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GENERAL MORPHOPATHOLOGY

(Scientific adviser - V. Anestiade, academician)

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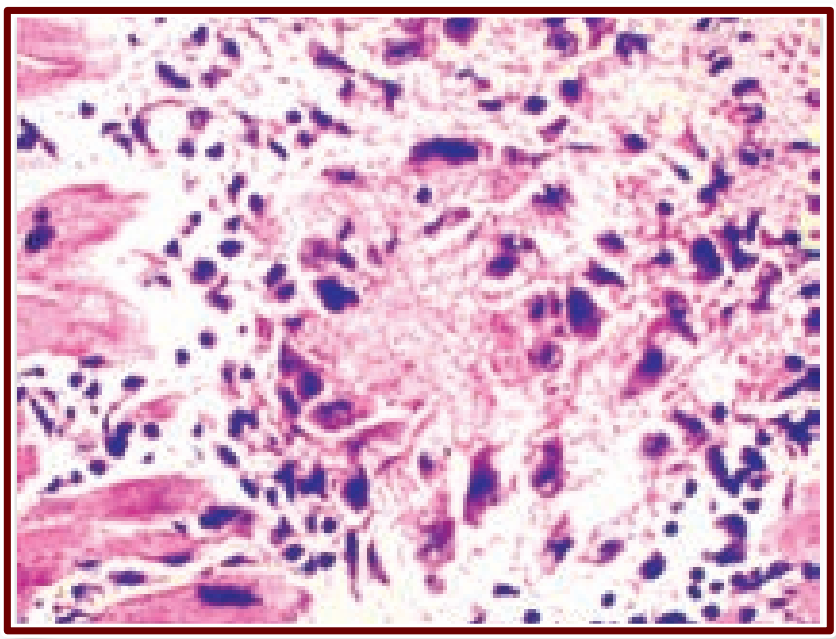

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INTRODUCTION TO MORPHOPATHOLOGY

The morphopathology or anatomical pathology (from the Greek –*morph* – form, *pathos* – suffering, disease and *logos* – science) studies morphological changes that occur in the human body during various diseases. Morphological lesions can be at different structural levels: macroorganism, system, organ, tissue, cellular, intracellular, molecular. Morphopathology is a fundamental discipline of medical education, being the main link between clinical and fundamental disciplines.

The role of anatomical pathology in medical practice is extremely important, particularly in making a diagnosis, correct interpretation of clinical symptoms, choice of therapeutic tactics, verification of the correctness of diagnosis and efficacy of treatment during the evolution of diseases. The identification of the morphological substrate of diseases is performed by studying structural lesions of tissues and organs. The sampling of tissular material is made using various investigation methods:

a) biopsy;
b) examination of postoperative pieces, including those of placentas;
c) necropsy.

Nowadays, there is an obvious increase of intravital morphopathological investigations (biopsies and postoperative material) in the global medical practice. About 80% of the working time of a pathologist is dedicated to the diagnosis of diseases and pathological processes based on the study of biopsic and surgical material, placentas and cytopathological pieces. **The intravital morphological diagnosis is the most exact of all medical diagnostic options.** It may influence decisively the quality of clinical diagnosis and treatment, especially in oncology.

BIOPSY

BIOPSY (from the Greek *bios* – *life* and *opsis* – vision, image) definition: sampling of tissue fragments or organs from a living organism, for microscopic examination, with the purpose of making a diagnosis ("operation for diagnosis"). Nowadays, biopsy is the main field of diagnostic activity of pathological service. The main goals of biopsy are the following:

a) making an exact diagnosis of a disease;
b) identification of the benign or malignant nature of tumor lesions. Only the histopathological investigation can determine whether a tumor is benign or malignant; in case of malignant tumors, their histological form is identified, for example, squamos cell carcinoma or glandular cancer (adenocarcinoma); the cell variant of sarcoma, melanoma, etc.;
c) staging of some diseases; it refers primarily to tumors – establishment of the stage and degree of histological differences of malignant tumor, which definitely

influence the therapeutic approach and prognosis. The histological examination is of great importance in revealing cancer metastases in regional and distant lymph nodes, in assessment of primary tumor extension. This information is necessary to classify tumors according to the TNM criteria (***t**umor*-**n***odus*-**m***etastasis*). It is also important to assess the severity of morphological lesions in non-tumoral diseases of parenchymatous organs, for example, those of liver, kidneys (chronic hepatitis, glomerulonephritis etc.);

d) collection of cells for cytopathological investigation and for cellular cultures.

There are several types of biopsies. They depend on the type of the organ (parenchymatous or hollow), character of lesions (superficial or deep) and the quantity of tissue necessary for histopathological or cytopathological examination. At present, a biopsy sample can be collected from any organ or tissue of the human body. The biopsy is sampled from tumor formations in the majority of clinical cases. Biopsy of macroscopically unchanged tissues is also used, for example, the skin biopsy in case of vasculitis, skin or buccal mucosa in case of amyloidosis, or biopsy of skeletal muscles in case of myositis or degenerative diseases, etc.

Biopsy types:

1. **surgical biopsy** – surgical collection of tissue material; it can be **incisional,** when only a part of formation or pathological area is sampled, and **excisional,** when the pathological area is removed completely, with the intact surrounding tissue, this intervention having also a therapeutic effect;
2. **endoscopic biopsy** – collection of tissue material from tubular/ hollow organs by means of an endoscope (a long, flexible, thin tube made of optical fiber and equipped with illumination system), which permits visualizing the inner surfaces of cavitary organs, after its introduction through natural orifices. It is applied in biopsy of organs accessible to endoscopy under visual control, for example, endoscopic biopsy of esophagus, stomach, colon, bronchi, urinary bladder, abdominal cavity (laparoscopic biopsy);
3. **curettage biopsy** – obtaining tissue material by abrasion (scraping) of the mucosal surfaces or of other superficial lesions with some curettes, for example, the diagnostic curettage of the endometrium, cervical canal, buccal mucosa, skin;
4. **needle aspiration biopsy** – sampling of biopsy by means of syringes or special devices with a fine needle (0.5-0.8 mm diameter) or a cutting needle (1.5-2.5 mm diameter). It is used to obtain a biopsy from deep organs/tissues, for example, from liver, kidneys, thyroid gland, bone marrow, prostate; the access is transcutaneous, while in prostate biopsy it is transrectal; it is usually associated with cell and tissue fragments aspiration. The sample of cellular material is obtained by fine needle puncture. After that, it is spread

on a glass slide, fixed, stained and studied by a cytopathologist. During the puncture with a cutting needle, a tissue fragment of cylindrical shape, of about 2 cm long and 1,0-1,5 mm thick is collected. It is subject to the usual histological processing and is embedded in paraffin; microscopic pieces are studied by a pathologist. The puncture of organs can be made directly, under the control of palpation or imaging guidance (echographic, computer-imaging), particularly in case of some deep intra abdominal tumors. In addition to making an exact diagnosis of some tumors, the needle aspiration biopsy is widely-used in various non-tumoral pathologies of liver and kidneys, in order to determine the degree of affection and the stage of the pathological process (chronic hepatitis, cirrhosis of the liver, glomerulonephritis etc.);

5. **aspiration biopsy** is the collection of tissue material from cavities, by aspiration of the fluid content, which is then centrifuged and the sediment rich in cells is spread on a glass slide, like a smear, stained and studied by the cytopathologist. The main purpose of aspiration biopsy is to determine benignity or malignity of a tumor. When necessary, a cytologic biopsy may be completed with a tissue one. The most eloquent example of aspiration biopsy is the biopsy of thyroid gland cysts;
6. **intraoperative biopsy** is the biopsy performed during a surgical intervention, in order to specify the diagnosis, extent of lesions, degree of penetration into tissues, something that is very important for a correct surgical act (assessment of the volume of an organ resection). The histopathological examination is performed on the spot, taking 15–20 minutes, sections being performed at a freezing microtome with inclusion on ice.

Besides the microscopic examination of sampled tissues (cells), these can be also subject to some histochemical, immunohistochemical, luminescent microscopical, ultramicroscopic analyses and other techniques of investigation. In many cases, more repeated biopsies are performed, in order to monitor the development of tumors and the efficacy of treatment.

EXAMINATION OF POSTOPERATIVE PIECES

According to the current requirements, all tissue and organs fragments, entire organs or parts of the body (for example, the limbs) removed during surgical interventions, as well as placentas, must be sent to a pathology department, where they are exposed to macroscopic and microscopic examination. First of all, the pathologist makes a detailed macroscopic description of postoperative pieces and a record of all lesions visible to the naked eye. Then, tissue fragments are sampled from all the revealed lesions, including, as much as possible, in the same fragment, both pieces of the changed macroscopic tissue and of the normal one. This is necessary to assess the correctness of resection of an organ, especially

in tumor pathologies, as well as to estimate the reaction of lesion adjacent tissues. Then, tissue fragments are processed histologically and embedded in paraffin blocks. After that, microscopic sections are removed from paraffin blocks, being stained by different methods. The specimens are studied by a pathologist, who makes an extended histological description and, on the basis of macroscopic and microscopic data, establishes a definitive pathologic diagnosis.

POSTMORTEM EXAMINATION (NECROPSY)

NECROPSY (from the Greek *nekros* – dead and *opsis* – vision, image).

Although recently the number of autopsies has been decreasing, they continue to be an important method of diagnosis and control of medical act. ***There is no other objective method to verify the correctness of diagnosis and treatment than the necropsy of the deceased.***

Necropsy is the direct research of morphological lesions on cadaver, occurred during diseases. Directly during the necropsy, macroscopic changes in all the tissues and organs are studied thoroughly. Based on this study, a presumptive anatomopathological diagnosis is established (by agreement with the treating physician, whose presence is obligatory at necropsy). Subsequently, fragments from all the organs are sampled and subject to histopathological processing. Histological specimens are studied microscopically, and, whenever necessary, other additional histochemical, bacterioscopic and luminescent microscopic methods are applied. At the end of all these investigations, a final anatomopathological diagnostic is established and recorded in a necropsy protocol and in the medical history of the patient. A necropsy protocol also includes the clinical–anatomical epicrisis, in which the pathologist motivates the diagnosis, indicates the cause of death, ascertains confrontation results of the anatomopathological diagnosis with the clinical one, and, in case when they do not match – points out the possible reasons of identified medical errors. The anatomo-clinical confrontation and the identification of medical errors constitute a permanent training and improvement school for physicians, regardless of their speciality.

Another way to collect the material for anatomopathological study of diseases is the experimental one. Creation of experimental models has contributed significantly to the knowledge of the pathogenesis and morphogenesis of many human diseases. Besides this, modelling of some diseases on animals gives adequate possibilities to test medicinal drugs and some new surgical techniques of treatment.

The basic principle of modern pathology is the anatomo-clinical orientation. It is a morphological discipline, from a methodical point of view, but it is a clinical discipline, from the point of view of medical practice. This mutual combination places pathology in the middle of human medicine. Pathology knowledge is indispensable for the study of other clinical disciplines in medical education, as well as for daily practical activity of clinical doctors.

DEATH OF THE BODY

Death is the final and irreversible cessation of vital functions of the body. The final interruption of biological processes at tissues and organs level leads to their death and disintegration with transformation of the living, organic matter into dead, inorganic matter and of the human body into a corpse (*lat. cadaver*). According to the causative factor, the following types of death can be distinguished: a) natural; b) violent; c) caused by diseases.

The natural death (physiological) occurs as a result of natural wearing of the body in people of advanced age.

The violent death is caused by some external factors: traumatic, physical, chemical, mechanical etc. Cases of violent deaths are studied by forensic medicine service.

The death caused by diseases (pathological death) is conditioned by changes that are incompatible with life, developing within various diseases and pathological processes. Usually, they settle slowly, reducing the vital functions of the body gradually. Cases of death caused by diseases are studied by the anatomopathological service.

Sometimes, *sudden*, unpredictable *death* takes place, occurring unexpectedly, apparently in full health, within 1 hour of the onset of clinical symptoms. The cause may be ischemic cardiomyopathy, first of all myocardial infarction and rarely aortic stenosis, congenital or acquired disorders of the heart conduction system, cardiomyopathies, electrolyte disorders etc. Cases of sudden death are subject to forensic medical examination.

Since various tissues and organs have different sensitivity to anoxia, the death process takes place in a certain dynamic, in stages. The real (irreversible) death is preceded by a series of phenomena, called *terminal states,* which means the final period of the disease, a state between life and death, when deep disorders of homeostatic parameters of the body appear. According to the clinical point of view, the periodization of terminal states is divided in *preagonia, agonia* and *clinical death*, each of them requiring different medical approaches. The moment of death of the entire body is considered the moment when the death of the brain is established (*the cerebral death – the equivalent of the body's death*). This aspect is especially important in the context of sampling of the organs/tissues from the corpse, with the purpose of transplantation.

Depending on the reversible or irreversible character of vital activities changes of the body, we distinguish *clinical* and *biological death.* Clinical death is characterized by cessation of respiration and of blood circulation (cardiac contractions). The duration of clinical death is ~ 5–6 min. – it is the duration of cortex survival in conditions of anoxia. During clinical death, the respiration and blood circulation are lacking, but the cellular metabolism continues through anaerobic glycolysis. The stocks of glycogen in the brain deplete gradually and irreversible lesions occur in the nervous tissue – death of cerebral cortex neurons. During the electroencephalographic examination (EEG), a flat track is recorded in the

frontal lobes activity (isoelectric line or "bioelectrical silence").

After that, biological death occurs – the irreversible cessation of vital activity of the body. The signs of certainty of biological death are:

1) *cooling of the corpse;*
2) cadaveric rigidity;
3) cadaveric lividities (spots);
4) dehydration (drying) of the corpse;
5) decomposition of the corpse.

The cooling of the corpse (*algor mortis*)

The decreasing of temperature starts on the surface of the body and becomes more obvious in uncovered places. Gradually, the body temperature is leveled with external environmental temperature. The rapidity of the process depends on the temperature and humidity of the atmospheric air, the volume of the corpse, the thickness of the subcutaneous adipose layer and the specificity of the pathological process. The cooling of the corpse occurs due to the stopping of heat production in the body, as a result of blood circulation cessation, suppression of oxidative processes, and heat loss in the external environment. Generally, it is considered that the temperature of the corpse drops one degree per hour, if external environmental temperature is half of body temperature. This rhythm depends, to a great extent, on the temperature of the body at the moment of death and the temperature of the external environment.

Cadaveric rigidity *(rigor mortis)*

Hardening and stiffness of the muscles appear in 2–5 hours after the death and spread gradually in craniocaudal dimension, from the face muscles (masseter and mimic muscles) to limbs, involving all muscle groups. In 24 hours, it reaches maximum level and in 2–3 days disappears in the same order. If handled with force, the muscle rigidity doesn't recover. The intensity and rapidity of cadaveric rigidity establishment depend on the degree of development of the body musculature and of specificity of the pathological process which preceded the death. For example, the rigidity appears more rapidly and is more intense in people with a strong musculature and in death preceded by convulsions (tetanus, cholera, intoxication with strychnine). The mechanism consists in decomposition of adenosine triphosphoric acid (ATP) in muscles after the death, accumulation of lactic acid and the increase of actinomyosin viscosity, leading to hardening of muscles. The resolution is based on the autolysis of muscle fibers.

Cadaveric lividities (spots) – spots of purple color on the declivous parts of the body. The localization of the spots depends on the position of the body at the moment of death and, as a rule, they lack in places exposed to pressure. They begin to appear in 3–6 hours after death. At first, they disappear at digital pressure and reappear after its cessation, and in 18–24 hours they have a red–rose color and do not disappear at digitopressure. The mechanism consists in redistribution and accumulation of blood in the vessels of declivous parts of the body, as a result of cessation of circulation and gravity (cadaveric hypostasis). In 18–24 hours after death, a cadaveric imbibition occurs, generated by the erythrocytes hemolysis and the diffusion of plasma in the tissues. The blood in the corpse is accumulated in veins, arteries being almost empty. The passing of the blood from arteries to the veins is determined by the rigidity of the smooth

muscles of the arterial walls. The *post mortem* coagulation of the blood caused by the suppression of blood circulation takes place in veins and in the right cavities of the heart. The blood does not coagulate in cases of asphyxia. Cadaver clots are more numerous, when death occurs slowly, and less numerous, when it occurs suddenly. Intensity and color of cadaver spots depend, to some extent, on the previous pathology. For instance, in cases of chronic heart failure, the spots are well marked and intensely colored, while in anemias and in cachectic conditions they are weakly pronounced.

Cadaveric dehydration (drying) of tissues, first of all, mucosas, skin and eyeballs. The skin, especially at the level of scrotum and digital pulp gains a parchment aspect. Mucosas, particularly of the lips, become dry, wrinkled, and dense, scleras lose their luster, cornea becomes opalescent, and a whitish spot appears at the level of the pupil (corneal clouding). These changes can be explained due to cessation of circulation and evaporation of water from the surface of the body. The intensity of dehydration of the corpse depends much on the temperature and humidity of external environment.

Decomposition of the corpse occurs as a result of corpse autolysis and putrefaction processes. *Cadaveric autolysis* – softening and liquefaction of cells and tissues, under the action of own enzymes. Glandular organs get autolysed faster, first of all the pancreas, liver, gastrointestinal and bronchial mucosa, the cells of which are rich in hydrolytic (proteolytic) enzymes. Gradually, *putrefaction processes* are associated, caused by aerobic and anaerobic microbial flora, which is more abundant in the intestine. Putrefaction intensifies cadaveric autolysis and is more evident in the abdominal cavity. Microbes produce hydrogen sulfide, which reacts with disintegrating products of hemoglobin, forming sulfhemoglobin of green color. This gives the respective color to the tissues and the abdominal wall. The green spot of putrefaction appears in approximately 24 hours from the moment of death. Putrefaction gases penetrate the tissues and organs, determining the appearance of cadaveric emphysema. The rapidity and the intensity of autolysis and putrefaction depend on the temperature of the external environment and on the specific character of pathological process, being better marked in cases of infectious diseases, septicemias, peritonitis. Keeping the corpse at low temperatures diminishes the effects of putrefaction and embalming provides long-term conservation.

CELLULAR AND EXTRACELLULAR REVERSIBLE LESIONS

Lesion or ***alteration*** is the change of the structure of the cells, intercellular substance, tissues and organs, which occurs in pathological conditions and manifests itself by disturbing their vital activity. These changes can be caused by excessive physiological stimuli or by pathological factors. The severity of cellular/tissular lesions depends not only on the specificity, length and intensity of action of the pathogenic agent, but also on many other factors referring to the cells themselves, for example their vulnerability, sensitivity to aggressive actions, degree of differentiation, blood supply, nutrition, antecedent condition, as well as the capacity to adapt to new conditions of existence. In most cases, as a response to a harmful agent, adaptive processes develop in the impaired cells, resulting in a new condition of structural–functional stability (a state of homeostasis), which ensures the survival and the functional activity of the cells in the modified microenvironment. If the limits of the adaptive response are exceeded, a cellular/tissular lesion takes place, being reversible up to a certain level of progressing of morphological changes, but, when the pathogenic factor acts permanently, or has a major intensity, irreversible lesions, which may result in cellular death, occur. The difference between reversible and irreversible cellular lesions is more of quantitative nature. A reversible lesion is insignificant, superficial, and after removement of the harmful factor, the cell returns to its normal state. But, if the alteration is severe or persistent, the restoration of the cell is impossible and the lesion becomes irreversible. The transition from a reversible lesion to an irreversible one is gradual and happens when the adaptive potential of the cell is exhausted.

So, the cellular response to harmful actions is manifested in the appearance of a wide range of morphological changes, which can be grouped as following:

- ✧ adaptive processes;
- ✧ reversible lesions;
- ✧ irreversible lesions;
- ✧ cellular death.

Adaptive processes (atrophy, hypertrophy, hyperplasia and metaplasia) are tackled in the chapter "Adaptive – compensatory processes".

2.1. CAUSES OF CELLULAR EXTRACELLULAR LESIONS

The causes of reversible and irreversible lesions of cells and extracellular matrix are similar. Initially, most of causative factors cause reversible lesions, but, if the harmful factor has a severe and prolonged action, the changes progress and the cell achieves a "non–return" point, when irreversible lesions occur, which result in cellular death. Etiological factors of cellular lesions vary from severe mechanical traumas with crushing of tissues, wounds, up to molecular defects at genes level, which are the basis of congenital metabolic diseases. Etiological factors of cellular lesions can be divided in many groups, and namely:

1. Hypoxia (anoxia) caused by disturbances of cardiovascular and respiratory systems, anemias, intoxications with carbon monoxide etc. Hypoxia induces disturbances of aerobic breathing in the cells, the decreasing of synthesis of ATP and the compensatory activation of anaerobic glycolysis. A rapid exhaustion of intracellular resourses of glycogen occurs, as well as an accumulation of lactic acid, a decrease of pH and an impairment of the activity of most cellular enzymes. A reduction of ATP synthesis by more than 5–10%, in comparison with the norm, influences many critical cellular systems, and, first of all, the membrane sodium pump, which causes the intracellular accumulation of sodium, water retention and tumefaction of the cell. Example: the reduction or suppression of the arterial blood supply to myocardium, as a result of stenosing atherosclerosis of coronary arteries, causes ischemic dystrophy or myocardial infarction.
2. Physical agents: mechanical, thermal traumas, radiations. In some cases, a direct destructive action of the causative factor takes place on tissues/cells, in others, like ultraviolet and ionizing radiation, the pathogenic effect is manifested by an excessive accumulation of the oxygen free radicals, which acts harmfully on lipids, proteins and cellular DNA. Example: solar burns of the skin in excessive ultraviolet radiation.
3. Chemical agents: exo- or endogenous toxins, drugs, medicines. Example: liver dystrophy and its necrosis in case of intoxications with poisonous mushrooms.
4. Infectious agents: viruses, bacteria, rickettsias, fungi, parasites. Example: the lesion of respiratory tract mucosa by the influenza virus.
5. The immune responses (autoimmune). Example: pathology of the cell nuclei in disseminated lupus erythematosus, caused by antinuclear and antinucleolar autoantibodies.
6. Impairment of the trophic function of the neuroendocrine system. Example: the dystrophy and atrophy of tissues in innervation disturbances.
7. Genetic disorders (genetic or chromosomal defects). Example: hereditary enzymopathies or thesaurismoses (storage diseases).
8. Nutritional disorders: insufficiency or excess of some substances in nutrition (iron, vitamins, proteins, lipids, etc.). Examples: fatty dystrophy of the liver in cases of fat misuse in nutrition, development of diabetes mellitus type II in obesity.

2.2 MORPHOLOGY OF CELLULAR AND EXTRACELLULAR REVERSIBLE LESIONS

Cellular and extracellular reversible lesions are also called ***dystrophies*** or degenerative processes (degenerescences). The notion currently used of **"cellular/extracellular reversible lesions"** is identical with the classical notion of **"dystrophies"**. Further on, the term **"dystrophy"** will be used.

Dystrophy ***(cellular/extracellular reversible lesion)*** is a pathological process, caused by disturbances of the cellular metabolism (intercellular), inducing structural changes. All pathological processes start at the molecular level and any cellular response to an aggressive action is first of all manifested by

cellular metabolic disturbances. By progressing, they lead to structural changes noticeable at the level of cellular compartment or intercellular structures. Cellular lesions ensue from functional and biochemical disturbances of one or more cellular components. The most important and sensible to harmful stimuli are: 1) mitochondria, which ensure the breathing and energetic resources of the cell; 2) the cellular membrane, which regulates the ionic and osmotic homeostasis of the cell; 3) the cytoskeleton, which ensures such cell functions like support, transport, contraction and motor; 4) the synthesis of proteins and 5) the cellular genetic apparatus. The possibilities to detect these changes depend on the sensibility of the applied methods of morphological investigation. Histochemical and electron microscopy techniques allow identifying the dysmetabolic lesions in a short time (minutes, hours) from the onset of the harmful action, and, macroscopically or microscopically, they become visible much later. Example: dystrophic lesions caused by the myocardial ischemia can be tracked by histochemical reactions in 30 minutes–2 hours from the onset of ischemia (histochemical methods for glycogen and oxidoreductive enzymes), while, by means of an optical microscope – in 12–20 hours.

Morphologically and biochemically, dystrophies are manifested by quantitative and qualitative changes of some metabolic products in the cells and/or intercellular spaces. There may be the following variants:

a) accumulation in the cells or/and in interstitium of some usual chemical substances in excessive amounts, in comparison with the norm (intracellular accumulations); they can be of intracellular or extracellular origin;
b) decreasing of some structural substances which are encountered in physiological conditions;
c) storage in cells or/and in intercellular spaces of some usual substances, but in unusual places;
d) appearance and storage in the cells or/and in interstitium of some substances that are not encountered in the organism in normal conditions.

These quantitative and qualitative changes of different metabolic products can be made through the following morphogenic stereotype mechanisms:

1. **Infiltration** – excessive penetration in cells (intercellular spaces) of some metabolic products from blood, lymph, urine and their further storage, as a result of insufficiency of enzymatic systems to metabolize them. Example: infiltration of epithelial cells of renal tubes with glucose in diabetes mellitus or infiltration with lipids of the hepatic lobules in obesity (lipemia).

2. **Decomposition** (phanerosis) – break down (decomposition) of some complex chemical substances and the storage of their components in the cells or in the extracellular compartment. Example: break down of lipoproteic complexes of membranous structures in hypoxia, intoxications or decomposition of the glycoproteic complexes from the ground substance of connective tissue in rheumatic diseases.

3. **Transformation** – formation of one type of metabolic products from precursor substances, common to all types of metabolism (proteins, lipids and glucides). Example: transformation of the components of glucides in fatty acids or of amino acids in glucides.

4. **Pathological synthesis** – the synthesis of some substances not usually seen in cells and tissues in physiological conditions. Example: the synthesis of the abnormal glycogen in some hereditary glycogenoses.

The classification of dystrophies, according to various criteria, is presented in the Table 2.1.

Table 2.1

Classification of dystrophies

Classification criterion	Varieties of dystrophies according to the given criterion
Predominant localization of metabolic enzyme disturbances	a) Cellular (parenchymatous) b) Extracellular (mesenchymal, stromal-vascular) c) Mixed (intra- and extracellular)
Type of altered metabolism	a) Proteic (disproteinoses) b) Lipidic (dislipidoses) c) Glucidic d) Mineral
Extension of dystrophic lesions	a) Systemic (generalized) b) Localized
Mechanisms of development (role of genetic and acquired factors)	a) Acquired b) Hereditary (congenital)

2.3. CELLULAR LESIONS (PARENCHYMATOUS CELLULAR DYSTROPHIES)

Metabolic disturbances in this group of dystrophies take place in parenchymatous cells, which perform the specialized function of these organs. Morphological changes take place both at the level of cytoplasm and at the nucleus level and may be qualitative and quantitative. According to the impaired type of metabolism, parenchymatous dystrophies are subdivided into proteic, lipidic and glucidic dystrophies (Table 2.2).

Table 2.2

Classification of cellular dystrophies

I – Proteic dystrophies	➢ granular dystrophy ➢ cellular hyaline dystrophy ➢ hydropic dystrophy ➢ keratin dystrophy ➢ hereditary dystrophies with impairment of amino acids metabolism
II – Lipidic dystrophies	➢ fatty cellular dystrophy (steatosis) ➢ hereditary systemic lipidoses.
III – Glucidic dystrophies	➢ glycogenic dystrophy ➢ hereditary glycogenoses ➢ cellular mucous (mucinous) dystrophy

2.3.1. PROTEIC CELLULAR DYSTROPHIES (CELLULAR DISPROTEINOSES)

Granular dystrophy (cloudy intumescence) develops in parenchymatous organs, such as kidneys, myocardium and liver.

Microscopically, it manifests itself by the presence in the cells (nephrocytes, cardiomyocytes and hepatocytes) of a large number of tiny proteic granules. Macroscopically, the affected organs are somewhat larger in size and weight. They have a weakened capsule, flaccid consistency; luster is absent, opaque and pale aspect like of boiled meat, hence its name of *cloudy intumescence*.

When examined microscopically, the cells are bigger in size, tumefied, with unclear margins; the cytoplasm has a fine granular, reticulated aspect and contains proteic granules, small eosinophils spread uniformly (fig. 2–1a).

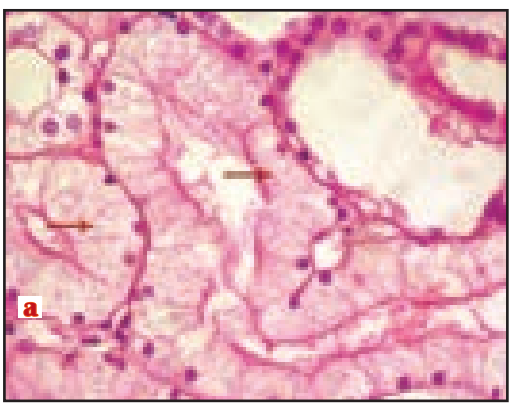
The electron microscopy detects dilatation of the endoplasmic reticulum, which contains agglomerations of proteic masses and an insignificant tumefaction of mitochondria (fig. 2–1b).

The function of the affected organs in granular dystrophy is slightly altered (for example: appearance of proteinuria in the granular dystrophy of kidneys).

Consequences. Granular dystrophy is the first sign of a cellular lesion, and it is reversible, if the causative factor is removed. In case the harmful action persists, the changes can advance to more severe lesions, like cellular hyaline dystrophy, hydropic or lipidic.

The appearance of some proteic granules in cytoplasm of the cells can be also observed in physiological conditions, reflecting the morpho– functional peculiarities of the cell (for example, elaboration of secretory granules in endocrine cells of the glands, physiological resorption of proteins by the epithelium of the proximal renal tubes etc.), intensification of the synthesis function of proteins (ex: in hepatocytes, secretory cells), hyperplasia and hypertrophy of cytoplasmic organelles in functional overstrain of parenchymatous organs etc.

Cellular hyaline dystrophy (*intracellular hyalinosis*) is characterized by the appearance in the cells of some homogenious, eozinophilic large dro-



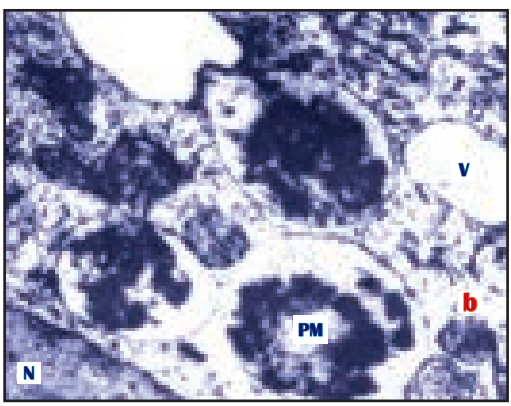


Fig. 2–1 a, b. Granular dystrophy of the epithelium of convoluted renal tubes: a – microscopic pattern (hematoxylin–eosin stain; ×70); b – electron microscopic image (×16000); V – vacuoles (dilated cisternae of endoplasmic reticulum); PM – proteic masses; N – nucleus;

plets of proteic origin, occupying the entire cytoplasm (Fig. 2–2). Macroscopically, the affected organs do not show any characteristic signs. The electron microscopy reveals a **destruction** of cytoplasmic organelles, homogenisation and their change into proteic hyalin structures.

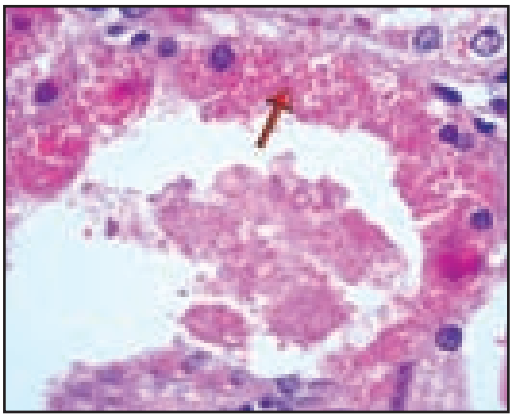


Fig. 2–2. Cellular hyaline dystrophy of the epithelium of the proximal renal tube (hematoxylin–eosin stain; ×200).

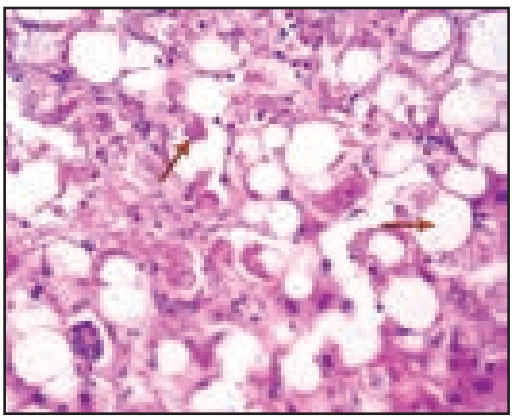


Fig. 2–3. Cellular hyaline dystrophy (Mallory corpuscles) and steatosis of hepatic cells (hematoxylin–eosin stain; ×110).

It can be seen more frequently in kidneys (epithelium of uriniferous tubes) and in the liver (hepatocytes). It can be observed in kidneys in cases of massive proteinuria, in glomerulonephritis, renal amyloidosis, diabetic glomerulopathy, paraproteinemic nephrosis, intoxications etc., when the permeability of glomerular filter increases and an excessive reabsorption of proteins from the urinary filtrate occurs. Similar lesions appear in hepatic cells, in case of alcoholic hepatitis and alcoholic cirrhosis - so called Mallory corpuscles or the alcoholic hyaline – intracytoplasmic hyaline accumulations of proteins (cytokeratins) of intermediate fibers, which may be considered as a result of cytoskeleton's alteration under the action of alcohol (Fig. 2–3). Other examples are the Russel corpuscles, representing storages of immunoglobulins in vesicles of rough endoplasmic reticulum of plasmocytes and hyaline cytoplasmic inclusions in viral infections. A similar process can be observed in the Alzheimer disease, when neurofibrillary plexus constituted of cytoskeletal proteins, especially of microtubules and neural fibers, are formed in neuronal cytoplasm.

It is an irreversible process leading to focal or entire necrosis of the cell. Clinically, it is manifested by severe disturbances of the organ's function (for ex: the appearance of proteins and hyaline cylinders).

Hydropic dystrophy (*vacuolar*) manifests itself by the appearance of some vacuoles filled with cytoplasmic fluid in the cytoplasm of the cells. At the microscope, vacuoles are optically empty, round or oval with pale nucleus (Fig. 2–4). It can be seen both in parenchymatous organs and in the skin (epidermis). Macroscopically, the affected organs are slightly changed.

The main mechanism of vacuolar dystrophy is the disturbance of the hy-

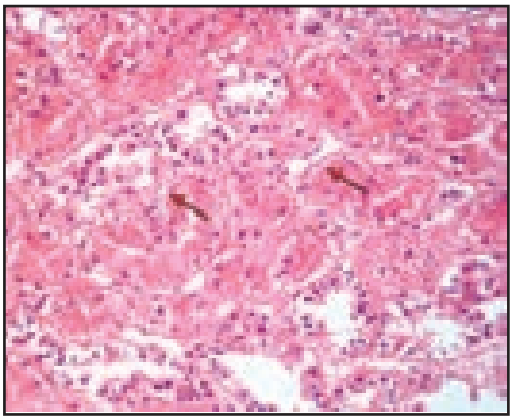


Fig. 2–4. Hydropic dystrophy of the epithelium of convoluted renal tubes (hematoxylin–eosin stain; ×70).

dro-electrolyte and proteic metabolism with change of intracellular colloid-osmotic pressure, which leads to penetration of water into the cell or the impairment of elimination of it from the cell, during the oxido-redox processes. An excessive accumulation of water leads to destruction of cellular ultrastructures and appearance of vesicles filled with cytoplasmic fluid (cell distention). This fluid accumulates in the vesicles of endoplasmic reticulum and in the mitochondria (Fig. 2–5). A certain diagnosis of hydropic dystrophy can be made only after the staining of microspecimen for glycogen and lipids (the absence of staining confirms the diagnosis).

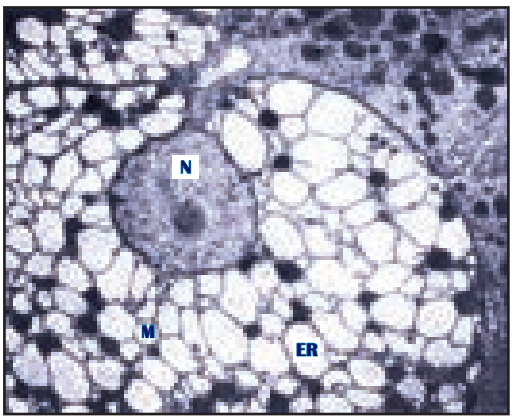


Fig. 2–5. Hydropic dystrophy of hepatic cell (electron microscopy ×7000); ER – endoplasmic reticulum; M – mitochondria; N – nucleus.

Vacuolar dystrophy is an irreversible process, resulting in a colliquative necrosis of the cell. It may result in a distended dystrophy of the cell as a manifestation of a focal colliquative necrosis. After that, severe functional disturbances appear in the respective organs. For example, hydropic dystrophy of epithelium of renal tubes is observed more frequently in nephritic syndrome, characterized by deep proteinuria and edemas. Vacuolar dystrophy of myocardium is manifested by a considerable reduction of the heart contractility function.

Hydropic dystrophy is noted in infectious diseases (mostly in viral hepatitis), intoxications (with phosphorus, arsenic, carbon tetrachloride), inanition states, avitaminoses, under the action of penetrant radiation etc.

Keratin dystrophy (*cornous*) is observed in the skin and mucosa covered with squamous and transitional epithelium. It shows an excessive formation of keratin in the pluristratified cornified squamous epithelium (hyperkeratosis) or an appearance of keratin in epithelium of mucosas, which is not cornous under normal conditions (leukoplakia).

Macroscopically, in hyperkeratosis foci, the skin is thickened, dry and has an aspect of fish scales or corns (Fig. 2–6a). Microscopically, the cornous layer of the epithelium is thickened considerably, as a result of an excessive formation of keratin (Fig. 2–6b). The chronic inflammation, viral infection, avitaminoses (particularly the lack of vitamin A), chronic irritations, some skin developmental disturbances, e.g.: congenital hyperkeratosis or the ichthyosis (from the Greek *ichtys* - fish + *osis* - pathological process) are significant in the etiology of lesion. Generalized congenital ichthyosis is a pathology that is incompatible with life.

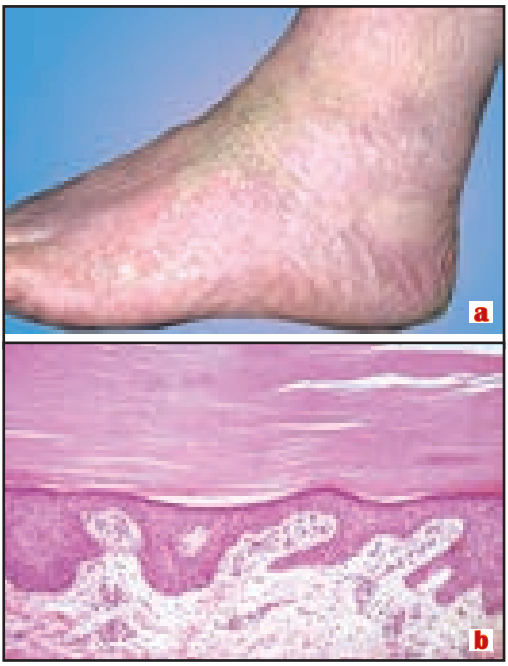


Fig. 2–6 a, b. The skin hyperkeratosis: a – macroscopic aspect; b – microscopic pattern (hematoxylin-eosin stain, ×70).

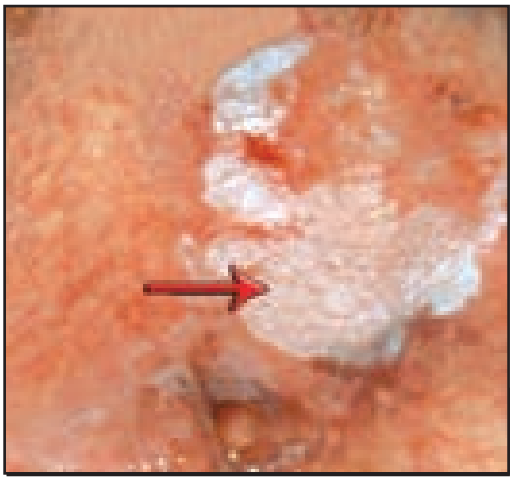


Fig. 2–7. Leukoplakia of buccal mucosa.

Leukoplakia is observed in oral cavity mucosa, tongue, lips, pharynx, larynx, vaginal portion of the uterine cervix, vagina, and urinary bladder. Macroscopically, it shows some slightly prominent, well-delimitated plaques of whitish color and a smooth or irregular surface, which can reach some centimeters in diameter (Fig. 2–7). Microscopically, the pluristratified squamous epithelium is thickened; the superficial layer is formed from keratinized, enucleated cells, and is covered with a keratin layer. Leukoplakia can also appear on mucosas covered with unistratified epithelium, if squamous metaplasia of mucosas took place initially (in bronchi, stomach, intestines, and endometrium).

Chronic inflammations, chronic irritations (smoking), traumatisms etc. are the most frequent causes of leukoplakia, which is considered to be a precancerous lesion.

Keratin dystrophy can advance towards restoration of the affected tissue or necrosis of the cells. The function of the skin and mucosas in the deteriorated areas is severely impaired.

2.3.2. LIPIDIC CELLULAR DYSTROPHIES (CELLULAR LIPIDOSES)

The metabolic disturbances of neutral lipids or *steatosis of the parenchymatous organs* are the most frequent of this group of dystrophies. Macroscopically, the affected organs have an increased volume and weight, a flaccid consistency and a yellow aspect (claylike). Microscopically, steatosis appears in cytoplasm of the cells like some droplets of neutral fats of various sizes (macro or microvesicular steatosis), without a limiting membrane. Optically, the lipidic droplets appear to be empty, in pieces processed in paraffin, since lipids dissolve in alcohol, chloroform etc. To keep the lipids in tissular fragments, their contact with lipophilic reagents during histological processing is avoided and sections are made in freezing microtome.

The following methods of staining are applied to identify the lipids:

- ✧ Sudan III or Scharlach - the lipids are stained in red;
- ✧ Sudan IV or Osmic acid – the lipids are stained in black;
- ✧ The Nile blue stains fatty acids in dark-blue and neutral fats - in red.

The heart in fatty dystrophy is increased in size, the compartments are enlarged, dilated, the myocardium has a flaccid consistency and, on the necropsy table, it extends and widens; it is opaque, pale–yellowish on cross section. Under the endocardium, mostly in the region of papillary muscles, an alternation of some yellowish fattish striae can be noted, with areas of usual color, the heart getting an aspect similar to the skin of a tiger (*"tiger heart"*, Fig. 2–8a). The tiger skin aspect of myocardium is explained by the inhomogeneous character of the fatty dystrophy, because deposition of lipids takes place mainly around veins and venules. This focal, segmentary character of lipidic inclusions occurs in case of a moderate hypoxia of myocardium. In severe lesions, for example in severe anemias, the myocardial steatosis is diffuse. Under the microscope, small or bigger droplets of lipids can be revealed in cardiomyocytes cytoplasm, which are colored in yellow–red, when processed with Sudan III (Fig. 2–8b). During electron microscopic examination, a lipidic inclusion has a characteristic white–black striation and adheres to membranes of cytoplasmic organelles, mostly of mitochondria (Fig. 2–8c). The membranes become dim and destroyed in areas of contact with lipidic inclusions.

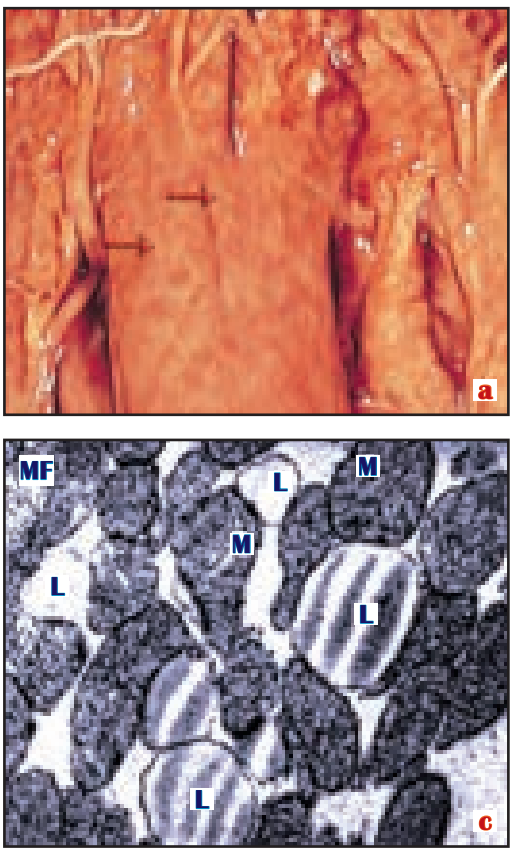


Fig. 2–8 a, b, c. Fatty dystrophy of myocardium (myocardial steatosis): a – macroscopic aspect ("tiger heart"); b – microscopic pattern (Sudan III stain; ×70); c – electron microscopic image (×21000); L – lipidic inclusions, M – mitochondria, MF – myofibrils.

It frequently happens in chronic cardiovascular insufficiency (rheumatic or congenital valvulopathies, cardiosclerosis, cardiomyopathies), anemias, severe infectious diseases, intoxications (with ethanol, phosphorus) etc. It is particularly characteristic for diphtheric myocarditis

and severe anemias. The predominant morphogenetic mechanism is decomposition or lipophanerosis – the splitting of lipoproteic compounds of intracellular membranes. The contractile function of the heart is decreased. Myocardial steatosis is considered as a morphological substrate of functional decompensation of the heart.

The liver in steatosis has an increased volume and mass, the fibrous capsule is distended and smooth, the borders are rounded, the consistency is soft, pasty, of a yellowish color on section (claylike aspect), homogenous or spotted, a layer of fat remaining on the blade of necropsy knife. The mass of the liver can be enlarged up to 3–4 kg, being 3–5 times bigger than the normal one. The lobular pattern is kept or even emphasized (in cases when the dystrophic process occurred only in some areas of the lobules – in the centre or at the peripheral area of the lobule), or it may be erased, dim in severe dystrophies with diffuse steatosis of hepatocytes; the final case is macroscopically similar with the "goose liver" (Fig. 2-9 a). Microscopically, initially, the granules of lipids appear in hepatocytes (pulverulent steatosis), subsequently - small droplets (microvesicular steatosis), which confluence in dynamics, forming large droplets (macrovesicular steatosis). In severe steatosis, the lipids blend and form a bigger dro-

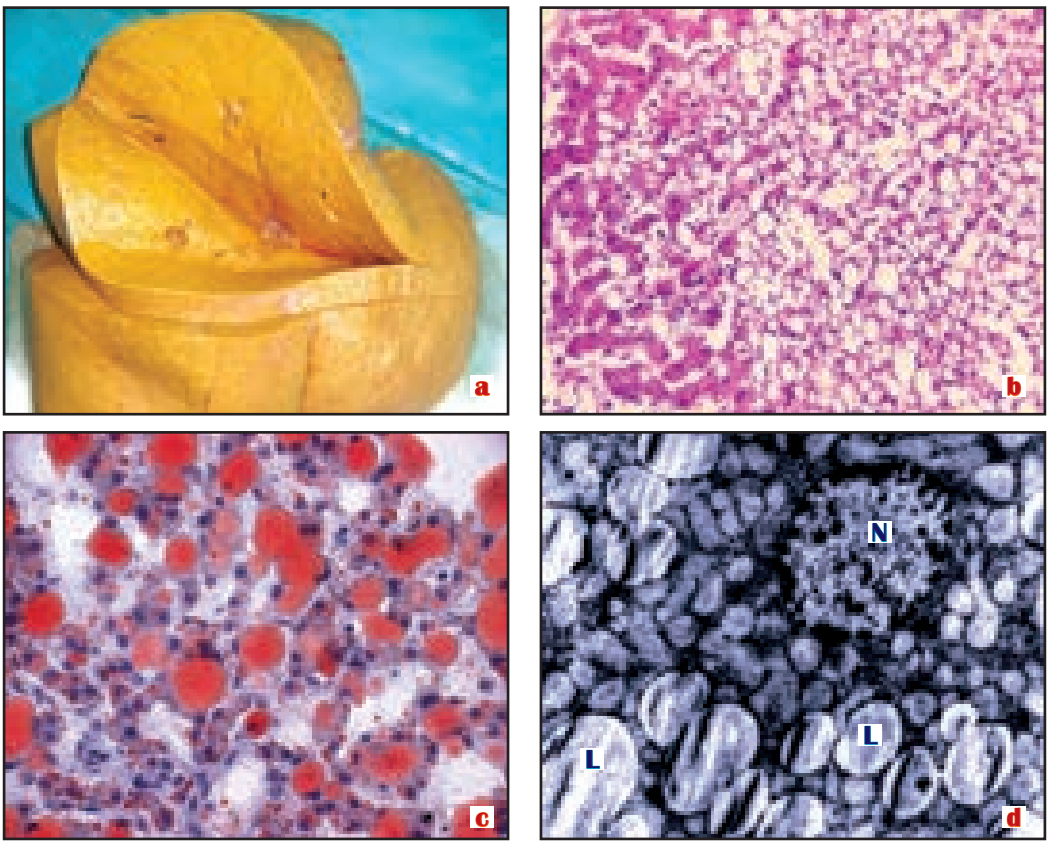


Fig. 2–9 a, b, c, d. Fatty dystrophy of the liver (hepatic steatosis): a – macroscopic aspect; b, c – microscopic pattern (b – hematoxylin–eosin stain, c – Sudan III – stain; ×70); d – electron microscopic image (×10000): L – lipidic inclusions; N – nucleus.

plet, pushing the nucleus to the edge and the hepatocyte becomes similar to the fatty cell (adipocyte). A rupture of membranes of hepatocytes and formation of some lipidic cysts may occur. Steatosis is observed more frequently in peripheral areas at the level of hepatic lobule, and more rarely - around the central vein and, in severe lesions, it becomes diffuse (Fig. 2–9 b and 2–9 c). Electronomicroscopically, it can be established that lipidic droplets are mainly placed in the perinuclear area of hepatic cells (Fig. 2–9 d).

The most frequent causes of hepatic steatosis are the lipidemia (in obesity, excess of fat in the diet, chronic alcoholism, diabetes mellitus, hormonal disorders), hepatotropic intoxications (with phosphorus, carbon tetrachloride, ethanol, chloroform etc.), nutrition disorders (lack of proteins or lipotropics factors, avitaminoses, digestive tract diseases etc.), tissular hypoxia (in heart failure, severe anemias, pulmonary diseases) etc. In clinical practice, the liver steatosis in alcoholism and diabetes mellitus associated with obesity are significant.

The predominant morphogenetic mechanism of peripheral areas of steatosis (*peripheral or periportal steatosis*) is the infiltration and it is observed in cases of hyperlipidemia (fats penetrate the liver with the blood of portal vein and infiltrate the peripheral areas of the lobules first) and of centrolobular areas (*centrolobular steatosis*) – decomposition, which may occur as example, in progressive hypoxia of the liver.

The function of the liver in fatty dystrophy remains normal for a long time. When the action of harmful factor persists, necrosis processes associate and, gradually, a micronodular cirrhosis begins (portal type).

2.3.3. GLUCIDIC CELLULAR DYSTROPHIES

The following methods of staining are used for the histochemical identification of glucides:

- ✧ PAS reaction (*periodic–acid–Schiff*) - to reveal the amount of glucides – it is colored in red; in order to identify the glycogen, the amylase – an enzyme which dissolves the glycogen - is applied additionally on colored sections with PAS reaction. The disappearance of staining after being processed with amylase confirms the presence of glycogen;
- ✧ reaction with Best carmine to trace out the glycogen (it is colored in red);
- ✧ reaction with toluidine or alcian blue to identify glycosaminoglycans, stained in red–purple (*metachromatic – the tissue appears colored differently compared to the staining solution),* the normal tissue being colored in blue (*orthochromatic – the color of the stain*).

