they are therefore called immunoglobulins. Lipids are transported in the blood, but since they are insoluble in water, they are coupled to different plasma proteins. The cellular elements of the blood are summarized in Table 5.
**Erythrocytes (red blood cells)** do not have a cell nucleus; they contain hemoglobin, which carries the oxygen. Their life span is about 120 days. **Anemia** is a pathologic condition when the hemoglobin concentration of the blood (and the number of erythrocytes) is below the normal level. The **platelets** or **thrombocytes** are also anucleated membrane–bound corpuscles which are the cytoplasmic fragments of large **megakaryocytes** of the bone marrow. The **leukocytes** (white blood cells) are heterogenous, comprising the neutrophilic, eosinophilic and basophilic **granulocytes**, the **monocytes** and the **lymphocytes**. The granulocytes are named on the basis and staining properties of their cytoplasmic granules.

1. **Neutrophilic granulocytes** (neutrophils, polymorphonuclear cells) are easily recognized from their highly characteristic nucleus, consisting of two or more lobules connected by narrow strands. The number of lobules depends on the age of the cell. They contain intracytoplasmic granules which have little affinity for dyes; the cytoplasm is therefore pale. Their life span is about 8 days.

2. **Eosinophilic granulocytes** (eosinophils) are easily recognized in consequence of their coarse cytoplasmic granules, which stain pink with blood smear stains. Their nucleus is regularly bilobed. Their life span is about 8-12 days.

3. **Basophilic granulocytes** (basophils) have an elongated, often bent, sometimes bilobed nucleus. The cytoplasmic granules are large and stain deep purple.

4. **Monocytes** have a large cytoplasm, which stains grayish-blue because of the small cytoplasmic granules. The cell nucleus is eccentric, oval or bean-shaped. Monocytes originate from the red bone marrow, enter the circulation and, after spending 1-2 days in the blood, migrate into the connective tissues of the different organs, where they differentiate into tissue–specific macrophages.

5. **Lymphocytes** are rounded cells with a spherical, slightly indented cell nucleus. The nucleus is surrounded by a thin rim of clear blue cytoplasm.

The **platelets** or **thromboplastids** are minute, colorless, membrane–bound corpuscles. They do not contain nucleus and have only a few mitochondria and cytoplasmic granules. Their main function is to pave small endothelial defects and to limit bleeding by promoting the local coagulation of blood.

Leukocytes migrate into peripheral loose connective tissues in large numbers during inflammations and participate in different immunologic reactions. Erythrocytes, platelets and leukocytes are generated by the colony–forming progenitor cells of the red bone marrow. The proliferation and differentiation of blood cells takes place in the red bone marrow; only
mature cells are released into the blood circulation. The cells of the blood are easily accessible for medical investigation; peripheral blood smears can be stained with different methods, which allow study of the shape, size and quantity of the cells under the light microscope.

Table 5
The cells of the peripheral blood. The absolute numbers of all leukocytes are shown. The quantities of the different cell types are shown as percentages of this absolute number.

<table>
<thead>
<tr>
<th>CELL TYPE</th>
<th>SIZE (in μm)</th>
<th>NUMBER IN 1 μl BLOOD</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERYTHROCYTES</td>
<td>6-8</td>
<td>4-6 x 10⁶</td>
<td>CO₂ and O₂ transport</td>
</tr>
<tr>
<td>LEUKOCYTES</td>
<td></td>
<td>6-10 x 10³</td>
<td></td>
</tr>
<tr>
<td>Neutrophilic granulocytes</td>
<td>12-15</td>
<td>60 - 70 %</td>
<td>Phagocytosis</td>
</tr>
<tr>
<td>Eosinophilic granulocytes</td>
<td>12-15</td>
<td>2 - 4 %</td>
<td>Allergic reactions</td>
</tr>
<tr>
<td>Basophilic granulocytes</td>
<td>12-15</td>
<td>0 - 1 %</td>
<td>Histamine release</td>
</tr>
<tr>
<td>Monocytes</td>
<td>12-20</td>
<td>3 - 8 %</td>
<td>Phagocytosis</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>6-12</td>
<td>20 - 30 %</td>
<td>Immunologic reactions</td>
</tr>
<tr>
<td>PLATELETS</td>
<td>2-4</td>
<td>2-4 x 10⁵</td>
<td>Clotting of blood</td>
</tr>
</tbody>
</table>

VII. ANATOMY OF THE LYMPHOID ORGANS AND HISTOLOGY OF THE IMMUNE SYSTEM
The lymphoid organs are parts of the immune system, which provides surveillance and defense against infectious agents. The lymphoid organs contain, store and generate the cells of the immune system; the lymphocytes. The lymphocytes originate from the stem cells of the red bone marrow, and invade the lymphoid organs, where they differentiate and proliferate, resulting in different cell types (Table 6).
Table 6
Cell types of the immune system. The main cell groups are written in capitals, whilst the subgroups are listed underneath.

<table>
<thead>
<tr>
<th>CELL TYPE</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. B–LYMPHOCYTES</td>
<td>Humoral immune response</td>
</tr>
<tr>
<td>1.1. Plasma cells</td>
<td>Production of antibodies</td>
</tr>
<tr>
<td>1.2. Memory cells</td>
<td>Immunological memory</td>
</tr>
<tr>
<td>2. T–LYMPHOCYTES</td>
<td>Cellular immune response and regulation of the immune system</td>
</tr>
<tr>
<td>2.1. Helper cells</td>
<td>Stimulate differentiation of B–lymphocytes</td>
</tr>
<tr>
<td>2.2. Suppressor cells</td>
<td>Regulate cellular and humoral immunity</td>
</tr>
<tr>
<td>2.3. Cytotoxic cells</td>
<td>Destroy foreign cells</td>
</tr>
<tr>
<td>2.4. Memory cells</td>
<td>Immunological memory</td>
</tr>
<tr>
<td>3. NATURAL KILLER</td>
<td>Kill virus–infected cells and tumor cells</td>
</tr>
<tr>
<td>LYMPHOCYTES</td>
<td></td>
</tr>
<tr>
<td>4. ANTIGEN PRESENTING CELLS</td>
<td>Ingest foreign proteins and present selected parts of these proteins to lymphocytes</td>
</tr>
</tbody>
</table>

The lymphoid organs are the **thymus, spleen, tonsils, lymph nodes** and **lymph vessels**. The **thymus** is located behind the sternum, in the upper part of the thoracic cavity. It is subdivided into lobes, which contain T–lymphocytes, blood vessels and reticular connective tissue. The T–lymphocytes differentiate to a certain degree, then leave the thymus and settle in the spleen, lymph nodes and lymphoid follicles. At around puberty, the thymus stops functioning, the lymphoid tissue disappears and fat tissue occupies the organ. The **spleen** is located in the upper left part of the abdominal cavity, close to the stomach and pancreas. Its main function is to participate in the metabolism of hemoglobin; old erythrocytes are destroyed and their hemoglobin content is recycled and stored in the spleen. The **tonsils** are situated in the pharynx, where they defend the human body against infectious agents coming through the nasal and oral cavities. They contain hundreds of thousands of lymphocytes and reticular connective tissue. The lymphocytes and reticular cells form large groups, the **lymphoid follicles**, which are the sites of proliferation and differentiation of lymphocytes. Lymph nodes
are small (5–10 mm), bean–shaped organs, which are connected to each other by means of delicate lymph vessels, and so they form groups or chains in different body parts. The invasion of a lymph node by bacteria causes the inflammation of this small organ; this is lymphadenitis. Inflamed lymph nodes are enlarged and painful and the skin above them is often red. Lymphadenitis can be an early and useful sign of certain bacterial infections. Lymph vessels are thin–walled tubular structures lined with endothelium. Small vessels are collected into larger ones and finally into seven main vessels, the thoracic duct, the right and left bronchomediastinal trunks, the right and left jugular trunks and the right and left subclavian trunks, which open into the system of the superior vena cava. The lymph is the extracellular fluid collected from various organs and tissues. It circulates, coming from and returning into the blood. During circulation, it goes through several lymph nodes (or tonsils), where any foreign or infectious particle can be captured by the mononuclear phagocytes. The antigenic molecules of these particles will be presented immediately to the lymphocytes, which develop an immune response against the particle. The immune response can be the production of specific antibodies or the proliferation of cytotoxic and natural killer lymphocytes, which aim to eliminate it.

VIII. ANATOMY AND HISTOLOGY OF THE RESPIRATORY ORGANS

The respiratory system includes the airways, which lead to the respiratory surface of the lungs. The airways begin with the nasal cavity, which continues in the pharynx, the larynx, the trachea (or windpipe), the main bronchi and the bronchial tree inside the lungs. The bronchi divide into bronchioli, which terminate in the respiratory epithelium of the alveolar ducts and the alveoli.

VIII. 1. The nasal cavity and the pharynx

The nasal cavity is part of the viscerocranium. The cavity is subdivided into two halves by the nasal septum, and is connected to the air–filled paranasal sinuses, which are the cavitations of some skull bones. There are frontal, maxillary, sphenoidal and ethmoidal sinuses. The paranasal sinuses are connected to the nasal cavity via narrow ducts and openings. The nasal cavity and the sinuses are lined with a well–vascularized mucous membrane. The mucous membrane is covered with ciliated columnar epithelium and contains goblet cells and mucous glands. On the roof of the nasal cavity, there is a small area covered with olfactory
epithelium. The olfactory epithelium is a primary sensory epithelium from which the olfactory nerve arises. Inflammation of the nasal cavity is rhinitis. The nasal cavity joins the upper part of the pharynx (called the nasopharynx), which is a muscular tube covered with mucous membrane. This part of the pharynx displays accumulations of lymphoid tissue in the mucous membrane; this is the pharyngeal tonsil. The tympanic cavity of the middle ear opens into the nasopharynx with a cartilaginous tube, the auditory tube.

VIII. 2. The larynx

The larynx commences at the lowest (or laryngeal) part of the pharynx. It is anterior to the pharynx and it is therefore palpable on the surface of the neck. It consists of five large laryngeal cartilages, linked to each other by means of movable articulations. The movements of the laryngeal cartilages are mediated by cross-striated laryngeal muscles. These muscles are important in vocalization. The cavity of the larynx is covered by a mucous membrane, containing glands and goblet cells. The entrance to the cavity is protected from above by one of the laryngeal cartilages, the epiglottis. The cavity is subdivided into an upper part, called the vestibule, a middle part, called the glottis, and a lower, subglottic space. At the lower edge of the vestibule, we find two folds of mucous membrane; these are the vestibular folds (or false vocal folds). Below the vestibular folds, the glottis contains the vocal folds or vocal cords, which are movable and can close the cavity completely. The vocal folds are essential in vocalization; the air flowing through the glottis causes the vocal folds to vibrate and this, together with the resonator cavities of the pharynx, mouth, nose and paranasal sinuses, results in different sounds. The mucous membrane of the larynx may swell in certain pathological conditions; this life-threatening situation is called edema of the larynx. The inflammation of the larynx is laryngitis.

VIII. 3. The trachea and the main bronchi

The trachea or windpipe is a cartilaginous tube about 11 cm long, which commences below the larynx and divides into two main bronchi in the thoracic cavity behind the upper part of the sternum. The wall of the trachea contains not only cartilage, but also smooth muscles and a well-developed mucous membrane. The mucous membrane is lined with ciliated columnar epithelium, containing goblet cells. The goblet cells and the glands secrete a thin layer of mucus, which covers the epithelium and which is continuously pushed towards the nasal cavity by means of the movements of the cilia. This mechanism serves to eliminate dust particles present in the inhaled air. The trachea divides into the right and left main bronchi,
the right being the shorter and the wider. The consequence of this anatomical situation is that any foreign body which enters the airways drops into the right main bronchus.

**VIII. 4. The lungs and the bronchial tree**

**VIII. 4. 1. The lungs (lung=pulmo)** are pinkish, spongy, very elastic organs, located in the right and left sides of the thoracic cavity. The space in the middle, between the two lungs, is called the *mediastinum*. The mediastinum contains the heart, the superior vena cava, the ascending aorta and the aortic arch, the right and left pulmonary arteries and veins, the trachea and the main bronchi, the esophagus, the phrenic and vagus nerves, a series of lymph nodes and the thoracic duct. The lungs have a conical apex which extends above the level of the first rib, and a flattened base which lies on the surface of the diaphragm. The lungs and the inner surface of the thoracic cavity are covered with two separate layers of a large serous membrane, the *pleura*. The lungs are divided into lobes: three in the right and two in the left lung. The lobes contain anatomical units which are the bronchopulmonary segments. The segments are demarcated by connective tissue, and they can therefore be resected surgically.

**VIII. 4. 2. The bronchial tree** is found inside the lungs. The main bronchi reach the mediastinal surface of the lungs and divide into lobar bronchi. The *lobar bronchi* enter the lung tissue and divide into segmental branches, which enter the bronchopulmonary segments. Each *segmental bronchus* gives off smaller branches, which finally branch into the bronchioles. The walls of the bronchi contain cartilage and smooth muscle. The mucous membrane is lined with ciliated columnar epithelium, while the lamina propria contains lymphocytes and mast cells. The *bronchioles* lose the cartilage, but the amount of smooth muscle and elastic fibers increases. The smooth muscle of the bronchi and the bronchioles is innervated by autonomic nerves. The smooth muscle regulates the diameter of the bronchioles; its constriction increases, and its relaxation decreases the resistance of the airways. Stimulation of the sympathetic nerve fibers relaxes the smooth muscle and decreases the airway resistance, whereas the stimulation of the parasympathetic fibers (which arrive in the vagus nerve) has the opposite effect: smooth muscle constriction and the increase of airway resistance. *Asthma* is a consequence of an increased of the resistance of the airways, partly because of smooth muscle contraction, and partly because of the chronic inflammation of the mucous membrane in the bronchial tree.

**VIII. 4. 3. Respiratory portion of the lung**

The smallest bronchioles are called *respiratory bronchioles* because they contain alveoli in their wall. The respiratory bronchioles continue into the *alveolar ducts*, from where the
alveoli open. The alveoli are ball–like thin–walled structures covered with the respiratory epithelium, where the exchange of $O_2$ and $CO_2$ takes place. The alveolar epithelial cells and the capillary endothelial cells are separated only by the basal lamina, and these three layers together form the blood–air barrier, through which the gas exchange takes place. The alveolar epithelial cells are of two kinds: type I and type II. Type I cells participate in the formation of the blood–air barrier, whilst type II cells secrete an extracellular alveolar coating, called pulmonary surfactant, which reduces the surface tension in the alveoli; without the surfactant, the alveoli tend to collapse during expiration. The synthesis of the surfactant commences at around the 7th month of pregnancy. In premature births, when the amount of surfactant is less than necessary, the infant has serious difficulties in breathing; this is the respiratory distress syndrome. Another cell type in the wall of the alveoli is the alveolar macrophage, which is the phagocyte of the lung. The wall contains elastic fibers and fibroblasts too. Inflammation of the bronchial tree is called bronchitis or bronchiolitis (if the bronchiolar segment is more involved). Inflammation invading the alveoli is called pneumonia.
IX. ANATOMY AND HISTOLOGY OF THE DIGESTIVE (ALIMENTARY) SYSTEM

The digestive system commences with the mouth and the oral cavity and ends with the rectum and anus. The organ system consists of several tubular organs and large exocrine glands. Its proper function depends on the presence of a huge mucous membrane surface where the decomposition and absorption of food take place.