In order to keep the glycogen, fragments of tissues are fixed in alcohol in order to avoid the contact with water, which dissolves the glycogen. Glucides metabolism disturbances are subdivided into:

- ✧ glycogenic dystrophy;
- ✧ dystrophy of glycoproteins or parenchymatous mucinous dystrophy.

Glycogenic dystrophy manifests itself as an excessive accumulation of glycogen in the cytoplasm of the cells and it can be seen more frequently in diabetes mellitus. In kidneys, changes appear as a result of hyperglycemia and glucosuria, determined by the impairment of the process of taking (using) of glucose by tissue, related to insufficient secretion of insulin by beta cells of the pancreas isles (Langerhans). Renal tubes epithelial cells have a clear, vacuolized cytoplasm, and, at Best carmine staining,

glycogen granules of different sizes, red-colored can be revealed (Fig. 2–10). The cells of the thin segment and distal portions of the convoluted tubes are affected most of all; glycogen granules can be seen in the tubes lumen too. The main morphogenetic mechanism of renal glycogenic dystrophy is the infiltration, as a result of glucosuria. A thickening of basement membranes of capillaries and depositions of polysaccharides (intercapillary glomerulosclerosis) in mesangium can be seen in the renal glomeruli. The process may be reversible.

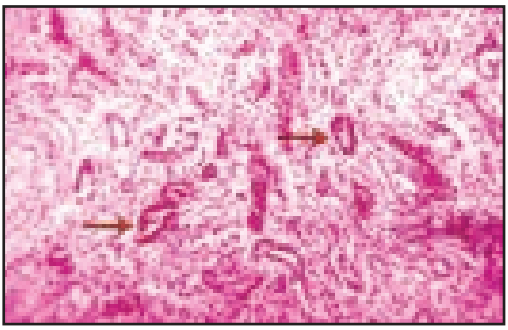


Fig. 2–10. Glycogenic infiltration of epithelium of renal convoluted tubes in diabetes mellitus (carmine stain; ×70).

Parenchymatous mucinous dystrophy is characterized by exaggerated secretion and accumulation of mucus (mucin) in the cytoplasm of the mucosecretory cells, as well as change of physicochemical properties of the mucus. It can be seen in the mucosas of the bronchi, digestive tract, uterus and in glandular organs (pancreas, sudoriparous, lacrimal and mammary glands) in cases of chronic inflammations (chronic bronchitis, bronchial asthma, muciparous cancer, especially in signet ring cell cancer (Fig. 2–11), mucoviscidosis (hereditary enzymopathy).

Macroscopically, the harmed organs (tissues) show an excess of mucus, an obstruction of glandular ducts and of secretory canals and a formation of cystic cavities. As a result of parenchymatous mucinous dystrophies, necrosis and desquamation of the affected cells occur. Sometimes, mucoid or pseudomucin substances accumulate in glandular structures.

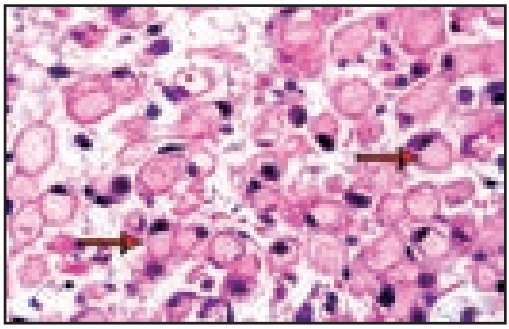


Fig. 2–11. Mucinous gastric cancer with "signet ring" cells (hematoxylin–eosin stain; ×110).

When condensed, they have a colloid aspect (colloidal dystrophy) with a gelatinous consistency. It can be seen in colloid goiter, adenomas and colloid carcinomas of the thyroid gland.

A particular form of mucinous dystrophy occurs in *mucoviscidosis* – a hereditary disease, characterized by a change of the mucus secreted by the mucosecreting epithelium of mucosas and exocrine glands. The mucus becomes viscous, dense, it is eliminated with difficulty, leading to retention of evacuation of secretions and formation of mucus "plugs". Inflammatory processes, cystic dilatation and deformation of excretory ducts, sclerosis, atrophic processes of glandular parenchyma become associated. Most frequently, the exocrine pancreas is affected (the fibro–cystic disease of the pancreas), but also the bronchi, salivary glands, sudoriparous and lacrimal glands, the small intestine, genitourinary organs. The development, clinical manifestations and complications of mucoviscidosis depend on the preponderant localization of lesions.

2.4. EXTRACELLULAR DYSTROPHIES (MESENCHYMAL OR STROMAL-VASCULAR)

In extracellular or mesenchymal (stromal-vascular) dystrophies, the metabolic disturbances take place in ground substance and fibrillar elements of the connective tissue, particularly in stroma of organs and in walls of vessels (the basement membrane of blood vessels consists of ground substance and reticulinic fibers). They are manifested by deposition of some metabolic products, which are changed quantitatively and qualitatively, in interellular substance of stroma of the organs and of vascular walls. The morphogenetic mechanisms of mesenchymal dystrophies are: infiltration, decomposition, transformation and pathological synthesis.

According to the type of altered metabolism, the mesenchymal dystrophies is divided into proteic, lipidic and glucidic dystrophies (Table 2.3).

Table 2.3

Classification of extracellular dystrophies

I. Proteic	a) mucoid intumescence; b) fibrinoid intumescence; c) hyalinosis; d) amyloidosis.
II. Lipidic	**I – neutral fats metabolism disturbances:** a) generalized: 1) – obesity; 2) – cachexia; b) localized: 1) segmental lipomatoses (adiposities); 2) regional lipodystrophy; **II – disturbances of cholesterol and its esters metabolism (in atherosclerosis of arteries and familial hypercholesterolemic xanthomatosis);**
III. Glucidic	a) – mesenchymal mucous dystrophy (myxomatosis of tissues); b) – mucopolysaccharidoses (Hurler disease or gargoilysm)

2.4.1. PROTEIC EXTRACELLULAR DYSTROPHIES (EXTRACELLULAR DISPROTEINOSES)

The following varieties of extracellular disproteinoses can be distinguished: mucoid intumescence, fibrinoid intumescence (degenerescence), hyalinosis and amyloidosis. The first three can be consecutive phases of the one and the same process of disorganization of connective tissue (ex: in rheumatic diseases).

2.4.1.1. MUCOID INTUMESCENCE

The mucoid intumescence represents a superficial and reversible disorganization of connective tissue, characterized, from biochemical point of view, by accumulation and redistribution of glycosaminoglycans (especially of hyaluronic acid) in ground substance. Hydrophilia of glycosaminoglycans induces a significant increase of vasotissular permeability, which leads to infiltration of ground substance with plasmatic proteins (albumins and gammaglobulins), hydration and intumescence of interstitial tissue. Collagenic fiber fascicles are tumefied; interfibrillar spaces are considerably enlarged, as a result of hyperhydration, and contain microgranular proteic masses. The collagenic fibers keep their normal structure and transversal striation, being only tumefied (mucoid, chromotrope or myxomatous edema) (Fig. 2–12a).

The macroscopic aspect of the organs is unchanged, the lesions can be revealed only at a microscopic examination with histochemical reactions to highlight the glycosaminoglycans. When stained with toluidine blue, the dystrophic foci are colored metachromatically in purple or red, like mucins, on a blue (orthochromatic) background of intact connective tissue (*hence the name "mucoid intumescence"*) (Fig. 2–12b).

Mucoid intumescence is present in different organs and tissues, but mostly in the walls of arteries, the heart valves and parietal endocardium in hypoxia, in various infectious, allergic, rheumatic diseases, atherosclerosis, etc.

It is a reversible process, but it can develop into fibrinoid degenerescence, if the causative factor is not removed. The function of organs in mucoid intumescence is slightly impaired.

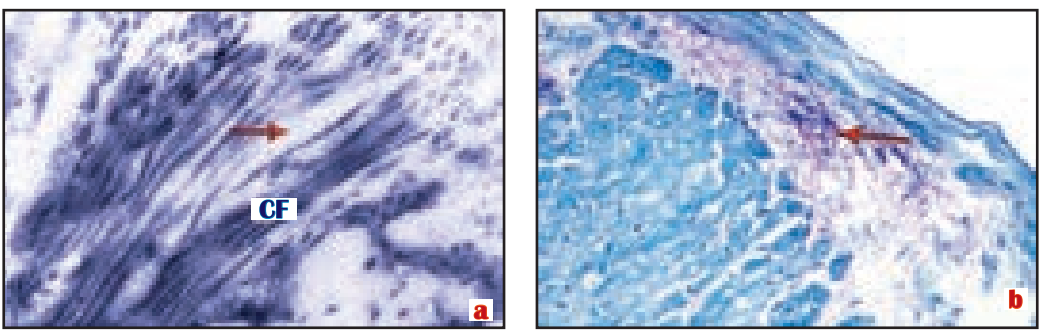


Fig. 2–12 a, b. Mucoid intumescence of the connective tissue: a – electron microscopic image (×35000); CF – collagenic fibers; b – microscopic pattern (stain with toluidine blue ×110).

2.4.1.2. FIBRINOID INTUMESCENCE

This is an irreversible process of disorganization of the connective tissue. It is characterized by the distruction of the ground substance and of collagen fibers, by a considerable increase of vasotissular permeability and fibrinoid formation. The fibrinoid is a complex substance, consisting of proteins and polysaccharides resulted from collagenic fibers and ground substance degradation, as well as from plasmatic proteins, extravasated as a result of an

increased permeability of vessels. The main component of fibrinoid is the fibrin (Fig. 2–13). Consequently, the fibrinoid has tinctorial properties similar with the fibrin, from which the name derives. No characteristic changes are noted macroscopically. The function of the organs is severely impaired.

We distinguish the fibrinoid degenerescence of connective tissue and of blood vessels. When progressing, the fibrinoid changes lead to fibrinoid necrosis of the connective tissue, which turns into a homogeneous mass with eosinophilic tinctoriality (Fig. 2–14).

A macrophage and lymphocytic infiltration can be seen around the foci of necrosis. As a result, sclerosis (cicatrization) and hyalinosis processes appear on the territories of fibrinoid changes, with important functional alterations of the given organ.

It can be seen in some allergic, autoimmune, angioneurotic, dysmetabolic, infectious diseases, etc. (rheumatic diseases, glomerulonephritis, arterial hypertension, atherosclerosis). Fibrinoid necrotic foci of connective tissue with cellular cord constitute the morphological substrate of rheumatic granulomas (Aschoff granulomas).

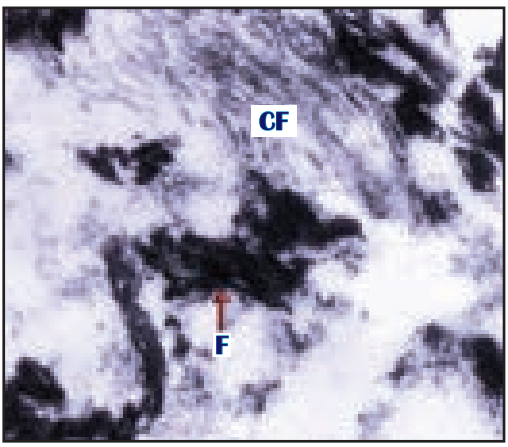


Fig. 2–13. Fibrinoid intumescence of connective tissue (electron microscopy; ×35000): CF – collagenic fibers; F – fibrin.

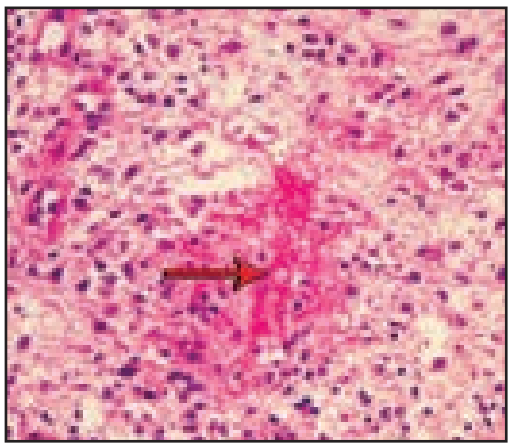


Fig. 2–14. Fibrinoid necrosis of connective tissue in rheumatism (hematoxylin–eosin stain; ×110).

2.4.1.3. EXTRACELLULAR HYALINOSIS (HYALINE DYSTROPHY)

It is characterized by the appearance of hyaline in tissues – a semitransparent whitish mass of hard consistency, with a glassy aspect, similar to hyaline cartilage and deposited extracellularly. Hyaline is a substance of proteic origin (fibrillar protein), which, microscopically, appears unstructured, homogeneous, eosinophylic; it is resistant to the action of enzymes, acids and bases. The main mechanism of hyalinosis production is the destruction of fibrillar structures of connective tissue and the increase of vasotissular permeability (plasmorrhagia). Hyalinosis may develop as a result of: a) fibrinoid intumescence, b) plasmatic imbibition (plasmorrhagia), c) chronic inflammation; d) necrosis; e) sclerosis.

We distinguish hyalinosis of connective tissue and hyalinosis of blood vessels.

Hyalinosis of vessels appears mostly in small arteries and arterioles, preceded by the increase of vascular

permeability and plasmatic imbibition (plasmorrhagia) of the vessel walls. Vascular hyaline is formed from plasmatic precursors, especially from blood plasma proteins, accumulating initially in the subendothelial space. The smooth muscle cells and fibrillar elements of vascular walls become atrophied gradually and imbued with fibrin and other plasmatic components. Later, the affected vessel turns into a hyaline tube (becomes similar with a glass tube) with a thickened wall and a very narrow or completely closed up lumen (Fig. 2–15). These alterations lead to ischemia and hypoxia of the organ, atrophy of parenchyma and perivascular proliferation of connective tissue.

These lesions are characteristic particularly for arterial hypertension and diabetes mellitus. First to be affected are the small arteries of the brain, heart, kidneys, retina, endocrine glands etc. In such cases, the process of arterial hyalinosis has a generalized character.

Local hyalinosis of arteries can be noted in the spleen, representing a physiological process, determined by the morphofunctional specific features of the spleen, as a blood storage organ.

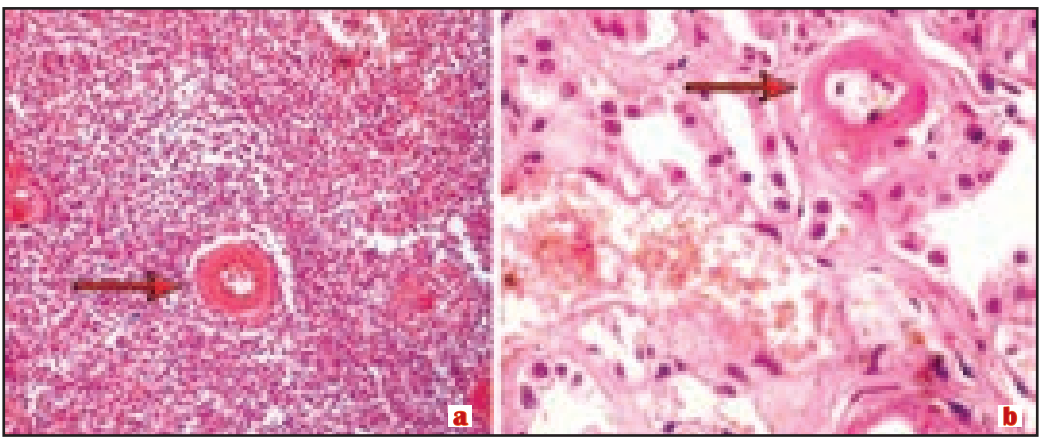


Fig. 2-15. Hyalinosis of lienal arteries (a) and of renal arterioles (b); hematoxylin–eosin stain ×110.

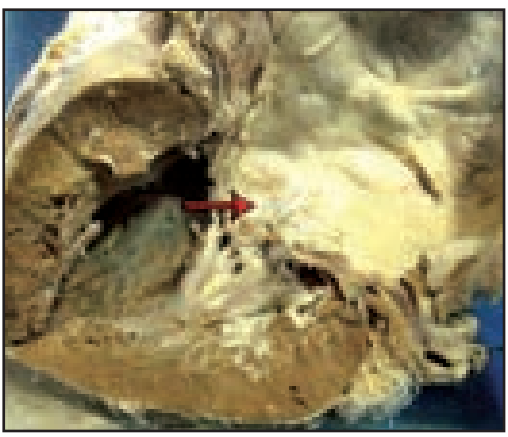


Fig. 2–16. Hyalinosis of mitral valve (rheumatic valvulopathy).

First of all, **the hyalinosis of the connective tissue** can be seen in rheumatic diseases, preceded by fibrinoid intumescence of connective tissue. In these cases, the hyaline is formed from fibrinoid masses. A characteristic example may be the sclerosis and hyalinosis of the heart valves in rheumatism and other rheumatic diseases, leading to their thickening and deformation, and forming of cardiac valvulopathies (Fig. 2– 16). The hyalinosis of the connective

tissue in these diseases has a generalized character.

Local hyalinosis is noted in gastric ulcer, keloid scars (Fig. 2–17), adherences, in the spleen capsule in ascites ("icing-sugar" or „sugar-coated" spleen) (Fig. 2– 18).

Hyalinosis is usually an irreversible process, which may end in functional disturbances and severe complications (for example, arteriolosclerotic nephrosclerosis with wrinkling of kidneys in arterial hypertension, rheumatismal cardiac valvulopathies, diabetic glomerulosclerosis and retinopathy etc.)

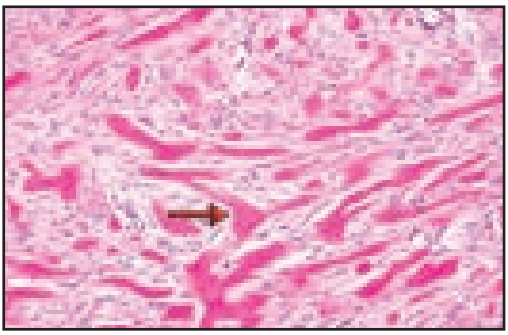


Fig. 2-17. Hyalinosis of connective tissue (hematoxylin–eosin stain; ×110).

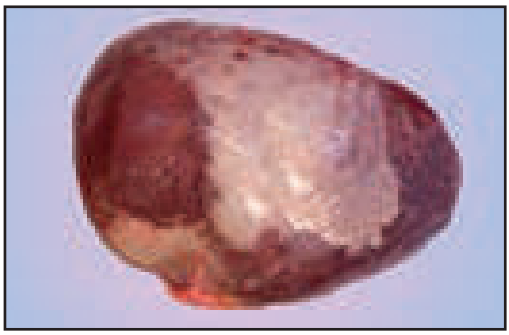


Fig. 2-18. Hyalinosis of spleen capsule.

2.4.2. LIPIDIC EXTRACELLULAR DYSTROPHIES

Metabolic disturbances of neutral fats are located at the level of adipose tissue. An excessive growth (obesity) or decrease (cachexia) of fatty deposits may occur.

Obesity may be *primary*, determined by constitutional–hereditary factors (the need of nourishment with an increased caloric value is determined genetically), and *secondary*, which is symptomatic and is observed in some cerebral, endocrine and hereditary diseases. The following variants of secondary obesity can be observed, from this point of view:

a) food obesity – caused by an excessive nutrition and hypodynamia (sedentary lifestyle);
b) cerebral – in various cerebral tumors, traumatisms, neurotropic infections;
c) endocrine – in various pathologic processes of endocrine glands, for example,
   ✧ in hypercorticism – hypersecretion of the corticosteroid hormones (basophilic adenoma of the anterior lobe of pituitary gland or hormonal active tumors of corticoadrenals);
   ✧ in hypothyroidism – diminishing of the function of the thyroid gland (myxedema);
   ✧ in hypogonadism – hyposecretion of androgenic hormones (inflammatory processes, tumors of testicles, in cases of castration, in climacterium;
   ✧ in hyperinsulinism – insulin hypersecretion (adenoma from *beta* cells of pancreatic islets).
d) hereditary – caused by genetic defects (including hereditary enzymopathies).

From the morphological point of view, obesity manifests itself by growth of deposition of fats in subcutaneous tissue, epiploon, mediastinum, mesentery, retroperitoneal tissue, the bed and stroma of some internal organs (heart, pancreas, kidneys, and liver). In primary obesity, a hypertrophy of fat cells occurs, leading to their diminished sensitivity to

insulin. In all the forms of obesity, the heart lipomatosis occurs. The fat cells infiltrate the myocardium, dissociating the muscular fiber bands, which later on become atrophied (Fig. 2–19 a). Macroscopically, the heart becomes enlarged in size, abundant deposits of fat appear under the epicardium, surrounding the heart like a muff (Fig. 2–19 b). These manifestations are more profound in the right ventricle, whose thickness may achieve 1–2 cm (the normal one should be 2–3 mm). The contractile power of the heart drops, developing a cardiac insufficiency; even a rupture of the right ventricle wall may occur, with a tamponade of pericardial sac and sudden death. It should be mentioned that obesity (including the heart lipomatosis) is one of the risk factors of ischemic heart disease (ischemic cardiopathy).

The local increase of the adipose tissue content takes place in **lipomatosis**, for example in the Dercum disease. It is characterized by the appearance of some nodules, formed of fats, in the subcutaneous tissue of the extremities and of the trunk, sometimes painful (lipomatosis dolorosa), reminding lipomas. This is endocrine polyglandular pathology.

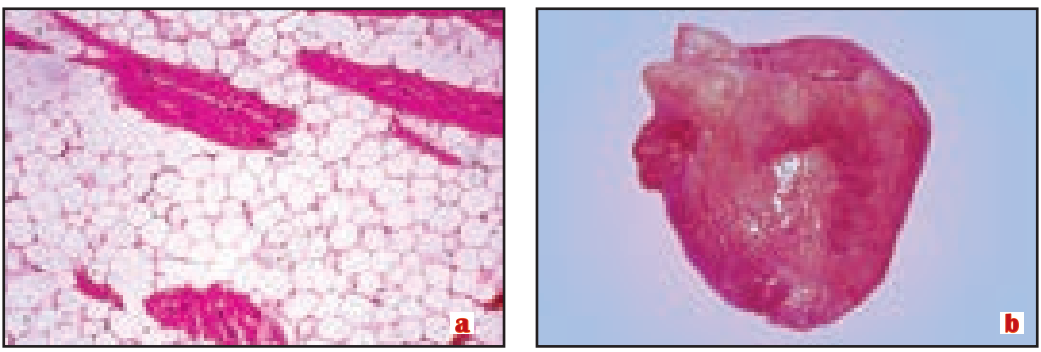


Fig. 2–19 a, b. Heart lipomatosis: a – microscopic pattern (hematoxylin–eosin stain; ×70); b – macroscopic aspect.

2.4.3. GLUCIDIC EXTRACELLULAR DYSTROPHIES

Mesenchymal mucous dystrophy (myxomatosis of tissues). This variant of extracellular dystrophy presents disturbances of glycoproteins metabolism from ground substance of connective tissue. The main glycoproteins are the mucoids, secreted by the cells of the connective tissue (fibroblasts, chondroblasts and osteoblasts), an important component of ground substance. In case of metabolic disorders, the mucoids accumulate excessively in the connective tissue and the collagenic fibers are substituted with a mucoid mass. The connective tissue gets a myxomatous, gelatinous aspect, similar with the myxoid tissue of the fetus and umbilical cord. It can be observed in connective tissue in myxedema and cachexies, in cardiac valves in Marfan syndrome etc. The phenomenon of myxomatosis is frequently observed in tumors of connective, cartilaginous and osseous tissues. It is very characteristic for myxomas. The cells of the connective tissue acquire a stellate shape. The myxomatosis can develop in some tumors as a manifestation of secondary lesions. The processes of myxomatosis may result in tissue necrosis and formation of some cystic cavities, filled with mucus.

2.5. ACCUMULATION DISEASES (THESAURISMOSES OR STORAGE DISEASES)

This is a group of diseases characterized by insufficiency or absence of enzymes in the body, which leads to accumulation of some intermediate substances in the organs and tissues, which cannot be metabolized. They are hereditary diseases based on defects of genes, which codify certain enzymes (hereditary, congenital enzymopathies). These diseases can be diagnosed antenatally by amniocentesis, justifying the importance of a genetic consultation before giving birth.

The thesaurismoses can be grouped conventionally into:

- ✧ congenital disorders of amino acids metabolism,
- ✧ lysosomal diseases of accumulation (lysosomal storage diseases).

2.5.1. HEREDITARY DISORDERS OF AMINO ACIDS METABOLISM

The main diseases of this group are cystinosis, tyrosinosis, phenylketonuria and alkaptonuria.

Cystinosis is determined by alteration of metabolism of cystine, as a result of a congenital enzymatic deficiency. It is characterized by deposition of cystine crystals in the kidneys, liver, spleen, cornea, bone marrow and other tissues. Clinically, it is manifested by the disturbance of kidney function (urinary calculosis), physical development delay, and changes of the skeleton, similar with rickets (vitamin resistant rickets).

Tyrosinosis is a manifestation of tyrosine metabolic disturbance, caused by tyrosine aminotransferase deficiency. Clinically, it is manifested by hypertyrosinemia, liver, kidneys and bones impairment.

Phenylketonuria is a disturbance of phenylalanine metabolism, conditioned by hereditary insufficiency of phenylalanine–hydroxylase enzyme, leading to hyperphenylalaninemia and phenylketonuria. The excess of phenylalanine and its derivatives impairs the development of the brain by the inhibition of amino acids supply, synthesis of neuromediators and myelin, causing a state of mental retardation of the child (dementia or phenylpyruvic oligophrenia).

Alkaptonuria is characterized by metabolic disturbance of phenylalanine and accumulation of homogentisic acid in connective tissue of all organs, as a result of insufficiency of homogentisic acid oxidase enzyme. Clinically, it is manifested by dystrophic lesions of joints, determined by the storage of homogentisic acid in joints cartilages and intervertebral discs.

2.5.2. THE LYSOSOMAL ACCUMULATION DISEASES (LYSOSOMAL STORAGE DISEASES)

They represent a group of hereditary diseases, characterised by accumulation in lysosomes of some intermediate, non-metabolized substances. They are caused by lack or congenital insufficiency of lysosomal acidic hydrolases. According to the nature of disturbed metabolism, we distinguish: **systemic lipidoses, glycogenoses and mucopolysaccharidoses.**

2.5.2.1. SYSTEMIC LIPIDOSES OR LIPID STORAGE DISEASES

According to the type of lipids accumulated in cells, they are subdivided in the Gaucher, Tay–Sachs and Niemann–Pick diseases.

The Gaucher disease or cerebroside lipidosis is caused by the lack of glucocerebrosidase enzyme and is characterized by an accumulation of glucocerebrosides in the reticuloendothelial cells, with the appearance of the so-called Gaucher cells - macrophages filled with lipids. Clinically, it manifests itself by hepatosplenomegaly and bone lesions.

The Tay–Sachs disease or ganglioside lipidosis is an accumulation of gangliosides in the lysosomes of neurons and macrophages. Clinically, it is manifested by psychic disturbances and amaurosis (blindness), hence the name of *amaurotic idiocy*. A deficiency of hexosaminidase enzyme is registered biochemically.

The Niemann–Pick disease or sphingomyelin lipidosis is manifested by accumulation of sphingomyelin in parenchymatous and reticuloendothelial cells. The biochemical mechanism consists in the deficiency of sphingomyelinase enzyme, which divides the sphyngomyelin. Clinically, there are neurologic signs, jaundice, and hepatosplenomegaly.

2.5.2.2. GLYCOGENOSES OR GLYCOGEN STORAGE DISEASES

They are manifested by accumulation of glycogen in tissues and organs with normal or deteriorated structure.

The Gierke disease is characterized by excessive accumulation of glycogen in parenchymatous organs, particularly in the liver and kidneys. It is caused by the deficiency of glucose–6–phosphatase enzyme. Clinically, a hepato- and renomegaly is registered, and, microscopically - massive deposits of glycogen in the liver, kidneys, muscles, the mucosa of the digestive tract and the nervous system.

The Pompe disease is an excessive accumulation of glycogen in myocardium, smooth and skeletal muscles. It is caused by the alpha-glucosidase deficiency. Clinically, a massive cardiomegaly and a severe cardiac insufficiency are registered.

The McArdle disease is caused by insufficiency of muscle phosphorylase and manifests itself by accumulation of glycogen in myocytes, and clinically - by myopathy.

The Forbes–Cori disease is based on the hereditary deficiency of amylo–1,6–glucosidase, resulting in accumulation of glycogen, with abnormal structure in the liver, muscles and heart.

Besides generalized glycogenoses, there are localized accumulations of glycogen, for example, in some tumors, like seminoma and clear cells renal carcinoma.

2.5.2.3. MUCOPOLYSACCHARIDOSES

The mucopolysaccharidoses are characterized by tissular accumulation of glycosaminglycans (mucopolysaccharides) and their elimination via urine in increased amount. **The Hurler syndrome** is most frequently observed, being caused by the hereditary deficiency of the alpha –iduronidase enzyme. It is manifested by accumulation of heparan sulphate and dermatan sulphate in parenchymatous organs and blood vessels and, clinically, by distortion of the face, low height, osseous and articulation lesions, hepatosplenomegaly, mental retardation. Microscopically, one reveals mucopolysaccharide deposits in phagocytic cells, fibroblasts, endotheliocytes and smooth muscle cells of vascular walls. The clinical syndrome is called **gargoylism** (from the Latin *gargulio* – throat).

ESSENTIAL TERMS

on the subject "Reversible cellular and extracellular lesions"

accumulation disease	hyalinosis	obesity
alcoholic hyaline	hydropic dystrophy	orthochromasia
alkaptonuria	hyperkeratosis	pathologic synthesis
alteration	ichthyosis	phanerosis
cellular hyaline dystrophy	„icing-sugar" spleen	phenylketonuria
cloudy intumescence	infiltration	plasmatic infiltration
cystinosis	lesion	Pompe disease
decomposition	leukoplakia	Russel corpuscles
dystrophy	lipomatosis	steatosis
fibrinoid intumescence	Mallory corpuscles	storage disease
Forbes–Cori disease	McArdle disease	„sugar-coated" spleen
gargoylism	metachromasia	Tay-Sachs disease
Gaucher disease	mucoid intumescence	thesaurismosis
Gierke disease	mucopolysaccharidosis	tiger heart
glycogenosis	mucoviscidosis	transformation
granular dystrophy	myxomatosis	tyrosinosis
Hurler disease	Niemann–Pick disease	vacuolar dystrophy

TESTS

on the subject "REVERSIBLE EXTRACELLULAR AND CELLULAR LESIONS"

SET I

Multiple-choice questions with one correct answer

1. *Which of the signs listed below characterize the granular dystrophy:*
   a) large, homogeneous, hyaline droplets in cells cytoplasm;
   b) formation of vacuoles in cytoplasm and nucleus;
   c) small eosinophilic granulations in the cells cytoplasm;
   d) pathologic keratinization;
   e) granules of glycogen in cytoplasm.
2. *Definition of leukoplakia:*
   a) excessive keratinization of the skin;
   b) vacuolar dystrophy of the skin;
   c) parakeratosis;
   d) formation of keratin pearls;
   e) pathological keratinization of the mucous membranes.
3. *Which of the listed terms indicate the accumulation of lipids in parenchymatous cells:*
   a) lipomatosis;
   b) steatosis;
   c) systemic lipoidosis;
   d) sphyngolipidosis;
   e) lipofuscinosis.
4. *Which is the main cause of myocardial steatosis:*
   a) hypoproteinemia;
   b) hypoxia;
   c) hypocalcemia;
   d) hypoglycemia;
   e) hyperuricemia.

5. Which of the listed processes characterize the mucoid intumescence:
a) develops in the cells of connective tissue;
b) develops in ground substance of connective tissue;
c) accumulation of lipids;
d) accumulation of glycogen;
e) accumulation of proteins.

SET II.

Multiple-choice questions with 2, 3 or more correct answers

1. Macroscopic changes of organs, characteristic for granular dystrophy:
a) enlarged in size;
b) diminished in size;
c) flaccid consistency of the organ;
d) cloudy aspect on the section;
e) densification of the organ;
f) the organ maintains its usual luster.

2. Which of the signs listed below are characteristic for the "tiger heart":
a) enlarged size;
b) dilated cavities;
c) subepicardial adipose tissue deposits;
d) brown color of the myocardium on the section;
e) white–yellowish stripes under the endocardium of the papillary muscles;
f) adipose tissue in the stroma of myocardium;
g) dense consistency of myocardium.

3. Which of the listed dystrophies are characteristic for rheumatism:
a) cloudy intumescence;
b) mucoid intumescence;
c) glycogenosis of cardiac valves;
d) fibrinoid intumescence;
e) intracellular hyalinosis;
f) extracellular hyalinosis.

4. Which of the listed lesions of arteries occur in arterial hypertension:
a) amyloidosis of arteries;
b) hyalinosis of small caliber arteries;
c) lipidic infiltration of arteries;
d) plasmatic infiltration of arteries;
e) glycogenic infiltration of arteries.

5. Which of the listed signs are characteristic for fibrinoid intumescence:
a) considerable increasing of vascular permeability;
b) it is a reversible process;

SET III.

Classification tests include 2–4 subjects and a series of answers. Indicate the correct answers for each subject separately.

c) collagenic fibers destruction;
d) positive reaction to fibrin;
e) formation of fibrinoid.

1. *Which of the morphologic signs listed below are characteristic for:*
I – cellular hyaline dystrophy;
II – granular dystrophy;
a) large proteic droplets, confluent in the cell cytoplasm;
b) tumefaction of mitochondria;
c) fine proteic granules in cytoplasm;
d) destruction of cytoplasmic organelles.

2. Which of the morphological changes are characteristic for:
I – hydropic dystrophy of myocardium;
II – fatty dystrophy of myocardium;
a) yellowish stripes under the endocardium;
b) presence of some vacuoles in sarcoplasma, filled with cytoplasmic fluid;
c) presence of some droplets in sarcoplasma, stained with Sudan III;
d) the myocardium is not changed macroscopically;

e) dilatation of endoplasmic reticulum cisterns.

3. In which of the listed diseases one notices:
I – the liver steatosis;
II – hydropic dystrophy of the liver;
a) thyrotoxic goiter;
b) excess of fats in food;
c) ethanol intoxication;
d) avitaminoses;
e) chronic pulmonary pathology;
f) viral hepatitis.

4. Which of the listed signs are characteristic for:
I – liver steatosis;
II – myocardial lipomatosis;
a) lipidic vacuoles in cytoplasm of cardiomyocytes;
b) it is most frequently noted in obesity;
c) accumulation of adipocytes among myocardial fibers;
d) deposits of fats under epicardium;
e) stripped aspect of myocardium on section;
f) the cardiomyocytes are enlarged in size;
g) it is the morphological substrate of the contractile activity decompensation of the heart.

5. Which of the listed signs are characteristic for:
I – mucoid intumescence;
II – fibrinoid intumescence;
a) it is a reversible process;
b) the destruction of collagenic fibers occurs;
c) it is an irreversible process;
d) the fascicular structure of collagenic fibers is maintained;
e) it is revealed when stained with toluidine blue;
f) hyaluronic acid accumulation occurs.

SET IV. SITUATIONAL PROBLEMS

Daily practice cases are presented with clinical and morphological data from clinical histories and/or from necropsy protocols. Each subject includes simple or multiple-answer questions, with 1, 2 or more correct answers.

1. A patient with pandemic influenza had tachycardia and traces of proteins in urine. The activity of the heart and the characteristics of the urine became normal after treatment.

Questions:

A) Which dystrophic process took place in the myocardium and kidneys:
a) fatty dystrophy;
b) hydropic dystrophy;
c) granular dystrophy;
d) glucidic dystrophy;
e) amyloidosis;
f) cellular hyalinosis.

B) Which morphogenetic mechanism of dystrophy prevails in myocardium (1) and kidneys (2):
a) infiltration;
b) decomposition;
c) transformation;
d) denatured synthesis.

2. An 18 year-old patient had throat pains and a fever up to 39 °C, enlarged cervical lymph nodes, membranes of white–grayish color on mucosa of the palatine tonsils, which detach with difficulty, leaving bleeding ulcerations. A diagnosis of diphtheria was made. In 8 days, the patient died because of acute heart failure. During the necropsy, the myocardium had a very flaccid consistency and a claylike aspect on the section; the heart cavities were considerably dilated.

Question:

Which pathological changes can be revealed in cardiomyocytes:
a) glucidic dystrophy;
b) vacuolar dystrophy;
c) fatty dystrophy;
d) intracellular hyaline dystrophy;
e) granular dystrophy.

3. A patient died because of chronic alcoholic intoxication and, at necropsy of the corpse, the following macroscopic changes of the liver were revealed: increased mass up to 4,5 kg (the average norm being 1,5– 1,6 kg), flaccid consistency and yellow color.

Questions:

A) Which histological changes can be revealed in the liver biopsy:

a) accumulation of glycogen in hepatocytes;
b) presence of fat droplets in hepatocytes;
c) proliferation of fatty (adipose) tissue through hepatic trabeculae;
d) accumulation of amyloid in the liver.

B*) Which method of staining should be applied to make a correct diagnosis:*

a) hematoxylin and eosin;
b) Sudan III;
c) carmine;
d) Congo red.

4. A focus of tumefaction of collagenic fibers was revealed during the microscopic examination of the biopsy from the capsule of the knee joint of a patient with rheumatoid arthritis. It was stained in red with toluidine blue.

Question:

Which are the substances that reflect this microscopic pattern, when accumulated:

a) glycogen;
b) lipoproteins;
c) hyaline;
d) amyloid;
e) glycosaminoglycanes;
f) neutral fats.

5. A 45 year-old patient died suddenly because of a heart attack. The necropsy revealed grade III obesity, universal type, rupture of the right ventricle wall with pericardial tamponade (more than 350 ml of bloody fluid and clots in the pericardial sac), the heart in systole state, abundant deposits of adipose tissue under the epicardium, the thickness of the right ventricle wall - 1,8 cm. The histological examination revealed agglomerations of adipocytes, infiltrating the stroma of the myocardium, the muscular fibers being atrophied.

Question:

Which pathological process of those listed occurs in the given case?

a) myocardial steatosis;
b) arterial hypertension;
c) ischemic cardiomyopathy;
d) acute myocardial infarction;
e) heart lipomatosis.

2.6. REVERSIBLE MIXED INTRA - AND EXTRACELLULAR LESIONS (MIXED DYSTROPHIES)

In cases of mixed lesions (dystrophies), metabolic disturbances take place both in the parenchyma of organs and tissues (intracellular) and in the stromal connective tissues (extracellular). Usually, it is alteration of mixed proteins metabolism (chromoproteins, nucleoproteins, lipoproteins, glycoproteins) and of mineral substances. It is manifested through quantitative and qualitative changes of respective substances in the cells and intercellular compartment.

2.6.1. CHROMOPROTEINS DYSTROPHIES

The chromoproteins or pigments of endogenous origin are colored complex proteins synthesized in the organism, unlike the exogenous pigments, which enter the body from the external environment. They are classified in three groups (Table 2.4).

Table 2.4

Classification of endogenous pigments dystrophies

Groups of pigments	The pigments
Hemoglobinogenic pigments	**Physiological hemoglobinogenic pigments** a) ferritin b) hemosiderin c) bilirubin **Pathological hemoglobinogenic pigments** a) hematoidin b) hematins ➢ hemomelanin ➢ hydrochloric hematin ➢ formalin pigment c) porphyrin
Proteinogenic pigments	melanin
Lipidogenic pigments	a) lipofuscin b) lipochromes

Morphologically, metabolic disturbances of chromoproteins can manifest themselves by increasing or diminishing the quantity of pigments present in the organism normally or by the appearance and deposition of some pigments, formed only in pathologic conditions. The pigment metabolism can be disturbed secondarily in many diseases and pathological processes. In other cases, these disturbances develop primarily, representing morphological substrate of some diseases itself.

2.6.1.1. HEMOGLOBINOGENIC PIGMENTS DYSTROPHIES

These pigments are formed as a result of hemolysis of erythrocytes and degradation of hemoglobin, having the following specific features:

a) **Ferritin** – ferroprotein, the main iron storage in the body. It is formed in the organs of the reticuloendothelial system (liver, spleen, bone marrow, lymph nodes). The level is increased in hemosideroses.

b) **Hemosiderin** – an amorphous pigment of brown color, containing iron. It is formed intracellularly in reticuloendothelial (sideroblasts) cells. It appears in the first 24 hours, in cases of hemorrhages. The level is increased in generalized and localized hemosiderosis and hemochromatosis. The Pearls reaction is used to identify the hemosiderin in histological samples: blue granules of ferrous ferricyanide are formed (also called Berlin or Prussian blue) on treating microscopic sections with potassium ferrocyanide and hydrochloric acid.

c) **Bilirubin** – a crystalline pigment of yellow color that doesn't contain iron. The indirect (free, unconjugated) bilirubin is formed in reticuloendothelial cells, being eliminated later in blood plasma. The direct (conjugated) bilirubin is formed in hepatocytes, by conjugation of free bilirubin with glucuronic acid, and is excreted in the bile. The level is increased in jaundice syndromes.

d) **Hematoidin** – a crystalline pigment of orange color that doesn't contain iron. It is identical to bilirubin and it is also called *tissular bilirubin*. It is accumulated extracellularly in areas of limited oxygen supply, remoted from viable tissues, mostly in necrotic masses. In hemorrhagic foci, it is formed in 5–10 days after the hemosiderin. It is revealed in old hematomas, hemorrhagic infarctions, hemangiomas - in their central areas, situating themselves freely in necrotic masses. The hemosiderin can be revealed in large hemorrhagic foci, at the periphery, while the hematoidin - in the centre. The Pearls reaction indicates the lack of iron in hematoidin (Fig. 2–20).

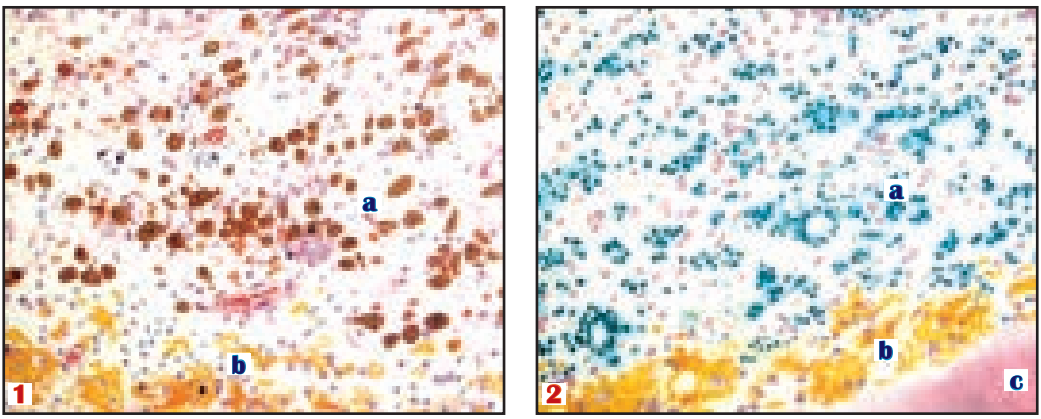


Fig. 2–20. Old cerebral hemorrhage (old cerebral hematoma) (hematoxylin – eosin stain (1) and Pearls reaction (2); ×70): a – hemosiderin; b – hematoidin; c – necrotic focus.

e) ***The hematins***:

1) **hemomelanin** or **malarial pigment** – a crystalline pigment of brown-black color that contains iron. It is formed in erythrocytes, under the action of malaria plasmodia. The level is increased in patients with malaria (hemomelanosis). It penetrates the blood after the destruction of erythrocytes and is phagocyted by circulating and tissular macrophages.

2) **hydrochloric hematin** – a crystalline pigment of brown-black color that contains iron. It is formed under the influence of the digestive enzymes and of the hydrochloric acid from gastric juice. It gathers on the bottom of erosions and gastric ulcers, staining them in black (Fig. 2–21).

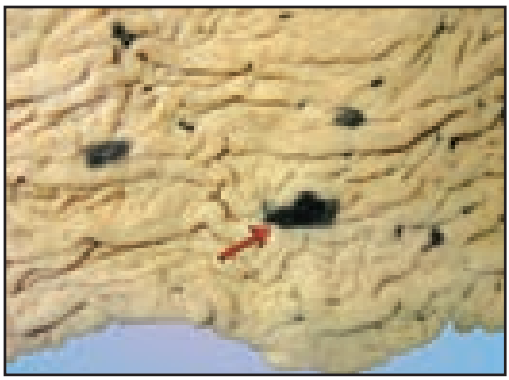


Fig. 2–21. Hydrochloric hematin on the bottom of gastric mucosal erosions.

3) **formalin pigment** – a brown–black pigment, formed in tissues fixed in acid formalin.

f) **the porphyrin** does not contain iron and has a red luminescence in ultraviolet rays; it is revealed in small quantities in blood, urine, tissues; it increases the sensitivity of the skin to light, the level is high in *porphyria*, which can be congenital or acquired.

The hemoglobinogenic pigments dystrophies can manifest themselves by the increased quantity of pigments formed in physiological conditions (ferritin, hemosiderin and bilirubin) or by the appearance of some pigments that appear only in pathological conditions (hematoidin, hematin and porphyrin). The most common dystrophies of the hemoglobinogenic pigments are: **hemosiderosis, hemochromatosis, jaundice, hemomelanosis and porphyria.**

Hemosiderosis can be generalized and localized:

Generalized hemosiderosis is caused by intravascular hemolysis of erythrocytes; it occurs in hemolytic anemias, leukemias, severe infectious diseases (septicemias), intoxications (*for example, with snake venom*), and incompatible blood transfusions. The storage of hemosiderin takes place in the cells of the reticuloendothelial system and of parenchymatous organs. Concomitantly, an increase of ferritin and bilirubin synthesis is noticed. The affected organs (spleen, liver, bone marrow, lymph nodes and kidneys) have a rust color. Granules of hemosiderin can be revealed microscopically in the cytoplasm of cells (Fig. 2–22 and 2–23).

Localized hemosiderosis is caused by extravascular hemolysis of erythrocytes. It occurs in hemorrhages, hemorrhagic infarctions, chronic venous stasis of the organs and tissues. Morphologically, is noticed a localized, circumscribed deposition of hemosiderin in different organs and tissues, which gives them a brown color (Fig. 2–24). At the microscope, granules of hemosiderin can be revealed in the cytoplasm of mesenchymal and epithelial cells. Initially, the

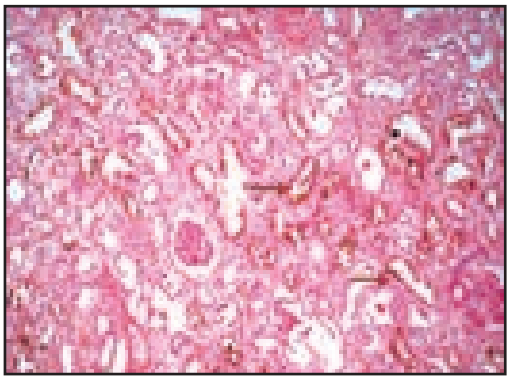


Fig. 2–22. Hemosiderosis of the kidney (hematoxylin–eosin stain; ×70).

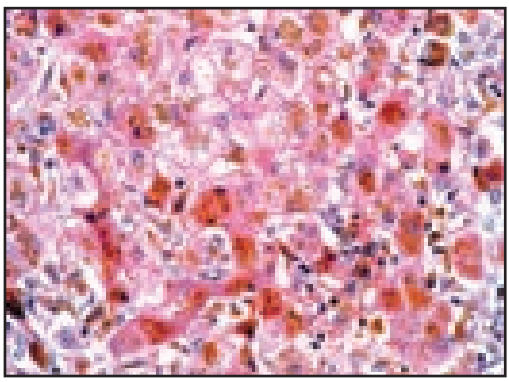


Fig. 2–23. Hemosiderosis of the liver (hematoxylin–eosin stain; ×110).

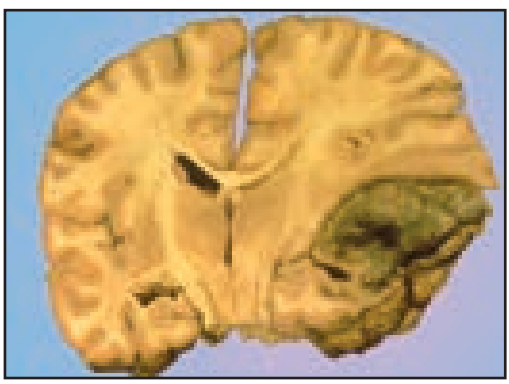


Fig. 2–24. Cerebral hematoma.

subcutaneous suggillations have a blue violet (purple) color, but, within 7–10 days, they get a yellow – greenish shade, as a result of consecutive formation of various hemoglobin pigments: hemosiderin (brown), hematoidin (yellow) and biliverdin (greenish).

Hemochromatosis can be primary and secondary:

a) **Primary hemochromatosis** is a thesaurismosis with a familial character, caused by a congenital defect of enzymes, which regulates the use (metabolism) of iron in the organism. An excessive absorption of the exogenic iron (alimentary) occurs in the duodenum. The content of iron in the body rises dozens of times. Morphologically, is noticed a deposition of hemosiderin and ferritin in organs and tissues and of melanin - in the skin. The affected organs have a dark brown color and a hard consistency. At the microscope, is observed granules of hemosiderin in the cytoplasm of the cells and an excessive proliferation of connective tissue. The liver, pancreas, skin, heart, endocrine glands, and gastric mucosa become affected. The cardinal signs are: pigment hepatic cirrhosis, diabetes mellitus, brown (bronze) color of the skin and cardiomyopathy. The disease is also called *bronze diabetes* because of the hyperpigmentation of the skin.

b) **Secondary hemochromatosis** is conditioned by insufficient use of iron in the processes of hematopoiesis. It can be noticed in massive hemolysis of erythrocytes, excessive intake of alimentary iron, repeated blood transfusions and hemoglobinopathies. Morphologically, a deposition of hemosiderin and ferritin is revealed in organs and tissues (liver, pancreas, myocardium etc). The affected organs have a dark–brown color and an increased consistency.

Jaundice may be hemolytic, parenchymatous and mechanical.

a) **Hemolytic jaundice** (prehepatic) is related to excessive hemolysis of erythrocytes. It can be observed in hemolytic anemias, leukemias, intoxications, infectious diseases, incompatible blood transfusions. The level of the free (indirect, unconjugated) bilirubin is increased in blood plasma. At an exterior examination, is noticed the yellow coloration of all organs and tissues, especially of the teguments, mucosas, scleras and serosas.

b) **Hepatic jaundice** (parenchymatous) is caused by destructive lesions of hepatocytes in hepatitides, hepatoses, and hepatic cirrhoses. An increase of the free and conjugated bilirubin in blood plasma is noticed.

c) **Mechanical jaundice** (subhepatic, obstructive) is related to the impairment of bile ducts permeability (bile stasis) (Fig. 2–25). It can be seen in cases of bile

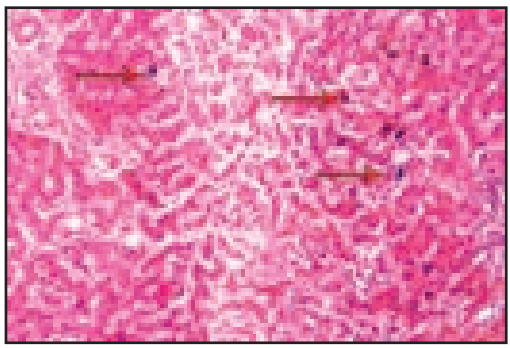


Fig. 2–25. The liver with bile stasis in mechanical jaundice (hematoxylin–eosin stain; ×70).

ducts occlusion by gallstones, tumors of bile ducts, parasites, malformations or by external compression (metastases of cancer in lymph nodes of the hepatic hilum, tumors of the head of the pancreas, tumors of duodenal papilla/ampulla of Vater, adherences). From the clinical point of view, there is an excess of direct (conjugated) bilirubin in the blood, which determines a yellow–green pigmentation of tissues, including the skin and sclerae. Besides the intensive coloration

of teguments in obstructive jaundice, is noticed a general intoxication induced by bile acids, hemorrhagic syndrome, dystrophic lesions of kidneys, hepatorenal insufficiency. Bile stasis may complicate with the inflammation of the bile ducts (cholangitis), and when the process becomes chronic, biliary cholestatic cirrhosis may develop.

Hemomelanosis occurs in malaria. A deposition of hemomelanin (malarial pigment) occurs in organs and tissues, both at the intracellular and extracellular levels (in the spleen, bone marrow, liver, lymph nodes, as well as in the brain in cases of malarial coma). The pigment appears under the action of malaria plasmodia, which parasite in erythrocytes. At the same time, hemosiderin and bilirubin are deposited. The affected organs get a dark grayish nuance. Granules of hemomelanin in macrophages can be revealed at the microscope (Fig. 2–26).

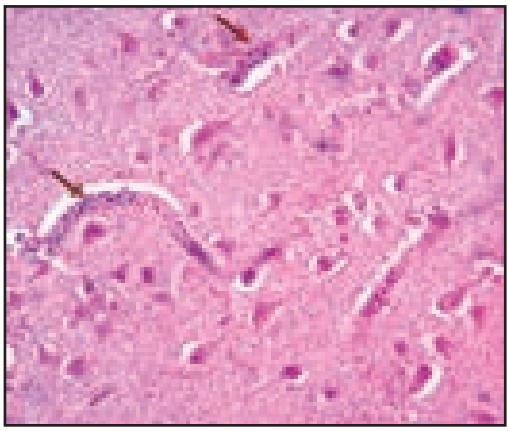


Fig. 2–26. Cerebral hemomelanosis in malaria (hematoxylin–eosin stain; ×110).

Porphyria may be congenital or acquired:

a) **Congenital porphyria** is caused by disturbances of metabolism of porphyrins in the body, as a result of hereditary insufficiency of enzymes that regulate the metabolism of porphyrins in erythroblasts and liver. An increase of porphyrins in the blood and urine and their deposition in the tissues occur. Erythema, photodermatitis, ulcerations, scars, depigmentated foci are observed on the skin, in the liver – fatty dystrophy of hepatocytes, depositions of hemosiderin, in bones and teeth - a brown coloration.

b) **Acquired porphyria** is noticed in intoxications, avitaminoses.

2.6.1.2. DYSTROPHIES OF PROTEINOGENIC PIGMENTS

Melanin (from the Greek *melas* – black) is a pigment of a brown – black color, which in physiological conditions is contained in the skin, hair, ocular membranes (choroid, iris, retina), brain, leptomeninges. The pigment determines the coloration of the skin, hair and eyes. It is formed exclusively in melanocytes by oxidation of tyrosin in dihydroxyphenylalanine (DOPA), the reaction being catalyzed by tyrosinase. Although it is synthesized only in melanocytes, it is also accumulated in keratinocytes of the basal layer of the epidermis and in dermal macrophages (melanophages – histiocytes that phagocytize melanin). At the microscope, it has an aspect of fine granules situated intra – or extracellularly. It is not different from other pigments (hemosiderin, lipofuscin) at usual staining with hematoxylin–eosin. The reaction Fontana–Masson with an ammonia solution of silver nitrate is used to make a differential diagnosis. Melanin reduces the silver nitrate to metallic silver, seen at the microscope as granules of black color. The pigment has a protective role: it protects the skin from ultraviolet radiation action. When exposed to the sun, the melanin synthe-

sis increases, that being a protective biological reaction. The content of melanin varies much according to individual and racial features. The melanogenesis is controlled by the central nervous system and endocrine glands. The disturbances of melanin metabolism manifest themselves by hyperpigmentation (hypermelanosis, melanodermia) or hypopigmentation (hypomelanosis) and each of them can be generalized or localized, acquired or congenital.

The most characteristic example of **generalized** acquired **hypermelanosis** is the Addison disease. The skin in this disease turns intensively pigmented, getting a bronzed aspect. At the microscope, is observed increased quantities of melanin in cells of the basal layer of epidermis, numerous melanophages filled with melanin granules in the subepidermal areas of the dermis (Fig. 2–27).

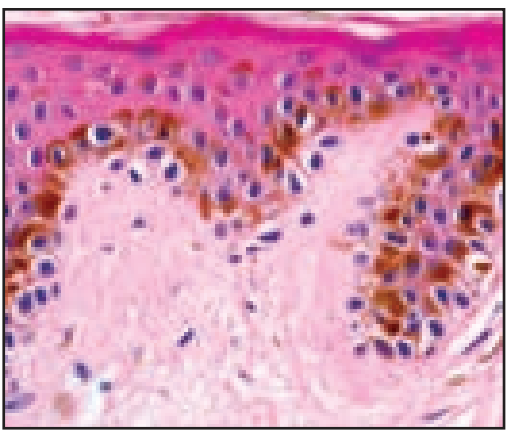


Fig. 2–27. Hyperpigmentation of the skin in Addison disease (hematoxylin–eosin stain, ×110).

It is caused by chronic insufficiency of the adrenal glands, i.e. abolition or diminution of the hormones production of these glands. The most frequent causes are: tuberculosis of adrenal glands (in more than 70% of cases), amyloidosis, primary or bilateral metastatic tumors etc. The hyperpigmentation of the skin can be explained by the fact that, as a result of destruction of the adrenal glands and diminution of the amount of adrenal hormones in the blood, an increase of ACTH secretion takes place, which exerts a melanocyte–stimulatory action and intensifies the synthesis of melanin in the skin. The hypermelanosis of the skin occurs in other endocrine diseases (hypogonadism, hypopituitarism), hemochromatosis, avitaminoses (pellagra, scurvy) and cachexies.

The generalized congenital hypermelanosis or xeroderma pigmentosum is a hereditary disease, with a familial character, caused by congenital deficiency of endonuclease - the enzyme regulating the repairing processes of the DNA defects, as a result of ultraviolet radiation action. It manifests itself by hypersensitivity to the sunlight. It is characterized by hyperpigmentation of the skin in the form of spots that are more emphasized on uncovered parts of the body, exposed to sun radiations, ulcerations, atrophies, scars, deformations. It is a precancerous condition.

The local acquired **hypermelanoses** have different variants of spots or hyperpigmented areas, for example:

- ephelides (freckles) – small pigmented spots (1–10 mm), which appear after exposing to the sunlight and are particularly characteristic for people with blond or red hair and bear a seasonal character; at the microscope, the number of melanocytes is normal, but the content of melanin in the keratinocytes of the basal layer of epidermis is increased;
- lentigo – spots of 5–10 mm, which do not become more pigmented under the action of the sun radiation; at the microscope, is observed the hyperplasia of melanocytes and their hyperpigmentation;
- hyperpigmentated areas of the skin,

which appear in ovarian tumors, as a result of a prolonged use of hormonal contraceptives, during pregnancy (chloasma or melasma of the pregnant women);

- acanthosis nigricans – the appearance of some pigmented patches, most frequently located in the flexural parts of the body (axillary, nape, anorectal, inguinal regions), in endocrinopathies (diabetes mellitus, pituitary adenoma, hyperthyroidism), and, in some cases, it is associated with certain forms of cancer of the visceral organs, being a manifestation of the paraneoplastic syndrome.

Another example of local hypermelanosis is the pigmentary nevi, considered congenital or acquired hamartoma of the skin (a hamartoma is a pseudotumoral formation, consisting of cells and tissues - normal components of the given organ). Macroscopically, they look like spots or papules of up to 6 mm in size, with smooth or verrucous surface, of brown or dark–brown color, sometimes covered with hairs (Fig. 2–28). Microscopically, it represents an agglomeration of nevic cells – cells that come from Schwann cells and can synthesize melanin.

The malignant melanoma is another example of local acquired hypermelanosis. It is one of the most malignant tumors in humans. A more frequent localization is at the skin level, but there can be extracutaneous localizations. In malignant melanoma, there is a synthesis of some excessive quantities of melanin, which is also present in hematogenic metastases of melanoma that can be localized in various organs and tissues (Fig. 2–29).

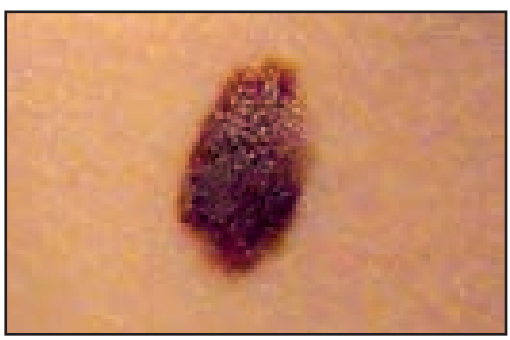


Fig. 2–28. Pigmentary nevus.

The hypomelanosis can be generalized or localized. Generalized hypopigmentation or albinism appears as a result of hereditary insufficiency of the tyrosinase, which catalyzes the formation of melanin from tyrosine. It is characterized by the absence of melanin in hair, skin, iris and retina. People have pale teguments, the hair is blond-white, the iris and the choroid are depigmented, the pink eyeground turning visible with naked eye. The microscopic and electronoptic examination shows that melanocytes exist in a normal number and have a normal structure, the pre-melanosomes being present, but without melanin. Patients with oculo-cutaneous albinism have severe photophobia, an extremely sensitive skin to sun radiation, photodermatitides, ulcerations and a high risk of squamous or basal cell cancer of the skin.

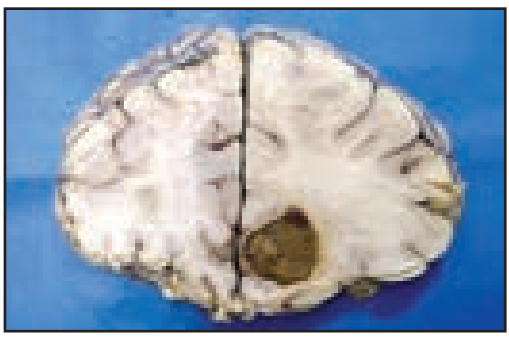


Fig. 2–29. Melanoma metastasis in the brain.

The localized hypomelanosis is called *leucodermia* or *vitiligo* (partial albinism). It is manifested by the appearance of some white spots of different shape and size, sometimes symmetrical, clearly defined, surrounded by a hyperpigmented border most of the times (Fig. 2–30).

It may occur in some endocrine diseases (hyperparathyroidism, thyrotoxic goiter, diabetes mellitus) related to melanogenesis disorder, as a result of diverse inflammatory and necrotic lesions of the skin (in burns, syphilis, leprosy). Vitiligo may have an autoimmune origin, being caused by the appearance of autoantibodies against tyrosinase or melanocytes. Electron microscopic studies revealed a reduction of the number of melanocytes in affected areas, in comparison to albinism, where melanocytes are present, but are not functional. The localized melanin depigmentation may be congenital.

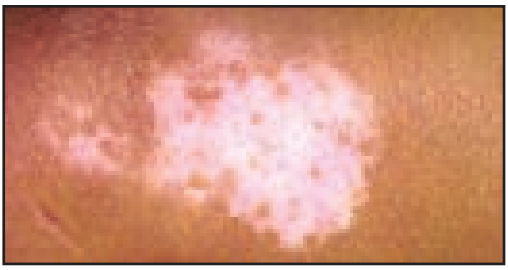


Fig. 2–30. Leucodermia (vitiligo).

2.6.1.3. DYSTROPHIES OF LIPIDOGENIC PIGMENTS

The main pigments of this group are lipofuscin, ceroid and lipochromes.

The lipofuscin (from the Latin *fuscus* – yellow) is an insoluble intracellular pigment, in the form of fine yellow–brown granules, placed in cytoplasm mostly in the perinuclear space (Fig. 2–31 and 2–32).

It consists of complex lipids (phospholipids) and proteins, which appear as a result of peroxide oxidation of unsaturated lipids of subcellular membranes in autophagia process of the own degradated and aged components of the cell. The accumulation of lipofuscin in organs and tissues – the acquired lipofuscinosis - occurs in cachectic diseases, senile atrophy, hypoxia and is observed more frequently in myocardium, liver, brain, adrenal cortex. Macroscopically, the tissues and respective organs get a brown appearance, hence the name *brown atrophy* (Fig. 2–33). Due to this, lipofuscin is also called "wear and tear pigment" or "age pigment".

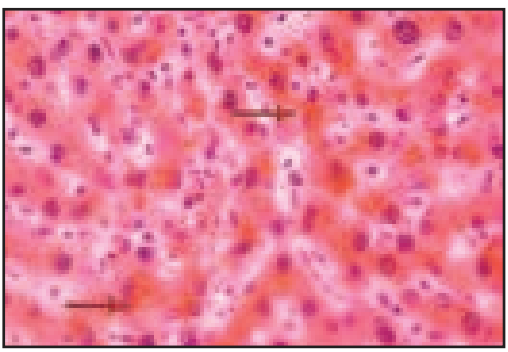


Fig. 2–31. Liver lipofuscinosis (hematoxylin–eosin stain; ×110).

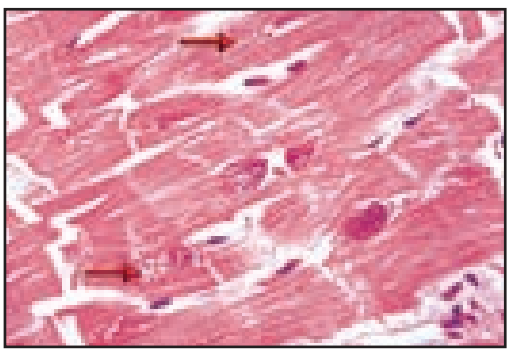


Fig. 2–32. Myocardial lipofuscinosis (hematoxylin–eosin stain; ×110).

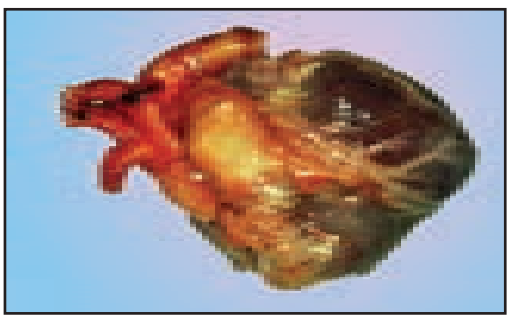


Fig. 2–33. Brown atrophy of the heart.

The ceroid (from the Latin *cera* – wax) is a lipopigment, which appears in macrophages, as a result of phagocytosis of some products containing lipids. The lipids are not disintegrated by lysosomal enzymes and remain in cells, forming residual bodies – *telolysosomes*. It is mostly formed in the necrosis of tissues, for example, in the liver - in acute viral hepatitis (in the resorption phase) or in granulation tissues in the course of maturation.

The difference between lipofuscin and ceroid is not distinct; the first lipopigment appears in parenchymatous cells of the organs, as a result of autophagy, the second – in macrophages, as a result of heterophagy processes.

The lipochromes determine the yellow coloration of the adipose tissue, ovarian corpus luteum, adrenal cortex, testicles, blood serum and transudate.

Exogenous pigmentations. The inclusions of coal dust, which enter the organism by respiration, occur most frequently. The inhaled dust is phagocyted by alveolar macrophages and taken lymphatically to the tracheobronchial lymph nodes. The pigment accumulations give the lymph nodes and pulmonary parenchyma a black color. A prolonged inhalation of the coal dust causes an occupational pathology of respiratory system – *anthracosis* - morphologically manifested by pneumosclerosis and pulmonary emphysema.

Tattooing is an exogenous localized pigmentation of the skin. The respective stain, when introduced into the skin, is phagocyted by the macrophages from dermis, where it remains forever.

Exogenous pigmentation of the skin may also occur in persons working with different chemical dyes.

2.6.2. DYSTROPHIES OF NUCLEOPROTEINS

The metabolic disturbances of nucleoproteins manifest themselves by excessive formation of uric acid and its salts, which can be stored in tissues. It can be observed in gout and urinary lithiasis especially.

Gout (podagra) is characterized by hyperuricemia and hyperuricuria. There are 2 forms of gout: primary (idiopathic) and secondary. **Primary gout,** the most frequent form, constitutes 90% of cases. It is caused by congenital, hereditary disturbances of the purine metabolism. A hyperproduction of uric acid with its normal excretion takes place, or its normal production with a reduced elimination. Alcohol and obesity constitute predisposing factors. A disorder of the activity of enzymes involved in uric acid metabolism can be observed in a certain number of cases.

Secondary gout is noticed in 10% of cases and can be a complication of some diseases with massive cellular destructions, for example, in chronic hemolysis, polycythemia, leukemias and lymphomas, which lead to an increase of the uric acid level in the blood. Secondary gout may appear related to an exaggerated consumption of animal proteins.

The pathognomonic lesion is the **gouty tophus** that presents deposits of salts of uric acid, crystalline or amorphous, surrounded by perifocal reactive inflammation with macrophages, lymphocytes, fibroblasts, and giant polynucleated cells "of foreign bodies" (Fig. 2–34 a).

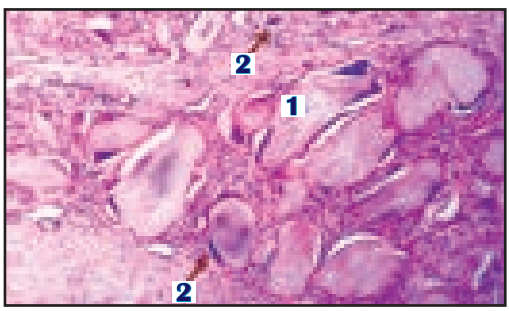


Fig. 2–34 a. Gouty tophus - microscopic pattern (hematoxylin–eosin stain; ×70): 1 – urate deposits, 2 – giant polynucleated cells of foreign bodies.

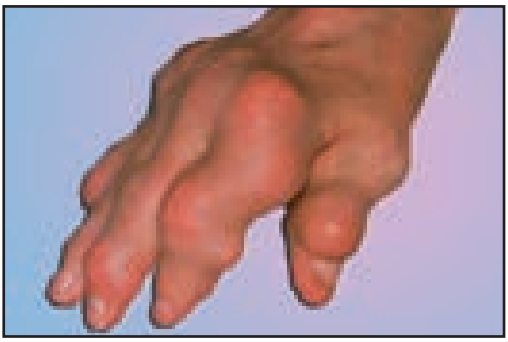


Fig. 2–34 b. Gouty nodules (gouty tophi), macroscopic aspect.

Subsequently, sclerosis processes develop, painful nodules form and deformation of joints may appear (Fig. 2–34 b).

The elbow, knee, fingers joints are affected, as well as the ear. Urate salts of sodium are deposited in the synovial membranes, cartilages, tendons, ligaments, articular capsule. 90% of patients with chronic gouty arthritis develop renal lesions: acute or chronic nephropathy, urinary calculi.

2.6.3. MINERAL DYSTROPHIES. PATHOLOGIC CALCIFICATION

Disturbances of calcium metabolism prevail among mineral dystrophies. The main factors which ensure the maintenance of the normal calcium level in organism are: the parathormone, calcitonin, food intake, vitamin D, as well the function of calcium excretory organs (kidneys, colon). Calcium is revealed in histological section by von Kossa reaction with silver nitrate. Pathological calcification manifests itself by abnormal depositions of calcium salts in soft tissues. There are two variants of calcification: a) dystrophic and b) metastatic.

Dystrophic calcification (petrification) occurs in nonviable, necrosed tissues, the calcium level in the blood plasma being normal. The development mechanism consists in physico–chemical changes of tissues in foci of dystrophy, necrosis, sclerosis, which stimulate calcium absorption from blood and interstitial fluid. Local increase of alkalinity of tissues and of the activity of phosphatases occur, and this favors the calcium absorption and precipitation. Dystrophic calcification has a local character. It can be seen in tuberculosis (in foci of caseous necrosis) (Fig. 2 –35), syphilis (syphilitic gummas), atherosclerosis of arteries (Fig. 2–36), foci of necrosis (Fig. 2–37), infarctions, scars (cutaneous keloids, postinfarction scars), adherences, mortified parasites (echinococcus), cardiac

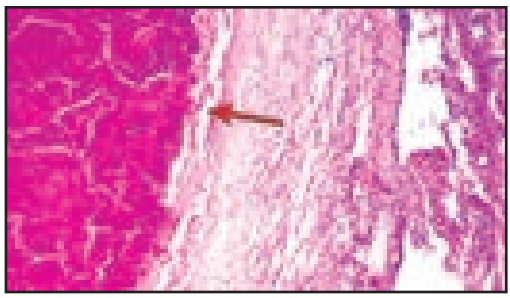


Fig. 2–35. Dystrophic calcification of pulmonary tissue (hematoxylin–eosin stain; ×70).

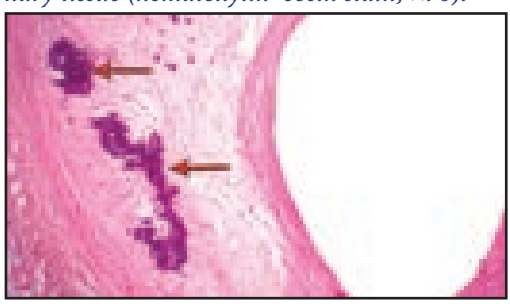


Fig. 2–36. Dystrophic calcification of coronary artery in atherosclerosis (hematoxylin–eosin stain; ×110).

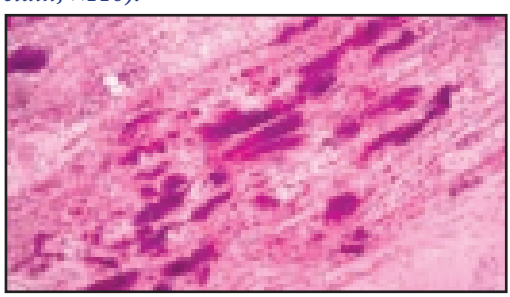


Fig. 2–37. Dystrophic calcification of striated muscle (hematoxylin–eosin stain; ×110).

valvulopathies. Macroscopically, the foci of calcification have a whitish color and a stony consistency. Microscopically, calcium is revealed both intra and extracellularly.

Metastatic calcification (calcareous metastases) is caused by excess of calcium in blood plasma (hypercalcemia), determined, in its turn, by the mobilization of calcium from bones or by disturbance of elimination processes of calcium from the organism. It is observed in primary hyperparathyroidism (parathyroid adenoma) or secondary one (as a result of ectopic secretion of parathormone in malignant tumors, for example, in pulmonary cancer, bone tumors (multiple myeloma, bone metastases), multiple bone fractures, hypervitaminosis D, osteoporosis, osteomalacia, chronic nephritis.

Morphologically, it is manifested by appearance of calcium focal deposits (metastases) in different intact organs and tissues, but more frequently - in arterial walls (tunica media), lungs, gastric mucosa, myocardium, kidneys) (Fig. 2–38 and 2–39).

There is a local alkalosis in these organs, because they eliminate acidic products, encouraging the precipitation

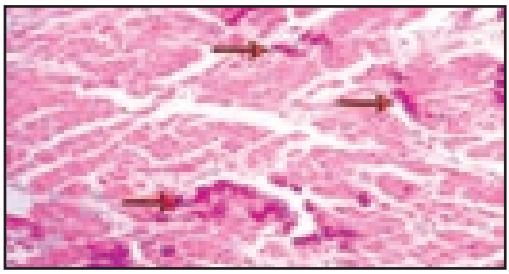


Fig. 2–38. Metastatic calcification of myocardium (hematoxylin–eosin stain; ×110);

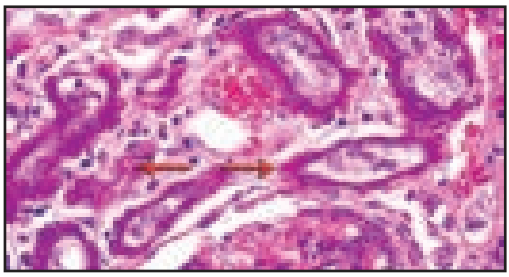


Fig. 2–39. Metastatic calcification of kidney (hematoxylin–eosin stain; ×110), deposition of calcium salts in the renal tubes and in stroma.

of calcium salts (the stomach - hydrochloric acid, the kidneys – uric acid, the lungs – carbon dioxide and the myocardium and arteries are in constant contact with the arterial blood and have a low content of carbon dioxide). Macroscopically, calcium deposits have the same aspect of whitish foci of a hard consistency, like in dystrophic calcification.

2.6.4. CALCULOGENESIS (LITHIASIS)

Calculi or concrements are formations of dense consistency, which are formed in the lumen of hollow organs or in excretory ducts of glands, being constituted of secretion components of the respective organs or ducts.

Calculi appearance, the *calculogenesis,* is determined by a range of general and local factors:

- ✧*general factors*: lipidic, mineral, proteic, glucidic metabolism disturbances. The character of alimentation, the quality of drinking water, the geographic area, the hereditary factors play a certain role. The association of the biliary calculosis with obesity, atherosclerosis and of the nephrolithiasis with gout is well-known.
- ✧local factors:
  1) inflammatory lesions of hollow/tubular organs;
  2) disorder of secretion and reabsorption processes, leading to change of physicochemical features of secret, the increase of concentration of certain components and their precipitation from the solution;

3) retention of secretion, its condensation due to the reabsorption of fluid components.

The presence of some nuclear factors like cellular debris, necrotic residuals, mucus, bacteria, leukocytes, desquamated cells is important and constitutes the organic matrix in which the salts are deposited.

Most frequently, calculi are formed in biliary and urinary ducts. Macroscopically, they can have different sizes, shapes, and colors, smooth or rugged, granular surface, hard consistency. They can be solitary or multiple numerically (Fig. 2–40 and 2–41).

According to chemical structure, biliary calculi may be cholesterolic, pigmented or mixed. Biliary calculosis may complicate with cystic duct obstruction, retention of bile and development of gallbladder hydrops or mucocele, appearance of acute or chronic cholecystitis, perforation of vesical wall and overflowing of bile in peritoneal cavity with consecutive biliary peritonitis.

According to chemical composition, urinary calculi are frequently formed of calcium oxalate, calcium phosphate, uric acid and its salts (oxalates, phosphates and urates). Renal pelvis calculi cause the retention of urine, distention of pelvis and calyces, atrophy of renal parenchyma, repeated hydronephrosis; ureteral calculi cause hydroureter. It is usually associated with chronic pyelonephritis.

Fig. 2–40. Calculi in gallbladder.

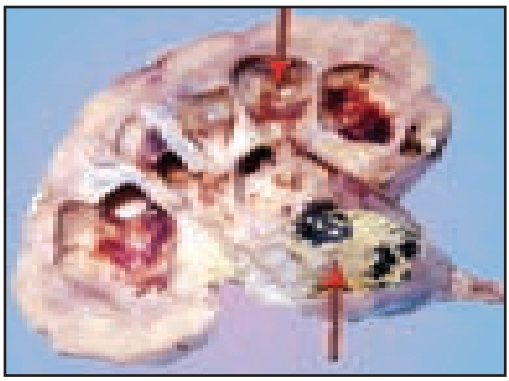


Fig. 2–41 Urinary calculus in renal pelvis with hydronephrosis (dilatation of calyces).

Calculi can also form in other hollow/tubular organs, for example, in bronchi (broncholiths), pancreatic ducts (pancreatoliths), salivary glands (sialoliths), intestine (coproliths).

ESSENTIAL TERMS

on the subject "MIXED EXTRA- AND INTRACELLULAR LESIONS (mixed dystrophies)"

acanthosis nigricans	gout	leucodermia
Addison disease	gouty tophus	lipochrome
albinism	hamartoma	lipofuscin
anthracosis	hematin	lipofuscinosis
bilirubin	hematoidin	mechanical jaundice
broncholithiasis	hemochromatosis	melanodermia
calcification	hemolytic jaundice	melasma
calculogenesis	hemomelanin	metastatic calcification

ceroid	hemomelanosis	nephrolithiasis
chloasma	hemosiderin	nevus
cholelithiasis	hemosiderosis	podagra
chromoproteins	hepatic jaundice	porphyria
coprolithiasis	hydrochloric hematin	porphyrin
dystrophic calcification	hypermelanosis	sialolithiasis
ephelides	hypomelanosis	urolithiasis
ferritin	lentigo	vitiligo

TESTS

on the subject "REVERSIBLE EXTRACELLULAR AND CELLULAR LESIONS"

SET I.

Multiple-choice questions with only one correct answer

1) Which process induces the development of generalized hemosiderosis:
a) extravascular hemolysis;
b) hemorrhages by diapedesis;
c) intravascular hemolysis;
d) hemangioma;
e) mechanical jaundice.

2) Indicate the lipidogenic pigment:
a) porphyrin;
b) the "wear and tear" pigment;
c) hemomelanin;
d) hemosiderin;
e) bilirubin.

3) Which organ participates in the regulation of calcium metabolism:
a) the liver;
b) the lung;
c) the bone marrow;
d) the parathyroid glands;
e) the kidneys.

4) Variant of tissular calcification, according to the development mechanism:
a) atrophic;
b) necrotic;
c) dystrophic;
d) diffuse;
e) local.

5) In which of the listed diseases occurs the impairment of nucleoproteic metabolism:
a) hemosiderosis;
b) hemochromatosis;
c) gout;
d) Gaucher disease;
e) amyloidosis.

SET II.

Multiple – choice questions with 2, 3 and more correct answers

1) Which of the listed signs are characteristic for local hemosiderosis:
a) it can be seen in chronic venous stasis in the lungs;
b) intravascular hemolysis of erythrocytes;
c) extravascular hemolysis of erythrocytes;
d) it occurs in subcutaneous hemorrhages;
e) intoxications with hemolytic toxins.

2) Which of the listed causative factors may cause the accumulation of lipofuscin in organ:
a) arterial hyperemia;
b) cachectic diseases;
c) atrophic processes;
d) the aging of the body;

e) perivascular hemorrhages.

3) *Localization of deposits of fat in heart lipomatosis:*
   a) under epicardium;
   b) in cytoplasm of cardiomyocytes;
   c) in walls of coronary arteries;
   d) in walls of lymphatic vessels;
   e) in stroma of myocardium;
   f) under endocardium.

4) *Which of the listed signs characterize the gout (podagra):*
   a) increase of the urea level in the blood;
   b) deposition of calcium salts in joints;
   c) deposition of uric acid salts in joints;
   d) hyperuricemia;
   e) formation of nodules in the area of joints;
   f) increase of the uric acid in the urine.

5) *What changes in organs and tissues anticipate dystrophic calcification:*
   a) mucoid intumescence;
   b) necrosis;
   c) hyalinosis;
   d) severe dystrophy;
   e) hemosiderosis.

SET III.

The classification tests include 2 – 4 subjects and a series of answers. Indicate which answers are correct for each separate subject.

1. *Which hemoglobinogenic pigments are formed in the organism in:*
   I – physiological conditions;
   II – pathological conditions;
   a) hematoidin;
   b) hemosiderin.
   c) porphyrin;
   d) ferritin;
   e) bilirubin;
   f) hematins.

2. *Which of the listed sings characterize:*
   I – hemosiderin;
   II – hematoidin;
   a) yellow color;
   b) brown color;
   c) is formed in 24 – 48 hours after hemorrhage;
   d) is formed in 5 – 10 days after hemorrhage;
   e) is formed in the presence of oxygen;
   f) accumulates extracellularly;
   g) is formed intracellularly.

3. *In which organs (tissues) do the lipidogenic pigments accumulate:*
   I – lipofuscin;
   II – lipochrome;
   a) the ovarian corpus luteum;
   b) myocardium in decompensated valvulopathies;
   c) adrenals;
   d) blood serum;
   e) the liver in cachectic diseases;
   f) the liver and other organs in senile period.

4. *Which of the listed signs are characteristic for calcification:*
   I – metastatic;
   II – dystrophic;
   a) hypercalcemia;
   b) normal level of calcium in the blood;
   c) systemic deposits of calcium salts;
   d) focal deposits of calcium salts.

5. *Which of the listed diseases may cause:*
   I – mechanical jaundice;
   II – gallbladder hydrops;
   a) occlusion of common hepatic duct by calculi;

SET IV. SITUATIONAL PROBLEMS

b) occlusion of choledoch duct by calculi;
c) duodenal papilla cancer;
d) cancer metastases in subhepatic lymph nodes;
e) chronic cholecystitis with stenosis of the cystic duct lumen.

SET IV. SITUATIONAL PROBLEMS

Daily practice cases are presented with clinical and morphological data from clinical histories and/or from necropsy protocols. Each subject includes simple or multiple - answer questions, with 1, 2 or more correct answers.

1. *A sportsman had a trauma of the soft tissues in the region of the hip, during his training. On the second day, the area became bluish-grey, and, in a week, it became yellow, later - greenish.*

Question:

Which hemoglobinogenic pigments were formed in the region of trauma:
a) hematoidin;
b) hemomelanin;
c) hemosiderin;
d) lipofuscin;
e) bilirubin.

2. *At a microscopic examination of cardiomyocytes and hepatocytes of a patient who died of pulmonary cancer, pigment granules of brown color, which did not stain positive at Pearls reaction, were revealed.*

Question:

Which pigment was detected in this case:
a) melanin;
b) hemomelanin;
c) hemosiderin;
d) lipofuscin;
e) lipochrome.

3. *A patient addressed a traumatologist because of pains in the small joints of hands and legs. During a clinical examination, a deformation of the fingers and some painful nodules was revealed. A nodule was removed for diagnosis purposes. A histological examination revealed focal deposits of crystals and amorphous masses, surrounded by gigantocellular inflammatory reaction.*

Questions:

A) Which disease can be suspected in this patient:
a) rheumatic arthritis;
b) gout;
c) rheumatoid arthritis;
d) exostoses;
e) osteoporosis.

B) Which biochemical investigation of blood and urine is indicated to specify the diagnosis:
a) calcium content;
b) uric acid content;
c) sodium content;
d) potassium content;
e) ketone bodies content.

4. *A patient, who suffered from multiple myeloma that affected vertebrae, ribs, skull bones, died of renal failure. At microscopical examination of cadaveric material, foci of calcification in myocardium and kidneys were revealed.*

Questions:

A) Which calcification variant had this patient:
a) metastatic;
b) dysfunctional;
c) dystrophic;
d) metabolic;
e) physiological.

B) In which organs can be revealed foci of calcification in this case:
a) stomach;
b) lungs;
c) skin;
d) arteries;
e) brain.

5. *A patient suffering from biliary lithiasis started to feel pains in the right costal part and jaundice.*

Question:

A) Which localization of calculi can be suspected in this patient:
a) choledoch duct;
b) common hepatic duct;
c) cystic duct;
d) intrahepatic ducts;
e) duodenal papilla.

B) Which variant of jaundice has this patient:
a) hemolytic;
b) subhepatic;
c) hepatic;
d) prehepatic;
e) parenchymatous.

IRREVERSIBLE CELLULAR LESIONS NECROSIS AND APOPTOSIS

3.1. NECROSIS

Necrosis is the localized death of cells and tissues in a living organism. It may include a portion of cell, separate cells, cell groups, segments of tissues and organs or entire organs, parts of the body. The necrotic process has an evolution of 4 stages:

1) **pre-necrosis stage** – the state of the cell/tissue preceding the necrosis; it includes potentially reversible cellular lesions, which occur as a result of the action of harmful exo - and endogenous factors;
2) **necrobiosis stage** – a transition period from life to death, which shows the evolution of cell to necrosis. There is a progressive accumulation of irreversible lesions of structural components in the cell, but it remains viable as a system and may restore in favorable conditions. This stage may lack in cases when necrosis occurs suddenly, due to the action of some strong destructive factors, for example, the electric power, but it may last for a long time;
3) **necrosis stage** – morphological manifestation of the death of the cell; at this stage, cellular death signs can be revealed at electron and optical microscopy (the appearance of morphological signs of cellular death is called *necrophanerosis);* the exact moment of death of the cell (a non – return point of viability of a biological object) cannot be established with certainty, because different cellular elements die at different periods of time;
4) **autolysis stage** *(postnecrosis)* – disintegration and lysis of necrotic cells, under the action of the own hydrolytic lysosomal enzymes of necrotic cells (autolysis) and of neutrophil leukocytes and macrophages *(heterolysis)*.

Necrosis can be conditioned by different causative agents, both of exogenous and endogenous origin. According to the etiological factor, the following varieties can be distinguished:

a) traumatic necrosis – caused by the action of some physical or chemical factors (*mechanical trauma, thermal or chemical burns, chilblains, radiation sickness etc.);*
b) toxic necrosis – caused by the acti-

on of some bacterial toxins, exo- or endogenous toxic chemical substances, enzymes, drugs, etc. *(in some infectious diseases, acute massive necrosis of the liver, acute tubular renal necrosis, steatonecrosis, etc.);*

c) trophoneurotic necrosis – caused by the impairment of the trophic function of the central and/or the peripheral nervous system (in traumatisms, tumors of brain, spinal cord, peripheral nerve trunks; cerebral infarctions and hemorrhages; leprosy etc. (*eschars, trophic ulcerations, gangrene);*

d) vascular necrosis *(circulatory, ischemic)* – caused by the reduction or suppressing of arterial circulation in an organ or tissue; vascular necrosis of parenchymatous organs is called *infarction*;

e) allergic necrosis – related to harmful action of immune complexes, antibodies in a sensitized organism (immediate hypersensitivity reaction), for example, in allergic infectious diseases *(rheumatism, tuberculosis),* autoimmune diseases *(disseminated lupus erythematosus, autoimmune glomerulonephritis etc.)*

According to the action mechanism of the harmful agent, the necrosis can be direct and indirect. In case of direct necrosis, there is a direct action on the tissues of different causative agents, for example, in traumatic, toxic or allergic necrosis. The indirect necrosis occurs as a result of disturbance of tissues (*cells*) trophicity, for example, in trophoneurotic or vascular necrosis.

Morphological changes of the cells and tissues in the necrosis process occur as a result of destructive actions of catalytic enzymes, which are released from lysosomes of necrosed cells (autolysis) or from the lysosomes of leukocytes (heterolysis). Two competitive processes develop: denaturation of proteins, disintegration and dissolution of the cells.

The microscopic changes in necrosis occur at the level of the cells (nucleus and cytoplasm) and intercellular matrix.

Changes of the nucleus (Fig. 3–1):

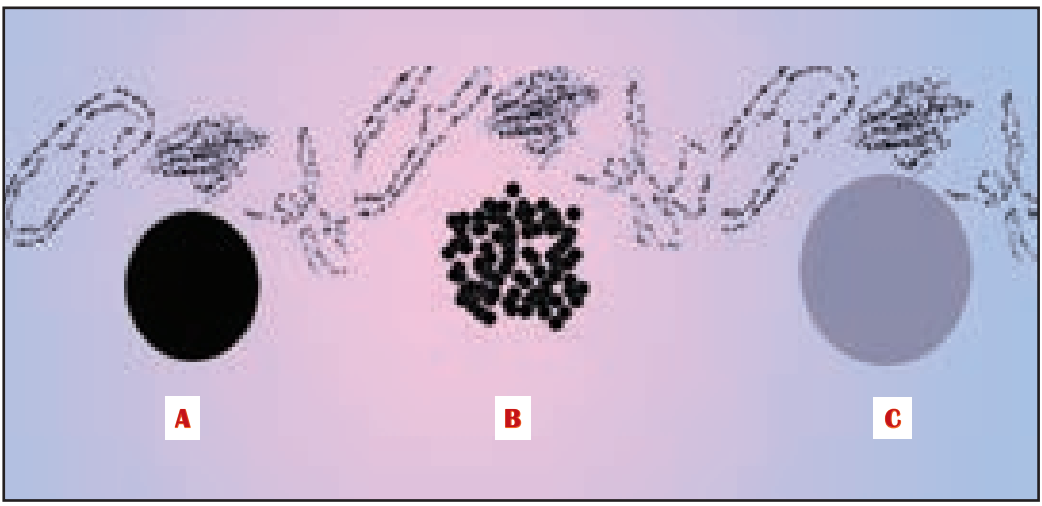


Fig. 3–1. Schematic presentation of the cellular nucleus changes in necrosis; a) karyopyknosis; b) karyorrhexis; c) karyolysis.

- **karyopyknosis** – condensation of chromatin and shriveling of nucleus; the nucleus has a reduced volume, intensely basophilic, the membrane is wrinkled, shriveled, the karyoplasma is dense, compact and the nucleolus is not differentiated (Fig. 3–2 and 3–3);
- **karyorrhexis** – fragmentation of the nucleus (chromatin) in small granules, spread in cytoplasm;
- **karyolysis** – dissolution of the nuclear chromatin in cytoplasm, as a result of the action of endonucleases; the disappearance of the nucleus is the marker–sign of the cell necrosis (Fig. 3–4).

These changes of the nucleus can be consecutive stages or independent forms of the cellular nucleus reaction to harmful action. Karyopyknosis may persist a relatively long time, after which karyorrhexis may happen and later karyolysis.

Cytoplasm lesions:

- denaturation and coagulation of cytoplasmic proteins (plasma coagulation); the cytoplasm becomes eosinophilic, as a result of increased acidophilia of denatured proteins and of diminishing of cytoplasmic DNA content. Intensive eosinophilia of cytoplasm is also a marker–sign of the cell necrosis (Fig. 3–3);
- plasmorrhexis – fragmentation of cytoplasm in blocks (Fig. 3–5);
- plasmolysis – liquefaction and hydrolysis of cytoplasm (Fig. 3–6).

The intercellular matrix registers the tumefaction and liquefaction of ground substance, disintegration and lysis

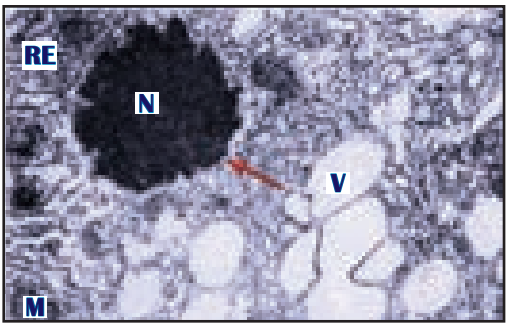


Fig. 3–2. Necrosis of the cell; karyopyknosis (electron microscopy; ×17500): N – nucleus, ER – endoplasmic reticulum; M – mitochondria; V – vacuoles.

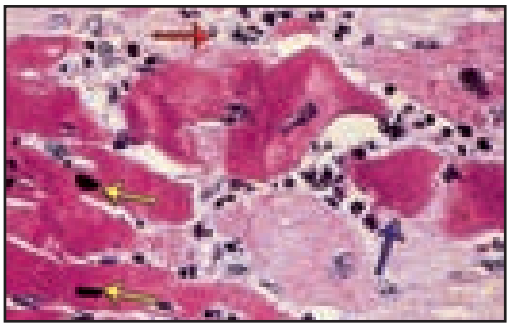


Fig. 3–3. Karyopyknosis and eosinophilia of the sarcoplasm of cardiomyocytes in acute myocardial infarction (the red arrow – leukocyte infiltration) (hematoxylin–eosin stain ; ×110).

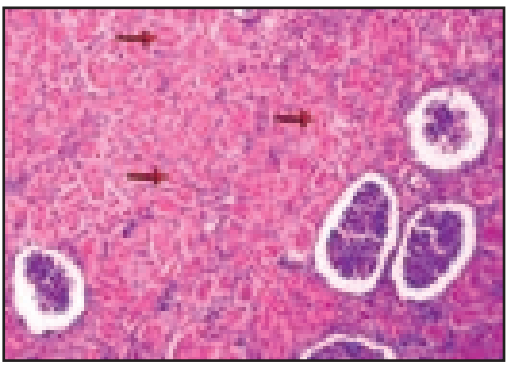


Fig. 3–4. Necrosis of the epithelium of renal convoluted tubes (hematoxylin–eosin stain; ×70).

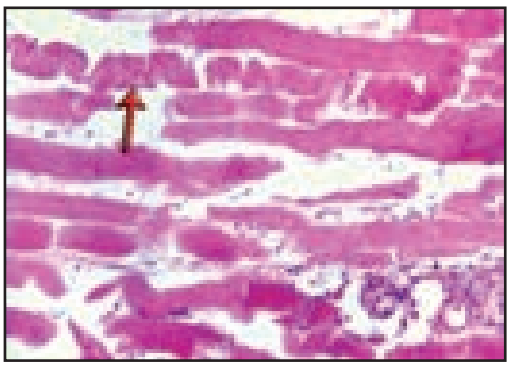


Fig. 3–5. Waxy (Zenker) necrosis of striated muscle (karyolysis and plasmorrhexis) (hematoxylin–eosin stain; ×70).

of fibrillar elements (collagenic, reticular and elastic fibers) under the action of proteases and lipases.

Following the destruction and autolysis of mortified tissues, a tissular debris is formed in the necrotic focus. It is an amorphous substance, consisting of cells debris and degraded fibers.

Microscopically, necrotic lesions are best revealed in the autolysis stage, which is not identical to necrosis, but morphologically usually coincides with it. According to experimental data, irreversible changes in cardiomyocytes occur in 20 minutes from the moment of alteration, in liver and kidney cells - in 25–40 minutes, but the first obvious histologic signs of cellular death can be revealed only in 6–12 hours from the onset of ischemia. These aspects have a particular significance in the morphological diagnosis of sudden death.

The periphery of necrotic focus reveals an edema area, hyperemia of vessels and infiltration with neutrophil leukocytes – a zone of *demarcation inflammation* (Fig. 3–7), determined by the action on viable surrounding tissues of different biologically active substances released in the necrotic focus, both from necrotized cells and from neutrophils and macrophages. The inflammation contributes to the delimitation of the affected zone and to the resorption of necrotic masses with subsequent restoration (regeneration) of injured tissues.

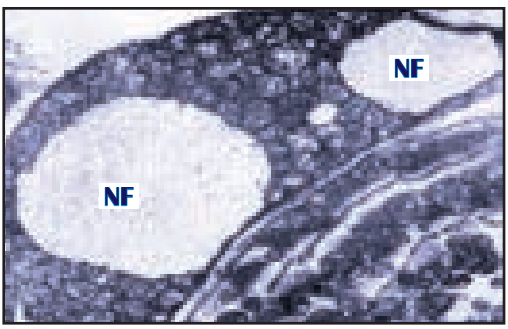


Fig. 3–6. Focal (partial) necrosis of cytoplasm of cardiomyocyte (electron microscopy; ×10000); NF–necrotic focus.

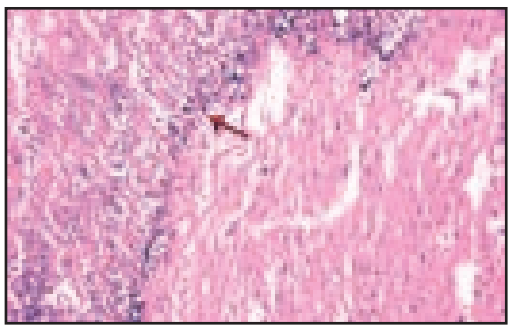


Fig. 3–7. Demarcation inflammation in myocardial infarction, leukocyte infiltration at the limit between necrosis and persistent myocardium (hematoxylin–eosin stain; ×70).

3.1.1. CLINICAL AND MORPHOLOGICAL FORMS OF NECROSIS

The following clinical and morphological varieties of necrosis are distinguished:

1) dry or coagulative necrosis;
2) wet or liquefactive necrosis;
3) gangrenous necrosis (gangrene);
4) infarction (vascular, ischemic necrosis);
5) caseous necrosis;
6) steatonecrosis (fat necrosis);
7) waxy necrosis (Zenker);
8) fibrinoid necrosis;
9) sequestrum.

Dry necrosis (*coagulative*) is characterized by predominance of densification, denaturation and dehydration (drying) processes of the tissues. It is the most frequent form of necrosis; the

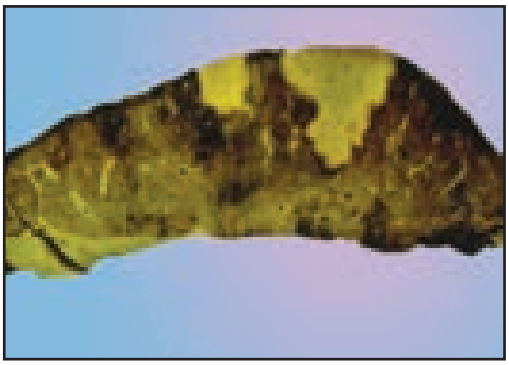


Fig. 3–8 a. Ischemic infarction of the spleen: macroscopic aspect.

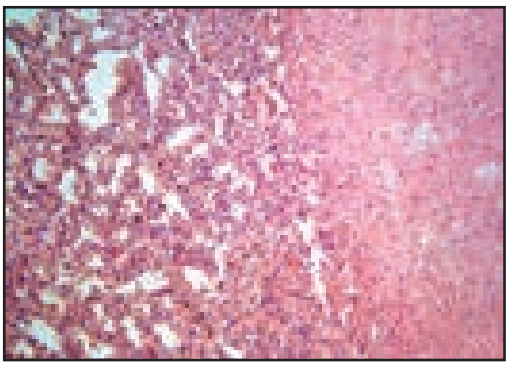


Fig. 3–8 b. Ischemic infarction of the spleen: microscopic pattern (hematoxylin–eosin stain; ×70).

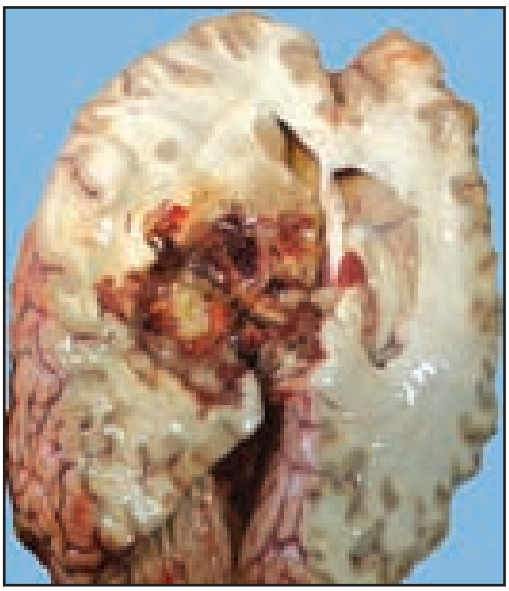


Fig. 3–9. Cerebral ischemic infarction (white softening, encephalomalacia).

necrotic masses are dry, dense, of a whitish–yellow color, they are not subject to enzymatic decomposition for a long time. It is considered that the action of harmful factors and the intracellular acidosis condition the denaturation not only of the structural proteins, but also of enzymes and that stops the cell autolysis. Consequently, the necrotic focus maintains the outlines of the tissular elements. It is more frequently seen in poor in water tissues, practically in all the organs and tissues, except the brain and spinal cord. As a rule, it is caused by hypoxia and ischemia. The typical coagulative necrosis occurs in myocardial, lienal and renal infarction (Fig. 3–8 and 3–8 b).

Wet necrosis (*liquefactive* or *colliquative*) prevails the processes of moistening, liquefaction and autolysis of dead tissues; the necrotic masses contain an increased content of fluid, have a soft, flaccid consistency similar to a porridge. It occurs in tissues rich in water, in which hydrolytic processes are particularly intense. Firstly, it is found in brain and spinal cord infarction (*grey or white cerebral softening, encephalomalacia,* Fig. 3–9), but it can also be seen in purulent inflammation foci, for example, in abscesses.