IX. 1. The oral cavity

The oral cavity contains the teeth and the tongue. The oral and nasal cavities are separated from each other by the palate. The oral cavity has two parts: the vestibule (the slit between the lips, the cheeks and the teeth) and the oral cavity proper. The palate consists of the bony hard palate and the muscular soft palate. The teeth articulate with the upper and lower jaws. The crown of the tooth is covered with enamel, which is the hardest substance in the body. The neck of the tooth is surrounded by the gums (gingiva) and the roots extend into the sockets of the jaws. The bulk of the tooth is composed of dentin, which is a calcified connective tissue. The dentin is actively produced throughout life by the odontoblast cells. Inside the dentin, the tooth contains the pulp cavity, which contains the nerves and capillaries supplying the tooth. The odontoblasts line the cavity from inside. Local destruction of the enamel by acids produced by some bacteria is called dental caries.

The tongue (lingua or glossa) is a muscular organ, important in chewing, deglutition and speaking. Some muscles of the tongue are attached to the mandible and the hyoid bone. Other muscles remain inside the tongue and run transversely, longitudinally or vertically. The muscles mediate the various movements and changes in shape and size. The upper (dorsal) surface of the tongue is covered with a thick and strong stratified squamous epithelium which forms the papillae. The papillae fulfil a mechanical function and also contain special sense organs, the taste buds. The lower (ventral) surface of the tongue is covered with a thinner mucous membrane (also with stratified squamous epithelium). This surface is directly related to the bottom of the oral cavity and connected to it by a fold of the mucous membrane, the frenulum of the tongue. On the lower surface of the tongue, the branches of the sublingual vein are visible. Due to the thin mucous membrane and the presence of the large veins, drugs deposited below the tongue are absorbed rapidly.

Three pairs of large salivary glands open into the oral cavity: the parotid, the submandibular and the sublingual glands. Apart from these, the mucous membrane of the
oral cavity contains abundant small salivary glands. The oral cavity opens into the pharynx with the isthmus of the fauces, which is bordered by the soft palate and palatine tonsils (above and laterally) and the root of the tongue (below). Behind the root of the tongue we find the epiglottis, which protects the entrance of the larynx during swallowing. Inflammation of the oral cavity is called stomatitis.

IX. 2. The pharynx and the esophagus

The pharynx is a muscular tube; the muscles are cross–striated. Its cavity is subdivided into nasal, oral and laryngeal parts, communicating with the appropriate cavities. The inflammations are called pharyngitis. The esophagus (or gullet) is the direct continuation of the pharynx. It is about 25 cm long and is located in the posterior mediastinum. The wall of the esophagus contains cross–striated (in the upper third) and smooth muscles (in the lower two–thirds) which are innervated by the vagus nerve. The lower part of the esophagus pierces the diaphragm and opens into the stomach. The junction of the stomach and the esophagus is called the cardia.

IX. 3. The stomach (ventriculus, gaster)

The stomach is located in the upper left–middle part of the abdominal cavity, immediately below the diaphragm. It is a pouch–like reservoir for food and has distinct anatomical parts. At the cardia we find the fundus, then the body and finally, close to the duodenum, the pyloric part (or pylorus). The inner surface is folded and covered with mucous membrane. The lamina propria of the mucous membrane is filled with the gastric glands; these glands secrete the gastric juice, which contains hydrochloric acid, digestive enzymes and mucus. The mucus protects the surface from the effects of hydrochloric acid. The juice also contains a special glycoprotein, called the intrinsic factor, which is absolutely necessary for the absorption of vitamin B₁₂. The outer wall of the stomach is built up from several layers of smooth muscle. This smooth muscle is thickened at the gastroduodenal junction forming the pyloric sphincter. The stomach is covered completely with peritoneum. Inflammation of the gastric mucosa is gastritis.

IX. 4. The small intestine

The digestion takes place in this approximately 7–m–long tube. It has three anatomical segments: the duodenum, the jejunum and the ileum. The lumen is covered with mucous membrane, which forms folds and the intestinal villi. The intestinal villi are microscopic, finger–like projections of the mucous membrane which are specialized for the absorption of nutrients. The columnar epithelial cells (enterocytes) have a brush border and contain several
enzymes on their surface (e.g. alkaline phosphatase, aminopeptidase and glucosidase). Goblet cells are present between them. The glands of the mucous membrane open between the villi. These intestinal glands are the reservoirs of young, undifferentiated cells, which are the supply of the enterocytes. They also produce enzymes which regulate the bacterial flora of the small intestines. Inflammations of the small intestine are called enteritis (enteron=intestine).

IX. 4. 1. The duodenum is the first and shortest segment; it is about 25 cm long. It is the continuation of the stomach; the two organs are separated by the pyloric sphincter. The duodenum is fixed to the posterior abdominal wall and located below the liver, on the right side of the vertebral column. The liver and the pancreas are connected to the cavity of the duodenum through their excretory duct systems. The liver secretes the bile, which flows through the common bile duct and discharges into the duodenum. The excretory ducts of the pancreas, the main and the accessory pancreatic ducts open into the duodenum too. The common bile duct and the main pancreatic duct may join and form a short, common duct called the ampulla of Vater, which is surrounded by a smooth muscle ring, the sphincter of Oddi.

IX. 4. 2. The jejunum and the ileum are the rest of the 7-m-long small intestine. They are similar anatomically, although there are some histological differences. The ileum contains abundant large lymphoid follicles in the mucous membrane; these are Peyer’s patches. The jejunum and the ileum are invested completely by the peritoneum. The large peritoneal ligament running to the jejunum and ileum forms the mesentery, where the blood vessels, nerves and lymph vessels and nodes supplying the intestine are located. The coils and loops of the jejunum and ileum fill most parts of the abdominal cavity.
IX. 5. The large intestine (colon)
The continuation of the ileum is the large intestine, which is larger in caliber and has a sacculated appearance. The colon is lined with mucous membrane, which forms transverse folds, but there are no intestinal villi. The intestinal glands are present in large numbers. Anatomically there are five different portions: the cecum, the ascending, the transverse, the descending and the sigmoid colon. The cecum is located in the right lower part of the abdomen. The ileum joins it directly at the ileocecal junction. Inside we find the ileocecal valve, which is a large intestinal fold. The cecum has a finger-like projection, 3–4 mm thick and 5–8 cm long, which is the appendix (or vermiform process). It is a lymphoid organ containing many lymphoid follicles. Its inflammation is appendicitis. The ascending colon is on the right-hand side of the abdomen; it extends to the liver, where it bends and forms the transverse colon. The latter crosses the abdominal cavity, extends to the spleen, and then turns down on the left side and forms the descending colon. The last portion is the sigmoid colon, which is located in the upper part of the pelvis (above the urinary bladder and uterus). The large intestine is invested completely by the peritoneum. Inflammation of the large intestine is called colitis.

IX. 6. The rectum and the anal canal
The last segment of the alimentary canal is located in the pelvis. The histological structure of the rectum is similar to that of the colon. The last 3–4 cm is the anal canal, which opens onto the perineum with the anus. The opening is surrounded by a voluntary (cross–striated) sphincter muscle. The anal canal is the site of epithelial transition, where the intestinal mucous membrane (and the columnar epithelium) gradually turn into stratified squamous, then keratinizing stratified squamous epithelium and skin structure. Large venous plexuses are present in the mucosa and submucosa layers, which often cause complaints as varicosities (or hemorrhoids). The presence of the mucous membrane in the upper part of the anal canal gives the opportunity for the delivery of drugs in the form of a suppository.

IX. 7. The liver (hepar)
The liver is a large gland and the center for the metabolism of absorbed foodstuffs. This is the largest organ of the body, weighing about 1.4 kg. It is located in the right upper part of the abdominal cavity, immediately below the diaphragm and has two (right and left) lobes. It has two surfaces: the upper or diaphragmatic and the lower or visceral surface. The visceral surface includes the porta hepatis, which is the entrance or gate for the blood vessels (the hepatic artery and the portal vein) and the common excretory duct of the bile duct system.
(the hepatic duct). The gallbladder (cholecyst) resides on the right side of the visceral surface. The liver secretes the bile, which is a greenish fluid containing water, inorganic salts, bile acids, bilirubin and cholesterol. The bile is carried via the hepatic duct, which joins to the cystic duct soon after leaving the liver. The cystic duct comes from the gallbladder and unites with the hepatic duct, and together they form the common bile duct, which runs down to the duodenum.

The histological structure of the liver is uniform and simple: the hepatocytes build up the liver lobules, which are separated by connective tissue. Inside the lobules, we find an extensive system of sinusoid capillaries, the liver sinusoids. In the liver sinusoids, Kupffer cells are anchored to the endothelial surface. The Kupffer cell is a typical mononuclear macrophage. The hepatocytes are located alongside the endothelial wall of the sinusoids. The sinusoids converge to the center of the lobule and discharge into the central vein. The central veins form the sublobular veins, which finally discharge into the hepatic veins. The hepatic veins join the inferior vena cava. The hepatocytes take up various nutrients and other substances (e.g. drugs) from the blood. The other capillary system in the lobule is that of the bile capillaries. The bile is secreted by the hepatocytes and drained from the lobule by the bile capillaries. The bile capillaries flow into excretory ducts, which become larger and larger and finally form the hepatic duct. Between the sinusoids and the hepatocytes, scattered fat-storing cells (the Ito cells) are located, which play a role in the metabolism of vitamin A. The liver has a fairly large regenerative capacity; it contains young, undifferentiated cells which, replace the dying hepatocytes. This regeneration is very important during the healing of benign hepatitis.

**IX. 8. The pancreas**

The pancreas is the other large gland associated with the alimentary tract. It secretes the pancreatic juice, which digests fat, carbohydrates and proteins. The gland is located transversely in front of the lumbar vertebrae. Anatomically, it is subdivided into a head (on the right side), body and tail (on the left side). The head is surrounded by the duodenum, while the body and the tail are located behind the stomach. The excretory ducts, which are the main and the accessory ducts, open into the duodenum. Histologically, the pancreas is subdivided into exocrine and endocrine parts. The exocrine part produces the digestive juice, and the endocrine cells synthesize insulin and glucagon, which are hormones regulating the glucose metabolism of the body.

**IX. 9. The peritoneum**
Most of the abdominal organs and the wall of the abdominal cavity are covered with a shiny, smooth, thin sheet of tissue: the peritoneum. The peritoneum is a serous membrane with one layer of squamous epithelium and some loose connective tissue attached to it. The capillaries in the loose connective tissue secrete a small amount of clear fluid (the peritoneal fluid), which lubricates the surface. This slightly lubricated smooth epithelial surface helps the movements of the stomach and the intestines. The liver, the stomach and the intestines are completely ensheathed (with the exception of parts of the duodenum) by the peritoneum. The peritoneum not only covers, but also fixes these organs with the help of its duplicatures or ligaments. The mesentery is the largest peritoneal ligament. These ligaments carry the blood and lymph vessels and nerves to the organs. Inflammation of the peritoneum is peritonitis.

**IX. 10. The blood supply of the abdominal viscera**

The abdominal viscera are supplied by the branches of the abdominal aorta. The organs of the alimentary tract and the spleen are supplied by the arteries, which branch into capillaries in the wall of the viscera. The capillaries are collected as veins and these organ veins (e.g. the mesenteric veins, the splenic vein, and the gastric veins) discharge into the portal vein, which is the largest vein in the abdomen. The portal vein enters the liver together with the hepatic artery at the porta hepatis, and forms smaller and smaller branches and finally the sinusoid capillaries. The sinusoid capillaries are gathered in the central veins, which flow into larger and larger veins, and finally into the hepatic veins. The hepatic veins join the inferior vena cava. This portal circulation means that the veins coming from the organs (stomach, gut, pancreas and spleen) form a second capillary system in the liver and all the substances absorbed from the gut and coming from the tissues of the organs flow through the liver. These nutrients, hormones, drugs, toxic chemicals, vitamins and minerals reach the cells of the liver and become metabolized. The metabolized products are released into the blood of the sinusoids.

**IX. 11. Enteroendocrine cells**

The gastrointestinal epithelium and the glands contain a widespread, scattered system of single cells and small cell groups which secrete hormones into the local capillaries or into the local tissue. The following hormone-like substances have been identified so far: somatostatin, gastrin, cholecystokinin, neurotensin, motilin, secretin, pancreatic polypeptide, serotonin and histamine. The enteroendocrine cells are most numerous in the duodenum, stomach, jejunum and ileum. Their number is limited in the colon and in the epithelium of the gallbladder and biliary ducts. The cells of the islets of Langerhans also belong to the enteroendocrine system.
X. ANATOMY AND HISTOLOGY OF THE UROGENITAL ORGANS

The urinary organs are the kidneys, the ureters, the urinary bladder and the urethra. Apart from the urethra, the urinary organs do not differ in the two sexes.

X. 1. The kidney (ren, nephros)

The kidneys are bean-shaped, reddish-brown organs, measuring 12 cm in height, 7 cm in width and 2.5 cm in thickness. They are paired, attached to the posterior abdominal wall at the level of the 12th vertebra and the last rib, on the two sides of the vertebral column.

The kidney is the excretory organ producing the urine, which is collected in the renal pelvis (pyelon) and transported by the ureter to the urinary bladder. The kidney has an outer cortex and an inner medulla. The cortex contains the histological structures responsible for urine excretion (see later). The medulla contains the collecting tubules or ductules, which transport the urine into the renal pelvis. The medulla forms triangular structures, the renal pyramids, which are separated from each other by the cortex, forming the renal columns. The tip of the pyramid is the renal papilla, connected to the renal pelvis by the calyces, which are the cup-like extensions of the renal pelvis. The renal pelvis is the upper, dilated part of the ureter. The shape of the calyces and pyelon can be studied by means of X–radiography: this method is called pyelography.

The blood supply of the kidney is from the renal artery which is a branch of the abdominal aorta. Venous blood is drained by the renal vein into the inferior vena cava.

X. 2. The ureters and the urinary bladder (urocysta)

The ureters are paired muscular tubes 28-34 cm in length, which convey the urine from the kidneys to the urinary bladder. The bladder is situated behind the pubic symphysis in the anterior part of the lesser pelvis, covered from above by the peritoneum. In the male, the rectum is behind and the prostate is below the bladder. In the female, the body and the fundus of the uterus is above and the cervix and the vagina are behind the urinary bladder.