Softening of necrotic tissues happens as a result of proteo- and lipolytic lysosomal enzymes action, both from necrosed and inflammatory cells. In cerebral tissues, the softening and the resorption of liquefied necrotic masses condition the formation of cystic cavities, filled with a semi-fluid mass. The fluid penetrates from the adjacent tissue.

Gangrene (gangrenous necrosis) is the necrosis of the tissues in contact with the external environment (air, bacteria). The dead tissues have a grayish–brown or black color. Preferential localization is in limbs, superficial soft tissues, digestive tube, lungs, uterus and urogenital tract. The most frequent causes of the gan-

grene of limbs are: thrombosis, arterial thromboembolism in atherosclerosis, diabetes mellitus, obliterating endarteritis. It can develop in burns, chilblains, vibration disease etc.

There may be dry, moist and gas (anaerobic) gangrene.

The processes of drying, densification and shriveling of dead tissues prevail in **dry gangrene.** The tissues become dry, wrinkled, mummified, as a result of evaporation or absorption of water by the normal neighboring tissues. They are black and have a dense consistency; there is an obvious line of delimitation (demarcation inflammation) between the live and the dead tissue. The black color is determined by the iron sulphite, which appears after a contact of hemoglobinogenic pigments with the atmospheric air and hydrogen sulphide produced by bacteria in mortified tissues (Fig. 3–10).

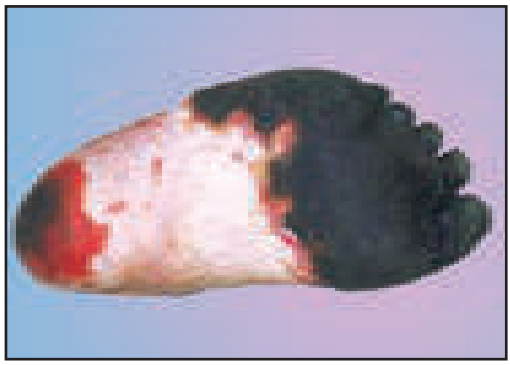


Fig. 3–10. Dry gangrene of the foot.

In **wet (moist) gangrene,** the tissues are tumefied, imbued with fluid, have a soft consistency, a grayish–blue or blackish color, a putrefaction smell and the demarcation line is missing. It occurs mostly in inferior limbs, in cases of diabetes mellitus (Fig. 3–11), in lungs as a complication of pneumonias, pulmonary abscesses and infarctions, in intestines - in atherosclerosis of mesenteric arteries (Fig. 3–12).

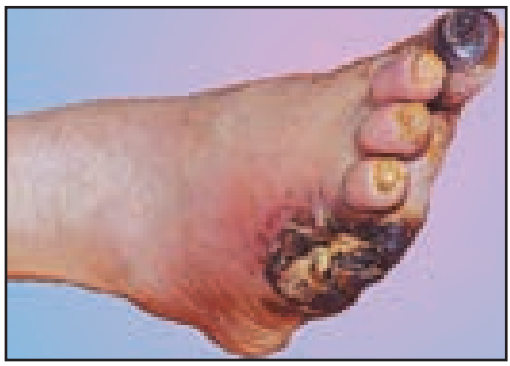


Fig. 3–11. Wet gangrene of the foot.

It develops as a result of the action of saprophytic bacteria of putrefaction (Bacteria fusiformis, putrificans, proteus etc.), which become pathogenic in dead tissues. Initially, a coagulative necrosis develops and a bacterial infection associates on its background. Due to the action of bacterial proteolytic enzymes, the autolysis and liquefaction of necrosed tissues occur. Clinically, a severe toxemia happens, caused by the absorption of toxic products from deteriorated tissues. Wet gangrene is encouraged by the venous stasis.

Fig. 3–12. Gangrene of small intestine.

A rare variant of wet gangrene is *noma* or gangrenous stomatitis, which starts at the gum line of the mandible and spreads progressively over the soft tissues of the face, predominantly over lips and cheeks. It is observed in children with severe infections, nutrition disturbances and avitaminoses. It is caused by the putrefaction bacteria.

Anaerobic or gas gangrene develops at contamination of affected tissues by bacteria from the anaerobic group of microorganisms (*Clostridium perfringens, oedematiens, histolyticum, septicum* etc.). The gangrenated zone gets an emphysematous aspect, it crepitates on palpation due to the infiltration with gas bubbles and it has a greenish–grey color and a fetid smell. The process extends extremely fast in neighboring tissues along muscles, connective tissues, vessels and other tissues with their necrosis. The respective microorganisms produce exotoxins, which determine a severe intoxication, favouring the spreading of necrotic process. It constitutes a complication of open extended wounds, produced in war circumstances, road or work accidents, with massive destruction of muscular and bone tissues. It is considered an independent infectious disease (*primary gangrene*).

Decubitus or eschar is a variant of gangrene. It has foci of necrosis in soft superficial tissues of bluish–black color, the skin often being ulcerated. It appears in severe cachectic patients, with circulatory and neurological disturbances, especially in areas exposed to local and prolonged mechanical compressions, especially above bony prominences, for example, in sacral, trochanteric, scapular, calcaneal regions etc. It can often be noticed in patients with malignant tumors, severe infectious diseases, chronic cardiac insufficiency, cerebrovascular diseases, etc., patients who remain confined to bed for a long time and in the same position. The irregularities of the bed, the folds of underwear and bed clothes etc. may be the predisposing factors. It is a necrosis of neurotrophic origin.

Infarction is a necrosis of parenchymatous organs, caused by arterial or venous circulation impairment (vascular, ischemic, angiogenic necrosis). It occurs in myocardium, lungs, brain, spleen, (Fig. 3–7 – 3–9), kidneys and rarely in liver, intestine. It develops as a result of thrombosis, embolism, prolonged spasm of arteries or functional overstrain of the organ in conditions of insufficient blood flow. It is the most frequent form of necrosis, observed in atherosclerosis of arteries, arterial hypertension, arteritides, thrombotic endocarditis etc.

Caseous necrosis is most frequently observed in tuberculosis, but also in syphilis, Hodgkin disease, leprosy, in some mycotic granulomas. It is a variant of coagulative necrosis. The necrotic masses have a dense consistency, a yellowish–white color; they are friable, reminding macroscopically the dry cheese ("cheese like" aspect, Fig. 3–13). Histologically, the necrotic area is amorphous, microgranular, astructurated, eosinophilic stained (Fig. 3–14). A complete loss of architectonics of tissue is characteristic, the cellular and tissular structures disappearing completely.

Fig. 3–13. Caseous necrosis of pulmonary tissue.

Steatonecrosis (fat necrosis) – necrosis of the adipose tissue. It is a form of enzymatic necrosis caused by the action of lipase and trypsin, released from pancreatic acinar cells in case of acute pancreatitis (pancreonecrosis). The lipase

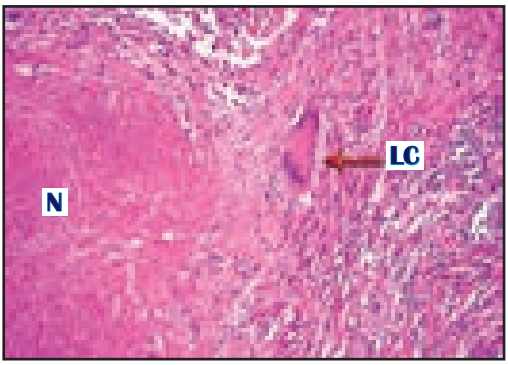


Fig. 3–14. Caseous necrosis of lymph node in tuberculosis (hematoxylin–eosin stain; ×110): N – necrotic focus; LC – giant polynucleated Langhans cell.

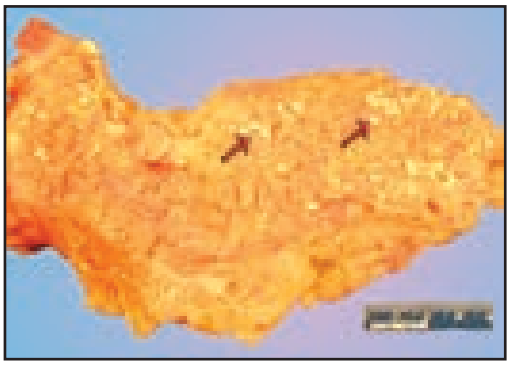


Fig. 3–15 a. Steatonecrosis in acute pancreatitis – macroscopic aspect.

penetrates adipocytes, induces their necrosis and transforms the lipids in soaps (calcium salts of the fatty acids), which give the necrotic foci an aspect of stearin spots of yellowish–white color, dense consistency and a clear outline. In acute pancreatitis, steatonecrotic foci are noticed in pancreas, peripancreatic tissue, omentum, epiploon and in the adipose tissue from other areas (Fig. 3–15 a). Microscopically, the adipocytes become unclear, with blurred outlines, basophilic colored (in blue), as a result of an increased content of calcium salts (Fig. 3–15 b). It is also observed in traumatisms of adipose tissues, for example, of mammary gland.

In **waxy necrosis** (*described by Zenker*), the necrotic masses have a dense consistency (coagulation necrosis), a macroscopic yellowish–white aspect, similar with the bees-wax. It is observed in striated muscles, in some severe acute infectious diseases (*typhoid fever, exanthematous typhus*), muscular traumatisms, electric shock. Optical microscopy shows that striated myocytes have a homogenous, astructured aspect; the transversal striation is missing (Fig. 3–5).

In **fibrinoid necrosis**, the connective tissue is destructed (the ground substance and collagenic fibers). Arteries of small caliber and stroma of organs are affected more often. The necrotic masses are infiltrated with plasmatic proteins, where the fibrin prevails (hence the name of *fibrinoid* necrosis); microscopically, they have a homogenous, eosinophilic aspect (Fig. 3–16).

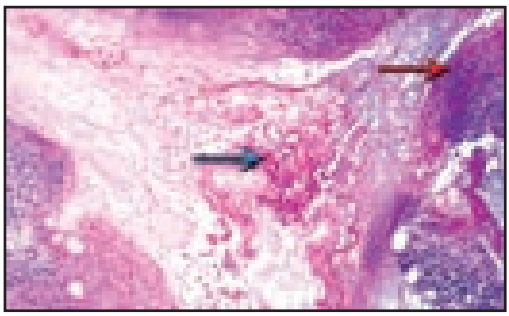


Fig. 3–15 b. Steatonecrosis in acute pancreatitis - microscopic pattern (hematoxylin–eosin stain; ×70).

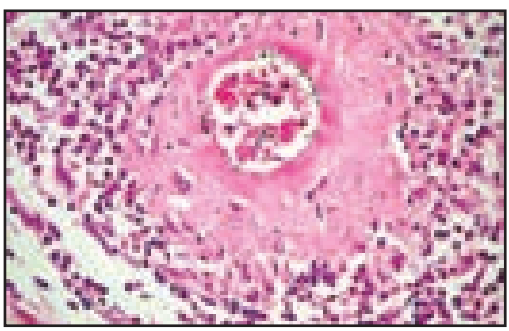


Fig. 3–16. Fibrinoid necrosis of vascular wall in polyarteritis (periarteritis) nodosa (hematoxylin–eosin stain; ×110).

It is usually seen in arterioles, small caliber arteries and glomerular capillaries in autoimmune diseases (for example, in systemic lupus erythematosus, glomerulonephritis) and in malignant arterial hypertension. The fibrinoid necrosis of arterioles and small arteries is characteristic in hypertensive crises (emergencies).

Sequestrum is a portion of dead tissue, detached completely from viable surrounding tissues and situated freely in a sequestrial cavity (Fig. 3–17). It appears when the necrosed tissue is not exposed to autolysis, organization or encapsulation. It often occurs in bones, multiple fractures with small pieces, in tuberculosis, sepsis. Sometimes, external fistulas are formed – canals in soft tissues with orifice at the skin level, through which the pus is let out periodically from sequestrial cavity and fragments of necrosed bone tissue can be eliminated. The sequestration of Peyer's patches in typhoid fever, of pulmonary infarction, eschars can occur, etc.

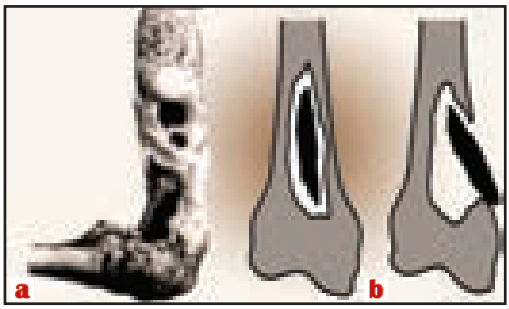


Fig. 3–17. Chronic purulent osteomyelitis with formation of sequestra; a – macroscopic aspect; b – schematic presentation.

3.1.2. EFFECTS AND CONSEQUENCES OF NECROSIS

The effects and consequences of necrosis depend on the extension of the necrotic process and functional importance of the affected tissues. For instance, the necrosis of convoluted tubes of kidneys leads to acute renal failure, massive necrosis of the liver – to hepatic failure (coma), necrosis of cerebral tissue – to paralyses, necrosis of myocardium – to impairment of the heart functions etc. Small size necrosis in the spleen, kidneys and lymph nodes may have minimum effects, without major functional disturbances. During necrotic processes in different tissues and organs, there is a release of enzymes from necrotized cells, which results in enzymemia – growth of the level of some enzymes in the blood. This phenomenon constitutes the basis for clinical diagnostic tests of necrosis of different internal organs. For example, in myocardial infarction, the level of creatine-phosphokinase (myocardial form – CK–MB) in the blood increases, in hepatic necrosis – the level of alanine-aminotransferase (ALAT), in necrosis of exocrine pancreas – the level of amylase.

The direct consequences of necrosis depend on the potential of regeneration and the preexisting state of the deteriorated tissues. Among the consequences of necrosis we distinguish:

1. **Complete restoration** of the preexistent tissue through regeneration (restitution). It is observed in organs/tissues with the cellular form of regeneration, for example, in the liver, kidneys, mucosas.
2. **Organization** (***cicatrization***) – substitution of necrotic focus with connective tissue, for example, in myocardium, the necrotic debris is resorpted by phagocytes, and a connective tissue scar (substitution) appears in the area of necrosis (Fig. 3–18 a, b).
3. **Encapsulation** – formation of a membrane (capsule) of connective tissue around the necrotic focus; it can be observed most frequently

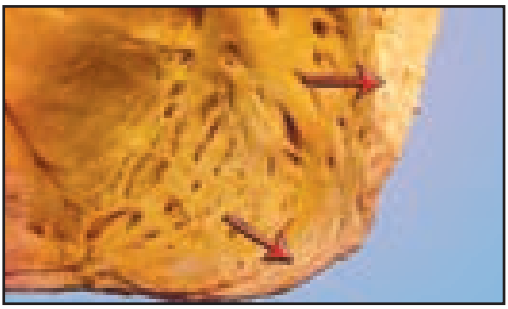


Fig. 3–18 a. Organization of myocardial infarction (macrofocal postinfarction cardiosclerosis) – macroscopic aspect.

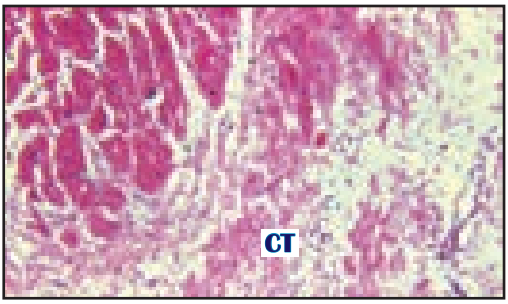


Fig. 3–18 b. Organization of myocardial infarction (macrofocal postinfarction cardiosclerosis) – microscopic pattern: CT – cicatricial connective tissue (hematoxylin–eosin stain; ×110).

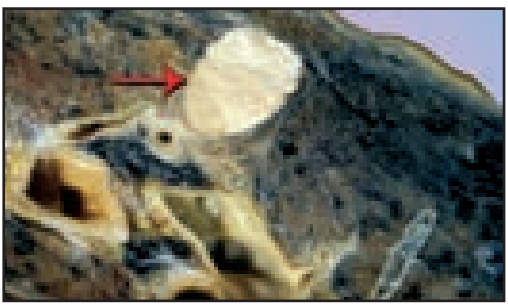


Fig. 3–19. Encapsulated petrification in pulmonary tissue.

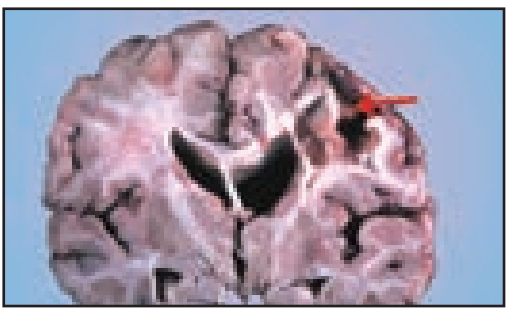


Fig. 3–20. Postnecrotic cerebral cyst.

in foci of caseous necrosis in tuberculosis (Fig. 3–19).

4. **Calcification (*petrification*)** – deposits of insoluble calcium salts in necrotic masses (dystrophic calcification). It is characteristic for caseous necrosis in tuberculosis (Fig. 3–19), waxy necrosis of striated muscles etc.
5. **Ossification** – substitution of necrotic focus with newly- formed bone tissue.
6. **Formation of cysts** (***cystic transformation***) – appearance of some cavities, as a result of lysis and resorption of mortified tissue in liquefactive necrosis (Fig. 3–20).

It is more frequently observed in the brain and spinal cord. The newly-formed cavities are actually pseudocysts, because they do not have an epithelial lining and their wall is from the cerebral tissue adjacent with necrotic and softening focus.

7. **Sequestration** – complete detachment of the dead tissue from the live one. It is mostly seen in bone tissues (Fig. 3–17).
8. **Autoamputation** – complete detachment from the organism of some limbs or organs, for example, in the dry gangrene of fingers.
9. **Mummification** – drying of dead tissues in gangrene.
10. **Purulent lysis** – disintegration (melting) of necrotic masses, under the action of polymorphonucleated leukocytes, in cases of pyogenic overinfection.

Organization, encapsulation, calcification (petrification), ossification and sequestration occur mostly in dry necrosis. Cysts formation and purulent lysis are usually observed in wet necrosis. Autoamputation and mummification may occur in dry gangrene.

3.2. APOPTOSIS

The apoptosis is a specific, morphologically distinct form of cellular death, which differs from the usual coagulative necrosis. It is a programmed genetic process, controlled and energetically dependent, responsible for the inactivation and elimination of over numerical, nonfunctional or deteriorated cells. Apoptosis provides a permanent renewal of tissues and the maintenance of structural homeostasis in the human body. The elimination of cells through apoptosis constitutes the main mechanism of cellular death, both in physiological conditions and in various pathological processes.

Examples of physiological apoptosis:

- ✧ elimination of excess cells during embryonic development of organs and tissues. An eloquent example is the disappearance of interdigital folds from the membranes of the embryo, which is occurred through apoptosis, and the disorder of this process causes syndactylia (a congenital defect consisting in fusing the fingers and toes together);
- ✧ elimination of cells in the involution of some organs (tissues), for example, in physiological involution of the thymus;
- ✧ elimination of cells from hormone-dependent tissues, such as the endometrium (changes of uterine lining in menstrual cycle), the mammary gland (involution of epithelium after cessation of lactation), the prostate (atrophy of prostate in case of decrease or abolition of testosterone secretion) etc.
- ✧ clonal selection of lymphocytes in the process of formation of immunological tolerance, for example, deletion of autoreactive T-lymphocytes in thymus (which can react with their own tissues);
- ✧ elimination of cells in the tissues that have a rapid cellular turnover, for example, in intestinal epithelium.

Examples of pathological apoptosis:

- ✧ elimination of the cells with defects at DNA level, caused by viral infection, ionizing or ultraviolet radiations, cytotoxic agents (drugs) etc;
- ✧ destruction of virus-infected cells by cytotoxic T-lymphocytes, for example, in viral hepatitis, the cytotoxic T-lymphocytes have the ability to interact directly with the cytoplasmic membrane of the target cells, releasing substances which induce the apoptosis in the virus-infected cells;
- ✧ death of T-helper cells (CD4) infected with the human immunodeficiency virus (HIV infection);
- ✧ elimination of neoplastic cells; the balance between apoptosis and cellular proliferation is disturbed in tumors;
- ✧ death of nerve cells in neurodegenerative diseases (Alzheimer disease, amyotrophic lateral sclerosis, Parkinson disease).

Apoptosis is initiated by an intracellular signaling complex and a range of enzymatic processes. The main role belongs to the caspases – a group of proteolytic cysteinic enzymes, which act in cascade (for example, the complement). They are present in cells in an inactive form and are activated by apoptotic stimuli. Some caspases activate, in their turn, other caspases, which alter the components of the cytoskeleton, as well as the endonucleases that disintegrate the nuclear DNA, and phospholipases which change the configuration of the cellular membrane. Usually, apoptosis appears

in individual, solitary cells (*the so-called "cellular suicide"*). Initially, there is a disorganization of superficial structures in the cell in apoptosis - the loss of microvilli and intercellular junctions; the cell gets a spherical shape, it detaches from the neighbor cells and isolates. Later, the cell shrinks, diminishes in size, the nucleus shrivels. Chromatin condenses forming aggregates that stay in the marginal zone of nucleus, along the membrane. Cytoplasmic organelles condense, but remain intact from the structural point of view. Concurrently, the cells form exvaginations of cytoplasmic membrane because of cytoskeleton alteration, which, later, break away from the cell body (*hence the name of apoptosis – in Greek "the falling of leaves from the trees"*). The splitting of the cell occurs in more fragments – apoptotic bodies that contain cytoplasm, organelles, pieces of nucleus and are covered by cytoplasmic membrane (Fig. 3–21).

Apoptotic bodies penetrate the extracellular space. In histological sections, they have an aspect of oval or round formations with an intensely eosinophilic cytoplasm, containing fragments of nuclear chromatin, mitochondria and other intact cytoplasmic organelles (Fig. 3–22).

In the final phase, apoptotic bodies become recognized, phagocyted and digested by both macrophage and parenchymatous neighboring cells. Apoptotic bodies can be eliminated via secretions, lymph or blood. The rapid clearance of apoptotic remains (in several hours) prevents the inflammatory response, because there is no draining of cytoplasmic content in the extracellular space. The absence of inflammatory reaction is an essential feature of apoptosis, due to which the death of one cell does not affect the neighbor cells, the tissular and cellular architectonics of adjacent tissue remaining intact.

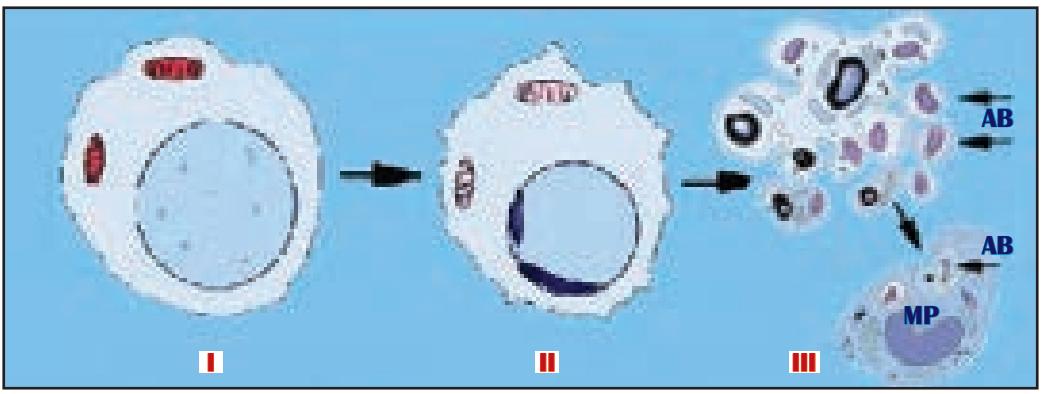


Fig. 3–21. Schematic presentation of apoptosis: I – normal cell; II – shriveling of the cell and the chromatin disposition under nuclear membrane; III – phagocytosis of apoptotic bodies; AB – apoptotic bodies; MP – macrophage.

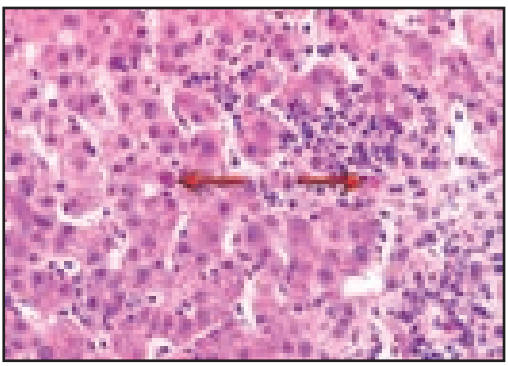


Fig. 3–22. Apoptosis of hepatocytes in acute viral hepatitis (hematoxylin–eosin stain; ×110).

Apoptosis can be stimulated or inhibited by certain pro- or antiapoptotic factors, for example: the protein Bcl–2 (B–*cell lymphoma*) inhibits apopto-

sis, prevents the death of the lymphoma lymphocytes, transforming them into "immortal" cells; the protein p53 is an inductor of apoptosis: it regulates the DNA replication, proliferation and death of cells. It is considered that exactly this protein can prevent the spreading of genetically altered cells in tissues. The absence or mutation of p53 protein was revealed in colon, pulmonary and mammary cancer and in other malignant tumors.

The accumulation of cells through suppression of apoptosis may contribute to the appearance and evolution of neoplasms, to persistence of viral infections, and excessive death through apoptosis may result in different degenerative diseases. The main criteria of differentiation between apoptosis and necrosis are exposed in table 3.1.

The main difference between necrosis and apoptosis consists in the fact that necrosis is always a pathological process, while apoptosis occurs in normal, physiological conditions and does not obligatory associate with necrosis. But still, in some pathological processes, both forms of cellular death can be involved. For example, in the central zone of myocardial infarction, the processes of necrosis prevail, while the apoptosis prevails in the peripheral zone, where the intensity of hypoxia is lower.

Another form of genetically-programmed cellular death is **autophagia** (autodigestion). In the process of autophagia occurs the lysosomal autodigestion of the own components of the cell. Initially, the sequestration of some intracellular organelles and portions of cytosol with formation of autophagic vacuoles, delimited by the membrane of the rough endoplasmic reticulum is produced. Later, the vacuoles fuse with lysosomes, forming autophago-lysosomes, in which cellular components are digested by lysosomal enzymes. The undigested remains are eliminated through exocytosis, and a part of them remains

Table 3.1

APOPTOSIS versus NECROSIS

Criteria of differentiation	*NECROSIS*	*APOPTOSIS*
Induction	It is caused only by harmful factors.	It may be caused by different physiological and pathological factors.
Extension	Groups of cells	Solitary, individual cells
Biochemical aspects	The lysosomes release lytic enzymes	Nuclear DNA fragmentation. The lysosomes are intact.
Morphological pattern	Tumefaction and lysis of the cell, cytoplasmic membrane is altered	Condensation of chromatin and fragmentation of nucleus, formation of apoptotic bodies. Cytoplasmic membrane is intact.
Inflammatory reaction	Present	Absent
Consequences	Phagocytosis of dead cells by neutrophils and macrophages.	Phagocytosis of apoptotic bodies by parenchymatous neighboring cells ("non–professional" phagocytes) or by macrophages.

in cytoplasm, like residual corpuscles. The process of autophagia is regulated by a complex of cellular proteases named ubiquitins. Thus, an elimination of supernumerary, aged, degraded and altered organelles occurs. Autophagia is also involved in the maintenance of cellular homeostasis in conditions of insufficiency of nutritive substances. Autodigestion of own components in such conditions provides the cells with metabolic and energetic substrates, which ensure their survival in certain pathological conditions. Autophagia can be induced by hypoxia, hormones and intracellular stress, and is involved in some neurodegenerative diseases, myopathies, and tumoral processes. Currently, the autophagic death is considered the second type of programmed cellular death (after apoptosis). Autophagia and apoptosis can be independent or may coexist.

ESSENTIAL TERMS

on the subject "IRREVERSIBLE CELLULAR LESIONS. NECROSIS AND APOPTOSIS"

agony	dehydration	myomalacia
apoptosis	demarcation inflammation	necrobiosis
apoptotic body	direct necrosis	necrosis
autolysis	encapsulation	noma
autophagia	encephalomalacia	organization
calcification (calcinosis)	eschar	ossification
caseous necrosis	fibrinoid necrosis	petrification
coagulative necrosis	gangrene	plasmolysis
colliquative necrosis	indirect necrosis	plasmorrhexis
Councilman corpuscle	infarction	purulent lysis
cyst	karyolysis	sequestrum
cytolysis	karyopiknosis	steatonecrosis
debris (cellular, tissular)	karyorrhexis	waxy necrosis (Zenker)
decubitus	mummification	

TESTS

on the subject "IRREVERSIBLE CELLULAR LESIONS. NECROSIS AND APOPTOSIS"

SET I.

Multiple-choice questions with only one correct answer.

1. *Which of the changes of the nucleus characterize the karyopyknosis:*
   a) dilatation of endoplasmic reticulum cisternae;
   b) margination of chromatin;
   c) destruction of mitochondria;
   d) condensation of chromatin;
   e) size-increasing of nucleoli.

2. *What is the correct definition of gangrene:*
   a) vascular necrosis;
   b) dry necrosis;
   c) toxic necrosis;
   d) necrosis of tissues in contact with the external environment;
   e) allergic necrosis.

3) Which of the listed diseases develop more frequently in wet gangrene:
   a) atherosclerosis;

b) diabetes mellitus;
c) hepatic cirrhosis;
d) myocardial infarction;
e) arterial hypertension.

4) Which of the listed causes induce the development of infarction:
a) autoimmune conflict;
b) damage of peripheral nerves;
c) action of some bacterial toxins;
d) traumatisms;
e) reduction of arterial blood supply.

5) Which etiological variant of necrosis occurs in eschars:
a) vascular;
b) trophoneurotic;
c) traumatic ;
d) toxic;
e) liquefactive.

SET II.

Multiple-choice questions with 2, 3 or more correct answers.

1. Indicate the microscopic changes of the cells cytoplasm in necrosis:
a) coagulation;
b) karyorrhexis;
c) plasmorrhexis;
d) plasmolysis;
e) karyopyknosis.

2. Characteristic signs of dry gangrene:
a) dense consistency of mortified tissues;
b) dehydration of tissues;
c) flaccid consistency of tissues;
d) whitish color of tissues;
e) black color of tissues.

3. Which consequences of necrosis occur more frequently:
a) organization;
b) encapsulation;
c) autoamputation;
d) calcification;
e) formation of a cystic cavity.

4. The infarction can develop in which of the listed organs:
a) uterus;
b) brain;
c) kidneys;
d) vermicular appendix;
e) liver.

5. Caseous necrosis occurs more frequently in which diseases:
a) lobar pneumonia;
b) gastric ulcer;
c) Hodgkin disease;
d) tuberculosis;
e) appendicitis.

SET III.

Classification tests include 2–4 subjects and a series of answers. Indicate the correct answers for each subject separately.

1) Which of the listed signs characterize:
I – necrosis;
II – apoptosis;
a) absence of the inflammatory reaction;
b) intact cytoplasmic organelles;
c) destruction of cytoplasmic organelles and cellular membrane;
d) disappearance of cellular nucleus;
e) phagocytosis of cellular fragments by adjacent cells;
f) phagocytosis of cellular debris by emigrated blood leukocytes;
g) disintegration of the cell in fragments with intracellular organelles and debris of nuclei, delimited by the membrane;
h) appearance of perifocal inflammatory reaction.

2) In which organs and tissues occurs more often :
I – coagulative necrosis;

II – colliquative necrosis;
a) limbs;
b) myocardium;
c) spleen;
d) brain;
e) liver;
f) kidneys;
g) spinal cord.

3) Indicate which disease is characteristic for:
I – caseous necrosis;
II – fibrinoid necrosis;
a) leprosy;
b) tuberculosis;
c) rheumatism;
d) arterial hypertension;
e) Hodgkin disease;
f) syphilis.

4) Indicate the correct definition:
I – of infarction;
II – of gangrene;
III – of sequestrum;
IV – of coagulative necrosis;
V – of colliquative necrosis;
VI – of allergic necrosis;
a) necrosis in which processes of liquefaction and autolysis of dead tissues prevail;
b) tissues necrosis caused by circulatory disturbances;
c) necrosis caused by an immune conflict;
d) necrosis in which processes of denaturation and dehydration of tissues prevail;
e) necrosis of tissues contacting with atmospheric air;
f) necrosis in which mortified tissues cannot be phagocyted.

5) In which of the organs listed below may develop more frequently:
I – the gangrene;
II –the infarction.
a) myocardium;
b) lungs;
c) intestine;
d) limbs;
e) uterus;
f) vermicular appendix;
g) gallbladder;
h) kidneys;
i) brain;
j) palatine tonsils.

SET IV. SITUATIONAL PROBLEMS

Daily practice cases are presented with clinical and morphological data from clinical histories and/or from necropsy protocols. Each subject includes simple or multiple – answer questions, with 1, 2 or more correct answers.

1. *The microscopic examination of the renal biopsy sampled from a patient suffering of tuberculosis revealed foci of caseous necrosis with chromatin granules at periphery.*

Question:

At what stage of cellular nucleus lesions in necrosis do such changes appear:
a) karyopyknosis;
b) karyorrhexis;
c) karyolysis;
d) karyokinesis;
e) marginal hyperchromatosis of nucleus.

2. *The microscopic examination revealed rheumatic granulomatous myocarditis in a 38 year-old patient, who died of chronic and progressive cardiac insufficiency. Granulomas from macrophages with a necrotic focus in the center were revealed in myocardium stroma.*

Question:

Which necrosis variant occurs in the center of rheumatic granuloma:
a) fibrinoid;
b) steatonecrosis;

c) caseous;
d) Zenker;
e) coagulative.

3. *A 75 year-old patient was taken urgently to the hospital with symptoms of acute abdomen. During laparotomy operation, the surgeon established that about 80 cm of the small intestine had a black color, the peritoneum was opaque and in hyperemia, and the lumen of the superior mesenteric artery was obstructed by thrombotic masses.*

Question:

Which clinical and morphological variant of necrosis occurred in the intestine in this case:

a) eschar;
b) white infarction;
c) coagulative necrosis;
d) gangrene;
e) white infarction with hemorrhagic border.

3. *Areas of black color and edema appeared in the sacral, scapular, calcaneal regions of an elderly patient with a femoral neck fracture, who has been confined to bed for a long time. The epidermis was desquamated in some places and ulcerations were formed.*

Question:

Which pathological process of the listed below occurs in this case:

a) apoptosis;
b) dry gangrene;
c) infarction;
d) eschars;
e) wet gangrene.

5. *A chronic osteomyelitis with fistulae, through the orifices of which necrosed bone fragments are released, developed in a patient with an open comminuted fracture (with more segments) of the leg bones.*

Question:

Which of the listed necrosis variants occurs in this case:

a) sequestrum;
b) gangrene;
c) infarction;
d) waxy necrosis;
e) caseous necrosis.

DISTURBANCES OF BLOOD AND LYMPHATIC CIRCULATION

4.1. HYPEREMIA

Hyperemia is the increasing of blood volume in an organ or tissue. It can be arterial and venous, generalized and local.

4.1.1. ARTERIAL HYPEREMIA

Arterial hyperemia consists in increasing of blood mass in an organ or tissue, as a result of increased blood flow in arteries. Macroscopically, it manifests itself by a red color of teguments and increasing of local temperature, and, microscopically, by active dilatation of arterioles.

It may have a *general* character, when the volumes of the circulating blood or the number of erythrocytes are increased, and it may be *local.* Local arterial hyperemia is more frequent and it may be observed both in physiological and pathological conditions. Examples of physiological hyperemia may be: hyperemia of teguments in different emotional conditions, hyperemia of gastric and intestinal mucosa during digestion, hyperemia of muscles during a physical effort, hyperemia of skin under the action of the sun rays etc.

Arterial pathological hyperemia can be: a) angioneurotic; b) collateral; c) postanemic; d) hyperemia *ex vacuo* and e) inflammatory.

Angioneurotic hyperemia appears as a result of some innervation disorders with exitation of vasodilator nerves or paralysis of the vasoconstrictor nerves. It may occur in some infectious diseases, like scarlet fever, typhoid fever, measles.

Collateral hyperemia appears in case of occlusion of the magistral vessel with a thrombus or embolus, when dilatation and hyperemia of collateral arteries occur. This reaction can compensate partially or totally the ischemia caused by the occlusion of the magistral artery.

Postanemic hyperemia is noticed in cases when a vessel has been compressed by a tumor, ligature, adherences, a collection of fluid etc. and, at a sudden removal of the respective factor, a rapid hyperemia of the previously ischemized area occurs, which may result in rupture of vessels, hemorrhages. Besides these, there may appear debilitation of other organs, like the brain, as a result of sudden redistribution of blood.

Hyperemia ex vacuo appears as a result of decrease of barometric pressure and it occurs in divers and caisson workers, at their rapid lifting from high pressure to the normal one; and has a generalized character. Local hyperemia conditioned by an analogical mechanism occurs when applying cupping glasses on the skin.

Inflammatory hyperemia is a manifestation of exudative phenomena in inflammatory processes and constitutes a clinical sign characteristic for inflammation.

4.1.2. VENOUS HYPEREMIA (OF STASIS OR CONGESTIVE)

Venous hyperemia is caused by the diminution of venous blood flow in conditions of normal arterial circulation. It is manifested through passive dilatation of veins and capillaries with an excess of blood in these vessels. It may be generalized and localized, acute or chronic.

4.1.2.1. GENERALIZED VENOUS HYPEREMIA

It is a consequence of acute or chronic cardiac insufficiency, based on the disturbance of the heart contractile activity (heart decompensation).

Acute cardiac insufficiency is observed in myocardial infarction, acute myocarditis, acute endocarditis with valvular ruptures, hypertensive crisis etc. It is manifested by acute generalized venous hyperemia; the dilatation and hyperemia of veins and capillaries appear in organs and tissues, as well as the plasmatic infiltration (plasmorrhagia) and edema, multiple perivascular hemorrhages through diapedesis, dystrophic and necrotic lesions resulting from acute hypoxia and mechanical compression of perivascular parenchymal elements by the dilated vessels.

Chronic cardiac insufficiency is observed in chronic cardiac diseases, such as valvulopathies, cardiosclerosis, severe impairments of the rhythm and conduction, chronic myocarditis, constrictive pericarditis etc. It manifests itself by dilatation and chronic hyperemia of the veins, plasmorrhagia and edema, erythrodiapedesis, hemosiderosis, atrophy and disappearance of parenchymal cells and sclerosis of organs and tissues. These changes are stereotyped and occur both in generalized and localized venous hyperemia. The main pathogenic mechanism of morphological lesions in venous hyperemia is the tissular hypoxia (venous or congestive hypoxia).

The characteristic macroscopic aspects of the organs in chronic congestive hyperemia are the following:

a) the dimensions and the mass are increased;
b) the capsule of organs is smooth, extended (under pressure);
c) the consistency is increased and dense;
d) the color on the section is dark–red–purple – the color of deoxygenated venous blood;
e) when sectioned, the blackish–red blood drains out abundantly from the surface of the section.

Changes of different organs and tissues in chronic venous congestion (stasis) have many common features and are named **cyanotic or stasis induration.** At the same time, certain specific features can be seen in some organs, which are conditioned by their angioarchitectonic particularities, especially in the liver and lungs.

The skin has a cyanotic aspect of bluish–violet color and a low temperature; it is particularly clear seen in the face area (nose, lips) (Fig. 4– 1).

Fig. 4–1. Cyanosis of the face skin and mucosa of lips.

The phenomenon is generated by the deoxygenated venous blood in dilated veins and capillaries. It is a certain symptom of cardiac insufficiency.

The subcutaneous adipose tissue is edematous, tumefied. The lax tissues in the region of lower limbs, external genital organs, eyelids are affected more often and intensely. Generally, the edema is more marked in the lower part of the body. When pressed with a finger, a pitting depression remains and does not disappear for several seconds or minutes (Fig. 4–2).

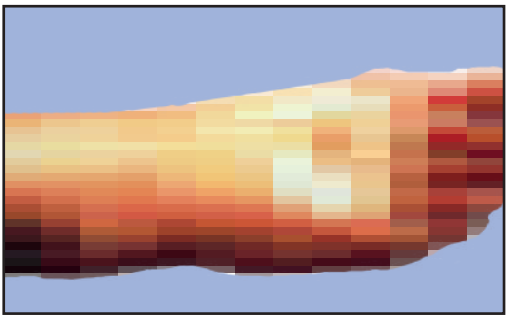


Fig. 4–2. Edema of the lower limb, pitting symptom.

A varicose dilatation of the veins, a skin hemosiderosis, trophic ulcerations may develop, which are hardly healed.

The kidneys and the spleen – cyanotic (stasis) induration. The dimensions and the mass of organs are increased, the surface is smooth, the capsule is extended, under tension, the consistency

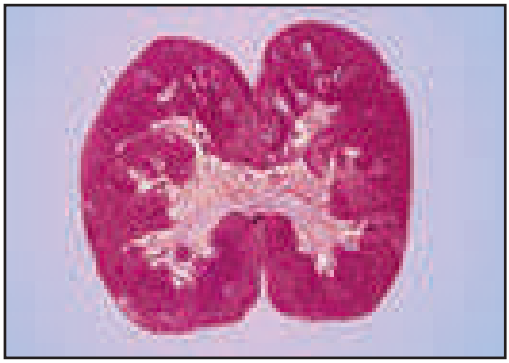


Fig. 4–3. Cyanotic induration of the kidney (stasis kidney).

is increased. The parenchyma has a dark red color on the section and the venous blood drains out abundantly (Fig. 4–3).

Microscopically, one observes the dilatation and hyperemia of glomerular and peritubular capillaries, dystrophic lesions of epithelium of convoluted tubes, excessive proliferation of connective tissue in the stasis kidney. At microscopic examination of the spleen, the red pulp is extensively hyperemic, flooded with blood, the sinuses are dilated, filled with erythrocytes; there can be hemorr-

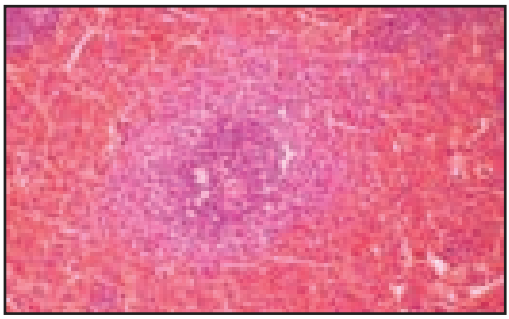


Fig. 4–4. Chronic venous hyperemia of the spleen (hematoxylin-eosin stain; ×70).

hagic foci, the walls are fibrosed and the white pulp is reduced and poorly highlighted (Fig. 4–4).

In the **serous cavities** accumulations

of edema appear – **hydrops** of the respective cavities (hydrothorax, hydropericardium, ascites or hydroperitoneum).

The liver is enlarged in size and mass, it has a smooth extended capsule, dense consistency, the anterior margin is rounded with a very emphasized lobular pattern on section, a characteristic spotted aspect, similar with the American nut kernel or nutmeg (Fig. 4–5 a),

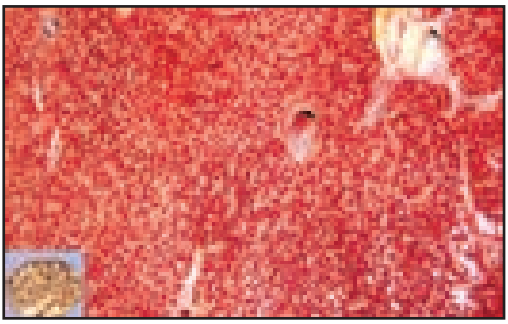


Fig. 4–5 a. Chronic venous hyperemia of the liver (nutmeg liver): macroscopic aspect: below – a nutmeg.

due to alternation of some small, punctiform, dark red foci (centrolobular areas of hepatic lobules) with other foci of a brown–yellow color (peripheral areas of the lobules).

This variegated aspect of the stasis liver is determined by the blood circulation features and angioarchitectonics of the organ. Microscopically, the central veins of the hepatic lobules and adjacent portions of sinusoidal capillaries are dilated, full of blood, and there are diapedetic hemorrhages in the center of the lobules ("blood lakes"), the hepatocytes are atrophied, the central portions of hepatic trabeculae are thin (these pericentrolobular areas have a dark red color under the microscope). There is a fatty dystrophy of hepatocytes in intermediary zones of the lobules (they appear brown–yellow macroscopically), but, in the peripheral areas, the sinusoidal capillaries and hepatocytes are not changed, the trabecular structure is maintained (the color of these areas is brown–red macroscopically - the usual aspect of the hepatic parenchyma) (Fig. 4–5 b).

Selective hyperemia of central areas of the lobules can be explained by the fact that venous stasis covers hepatic and collecting veins firstly, and, at the lobules level – the centrolobular and the neighboring portions of sinusoidal capillaries. However, the stasis does not extend to the periphery of lobules, due to the speed and pressure of blood, which is higher in peripheral areas of the sinusoids where the arterial capillaries penetrate from the hepatic artery system (at the border between the external third and the medium third of the hepatic lobules). Such being the case, the center of the hepatic lobule is hyperemiated, but the periphery is not, and this is what determines the variegated ("nutmeg-like") aspect of the stasis liver. The mechanism of development of nutmeg liver is schematically illustrated in the Fig. 4–6.

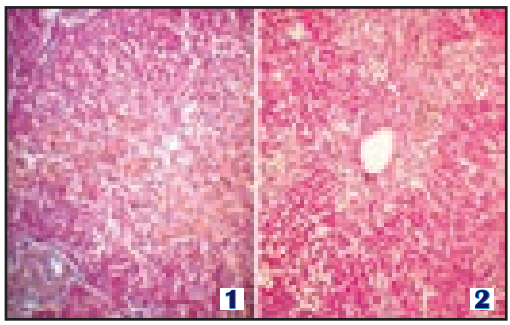


Fig. 4–5 b. Chronic venous hyperemia of the liver (nutmeg liver): microscopic pattern: 1 – initial stage; 2 – advanced stage with atrophy of pericentrolobular hepatocytes (hematoxylin–eosin stain; ×*70*).

The stasis cirrhosis (cardiac) of the liver develops as a result of chronic venous hyperemia. Frequently, it is established in the right cardiac insufficiency (stasis in greater circulation). A similar

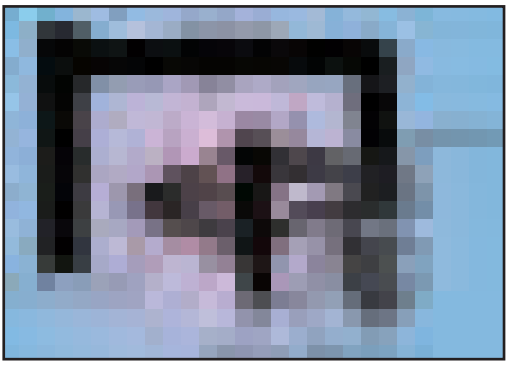


Fig. 4–6. The scheme of blood circulation in hepatic lobule.

pattern can develop in hepatic veins thrombosis (the Budd–Chiari syndrome).

The lungs in chronic venous stasis are enlarged in volume and mass, has a dense consistency, a brown color on the section and the pulmonary porosity of the parenchyma is diminished (Fig. 4–7 a).

The increased consistency of the lungs is a consequence of excessive proliferation of the connective tissue in the alveolar walls; their coloration derives from the accumulation of hemosiderin pigment. The decreased porosity is due to the thickening of alveolar septa, because of hyperemia of vessels and sclerosis. Microscopically (Fig. 4–7 b), the interalveolar septa are thickened, sclerosed, the veins and capillaries are dilated, hyperemiated, with thickened walls. The alveolar spaces contain agglomerations of phagocyte cells (alveolar macrophages), filled with hemosiderin granules (siderоblasts and siderophages); some alveoli contain edema fluid, whole erythrocytes

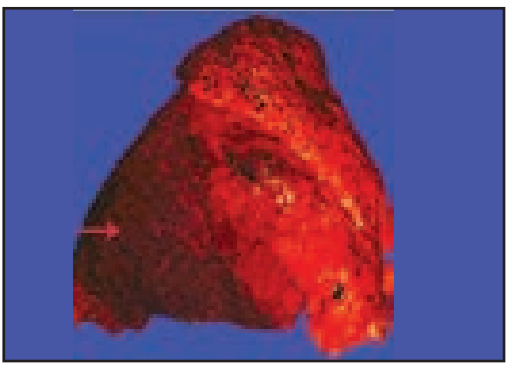


Fig. 4–7 a. Chronic venous hyperemia of the lung (brown induration of the lung): macroscopic aspect.

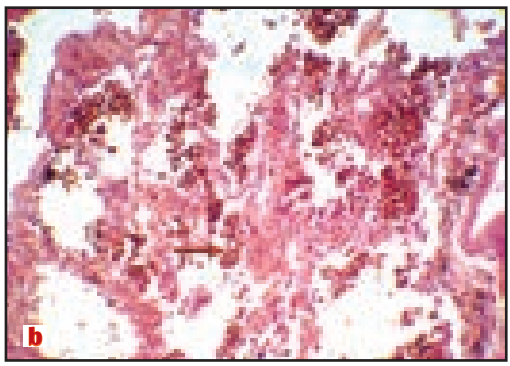


Fig. 4–7 b. Chronic venous hyperemia of the lung (brown induration of the lung): microscopic aspect (hematoxylin–eosin stain; ×70).

or parts of disintegrated erythrocytes. The lesions are more emphasized in lower posterior areas of the lungs.

Stasis hyperemia of the lungs occurs especially in the left cardiac insufficiency, first of all in mitral stenosis (hence the name "cardiac lung"). Macrophages with hemosiderin granules in cytoplasm can be found in the sputum of the patients with cardiac insufficiency and are called "cardiac cells". The presence of hemosiderin pigment gives the sputum rust–colored nuance. Diapedetic hemorrhages, hemosiderosis and proliferation of connective tissue are related with venous tissular hypoxia, which determines the increasing of vascular permeability and of the synthetic activity of fibroblasts of the alveolar septa.

4.1.2.2. LOCALIZED VENOUS HYPEREMIA

Localized venous hyperemia is observed in the case of disorder of venous blood reflux from one organ or part of the body, due to the occlusion of the lumen of the veins by a thrombus or embolus, veins compression from exterior by tumors or adherences etc. *Examples:* a) acute venous hyperemia of the abdominal cavity organs in thrombosis of the portal vein, or chronic in case of portal hypertension in hepatic cirrhosis; b) liver venous hyperemia with development of nutmeg liver as a result of inflammation and thrombosis of hepatic veins in the Budd–Chiari syndrome; c) kidneys venous hyperemia with their stasis induration, in cases of renal veins thrombosis; d) venous stasis of limbs in varicose disease and thrombophlebitis.

4.2. ISCHEMIA

The ischemia is the reduction or suppression of the arterial blood flow in a tissue, organ or a part of an organ. Thrombosis, embolism and angiospasm are the most frequent causes of this phenomenon. Macroscopically, the ischemiated organ is reduced in size, has a low temperature and a pale color. The effects of ischemia depend on many factors, of which the main are:

a) rapidity of occlusion onset (sudden or slow, gradual);
b) degree of obstruction (partial or complete);
c) level of obstruction (major or minor ramifications of arteries);
d) specific features of the causative agent (spasm, thrombus, embolus);
e) the state of collateral circulation;
f) duration of obstruction (ischemia);
g) sensitivity of tissue to insufficiency or lack of oxygen. For instance, the skeletal muscle can recover in 2–3 hours after the ischemia, while the cardiac muscle dies in 20–30 minutes. The organs with high glycolytic capacity may survive the reduction of oxygen quantity and oxidative phosphorylation (ex. the liver), rather than the organs with a reduced potential of anaerobic glycolysis (ex. the brain).
h) the state of tissular metabolism;
i) functional state of the organ at the moment of ischemia onset (a state of effort or pause).