X. 3. The urethra

As concerns the anatomy and histology of the urethra, considerable differences exist between males and females. The male urethra is 17-20 cm long; it begins at the internal orifice in the urinary bladder, and opens at the external orifice which is on the glans penis. The prostatic glands, the ejaculatory ducts and the bulbourethral glands open into the upper part of the
urethra. The lower part or penile portion is the longest: about 15 cm. It is embedded in the corpus spongiosum of the penis.

The female urethra is very short (about 4 cm); it has the internal orifice in the bladder and the external orifice in the vestibule of the vagina. It is closely related to the anterior wall of the vagina. Micturition is controlled by the sphincter urethrae, which is a voluntary, cross-striated muscle.

X. 4. Histology of the urinary organs

The **nephron** is the histological and functional unit of the kidney. The nephron performs the excretion process by means of an arterial capillary network and an elongated and differentiated epithelial tubular system, the proximal and distal convoluted tubules. Most parts of the nephron are located in the cortex; some segments of the tubular system extend into the medulla. The medulla also includes the **collecting tubules** and **collecting ducts**, which finally open into the minor calyces. The parts of the nephron are as follows:

- **The renal corpuscle**, which contains a capillary network called the glomerulus and is surrounded by a double-walled epithelial capsule, Bowman's capsule. Bowman's capsule has a vascular pole where the blood vessels enter, and a urinary pole on the opposite side, where it opens into the proximal convoluted tubule. The capillaries of the glomerulus are fenestrated and lined by a thick basal lamina, which has strong selective filtration barrier properties because of its macromolecular organization.

- **The proximal convoluted tubule** commences at the urinary pole of Bowman’s capsule. It is lined by a simple columnar or cuboidal epithelium covered by a brush border and containing thousands of mitochondria.

- **The loop of Henle** is a U-shaped tubular structure; it extends into the medulla and connects the proximal and distal convoluted tubules. The loop consists of a **thick descending limb**, very similar to the structure of the proximal convoluted tubule; a **thin descending limb** and a **thin ascending limb** (both covered with a flattened epithelium); and a **thick ascending limb** that closely resembles the distal convoluted tubule. The physiological roles of the thin and thick limbs are fundamentally different.

- **The distal convoluted tubule** is lined by a simple cuboidal epithelium without a brush border. This part of the nephron is an ion–exchanger: in the presence of aldosterone, sodium ion is absorbed and potassium ion is secreted. It also secretes hydrogen and ammonium ions into the urine.
The distal tubules open into the collecting ducts, which finally lead the urine into the renal pelvis. The collecting duct contributes to ion and water transport; its epithelium is the site of action of the antidiuretic hormone (ADH). The renal pelvis, the ureter, the urinary bladder and some parts of the urethra are lined with mucous membrane, covered with stratified epithelium called urothelium.

**X. 6. The male genital organs**

The genital organs are very different and diverse in the two sexes, and their anatomy and histology are therefore discussed separately.

The male genital organs comprise the testis, the epididymis, the vas deferens, the seminal vesicles, the prostate, the penis, the scrotum and the bulbourethral glands. The testis and the epididymis are found in the scrotum, while the prostate and the seminal vesicles are situated in the lesser pelvis. The vas deferens originates in the scrotum and enters the lesser pelvis through the inguinal canal. The penis is the male external genital organ. The bulbourethral glands are embedded into the tissues of the perineum.
X. 6. 1. The testis (orchis, didymos)
This is an oval, slightly flattened, plum-shaped, whitish, paired organ in the scrotum (size: 4 x 2.5 cm). The left one is usually slightly lower than the right. It is covered by a small portion of the peritoneum on the anterior, medial and lateral sides. Due to the presence of the peritoneum, the slightest injury to the testis is very painful. The testis is covered with a whitish connective tissue capsule, the tunica albuginea. The testis contains a delicate tubule system, which is the site of spermiogenesis.

X. 6. 2. The epididymis
This is a system of tortuous tubules and ducts which finally constitute a single duct, the duct of the epididymis. The thickened continuation of the duct of the epididymis is the vas deferens. The tubules and the duct of the epididymis are the route and reservoir (receptacle) for the sperms. In the scrotum, the organ is attached to the posterior side of the testis.

X. 6. 3. The vas deferens
This is a muscular tube, about 45 cm long; it commences in the scrotum, and then enters the abdominal cavity through the inguinal canal. It is directed toward the urinary bladder, where it takes the duct of the seminal vesicle and then pierces the prostate and discharges into the prostatic part of the male urethra. This last portion is called the ejaculatory duct. During ejaculation, the rhythmic contractions of the vas deferens propel the sperms towards the urethra.

X. 6. 4. The seminal vesicle is a pair of glands, that secrete a slightly alkaline fluid which, together with the prostatic fluid, constitutes the bulk of the semen. The seminal vesicle is firmly attached to the urinary bladder. It has a short duct which discharges into the vas deferens.

X. 6. 5. The prostate is a chestnut-shaped organ, immediately below the urinary bladder. It contains connective tissue, smooth muscle and glands. It surrounds the urethra and the prostatic glands open directly into the urethra.

The semen is the fluid which is discharged during ejaculation; it contains the secretions of the seminal vesicles and the prostatic glands, plus the spermatozoa. The semen is slightly alkaline and it contains fructose, amylase and acid phosphatase. Its volume is approximately 3.5 ml; the sperms account for 10% of this volume (this means about 2–3 x 10^8 spermatozoa).
X. 6. 6. The bulbourethral gland  is a pair of small, pea-sized glands on the perineum which open into the membranous portion of the male urethra. They secrete a mucous fluid which lubricates the urethra during erection.

X. 6. 7. The penis has a fixed root on the perineum and a body which hangs free. The root is made up of three erectile tissue bodies: the left and right crus of the penis and the bulb of the penis. The crura are fixed to the pubis and covered by muscles. The bulb is attached to the outer surface of the perineum and is also covered by a muscle. The body is composed of three cylinders of erectile tissue: the two corpora cavernosa and the corpus spongiosum. At its distal extremity, the corpus spongiosum expands to form the glans penis. The glans is covered by a thin skin duplicate, the prepuce or foreskin. It is connected to the glans below by the frenulum. At the tip of the glans, we find the external orifice of the urethra.

X. 6. 8. The scrotum is an outpouching of the lower abdominal wall. It contains the testes, the epididymides and the lower end of the vas deferens. There is a muscle in the wall of the scrotum which slightly elevates the testis. This is the cremaster reflex. The reflex can be initiated with a scratch on the medial side of the thigh; this stimulus elicits the contraction of the muscle which raises the testis and the scrotum on one side.

X. 7. The female genital organs
There are both internal and external female genital organs. The internal organs are the ovaries, the uterine tube, the uterus and the vagina. The external organs are the greater and lesser lips, which cover the vestibule of the vagina and the clitoris.

X. 7. 1. The ovary
The ovary is a paired almond-shaped body in the pelvic part of the abdominal cavity. It is covered partly by the peritoneum, and partly by a simple cuboidal epithelium. The peritoneum fixes the ovaries to the surface of the broad ligament (see below). The ovary contains the ovarian follicles, which are endocrine structures that help the ripening of the egg cells. The tissue between the follicles is called the interstitium. The ovarian cycle involves the process of ripening of the egg cell, the development and rupture of the ovarian follicle and the build-up of the corpus luteum. Depending on the size and complexity, we distinguish primary, secondary and mature (or Graafian) follicles. The rupture of the Graafian follicle expels the egg cell or ovum into the abdominal cavity; this process is ovulation. The remains of the follicle are the granulosa and theca cells, which begin to proliferate rapidly after ovulation and build up the corpus luteum, which is an endocrine gland secreting estrogens and progesterone. If pregnancy occurs, the corpus luteum flourishes and functions as an
endocrine organ. This is the corpus luteum of pregnancy. When pregnancy does not occur, the corpus luteum degenerates by the end of menstruation. This is the corpus luteum of menstruation. The endocrine cells are replaced by a fibrous scar tissue and this structure is called the corpus albicans.

X. 7. 2. The uterine tube (Fallopian tube, oviduct)
The uterine tube is essentially a part of the uterus, from which it extends laterally, similarly to the extended wings of a bird. The muscular tube has two openings: one is inside the uterus (uterine opening) and the other (abdominal opening) is very close to the ovary. The abdominal opening is as wide as a mouth and has 8-10 finger-like processes (the fimbriae), which hang around the ovary. One fimbria touches that point of the ovary where the Graafian follicle ripens (fimbria ovarica). During ovulation, the egg cell uses this fimbria as a ladder to reach the uterine tube. The main function of the uterine tube is to transport the ovum towards the uterus. The contractions of the smooth muscle and the fluid secreted by the mucous membrane of the oviduct help this function. The fertilization regularly takes place in the oviduct. Obstruction of the Fallopian tube (e.g. in chronic inflammations) causes infertility.

X. 7. 3. The uterus (womb)
The uterus is located between the urinary bladder and the rectum in the female lesser pelvis. Its size approximates to that of the fist. It has a strong muscular wall, called the myometrium, and an inner mucous membrane, called the endometrium. The endometrium displays cyclic histological changes; this is the menstrual cycle. The uterus has three anatomical parts, the fundus, the body and the neck (cervix). The oviduct joins it between the fundus and the body, and the vagina is connected to the cervix. One part of the cervix is visible inside the vagina: this is the vaginal part or portio vaginalis. The vaginal part of the cervix can easily be investigated from the vagina. This method is called colposcopy (colpos = vagina), and it is extremely important as a screening examination for uterine cancer. The uterus and the tubes are covered outside with a layer of peritoneum; the peritoneum on both sides of the uterus forms a duplicature, the broad ligament. The broad ligament supports the uterus, the oviduct and the ovary.

X. 7. 4. The vagina
The vagina is the female organ for copulation. It is connected to the uterus by means of the cervix, and the spermatozoa deposited in the upper part of the vagina have to pass through the cervical canal in order to reach the cavity of the uterus. The vagina is very closely related
anteriorly to the female urethra. Mechanical injuries during childbirth therefore often damage not only the wall of the vagina, but also the voluntary sphincter muscle of the urethra. This injury causes *urinary incontinence*, which means that the patient is not able to control her micturition. These patients have to be treated surgically.

**X. 7. 5. The external genital organs**

The vagina and the female urethra open into the vestibule, which is covered by the lesser lips (*labia minora*). The urethral opening is anterior to that of the vagina. In virgins, the vaginal opening is flanked by folds of the mucous membrane, the *hymen*, which ruptures during the first copulation. Two small glands open into the vestibule: the *vestibular glands* (or *Bartholin’s glands*), which secrete during sexual excitement. Anteriorly, the two lesser lips reach the *clitoris*, which is an erectile body richly innervated by sensory nerve endings. The lesser lips are covered by the greater lips, which are cutaneous folds, covered with the pubic hair. The slit between them is called the *pudendal cleft*. Anteriorly, the greater lips are continuous with the *mons pubis*, a rounded, hairy eminence on the body surface.

**X. 7. 7. Ovarian and uterine cycles**

At the time of puberty, the female endocrine activity begins to undergo monthly changes. These changes occur as regular 28–day cycles affecting mainly the genital organs. The cycles are regulated by the gonadotropins of the anterior pituitary: the *follicle stimulating hormone* (FSH) and the *luteinizing hormone* (LH). These two hormones act on the ovary and regulate the maturation of the ovarian follicles (FSH), and the development of the corpus luteum (LH). Estrogens are produced by the granulosa and theca cells of the follicle, whilst progesterone is the product of the corpus luteum. The cyclic changes in the ovary regulate the cyclic changes in the endometrium. The timing of the menstrual cycle begins on the first day of the bleeding or *menses*. The menses is the discharge of the tissue debris of the degenerated endometrium plus the clotted blood originating from the disrupted blood vessels. During the last days of the menses, the endometrium begins to heal; the epithelium regenerates from the remains of the glands. During the *follicular phase*, under the effects of estrogens, the endometrium proliferates, and new glands and stroma are produced. The progesterone of the corpus luteum stimulates the secretion of the glands and the transformation of the stroma cells. The degeneration of the endometrium is precipitated by an abrupt decline in blood progesterone level; because of the degeneration, the blood vessels rupture, blood infiltrates the stroma, and the new menses begins. The changes in the blood hormone levels, the ovary and the endometrium are summarized in Table 7.
Table 7
Correlation of the pituitary and ovarian hormone levels and the histological changes in the ovary and uterus during an idealized 28–day menstrual cycle.

<table>
<thead>
<tr>
<th>PHASE OF THE CYCLE</th>
<th>MENSTRUATIONAL</th>
<th>FOLLICULAR</th>
<th>OVULATION</th>
<th>LUTEAL</th>
<th>PREMENSTRUATIONAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAYS</td>
<td>1–5</td>
<td>4–13</td>
<td>12–16</td>
<td>15–25</td>
<td>26–28</td>
</tr>
<tr>
<td>FSH PRODUCTION</td>
<td>increasing</td>
<td>high, then declining</td>
<td>low</td>
<td>low</td>
<td>increasing</td>
</tr>
<tr>
<td>LH PRODUCTION</td>
<td>low</td>
<td>low, then increasing</td>
<td>high</td>
<td>high</td>
<td>decreasing</td>
</tr>
<tr>
<td>OVARY</td>
<td>degeneration of corpus luteum, beginning of follicular development</td>
<td>growth and maturation of follicle</td>
<td>rupture of Graafian follicle</td>
<td>active corpus luteum</td>
<td>degeneration of corpus luteum</td>
</tr>
<tr>
<td>ESTROGEN PRODUCTION</td>
<td>low</td>
<td>increasing</td>
<td>high</td>
<td>decline and a second rise</td>
<td>decreasing</td>
</tr>
<tr>
<td>PROGESTERONE PRODUCTION</td>
<td>none</td>
<td>none</td>
<td>low</td>
<td>increasing</td>
<td>decreasing</td>
</tr>
<tr>
<td>ENDOMETRIUM</td>
<td>degeneration and desquamation of endometrium, early regeneration</td>
<td>regeneration and proliferation of endometrium</td>
<td>proliferation of glands</td>
<td>secretion, glandular dilatation, edema of stroma, enlargement of stroma cells</td>
<td>end of secretion and beginning of degeneration</td>
</tr>
</tbody>
</table>
XI. ENDOCRINE GLANDS

XI. 1. The pituitary gland (hypophysis cerebri)

The pituitary gland is anatomically connected to the hypothalamus (diencephalon). It is divided into the neurohypophysis, the adenohypophysis and the intermediate lobe.

The neurohypophysis (posterior lobe) consists of diencephalic tissue at the base of the hypothalamus; it contains the nerve endings of the paraventricular and supraoptic nuclei, which secrete their peptide hormones (oxytocin and vasopressin) into the capillaries of the neurohypophysis.