Dystrophic and necrotic lesions appear in acute ischemia, they being related to depriving the tissue of oxygen and nutritive substances and accumulation of some metabolic products. These lesions are preceded by certain histochemical and ultrastructural changes: disappearance of glycogen from the ischemiated tissue, diminution (disappearance) of activity of the oxidoreductive enzymes, tumefaction and destruction of mitochondria. A prolonged obstructive ischemia may induce ischemic necrosis – infarction.

4.2.1. VARIANTS OF ISCHEMIA

1) **Angiospastic** – caused by the spasm of the artery, under the action of various vasoconstrictive factors (in arterial hypertension, atherosclerosis, obliterative endarteritis).

2) **By obturation** – caused by thrombosis, embolism, inflammation of arterial wall, proliferation of connective tissue (in artery atherosclerosis, obliterative endarteritis, productive vasculitis).

3) **By compression** – caused by compression of the artery from exterior, in tumors, accumulations of fluid, ligatures, exostoses.
4) **By blood redistribution** – in cases when there is a penetration of an important amount of blood in an area, which has previously been ischemiated (for example, ischemia of the brain, after a rapid elimination of the ascites fluid from the abdominal cavity, in patients with hepatic cirrhosis).

The infarction is the necrosis of an organ's portion or of a whole organ caused by the cessation of blood irrigation, as a consequence of ischemia (vascular or ischemic necrosis).

4.3. INFARCTION

The direct causes of infarction can be:
a) a prolonged spasm;
b) thrombosis;
c) embolism;
d) functional overstrain of the organ in conditions of its insufficient blood irrigation; an imbalance appears between arterial blood flow and the need of the organ in oxygen.

There are two successive stages in evolution of infarction: ischemic (prenecrotic) and necrotic. In order to diagnose the early ischemic lesions (the ischemic stage of infarction), histochemical, electron microscopic methods are used, as well as luminescence microscopy, for example:

1) Electron microscopy – observes the tumefaction and destruction of mitochondria, reduction and disappearance of glycogen from the sarcoplasm of cardiomyocytes (Fig. 4-8 b); lesions start in 10–20 minutes, developing up to the rupture of mitochondrial membranes in 1–2 hours after ischemia onset.

2) Histochemical methods:
- ✧ histochemical identification of glycogen (PAS-reaction or Best reaction with carmine) – glycogen granules are colored in red (after treated with amylase, the glycogen disappears), the rapid disappearance of glycogen from sarcoplasm of cardiomyocytes is one of the early signs of myocardial ischemia;
- ✧ determination of the activity of oxidoreductive enzymes (succinate dehydrogenase, NAD-diaphorase); the reaction product – granules of formazan are colored in blue–violet; the reaction mechanism consists in reduction of tetrazolium salts under the action

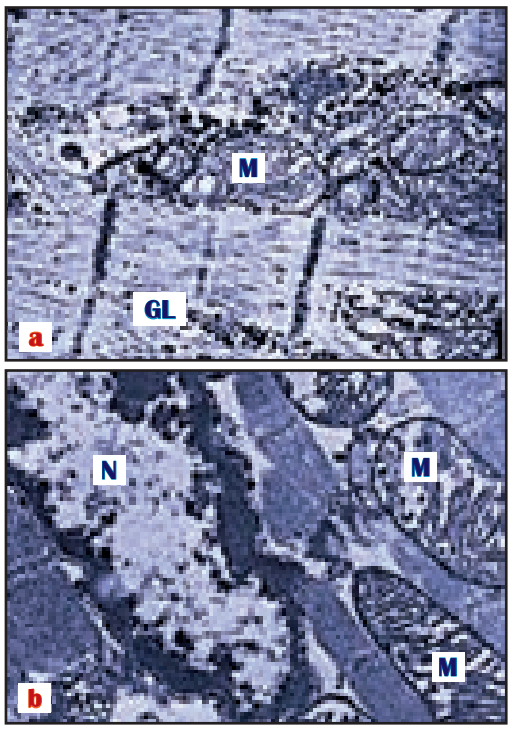


Fig. 4–8 a, b. Ischemia stage of myocardial infarction (electron microscopy; ×10000): a – normal cell; b – ischemiated cell; N – nucleus, M – mitochondria; Gl – glycogen.

of the succinate dehydrogenase. The ischemiated areas register a diminution and disappearance of glycogen from the cells (starting in 5–15 minutes after the onset of ischemia), a decreasing and abolition of oxidoreductive enzymes activity (Fig. 4 – 9).

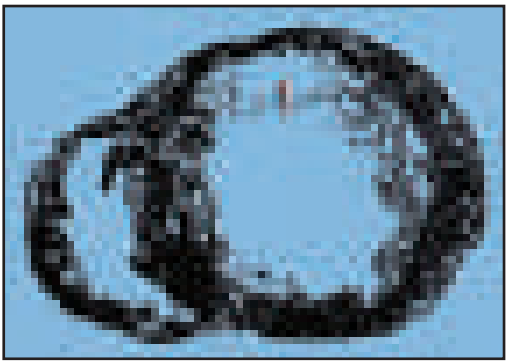


Fig. 4–9. Recent myocardial infarction: a histotopographic reaction with nitroblue tetrazolium for identification of succinate dehydrogenase, diminution (disappearance) of enzymatic activity in the ischemic area.

The reaction to SDH–ase and other oxydoreductive enzymes disappear in 12 hours from the onset of ischemia.

3) Luminescent microscopy:

✧ staining of specimens with acridine orange – ischemic areas have a luminescence of yellow–greenish color, more intense than the intact tissue (Fig. 4 – 10).

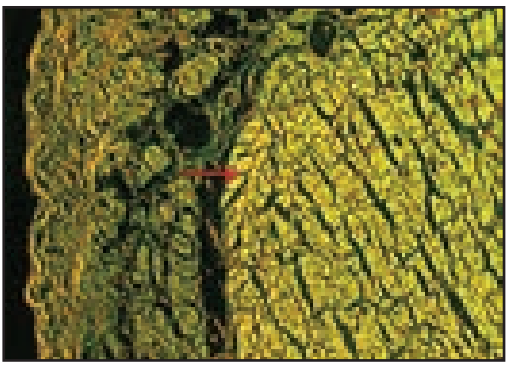


Fig. 4–10. Ischemic stage of myocardial infarction, luminescent microscopy with acridine orange staining; ×70).

Photochemical fluorochroming (treatment of samples with short wave UV rays); the luminescent intensity of ischemic foci is greater comparatively with intact areas. The changes of sarcoplasm fluorescence of cardiomyocytes are due to physicochemical disturbances of myofibrillar proteins, first of all of the myosin in conditions of ischemia. These changes determine a more intense fixation of acridine orange by the myosin and the increase of luminescence intensity of the ischemic cells.

The length of ischemic stage of infarction is approximately 18–24 hours. The necrotic stage develops after this interval, characterized by autolysis of mortified tissue and all macro- and microscopical signs of necrosis, the area of infarction becoming visible macroscopically (Fig. 4– 11 a, 4–11 b).

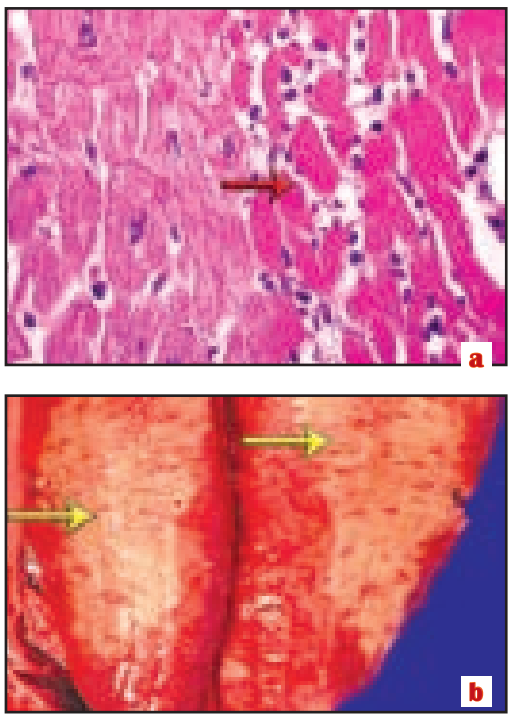


Fig. 4–11 a, b. Myocardial infarction, necrotic stage; a) microscopic pattern; karyolysis of cardiomyocytes (hematoxylin–eosin stain; ×110); b) macroscopic aspect.

According to exterior aspect (color) and mechanism of formation, there are 3 variants of infarction:

- ✧ white (ischemic);
- ✧ red (hemorrhagic);
- ✧ white with a red border (ischemic with hemorrhagic belt).

White infarction (ischemic) occurs in cases of collateral circulation insufficiency. It happens most frequently in the spleen.

Red infarction (hemorrhagic) is registered in cases of double vascularization of the organ and venous stasis; it happens in the lungs, intestine.

White infarction with red border (ischemic with hemorrhagic belt) is related to the spasm of the vessels from peripheral area of infarction, followed by their dilatation, hyperemia and diapedetic hemorrhages; it happens in myocardium, kidneys.

According to geometric shape, infarctions can have a **triangular** (conical) shape – in the organs with a magistral type of vascularization (in the spleen, lungs, kidneys), and an **irregular** shape - in cases of a rich anastomotic circulation of the organ (in myocardium, brain, intestine).

According to necrosis type, infarctions may belong to the dry (coagulative) type of necrosis – in myocardium, spleen, kidneys and to the liquefactive (colliquative) type of necrosis – in the brain, intestine.

4.3.1. MORPHOLOGIC CHARACTERISTICS OF INFARCTIONS OF DIFFERENT ORGANS

Lienal infarction. The infarction area is well delimited, of a triangular (conical) shape, with the tip of it pointed towards the hilum of the organ and the base - towards the capsule. It has a white color and a dense consistency, because it is a coagulative necrosis. (Fig. 4–12).

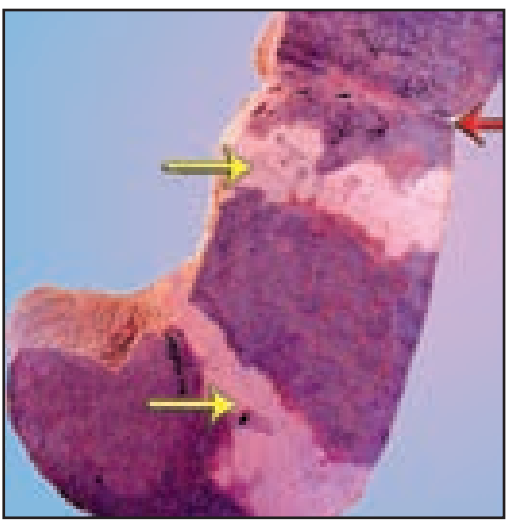


Fig. 4–12. White infarction (ischemic) of the spleen and post infarction scar.

In those areas in which the infarction extends up to the surface of the spleen, the capsule is rugged, covered with deposits of fibrin (reactive fibrinous perisplenitis), causing pains in the left hypochondrium. The most frequent cause of the splenic infarction is the lienal artery thrombosis or embolism. It occurs also in verrucous rheumatismal endocarditis, infective endocarditis, leukemias, ischemic cardiopathy, arterial hypertension etc. The conical shape and white color are determined by the magistral type of vascularisation of the spleen and by the poor collateral circulation, which excludes the possibility of blood penetration in infarction area through collaterals. There is an infiltration with polymorphonucleated leukocytes at the periphery of infarction, as a manifestation of demarcation inflammation delimiting the necrosed area. It is determined by the harmful action of toxic substances released from necrotic masses.

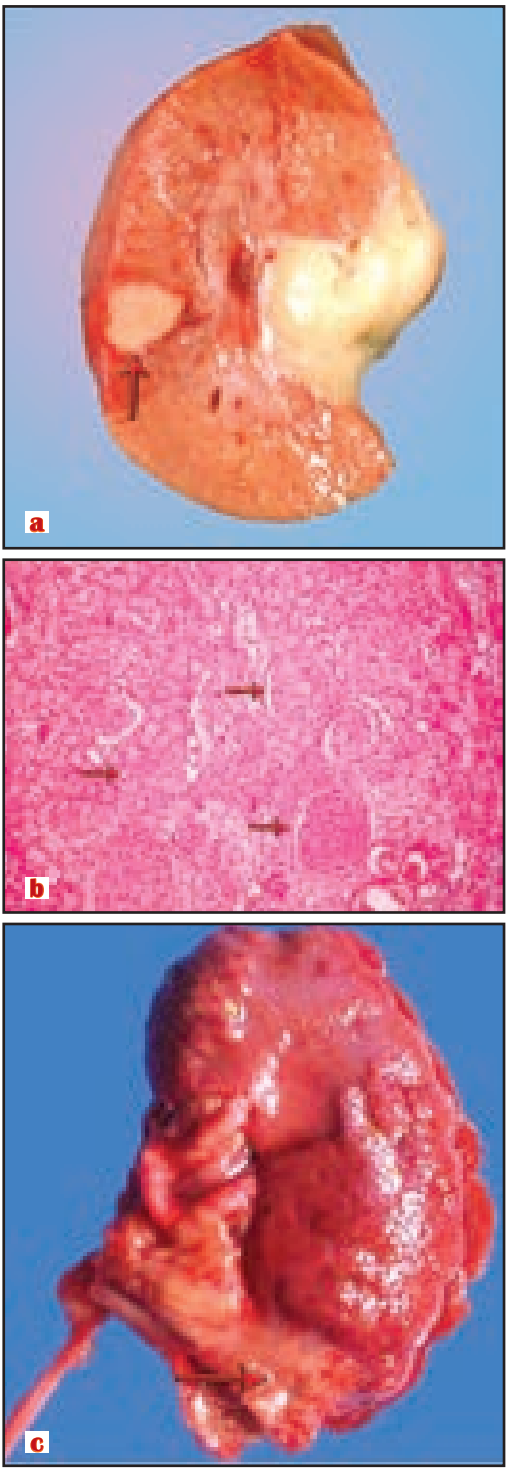


Fig. 4–13 a, b, c. Renal infarction: a – macroscopic aspect; b – microscopic pattern (karyolysis of all the cellular elements) (hematoxylin–eosin stain; ×110); c – post infarction scar.

Usually, the spleen infarction has a benign evolution, but in some cases a rupture of the spleen may happen, with hemorrhage in abdominal cavity, abscess, and total necrosis of the organ. The most frequent consequence is organization and cicatrization of infarction and deformation of the spleen. Perifocal inflammation of the capsule often leads to the appearance of adherences between the spleen capsule and diaphragm, parietal peritoneum, intestinal loops.

The red infarction with massive hemorrhages in the necrosed tissue develops less frequently in the spleen. It occurs in thrombosis or compression of lienal artery on background of venous stasis of the spleen (venous hemorrhagic infarction).

Renal infarction. A well delimited, extended area of triangular shape is observed in kidneys, with the tip oriented to the renal pelvis and the base - to the capsule, of white–yellowish color, surrounded by red belt (white infarction with hemorrhagic belt), an increased consistency (Fig. 4–13 a and 4 – 13 b).

Fibrinous deposits can be found on the surface of the capsule. Usually, the necrotic process is related to both layers of the renal parenchyma. As a result of the hemorrhagic rim, the renal infarction is clinically manifested by hematuria and the inflammation of the capsule determines the appearance of pains in lumbar region. The most frequent causes of renal infarction are the renal artery thromboembolism or thrombosis. It can be observed in rheumatic and infective endocarditis, atherosclerosis, arterial hypertension, ischemic cardiomyopathy etc. The red infarction (venous) develops rarely in kidneys – in cases of renal vein thrombosis. The most frequent consequence of renal infarction is cicatrization (organization) (Fig. 4 – 13 c).

Pulmonary infarction. The infarction area has a conical shape, the base

towards pleura, a dark red color, hard consistency, non-aerated, full of blood; fibrinous deposits are observed on the pleura (Fig. 4–14 a). Microscopically (Fig. 4–14 b), the alveoli are filled with extravasated erythrocytes; the alveolar septums are thickened, edematous, with dilated and hyperemic capillaries, with agglomerations of erythrocytes in alveoli. The cause of pulmonary infarction is obstruction of a branch of pulmonary artery by thrombosis or embolism (with a starting point from peripheral venous

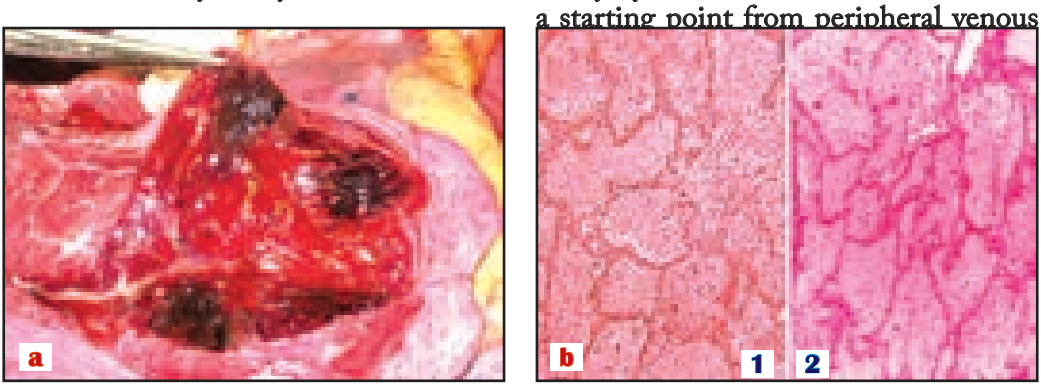


Fig. 4–14 a, b. Pulmonary hemorrhagic infarct: a - macroscopic aspect, b - microscopic pattern (1 – recent stage, 2 - advanced stage with karyolysis of alveolar septa and hemolysis of erythrocytes); (hematoxylin–eosin stain; ×110).

system, particularly of the lower limbs veins). The hemorrhagic character of infarction is determined first of all by the double circulation of pulmonary tissue: from the pulmonary artery (small circulation) and bronchial artery (great circulation); there are multiple anastomoses between these arteries, which do not function in physiological conditions. The obstruction of pulmonary arteries is followed by the reflex opening of anastomoses and penetration of the blood under pressure from the great circulation system (bronchial artery) into the ischemiated area. This induces the rupture of the walls of pulmonary capillaries and venules and blood overflowing the infarction area (interalveolar septums and alveoli spaces). The second factor determining the hemorrhagic character of pulmonary infarction is the venous stasis, because it encourages the retrograde circulation of blood through the veins and flooding the ischemiated zone. Venous stasis takes place in the left cardiac insufficiency, mainly in mitral stenosis. Clinically, pulmonary infarction is manifested through hemoptysis (the presence of blood in sputum) and pleural friction (frottage) at auscultation.

The usual consequence of pulmonary infarction is cicatrization. Possible complications are: post infarct pneumonia, pulmonary abscess, pleural empyema, pneumothorax, pulmonary gangrene. The white infarction (ischemic) occurs rarely in lungs – in cases of obstruction of bronchial artery through sclerosis and obliteration.

Cerebral infarction. It settles more frequently in subcortical nuclei and the occipital zone. Necrotic foci are soft, of white–grayish color (colliquation necrosis) and irregular shape. These changes are called encephalomacia or white softening. Microscopically, one observes a rarefaction of cerebral tissue, gradual disappearance of nervous cells, infiltration of affected area with numerous monocytic and microglial macrophages (granulous bodies), hyperplasia of astrocytes (Fig. 4–15).

It is more frequently seen in atherosclerosis of cerebral arteries or ma-

gistral arteries of the head (carotid and vertebral) and in arterial hypertension, the direct causes being the spasm, thrombosis or the embolism of arteries.

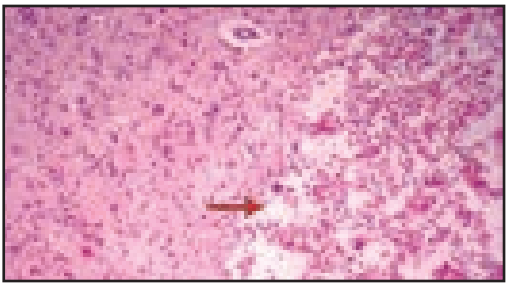


Fig. 4–15. Ischemic cerebral infarction, necrosis and disintegration focus of cerebral tissue with a large number of granulous bodies (hematoxylin–eosin stain; ×110).

It is also observed in cases of intracardiac thrombosis (for example, in acute transmural myocardial infarction, cardiac aneurysm) and rheumatic verrucous endocarditis. Clinically, it is manifested by psychic or neurological distrurbances, depending on localization of necrotic process, for example, the affection of subcortical nuclei and lesion of conduction ways leads to paralysis. As a result of the ischemic cerebral infarction of smaller dimensions, a connective glial scar is formed, and the extended softening suffers a cystic transformation (Fig. 4–16 a and 4–16 b).

Myocardial infarction. It is the most frequent and important form of ischemic cardiopathy. Etiologically and pathogenetically, it is related to atherosclerosis of the coronary arteries and arterial hypertension. In the majority of cases, according to macroscopical aspect, it is a white infarction with a red border, the central necrosis zone having a white–yellowish color, while the periphery is red. The consistency of the necrosis zone becomes flaccid, the process of softening being called myomalacia. A red myocardial hemorrhagic infarction is registered in 1–1,5 % of cases. At the limit between the necrosis zone and the persistent myocardium, there appears the demarcation inflammation with a more or less intensive leukocyte reaction, due to which there is a resorption of necrotic masses and a gradual substitution of infarcted zone with connective tissue. It is more frequently localized in the anterior wall of the left ventricle. There may be an anterior isolated or anteroseptal infarction, with involvement of the interventricular septum. Depending on the extension of the necrosis zone into the thickness of the ventricular wall, we distinguish subendocardial, intramural, subepicardial and transmural infarction. The transmural infarction may complicate with fibrinous pericarditis and/or thromboendocarditis. The most frequent consequence of myocardial infarction is organization (cicatrization) of necrosis zone (postinfarction macrofocal cardiosclerosis).

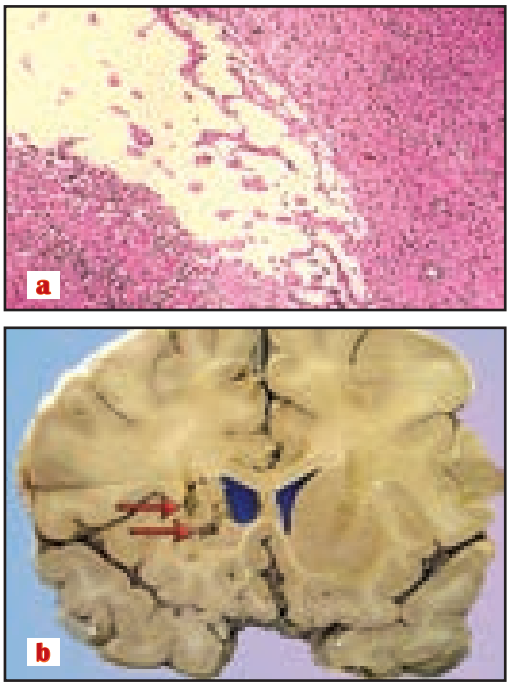


Fig. 4–16 a, b. Postinfarction cerebral cyst: a – microscopic pattern (hematoxylin–eosin stain; ×110); b – macroscopic aspect.

The clinical importance and the infarction effects depend on its localization and extension. In some cases,

infarction may unfold asymptomatically, without functional significance, but in case of lesion of some organs of vital importance, it may result in severe complications, including a lethal outcome (cerebral, myocardial infarction). The general phenomena in case of infarction are manifested by fever and leucocytosis.

Possible consequences of infarction of different localization are the following:

a. autolysis, resorption of necrotic masses and restoration of the preexistent tissue;
b. organization (cicatrization);
c. encapsulation;
d. petrification (calcification);
e. formation of cysts (cystic transformation);
f. hemosiderosis;
g. purulent lysis (suppuration).

4.4. HEMORRHAGE

Hemorrhage is the blood exiting from the vessels lumen or from the cavities of the heart.

According to the origin, hemorrhages are subdivided into:

- ✧ **cardiac** – caused by a penetrant wound of the thorax or a rupture of the ventricular wall, as a result of myocardial infarction or cardiac aneurysm;
- ✧ **arterial** – as a rule, a consequence of a trauma or a rupture of aneurysm;
- ✧ **capillary** – conditioned more frequently by traumas or surgical interventions, but it may also be observed in some diseases with the increasing of vascular wall permeability (ex., in avitaminosis C) or thrombocytopathies (ex., in idiopathic thrombocytopenic purple);
- ✧ **venous** – it occurs frequently in traumas and surgical interventions.

Hemorrhage may be **external** – the blood drains out of the organism, and **internal** – when blood accumulates in tissues, organs or preexistent cavities.

4.4.1. MECHANISMS OF HEMORRHAGES

1) by vessels rupture *(per rhexin)* – is observed in arterial hypertension, atherosclerosis, arterial aneurysm, cardiac aneurysm, myocardial infarction, venous varicosities, traumatisms, leukemias (Fig. 4–17 and 4–18).

2) by vascular wall erosion *(per diabrosis)* – it occurs in ulcer disease, ty-

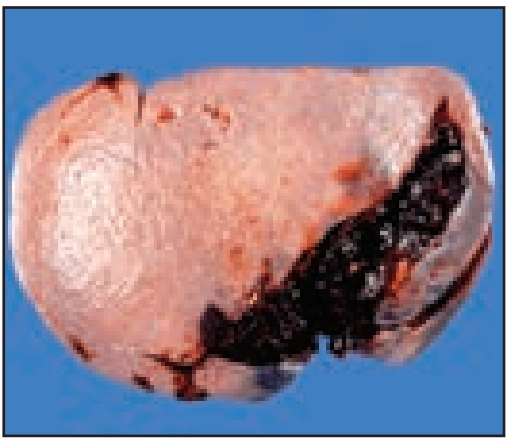


Fig. 4–17. Rupture of the spleen.

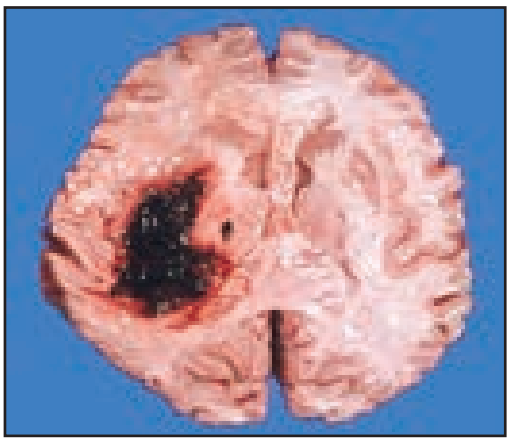
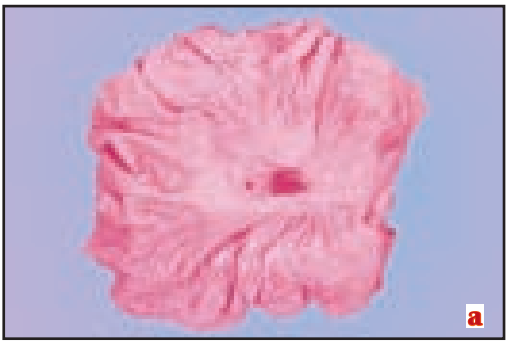


Fig. 4–18. Cerebral parenchymatous hemorrhage (hematoma).

phoid fever, dysentery, tuberculosis, abscess, malignant tumors (cancer, sarcoma), tubal pregnancy (Fig. 4–19 a and 4–19 b);



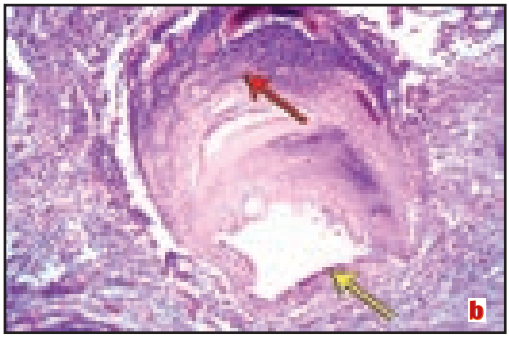


Fig. 4–19 a, b. Chronic gastric ulcer, erosion of an artery on the bottom of ulcer: a) macroscopic aspect; b) microscopic pattern (hematoxylin–eosin stain; ×110);

3) by diapedesis *(per diapedesis)* – caused by increase of permeability of vessels. It is observed in tissue hypoxia (ex: cardiovascular insufficiency, respiratory, anemias), avitaminosis C, arterial hypertension, infectious diseases (ex: influenza, smallpox, anthrax, septicemia), leukoses, systemic vasculitis (Fig. 4–20).

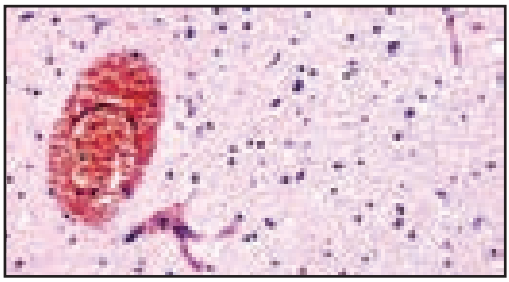


Fig. 4–20. Cerebral diapedetic perivascular hemorrhage (hematoxylin–eosin stain; ×110).

4.4.2. TERMINOLOGY OF HEMORRHAGES

(A) External hemorrhages:

1) Epistaxis *(rhinorrhagia)* – nosebleed; it occurs in traumatisms, tumors, arterial hypertension, hemophilia, sinusitis.

2) Hemoptysis – oral expulsion of blood, caused by a bronchopulmonary hemorrhage; it occurs in lung cancer, tuberculosis, abscess, bronchiectases.

3) Hematemesis – vomiting blood, a sign of upper gastrointestinal hemorrhage, localized higher than the ligament of Treitz (the duodeno-jejunal flexure), more frequently from stomach or esophagus. It occurs in gastric ulcer, erosive gastritis, esophageal/gastric varicosities in hepatic cirrhosis, Mallory–Weiss syndrome, esophageal and gastric cancer. The emetic masses may contain fresh or digested blood with a "coffee ground" aspect (blood clots condition this characteristic aspect); the color is determined by the hydrochloric hematin pigment, produced from hemoglobin, under the action of the hydrochloric acid from gastric juice; the blood gets a "coffee ground" aspect after staying in the stomach for some hours.

4) Melena – elimination of a stool

with black, digested, tarry blood, of pasty consistency; it is observed in upper gastrointestinal hemorrhages (ex: in those listed above). The black color is determined by the appearance of iron sulphite, as a result of an interaction between the hemoglobin and the hydrogen sulphide from the intestine. Melena appears in severe blood losses, of at least 60–80 ml, from upper digestive segments, at an intestinal transit of at least 8 hours.

5) **Hematochezia** – rectal bleeding, presence of fresh, red, indigested blood in feces. Usually, the localization of the hemorrhage is in the lower gastrointestinal segments, lower than the ligament of Treitz, for ex: in intestinal polyposis, ulcerative colitis, Crohn's disease, intestinal cancer and diverticulosis, hemorrhoids, it may also be in massive upper gastrointestinal hemorrhage, with rapid transit through the intestines.

6) **Rectorrhagia** – rectal bleeding, a generic term indicating a hemorrhage from any segment of the gastrointestinal tract.

7) **Metrorrhagia** – intermenstrual uterine bleeding, having no relation with the menstrual cycle. It is observed in extrauterine pregnancy, abortion, polyposis, glandular hyperplasia of endometrium, benign and malignant uterine tumors.

8) **Menorrhagia** – heavy menstrual bleeding (abundant prolonged menstruation) in different diseases of the female genital tract (including those mentioned above).

9) **Menometrorrhagia** – menstrual bleeding that does not stop in several days after the onset.

10) **Hematuria** – blood elimination with the urine. It may be classified as macroscopic, visible to the naked eye, and microscopic, revealed only at the microscopic examination of the urinary sediment. It is a sign of the urinary system pathology, for example, of glomerulonephritis, pyelonephritis, urinary calculi, cystitis, renal or bladder tumors.

11) **Otorrhagia** – hemorrhage from the ears.

12) **Stomatorrhagia** – hemorrhage from buccal mucosa.

(B) Hemorrhages in serous cavities and cavitary organs (the term is formed by the prefix hemo - or hemato - and the name of the respective anatomic portion):

1) **Hemopericardium** – hemorrhage in pericardial sac.
2) **Hemothorax** – hemorrhage in pleural cavity;
3) **Hemoperitoneum** – accumulation of blood in peritoneal cavity;
4) **Hemarthrosis** – hemorrhage in the cavity of a joint.
5) **Hematocele** – hemorrhage in the tunica vaginalis of the testicle or in scrotal tissues;
6) **Hemosalpinx** – hemorrhage in the lumen of the Fallopian tube.
7) **Hemocholecyst** – hemorrhage in the cavity of the gallbladder.
8) **Hemoamnion** – hemorrhage in amniotic fluid through the rupture of umbilical cord vessels.
9) **Hematometra** – blood accumulation in uterine cavity.

(C) Variants of hemorrhages according to size and specific features:

1) **Petechia** – punctiform hemorrhage of less than 1mm, usually of capillary origin.
2) **Ecchymosis** – hemorrhages in the skin, mucous or serous membranes,

manifest by spots of thumb-nail or a little larger, which are not prominent; they are of capillary origin or from small vessels.

3) **Hemorrhagic suffusion** – flat hemorrhage under a covering layer (skin, mucous, serous membranes), which may reach a large size.

4) **Apoplexy** – acute massive hemorrhage into an organ, with a more or less complete suspension of the organ's functions (cerebral, ovarian, suprarenal apoplexy).

5) **Cephalhematoma** – cranial subperiosteal hematoma in newborn, as a result of obstetrical traumatism; it may be external and internal (between dura mater and periosteum).

6) **Purpura** – syndrome characterized by appearance of some multiple hemorrhages in the skin and mucous membranes, in the form of petechiae and ecchymoses. It can be observed in thrombocytopenia, infectious diseases (septicemia), intoxications, systemic vasculitis, DIC syndrome.

(D) Morphologic variants of interstitial (in tissues) hemorrhages:

- ✧ **hemorrhagic infiltration** – interstitial hemorrhage, when the blood penetrates between tissular elements that maintain the structural integrity;
- ✧ **hematoma** – circumscribed blood accumulation in a tissue and formation of a cavity, as a result of compression and destruction of the adjacent tissue; the blood may be fluid or coagulated.

4.4.3. THE MOST FREQUENT CONSEQUENCES OF INTERNAL HEMORRHAGES

1) blood resorption;
2) organization;
3) encapsulation (encystation);
4) formation of cystic cavities (ex. in the brain);
5) suppuration.

4.5. PLASMORRHAGIA

Plasmorrhagia is the escape of plasma from the vascular bed with imbibitions of the vessels walls and surrounding tissue (Fig. 4 – 21).

It is determined by increase of vascular permeability and is frequently observed in arterial hypertension and atherosclerosis, cardiac insufficiency, infectious diseases, diabetes mellitus. Plasmatic infiltration leads to subsequent hyalinosis of arterial walls.

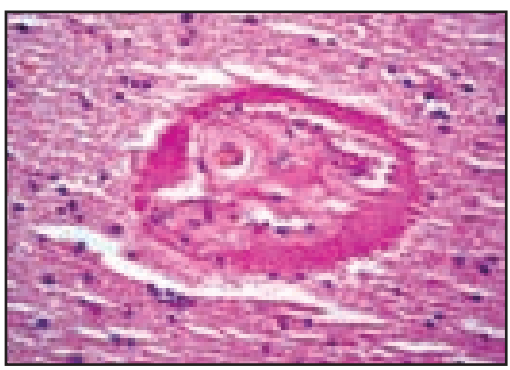


Fig. 4–21. Plasmatic infiltration of cerebral arteriole (hematoxylin–eosin stain; ×110).

ESSENTIAL TERMS

on the subject "DISTURBANCES OF BLOOD CIRCULATION: hyperemia, ischemia, infarction, hemorrhage"

anasarca	hematuria	hydropsy
apoplexy	hemoamnion	hydrothorax
ascites	hemocholecyst	hyperemia
Budd–Chiari syndrome	hemopericardium	infarction
cephalhematoma	hemoperitoneum	melena
cyanosis	hemoptysis	menorrhagia
cyanotic induration	hemorrhage	nutmeg liver
ecchymosis	hemorrhage per diabrosis	metrorrhagia
encephalomalacia	hemorrhage per diapedesis	myomalacia
epistaxis	hemorrhage per rhexin	otorrhagia
hemarthrosis	hemorrhagic infiltration	petechia
hematemesis	hemorrhagic suffusion	plasmorrhagia
hematocele	hemosalpinx	purpura
hematochezia	hemothorax	rectorrhagia
hematoma	hydropericardium	stasis
hematometra	hydroperitoneum	stomatorrhagia

TESTS

on the subject "DISTURBANCES OF BLOOD CIRCULATION: hyperemia, ischemia, infarction, hemorrhage"

SET I.

Multiple-choice questions with one correct answer.

1. ***Which sign is characteristic for the left cardiac insufficiency:***
   a) hepatomegaly;
   b) splenomegaly;
   c) ascites;
   d) inferior limbs edema;
   e) dyspnea.
2. ***All the listed clinical signs are characteristic for the right cardiac insufficiency, except:***
   a) pulmonary edema;
   b) ascites;
   c) nutmeg liver;
   d) chronic venous hyperemia of the spleen;
   e) chronic venous hyperemia of kidneys.
3. ***Which of the pathological processes listed below usually associate with mitral insufficiency:***
   a) thrombosis of pulmonary veins;
   b) thromboembolism of pulmonary artery;
   c) pulmonary edema;
   d) fibrinous pleuritis;
   e) pericardium tamponade.
4. ***Which of the listed signs is characteristic for the infarction caused by venous occlusion:***
   a) it can be white or red;
   b) it occurs only in the lungs;
   c) it is always red (hemorrhagic);

d) it is always white (ischemic);
e) it is white with hemorrhagic border.

5. As a rule, the pulmonary infarction is:
a) white;
b) liquefied;
c) bilateral;
d) septic;
e) hemorrhagic.

SET II.

Multiple-choice questions with 2, 3 or more correct answers.

1. Which of the listed diseases may cause generalized venous hyperemia:
a) portal vein thrombosis;
b) decompensated cardiac valvulopathies;
c) disturbances of rhythm and cardiac conduction;
d) thrombosis of hepatic veins;
e) thrombosis of femoral artery;
f) myocardial infarction.

2. Which of the morphological lesions listed below are characteristic for the chronic venous hyperemia of the organs:
a) increased size;
b) decreased size;
c) flaccid consistency;
d) dense consistency;
e) smooth, extended capsule;
f) shriveled, wrinkled capsule;
e) red–violaceous (cyanotic) color;
h) bright red color.

3. Which of the morphological lesions listed below are observed in chronic venous hyperemia of the lungs:
a) diffuse hemosiderosis of pulmonary tissue;
b) diffuse pneumosclerosis, more evident in posterior inferior areas;
c) fibrinous pleuritis;
d) pulmonary emphysema;
e) sclerosis of pulmonary blood vessels.

4. Which of the listed pathological processes develop as a result of stasis in the inferior vena cava:
a) nutmeg liver;
b) cyanotic induration of the spleen;
c) edema in lower extremities;
d) ascites;
e) pulmonary edema.

5. Which of the macroscopic changes listed below are observed in the ischemia of organs:
a) enlarged size;
b) flaccid consistency;
c) dense consistency;
d) smooth, extended capsule;
e) shriveled, wrinkled capsule;
f) pale color;
g) bright red color;
h) increased local temperature.

SET III.

Classification tests include 2–4 subjects and a series of answers. Indicate the correct answers for each subject separately.

1. Which of the pathological processes listed below are characteristic for:
I – left cardiac insufficiency;
II – right cardiac insufficiency;
a) nutmeg liver;
b) brown induration of the lungs;
c) hydropsy of the serous cavities;
d) subcutaneous edemas in lower extremities;
e) pulmonary edema;
f) cyanotic induration of kidneys;
g) stasis induration of spleen.

2. Which of the enumerated etiological factors may cause:

I – brown induration of the lungs;

II – nutmeg liver;

a) mitral stenosis ;
b) insufficiency of the mitral valve;
c) tricuspid valve insufficiency;
d) thrombosis of pulmonary veins;
e) stenosis of pulmonary artery;
f) thrombosis of hepatic veins;
g) stenosis of aorta;
h) obliteration of pericardial cavity.

3. Which of the pathological processes may develop in case of stasis:

I – in the portal vein system;

II – in the hepatic veins system;

a) nutmeg liver;
b) ascites;
c) stasis induration of spleen;
d) congestive enterocolonopathy;
e) collateral hyperemia of esophageal veins.

4. In which of the listed organs one observes more frequently:

I – ischemic infarction;

II – hemorrhagic infarction;

III – ischemic infarction with hemorrhagic border;

a) the spleen;
b) the kidneys;
c) the myocardium;
d) the lungs;
e) the brain;
f) the intestine.

5. Which of the listed pathogenetic factors may determine the appearance of:

I – the white infarction;

II – the red infarction;

a) magistral type of the organ's vascularization;
b) venous stasis;
c) double vascularization of the organ;
d) insufficiency of collaterals;
e) diffuse type of vascularization of the organ with a rich anastomotic circulation.

SET IV. SITUATIONAL PROBLEMS

Daily practice cases are presented with clinical and morphological data from clinical histories and/or from necropsy protocols. Each subject includes simple or multiple-answer questions, with 1, 2 or more correct answers.

1. In a patient after rheumatic pericarditis, adherences between the sheets of the pericardium were formed and a complete obliteration (closing) of the pericardial sac occurred. Later, signs of cardiovascular insufficiency with dyspnea on effort appeared, as well as edemas at the legs level, sensations of heaviness in the right costal part of the body; on palpation, the liver was enlarged, painful, the anterior margin was rounded.

Questions:

A) What pathological process developed in the patient's liver:

a) fatty liver;
b) cardiac liver;
c) nutmeg liver;
d) goose liver;
e) amyloid liver.

B) What pathological process may develop in the liver during the progress of cardiac insufficiency:

a) complete recovery;
b) subtotal necrosis of the liver;
c) cardiac cirrhosis;
d) chronic hepatitis;
e) biliary stasis.

2. A patient suffered from mitral ste-

nosis of rheumatic origin. Clinically, he presented dyspnea, cyanosis, edemas of the lower extremities, enlarged and painful liver, and cough with sputum of a rust color.

Questions:

A) How can the rust color of the patient's sputum be explained:

a) presence of hemosiderin;
b) mucus;
c) unchanged erythrocytes;
d) presence of eosinophils;
e) coal dust.

B) Which of the listed cells appear in the sputum of patients with left cardiac insufficiency:

a) giant cells;
b) cardiac cells;
c) atypical cells;
d) foreign body cells;
e) Langhans cells.

C) What kind of acute pulmonary complication may occur in this patient:

a) brown induration;
b) pneumosclerosis;
c) status asthmaticus;
d) alveolar edema;
e) emphysema.

3. A patient with the clinical diagnosis of acute myocardial infarction died due to ventricular fibrillation. At necropsy, a focus of white–yellowish color was revealed in the anterior wall of the left ventricle of the heart. It had a flaccid consistency and occupied the whole thickness of the ventricular wall.

Questions:

A) How does one call the myocardial infarction, which occupies the whole thickness of the cardiac wall:

a) circular;
b) subepicardial;
c) intramural;
d) transmural;
e) subendocardial.

B) Which favorable consequence is more frequent in myocardial infarction:

a) heart rupture;
b) myomalacia;
c) cardiac aneurysm;
d) cicatrization;
e) calcinosis.

4. A patient with post infarction cardiosclerosis (old myocardial infarction) died due to cardiac insufficiency. At necropsy, on the background of chronic congestive hyperemia, a non-aerated, dark–red area of dense consistency was revealed, being situated in the subpleural region of the right lung.

Questions:

A) What pathological process developed in this patient's right lung:

a) hematoma;
b) cancer;
c) abscess;
d) pulmonary hemorrhage;
e) hemorrhagic infarction.

B) What kind of changes may appear on the visceral pleura:

a) pleural empyema;
b) pleural mesothelioma;
c) fibrinous pleuritis;
d) hydrothorax;
e) pneumothorax.

5. A patient, who suffered from infectious endocarditis affecting the aortic valve, suddenly presented signs of stroke with paralysis of the right part of the body and aphasia (loss of speech capacity). He died in 24 hours after the cerebral edema. At necropsy, a focus of softening of cerebral substance of irregular form was revealed in the brain, with a diameter of ~4,5 cm, localized in the subcortical area on the left.

Question:

Which pathological process of the listed below occurred in this patient:

a) cerebral hematoma;
b) cerebral ischemic infarction;
c) cerebral abscess;
d) cerebral tumor;
e) parenchymatous intracerebral hemorrhage.

4. 6. THROMBOSIS

Thrombosis represents the process of coagulation of blood in the vessel lumen or in the heart cavities during lifetime. The clots formed in the vessel interior, in circulating blood or in the heart chambers, are called **thrombi** and the ones formed postmortem or in sample tubes – **clots**. The clot is formed from normal constituents of the blood.

4.6.1. THROMBOGENESIS MECHANISMS

The main factors encouraging the formation of thrombi (*the so-called* **Virchow's triad**, *1845*) are the following:

a) local lesions of the vessel walls or the heart;
b) disorders of blood circulation;
c) changes in blood composition with its coagulation impairment.

I. Local lesions of the vessel walls or of the heart represent the dominant factor in the process of thrombus formation. The changes of the vascular endothelium are involved in thrombogenesis through 2 mechanisms:

1. damaged endotheliocytes produce and release procoagulant factors (for example, thromboplastin, von Willebrand factor, inhibitors of plasminogen activator), but the synthesis of anticoagulant substances (thrombomodulin, antithrombin III, nitrogen monoxide and plasminogen activators) is reduced.
2. destruction and desquamation of endotheliocytes expose the underlying basement membrane of the vascular wall and blood platelets adhere to these structures. Binding of platelets to the vascular wall, mediated by von Willebrand factor, leads to formation of platelet aggregates and initiates the formation of thrombus.

The damage of the vascular endothelium and respectively the high risk of thrombosis are observed in such diseases like atherosclerosis, arterial hypertension, vasculitis, especially phlebitis, infections (bacterial toxins), autoimmune disturbances (periarteritis nodosa), metabolic disturbances (hyperlipidemia, homocystinemia), infective or rheumatic endocarditis, myocardial infarction, traumas, surgical interventions.

II. Changes of blood circulation. The slowing down and turbulence of blood circulation has an essential role in development of thrombi. In these conditions, platelets come in contact with the vascular wall and gather at the level of endothelium, starting the process of thrombogenesis. The slow circulation encourages the formation of platelet microaggregates, which are not eliminated with the blood flow. Besides this, the stasis reduces the inflow of fresh blood that contains natural anticoagulants. Mechanical lesion of endothelial cells, caused by turbulent flow and hypoxia of endothelium in conditions of stagnant circulation, constitute additional favoring factors in development of thrombi.

As a rule, blood stasis is noticed in dilated veins, and especially in varicose veins, representing the most frequent cause of venous thrombosis (Fig. 4–22).

Turbulent blood circulation occurs in arterial and cardiac aneurysms, as well as in the atrial fibrillation, when the dilated heart chambers do not contract regularly. According to a similar mechanism, the thrombosis of the heart auricles in dilated atria with stagnant blood develops in patients with chronic

cardiac insufficiency (mitral stenosis, decompensated pulmonary heart, etc.) (Fig. 4–23 and 4–24).

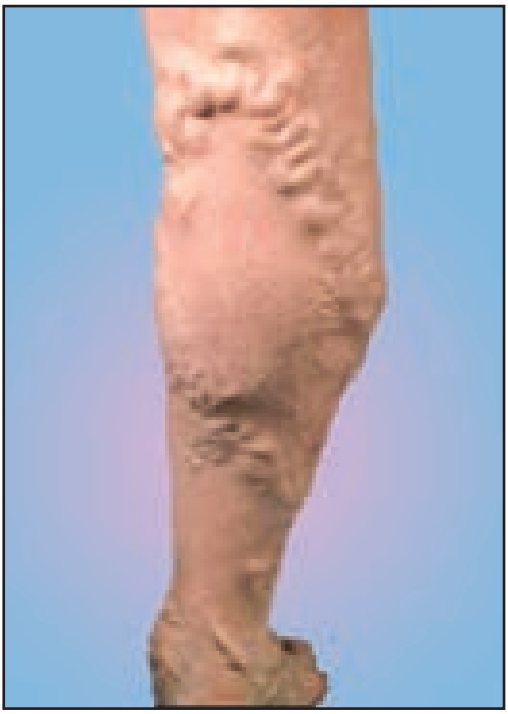


Fig. 4–22 Varicose dilatation of the lower extremities veins.

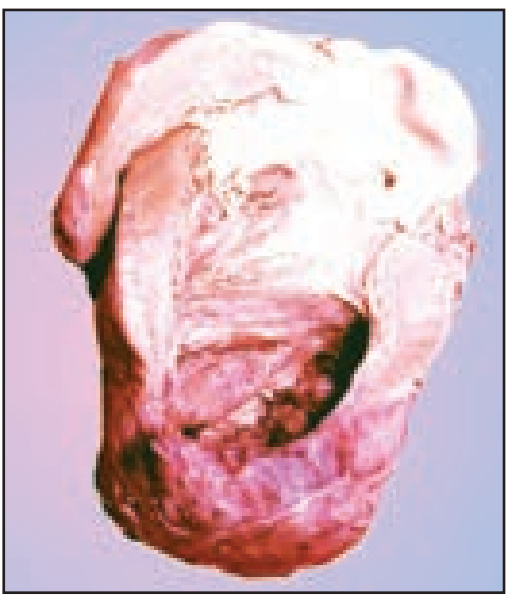


Fig. 4–23. Chronic cardiac aneurysm with thrombosis.

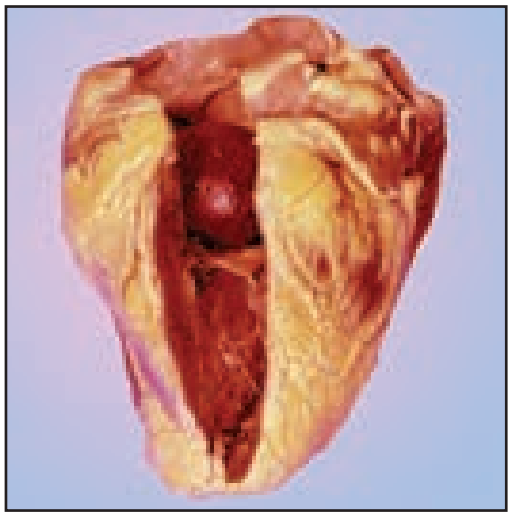


Fig. 4–24. Spherical thrombus in the left atrium, in stenosis of the left atrioventricular orifice (mitral stenosis).

III. Changes in blood composition. In some pathological conditions, one notices an increase of concentration of coagulation factors and a decrease of natural anticoagulants, which leads to a balance disorder between pro- and anticoagulant factors and to hypercoagulability of blood.

The most frequent causes: thrombocytosis (the increase of the number of platelets in the blood), severe traumatisms, including surgical interventions, where there is an increase of tissular thromboplastin level as a result of tissue lesions, malignant tumors (tumoral cells release procoagulant substances), the increase of blood viscosity conditioned by the high content of macro-dispersed proteins, for example, in malignant myeloma.

Other factors that increase the risk of thromboses by hypercoagulability of blood are an advanced age, obesity, smoking, oral contraceptives, etc.

In order to memorize the main causes of thrombogenesis, one can use the English abbreviation **THROMBI**:

Tissue damage – tissular damage (traumatisms, burns, surgical interventions).

Hereditary conditions – hereditary anomalies of the coagulation system (deficiency of antithrombin III, proteins C and S, etc.)

Rest – treatment of long-term bed rest (after surgical interventions, bone fractures, etc).