The adenohypophysis (anterior lobe) is larger: it constitutes 75% of the total weight of the gland. The adenohypophysis consists of irregular cords and nests of glandular epithelial cells, a sparse network of connective tissue and blood vessels. The connective tissue forms a collagenous capsule around the gland. The blood vessels come from a portal circulation and are mainly thin-walled sinusoidal capillaries spread out between the epithelial cells. The glandular cells may be stained differentially by a number of methods. Depending on their staining characteristics, we may divide them into three groups. The acidophilic cells produce growth hormone (somatotropin) and prolactin. Basophilic cells produce glycoprotein hormones; thyroid stimulating hormone (TSH), LH and FSH. They also produce adrenocorticotrophic hormone (ACTH) and melanocyte stimulating hormone (MSH).

Chromophobic cells are degranulated cells. They do not stain with the above methods; their cytoplasm is pale. Specific identification of the cells is possible by means of immunohistochemistry. The adenohypophysis may undergo functional hypertrophy when the number of the gland cells increases. This normally occurs during pregnancy.

The intermediate lobe is rudimentary in man; it contains some follicular structures which secrete MSH.

XI. 2. Pineal gland (epiphysis cerebri)

This endocrine gland is part of the epithalamus, located above the roof of the third ventricle and attached to the diencephalon. The pineal gland consists of some connective tissue framework, glial cells, pinealocytes and nerve terminals. There are no neuronal cell bodies in the gland. Sympathetic nerve fibers enter from the subarachnoid space and originate from the superior cervical ganglion. The pinealocytes are phylogenetically related to photoreceptors, although in most mammalian species they are not sensitive to light. The pinealocytes secrete melatonin into the capillary perivascular spaces.

XI. 3. Thyroid gland
The gland is located in the neck around the upper part of the trachea, close to the larynx. It has two lobes and a connecting segment. The parathyroid glands are embedded into it. The thyroid gland contains **follicles**, which are rounded (ball-like) groups of endocrine cells. The follicle has a cavity inside, which is filled with a gelatinous substance, the **colloid**, which contains thyroglobulin, an iodinated large glycoprotein. Thyroglobulin is synthesized by the follicular cells. The necessary iodide is taken up from the blood. The gland secretes a mixture of two iodinated hormones, **thyroxine** or **tetraiodothyronine**, and **triiodothyronine**. The hormones are produced from thyroglobulin. Some isolated clusters of **parafollicular cells** are located between the follicles. The parafollicular cells secrete another hormone, called **calcitonin**, whose main effect is to lower blood calcium levels via inhibition of the activity of osteoclast cells in bones.

**XI. 4. Parathyroid glands**
The parathyroids are four small glands embedded into the capsule of the thyroid gland. The glands secrete the **parathyroid hormone**, which acts on bone tissue by increasing the number and activity of osteoclasts.

**XI. 5. Suprarenal glands**
The suprarenal glands are yellowish, triangular bodies sitting on the upper pole of the kidneys. They have an outer **cortex** and an inner **medulla**, which are entirely different in function. The endocrine cells of the **adrenal cortex** are regulated by the corticotropin hormone (ACTH) of the anterior pituitary, and secrete steroid hormones: glucocorticoids, mineralocorticoids and androgens. The adrenal medulla is part of the sympathetic nervous system; the endocrine cells are innervated by cholinergic preganglionic sympathetic nerve fibers. Upon stimulation of the preganglionic fibers, the medullary cells release adrenaline and noradrenaline into the blood.

**XI. 6. Endocrine pancreas**
The endocrine cells of the pancreas form cell groups, the **islets of Langerhans**. These cellular islets produce several hormones: **insulin**, **glucagon**, **somatostatin** and **pancreatic polypeptide**. The islets are innervated by sympathetic and parasympathetic postganglionic nerve fibers, which contribute to the regulation of the secretory activity. Destruction of the islets (e.g. during the inflammations of the pancreas) leads to a serious disturbance of the glucose metabolism, called **diabetes mellitus**. These patients must take insulin daily in order to maintain their blood glucose level.

**XI. 7. The gonads**
The testis and the ovary have endocrine functions which are regulated by the hormones of the anterior pituitary. The interstitial cells (or Leydig cells) in the testis synthesize the male hormone called testosterone, which is responsible for the secondary male sex characteristics (pubic hair, size of the penis, etc.). The ovary contains several endocrine cells which produce estrogens and progesterone, depending on the phase of the menstrual cycle. These hormones are secreted mainly by the theca cells and the granulosa cells of the follicles. The interstitial cells of the ovary synthesize small amounts of androgens.

XII. ANATOMY AND HISTOLOGY OF THE NERVOUS SYSTEM

The human nervous system consists of the central nervous system (CNS) and the peripheral nervous system (PNS). The spinal cord and the brain comprise the CNS, whereas the PNS consists of the autonomic nervous system, the peripheral nerves and the sensory ganglia.

XII. 1. Histology of the CNS

The CNS consists of the brain and the spinal cord, which are grayish, soft tissues in the living body, sheltered by the strong bony structures of the skull and the vertebral column. The tissues of the CNS contain neurons and glial cells, which are heavily interconnected and build up a particular architecture, i.e. a structured system of cell groups and their orderly connections in different CNS areas. The CNS has a very small extracellular space and no connective tissue inside.

The neurons are highly--specified, non-dividing cells equipped with processes, which are the elongations of the cell body. These processes are the dendrites and the axon. The neuron may have several dendrites, but only one axon. Both dendrites and axons conduct electric impulses (e.g. action potentials). The connections between the neurons are called synapses. The synapse is a highly--organized intercellular contact, the structural details of which are visible only with the electron microscope. Synapses have two sides: a presynaptic nerve ending is connected to a postsynaptic dendrite, axon or cell body. The presynaptic and postsynaptic membranes are separated by a tiny cleft (the synaptic cleft) and a macromolecular meshwork which fills the synaptic cleft. Presynaptic nerve endings contain
chemical substances (mainly peptides and amino acids), which are called **transmitters**, simply because these molecules transmit electric signals from one cell to another. Transmitters are stored in small vesicles, the **synaptic vesicles**. Each transmitter molecule has its own **receptor** in the cell membrane of the neuron; these receptors are the targets of numerous neuroactive drugs. Transmitter receptors activate **ion channels** in the membrane directly or via second messengers, resulting in a change in the postsynaptic membrane potential. In response to the nerve impulse, transmitters are released from the presynaptic nerve ending, penetrate the synaptic cleft and bind to their receptors on the postsynaptic side. Neurons and their elongations form the **gray matter** of the CNS.

The **glial cells** outnumber the neurons in every part of the CNS. They are smaller than neurons and they are able to proliferate (dividing cells). Glial proliferation needs specific (mostly pathological) signals. We distinguish three types of glia in the CNS: the **astrocyte**, the **oligodendrocyte** and the **microglia**. Glial cells and some axons form the **white matter** in the CNS. **Astrocytes** have processes which surround the neurons, the synapses and the blood vessels, including the capillaries. They participate in the uptake and synthesis of transmitters, in the regulation of ion concentrations around neurons, in the elimination of CO₂ from nervous tissue and in the transport of metabolites from and to the capillaries. Neuronal death induces the proliferation of astrocytes, which then contribute to the scar tissue inside the CNS. **Oligodendrocytes** form a **myelin sheath** around the axons of the CNS, and also help to regulate the microenvironment around neurons. The myelin sheath is built up from the cell membrane of the oligodendrocyte processes. The **microglia** is the mononuclear phagocyte of the CNS. Its main function is phagocytosis and participation in immunologic reactions of the CNS.

Apart from these highly-specialized cells, the brain and the spinal cord contain numerous blood vessels. Large blood vessels run on the surface of the brain and spinal cord. There are small vessels and continuous capillaries inside the CNS, which are structurally and functionally different from those in other tissues. The wall of these blood vessels is very tight and the transport of the materials (oxygen, carbon dioxide, sugar, amino acids, vitamins, drugs, etc.) is strictly regulated by the needs of the nervous tissue. The structural basis of this strict regulation is called the **blood-brain barrier** (BBB). Any breakdown of the BBB leads to serious pathological consequences, mainly **brain edema**. Injuries to larger CNS vessels cause **stroke**, **brain infarction** or **intracranial bleeding**, all of which may threaten the life of the patient, or at least cause the death of some neurons and the proliferation of astrocytes and
microglial cells. The glial proliferation may destroy CNS structures by scarring. The neurons of the CNS are not able to divide, and there is therefore no structural regeneration in the brain and spinal cord.

The choroid plexus of the brain is responsible for the production of much of the cerebrospinal fluid (CSF). Every cerebral ventricle has its own choroid plexus, which is supplied by the choroidal arteries. The choroid plexus consists of extremely well-vascularized connective tissue and an epithelium which covers it. The epithelium is simple cuboidal, with basement membrane and microvilli on the CSF surface. The epithelial cells are connected with tight junctions, which form the blood-CSF barrier. The choroid plexus epithelium contains high concentrations of angiotensin converting enzyme, which is localized on the microvillar surface.

The mammalian choroid plexus contains noradrenergic, cholinergic and peptidergic nerves and nerve terminals. The nerves originate from the superior cervical ganglion. The nerves probably regulate the vasculature and the choroid epithelial cells. The choroid plexus epithelium contains a number of receptors: adrenergic, dopamine, histamine, serotonin, melatonin, muscarinic, vasopressin, oxytocin, angiotensin II, insulin, prolactin, growth hormone and benzodiazepine receptors have been demonstrated. Hormones may enter from the blood through the choroid plexus into the CSF. This system could therefore constitute an important pathway for neuroendocrine signaling in the brain.
XII. 2. The histology of the PNS

The peripheral accumulations of neurons and glial cells form the peripheral ganglia. These are grayish structures surrounded by loose connective tissue. We distinguish sensory and autonomic ganglia. They differ considerably in their structures. The sensory ganglion contains the primary sensory neurons (and some glial cells too), which have long peripheral processes ending in the skin, joints, muscles, blood vessels and viscera. The other process of the primary sensory neuron enters the brain stem or the spinal cord, establishes synapses on the CNS neurons and thus conveys the different senses to the CNS. The primary sensory neurons contain a large variety of neurotransmitters, but their principal transmitter substance is an excitatory amino acid. The amino–acidergic transmission is modulated by a number of peptides (somatostatin, substance P, cholecystokinin, etc.) and non–peptide (e.g. adenosine) modulators. The result of this process is called sensory perception. The autonomic ganglion contains multipolar neurons which mediate the autonomic motor functions (such as sweating, salivation, gut movements and blood vessel constriction). Glial cells are present in the autonomic ganglia too.

The long axonal processes of the sensory ganglion cells and the motor neurons of the CNS form the peripheral nerve. The peripheral nerve is a whitish structure, surrounded by loose connective tissue. It is easily separable from other anatomical structures such as blood vessels, muscles and viscera. Peripheral nerves contain the axons of motor, sensory and autonomic neurons. These axons are surrounded by a special glial cell, the Schwann cell. Most of the Schwann cells form an insulating myelin sheath around axons. This myelin sheath consists of closely apposed layers of the glial cell membrane, similar to that in the CNS. The importance of myelin sheaths becomes obvious in disease: in demyelinating diseases (such as peripheral neuropathy, when the myelin sheath is partly destroyed and the axons degenerate), there are serious difficulties in the conduction of nervous impulses, causing pathological symptoms and signs. Following different kinds of injuries, the peripheral nerves are able to regenerate. If they are cut or crushed, the axons sprout and grow out from the proximal nerve stump and the Schwann cells proliferate. The growing axons and their Schwann cells reach and reinnervate their peripheral targets (such as sensory receptors, muscles and autonomic nerve plexuses). This phenomenon takes months to be completed, but it is of huge importance and has a large impact in medical practice. Injuries to the vertebral column or to the limbs may destroy peripheral nerves and, as direct and immediate consequences, the skin loses its sensory innervation and the muscles become paralysed.
Careful surgical treatment of these patients promotes the regeneration of the peripheral nerve, which restores the functions lost after the injury.

The peripheral nerves originating from the spinal cord form **nerve plexuses** (such as the brachial plexus or the lumbar plexus). The nerves inside the plexuses are anatomically and topographically related to each other. They have similar destinations (this means that they supply certain parts of the body, *e.g.* the upper limb), which are determined during the early development of the embryo. Because of their close topographical relation, certain injuries may damage the entire plexus. The brachial plexus is particularly prone to such bulk damage.
XII. 3. The anatomy of the CNS

The CNS develops from the neural tube, the cranial part of which forms vesicle–like dilatations; the primary brain vesicles. These develop further into secondary brain vesicles, which finally differentiate into the structures of the CNS. Table 8 summarizes the ontogenetic origin of the human CNS.

<table>
<thead>
<tr>
<th>PRIMARY BRAIN VESICLES</th>
<th>SECONDARY BRAIN VESICLES</th>
<th>ADULT CNS STRUCTURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>RHOMBENCEPHALON</td>
<td>MYELENCENCE-PHALON</td>
<td>MEDULLA OBELONGATA</td>
</tr>
<tr>
<td></td>
<td>METENCEPHALON</td>
<td>PONS, CEREBELLUM</td>
</tr>
<tr>
<td>MESENCEPHALON</td>
<td>MESENCEPHALON</td>
<td>MESENCEPHALON</td>
</tr>
<tr>
<td>PROSENCEPHALON</td>
<td>DIENCEPHALON</td>
<td>THALAMUS, HYPOTHALAMUS, METATHALAMUS, EPITHALAMUS, SUBTHALAMUS</td>
</tr>
<tr>
<td></td>
<td>TELEENCEPHALON</td>
<td>BASAL GANGLIA, LIMBIC SYSTEM, CEREBRAL CORTEX, HEMISPHERES</td>
</tr>
</tbody>
</table>
The embryonic brain vesicles contain cavities; these cavities persist and grow, and in the adult brain we call them cerebral ventricles. The lateral ventricles are found in the cerebral hemispheres, the third ventricle is inside the diencephalon and the fourth ventricle is between the brain stem and the cerebellum. The lateral and the third ventricles communicate through the interventricular foramen, and the third and fourth ventricles communicate through the cerebral aqueduct, which is inside the mesencephalon. The fourth ventricle has three small openings, which communicate with the subarachnoid space. The CSF is continuously produced by the choroid plexuses inside the ventricles, and flows from the lateral ventricles towards the fourth, from where it enters into the subarachnoid space. In the subarachnoid space, the CSF is absorbed into the large venous sinuses of the brain. The production of surplus CSF or obstruction of the route of CSF flow results in an accumulation of the fluid in the ventricles, a disease called hydrocephalus.

XII. 3. 1. The spinal cord
The spinal cord (medulla spinalis), the lower part of the neuraxis is located in the vertebral canal. In adults, its length is approximately 45 cm and its weight is about 30 g. There are 31 pairs of spinal nerves which are anatomically connected to the spinal cord and constitute a large part of the PNS. Each spinal nerve pair belongs to a thin transverse slice of the spinal cord: this transverse slice is the spinal segment. The spinal nerves form ventral and dorsal roots, which are attached to the cord on its ventral and dorsal surfaces, respectively. The dorsal root has a swollen portion at the site of the dorsal root ganglion. The cord is surrounded by the meninges, the subarachnoid space of which contains CSF. The meningeal sheath is considerably longer than the spinal cord; it ends at the level of the second sacral vertebra. Between the second lumbar and second sacral vertebral levels, the meningeal sac contains the lumbosacral spinal nerve roots: this collection of fibers is called the cauda equina. This part of the subarachnoid space is the lumbar cistern, the site of the lumbar puncture. There are two uninterrupted grooves in the midline: the anterior median fissure and the posterior median sulcus. The spinal cord contains an outer white matter and inner gray matter. The central canal, the cavity (“ventricle”) of the cord, is located in the gray matter.
ANATOMY OF THE GRAY MATTER
The gray matter contains nerve cells, glial cells, blood vessels and some nerve fibers. It is arranged in longitudinal columns, which appear on the transverse section as gray “horns”. The dorsal horn is posterior and deals mainly with sensory information, while the ventral horn is anterior and has mainly motor functions. The ventral horn contains large groups of α- and γ-motor neurons, which innervate the skeletal muscles of the body. There is a prominent lateral horn at thoracic levels, which contains preganglionic sympathetic neurons. The gray matter of the two sides is connected with the gray substance around the central canal.

THE ANATOMY OF THE SPINAL SEGMENT
The spinal segments are the anatomical and functional units of the spinal cord. There are no visible borders between them: the spinal roots determine their location. Each segment contains one pair of spinal nerves, the dorsal root ganglion, the ventral and dorsal roots, and a complete set of sensory and motor neurons, which are interconnected and form the anatomical basis of the reflex arcs. The sensory axon enters through the dorsal root ganglion and dorsal root, and synapses with interneurons in the dorsal and/or ventral horns. The interneurons make another synapse on the motor neuron. However, the sensory primary afferent axon may also terminate directly on the motor neuron. The axon of the motor neuron leaves the cord through the ventral root and reaches the skeletal muscle by means of the spinal nerve.

THE ANATOMY OF THE WHITE MATTER
The white matter contains nerve fibers, glial cells and blood vessels. The white matter surrounds the gray matter. The ventral and dorsal horns subdivide the white matter into funiculi: we distinguish dorsal, lateral and anterior funiculi. Every funiculus contains thousands of myelinated axons. The nerve cell axons of similar destinations form large groups which we call a tract or pathway. We distinguish two types, the ascending and the descending tracts. They are anatomically and functionally different and have to be discussed separately. The tracts are located in the dorsal, lateral and anterior funiculi of the white matter.
ASCENDING TRACTS

The ascending tracts originate in the spinal cord and terminate in higher brain centers, such as the brain stem and thalamus. The fibers are arranged in a certain somatotopy: the axons of lower segmental origin are located more superficially in the white matter.

- **Dorsal column pathways** contain the central axons of **primary afferent** sensory ganglion cells: they therefore originate from the dorsal root ganglion; these axons ascend in the dorsal funiculus and terminate in the brain stem. These tracts convey vibration, pressure, and exteroceptive tactile and proprioceptive stimuli.

- **Spinocerebellar pathways** contain the axons of spinal cord gray matter neurons and originate in the gray matter of the spinal cord. The pathways are located in the lateral funiculus. They propagate stimuli from skin and muscle: from mechanoreceptors and proprioceptors. Spinocerebellar pathways also carry information generated in the spinal cord in association with program-controlled movements such as walking.

- **Spinothalamic tracts** are the largest sensory tracts in the lateral and anterior funiculi. The tracts are found throughout the whole spinal cord and terminate mainly in the thalamus. These are the major pathways for somatic pain and thermal senses.

DESCENDING TRACTS

Most of these pathways terminate in the ventral horn and influence the motor neurons of the anterior horn. The pathways originate from the cerebral cortex and the brain stem.

- **Corticospinal tracts**: These large pathways run in the lateral and anterior funiculi. They originate in the cerebral cortex, and descend in the internal capsule and brain stem, and most of the axons decussate in the medulla. The axons terminate in the ventral horn. Damage to this pathway (*e.g.* stroke) causes paresis of the skeletal muscles.

- **Reticulospinal tract**: The tract originates from the neurons of the reticular formation of the brain stem. The fibers innervate motor neurons and interneurons in the ventral horn.

- **Vestibulospinal tract**: This is derived from the vestibular nuclei of the brain stem. It influences motor neurons.

These pathways are examples of the more than 24 pathways currently known to exist in the human spinal cord. For a complete list of spinal cord pathways, comprehensive neuroanatomy textbooks should be consulted.

The **meninges** surround the spinal cord and in adults extend down to the level of the second sacral vertebra. The space surrounded by the meninges can be used for local anesthesia
(epidural anesthesia) and CSF sampling (lumbar puncture). The meninges consist of the outer dura mater and the inner arachnoid–pia mater layers. The blood supply of the spinal cord originates from three longitudinally coursing arteries that arise around the level of the foramen magnum from the vertebral arteries.

XII. 3. 2. The brain stem and the cerebellum

The brain stem is the upper continuation of the spinal cord. It is located in the skull and can be divided into three different anatomical parts:
1. the medulla oblongata (continuous with the spinal cord),
2. the pons,
3. the mesencephalon or midbrain (at its upper part it is continuous with the diencephalon).

The brain stem contains the nuclei of ten cranial nerves (see Table 9). The first two cranial nerves (the olfactory nerve and the optic nerve) are sense organ nerves, which are not related anatomically to the brain stem. The olfactory nerve originates from the olfactory epithelium of the nasal cavity and terminates in the olfactory bulb, which is part of the rhinencephalon (nose–brain). The rhinencephalon belongs to the limbic system. The optic nerve comes from the retina of the eyeball and terminates in the diencephalon as the optic tract. The other sensory and motor cranial nerve nuclei are located in the medulla, pons and midbrain. Apart from the cranial nerve nuclei, the brain stem contains several autonomic parasympathetic nuclei which, regulate the secretion of the salivary and lacrimal glands and the movements of the pupil. A large part of the brain stem is occupied by sensory tracts or pathways coming from the spinal cord or originating in the brain stem sensory nuclei. The motor tracts of the brain stem include the corticospinal and the corticobulbar tracts; both originate in the cerebral cortex. The corticobulbar tract contains the motor fibers which terminate on the motor nuclei of the cranial nerves. Finally, the brain stem contains a system of nuclei and scattered nerve cells which build up the reticular formation, the huge neuronal system which contains transmitter substances such as noradrenaline, adrenaline, dopamine, serotonin and acetylcholine. Neurons containing a particular neurotransmitter tend to form separate nuclei. The substantia nigra of the mesencephalon is the best-known structure accommodating the dopaminergic neurons. These neurons project to the striatum. Injuries to the dopaminergic system results in parkinsonism. The serotonergic neurons reside in the midline of the medulla, pons and mesencephalon, forming the raphe nuclei. The noradrenergic neurons are concentrated in the locus coeruleus. These neurons form ascending and descending tracts, which innervate almost every part of the CNS. The
monoaminergic axons release their transmitters into the extracellular space and influence large neuron populations at the same time. The reticular formation of the medulla oblongata participates in vital functions such as the regulation of circulation and respiration. Another very important function of the reticular formation is the regulation of alertness. The brain stem reticular formation is connected to the diencephalon and through the thalamus it may regulate the arousal reaction of the cerebral cortex.

The cerebellum has strong developmental and anatomical relations to the brain stem. It is protected by the posterior, occipital part of the skull. It has two hemispheres and the vermis between them. Its surface displays parallel transverse grooves which border the cerebellar folia (leaves). The folia include the cerebellar cortex (gray matter) and the subcortical white matter. The cortex contains large neurons, the Purkinje cells, which are inhibitory cells and project to the deep cerebellar nuclei. The cerebellum deals with sensory information coming from the muscles, the tendons and the skin, mainly through the spinocerebellar pathways. The other important sources of cerebellar afferents are the vestibular part of the vestibulocochlear nerve and the vestibular nuclei of the brain stem. The cerebellum also receives information from the cerebral cortex. The cerebellum sends its efferents mainly to the thalamus and from there to the motor neocortex. Other cerebellar outputs act on the reticular formation and the vestibular nuclei of the brain stem. These outputs influence the reticulospinal and vestibulospinal pathways. The main function of the cerebellar system is the regulation of balance–related muscular activity, posture and gait. An individual who suffers from cerebellar damage walks awkwardly with the feet well apart and has difficulty maintaining his or her balance; the gait is described as reeling and drunken. At the same time, there is usually a weakness or "hypotonia" of the skeletal muscles.
Table 9
List of the cranial nerves. Olfactory and optic nerves (I – II) are not shown.

<table>
<thead>
<tr>
<th>CRANIAL NERVE</th>
<th>LOCATION OF NUCLEI IN THE BRAIN STEM</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oculomotor nerve (III)</td>
<td>Mesencephalon</td>
<td>Motor innervation of eye muscles</td>
</tr>
<tr>
<td>Trochlear nerve (IV)</td>
<td>Mesencephalon</td>
<td>Motor innervation of eye muscles</td>
</tr>
<tr>
<td>Trigeminal nerve (V)</td>
<td>Mesencephalon, pons and medulla oblongata</td>
<td>Motor and sensory innervation of masticatory muscles, sensory innervation of skin of head, mucous membranes of nasal and oral cavities, teeth and eyeball</td>
</tr>
<tr>
<td>Abducent nerve (VI)</td>
<td>Pons</td>
<td>Motor innervation of eye muscles</td>
</tr>
<tr>
<td>Facial nerve (VII)</td>
<td>Pons</td>
<td>Motor innervation of muscles of facial expression, sensory innervation of taste buds of the tongue</td>
</tr>
<tr>
<td>Vestibulocochlear nerve (VIII)</td>
<td>Pons and medulla oblongata (cochlear and vestibular nuclei are separated)</td>
<td>A specific sense organ nerve: originating in vestibular and auditory receptors of the inner ear</td>
</tr>
<tr>
<td>Glossopharyngeal nerve (IX)</td>
<td>Medulla oblongata</td>
<td>Motor innervation of pharyngeal musculature, sensory innervation of pharyngeal mucous membrane and some taste buds in the tongue</td>
</tr>
<tr>
<td>Vagus nerve (X)</td>
<td>Medulla oblongata</td>
<td>Motor innervation of soft palate, pharyngeal and laryngeal muscles and esophagus, sensory innervation of pharynx, larynx, and viscera of thorax and abdomen</td>
</tr>
<tr>
<td>Accessory nerve (XI)</td>
<td>Medulla oblongata and cervical spinal cord</td>
<td>Contributes to motor innervation of pharynx; spinal part innervates sternocleidomastoid and trapezius muscles</td>
</tr>
<tr>
<td>Hypoglossal nerve (XII)</td>
<td>Medulla oblongata</td>
<td>Motor innervation of tongue muscles</td>
</tr>
</tbody>
</table>
XII. 3. 3. The diencephalon

The diencephalon is located in the deep, medial aspect of the forebrain and includes the thalamus, metathalamus, hypothalamus and epithalamus (pineal gland). It has a narrow cavity, the third ventricle.

THE THALAMUS

The thalamus is an ovoid (egg-shaped) nuclear structure about 4 cm long, immediately lateral from the third ventricle. It consists of mainly gray matter nuclei which are separated from each other by white matter laminae. The white matter separates four large nuclear groups: the anterior, lateral, ventral and medial groups of nuclei. The ventral group is located below the lateral group and is subdivided into ventral anterior, ventral lateral and ventral posterior nuclei. The largest of them is the ventral posterior, which is divided into a ventral posterolateral and a ventral posteromedial nucleus.

Large sensory tracts approach the thalamus from the brain stem and enter the thalamic nuclei. These are listed in Table 10.

<table>
<thead>
<tr>
<th>SENSORY PATHWAY</th>
<th>THALAMIC TERMINATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinothalamic tract</td>
<td>Ventral posterolateral nucleus</td>
</tr>
<tr>
<td>Medial lemniscus</td>
<td>Ventral posterolateral nucleus</td>
</tr>
<tr>
<td>Trigeminal lemniscus</td>
<td>Ventral posteromedial nucleus</td>
</tr>
<tr>
<td>Auditory pathway</td>
<td>Medial geniculate body</td>
</tr>
<tr>
<td>Optic tract (continuation of optic nerve)</td>
<td>Lateral geniculate body</td>
</tr>
</tbody>
</table>

The metathalamus is a purely anatomical distinction, referring to the medial and lateral geniculate bodies (MGB and LGB), which are important specific sensory nuclei. The MGB is related to the auditory pathway; the LGB is a relay station of the visual system.

THE HYPOTHALAMUS

The hypothalamus is mostly concerned with visceral, autonomic and endocrine (neuroendocrine) functions. However, since it is part of the diencephalon (i.e. it occupies a central part in the forebrain), all of these functions are intimately related to human emotional and affective behavior. On the basal surface of the brain, the hypothalamus is marked by the optic chiasma and the mamillary bodies. Between these we see the infundibulum and the
tuber cinereum, which belong to the hypothalamus too. The area above the optic chiasm is called the preoptic region, which is the rostral continuation of the hypothalamus. Further rostrally we have the basal forebrain, which contains cholinergic nuclei. These cholinergic neurons innervate the neocortex. Degeneration of these cholinergic cells is characteristic of Alzheimer's disease.

The hypothalamus consists of numerous small nuclei which occupy the zone surrounding the third ventricle. The lateral area of the hypothalamus is more homogenous and is considered separately. The medial hypothalamus contains the magnocellular and parvicellular neurosecretory nuclei. These nuclei belong to the neuroendocrine system, because several of their neurons perform neurosecretion. Neurosecretion means that a CNS neuron synthesizes, transports and secretes hormones into the blood stream. Thus, the neuron exerts endocrine action; the brain secretes hormones into the blood (or into the CSF). These processes are very important in the regulation of the endocrine activities of the body; neuroendocrinology deals with these functions of the nervous system. The paraventricular and supraoptic nuclei belong to the magnocellular system. The magnocellular nuclei contain large neurosecretory neurons (although there are small neurons too), which send their axons to the neurohypophysis (posterior lobe of the pituitary). Both nuclei synthesize peptide hormones, i.e. oxytocin and vasopressin (or antidiuretic hormone; ADH), which travel along the axons and reach the neurohypophysis, where the axons terminate on the walls of the capillaries. The axon terminals empty their peptide-containing vesicles into the blood. The parvicellular system comprises mainly the arcuate (infundibular) nucleus, which is located in the tuberal region. These neurosecretory cells produce hypophyseotropic hormones and send their axons to the median eminence. The hypophyseotropic hormones are released into the capillaries of the median eminence. These capillaries are collected into small portal vessels, which branch again into sinusoid capillaries in the anterior lobe (adenohypophysis). Thus, the hypophyseotropic hormones can influence and regulate the secretory activity of the adenohypophysis. Other structures belonging to the parvicellular system include the medial preoptic and periventricular nuclei.