Obstetrics – different conditions associated to pregnancy (normal pregnancy, eclampsia, early detachment of placenta etc.).

Malignancy – malignant tumors.

Blood flow disturbances – disturbances of blood circulation (dilated varicose veins, hemorrhoids, cardiac or arterial aneurysms, venous stasis, etc.).

Immune mechanisms – immunopathological processes (disseminated lupus erythematosus, polyarteritis nodosa, antiphospholipid syndrome).

4.6.2. MORPHOGENETIC STAGES OF THROMBOSIS

The process of thrombus formation evolves in 4 stages (Fig. 4–25 a, b, c, d):

1) aggregation of platelets;
2) transformation of fibrinogen in fibrin;
3) agglutination of erythrocytes and other cellular elements of the blood;
4) precipitation of plasmatic proteins.

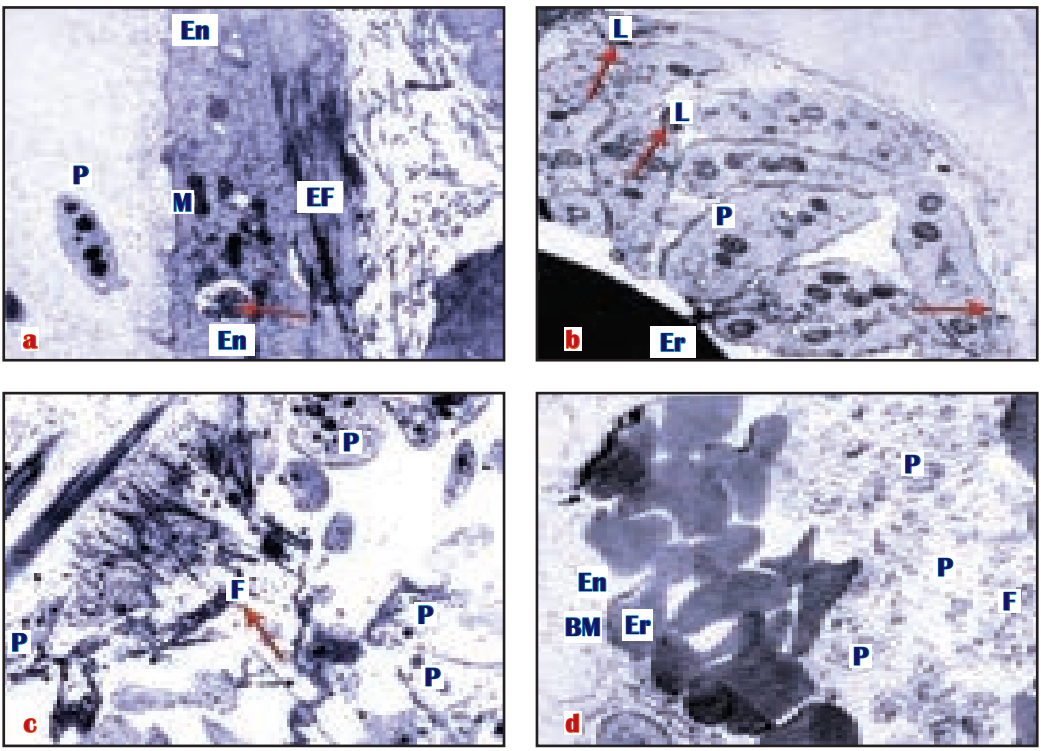


Fig. 4–25 a, b, c, d. Stages of thrombus formation: I (a, b) – aggregation of platelets; II (c) transformation of fibrinogen in fibrin and III (d) – agglutination of erythrocytes and other cellular elements of the blood (electronic microscopy; a ×9000, b ×56000, c ×7750, d ×58000); En – endothelium, P – platelets, M – mitochondria, EF – elastic fibers, Er – erythrocytes, L –lipids of lipoprotein complexes of peripheral areas of platelets, F – fibrin filaments, BM – basement membrane.

As a result of disintegration of platelets, an enzyme – *thrombosthenin (retractozyme)* – is released, which has a retractile action on the thrombus, and *serotonin*, which causes constriction (narrowing) of vessels. Under the action of these substances, the retraction of the thrombus and its densification occurs.

4. 6. 3. MORPHOLOGY OF THROMBI

Macroscopic aspects. The definitive thrombus has a dense consistency, it is dry, friable; the older the thrombus is, the more compact and harder it is (Fig. 4–26).

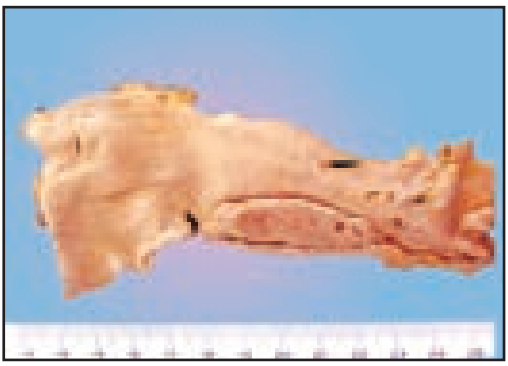


Fig. 4–26. Parietal thrombus in the iliac vein

The surface of the thrombus is irregular (goffered); the stripes (lines of *Zahn*) consist of agglutinated platelets and leukocytes, and are formed as a result of blood waves (*they resemble somehow sand stripes on the river banks or on the seaside)*, being an obvious sign that the process of blood coagulation occurred during lifetime. When sectioned, the thrombus usually has a stratified structure, one noticing an alternation of a white layer of fibrin and platelets and a red layer, made of erythrocytes.

Differentiation criteria of thrombus versus postmortem clot

The differential diagnosis between thrombi, as an intravital process and the postmortem clots, which appear because of cessation of the heart activity and blood circulation, is made during autopsy of corpses on the necropsy table. Under the action of the force of gravity, the postmortem clots appears usually stratified: the lower part is red, made of erythrocytes (resembling "currant jelly"), and the upper part is yellowish, made of plasma (resembling "chicken fat").

The main criteria of differentiation of thrombus from postmortem clot are exposed in the Table 4.1.

Table 4. 1.
Criteria of differential diagnosis between thrombus and postmortem clot

Thrombus	*Postmortem clot*
▪ adheres to the vessel wall	▪ does not adhere to the vessel wall
▪ a defect of the endothelium, with a rugged aspect, remains after detachment of the thrombus	▪ the endothelium remains intact, smooth, shiny after the removal of the clot
▪ rugged, irregular surface	▪ smooth surface
▪ opaque, dry aspect	▪ shiny, wet aspect
▪ increased, dense consistency	▪ flaccid, elastic consistency
▪ friable, brittle	▪ does not fill the lumen of blood vessels and does not dilate it

Most frequently, thrombi are formed in veins, particularly in the veins of lower extremities, hemorrhoidal, mesenteric, portal vein, more rarely - in arteries (coronary, cerebral, mesenteric, renal, pulmonary, aorta, etc.), especially in atherosclerosis. They may also appear in heart cavities, on the surface of mitral and aortic valves (in infective or rheumatic endocarditis), in the left atrium (for example, in mitral stenosis) or on cardiac cavities walls (parietal thrombosis in myocardial infarction, rheumatism, cardiomyopathies etc.).

Microscopically, the thrombus is made up of agglutinated platelets and fibrin filaments, among which erythrocytes and leukocytes can be found. Depending on the structural features and the exterior aspect, there are 4 types of thrombi: white, red, mixed and hyaline.

1) **The white thrombus** (of agglutination) consists of agglomerations of platelets, forming coral-like structures, leukocytes and a meshwork of fibrin filaments. It is mostly parietal and is usually observed in arteries and on the valves of the heart.
2) **The red thrombus** (of coagulation) is composed of a fibrin meshwork with erythrocytes, thrombocytes and a small number of neutrophils (Fig. 4–27). It is mostly observed in veins and is occlusive (obliterative).
3) **Mixed thrombus** (variegated, stratified or striped) consists of white and red thrombus elements and has a stratified structure. It is the most frequent variant of thrombi and their localization may be various. A mixed thrombus consists of three parts: head, body and tail. The head of the occlusive thrombus is oriented in veins towards the heart (the right ventricle) and in arteries - in the opposite direction. The parietal thrombus in veins, as well as in arteries, may develop both in the direction of the blood stream and opposite to it. The head adheres to the wall of the vessels (heart) and the body and the tail are free in the lumen.
4) **The hyaline thrombi** are usually multiple and localized in the vessels of the microcirculatory system. They can be seen in extreme conditions: shock, burn, massive tissues destruction. The hyaline thrombi have an amorphous, homogeneous, unstructured character, as a result of cellular elements destruction and precipitation of plasmatic proteins.

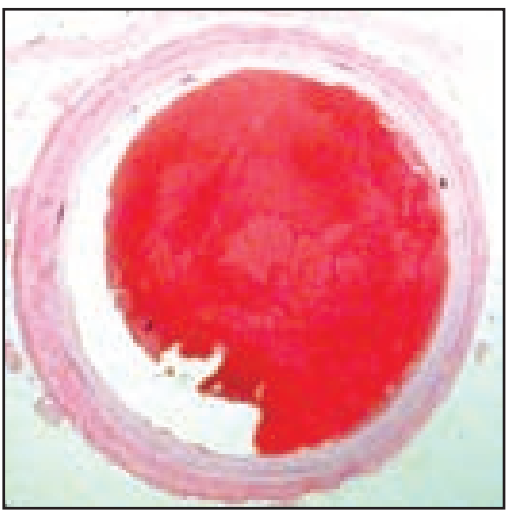


Fig. 4–27. Recent red vascular thrombus (hematoxylin–eosin stain; ×50)

The consequences of thrombi can be favorable and unfavorable:

I – *favorable consequences:*

a) resorption of thrombus;

b) aseptic autolysis (softening);

c) connective organization – substi-

tution of thrombus with granulation tissue, which contributes to consolidation of thrombus in the place of formation and excludes the threat of thromboembolism occurrence (Fig. 4–28);

d) vascularization and canalization (recanalization) (Fig. 4–29); the newly-formed vessels restore partially the permeability of the thrombosed vessel;

e) calcification (petrification).

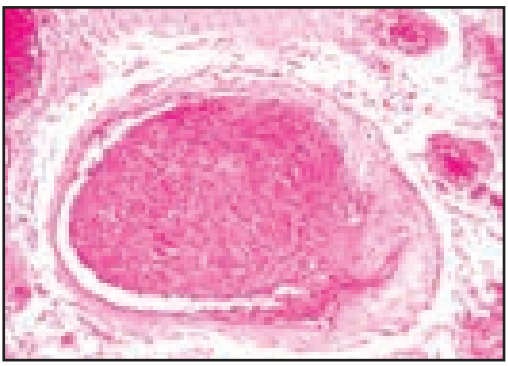


Fig. 4–28. Thrombus in course of organization (hematoxylin–eosin stain; ×70).

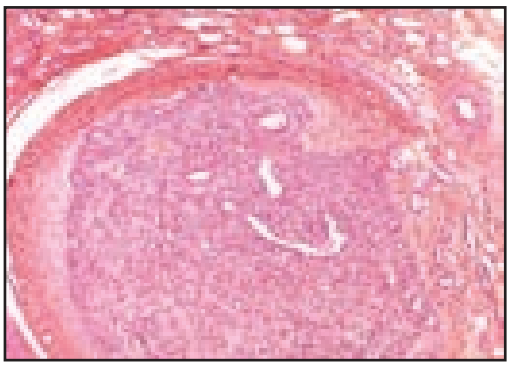


Fig. 4–29. Recanalized thrombus (hematoxylin–eosin stain; ×70).

II – *unfavorable consequences:*

a) septic autolysis (purulent softening);

b) rupture of thrombus and its transformation into thromboembolus.

The importance and clinical effects of thrombosis depend on localization, extension and rapidity of thrombus formation. The obliterative arterial thrombi may cause infarctions and gangrene. In case of parietal arterial thrombi, which are formed slowly, the collateral circulation is included and a threat of ischemic necrosis is avoided. The cardiac thrombi are a source of thromboembolism of the great circulation arteries. The thrombi from the aorta, magistral and visceral arteries can also cause thromboembolism of distal arterial branches towards the level of thrombus. Thrombosis of cardiac aneurysm can also have a beneficial role by "strengthening" of cardiac wall and prevention of its rupture. The effects of venous thrombi can be diverse at different levels and in different organs. First of all, vein thrombosis is a source of thromboembolism of the pulmonary artery. Thrombosis of the portal vein causes portal hypertension and ascites, thrombosis of hepatic veins – the Budd–Chiari syndrome, thrombosis of lienal vein – thrombophlebitic splenomegaly, thrombosis of mesenteric veins – intestine gangrene, thrombosis of venous sinuses of *dura mater* – disturbances of cerebral circulation etc. Thrombosis of the lower extremities veins in the varicose disease is frequently complicated by thrombophlebitis. A particular form of venous thrombosis can be seen in the Trousseau syndrome or migratory thrombophlebitis. This syndrome is frequently associated with gastric or pancreatic cancer. It manifests itself by thrombosis of superficial veins, which disappears spontaneously and reappears in another place. The phenomenon can be explained by the appearance of released thromboplastin from cancerous cells in the blood.

4. 7. EMBOLISM

Embolism is a pathological process, characterized by circulation of some particles in the cardiovascular (lymphatic) system, which do not appear in the blood (lymph) in normal conditions, and which produce complete or partial occlusion of the blood (lymphatic) vessels. The particles spread by the blood (lymph) are called ***emboli***. The emboli may be of exogenic or endogenic origin and, according to physical features – **solid** (thrombi, tissue fragments, groups of cells, foreign bodies, and microbial colonies), **fluid** (amniotic fluid, liquid fats) and **gaseous** (air, nitrogen, oxygen).

4. 7. 1. VARIANTS OF EMBOLISM ACCORDING TO THE COMPOSITION

a) Thromboembolism is an embolism with thrombi or fragments of detached thrombi; the starting point (the source) may be in veins, arteries or heart cavities. It happens in thrombophlebites, varicose disease of lower extremities veins, hemorrhoids, arterial atherosclerosis, arterial and cardiac aneurysms, infective or rheumatic thromboendocarditis, and myocardial infarction. It may end in infarctions, gangrene.

The thromboembolism of the pulmonary artery is more important clinically. The starting point of pulmonary emboli may be the thrombosis from the lower extremities veins, pelvic, intra-abdominal veins, cava veins, and the right cavities of the heart. Practically in 90–95% of the cases, the source of pulmonary emboli is thrombosis of the deep veins of the lower extremities (most frequently the popliteal vena). 60–80% of emboli have small size and develop clinically asymptomatically, due to the lysis of thrombus and compensation of circulation by the bronchial artery. Thromboembolism of small, terminal artery branches leads to installation of hemorrhagic pulmonary infarction. In cases when more than 60% of the pulmonary vessels become simultaneously blocked by multiple small emboli or by a big embolus, there occurs an acute right heart insufficiency (acute pulmonary heart) or a cardiovascular shock and sudden death. The occlusion of the common trunk or of the large branches of the pulmonary artery (the so-called thromboembolus alike "rider in its saddle") leads to sudden death because of pulmonary circulation occlusion with asphyxia and acute pulmonary heart (Fig. 4–30).

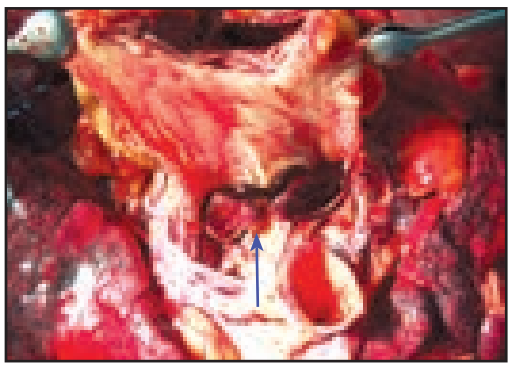


Fig. 4–30. Thromboembolism of the pulmonary artery.

In some cases, a sudden death may occur even from relatively small emboli through a pulmocoronary reflex with a spasm of pulmonary artery ramification, bronchi, coronary arteries and heart failure. The multiple thromboemboli, which do not occlude the pulmonary vessel lumen, can be substituted with connective tissue, this leading to thickening of the wall vessels and installation of pulmonary hypertension. Thromboembolism of the pulmonary artery is one of the severe complications in surgical interventions, particularly in the organs of the abdominal and pelvic cavities.

b) Fat embolism is an embolism with particles of endogenic or exogenic fats. Most frequently, it occurs in fractures of the tubular bones (especially of the femur and tibia), rarely – in contusions of the adipose tissue (subcutaneous, pelvic at the time of birth), intravenous introduction of some oleaginous substances. It results in embolism of pulmonary capillaries with acute asphyxia, when more than 2/3 of capillaries are blocked. Small drops of lipids, which penetrate the pulmonary capillary network, get into cerebral micro-vessels, causing small foci of necrosis and pericapillary hemorrhages. About 10% of the patients die. Fat embolism is identified by lipid coloration at autopsy (Sudan III) (Fig. 4–31).

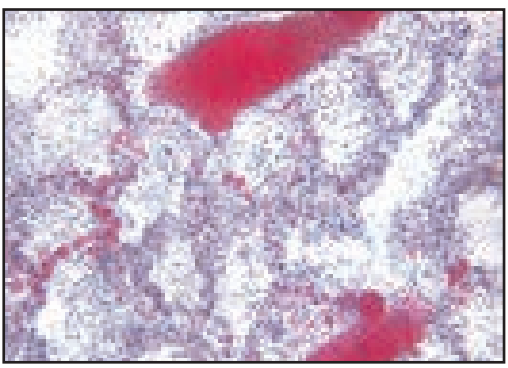


Fig. 4–31. Fat embolism of the pulmonary blood vessels (hematoxylin–eosin stain and Sudan III; ×70).

c) Air embolism is produced when the atmospheric air enters the venous or arterial system. It is noted in traumatisms or surgery on the neck area, after injury of the jugular vein or superior vena cava. Under the action of the negative pressure that exists in the thorax, the air is absorbed in the blood. An analogical mechanism takes place in traumas or surgeries on thorax, lungs, heart, laparoscopy, pneumothorax, pleural punctures. During external massage of the heart, there may be costal fractures that also present a threat of air embolism. During delivery or abortion, in cases of uterine atony in puerperal period, the air may penetrate the blood through the dehiscent uterine veins. Air embolism may appear as a result of injections or transfusions with technical defects. An accumulation of air during the small circulation vessel embolism occurs in the right compartment of the heart, blocking the blood circulation. To make a diagnosis, the right cavity of the heart is opened under water at autopsy (the water is poured into pericardial sac beforehand) (Fig. 4–32); air bubbles are eliminated eventually; the blood may have a foamy aspect.

Small quantities of air are absorbed and are not dangerous, but death occurs in case the air volume is more than 150,0 ml.

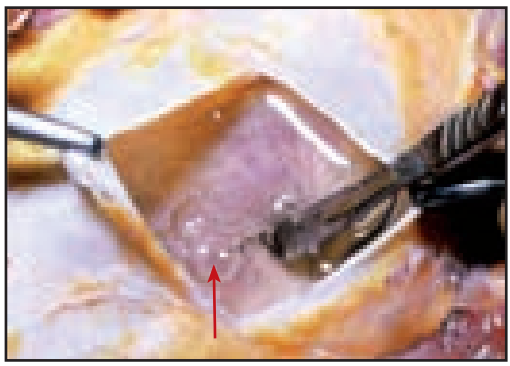


Fig. 4–32. The test to reveal air embolism at necropsy: the right ventricle is pierced with a scalpel under water; air bubbles are eliminated in case of a positive test.

d) Gaseous embolism – obstruction of vessels with nitrogen bubbles. Nitrogen is dissolved in the blood in physiological conditions, the soluble state being ensured by the atmospheric pressure. It occurs in divers, caisson workers, pilots, at a rapid passage of the organism from high or low atmospheric pressure to a normal one. It manifests itself by occlusion of capillaries of the brain, bones, soft tissues, spinal cord and other organs with appearance of ischemia and necrosis foci, punctiform hemorrhages and micro-

thrombi (the decompression or caisson disease). There may be multiple and extended infarctions in the organs with lethal outcome.

e) Tissular embolism *(cellular)* – embolism through isolated cells or tissue fragments. It is observed firstly in malignant tumors. The tumor cells infiltrate the walls of the blood and/or lymphatic vessels, proliferating extracellularly and form secondary, metastatic tumor nodules (cancer, sarcoma, melanoma – metastases) (Fig. 4–33 and 4–34).

The ischemic and necrotic lesions in tumor embolism are less important. The tissular embolism occurs also in ruptures of cardiac valves in infective endocarditis, in cerebral and hepatic traumatisms, amniotic fluid embolism (squamous cells, hair (lanugo), *vernix caseosa*, meconium) in puerperal women in cases of incomplete detachment of placenta, embolism with cerebral tissue in fetus and newborn in obstetrical trauma. Such an embolism may also appear in bone fractures, when the red bone marrow penetrates the blood flow. It is most frequently noticed

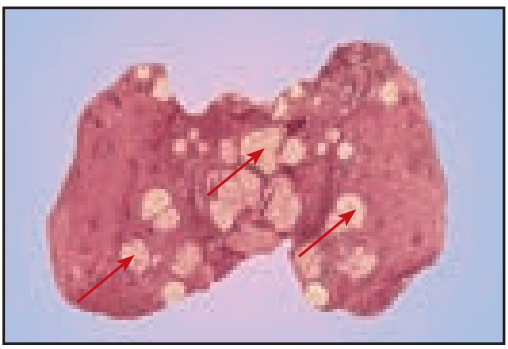


Fig. 4–33. Cancer metastases in the lungs.

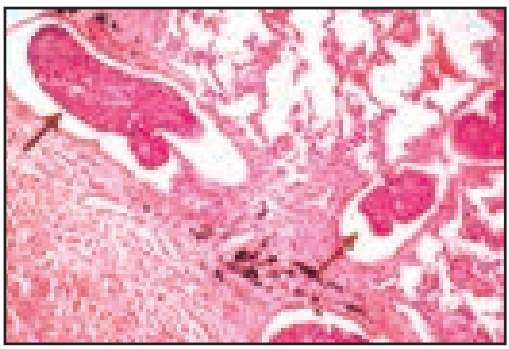


Fig. 4–34. Cancerous embolism of the pulmonary lymphatic vessels (hematoxylin–eosin stain; ×70).

in fractures of the ribs during the indirect massage of the heart. Particles of the hematopoietic tissue get into pulmonary arteries of small caliber together with the venous blood.

f) Microbial embolism – the embolus is made of agglomerations of microorganisms (colonies of microbes, fungi or parasites), which get into the blood from a septic focus. It can be seen in sepsis (septicopyemia), generating the appearance of ischemic and necrotic lesions and of purulent foci – metastatic abscesses in organs (Fig. 4–35 and 4– 36).

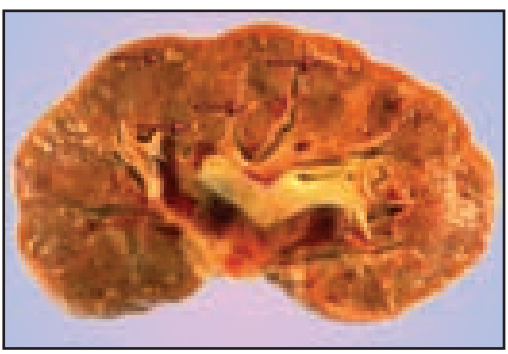


Fig. 4–35. Embolic purulent nephritis (metastatic abscesses in kidneys).

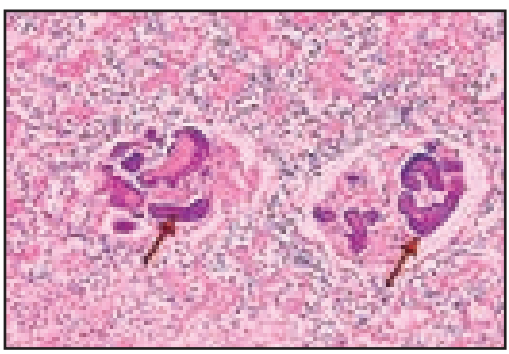


Fig. 4-36. Bacterial embolism of capillaries of the renal glomeruli (hematoxylin–eosin stain; ×70).

Such complications can also be observed in case of some fragments of infected thrombi ("sick thrombi"), for example, fragments of vegetations from the cardiac valve surface in infective endocarditis; the necrosis area is colonized by microbes and transforms into abscess. Thrombi become a favorable environment for bacterial development and are easily infected. The organization of the infected thrombi leads to thrombophlebitis.

g) Foreign body embolism – embolism with cotton, cloth fibers, talcum or starch crystals, fragments of catheters, needles, calcium salts, splinters, bullets etc. It can be observed in traumatisms, including surgical ones, in catheterization of vessels and heart, intravenous injecting of drugs etc. In the same context, one can observe the embolism with cholesterol crystals, which get into the arterial blood as a result of ulceration of atherosclerotic plaques, catheterization of aorta or surgical interventions in arteries. The foreign body embolism conditions the appearance of ischemic and necrotic foci in the organs. For example, embolism with cholesterol crystals of retina arteries may cause blindness, of arterioles and renal glomeruli capillaries – acute renal insufficiency.

4.7.2. VARIANTS OF EMBOLISMS ACCORDING TO THE DIRECTION OF THE EMBOLUS CIRCULATION

1) Direct (forward) embolism – the embolus circulates in the direction of the blood flow (Fig. 4–37):

✧ from the great circulation veins into the right compartments of the heart and into the small circulation vessels (in the pulmonary artery and its branches);

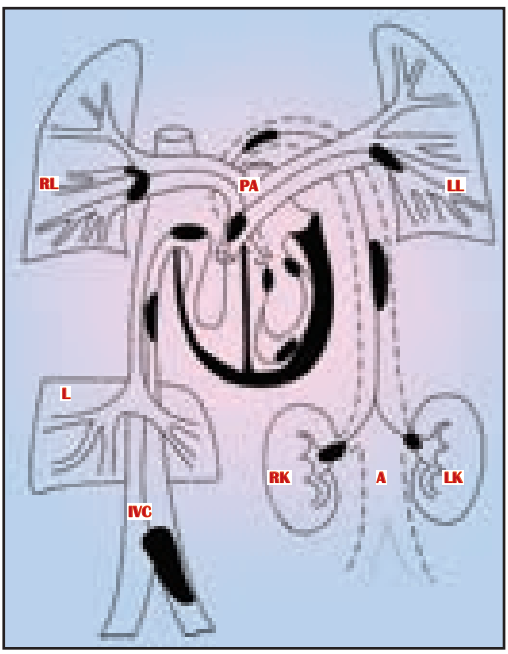


Fig. 4–37. The scheme of direct (forward) embolism A – aorta, IVC – inferior vena cava, L – liver , LL and RL – left and right lung, LK and RK – left and right kidney, PA – pulmonary artery.

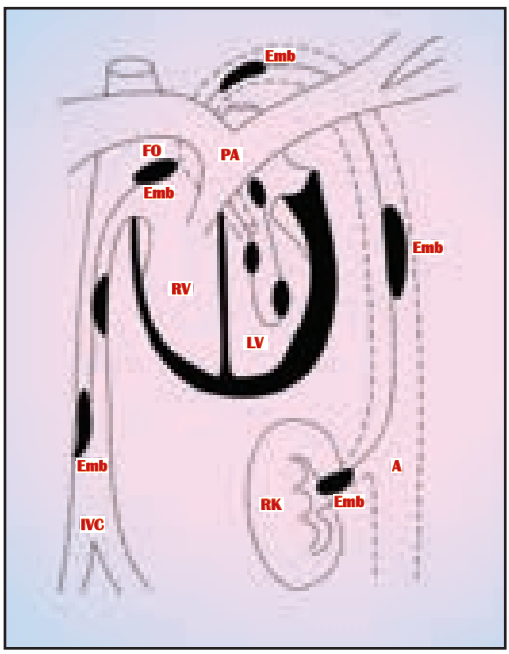


Fig. 4–38. Paradoxical embolism scheme: Emb – embolus, FO –foramen ovale, PA – pulmonary artery, A – aorta, IVC – inferior vena cava, LV and RV – left and right ventricles, RK – right kidney.

- ✧ from the pulmonary veins, the left compartments of the heart, aorta and major arteries into the great circulation arteries (lower and upper extremities arteries, celiac, lienal, mesenteric, renal, cerebral, coronary arteries);
- ✧ from the branches of the portal system into the portal vein trunk and liver.

2) Paradoxical (crossed) embolism – when the embolus from the big circulation veins reaches directly the left compartments of the heart and the great circulation system arteries, avoiding the small circulation system (the pulmonary capillary system) (Fig. 4–38).

It can be found in congenital heart diseases: the persistence of foramen ovale (interatrial communication) (Fig. 4–39), interventricular septal defect and arteriovenous shunts (communication) especially in cases of Botallo duct persistence; example – the thrombus from hemorrhoidal veins may reach the cerebral arteries.

3) Retrograde embolism – the circulation of embolus against the blood flow; for example, embolism of hepatic or renal veins, when the thromboembolus comes from the inferior vena cava at the moment of sudden increase of intraabdominal or intrathoracic pressure (during a cough access) (Fig. 4–40).

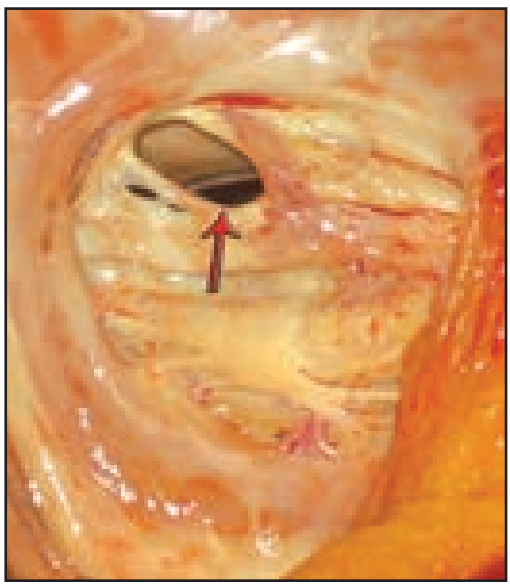


Fig. 4–39. Congenital cardiac malformation: interatrial septum defect.

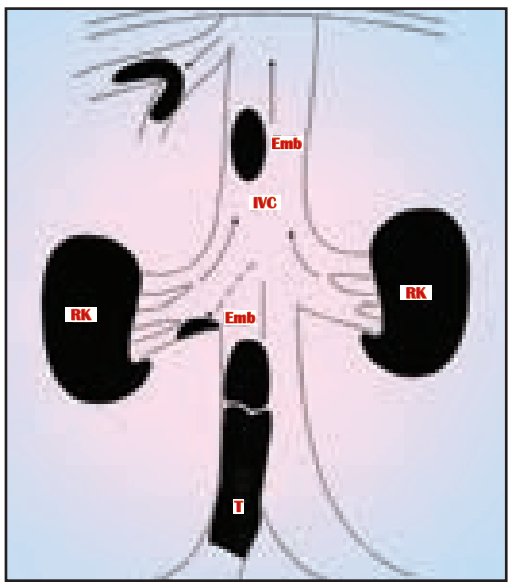


Fig. 4–40. Retrograde embolism scheme: Emb – embolus, T – thrombus, IVC – inferior vena cava, LK and RK – left and right kidney.

4.7.3. CONSEQUENCES OF EMBOLISM

The effects and consequences of embolism depend on the nature (structure), spreading and localization of emboli. The most frequent and severe effect of arterial embolism is ischemia, which leads to development of infarction or gangrene. The vascular occlusion consequences can be particularly dangerous in cerebral artery embolism (ischemic infarction, white cerebral softening), coronary (myocardial infarction), and pulmonary (pulmonary infarction or sudden death in pulmonary

artery thromboembolism). Air, gaseous and fat emboli can resorb but if the embolism is massive, severe complications may appear. Microbial (septic) embolism may generate metastatic abscesses, which, depending on the localization, may have a vital importance in the dissemination and generalization of the infection. The cellular (tissular) embolism in malignant tumors (cancer, sarcoma) is the main way of metastasis and generalization of the tumoral process (*the process of transfer of some pathological elements from one place to another in the organism, with the appearance of some secondary pathologic foci distanced from the primary focus is called metastatic process; the secondary focus that appears in this way is called metastasis).*

4. 8. STASIS (HEMOSTASIS)

Stasis is the stopping of blood in capillaries and venules with a dilated lumen, accompanied by aggregation (sticking) of erythrocytes in homogeneous columns (Fig. 4–41).

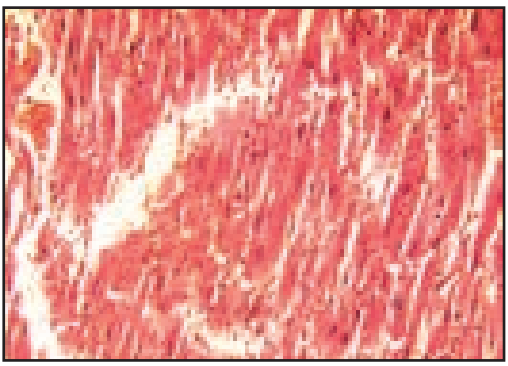


Fig. 4–41. Stasis in myocardium capillaries (hematoxylin–eosin stain; ×110).

A variant of stasis is the **sludging** condition (from the English **sludge** – mud), which consists in sticking of erythrocytes and other cellular blood elements, generating the increase of plasma viscosity and decrease of fluidity and perfusion of blood in the vascular system. It is conditioned by the changes of physical and chemical properties of erythrocytes. There is no hemolysis and coagulation of blood in stasis. It is a nonspecific process, which occurs in cases of severe circulation disturbances (cardiac valvulopathies, myocardial infarction), infectious diseases (malaria, typhus), intoxications, under the action of some physical factors (high temperature, cold). It is a reversible process, but a prolonged stasis causes hypoxia of the respective territory and dystrophic and necrotic lesions.

4. 9. SHOCK

The shock is a complex pathological condition, characterized by acute reduction of the blood flow (circulatory collapse), generalized hypoperfusion of tissues and insufficient oxygen and nutritive substances supply to the cells/tissues.

As a result of the critical decrease of blood circulation intensity at the level of micro-vessels, especially of capillaries, a severe energetic deficit and accumulation of intermediate products of metabolism occurs, with destructive lesions in tissues/organs and polyorganic insufficiency.

According to etiology and pathogenetic mechanisms, the following main varieties of shock are distinguished:

- ✧ **hypovolemic** – caused by the decrease of the volume of the circulating blood, dehydration of the organism or the peripheral vasodilatation; it appears in blood losses (gastro–intestinal hemorrhages, traumas, rupture of aortic aneurysm) or plasma losses (by vomiting, diarrhea, burns);
- ✧ **traumatic** – conditioned by many

pathogenetic factors, like pain, toxemia, hemorrhage; it develops in the syndrome of prolonged crush of the soft tissues (crush–syndrome), burns;

- **cardiogenic** – a result of such factors like contractile insufficiency of heart, fatal arrhythmias, pain; it may occur in the acute period of the myocardial infarction, thromboembolism of pulmonary arteries, myocardial contusion, pericardial tamponade, acute myocarditis;
- **septic** (toxico-infectious, endotoxic) – conditioned by bacterial endo- and exotoxins; it may be observed in peritonitis, pneumonia, urinary and biliary tract infection, pancreatonecrosis, puerperal sepsis, septic abortion;
- **neurogenic** – the starting moment is constituted by excessive afferent impulse, especially the painful one, or interruption of the sympathetic innervations; it appears in traumatisms of the spinal cord and complications of spinal anesthesia;
- **anaphylactic** – it appears as a result of immediate immune reaction, when reagin-type antibodies – IgE fix on mast cells and basophiles of the blood, causing histamine release; it can be seen in cases when the organism is sensitive to certain allergic substances, including medicines.

Morphological manifestations of the shock:

- redistribution of blood with its accumulation in the microcirculatory bed;
- the syndrome of disseminated intravascular coagulation;
- in kidneys – dystrophic lesions and necrosis of convoluted and straight tube epithelium (shock kidneys), in some cases – symmetrical cortical necrosis of kidneys;
- in adrenals – hemorrhages and necrosis of the cortical layer (Waterhouse–Friderichsen syndrome);
- in lungs – adult respiratory distress syndrome (shock lung);
- in liver – stasis, hydropic dystrophy of hepatocytes and centrolobular necrosis;
- in gastrointestinal tract – erosions of mucosa and acute multiple ulcers (stress ulcers);
- in brain – ischemia, with foci of hemorrhages and edema;
- in myocardium – dystrophic changes and small foci of necrosis of cardiomyocytes.

Morphological lesions, which appear in shock states, determine functional disturbances of the respective organs and the polyorganic insufficiency syndrome.

4. 10. DISSEMINATED INTRAVASCULAR COAGULATION (DIC SYNDROME)

DIC is characterized by formation of multiple thrombi in small blood vessels (arterioles, capillaries, venules), which generates the consumption of coagulation factors, fibrinogen (hypofibrinogenemia) and other procoagulant proteins (consumptive coagulopathy), reduction of the number of platelets (thrombocytopenia). Microthrombi cause severe dystrophic lesions and microinfarcts in all the organs, but more frequently in lungs, kidneys, brain, digestive tract, adrenals and skin. These microinfarcts are associated with the noncoagulability of the blood and the hemorrhagic syndrome with multiple hemorrhages in parenchymatous organs and teguments. It occurs in various shock conditions, severe infections (sepsis, me-

ningococcemia), intoxications, leukemias, traumatisms with massive tissue injuries, burns, obstetrical complications with amniotic fluid, eclampsia and uterine hemorrhages. The pathogenetic mechanism consists in the impairment of the balance between the coagulation and anticoagulation systems. Consequently, acute polyorganic insufficiency develops.

4. 11. EDEMA

Edema is the increase of fluid in tissues and serous cavities. The edema fluid is accumulated in the extracellular compartment (interstitium).

The edematous fluid or the transudate is transparent and contains up to 1–2 % of serum proteins, being slightly associated with the proteins and glycosaminoglycans of the ground substance of the interstitial tissue.

4. 11. 1. PATHOGENETIC MECHANISMS IN DEVELOPMENT OF EDEMAS

I. Vascular factors:

a. increase of hydrostatic pressure of the blood in small vessels;
b. decrease of oncotic pressure of blood plasma;
c. increase of permeability of capillary and venule walls;
d. lymphatic stasis.

II. Tissular factors:

a. retention of electrolytes in tissues, especially of sodium and water;
b. increase of oncotic pressure of interstitial fluids.

Macroscopically, the edematous tissues (organs) are increased in volume, tumefied; the lax tissue consistency is paste-like, gelatinous, a depression remains at digital pressure; the bony contours are erased in the region of extremities; the parenchymatous organs are increased, the capsule is distended, the consistency is increased, wet, shiny aspect on section, low temperature, the color is paler than normally (as a result of capillary compression), a colorless or pale–yellowish fluid leaks from the surface when sectioned.

Microscopically, one notices a dissociation of the fibrillar and cellular structures by the edema fluid, which, stained with hematoxylin–eosin, has a colorless or a slight eosinophilic (rosy) homogeneous aspect; the fluid is accumulated especially in the perivascular area; the lymphatic vessels are dilated (Fig. 4–42 and 4–43).

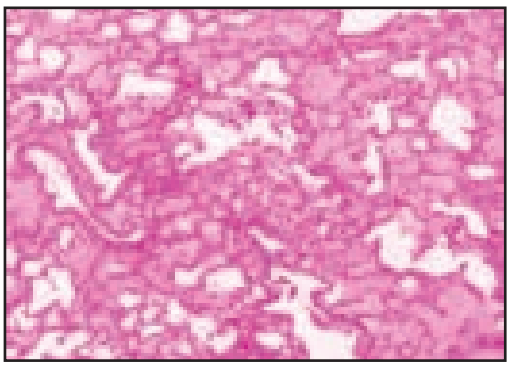


Fig. 4–42. Pulmonary edema (hematoxylin–eosin stain; ×70).

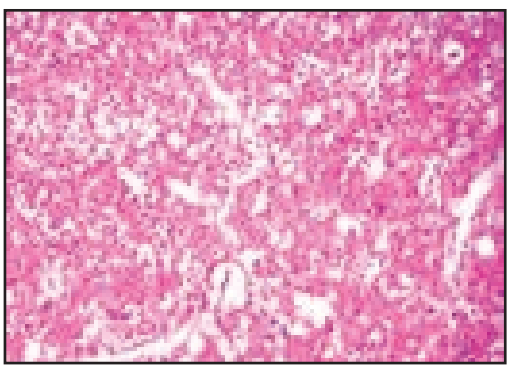


Fig. 4–43. Cerebral edema (hematoxylin–eosin stain; ×110).

4. 11. 2. CLASSIFICATION OF EDEMAS ACCORDING TO ITS PATHOGENETIC MECHANISMS

An edema may be generalized or localized, chronic or acute.

I. Generalized edemas:

Cardiac edema – the increase of hydrostatic pressure in veins, as a result of heart contractile insufficiency (decompensation of the heart); retention of sodium, as a result of increase of aldosterone secretion. The predominant edema localization is in the lower extremities (due to the gravity force); the teguments have a cyanotic aspect (cyanotic edema). It is seen in cardiac valvulopathies, infective endocarditis, diffuse myocarditis, pericarditis, diffuse cardiosclerosis, severe chronic cardiac arrhythmias, cardiomyopathies etc.

Renal edema - is the decrease of oncotic pressure, as a consequence of proteinuria, sodium retention. Initially, it appears in the lax connective tissue of the face (eyelids), further - on the dorsal surfaces of hands and legs, in the scrotum area; gradually, the edema becomes generalized; the teguments get a pale aspect (white edema). It occurs in nephrites, nephrotic syndrome and acute renal insufficiency.

Dystrophic edema (deficient, cachetic, starvational, nutritional) – the decrease of oncotic pressure due to protein insufficiency in the blood (hypoproteinemia); the increase of vascular permeability, as a result of intratissular tension decrease (disappearance of adipose tissue, muscular atrophy). The edematous tissues have a whitish appearance, the edema lodges particularly in lower extremities and abdominal cavity (ascites). It is noticed in cases of malnutrition, deficiency of proteins in the diet, malabsorption diseases (chronic enterocolitis), hypovitaminoses and cachexy conditions.

II. Localized edemas:

Stasis edema – the increase of pressure in veins or lymphatic vessels. The edema is lodged in the area of the occluded vessel and has a cyanotic aspect. It can be seen in thrombophlebites, in cases of compression of a vein or of a lymphatic vessel (by tumors, adherences, ligatures).

Inflammatory edema – hemodynamic disturbances in the microcirculatory system and increase of permeability of capillaries, due to the action of inflammatory mediators (histamine, serotonin). The edema lodges around the inflammatory focus. It can be seen in different inflammatory processes, especially in exsudatives.

Angioneurotic edema (*anaphylactic*) – the increase of vascular permeability, as a result of the action of histamine and other substances of histaminic type, released by labrocytes during allergic reactions (hypersensitivity) of immediate type. The edema has a white aspect and appears suddenly, more frequently in the facial area (eyelids, lips); larynx, glottis, trachea, bronchi, genital organs. It is seen in Quincke edema, nettle rash.

4. 11. 3. TERMINOLOGY OF EDEMAS

a. Hydropsy (Latin *hydrops*) – generalized edema, accumulation of edema fluid (transudate) in tissues and cavities of the body, especially in subcutaneous tissue, serous cavities and parenchymatous organs. It is mostly used to name the accumulation of fluid in serous cavities.

b. Anasarca (Latin *anasarca*) – accumulation of edema fluid in the subcutaneous adipose tissue (generalized edema of subcutaneous tissue).

c. **Ascites** or **hydroperitoneum** (Latin *ascites s. hydroperitoneum*) – accumulation of edema fluid in abdominal (peritoneal) cavity.
d. **Hydrothorax** (Latin *hydrothorax*) – edema in the pleural cavity (uni– or bilateral).
e. **Hydropericardium** (Latin *hydropericardium*) – pericardial hydropsy, accumulation of edema fluid in the pericardial sac.
f. **Hydrocele** (Latin *hydrocele*) – accumulation of fluid in the vaginal tunica of the testicle (testicular hydropsy).
g. **Hydrocephaly** (Latin *hydrocephalia*) – excessive accumulation of cerebrospinal fluid within the cranial cavity. It may be internal (in the cerebral ventricle cavities) and external (in the subarachnoid space).
h. **Hydrarthrosis** (Latin *hydrarthrosis*) – accumulation of edema fluid in the cavity of a joint.

4. 12. LYMPHATIC CIRCULATION DISTURBANCES

According to the character of disturbances, there are three types of lymphatic circulation insufficiency: mechanical, dynamic and resorptional.

I. Mechanical insufficiency of the lymphatic circulation is caused by the increase of the general venous pressure, local or regional, compression of lymphatic vessels (tumors, scars, adherences, ligatures), their occlusion (parasites, thrombi, tumoral emboli), interruption of lymphatic ways (surgical extirpation of vessels and lymph nodes, for example, in malignant tumors), insufficiency of lymphatic vessel valves, etc.

II. Dynamic insufficiency is determined by the discrepancy between the excess of fluid in tissues and its intensity (rapidity) of elimination. The main causative factor is the excessive filtration of the fluid in capillaries, formation of a large quantity of interstitial fluid, the lymphatic system being unable to eliminate it.

III. Resorptional insufficiency is conditioned by the decrease of lymphatic capillary permeability or by the change of tissular protein composition, causing water retention in tissues.

Lymphatic stasis is manifested morphologically through dilatation of lymphatic vessels (Fig. 4–44), appearance of collaterals, lymphangiectases (persistent dilatation of lymphatic vessels).

Consequently, there may develop a lymphedema (lymphatic edema), **lymphorrhage** or **lymphoreea** (the leakage of lymph from lymphatic vessels), lymphatic or lymphovenous fistulae, lymphogenic sclerosis of tissues. The lymphatic stasis has a sclerogenic action because it causes tissular hypoxia and excessive proliferation of connective tissue (activation of fibroblasts). Edematous tissues are increased in volume, the contours become erased, the skin is hard, thickened; these changes are called elephantiasis and occur more frequently in extremities and genitalia. Lymphorrhage may lead to appearance of **chylous ascites** (accumulation of lymph in peritoneal cavity) or **chylothorax** (accumulation of lymph in pleural cavities).

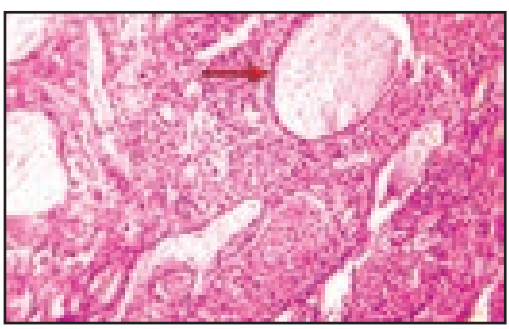


Fig. 4–44. Lymphatic stasis in the wall of the small intestine (hematoxylin–eosin stain; ×70).

ESSENTIAL TERMS
on the subject "THROMBOSIS. EMBOLISM. EDEMA. SHOCK"

air embolism	gaseous embolism	recanalization of thrombus
anaphylactic edema	hyaline thrombus	red thrombus
anaphylactic shock	hydrarthrosis	renal edema
anasarca	hydrocele	retrograde embolism
angioneurotic edema	hydrocephaly	septic shock
ascites	hydropericardium	shock
autolysis of thrombus	hydroperitoneum	"sick" thrombus
cardiac edema	hydropsy	stasis
cardiogenic shock	hydrothorax	stasis edema
cellular embolism	hypovolemic shock	thromboembolism
chylothorax	inflammatory edema	thrombolysis
chylous ascites	lymphedema	thrombosis
consumptive coagulopathy	lymphorrhage	thrombus
DIC-syndrome	lymphorrhea	tissular (cellular) embolism
direct (forward) embolism	lines of Zahn	transudate
dystrophic edema	microbial embolism	traumatic shock
edema	mixed thrombus	vascularization of thrombus
embolism	neurogenic shock	Virchow's triad
fat embolism	organization of thrombus	white thrombus
fibrinolysis	paradoxical embolism	
foreign body embolism	postmortem clot	

TESTS
on the subject "THROMBOSIS. EMBOLISM. EDEMA. SHOCK"

SET I.

Multiple-choice questions with one correct answer

1. Which of the listed factors has a determinant role in the venous thrombosis:
a) blood stasis;
b) reduction of number of platelets;
c) fibronectin;
d) cardiac output;
e) decrease of prothrombin level.

2. Thromboembolism from the lienal vein can occur in the vessels of which organ:
a) kidneys;
b) lungs;
c) liver;
d) brain;
e) stomach.

3. Thromboembolism, which starts in parietal thrombi from the left ventricle, can be in the vessels of all the listed organs, except for:
a) brain;
b) lungs;

c) colon;
d) spleen;
e) kidneys.

4. *Which of the statements that refer to thromboembolism of the pulmonary artery is correct:*
a) the majority of pulmonary thromboembolisms are fatal;
b) the majority of pulmonary thromboemboli originate from lower extremity veins;
c) the majority of pulmonary thromboembolisms occur in children and aged persons;
d) the majority of pulmonary thromboembolisms are of arterial origin;
e) all the statements are correct.

5. *All the listed pathological processes may cause edemas, except for:*
a) cardiac insufficiency;
b) renal insufficiency;
c) arterial occlusion;
d) lymphatic occlusion;
e) venous occlusion.

SET II.

Multiple-choice questions with 2, 3 or more correct answers.

1. *Which of the below listed pathological processes can cause per rhexin hemorrhage:*
a) arterial aneurysm;
b) enzymatic action on the vascular wall;
c) increase of permeability of the vascular wall;
d) transmural myocardial infarction;
e) arterial hypotension.

2. *Which of the listed diseases may complicate with hemorrhage per diabrosin:*
a) arterial hypertension;
b) gastric erosions;
c) tubal pregnancy;
d) pulmonary abscess;
e) vitamin C deficiency.

3. *Which of the listed signs are not characteristic for thrombi:*
a) smooth surface;
b) friable;
c) adherence to the vascular wall;
d) elastic consistency;
e) lines of Zahn.

4. *In the vessels of which organs paradoxical thromboembolism can occur, if the starting point of the emboli are the superficial veins of lower extremities:*
a) brain;
b) kidneys;
c) lower extremities;
d) lungs;
e) spleen.

5. *In the vessels of which organs direct thromboembolism from the femoral vein can occur:*
a) spleen;
b) lungs;
c) liver;
d) brain;
e) myocardium.

SET III.

The classification tests include 2 – 4 subjects and a series of answers. Indicate which answers are correct for each separate subject.

1. In the vessels of which organs listed below direct thromboembolism may occur, if the initial localization of the thrombus will be:

I – tricuspid valve;
II – aortic valves;
III – pelvic veins;
IV –aortic bifurcation area;
a) pulmonary vessels;
b) brain vessels;
c) lienal vessels;
d) kidney vessels;
e) intestinal vessels;
f) vessels of lower extremities.

2. Which of the elements listed below are characteristic for:

I – *air embolism*;
II – *gaseous embolism*;
a) it is seen in the atony of the uterus after delivery;
b) it is produced in cervical injuries;
c) it is frequently complicated with foci of ischemic necrosis in the brain and spinal cord;
d) it manifests itself by dilatation of the right heart cavities;
e) it may occur in pilots in case of rapid rising or landing;
f) to diagnose it, it is necessary to pierce the right heart under water, filling the pericardium with water beforehand.

3. Which of the elements listed below characterize the embolism:

I – *fat embolism*;
II – *cellular* (tissular) *embolism*;
III – *microbial embolism*;
a) it is often seen in multiple fractures of bones;
b) it is seen in traumas of subcutaneous adipose tissue in the obese;
c) it occurs in malignant tumors;
d) it occurs in septicemia;
e) to diagnose one uses the Sudan III stain;
f) destruction of cardiac valves in infective endocarditis.