Other nuclei of the medial hypothalamus do not belong to the neuroendocrine system. Among them we should mention the suprachiasmatic nucleus, which receives axons from the retina and is an important circadian pacemaker regulating diurnal rhythms. The neuronal connections of the hypothalamus include the thalamus, the limbic system, the amygdaloid nucleus, the brain stem and the spinal cord.
XII. 3. 4. The basal ganglia

The basal ganglia are large gray matter structures located deep inside the hemispheres. They comprise the caudate nucleus, the putamen and the globus pallidus (the latter two are located very close to each other, and are therefore called the lentiform nucleus), the claustrum and the amygdala. The caudate nucleus and the putamen together form the striatum, and the globus pallidus forms the pallidum; these are the main subcortical neuronal systems subserving the normal motor regulation. The amygdala belongs to the limbic system and the function of the claustrum is unknown. The caudate nucleus and the lentiform nucleus are lateral to the thalamus and are separated by a thick, curved bundle of white matter: the internal capsule. The internal capsule contains every corticospinal and corticobulbar axon coming from the neocortex; any damage to it (e.g. stroke) therefore destroys these nerve fibers. The aftermath of a stroke is a permanent muscular palsy.

The striatum and the pallidum are interconnected and are related to other thalamic and neocortical structures. The striatum is targeted by the dopaminergic axons of the substantia nigra. The complicated neuronal networks of the striatum and pallidum regulate the motor cortex. The important transmitter substances in the striatum are dopamine, acetylcholine and GABA (gamma–aminobutyric acid). Disturbances of the transmitter metabolism or degeneration in the striatum or pallidum cause severe motor disturbances, which are manifested as pathological and uncontrollable movements. Parkinson's disease (or parkinsonism) is one of these manifestations.

XII. 3. 5. The limbic system

The limbic system functions as the regulator of emotional and instinctive (including sexual) behavior. Anatomical structures belonging to the limbic system include the rhinencephalon, some nuclei of the hypothalamus, the thalamus, the amygdala and some areas of the cerebral cortex. One of these cortical structures is the hippocampal formation, which has a pivotal role in the process of memory formation. The amygdala is part of the emotional brain which plays important part in the regulation and impact of our emotions in our daily behavior.

XII. 3. 5. The cerebral cortex

The cerebral cortex is the most complicated and important structure of the human brain. It covers the cerebral hemispheres as gray matter approximately 1 cm thick, which forms different convolutions, the gyri. The gyri are separated by deep fissures, the sulci. Most of the gyri and sulci have specific names and in some instances well–defined functions. In general, we distinguish the phylogenetically old allocortex from the phylogenetically recent
neocortex. The large surface of the neocortex is subdivided into the frontal, parietal, temporal and occipital lobes. Every lobe contains several gyri and sulci. Very simply, the frontal lobe is concerned with somatomotor, intellectual and behavioral functions, the parietal lobe contains the main somatosensory and association fields, the occipital lobe is the center for vision, and the temporal lobe is concerned with hearing. There are two important speech areas: the motor speech center in the frontal lobe, and the sensory speech center in the parietal and temporal lobes. Damage to them causes long–lasting defects of speech performance. The two cerebral hemispheres are connected to each other via bundles of white matter, the cerebral commissures. The largest commissure is called the corpus callosum. The axons running in the corpus callosum form connections between the areas of the cerebral cortex of the right and left hemispheres.

XII. 4. The blood supply of the brain

The brain is supplied by two pairs of arteries; the vertebral arteries supply the brain stem and the cerebellum, and the internal carotid arteries supply the rest of the brain. The four arteries form a special system of anastomoses inside the skull: this is the arterial circle of Willis. The main arterial branches of the brain originate from this arterial circle. The veins are collected by the venous sinuses, which are formed by the dura mater of the brain. The dural sinuses are collected by the two internal jugular veins, which leave the skull and run in the neck toward the superior vena cava. The CSF from the cerebral ventricles is drained by the intracranial venous sinuses, so the venous circulation plays a pivotal role in the circulation of the CSF.

XII. 5. The meninges of the brain

The meninges are similar to those around the spinal cord. The outer layer, the dura mater or pachymeninx, forms a stiff, cage–like structure for the different parts of the brain. The next layer is the arachnoid layer, which connects the dura mater to the innermost pia mater, and at the same time forms spaces around the brain; this is the subarachnoid space, which is filled with CSF. The large vessels of the brain run in the subarachnoid space too. Rupture of these causes subarachnoid bleeding or hemorrhage, a very serious disease. The dura mater is very richly innervated by the trigeminal and vagus nerves; severe pain (headache) may originate from it.

XII. 6. Anatomy of the autonomic nervous system

The autonomic nervous system provides the innervation of the heart, blood vessels, viscera, glands and smooth muscles, including the smooth muscles of the eye and the skin. It has
components in the CNS and in the PNS. The autonomic nervous system is subdivided into the sympathetic and parasympathetic systems, which are basically functional subdivisions, but, at least in the CNS, the two systems are separated anatomically too. The parts in the CNS are the preganglionic neurons of the sympathetic and parasympathetic systems. These preganglionic neurons form nuclei in the brain stem and in the spinal cord. The peripheral part consists of the autonomic ganglia, the autonomic plexuses and the nerve pathways. The autonomic ganglia contain the postganglionic neurons of the sympathetic and parasympathetic systems. Anatomically, sympathetic ganglia are subdivided into paravertebral and prevertebral ganglia. The paravertebral ganglia and their related nerve trunks form the two sympathetic chains which are found alongside the vertebral column. The sympathetic chains are connected to the prevertebral ganglia by means of the splanchnic nerves. The prevertebral ganglia lie close to the abdominal aorta. Most sympathetic postganglionic neurons are noradrenergic and may also contain neuropeptides and ATP. The sympathetic postganglionic neurons innervating the sweat glands are exceptions, because they use acetylcholine as transmitter. The parasympathetic postganglionic neurons are located in small ganglia close to or inside their target organ. Parasympathetic postganglionic neurons are cholinergic and use neuropeptides too.

Two large autonomic plexuses are found in the gastrointestinal tract; the myenteric and submucosal plexuses contain enteric neurons, which are different from sympathetic and parasympathetic cells. Enteric neurons are innervated by cholinergic parasympathetic preganglionic, and noradrenergic sympathetic postganglionic axons. Most of the enteric neurons contain neuropeptides (vasoactive intestinal peptide; VIP, substance P and somatostatin), acetylcholine, nucleotide, nitric oxide and GABA. The enteric neurons and the postganglionic neurons elsewhere innervate their targets (glands and smooth muscles) with varicose axons.

XIII. THE SENSE ORGANS

XIII.1. The eye (oculus, ophthalmos)

The eye is located in and sheltered by the bony orbit. Inside, it is surrounded by the lacrimal gland, connective tissue, fat, blood vessels and nerves. On the face, it is covered by the eyelids. The tears are secreted by the lacrimal gland and drained by the lacrimal duct, which opens into the nasal cavity. The lacrimal duct is surrounded by the facial bones of the
skull. The eyeball itself is movable and the small cross-striated muscles inside the orbit perform the gazing movements. These extrinsic eye muscles are innervated by cranial nerves. The eyelids too are movable, and these movements are performed by certain facial muscles. The movements of the eyelids protect the eye. The eyeball consists of tissue layers or coats and refractive media inside. The outer fibrous coat is the sclera. The anterior part of the sclera is replaced by a refractive, transparent structure, the cornea. The rest of the anterior sclera is covered by a mucous membrane called the conjunctiva. The conjunctiva is highly-vascularized, loose connective tissue, covered by a thin stratified epithelium. It covers not only the eyeball, but also the inner surface of the eyelids. Its inflammation is called conjunctivitis. The next layer is the vascular coat. The layer lying immediately under the sclera is called the choroid portion. The anterior part of the vascular coat forms the ciliary body and the iris. The ciliary body contains smooth muscle and blood vessels. The smooth muscle regulates the thickness of the lens. The whole ciliary body serves for the fixation of the lens and the production of the aqueous humor, the fluid which fills the inner cavities of the eye. The iris is a rounded curtain attached to the ciliary body. It contains smooth muscle and an opening, the pupil. The size of the pupil is regulated by the smooth muscle, which is innervated by sympathetic and parasympathetic postganglionic nerve fibers. In bright light, the pupil becomes smaller; in dim light, it becomes larger. In this way, the pupil regulates the amount of light reaching the interior of the eye. This is the light reflex of the pupil. The innermost coat is the nervous coat or the retina of the eye. Developmentally, the retina is part of the CNS; it grows out from the embryonic prosencephalon. The retina contains several layers of receptor cells (the rods and the cones), different neurons and synapses. The optic nerve originates in the retina as the axons of the retinal ganglion cells. The right and left optic nerves enter the skull cavity and join each other at the optic chiasm. There is a partial decussation in the optic chiasm and the fibers continue as the optic tract. The optic tract terminates in the LGB of the thalamus. Thalamocortical fibers from the LGB form the optic radiation and reach the visual cortex in the occipital lobe. The retina is supplied by its own blood vessel, called the central artery of the retina. The branches of this artery are clearly visible with an ophthalmoscope.

The cornea is covered by a thin stratified epithelium, richly innervated by sensory nerve endings, and it is therefore very sensitive. Stimulation of these nerves elicits the cornea reflex, which results in closure of the eyelids. There are no blood vessels in it; if blood vessels do grow in it (e.g. in inflammations), the cornea loses its transparency. Behind the cornea, we
find a cavity which is the **anterior chamber** of the eye. The chamber contains a transparent fluid, the **aqueous humor**. The anterior chamber is bordered by the iris. Behind the iris, there is the crystalline lens of the eye and the **posterior eye chamber**. The aqueous humor is produced (secreted) by the ciliary body into the posterior chamber, from where it flows through the pupil into the anterior chamber. At the corneoscleral junction, we find the **canal of Schlemm**, which is the site of absorption of the aqueous humor. It drains the aqueous humor into the veins of the eye. The pressure of the aqueous humor builds up the **intraocular pressure**, which is reflected in the consistency of the eyeball. **Glaucoma** is a chronic eye–disease, with a permanent increase in the intraocular pressure. Behind the lens is situated a large, jelly–like refractive substance, the **vitreous body**. This helps to support the retina and to maintain the shape of the eyeball.
XIII. 2. The ear

The ear is anatomically subdivided into the **external ear** (the **auricle** and the **external acoustic meatus**), the **middle ear** (the **tympanic cavity** with the **auditory ossicles** and the **auditory tube**) and the **inner ear**. The external acoustic meatus and the tympanic cavity are separated by the **tympanic membrane**. The external meatus is covered by skin with hairs, sebaceous glands and modified sweat glands, which secrete the **cerumen** or ear–wax. The skin is richly innervated with sensory nerves, and inflammations (**otitis externa**) are painful. The tympanic cavity is covered with a thin mucous membrane. The cavity is connected to the cavity of the nasopharynx via a cartilaginous tube: this is the **auditory** or **Eustachian tube**.

The tympanic cavity contains three small auditory ossicles, which join each other with true articulations. The chain of ossicles connects the tympanic membrane to the oval window of the labyrinth and transmits the vibrations of the tympanic membrane to the perilymph of the labyrinth. Inflammation of the middle ear is called **otitis media**. The inner ear (or **labyrinth**) contains the receptors for hearing and the sense of position. The labyrinth is a complicated system of bony cavities filled with fluid (the **perilymph**), inside which we find a delicate system of duct–, canal– and sac–like membranous structures. These membranous structures contain the receptors which are innervated by the processes of primary sensory neurons. The receptor for hearing is found in the **cochlear duct**; the receptor is the **organ of Corti**. The organ of Corti contains a ciliated secondary sensory epithelium, which is innervated by the processes of the **spiral ganglion**; this ganglion forms the cochlear division of the **vestibulocochlear nerve**. The sense of position is felt by five receptors in the vestibular apparatus. Two of them are situated in the vestibule of the labyrinth; these receptors are the **macula of the saccule** and the **macula of the utricle**. Both contain secondary sensory epithelium, the ciliated cells of which are innervated by the **vestibular ganglion**, which forms the vestibular part of the vestibulocochlear nerve. The direction of movements are felt by the **cristae of the semicircular canals**. This secondary sensory epithelium is innervated by the vestibular nerve too. The membranous labyrinth contains fluid called **endolymph**. The vestibulocochlear nerve enters the brain stem and terminates in the cochlear and vestibular nuclei of the medulla and pons.
XIV. THE SKIN AND THE MAMMARY GLAND

The skin or integument covers the body, protects the underlying tissues and organs, regulates the body temperature, serves as a sense organ and produces vitamin D. These complex functions are maintained through the complex histological structure of the skin.

XIV. 1. The structure of the skin

We distinguish three layers: most superficial is the epidermis, which is a keratinizing, stratified squamous epithelium. The thickness of the keratinized layer varies considerably and depends on the mechanical function of the body part (e.g. the plantar skin). The epithelium is continuously regenerating and produces the keratinocytes, which become superficial and cornified (or keratinized) during differentiation. There are other cell types in the epidermis: the melanocytes, which produce pigment granules and give the color to the skin, and the Langerhans cells, which belong to the mononuclear phagocytes and play an important role in the immunologic skin reactions. The next layer is the dermis, which is separated from the epidermis by a basal lamina. The dermis contains connective tissue, abundant blood and lymphatic capillary networks and nerves. The loose connective tissue of the dermis is rich in elastic and collagen fibers, which give the strength, elasticity and extensibility to the skin. The capillaries extend close to the epidermis; these blood vessels nourish the epidermis and act in heat regulation. The nerves form different sensory nerve endings (e.g. tactile corpuscles, free nerve endings for pain, etc.). Beneath the dermis lies the subcutaneous tissue (hypodermis or tela subcutanea). This layer contains fat, loose connective tissue, the sweat glands and some nerve endings. The amount of fat in this layer differs from region to region, and reflects the eating habits very well. Free and encapsulated sensory nerve endings (skin receptors) occur in every layer. These nerve endings are the peripheral processes of the primary sensory neurons.

XIV. 1.1. The appendages of the skin

These are glands, hairs and nails. The glands are of two kinds: the sweat glands are located in the subcutaneous layer and secrete water, salts and some waste products (urea and uric acid). The sebaceous glands are located in the dermis and usually open into hair follicles. They secrete an oily substance called sebum, which covers the surface of the epidermis, keeping it soft and waterproof. The hairs are keratinized structures that grow out from the hair follicles, which are modified parts of the epidermis. The follicles extend to the deep layer of the dermis, but the shaft of the hair projects above the surface of the skin. The bottom of the
follicle, the hair bulb, contains the proliferating cells which keratinize and transform into hair. Because of the proliferation, the hair grows continuously. The nails are keratinized epithelial structures built up from a hard keratin. The nail is produced by the epidermis in the nail groove, where the root of the nail is fixed and grows continuously from the nail matrix. The pink color is due to the capillary network located in the nail bed (the epidermis immediately beneath the nail).