4. In which of the listed diseases develop the:

I – hypovolemic shock;
II – cardiogenic shock;
III – traumatic shock;
IV – endotoxic shock;
a) heart rupture;
b) severe infections;
c) massive hemorrhages;
d) multiple bone fractures;
e) extended burns;
f) repeated vomiting and diarrhea;
g) rupture of aortic aneurysm.

5. Which of the listed elements characterize the:

I – anasarca;
II – elephantiasis;
a) it can be seen in occlusion of lymphatic ways with cancerous cells;
b) it is accompanied by hydrothorax, ascites, hydropericardium;
c) it is caused by chronic cardiac insufficiency;
e) generalized edema with marked tumefaction of the subcutaneous tissue;
f) it is one of the consequences of extirpation of regional lymph nodes in different forms of cancer.

SET IV. SITUATIONAL PROBLEMS

Daily practice cases are presented with clinical and morphological data from clinical histories and/or from necropsy protocols. Each subject includes simple or multiple - answer questions, with 1, 2 or more correct answers.

1. A patient, who suffered a subendocardial myocardial infarction, lost suddenly the sight in her right eye. The ophthalmologist detected dilatation of the central artery of retina and a blood clot in its lumen. The echocardiography revealed a parietal thrombosis in the left ventricle.

Questions:

A) *Which is the cause of development of intracardiac thrombosis in case of subendocardial myocardial infarction:*
a) blood stasis;
b) reactive inflammation of endocardium;
c) blood flow turbulence;
d) thrombocytosis;
e) myomalacia.

B) *What pathological process caused the loss of sight:*
a) thrombosis;
b) artery spasm;
c) thromboembolism;
d) embolism with cholesterol crystals;
e) cellular embolism.

2. A 38-year-old patient underwent hemorrhoidectomy. In 6 hours after the surgery, there appeared signs of acute disturbances of cerebral circulation, paralysis of half of the body and, in 24 hours, the patient died because of cerebral edema with dislocation of brainstem (its enclave in the big occipital hole). One suspected of thromboembolism of cerebral arteries.

Questions:

A) *According to the direction of embolus circulation, which variant of embolism occurred in the given case:*
a) indirect;
b) retrograde;
c) direct;
d) collateral;
e) paradoxical.

B) *Which organ should be examined in details in order to confirm the diagnosis:*
a) lower extremities;
b) lungs;
c) heart;
d) spleen;
e) liver.

C) *Which variant of cerebral infarction has developed in this case:*
a) hemorrhagic;
b) ischemic;
c) ischemic with hemorrhagic border;
d) mixed;
e) hematoma.

3. An 18-year-old girl fell down from a swing and suffered multiple fractures of the leg bones from both sides. She was taken to traumatology department without immobilization of the fractured extremities. She died in 24 hours because of acute respiratory insufficiency.

Questions:

A) *What complication can be suspected in this case:*
a) fat embolism;
b) air embolism;
c) thromboembolism;

d) microbial embolism;
e) gaseous embolism.

B) *Which organ must be examined in details to confirm the diagnosis:*
a) heart;
b) liver;
c) lungs;
d) kidneys;
e) brain.

C) *What histochemical reactions should be applied to confirm the diagnosis:*
a) hematoxylin and eosin;
b) Congo red;
c) carmine;
d) Sudan III;
e) Sudan IV.

4. At the necropsy of a young man who died of polyorganic insufficiency due to a venous snake bite, multiple thrombi were revealed in the micro-vessels of the lungs, brain, kidneys, gastrointestinal tract, liver, adrenals and skin. Concomitantly, multiple petechiae hemorrhages were observed in the lungs, brain, as well as dystrophic lesions in tissues and organs.

Questions:

A) *Which variant of hemodynamic disorders has developed in this case:*
a) generalized venous hyperemia;
b) systemic thrombosis;
c) hemorrhagic syndrome;
d) DIC syndrome;
e) marantic thrombosis.

B) *What is the pathogenetic mechanism of the development of this syndrome:*
a) thrombocytosis;
b) erythrocytosis;
c) hyperfibrinogenemia;
d) consumptive coagulopathy;
e) thromboembolic syndrome.

5. A 17-year-old girl presents generalized edemas, more emphasized in lower extremities, which appeared after 3 weeks of artificial hunger in order to lose weight.

Questions:

A) *Which variant of edema has developed in this case:*
a) allergic;
b) angioneurotic;
c) hypoproteinemic;
d) renal;
e) cardiac.

B) *Which are the criteria of differentiation of transudate from exudate:*
a) transparent;
b) dim;
c) rich in proteins;
d) poor in proteins;
e) rich in cellular elements;
f) poor in cellular elements.

C) *The name of generalized edemas with accumulation of fluid in the subcutaneous adipose tissue:*
a) hydropsy;
b) hydrothorax;
c) hydroperitoneum;
d) anasarca;
e) ascites.

INFLAMMATION

Inflammation (Latin *inflammare* – kindling) – local organism reaction to tissue alteration, due to different pathogenic factors. It is a defensive reaction directed towards **elimination** (for example, bacteria elimination through exudates), **inactivation** (for example, bacteria phagocytosis) or pathogenic agent **delimitation** (for example, in foreign body granulomas) and reestablishment of structure and function of the injured tissue. The inflammatory process is firstly manifested by modification of the microcirculatory system, connective tissue and blood vessels. The inflammation occurs only in vascularized tissues.

5.1. CAUSES, MORPHOLOGY, TERMINOLOGY AND CLASSIFICATION OF INFLAMMATION

The inflammation can be caused by different physical, chemical and biological factors of exogenous and endogenous origin, which have a harmful action on tissues, causing cellular/tissular injuries.

Morphologically, one distinguishes 3 stages in the evolution of the inflammatory process: 1) alterative; 2) exudative; 3) proliferative.

Dystrophic and necrotic modifications are produced in the lesion focus, in the **first alterative stage** of inflammation. Both parenchymatous cells and ground substance, cellular and fibrillar elements of connective tissue (Fig. 5–1) are affected.

Consequently, some biologically active substances – the so–called *chemical mediators* of the inflammation are elaborated. These substances act on blood vessels, determine the evolution of the inflammatory process and the appearance of exudative reaction. The most important mediators are biogenic amines, coagulation factors, complement, arachidonic acid derivatives and cytokines. According to the origin, inflammation mediators can be cellular (tissular) and plasmatic. The most important source of active amines is mastocytes, which produce histamine, serotonin and heparin. Basophilic leukocytes, platelets, lymphocytes, monocytes, macrophages,

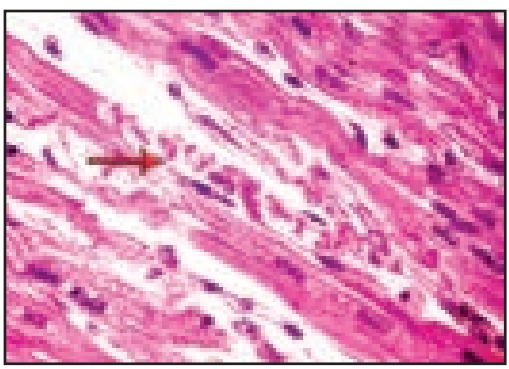


Fig. 5–1. Diphtheric myocarditis: vacuolar dystrophy and coagulation necrosis of cardiomyocytes, mononuclear cell infiltration (hematoxylin–eosin stain; ×70).

endotheliocytes also produce a wide range of pro-inflammatory mediators (leukotrienes, prostaglandins, thromboxanes, cytokines etc.). These substances can be eliminated from the cells via 2 ways: a) through *exocytosis* – a process which reminds secretion (it is observed in leukocytes) and b) through *degranulation* – expulsion of granules from cytoplasm and their further disintegration in the extracellular space (it is observed in mastocytes) (Fig. 5–2). An important role among plasmatic mediators is played by the kinins (bradykinin, kallikrein,) some components of the complement and coagulation and anticoagulation system of the blood.

The **II exudative stage** of the inflammation is determined by chemical mediators (primarily histamine and serotonin) and is manifested through 3 important processes:

a. dilatation of the microcirculatory system vessels and blood flow disturbance (modification of blood rheological properties);
b. exudation (extravasation) of plasma;
c. migration of blood cells.

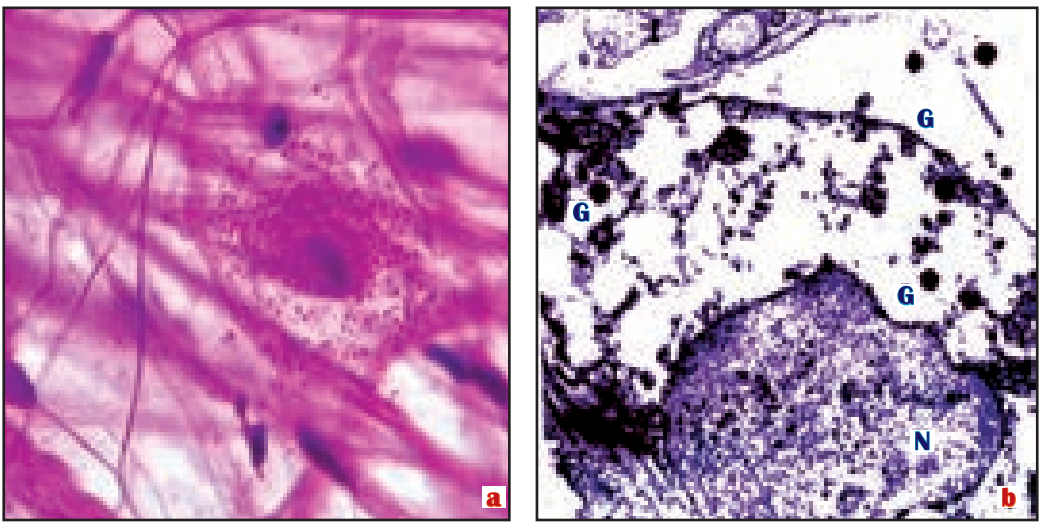


Fig. 5–2 a, b. Degranulation of mastocyte: a - microscopic pattern (azure–eosin stain; ×70); b – electron microscopic picture (×1000); G – granules of mastocytes, N – nucleus.

Dilatation of the microcirculatory bed **vessels**. Initially, a short-term vasoconstriction of arterioles appears in the inflammatory focus (some seconds or minutes). Later, a dilatation of arterioles, capillaries and venules (mainly of postcapillaries and venules) develops fast under the action of histamine; this determines an increased blood flow and active inflammatory hyperemia of the lesion focus. Clinically, these vascular modifications are manifested through *redness and local fever* (heat).

Extravasation from vascular bed is determined by the raise of the hydrostatic pressure and permeability of the microcirculatory system vessels, mainly of the venules. The increase of permeability, at the initial stage of the inflammation, is due to formations of some fissures among endothelial cells, which appear through contraction of endotheliocytes, under the action of bradykinin and histamine. Intensification of the *pinocytosis* processes takes place later in the endotheliocytes of the vascular walls and

plasma is evacuated through basement membrane, which also has an increased permeability (Fig. 5–3). These modifications are stimulated by the VEGF (*vascular endothelial growth factor*). Consequently, the active transendothelial transport of blood plasma, fluid accumulation in tissues (in the extravascular spaces) and appearance of *inflammatory edema and local tumefaction* are produced. Inflammatory edema is partly caused by the decrease of plasma oncotic pressure, as a consequence of loss of proteins with the extravasated plasma fluid.

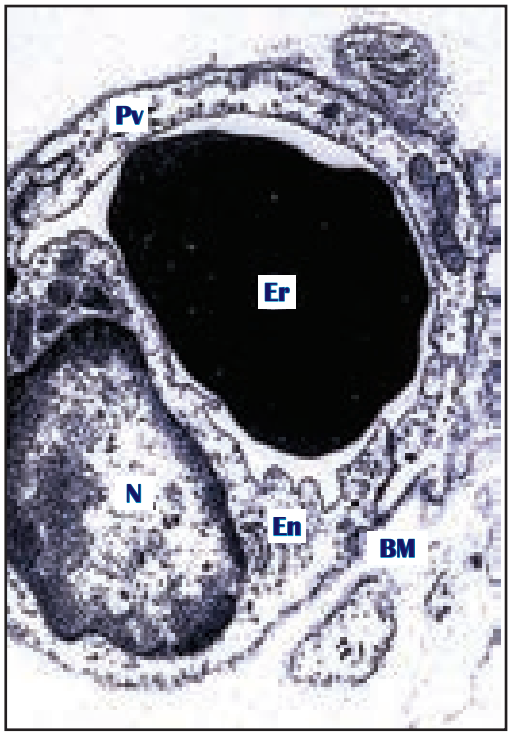


Fig. 5–3. Pinocytosis in the endothelium of capillary in inflammation (electron microscopy ×1000): Pv – pinocytic vesicles, En – endotheliocyte, Er – erythrocyte, BM – basement membrane, N – nucleus.

Migration of the blood cells represents the main aspect of the cellular stage of the inflammatory reaction. This process begins with neutrophil leukocytes margination, when they detach from the axial area of the blood column, constituted from cellular elements, moving towards the vascular wall (Fig. 5–4). Neutrophils extend on the endothelial surface and gradually form a continuous leukocyte layer. Activation of leukocytes and endotheliocytes leads to expression of adhesion molecules – integrins - and establishment of close contacts between

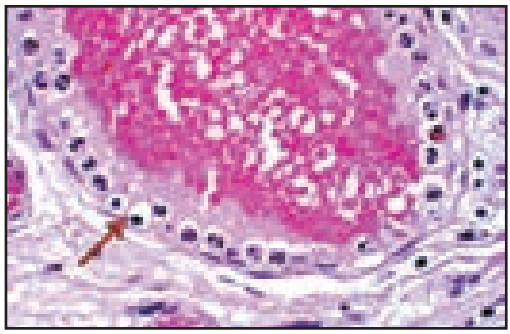
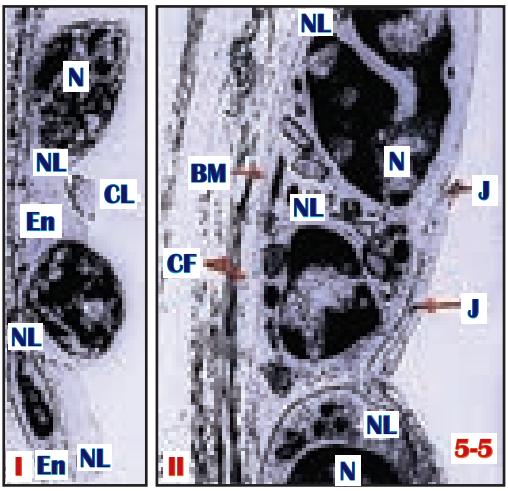


Fig. 5–4. Venule dilatation, hyperemia and leukocytes margination (hematoxylin–eosin stain; ×110).

these cells. Further on, leukocytes issue cytoplasmatic expansions (pseudopods), which slip actively at the junction level, among endotheliocytes (interendothelial), in the subendothelial space (Fig. 5–5). Leukocytes change their form during migration due to polymerization and redistribution of microtubules and microfilaments of the cellular cytoskeleton. After this, neutrophils penetrate the basement membrane within the thixotropy phenomenon (modification of colloidal state of the ground substance of the basement membrane) and penetrate in the perivascular connective tissue (Fig. 5–6). The fact that leukocytes secrete collagenases is also important, as they increase the permeability of the basement membrane. The leukocyte diapedesis takes place predominantly in postcapillaries and venules, and in the lungs – at the level of septal capillaries as



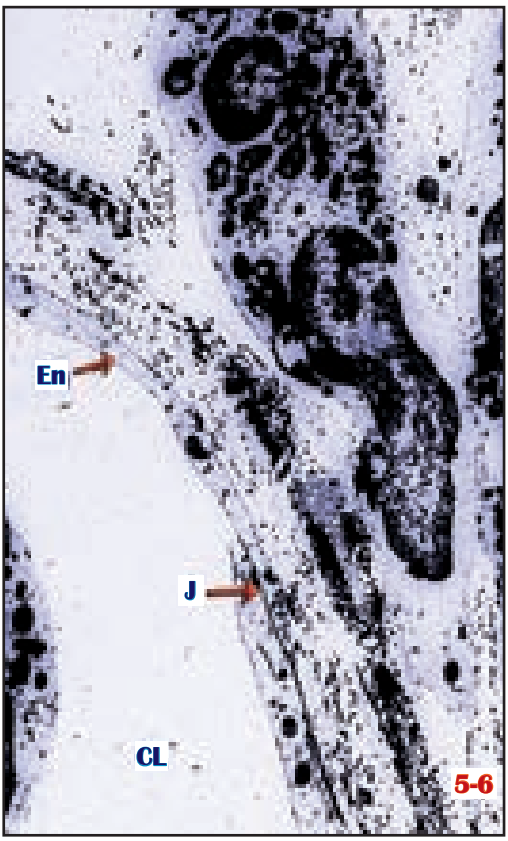


Fig. 5–5, and 5–6. Migration of neutrophil leukocytes in inflammation (electron microscopy; Fig. 5–5/I and 5-6 ×12000, Fig. 5–5/II ×20000): NL – neutrophil leukocyte, En – endothelium, BM –basement membrane, N – nucleus, J – junction between endotheliocytes, CF – collagen fibers, CL – capillary lumen.

well. Active migration of monocytes and eosinophils occurs according to the same mechanism, and lymphocytes cross the vascular wall through endothelial cell cytoplasm (transendothelial). Erythrocytes strain the vascular wall passively, through the same holes as neutrophils (Fig. 5–7). Basement membrane integrity is reestablished after cell migration.

Polymorphonuclear neutrophils that reached the perivascular space move actively towards the pathogenic agent by ameboid movements, by means of cyto-

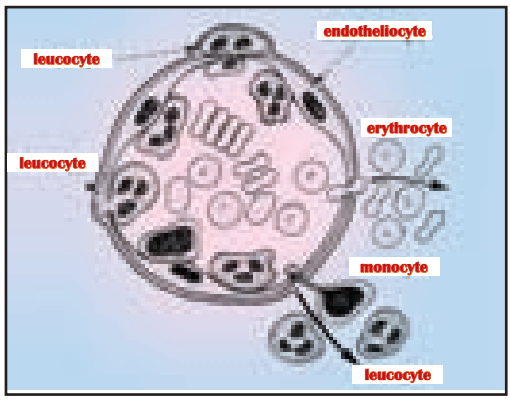


Fig. 5–7. Blood cell migration scheme in inflammation

plasm expansions, whose length can be 10 times longer than leukocyte's diameter. The travel speed of the neutrophil is nearly 0,02 mm per minute. This oriented (directed) movement of neutrophils is due to substances with a positive chemotactic action – the so–called attractant substances (immune complexes, complement activation products, bacterial exotoxins, arachidonic acid derivatives, mitochondrial polypeptides from the injured cells).

The main function of polymorphonuclear leukocytes and monocytes in the inflammation area is **phagocytosis** – engulfing of some microorganisms, tissular remnants, foreign micro-particles or

other substances and their intracellular destruction (digestion). Neutrophils are specialized cells which possess the capacity to phagocyte small bodies, especially microorganisms (*microphages*); monocytes and histiocytes phagocyte big particles, for example foreign bodies (*macrophages*). The phagocytosis process includes 2 main stages: 1) attachment of particles or microbes to the phagocyte membrane, its invagination and their penetration into the cytoplasm; 2) formation of phagocytic vacuoles (digestive vacuoles) around the engulfed particles and their intracellular digestion by the action of lysosomal enzymes (Fig. 5–8).

Bacteria attachment to the leukocyte membrane is facilitated by opsonins (*Greek opsonion = spice*) – proteic molecules which are normally found in blood plasma and in the interstitial fluid. The main opsonins are immunoglobulins G, the complement component C3, some pectins. The bactericidal action is made by means of different mechanisms: lysosomal enzymes, cationic proteins, hypochlorous acid and other bioactive substances. Neutrophil leukocytes undergo dystrophic modifications, especially fat dystrophy and die, but monocytes survive for a long time due to their capacity of new lysosomes production and resynthesis of lysosomal enzymes. Phagocytosis may be complete and incomplete. The latter may favor dissemination and generalization of infection. Phagocytosis is the key phenomenon of the inflammatory process.

As a consequence of these processes, firstly of plasmatic fluid extravasation and migration of blood cells, **exudates** (*inflammatory fluid*) are formed in tissues as an inflammation final product (Fig. 5–9 and 5–10).

The main components of the exudate are:

a) fluid part – water with proteins (albumins, globulins, fibrinogen),

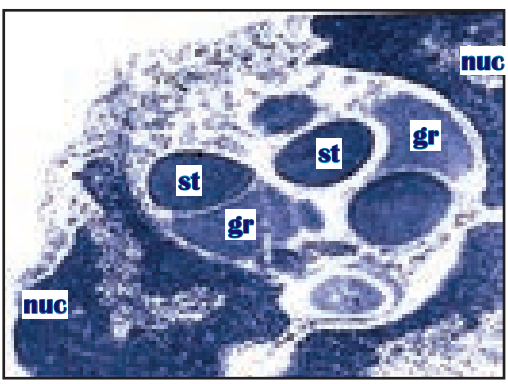


Fig. 5–8. Phagocytosis (electronic microscopy; ×1500): st – staphylococci, vac – digestive vacuole, gr – lysosomal granulations, which contain hydrolytic enzymes, nuc – nucleus.

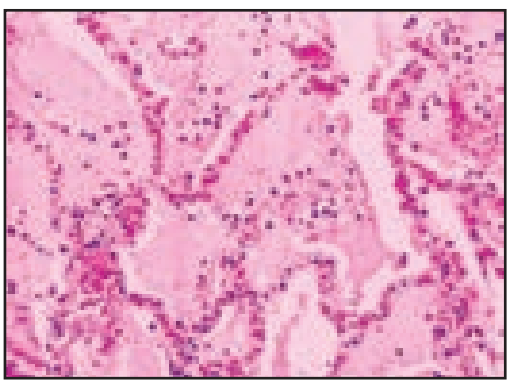


Fig. 5–9. Serous focal pneumonia (hematoxylin–eosin stain; ×110).

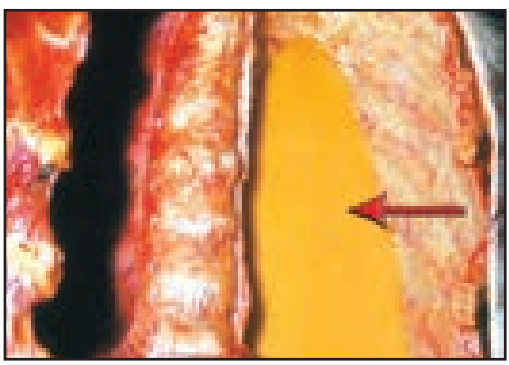


Fig. 5–10. Purulent pleuritis.

their content being higher than 3%;

b) cellular elements of hematogenic (especially leukocytes and mononuclear phagocytes) and histiogenic origin (local connective tissue cells and epithelial, parenchymatous cells);

c) products of tissue destruction (*tissue detritus*).

The consistency, aspect, color, character of the exudate depend on the proportion of its components.

Exudate accumulation in the inflammatory focus produces local tissue tumefaction and pain. The pain is generated by nerve endings compression due to tissular tension, caused by the inflammatory edema and their excitation by chemical mediators (bradykinin, prostaglandins). Pain and local tumefaction determines function disturbance of the inflamed organ (tissue).

Accordingly, the local clinical sings of inflammation are the following (Fig. 5–11, 5–12, 5–13):

1) redness (rubor);
2) local fever (calor);
3) tumefaction (tumor);
4) local pain (dolor);
5) loss of function (functio laesa).

General (systemic) manifestations of inflammation are fever, tachycardia, tachypnea, leukocytosis, ESR increase (erythrocyte sedimentation rate), general intoxication, which is manifested through poor appetite, tiredness, sleepiness etc.

The III *proliferative* stage of the inflammatory process manifests itself through cellular element multiplication in the inflammatory focus. Vessel hyperemia, plasma extravasation and cell migration in tissues diminish gradually, the affected area being delimited from the adjacent tissues.

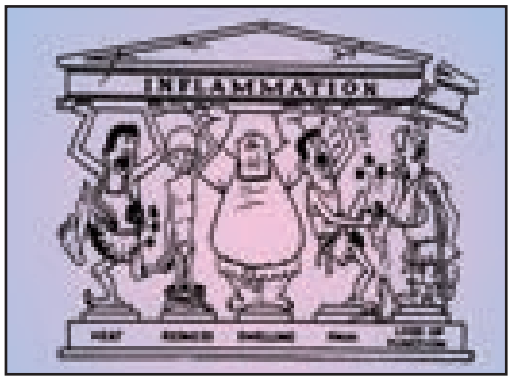


Fig. 5–11. Clinical signs of inflammation (heat, redness, swelling, pain, loss of function) (by D. A. Wiloughby and W. G. Spector, 1968).

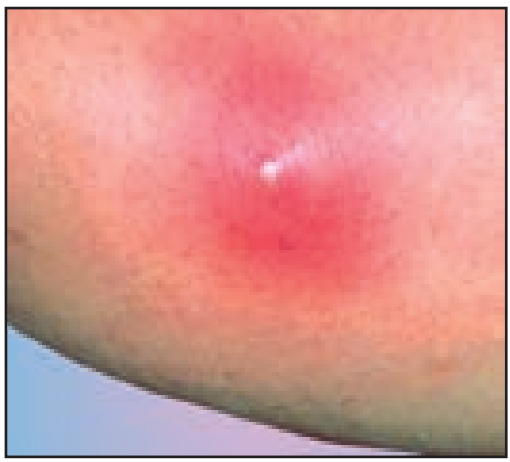


Fig. 5–12. Furuncle (purulent inflammation of the pilosebaceous follicle).

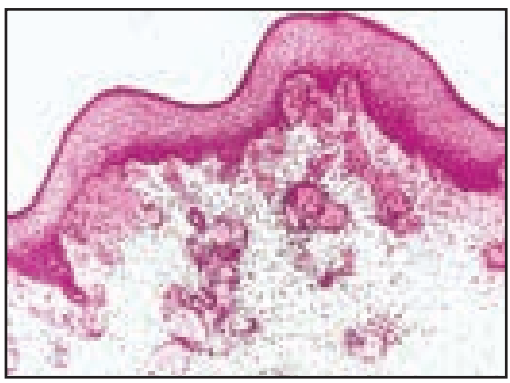


Fig. 5–13. Inflammatory hyperemia and edema of skin (purulent inflammation of the pilosebaceous follicle); (hematoxylin–eosin stain; ×70).

The localized agglomeration of cells in the inflammatory focus is called **inflammatory infiltrate.** It is composed of lymphocytes, plasmocytes, macrophages and their derivatives; leukocytes are rarely met (Fig. 5–14)

The cells from the infiltrate perform certain functions, for example, macrophages – phagocytosis, lymphocytes and plasmocytes – immune processes etc. A part of the cells die in time and others transform gradually in fibroblasts. Fibroblasts synthesize collagen and glycosaminoglycans, which assemble extracellularly in collagen fibrils and the inflammatory process ends with fibrillar connective tissue formation.

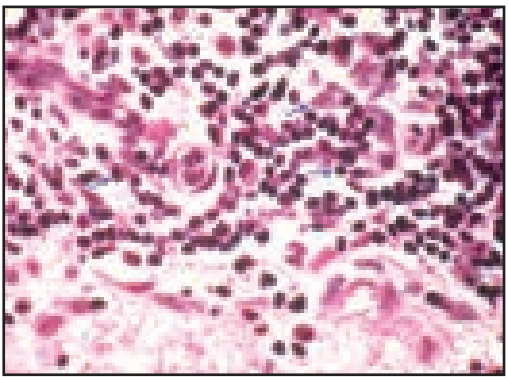


Fig. 5–14. Cellular inflammatory infiltrate in focus of inflammation (lymphocytes, plasmocytes, macrophages); (hematoxylin–eosin stain; ×70).

Consequences of inflammation – regeneration and recovery of altered tissues. In cases of small inflammatory foci, a complete recovery with exudate resorption and tissue detritus by means of phagocytes and their elimination takes place. In case of extensive and profound defects, the regeneration is incomplete, partial, the inflammatory focus being substituted with cicatricial fibroconnective tissue (*fibrosis* and *sclerosis*).

The inflammation character depends on:

a) causative factor features (for example, in lungs, pneumococcus causes more frequently fibrinous inflammation, staphylococcus aureus – purulent inflammation, influenza virus – hemorrhagic inflammation);
b) inflammatory process localization (the structural and functional particularities of the organ, for example, the lungs have a lax structure, the bones – a hard, compact structure);
c) reactivity state of the macroorganism (for example, in immune deficiency cases, the inflammatory reaction is more severe and extended, having the tendency for morbid process generalization).

Inflammation terminology: the suffix *–itis* is added to the Greek or Latin organ name root. For example, myocard–*itis*, gastr–*itis*, nephr–*itis*, hepat – *itis*, mening – *itis* etc. Latin or Greek terms are used in the medical literature concerning the inflammation of one or other organ. For example, fallopian tube inflammation – salpingitis (tube = Gr. – *salpinx*, Latin – *tubus*), kidney inflammation – nephritis (kidney = Gr. – *nephros*, Latin – *ren*) etc. The inflammation of some organs/tissues has specific names, for example *furuncle* – pilosebaceous follicle inflammation, *empyema* – inflammation of some cavities with accumulation of purulent exudate in them, *pneumonia* – pulmonary parenchyma inflammation with exudate formation in the alveoli, *pneumonitis* – inflammation of the interstitial tissue of the lungs etc.

Inflammation classification

Morphologically, inflammation is subdivided in:

1) exudative;
2) proliferative (productive).

A severe alterative reaction takes place in some cases of severe toxic in-

fections, allergic diseases, with tissues necrosis. Such inflammatory processes can be defined as alterative or necrotic inflammation, for example, alterative myocarditis in diphtheria, allergic necrotic vasculitis etc.

Clinically, the following forms of inflammation can be distinguished:

- ✧ acute (lasts not more than 2–3 weeks); it is usually an exudative inflammation;
- ✧ chronic (lasts months and years); the inflammation has a proliferative character.

5.2. ACUTE (EXUDATIVE) INFLAMMATION

It is an immediate reaction to a tissular lesion with a sudden, short time onset. It is characterized by predominance of reaction of microcirculatory bed vessels and formation of exudate in tissues and in body cavities.

According to the exudate features, one distinguishes the following exudative inflammation varieties: 1) serous; 2) fibrinous; 3) purulent; 4) putrid; 5) hemorrhagic; 6) catarrhal; 7) mixed.

5.2.1. SEROUS INFLAMMATION

The exudate is a yellowish, opalescent fluid, which contains 3–8 % of proteins (albumins); it resembles the blood serum and is poor in cellular elements (Table 5.1.).

Table 5.1

Main criteria of differentiation of exudate from transudate

Fluid characteristics	*Transudate*	*Exudate*
External aspect	Transparent	Diffuse, opaque
Consistency	Liquid	Viscous
Density	<1,015 g/ml	>1,020 g/ml
Protein concentration	<3 g/dl	>3 g/dl
Cell content	Insignificant number of mesothelial cells, lymphocytes, leukocytes	Numerous neutrophils
Coagulation	Does not coagulate	Coagulates
Bacteriologic examination	Sterile	Contains microbes

The serous inflammation localization can be various, the exudates accumulating in serous cavities, mucosas, meninges, skin (Fig.5-15 a, b), in interstitial spaces of parenchymatous organs (myocardium, liver, kidneys, lungs). Exudate reabsorption, with complete recovery of the altered tissue, takes place, as a **consequence** of serous inflammation.

As a rule, the serous inflammation evolutes acutely (1–2–3 weeks) or even very acutely (2–3 days), having usually a light clinical evolution. In some cases, serous inflammation can cause major clinical manifestations through compression of parenchymatous organs (in pericarditis, serous pleuritis) or through disturbance of their function (for example, in myocarditis, hepatitis, serous glomerulonephritis).

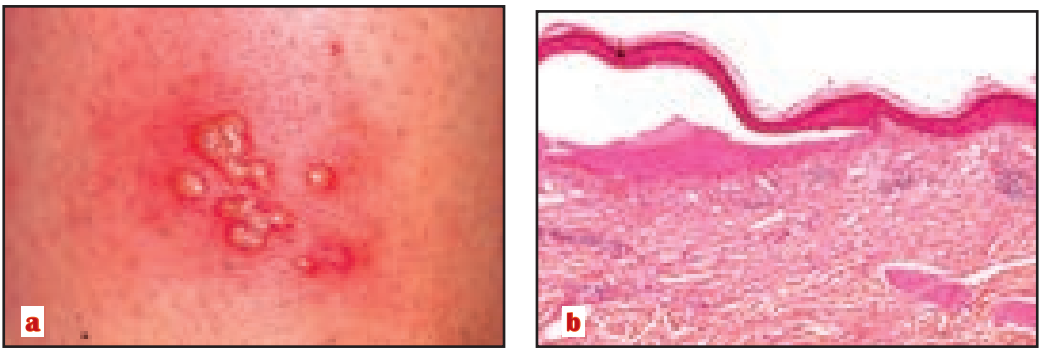


Fig. 5–15. Epidermal vesicles with serous exudate: a – macroscopic aspect; b – microscopic pattern (hematoxylin–eosin stain; ×110).

5.2.2. FIBRINOUS INFLAMMATION

It is characterized by formation of an exudate rich in fibrin. It is more frequently localized in mucous and serous membranes, but it is also met at the level of parenchymatous organs, for example, in the lungs (lobar pneumonia), kidneys (fibrinous glomerulonephritis) etc. It appears in cases when the causative agent provokes a marked increase of the vascular permeability, which favors fibrinogen extravasation. After the exit from vessels, fibrinogen coagulates in fibrin under the action of thromboplastin, which is eliminated as a result of tissue necrosis. It is met in infectious diseases (typical examples - diphtheria, dysentery, lobar pneumonia), intoxications (for example, in uremia) or under the action of some physical factors (for example, in burns).

The exudate has an aspect of false membrane or pseudomembrane of whitish–yellowish color on the mucous (Fig. 5–16 a, b and 5–17) and serous surfaces or an aspect of dense mass formed in parenchymatous organs, more frequently in lungs (Fig. 5–18). The pseudomembrane notion is used for differentiation of true anatomic membranes. The pseudomembranous inflammation is observed in the respiratory tract (pharynx, larynx, trachea, bronchi), in the stomach, small intestine, colon, endometrium. Lesions of mucosae constitute initially necrosis of superficial layers under the action of bacterial toxins. Furthermore, necrotized epithelial cells desquamate and combine with the fibrinous, mucous exudate, the content from lumen or respective cavity, forming a coating (pseudomembrane),

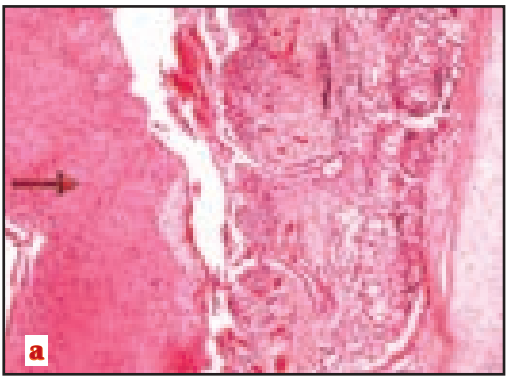


Fig. 5–16 a. Croupous tracheitis in diphtheria (diphtheric croup): microscopic pattern (hematoxylin–eosin stain; ×110).

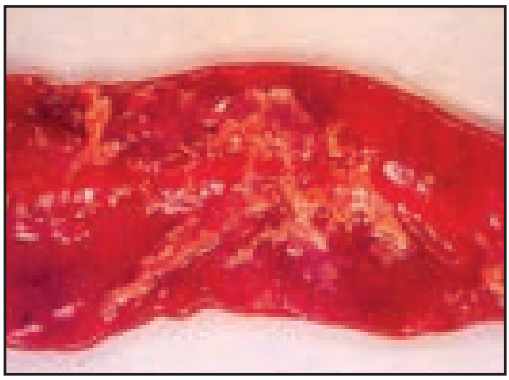


Fig. 5–17. Fibrinous enteritis.

Fig. 5–16 b. Croupous tracheitis in diphtheria (diphtheric croup): macroscopic aspect.

Fig. 5–18. Lobar pneumonia (gray hepatization stage).

which covers the defect and adjacent mucosa. Examined endoscopically, the respective coatings can be detached and the subjacent mucosa with the bleeding surface appears. The proteolytic activity of leukocyte enzymes at the limit level between live and necrotized tissue favors the detachment of pseudomembranes. The epicardium in fibrinous pericarditis is covered with a whitish–yellowish mass of fibrin, which has villous aspect due to the heart movements (Fig. 5–19 a, b). The heart gets a hairy or "cat's tongue" aspect (villous or hairy heart). It is met in rheumatism, tuberculosis, transmural myocardial infarction, uremia etc. The fibrinous inflammation on the pleura has a similar aspect (Fig. 5–20 a, b).

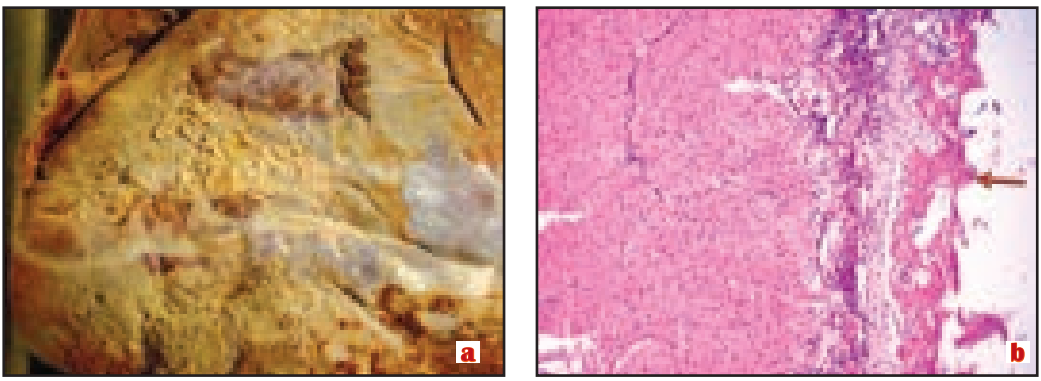


Fig. 5-19 a, b. Fibrinous pericarditis (villous heart): a – macroscopic aspect; b – microscopic pattern (hematoxylin–eosin stain; ×70).

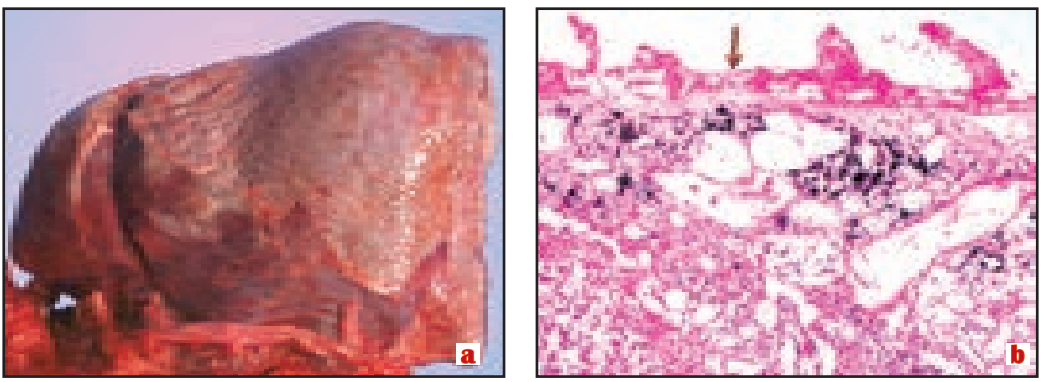


Fig. 5-20 a, b. Fibrinous pleuritis: a – macroscopic aspect; b – microscopic pattern (hematoxylin–eosin stain; ×70).

There are two forms of fibrinous inflammation: croupous and diphtheroid.

The fibrin membrane is thin, fine in **the croupous inflammation**, it adheres poorly to the subjacent tissues and detaches easily, due to the fact that the necrosis of mucosae and serosas is superficial.

The fibrin membrane is thicker in **the diphtheroid inflammation**, it adheres closely to the subjacent tissue, making the detachment more difficult. The necrosis in these cases is more profound; fibrin and necrotic mass form a compact common membrane, which leaves profound, sometimes bleeding ulcerations after detaching.

The croupous or diphtheroid character of the fibrinous inflammation depends not only on the depth of necrosis, but also on the type of the covering

epithelium of mucosae. Diphtheroid inflammation (buccal cavity, tonsils, plica vocalis, esophagus, uterine cervix) is observed on membranes covered with stratified squamous epithelium. Croupous inflammation (upper respiratory tract, gastrointestinal tract, endometrium, pleura, peritoneum and pericardium) is observed more on mucosae covered by glandular, monostratified epithelium and on serosas (mesothelium).

The consequences of the fibrinous inflammation can be various: in some cases, complete resorption of exudate takes place, due to the fibrinolytic action of leukocyte enzymes. In other cases, the fibrin is not reabsorbed, its organization being produced by appearance of some scars on the mucosae or some adherences (also called symphyses or synechiae) between the serous sheets, with partial or total cavity obliteration (pericardial, pleural, peritoneal) and functional disturbances of the respective organs.

The fibrinous pericarditis results often in exudate organization and formation of some adherences between pericardium sheets, later - in pericardial sac obliteration. In time, calcium salts are deposited in sclerotic serous membranes, which petrify or ossify ("heart in cuirass") and this leads to chronic progressive cardiac insufficiency. The formation of adherences in the pleura reduces the amplitude of the lung respiratory movements, and peritoneal adherences can cause intestinal occlusion.

5.2.3. PURULENT INFLAMMATION

It is characterized by predominance of neutrophil leukocytes in exudates, necrosis and lysis of tissues (histolysis).

The pus is a viscous, turbid liquid of yellowish–greenish color, composed of polymorphonuclear neutrophils, which undergo dystrophic modifications (mainly fat dystrophy) and disintegrate gradually (the so–called *pus globules* or *pyocytes*), tissular detritus and microbes. The purulent inflammation is more frequently caused by pyogenic bacteria (staphylococcus, streptococcus, meningococcus, bacillus coli etc.). Necrosis is generated both by direct injury action of pyogenic bacterial toxins on the tissues, and by circulatory disorders (related to vessel thrombosis or its compression by inflammatory edema). Histolysis (proteolysis) is produced through proteolytic enzymes eliminated by live neutrophil leukocytes or leukocytes in disintegration. A semi-liquid, viscous mass appears after the lysis of the altered and necrotized tissue.

There are two morphological variants: **abscess** and **phlegmon**.

The **abscess** is a focal purulent inflammation, circumscribed with tissue lysis and formation of a cavity filled with pus.

The abscess can be acute and chronic. The **acute abscesses** are delimited from the respective organ's tissue by a fibrinoleukocytic exudate or by granulation tissue (Fig. 5–21 a), **chronic abscesses**

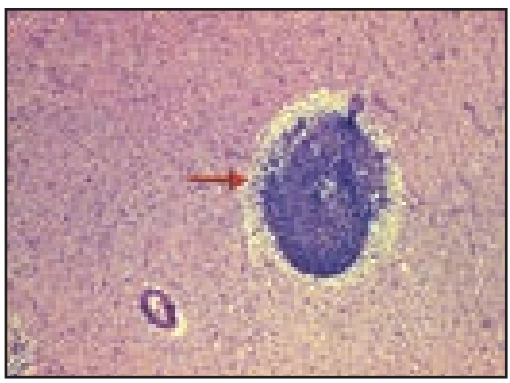


Fig. 5-21 a. Cerebral abscess – microscopic pattern (hematoxylin–eosin stain; ×70).

are delimited by the pyogenic membrane formed of granulation tissue, rich in capillaries, which produce intense leukocyte migration. Outwardly, the membrane is formed of fibrous connective tissue (Fig. 5–21 b, 5–22, 5–23 a, b).

Consequences of abscesses may be the following ones:

a) organization (cicatrization);
b) petrification (condensation and pus calcification);
c) fistulization – fistula formation,

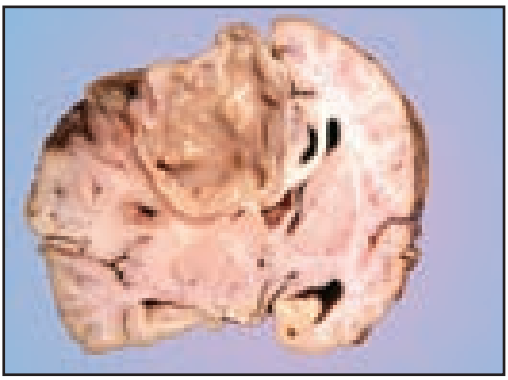


Fig. 5-21 b. Cerebral abscess – macroscopic aspect.

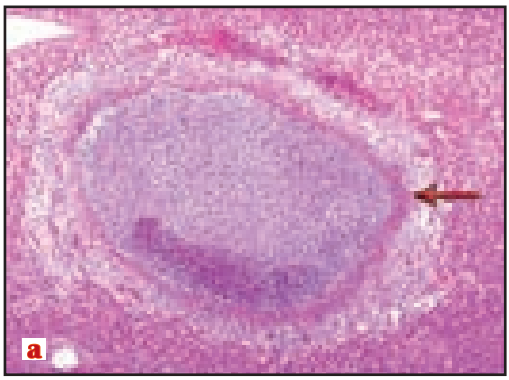


Fig. 5-23 a. Hepatic abscesses – microscopic image (hematoxylin–eosin stain; ×70).

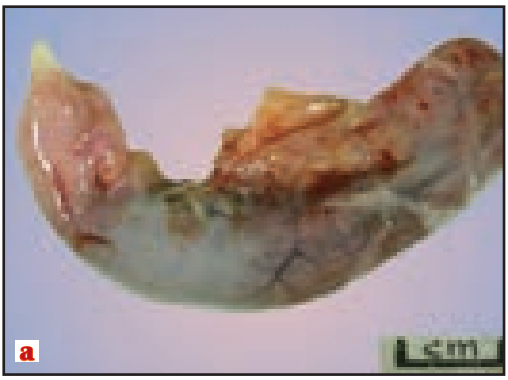
Fig. 5-22. Pulmonary abscesses.

Fig. 5-23 b. Hepatic abscesses – macroscopic aspect.

through which the pus is evacuated externally or in a preexistent cavity of the body. The pathologic channel through which the pus drains is called *fistula*. The fragments of tissue, which cannot be subject to autolysis or organization, or cannot get out because of their huge volume, are called *sequesters* (for example: osseous sequesters in chronic purulent osteomyelitis).

The **phlegmon** (phlegmonous inflammation) is a purulent inflammation without precise delimitation, where the exudate spreads diffusely among tissular elements. The pus spreads along intermuscular areas, adipose tissue, neurovascular trunks etc. It is caused mostly by the hemolytic streptococcus, which produces large quantities of hyaluronidase and fibrinolysin. The latter alter the ground substance and favor the spreading of inflammatory process. It is met in adipose tissues, muscles, walls of hollow and tubular organs (vermiform appendix, gallbladder, stomach, intestine etc.), in leptomeninges etc. (Fig. 5–24 a, b, 5–25 a, b).

Macroscopically, the inflamed area



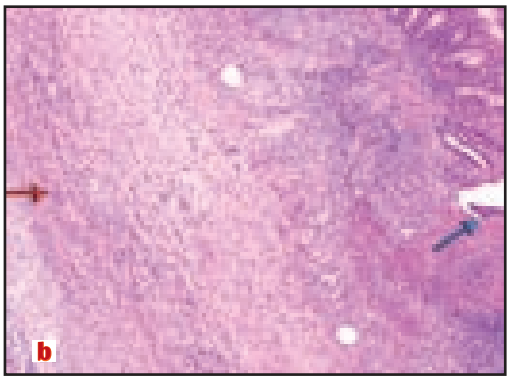
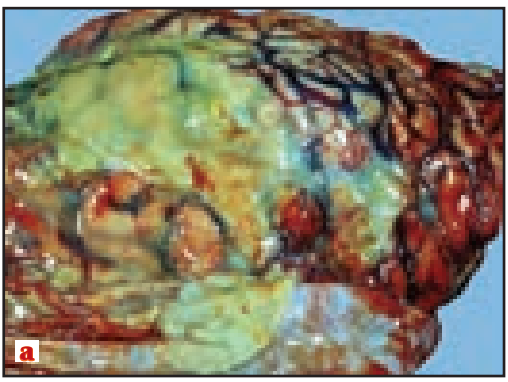


Fig. 5-24 a, b. Acute phlegmonous-ulcerative appendicitis: a – macroscopic aspect; b – microscopic pattern (hematoxylin–eosin stain; ×70).



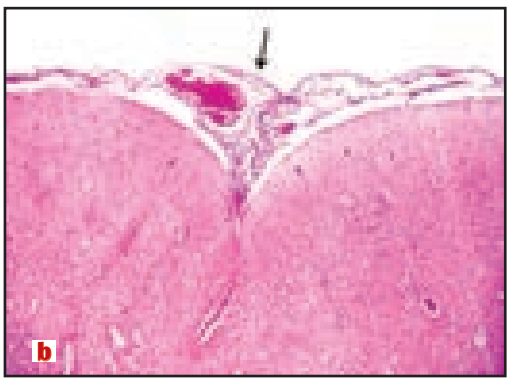


Fig. 5-25 a, b. Purulent leptomeningitis: a – macroscopic aspect; b – microscopic pattern (hematoxylin–eosin stain; ×70).

is tumefied, warm on palpation, imbued with pus. On section, it has a dim, yellowish–grayish color, either a hard, wood-like (*hard phlegmon*) or flaccid consistency (*soft phlegmon*), a fact which depends on the extension and gravity of

the necrosis processes in the respective area (the consistency is harder in cases of diffuse tissular necrosis).

The phlegmonous inflammation can be acute or chronic. The acute phlegmon can lead to sepsis. Secondary amyloidosis can occur in chronic forms of abscess and phlegmon.

5.2.4. PUTRID INFLAMMATION (ICHOROUS OR GANGRENOUS)

It develops as a result of superinfection of the inflammation focus with putrefaction bacteria (*colibacilli, Proteus vulgaris* etc.), causing tissue putrid disintegration processes. The exudate is a grayish–greenish mass, containing necrotic, liquefied tissue debris. The inflamed tissue has a dirty–grey aspect with unpleasant odor (fetid). It lodges in tissues that have contact with the external environment (buccal cavity, lungs, digestive tract, urogenital organs) – gangrenous tonsillitis, stomatitis, pneumonia, appendicitis, cholecystitis, colitis, endometritis.

5.2.5. HEMORRHAGIC INFLAMMATION

It is characterized by presence of a large number of erythrocytes in the exudate, which gets the aspect of hemorrhagic liquid (Fig. 5–26). Macroscopically, the hemorrhagic inflammation foci have a reddish color. It is met in flu, plague, streptococcus infection, anthrax, smallpox, especially in patients with hemorrhagic diathesis or cachexy. It is related to a marked increase of vascular permeability.

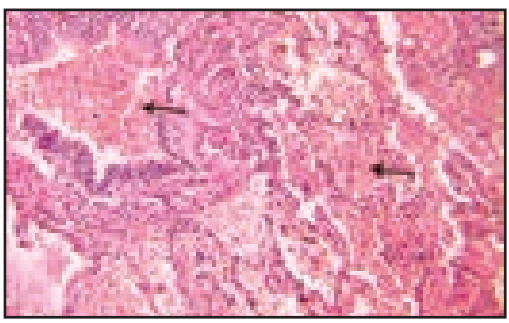
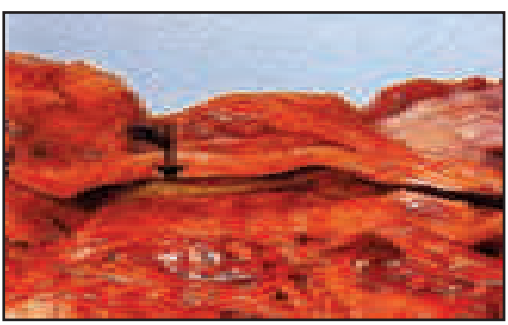


Fig. 5-26. Influenza hemorrhagic bronchopneumonia (hematoxylin–eosin stain; ×110).