XIV. 2. The mammary gland
The mammary glands develop from the ectoderm of the skin. The excretory ducts (called lactiferous ducts) of the glandular tissue open on the tip of the nipples. The nipples are surrounded by a pigmented area called the areola. The nipple and the areola contain smooth muscle, and the areola contains some modified sweat glands and sebaceous glands too. They are innervated by a rich network of sensory nerve endings. Each gland contains fat tissue and 15–25 glandular lobules, which secrete the milk after parturition. The milk contains lipids, proteins (caseins, lactalbumin and immunoglobulins) and lactose. The immunoglobulins enter it from the lymphocytes and plasma cells present in the interlobular connective tissue. The glandular epithelium grows and proliferates during pregnancy under the regulatory effects of estrogen, progesterone, the lactogenic hormone or prolactin (LTH) of the anterior pituitary and the human placental lactogen (hPL), which is a peptide hormone secreted by the placenta. The milk ejection is mediated by another pituitary hormone, oxytocin (a peptide of the neurohypophysis). The mammary gland displays cyclic changes during the menstrual cycle, which include swelling of the tissue and slight secretory activity of the glands in the luteal phase.
XV. GROWTH AND DEVELOPMENT OF THE HUMAN BODY

XV. 1. Development and differentiation of human germ cells

The germ cells (or gametes) appear very early in the human embryo, earlier than any other cell type. The testis and the ovary develop later (around week 8). Both of them are mesodermal in origin.

XV. 1. 2. Differentiation of the male germ cell (spermatogenesis)

Although the germ cells are already present in embryonic life, their differentiation begins only at around puberty. Spermatogenesis takes place in the epithelial tubules of the testis. The result of this process is a long (about 60 μm) cell, with a very small and condensed cell nucleus in the head piece, followed by a neck, a middle piece and a long tail piece. The tail piece exhibits the typical structure of a flagellum.

XV. 1. 4. Differentiation of the female germ cell (oogenesis)

Oogenesis begins earlier than spermiogenesis; it commences in fetal life at around week 11. However, the first phase of meiosis stops in fetal life, and the cells stay in this stage until the beginning of puberty (10-12 years). This extraordinarily long meiotic process makes these cells very vulnerable to environmental factors (radiation, drugs, etc.). The periods of oogenesis are in principle similar to those of spermatogenesis. At the end of oogenesis, the germ cell (ovum) accumulates lipids and glycogen, and develops a thick outer coat, the zona pellucida. The surrounding small cells, the follicular cells or granulosa cells, proliferate and the stroma cells of the ovary form an outermost cell layer around the whole structure. This outermost layer is the theca, consisting of the theca cells, which are highly specialized endocrine cells of great significance in the regulation of ovarian and uterine cycles. The whole structure is called a follicle. The follicle develops and grows and finally the Graafian follicle appears, which is a large structure (approximately 2.5 cm in diameter) containing the ovum, the follicular cells (or granulosa cells) and a cavity filled with fluid. The Graafian follicle is covered from outside by the theca cells.
XV. 2. Fertilization, cleavage and implantation

XV. 2. 1. Ovulation, fertilization and cleavage

At around day 14 of the menstrual cycle (see Table 7), the Graafian follicle ruptures and discharges into the abdominal cavity the secondary oocyte, which is surrounded by the thick zona pellucida and the follicular cells. This is ovulation, which precedes the fertilization process. The egg cell reaches the uterine tube and begins its journey towards the cavity of the uterus. The fertilization takes place in the cavity of the tube: the spermatozoa reach the egg cell and one of them penetrates the follicular cells and the zona pellucida. The two haploid cell nuclei fuse, resulting in a diploid cell (46 chromosomes), which is called a zygote. The development of the new organism (the new human being) begins with a series of mitotic divisions. The daughter cells of the zygote are called blastomeres. The basic events of the early development are summarized below:

<table>
<thead>
<tr>
<th>Fertilization</th>
<th>Zygote</th>
<th>Cleavage (mitotic divisions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blastocyst (50-60 blastomeres)</td>
<td>Morula (12-16 blastomeres)</td>
<td></td>
</tr>
</tbody>
</table>

XV. 2. 2. Implantation

The blastocyst reaches the uterus and becomes embedded into the endometrium. This is implantation. There are two different cell types in the blastocyst: trophoblasts (outer shell) and embryoblasts (inner cell mass). Each follows a separate line of development, the trophoblast giving rise to the placenta and some of the fetal membranes (chorion), and the embryoblast giving rise to the germ layers and then to the embryo and fetus. There may be errors in the implantation process, leading to abnormal implantation sites, which may lead to extrauterine pregnancy and placenta previa. All of these are serious complications which need urgent treatment and surgical intervention.

XV. 3. Differentiation of the trophoblast

The trophoblastic shell, which is one cell layer initially, differentiates into three cell layers and proliferates, growing rapidly. This growth of the trophoblastic shell is mainly responsible for the growth of the embryo during the first 2-3 weeks. The three layers are the syncytiotrophoblast (outer layer), the cytotrophoblast (middle layer) and the extraembryonic mesoderm (inner layer). These three layers form the chorion, or chorionic...
shell, which has a major role in the feeding of the embryo. The extraembryonic mesoderm, which takes part in the formation of the chorion, is also called the chorion mesoderm. The outer (syncyti-) layer is the thickest one, which invades the endometrium quickly, disrupting the wall of the uterine blood vessels and the uterine glands. The syncytiotrophoblast forms small cavities, the lacunae, which are surrounded by the syncytio cells. The disrupted blood vessels and uterine glands open directly into these lacunae, filling them with maternal blood and the secreted products of the glands. This is the first form of the feeding of the embryo: blood-borne substances reach the inner cells of the embryo by means of diffusion. The lacunae persist and grow together with the chorion and they become parts of the placenta.

XV. 3. 1. Changes induced in the endometrium by implantation

Fertilization and implantation induce specific histological and functional changes in the endometrium: this is the decidual reaction. The cells of the endometrium become large and pale, and they contain large amounts of glycogen and lipids. The endometrium of the pregnant uterus is called the decidua. At the site of implantation, we distinguish the decidua basalis and decidua capsularis. The remainder of the endometrium is called the decidua parietalis. The decidua basalis forms the maternal part of the placenta.

XV. 3. 2. Development and structure of the placenta

The mature human placenta develops from the decidua basalis (maternal part) and from embryonic structures, such as the trophoblast and chorion (fetal part).

1. DECIDUA BASALIS: The decidua forms septa (fences), which divide the chamber-like compartments which will contain the blood of the mother. The uterine blood vessels (veins and arteries) open directly into these chambers. These compartments develop from the lacunae of the syncytiotrophoblast and have the same function: they allow the blood of the mother to come into close contact with the trophoblastic surface.

2. TROPHOBLAST: This covers the surface of the chambers and the septa. The trophoblast covers the chorionic villus too. Since the trophoblastic surface is “washed” continuously by the blood of the mother, it is the most important interface (and barrier) between the fetal tissues and the maternal circulation.

3. CHORION: The chorion grows, proliferates and forms numerous finger-like processes (villous chorion), which build up a tree-like structure. This large and complicated villus is attached to the chorionic plate and to the decidua basalis. The villus is covered by trophoblasts. Inside the villus, we find connective tissue (the chorionic mesoderm) and blood vessels of the fetus. These blood vessels are the branches of the umbilical blood vessels.
During the second phase of childbirth, the placenta comes into the world too. However, the decidua basalis remains in the uterus and plays an important role during the subsequent regeneration process.

The human placenta has three main functions: (1) **metabolism**, *i.e.* synthesis of glycogen, fatty acids, *etc*.; (2) **transfer**, materials from the mother and from the fetus being transported through it; and (3) **endocrine secretion**, the syncytiotrophoblast synthesizing several placental hormones which are absolutely necessary for maintenance of pregnancy.

**XV. 4. Differentiation of the embryoblast: formation of the embryonic disc**

**XV. 4. 1. The bilaminar embryonic disc: formation of the amnion and yolk sac**

During the second week, two important changes take place in the inner cell mass (embryoblast cells). The cells lying close to the blastocyst cavity become flat, like the squamous epithelium; these cells form the hypoblast layer. The cells inside become tall and columnar and form another layer, the epiblast layer. The epiblast and the hypoblast lie on each other and form the **bilaminar embryonic disc**. On the other hand, a small cavity appears between the trophoblast and the epiblast, which grows and separates the bilaminar embryonic disc from the trophoblastic shell. The cavity is called the **amnion**. The hypoblast grows into the blastocyst cavity and separates another cavity inside. This will be the **yolk sac**. As a result, the embryonic disc will be surrounded by two cavities, the amnion above the epiblast and the yolk sac below the hypoblast.

**XV. 4. 2. The trilaminar embryonic disc: formation of the germ layers**

At the end of the second week, important changes take place in the bilaminar embryonic disc. Two small sites appear on the edge of the disc, where the epiblast and hypoblast firmly adhere together, and the hypoblast becomes tall and columnar too. The two sites mark the two poles of the disc, which is already oval in shape. One of them becomes the **oropharyngeal membrane** (the site of the subsequent mouth), and the other the **cloacal membrane** (this will later be the anus). These two sites determine the growth processes: the events during week 3 take place in the axis which connects the oropharyngeal and cloacal membranes. The axis will be the longitudinal axis of the embryo. First, the epiblast proliferates rapidly and the new cells are pushed towards the axis, where they cause a tiny elevation and a groove: the **primitive streak**. The new cells are pushed into the cleft between the epiblast and hypoblast, where they quickly fill the space and form an intermediate layer, the **mesoderm**. From this time on, the epiblast becomes the **ectoderm** (outer germ layer), and the hypoblast becomes the **endoderm** (inner germ layer). The mesoderm is now situated between the ectoderm and
endoderm. This is the **trilaminar embryonic disc**. The three **germ layers** give rise to every tissue of the human body.

**XV. 5. Early differentiation of the ectoderm and mesoderm**

**Neurulation** is the early differentiation of the ectoderm and gives rise to the **neural tube**. The brain and the spinal cord develop from the neural tube. On both sides of the neural tube, a longitudinal cord of ectodermal cells develops; this is the **neural crest**. In the meantime, the mesoderm on the two sides of the embryo thickens and forms two elongated columns. By the end of week 3, this mesoderm divides into cuboidal pieces along the axis of the embryo and the **somites** develop. The number of the somites increases until the end of the first month: at this time, 40-42 pairs of somites exist on both sides of the neural tube. The somites give rise to some parts of the skull, the vertebrae, muscles of the back and other musculoskeletal elements. Laterally from the somites the mesoderm forms knot-like structures: this is the **intermediate mesoderm**, which later gives rise to the tissues of the urogenital systems. The most lateral mesoderm (called the **lateral mesoderm**) forms a slit-like cavity which opens first into the blastocystic cavity. However, the slit-like space grows rapidly and loses its connection to the blastocystic cavity. It soon becomes the body cavity of the embryo and the fetus. This primitive body cavity is the forerunner of the **peritoneal, pleural and pericardiac** cavities.
**XV. 6. The derivatives of the germ layers**

ECTODERM: epidermis, hair, nails, glands of the skin, mammary gland, enamel of the teeth, inner ear, lens and anterior pituitary gland.

NEURAL TUBE (ECTODERM): CNS, retina, pineal gland and posterior pituitary.

NEURAL CREST (ECTODERM): sensory ganglia and peripheral nerves, autonomic ganglia and nerves, medulla of the adrenal gland, and pigment cells of the skin.

ENDODERM: epithelium and glands of the respiratory tract, epithelium and glands of the alimentary tract, liver, pancreas, thyroid gland, parathyroid glands, thymus, tonsils, pharynx, tympanic cavity, auditory tube (the epithelium and the glands only), and the posterior part of the tongue.

MESODERM: skeletal system (bones, joints and ligaments), muscles (skeletal muscle, smooth muscle and cardiac muscle), connective tissues everywhere, the dentin of the teeth, serous membranes (pleura, pericardium and peritoneum), cardiovascular system, blood and lymph cells, spleen, bone marrow, cortex of the adrenal glands, gonads (testicles and ovaries) and urogenital organs (the epithelium and the glands of these organs are mesodermal too).

**XV. 9. Summary of the events during the first two months (the embryonic period)**

WEEK 1: ovulation, fertilization, cleavage, blastocyst.

WEEK 2: implantation, chorion, bilaminar embryonic disc.

WEEK 3: trilaminar embryonic disc, germ layers, neurulation.

WEEK 4: neural tube, somites, intermediate and lateral mesoderm, folding begins.

WEEK 5: folding of the embryo, primitive heart and circulation, the branchial arches appear.

WEEK 6: the appearance of limb buds, differentiation of the branchial arches, the oral and nasal cavities begin to develop.

WEEK 7: the limbs are apparent, the face, eyes and ears are visibly human, the placenta differentiates.

WEEK 8: the external genital organs begin to develop, end of the embryonic age, length: 3 cm.
XV. 10. Landmarks of the fetal period, growth-rate of the fetus

After the first two months of the embryonic period, the development primarily involves the growth and differentiation of the tissues and organs. These seven months are called the fetal period of human development. The rate of body growth is rapid, especially between the weeks 9 and 20. The size of the body is given as the crown-rump (CR) length because the legs are bent under the belly and it is difficult to measure them precisely. This CR length is 36 cm at birth (at the end of the fetal period).

WEEKS 9-12: the CR length is 5 cm, the eyes are closed, the head is relatively large.

WEEKS 13-16: the CR length is 14 cm, ossification of the skeleton progresses rapidly.

WEEKS 17-20: the CR length is 19 cm, fetal movements are felt by the mother, the body is covered with fine hair, the lanugo.

WEEKS 21-25: the fetus gains weight, the skin is translucent, all organs are fairly well developed.

WEEKS 26-29: a fetus may survive if born prematurely, because the lungs are able to breathe, the CR length is 26 cm, subcutaneous fat is present.

WEEKS 30-34: the skin is smooth and pink, a pupillary light reflex is present.

WEEKS 35-38: the CR length is 36 cm, the fetus has a firm grasp and exhibits spontaneous orientation to light, the circumferences of the head and belly are approximately equal.

XV. 11. Anatomy and physiology of pregnancy

During the pregnant woman’s first visit to the doctor, the age of the pregnancy is estimated. The date of the last menstrual period (LMP) is a good guide, since most women remember the first day of bleeding exactly. The time counted from the first day of the LMP is the gestational age, which is obviously longer than the age of the child, because fertilization could occur on around day 14 of the cycle. If we deduct 2 weeks (14 days) from the gestational age, we get the fertilization age, which is more relevant to the fetus.

The signs of pregnancy are manifold. Most of the changes in the mother’s body are consequences of hormonal actions. One of these hormones can be used for the laboratory diagnosis of pregnancy: the presence of human chorionic gonadotropin (hCG) can be detected in the urine and this laboratory test, together with other signs and symptoms is widely used in pregnancy diagnosis. The cessation of the menses is another important sign. Subsequently, the increased pigmentation of the skin, the abdominal striation (visible skin furrows on the belly), the growth of the breasts and Hegar’s sign (the softening of the uterus upon palpation) are all useful. In later pregnancy (in the second trimester) the abdominal
enlargement is obvious. The enlarged uterus can be palpated above the symphysis at around week 12. Detection of the living fetus is also important: the heartbeats and the body can be detected by means of ultrasonography around weeks 17-19. At the same time, the mother clearly feels the movements of the child. The fetus comes to the world through the perineum. The perineal muscles are therefore of utmost importance: they can be exercised before parturition by special training that may facilitate delivery. However, in most cases, some of these muscles have to be cut by the obstetrician in order to help the delivery and prevent spontaneous rupture. This simple surgical procedure is called episiotomy.

**XV. 12. Congenital malformations**

Gross defects during the embryonic and fetal periods result in congenital malformations. **Teratology** is the study of birth defects, and **teratogens** are the factors which cause these birth defects. Human birth defects are caused by (1) **genetic factors**; (2) **infectious agents**; (3) **drugs, hormones** and **chemical agents**; (4) **ionizing radiation**; and (5) **other factors**.

The genetic factors are the numerical and structural aberrations of the chromosomes. Down's syndrome is a numerical aberration. Infectious agents may act during pregnancy. These are viruses, bacteria and parasites which infect the mother primarily, and then invade the fetus transplacentally. The rubella (German measles) virus causes serious heart defects, while the genital herpes virus infection results in mental retardation, retinal dysplasia and hepatosplenomegalia. Drugs, hormones and chemical agents include prescription and non-prescription drugs (e.g. diazepam, thalidomide, retinoic acid, methotrexate, and oral contraceptives), cigarette smoke, alcohol and illicit drugs (cocaine, LSD, etc.). Chemical agents such as lead or organic mercury compounds come from the external environment and reach the fetus transplacentally. Depending on the dose, ionizing radiation may kill the embryo or cause serious chromosome aberrations. Other factors include the malnutrition and diabetes of the mother and prenatal or perinatal hypoxia and asphyxia of the child, which may cause cerebral palsy.

**XV. 13. Characteristic features of the healthy newborn and the postnatal development of the organs and organ systems**

The newborn has palpable fontanelles on the skull, but no paranasal sinuses and no teeth. The skin is pinkish and covered by fine hairs (often not visible), and the nails are grown over the fingertips. The mammary glands may secrete (due to the hormones of the mother). A moderate umbilical hernia is considered to be normal. Just after birth, dramatic changes occur in the circulatory system:
1. Closure of the foramen ovale into a fossa ovalis.
2. Closure of the ductus arteriosus results in a ligament between the left pulmonary artery and the arch of the aorta.
3. Closure of the ductus venosus results in the development of a ligamentum venosum.
4. Closure of the umbilical vein proceeds slowly, the process taking 2–3 weeks. After that, the ligamentum teres (round ligament) will be present.
5. Closure of the umbilical arteries results in the medial umbilical folds and a connective tissue band connecting to the internal iliac artery.

Whilst the pulmonary circulation is established, the alveoli open up and remain open due to the presence of surfactant. In boys, the testicles are palpable in the scrotum; in girls, the greater lips cover the lesser lips completely. The external acoustic meatus short and cartilaginous and there are no mastoid air cells. The thymus is well developed, the liver and the suprarenal glands are large, and the kidneys are lobated. The muscles of the newborn are developed and move well. Although the myelination of the brain is still in progress, its functions and structures are well developed. The eyes and the ears function well; they too are completely developed.

XV. 13. 1. The skeletal system

Secondary centers of ossification appear (in the epiphyses of long bones) in the limbs. Ossification of the carpus and tarsus begins after birth, but the metacarpals and phalanges are well ossified. The growth of the upper limbs is such that the humerus grows in the proximal epiphysis, while the radius and ulna grow in their distal epiphyses. In the lower limbs, the femur grows in the distal epiphysis, and the tibia and fibula grow in their proximal epiphyses. The pelvis consists of different ossification centers which join in the region of the acetabulum. The sacrum of the newborn is perpendicular and weak. Standing and walking are important in the bone modeling of the pelvis, the vertebral column and the lower limbs. The epiphyseal lines disappear late (at around 20 years). This is of some pathological importance: the possibility of traumatic dislocation at these lines.

Since the brain is growing rapidly, the neurocranium grows faster than the face. The circumference of the skull is 33 cm at birth and 47 cm at 2 years. The fontanelles gradually disappear (the anterior one disappears during year 2, and the others somewhat earlier). The growth of the facial cranium is related to tooth development and mastication activity: mandibular movements, tongue movements and pharyngeal movements. The mandible is
very small at birth and consists of two halves joined by fibrous tissue. The two halves fuse during the first year.

**XV. 13. 2. The hemopoietic system**

At birth, red bone marrow is present in most of the medullary cavities of the bones of the body. At puberty, there is no red bone marrow in the long bones (except in the head of the femur and humerus). Red bone marrow is present only in the ribs, scapula, skull-calvaria, vertebrae, sternum and in hip bone.

**XV. 13. 3. The immune system**

The thymus is well developed and contains lymphoid tissue (thymus lymphaticus). Gradually, up to puberty, the lymphoid tissue disappears from it: fat and connective tissue remain (thymus adiposus). The tonsils are well developed in childhood, but they regress after puberty. Passive immunity (*i.e.* maternal antibodies coming from the milk of the mother) is present during the first 6 months; after that, vaccinations and diseases bring about the active immunity of the body.

**XV. 13. 4. The respiratory system**

At birth, the chest is relatively wide and short but it increases in size rapidly, which means that the capacity of the lungs increases too. The trachea becomes thicker and longer, and growth of the larynx results in the change in voice during puberty. The lungs grow actively: new alveoli, new alveolar ducts and bronchioli grow out and proliferate.
XV. 13. 5. The digestive system
The most spectacular change is the eruption of the teeth (first the decidous, and then the permanent ones). Eruption of the decidous teeth occurs during years 1-6, whilst the permanent teeth appear in years 6-13. The incisors are usually the first in both sequences. Growth dominates as feeding begins. Small children have a relatively large belly because the pelvis is small and the intestines are located in the abdomen proper.

XV. 13. 6. The urogenital organs
The lobulated kidneys grow quickly and the lobulation soon disappears. The urinary bladder is relatively large and extends into the abdomen. Testicular descensus through the inguinal canal proceeds before birth, regularly during the last two months of fetal development. In some rare cases, the testes remain in the inguinal canal; this is called cryptorchism; it is pathological and needs surgical intervention as spermatogenesis will otherwise not begin. Until puberty growth dominates; at puberty, the organs begin to function due to the effects of sex hormones. The uterus is relatively large at birth (because of the maternal hormones), but shrinks soon after it. Breast development begins before and around puberty with fat deposition and glandular proliferation. In girls at puberty, fat deposition occurs not only in the breasts, but also around the hips, and in the thighs and buttocks.

XV. 13. 7. The nervous system
In the newborn baby, the brain accounts for 10-12% of the body weight, and it doubles its weight in the first year. By the age of 5 or 6 years, it has tripled its weight, but after this the growth slows up rapidly, and thus the adult brain accounts for only about 2% of the body weight. The spinal cord is about 15-18 cm long and its lower end is opposite the third lumbar vertebra. The main feature of postnatal development is myelination. The major sensory tracts are myelinated earlier than the motor ones.

XV. 13. 9. The endocrine system
The hypothalamo-hypophyseal axis regulates body growth through somatotropin secretion. The gonadotropins (ICSH, FSH and LH), on the other hand, regulate the development of the reproductive system. The secretion of gonadotropins is controlled by the hypothalamus.
XV. 14. Indices of human maturity are diverse

Bone age depends on the structure and size of the bones, the presence of ossification centers and the extent of ossification. The dental age is determined on the basis of the eruption of deciduous and permanent teeth and dental wear (erosion of the enamel). The sexual age depends on the presence of secondary sexual indices, sexual phenotype, the pattern of pubic hair and axillary hair and the functioning apocrine sweat glands. The size and shape of the breasts, the size and function of the ovaries, the uterus (the appearance of the first menses, the menarche) and the pelvic diameters are important too. In boys, the size and function of the penis and the testis bear the same importance. The neural age is related to the development of coordinated eye movements, grasp, sitting, standing and crawling, walking, speech and the understanding of language.

XVI. VOCABULARY

ACETYLCHOLINE: An ester of choline that is stored in vesicles of the nerve terminal at the motor end-plate. It acts on the membrane of the muscle fiber, causing the generation of electric impulse and contraction. It is also a transmitter of the autonomic and central nervous systems.

ABDUCTOR: A muscle that, upon contraction, draws away from the middle.

ADDUCTOR: A muscle that draws a part toward the middle.

ALZHEIMER’S DISEASE: In diseases that abnormally intensify some of the aging processes, impairment of the cognitive and intellectual functions of the brain is frequent. These diseases are called dementias. Alzheimer’s disease is a common type of dementia, whose cause is unknown.

ANASTOMOSIS: A cross-connection between arteries and veins.

ANTAGONIST: A muscle that counteracts the action of another muscle.

ANTERIOR: The direction relating to what we see in front of us.

ATROPHY: A lack of nourishment. A wasting of muscular tissue due to lack of use.

BICEPS: A muscle with two heads or points of origin.

α-BUNGAROTOXIN: A snake venom which binds to the receptor of acetylcholine and prevents the normal function of the motor end-plate; causes paralysis of the muscles.

BURSA: A small space between muscles, tendons and bones that is lined with synovial membrane and contains a fluid, the synovia.
**CANALICULUS:** Diminutive of *canalis* (a canal), used to indicate a thin tunnel.

**CAUDAL:** The direction pointing toward the lower end of the vertebral column (*cauda* = tail).

**CONTRACTION:** The process of drawing–up and thickening of a muscle fiber.

**CRANIAL:** The direction pointing toward the skull.

**DEPRESSION:** Downward or inferior movement.

**DESMOSOME:** A specialized cell membrane contact between adjacent epithelial cells that ensures the mechanical stability of the tissue.

**DISTAL:** The direction pointing toward the tip of the upper or lower limbs.

**DORSAL:** The direction relating to the surface of the back.

**DORSIFLEXION:** At the ankle, to move the top of the foot toward the shin.

**ELEVATION:** An upward or superior movement.

**ENCAPSULATED RECEPTOR:** A nerve ending of the primary sensory neuron. The nerve terminal is surrounded (encapsulated) by supporting cells and connective tissue.

**EVERSION:** To face the soles of the feet away from each other.

**EXTENSION:** The angle between two bones increases; the process of straightening the flexed limb.

**FASCIA:** A whitish layer of connective tissue covering the muscle.

**FLEXION:** The angle between two bones decreases; the process of bending the limb.

**FREE NERVE ENDINGS:** Thin sensory nerve terminals without supporting cells and connective tissue capsule. Free nerve endings detect pain and temperature in the skin and in different organs.

**FRONTAL:** The plane of the human body which is in or parallel to the plane of the forehead.

**FUNICULUS:** Diminutive of *funis* = cord.

**GAP JUNCTION:** A connection between two cells, where the cell membranes come close to each other (the distance between the two membranes is approximately 2 nm) and they become connected by large protein complexes (connexins) which form ion channels. The two cells communicate freely through the ion channels.

**INFARCTION:** Necrosis caused by the thrombosis of blood vessels.

**INTERNEURON:** A nerve cell which sends its axon to the neighborhood. The axon is short and terminates in the vicinity.

**INTRAMUSCULAR:** Pertaining to within the muscle.
INVERSION: To face the soles of the feet toward each other.
LACUNA: A small cavity in a bone.
LATERAL: The directions pointing toward the right and left sides of the human body.
LEVATOR: A muscle that raises or elevates a part.
LONGITUDINAL: Something lying alongside the longest axis.
MEDIAL: The opposite of lateral; the direction pointing toward the midline of the body.
MONOAMINES: Adrenaline, noradrenaline, dopamine and serotonin are the monoamine transmitters. They are inactivated in the tissue by monoamine oxidase (MAO).
MOTOR NEURON DISEASE: A chronic disease due to destruction of the motor nerve cells in the spinal cord and brain stem. It is characterized by progressive muscular weakness, beginning in the limbs.
MYASTHENIA: Muscle weakness.
MYASTHENIA GRAVIS: A chronic disease due to a defect in the motor end-plate. It is characterized by progressive muscular weakness, primarily of the face and neck.
MYOBLAST: An embryonic cell that develops into a cell of muscle fiber.
MYOPATHY: Muscle disease.
NECROSIS: The destruction of a living tissue through the death of its cells.
NEUROMUSCULAR: Pertaining to both nerves and muscles.
PALSY: A loss of sensation or an impairment of motor function. Also called paralysis.
PARESIS: A slight, partial, or incomplete palsy.
PARKINSON'S DISEASE: The progressively worsening disease is associated with the loss of cells in the substantia nigra and dopamine levels in the striatum. Characteristic signs include abnormal movements, slow, monotonous speech, and loss of facial expression.
PERINEUM: A body part located between the thighs and buttocks; the external genital organs and the anus are found in the perineum.
PLANTAR FLEXION: At the ankle, to move the sole of the foot downward, as in standing on the toes.
PORTA: A gate, an entrance.
PROJECTION NEURON: A nerve cell with a long axon. The axon terminates on distant targets (e.g. spinal cord motor neurons).
PRONATION: To turn the palm down, or posteriorly.
PROTRACTION: The process of moving a body part forward.
PROXIMAL: The opposite of distal; a direction toward the shoulder or hip in the limbs.
QUADRICEPS: A muscle that has four heads or points of origin.

RETRACTION: The process of moving a body part backward.

ROTATION: The process of moving a body part around a central axis.

SAGITTAL: Body planes, running in or parallel to the cranio-caudal axis, and at the same time perpendicular to the frontal planes.

SOMATOTOPY: Representation of the body parts in the CNS, brought about by the orderly projections of neurons.

SQUAMOUS: Like a scale (*squama* = scale).

STROKE: Intracerebral bleeding or the sudden lack of blood circulation in a restricted part of the brain. It occurs often in the internal capsule, damaging the nerve fibers of the corticobulbar and corticospinal systems.

SUPINATION: To turn the palm up, or anteriorly.

SYNERGETIC: Pertaining to certain muscles that work together.

TIGHT JUNCTION: A sealing membranous junction between adjacent cells; the outer cell membranes are fused to each other and the intercellular space has disappeared. This junction is mechanical and prevents all material movement between the cells.

TRANSVERSE: Body planes which are horizontal in the erect posture. Transverse planes are perpendicular to both sagittal and frontal planes.

TRICEPS: A muscle having three heads with a single insertion.

VENTRAL: The direction relating to the belly (*venter* = belly).

VERTICAL: Perpendicular.