5.2.6. CATARRHAL INFLAMMATION

It appears at the level of respiratory tract mucosae (rhinitis, bronchitis) (Fig. 5–27a, b), digestive tract (gastritis, enteritis, colitis, cholecystitis), urogenital tract (endometritis, salpingitis, cystitis). Initially, the catarrh has a *serous* character,



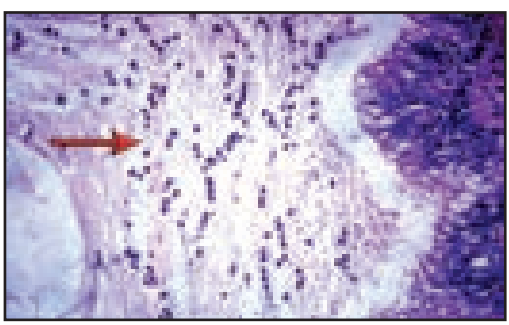


Fig. 5-27. Catarrhal tracheitis: a – macroscopic aspect; b – microscopic pattern (hematoxylin–eosin stain; ×110).

an abundant, yellowish–opaque liquid exudate draining on the mucosal surface, which thickens gradually, becoming *mucous* (*seromucous*) due to excessive mucus secretion, epithelial cell desquamation and migration of neutrophil leukocytes, gaining a *purulent* aspect (*mucopurulent*) in time.

According to its clinical evolution, the catarrhal inflammation can be acute and chronic. **The acute catarrh** heals in 1–2–3 weeks. **The chronic catarrh** can result in mucosal atrophy or hypertrophy, impaired function of the respective organs. The most frequent causes of catarrhal inflammation are: viral and bacterial infections, irritating gases, toxic substances (uremia), thermal factors etc.

5.2.7. MIXED INFLAMMATION

The association of one type of exudate with other takes place in a mixed inflammation (sero–fibrinous, sero–hemorrhagic, fibrino–purulent, fibrino–hemorrhagic inflammation etc.).

ESSENTIAL TERMS
on the subject "ACUTE (EXUDATIVE) INFLAMMATION"

abscess	endocytobiosis	migration
acute inflammation	exocytosis	phagocytosis
alteration	exudate	phlegmon
calor	exudative inflammation	pinocytosis
catarrhal inflammation	fibrinous inflammation	productive (proliferative) inflammation
cellular inflammatory infiltrate	functio laesa	purulent inflammation
chemotaxis	hemorrhagic inflammation	pus
chronic inflammation	gangrenous inflammation	putrid inflammation
complete phagocytosis	ichorous inflammation	pyocytes
croup	incomplete phagocytosis	rubor
croupous inflammation	inflammation	serous inflammation
degranulation	inflammatory mediators	subacute inflammation
diphtheroid inflammation	leukocytic margination	transudate
dolor	macrophage	tumor
empyema	microphage	

TESTS
on the subject "ACUTE (EXUDATIVE) INFLAMMATION"

SET I.

Multiple-choice questions with one correct answer.

1. *The characteristic morphological sign of fibrinous inflammation is:*
   a) serous liquid;
   b) pyogenic membrane;
   c) necrosis;
   d) whitish coating on the mucosal surface;
   e) sero–hemorrhagic exudate.

2. *Which definition of empyema is correct:*
   a) superficial fibrinous inflammation;
   b) focal purulent inflammation with formation of a cavity in the parenchymatous organs;
   c) pus accumulation in a preexistent anatomical cavity;
   d) catarrhal inflammation of mucosae;
   e) diffuse purulent inflammation.
3. *Catarrhal inflammation location is in:*
   a) serous membranes;
   b) myocardium;
   c) brain;
   d) mucosae;
   e) kidneys.
4. *Which cells react primarily in the acute inflammatory process:*
   a) activated B lymphocytes;
   b) activated T lymphocytes;
   c) mastocytes (labrocytes);
   d) plasmocytes;
   e) T-killer cytotoxic lymphocytes.
5. *All the listed cellular elements prevail in a chronic inflammatory process, with the exception of:*
   a) B lymphocytes;
   b) T helper lymphocytes;
   c) neutrophil leukocytes;
   d) plasmocytes;
   e) macrophages.

SET II.

Multiple-choice questions 2, 3 or more correct answers.

1. *Clinical signs of inflammation:*
   a) paleness;
   b) local temperature rise;
   c) cyanosis;
   d) swelling;
   e) redness.
2. *Morphological manifestations of alteration:*
   a) necrosis;
   b) metaplasia;
   c) dysplasia;
   d) dystrophy;
   e) atrophy.
3. *Fibrinous inflammation variants:*
   a) fibrinoid;
   b) diphtheroid;
   c) catarrhal;
   d) croupous;
   e) mixed.
4. *Purulent inflammation variants:*
   a) cyst;
   b) granuloma;
   c) papilloma;
   d) abscess;
   e) phlegmon.
5. *Exudate variants in catarrhal inflammation:*
   a) mucous;
   b) fibrinous;
   c) putrid;
   d) purulent;
   e) serous.

SET III.

The classification tests include 2 – 4 subjects and a series of answers. Indicate which answers are correct for each separate subject.

1. *Which of the enumerated signs refer to:*
   I – transudate;
   II – exudate;
   a) it is an edema fluid;
   b) contains numerous blood cells;
   c) contains more than 2% of proteins;
   d) it is a dim liquid;
   e) contains less than 2% of proteins;
   f) contains a reduced number of cells.
2. *Which of the listed morphologic lesions associate with inflammatory process stage:*
   I – of alteration;
   II – of exudation;
   a) dystrophic modifications of tissues;
   b) inflammatory hyperemia;
   c) epithelial cell desquamation;
   d) fibrinoid necrosis;
   e) migration of leukocytes;
   f) diapedesis of erythrocytes ;
   g) phagocytosis.
3. *What criteria characterize:*
   I – exudative inflammation;
   II – productive inflammation;
   a) it has a chronic evolution usually;
   b) it frequently leads to sclerosis of the affected organs;
   c) the morphological substratum is the inflammatory fluid;
   d) the morphological substratum is the inflammatory infiltrate;
   e) granuloma formation is frequently observed;
   f) it has an acute evolution more frequently;
   g) the complete reestablishment of the affected tissue takes place in the majority of cases.
4. *Which of the listed signs characterize:*
   I – abscess;
   II – phlegmon;
   a) the cavity filled with pus;
   b) diffuse purulent inflammation;
   c) presence of pyogenic membrane;
   d) focal purulent inflammation;
   e) the pus can extend unlimitedly.
5. *Which of listed morphological signs refer to:*
   I – croupous inflammation;
   II – diphtheroid inflammation;
   a) the fibrin coating is hardly eliminated;
   b) the fibrin coating detaches easily;
   c) the fibrinous exudate penetrates deeply in tissues;
   d) the fibrin coating adheres poorly to the adjacent tissue;
   e) it is seen on the mucosae membranes covered with stratified squamous epithelium;
   f) it is seen on mucosae covered with glandular epithelium;
   g) profound tissular necrosis;
   h) superficial tissular necrosis.

SET IV. SITUATIONAL PROBLEMS

Daily practice cases are presented with clinical and morphological data from clinical histories and/or from necropsy protocols. Each subject includes simple or multiple - answer questions, with 1, 2 or more correct answers.

1. *A patient touched the hot iron inadvertently and the forefinger became red, with edema, severe pain, and a few minutes later – a vesicle filled with yellow, transparent liquid appeared.*

Question:

Which variant of exudative inflammation developed in this case:

a) fibrinous;
b) purulent;
c) serous;
d) hemorrhagic;
e) gangrenous.

2. *In an 8-year-old child, the palatine tonsils are increased, edematous, hyperemic, covered with a whitish coat, which detaches easily.*

Question:

What is the correct diagnosis in the given case:

a) fibrinous tonsillitis;
b) purulent tonsillitis;
c) serous tonsillitis;
d) hemorrhagic tonsillitis;
e) gangrenous tonsillitis.

3. *Postoperative material: the gallbladder is increased in size; the wall is thickened, edematous, hyperemic, yellow–greenish fluid in the cavity, hyperemic serosa with punctiform hemorrhages, covered with a thin, whitish coat.*

Questions:

A) What kind of inflammation is in this case:

a) serous cholecystitis;
b) catarrhal cholecystitis;
c) purulent cholecystitis;
d) fibrinous cholecystitis;
e) gangrenous cholecystitis.

B) What is the name of the serous membrane inflammation of the gallbladder?

a) paracholecystitis;
b) endocholecystitis ;
c) pericholecystitis;
d) pancholecystitis;
e) mesocholecystitis.

C) What kind of inflammation developed in the serous membrane of the gallbladder:

a) catarrhal;
b) fibrinous;
c) purulent;
d) gangrenous;
e) serous.

4. *At the necropsy of a 28 year-old patient with rheumatism, rheumatic carditis, the following changes were detected: heart increased in size, opaque fluid in the pericardium, thickened epicardium, covered with whitish deposits, which give a rough appearance to the heart surface.*

Questions:

A) What kind of pericarditis is in this case:

a) serous;
b) catarrhal;
c) purulent;
d) fibrinous;
e) gangrenous.

B) What consequences are more common in this form of pericarditis:

a) resorption of exudate;
b) organization of exudate;
c) formation of adhesions between serous sheets;
d) pericardium cavity obliteration;
e) calcification of pericardium sheets.

5. *At necropsy in lungs was revealed a focus of irregular shape, consisting of necrotic decomposing black mass with a fetid smell.*

Questions:

A) Which type of inflammation is in the given case:

a) croupous;
b) serous;
c) purulent;
d) fibrinous;
e) gangrenous.

B) Which pathogenic agents from those listed below can be detected in this case:

a) flu virus;
b) diphtheria bacillus;
c) clostridium perfringens;
d) Staphylococcus aureus;
e) coli bacillus.

5.3. CHRONIC (PROLIFERATIVE, PRODUCTIVE) INFLAMMATION

Chronic inflammation develops independently or appears through chronicization of unresolved acute inflammation. The main pathogenetic mechanisms are the following:

- ✧ persistence of acute inflammation (for example, in slow-developing bacterial pneumonia);
- ✧ persistence of pathogenic agent due to impossibility of its rapid elimination through phagocytosis;
- ✧ long–lasting action of harmful factors (smoking);
- ✧ foreign bodies (for example, inhalation of dust in pneumoconiosis);
- ✧ autoimmune diseases;
- ✧ diseases of unknown etiology, such as Crohn disease, nonspesific ulcerative colitis, sarcoidosis etc.

Morphologically, as opposed to acute inflammation, which is mediated by neutrophil leukocytes, the chronic inflammation is mediated by mononuclear cells with nonsegmented nucleus. It is a productive (proliferative) inflammation, where the multiplying (proliferation) and cell transformation processes prevail. The morphological substratum of the chronic inflammation is the **cellular inflammatory infiltrate** – diffuse or focal mononuclear cell agglomeration. The most frequently encountered are mononuclear phagocytes (macrophages, epithelioid cells), lymphocytes, multinucleated giant cells and fibroblasts. Leukocytes, especially eosinophils (in allergic inflammations), are rarely met.

Classification:

- ✧ interstitial inflammation;
- ✧ granulomatous inflammation;
- ✧ polypoid inflammation (with polyps formation).

5.3.1. INTERSTITIAL INFLAMMATION

It is a type of productive inflammation, where the inflammatory process is lodged in the stroma (interstitium) of parenchymatous organs.

Most common *lodging* spots are in myocardium, kidneys, lungs, liver (*name – interstitial myocarditis, nephritis, pneumonia, hepatitis*).

Morphology: infiltrates, constituted of lymphocytes, monocytes, macropha-

ges, plasmocytes and fibroblasts are observed in the interstitial tissue of the organs (Fig. 5–28, 5–29 and 5–30); cellular infiltration is more pronounced around vessels (perivascular).

Etiology: viral infections (flu, measles, rubella), bacterial infections (scarlet fever, exanthematic typhus, meningococcal infection), sepsis.

Consequences: fibrosis, sclerosis and cirrhosis of organs (Fig. 5–31).

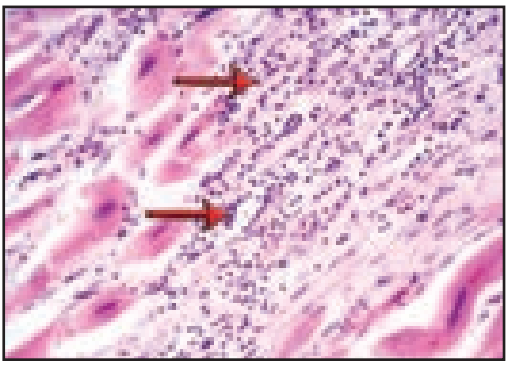


Fig. 5–28. Interstitial myocarditis (hematoxylin–eosin stain; ×70).

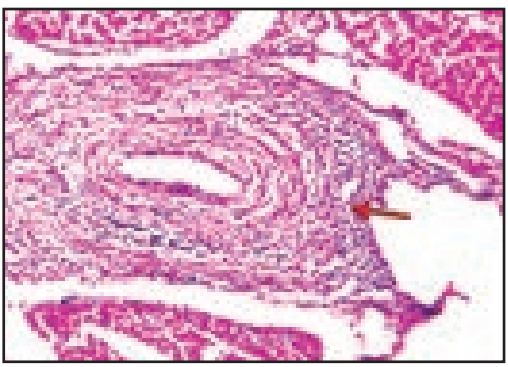


Fig. 5–29. Productive vasculitis in polyarteritis nodosa (hematoxylin–eosin stain; ×70).

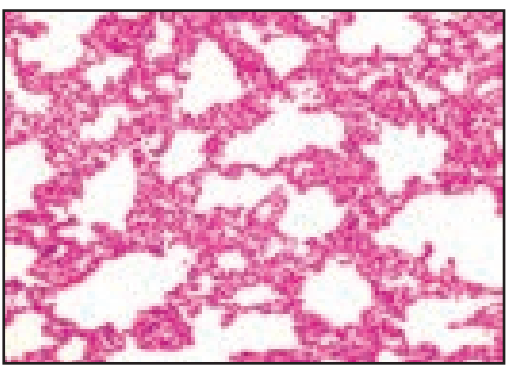


Fig. 5–30. Interstitial pneumonia (hematoxylin–eosin stain; ×70).

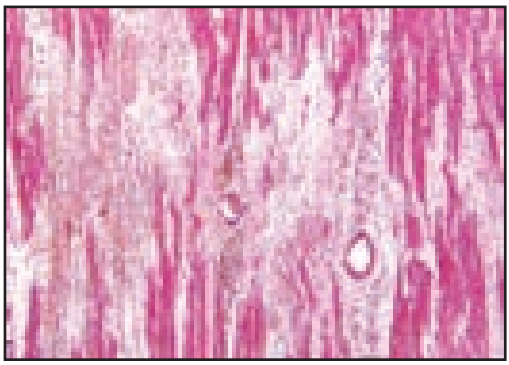


Fig. 5–31. Postmyocarditic cardiosclerosis (hematoxylin–eosin stain; ×70).

Fibrosis – connective tissue proliferation without organ's induration (for example, pneumofibrosis, myofibrosis).

Sclerosis – connective tissue proliferation resulting in diffuse or local induration of the parenchymatous organs (cardiosclerosis, pneumosclerosis, nephrosclerosis).

Cirrhosis – connective tissue proliferation, inducing pronounced deformation of organs (liver, lung and kidney cirrhosis).

It is a type of productive inflammation, characterized by formation of nodules of dense consistency in organs, called *granulomas*.

The granuloma is a focal cellular inflammatory infiltrate; usually it has a round or ovoid shape, a diameter of 1–2 mm up to 3–5 cm.

The structure of granuloma: in the center – necrosis focus (detritus, tissular debris), where the pathogenic agent can be; at the periphery – a cellular belt, surrounding the focus of necrosis, con-

5.3.2. GRANULOMATOUS INFLAMMATION

stituted of monocytes, lymphocytes and their derivatives (macrophages, epithelioid cells, giant cells, plasmocytes).

Granuloma types, according to cellular composition:

- ✧ macrophagic;
- ✧ epithelioid cell;
- ✧ gigantocellular.

The granuloma cells are of hematogenic (bone marrow) etiology. Epithelioid cells differ from normal macrophages by more abundant cytoplasm, filled with vacuoles and lysosomes, and lower phagocytic activity. They adhere closely to one another, reminding the spinous layer of the epidermis, hence the name. Being stable cells, arranged compactly in the structure of granulomas, they form a cellular belt that isolates the lesion focus and the pathogenic agent. The multinucleated giant cells subdivide into "*foreign body cells*" and *Langhans* cells; they are formed by fusion or incomplete division of epithelioid cells or of macrophages. The giant cells may have a diameter up to 150 μ and can contain up to 200 nuclei. In the giant foreign body cells, nuclei are distributed *chaotically* in the cytoplasm, and in Langhans cells – uniformly, along the cell membrane in the form of a *crown* or *horse shoe*.

Etiology. The granulomas appear when the pathogenic agent is resistant to phagocytosis and remains in the inflammatory focus for a long time. By granuloma formation, the isolation of harmful factor is produced, its delimitation from the rest of tissue/organ. The gradual degradation and elimination of pathogenic agent occur under the influence of granuloma cells.

The granulomatous inflammation is observed in more than 70 diseases (granulomatous diseases).There are:

I – **infectious granulomas**, for example, in typhoid fever, exanthematic typhus, tularemia, brucellosis, visceral fungi, parasitic diseases (echinococcosis, trichinellosis, cysticercosis, toxoplasmosis), in rheumatic diseases (Fig. 5–32 a, b);

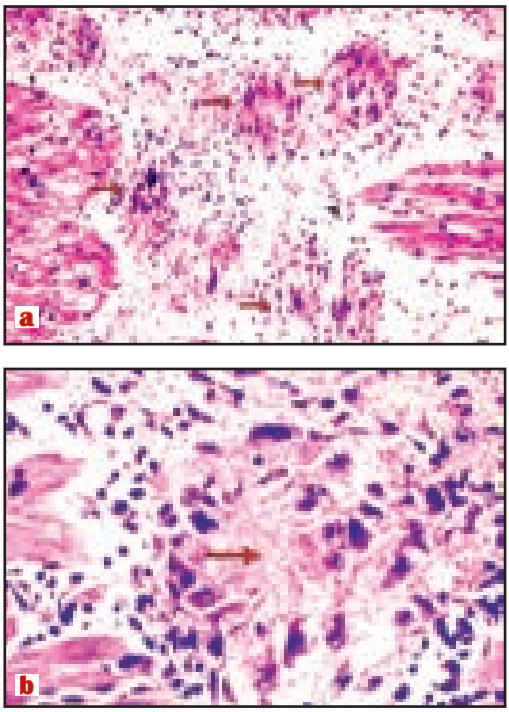


Fig. 5–32 a, b. Granulomatous inflammation of endo- and myocardium in rheumatism (Aschoff bodies) (hematoxylin–eosin stain; ×70 and ×110).

II – **non-infectious granulomas**, for example, in pneumoconiosis, foreign bodies, suture material (Fig. 5–33), oily substances etc.

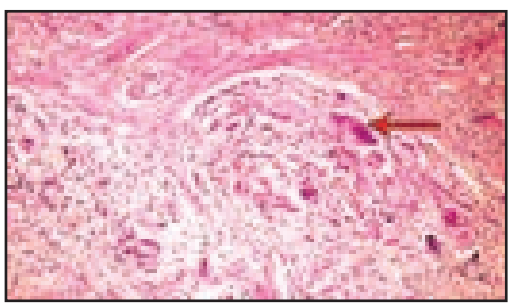


Fig. 5–33. Foreign body granuloma (suture granuloma) (hematoxylin–eosin stain; ×70).

III – **granulomas of unknown origin**, for example, Crohn's disease (Fig. 5–34), sarcoidosis.

Most common **consequences** of granulomas:

a) resorption of cellular infiltrate;
b) organization;
c) encapsulation;
d) calcification (petrification);
e) ossification;
f) secondary necrosis.

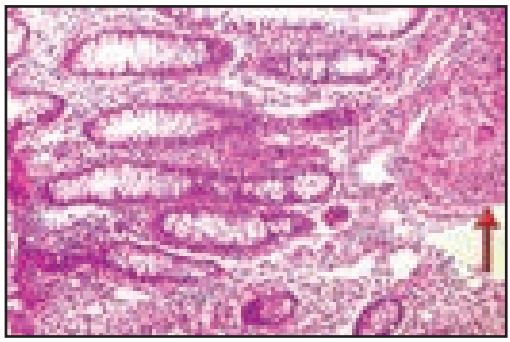


Fig. 5–34. Epithelioid cell granuloma in the colon in Crohn's disease (hematoxylin–eosin stain; ×70).

5.3.2.1. SPECIFIC GRANULOMATOUS INFLAMMATIONS

The specific inflammation differs from ordinary (nonspecific) inflammation by:

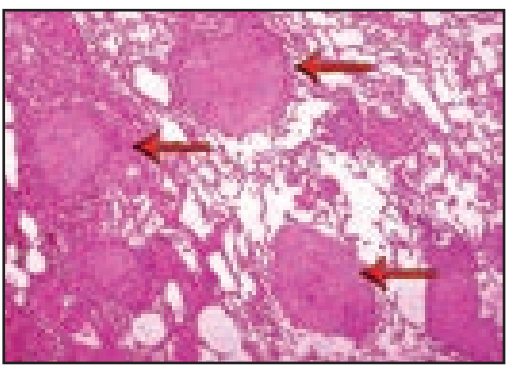
1) the formation of characteristic granulomas, which enable the morphological diagnosis of the respective disease without identification of the pathogenic agent;
2) undulate chronic evolution;
3) *primary* or *secondary* caseous necrosis of the altered tissue (*primary* necrosis appears at the initial penetration of the pathogenic agent, and *secondary* necrosis is preceded by exudative or proliferative reaction).

Etiology: tuberculosis, syphilis, leprosy, rhinoscleroma.

5.3.2.2. TUBERCULOUS GRANULOMATOUS INFLAMMATION

Causative agent – mycobacterium tuberculosis or Koch's bacillus.

Structure (Fig.5–35 and 5–36): in the centre – an amorphous, eosinophilic, caseous necrosis area, with no nuclei (macroscopically, the necrotic masses resemble the dry cheese); around the necrosis focus – a belt of cells arranged from the centre to periphery, in the following order: immediately around



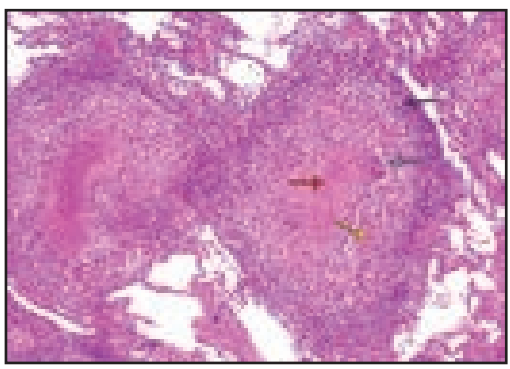


Fig. 5–35 and 5-36. Tuberculous granulomas in the lung (hematoxylin–eosin stain; ×70): focus of caseous necrosis, epithelioid cells, Langhans cells and lymphocytes.

necrosis, there are epithelioid cells with elongated, pale, radially arranged nuclei; giant multinucleated Langhans cells with eosinophilic cytoplasm and nuclei arranged in a crown or horseshoe form are observed among them; the Langhans cells are typical for tuberculosis; phagocytosed Koch bacilli can be found in their cytoplasm (Fig. 5–37a, b); a layer of lymphoid cells (small lymphocytes), among which macrophages and plasmocytes can be seen at the granuloma periphery. The tuberculosis nodules vary from the size of a millet grain in miliary tuberculosis (Fig. 5- 38 and 5–39) to bigger formations of few centimeters in diameter. They can be lodged in all tissues and organs.

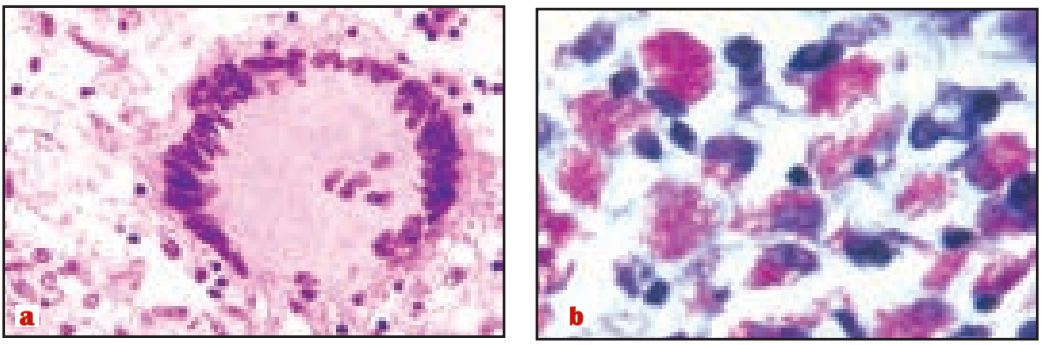


Fig. 5–37: a - Giant multinucleated Langhans cell (hematoxylin–eosin stain; x280); b - phagocytosis of mycobacterium tuberculosis (Ziehl-Neelsen stain; ×110).

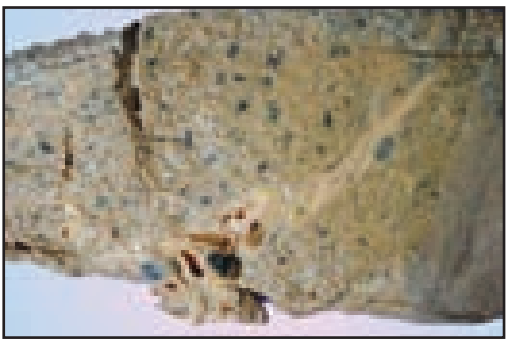


Fig. 5–38. Pulmonary miliary tuberculosis.

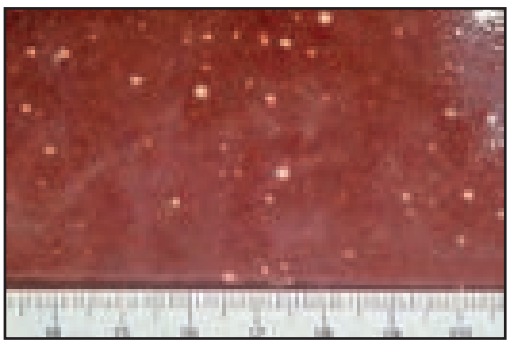


Fig. 5–39. Miliary tuberculosis of the liver.

Consequences of tuberculous granuloma:

I – in cases with favorable evolution (tuberculostatic treatment, high body resistance): *resorption, organization, encapsulation, petrification, ossification of inflammatory* focus;

II – in cases with unfavorable evolution: *secondary caseous necrosis.*

5.3.2.3. SYPHILITIC (LUETIC) GRANULOMATOUS INFLAMMATION

Causative agent – pale treponema. Lesions that are specific for syphilis appear in the tertiary period of the disease, which develops over 3–6 years after infection. They may have nodular or diffuse character and manifest themselves morphologically by the formation of granulomas in organs and tissues, called

syphilitic gummas or *gummous infiltrates*.

Syphilitic gummas can be solitary or multiple; *location* – visceral organs (liver, heart, kidneys), brain, teguments, soft tissues, bones, cartilages, nasal septum etc. Gummas diameter varies from 1 to 5–6 cm (Fig. 5–40 a). *Structure*: well–delimited nodule of grey–pink color with elastic consistency. Necrosis and softening of the preexistent tissue occurs in the centre of the gumma; this area becomes sticky, resembling the Arabic gum (*hence the name of gumma, from the Greek kommi – gum, rubber*).

Microscopically: necrosis focus in the centre surrounded by a cellular crown, consisting mainly of lymphocytes, plasmocytes and epithelioid cells; single giant Langhans cells are met, which are not typical for luetic inflammation (Fig. 5–40 b). The blood vessels are stored at the gumma's periphery, where a productive inflammation (proliferative endoperivasculitis) is observed. The syphilitic gumma consequences: organization, cicatrization, petrification. Sclerosis and cirrhosis with severe deformation of organs develop in parenchymatous organs, for example: macronodular liver cirrhosis (*hepar lobatum*).

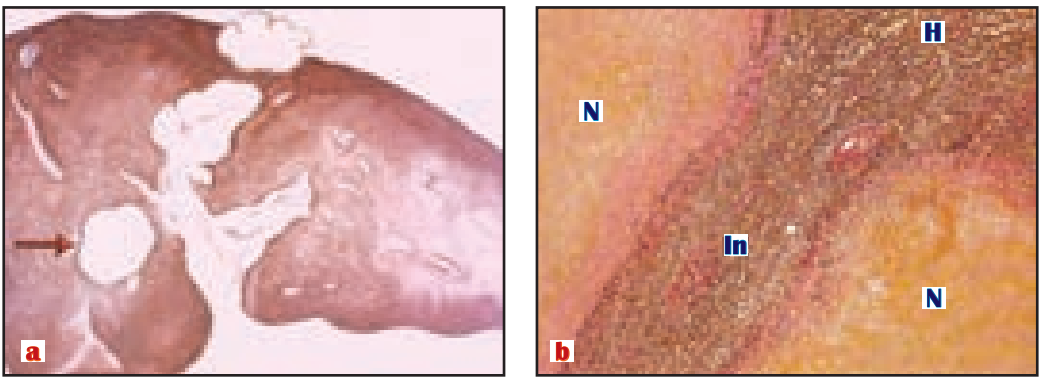


Fig. 5–40 a, b. Syphilitic gummas in the liver: a – macroscopic aspect; b – microscopic pattern (picrofuchsin van Gieson stain; ×70): N – necrosis, In – predominantly lympho-plasmocytic inflammatory infiltrate, H – adjacent hepatic parenchyma.

Gummous infiltrates are lymphoplasmocytic agglomerations of different dimensions in aorta (Fig. 5–41), myocardium, liver, bones, joints and other organs. The aorta is involved in 80–85% of patients with tertiary syphilis; the ascendant portion, arch and aortic valves are affected. The productive inflammation of *vasa vasorum* from adventitia and aortic media (syphilitic aortitis) develops, which leads to destruction of elastic membranes, decreased elasticity and aneurysm. Complications and death causes: severe cardiac insufficiency due to aortic valvular insufficiency or aneurysm rupture.

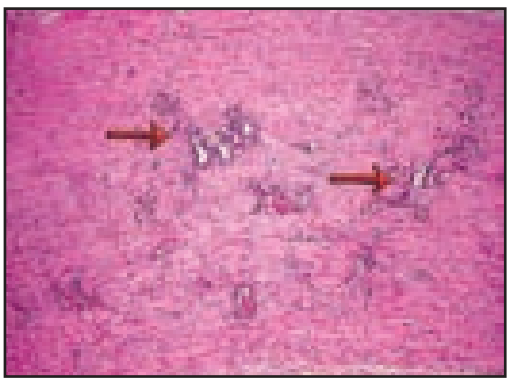


Fig. 5–41. Syphilitic mesaortitis, cell infiltrates in the aortic media, around the vasa vasorum (hematoxylin–eosin stain; ×70).

5.3.2.4. LEPROUS GRANULOMATOUS INFLAMMATION

Causative agent – mycobacterium leprae or Hansen bacillus. *Location* of inflammatory lesions: skin, subcutaneous tissue, upper respiratory tract, peripheral nerves.

The specific leprous granuloma – *leproma* appears in the lepromatous form of the disease. *Structure*: the leproma is composed of macrophages, lymphocytes, plasmocytes and giant cells with foamy (vacuolated) cytoplasm generated by lipid inclusions – the so–called leprous cells (*leprous globes or Virchow cells*). The latter are characteristic for leprosy and represent macrophages, with huge quantities of mycobacteria in their cytoplasm, which are arranged compactly, like cigarettes in a box. The granuloma is situated in the skin thickness (in dermis) and is separated from epidermis by a defined area of connective tissue (Fig. 5–42 a, b).

Macroscopically, lepromas have the appearance of nodules of different dimensions, lodged in the skin.

Consequences: lepromas can necrotize, and later they organize and form mutilating scars, which deform the patient's exterior aspect ("*leonine facies*").

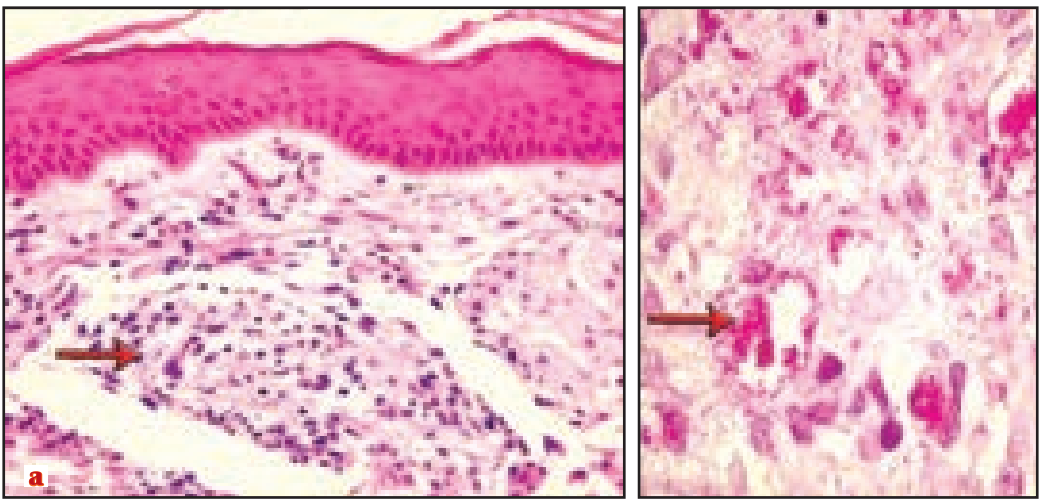


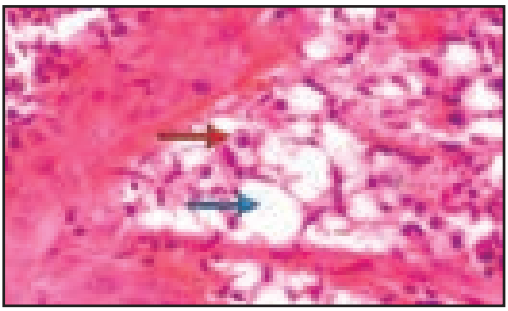
Fig. 5–42 a, b. Leprous granuloma in the skin: a – leprous granuloma (hematoxylin–eosin stain; ×70), b – Virchow cells (Ziehl-Neelsen stain; ×110).

5.3.2.5. GRANULOMATOUS INFLAMMATION IN RHINOSCLEROMA

Causative agent – Frisch bacillus. Inflammatory process *location*: mucosa of the upper respiratory tract, especially the nasal cavity.

Macroscopically, it manifests itself by proliferation of granulation tissue of dense consistency, with narrowing or obliteration of the respiratory tract; the inflammatory process can infiltrate adjacent tissues of the superior lip.

Microscopically, one observes productive inflammation with formation of some granulomas, constituted from plasmocytes, epithelioid cells and lymphocytes; the presence of big macrophages with foamy, clear cytoplasm - Mikulicz cells - is characteristic (contain many Frisch bacilli), as well as the



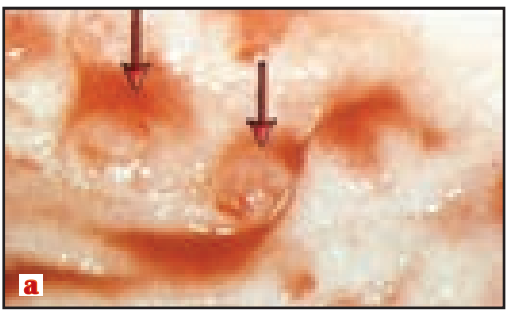
presence of Russel corpuscles (*hyaline spheres*), which appear as a result of dystrophic modifications of plasmocytes (Fig. 5–43).

Consequences: sclerosis and hyalinosis of the granulomatous tissue. Possible complications: respiratory disturbances (asphyxia).

Fig. 5–43. Rhinoscleroma in the nasal mucosa, inflammatory infiltrate with Mikulicz cells and plasmocytes (hematoxylin–eosin stain; ×110)

5.3.3.6. PRODUCTIVE INFLAMMATION WITH POLYP FORMATION

Polyps are formations with smooth or papillary surface, with the dimensions from 1–2 mm to some cm; they can be single or multiple, some of them have a cauliflower aspect. Location – mucous membranes covered with glandular epithelium of stomach (Fig. 5–44), intestine (Fig. 5–45 a, b), uterus and cervical canal (Fig. 5–46 a, b), nasal meatus (Fig. 5–47 a, b, c), bronchi, trachea. The polyps of inflammatory origin are called **hyperplastic polyps**. They develop on the background of some chronic inflammatory processes of respective mucosae, for example, gastritis, endocervicitis, endometritis, enterocolitis and chronic rhinosinusitis. Microscopically, they are formed of tortuous, cystically dilated glands, which contain mucus; the stroma is edematous, hyperemic, infiltrated



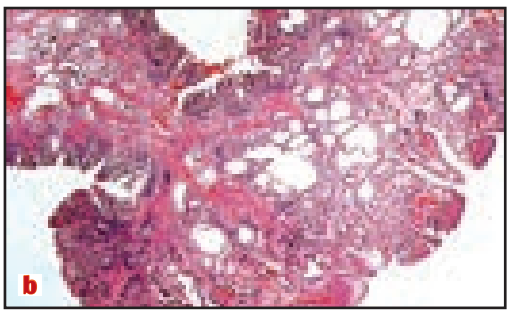
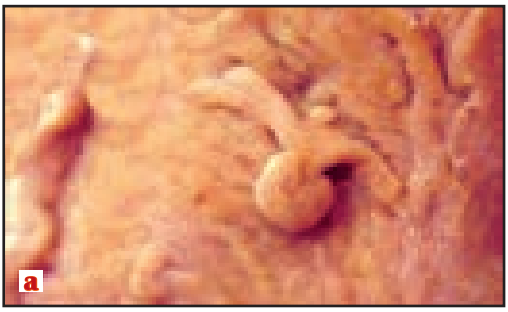


Fig. 5–44 a, b. Gastric polyps: a – macroscopic aspect; b – microscopic pattern (hematoxylin–eosin stain; ×50).



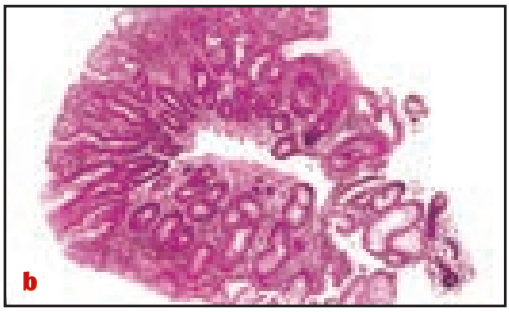
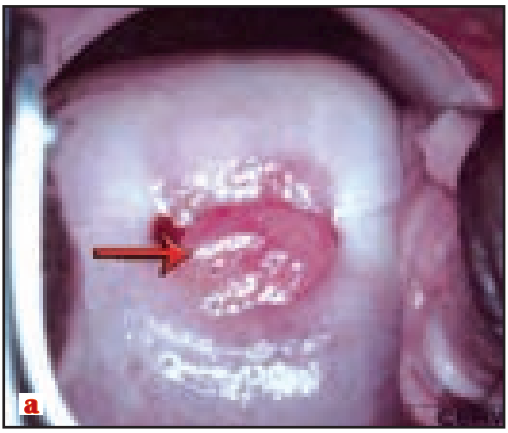


Fig. 5–45 a, b. Colonic polyp: a – macroscopic aspect; b – microscopic pattern (hematoxylin–eosin stain; ×50).



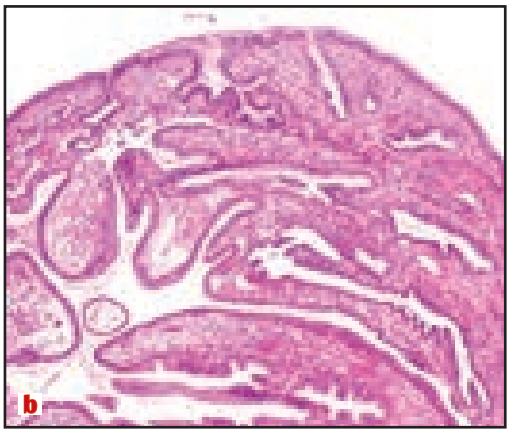
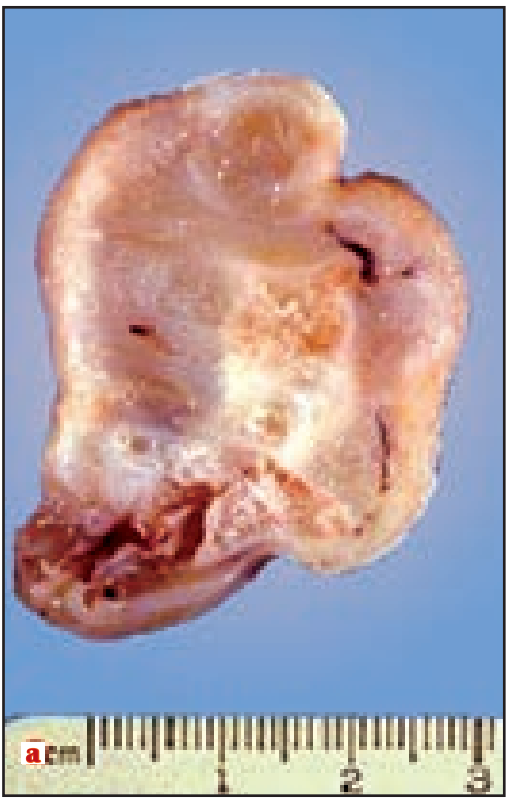


Fig. 5–46 a, b. Cervical canal polyp: a – macroscopic aspect at colposcopic examination; b – microscopic pattern (hematoxylin–eosin stain; ×50).



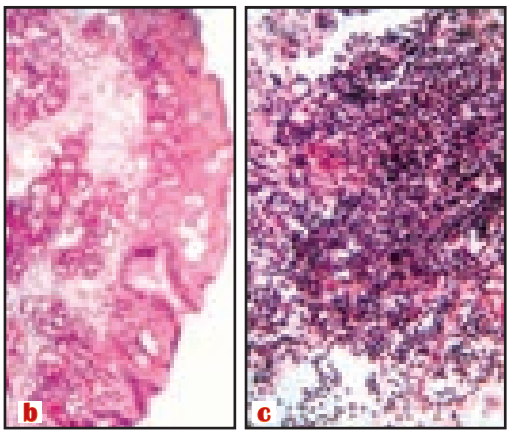


Fig. 5–47 a, b, c. Nasal polyp: a – macroscopic aspect; b, c – microscopic pattern (hematoxylin–eosin stain; ×40 and ×70).

with lymphocytes, macrophages and plasmocytes. There are groups of blood vessels with sclerosed, thickened walls in the area of polyp's pedicle. The nasal polyps have a large number of eosinophils in the inflammatory infiltrate, as a manifestation of allergic inflammation (allergic rhinitis).

Complications: hemorrhages, secondary inflammation, circulatory disturbances, stenosis of the lumen of tubular or hollow organs. Hyperplastic polyp malignization is observed very rarely.

Papillary formations covered with stratified squamous epithelium, called **condyloma acuminata** (*Greek kondylos – prominence, Latin acumen – tip*) can be met on the mucosae covered with stratified squamous epithelium and on the skin. They are located on the skin of the perineal area, cervical or urethral mucosa. They are caused by human papil-

loma virus (HPV). The irritant action of the urogenital secretions in gonorrhea, syphilis and other venereal diseases is important. Microscopically, the presence of **koilocytes** – intermediary cells of the stratified squamous epithelium with perinuclear halo (clear area), which appear under the influence of HPV, is characteristic. Chronic inflammatory infiltration is observed in the connective stroma of acuminate condylomas.

ESSENTIAL TERMS

on the subject: "CHRONIC (PROLIFERATIVE, PRODUCTIVE) INFLAMMATION"

cirrhosis	Langhans cell	scleromatous granuloma
condyloma acuminatum	leproma	sclerosis
epithelioid cell	mesaortitis	secondary necrosis
fibrosis	Mikulicz cell	specific granuloma
foreign body cell	nonspecific granuloma	suture granuloma
foreign body granuloma	primary necrosis	syphilitic gumma
granuloma	polyp	tuberculous granuloma
interstitial inflammation	Russel corpuscle	Virchow cell

TESTS

on the subject: "CHRONIC (PROLIFERATIVE, PRODUCTIVE) INFLAMMATION"

SET I.

Multiple-choice questions with one correct answer.

1. *Which is the characteristic morphologic substratum of the productive inflammation:*
   a) serous fluid;
   b) abscess;
   c) cellular infiltrate;
   d) necrosis;
   e) cystic cavity.
2. *What cells prevail in the inflammatory infiltrate in the final inflammation stage:*
   a) leukocytes;
   b) fibroblasts;
   c) sideroblasts;
   d) monocytes;
   e) T lymphocytes.
3. *What is the correct statement referring to plasmocytes:*
   a) derive from B lymphocytes;
   b) can transform into macrophages;
   c) the endoplasmic reticulum is hardly seen;
   d) it accumulates in the areas of hyperergic inflammatory reaction;
   e) can transform into multinucleated giant cells.
4. *What cells from those listed below are epithelioid cell forerunners:*
   a) neutrophil leukocytes;
   b) eosinophils;
   c) platelets;
   d) macrophages;
   e) T lymphocytes.
5. *The following microscopic aspects are elements that characterize tuberculous inflammation, with the exception of:*
   a) presence of epithelioid cell granulomas;
   b) evolution of granulomas to caseous necrosis;
   c) presence of Langhans cells;
   d) recent abscess formation;
   e) specific stains reveal Koch bacillus.

SET II.

Multiple-choice questions with 2, 3 or more correct answers.

1) The characteristic signs of chronic inflammation:
- a) long time evolution;
- b) mononuclear infiltration of tissue;
- c) sclerotic lesions in the inflammatory focus;
- d) secondary necrosis of tissue;
- e) predominance of the exudative reaction.

2) Morphogenetic stages of granuloma:
- a) accumulation of neutrophils;
- b) accumulation of young monocytic phagocytes;
- c) formation of macrophage granuloma;
- d) formation of epithelioid cell granuloma;
- e) accumulation of lymphocytes.

3) Which of the listed signs characterize the specific inflammation:
- a) acute evolution;
- b) formation of exudate;
- c) formation of granulomas;
- d) undulant chronic evolution;
- e) presence of a specific infectious agent.

4) Which of the listed cells are observed in the tuberculous granuloma:
- a) epithelioid cells;
- b) lymphocytes;
- c) mastocytes;
- d) foreign body giant cells;
- e) Langhans cells.

5) The microscopic signs characteristic for syphilitic gumma:
- a) necrosis;
- b) lymphocytes;
- c) Mikulicz giant cells;
- d) neutrophils;
- e) plasmocytes.

SET III.

The classification tests include 2–4 subjects and a series of answers. Indicate which answers are correct for each separate subject.

1. Which of the listed pathologic processes refers to:

I – exudative inflammation;
II – productive inflammation;
- a) gastric polyps;
- b) renal abscess;
- c) interstitial pneumonia;
- d) rheumatic granulomatous myocarditis;
- e) diphtheritic croup;
- f) villous heart;
- g) gummous mesaortitis;
- h) appendicular empyema.

2. Which of the listed signs characterize the:

I – acute inflammation;
II – chronic inflammation;
- a) predominance of the productive tissular reaction;
- b) rapid elimination of the pathogenic agent and recovery of altered tissues;
- c) intense exudative reaction;
- d) poorly pronounced exudative reaction;
- e) diffuse or focal mononuclear infiltration of tissues;
- f) prevalence of tendency towards sclerosis.

3. Which of the listed inflammation variants refer to:

I – ordinary inflammation;
II – specific inflammation;
- a) inflammation in tuberculosis;

b) interstitial nephritis;
c) polyps;
d) syphilitic inflammation;
e) rhinoscleromatous inflammation.

4. *Which of the listed cells belong to:*
I – monocytic series;
II – lymphocytic series;
a) epithelioid cells;
b) plasmocytes;
c) multinucleated giant cells;
d) natural killer cells;
e) circulating macrophages;
f) tissular macrophages;
g) cytotoxic cells.

5. *Choose the correct definition for each morphologic process:*
I – sclerosis;
II – necrosis;
III – cirrhosis;
IV – encapsulation;
V – inflammatory infiltrate.
a) excessive proliferation of the connective tissue with deformation of the organ;
b) excessive proliferation of the connective tissue with densification of the organ;
c) cellular death;
d) cell agglomerations in the inflammatory focus;
e) connective tissue proliferation around a lesion focus.

SET IV. SITUATIONAL PROBLEMS

Daily practice cases are presented with clinical and morphological data from clinical histories and/or from necropsy protocols. Each subject includes simple or multiple – answer questions, with 1, 2 or more correct answers.

1. *A 36-year-old patient with unclear cardiac pathology had a myocardium biopsy. The microscopic examination revealed mononuclear inflammatory infiltration of lymphocytes, histiocytes, plasmocytes, fibroblasts.*

Questions:

A) ***What is the diagnosis resulted from the microscopic pattern:***
a) serous myocarditis;
b) granulomatous myocarditis;
c) septic myocarditis;
d) purulent myocarditis;
e) interstitial myocarditis.

B) What kind of consequences can develop in the patient?
a) postmyocarditic cardiosclerosis;
b) atherosclerotic cardiosclerosis;
c) postinfarction cardiosclerosis;
d) ischemic cardiosclerosis;
e) hypoxic cardiosclerosis.

C) What complications may develop:
a) heart rupture;
b) cardiac insufficiency;
c) arrhythmias;
d) cardiac aneurysm;
e) sudden death.

2. *A 24-year-old patient complains of fever, weakness, inappetence. The biopsy of a supraclavicular lymph node was collected. The histological test revealed the presence of granulomas with caseous necrosis in the centre and a cellular belt of epithelioid cells, multinucleated giant Langhans cells with nuclei arranged in crown-form and lymphocytes.*

Question:

Which pathogenic agent must be identified in order to confirm the diagnosis:

a) Frisch bacillus;
b) Hansen mycobacterium;
c) Koch mycobacterium;
d) pale treponema;
e) actinomycetes.

3. *The necropsy revealed a round formation with a diameter of 1,5 cm in the liver, which, examined microscopically, had the following structure: in the centre – necrotic masses, and around them – granulation tissue with plasmocytes, lymphocytes, single giant Langhans cells and blood vessels with the signs of endo– and perivasculitis.*

Question:

What is the diagnosis in this case, taking into consideration the described morphologic pattern:

a) tuberculous granuloma;
b) leprous granuloma;
c) syphilitic gumma;
d) rhinoscleromatous granuloma;
e) actinomycotic granuloma.

4. *A 58-year-old patient was complaining of difficult nasal respiration, dyspnea. During the clinical examination, the otorhinolaryngologist found thickening of the nasal mucosa. The biopsy of the nasal mucosa revealed granulomatous inflammation with presence of lymphocytes, plasmocytes, Mikulicz cells, Russel corpuscles in granulomas.*

Question:

What is the diagnosis in this case, taking into consideration the described morphologic pattern:

a) rhinoviral rhinitis;
b) adenoviral rhinitis;
c) rhinoscleroma;
d) meningococcal nasopharyngitis;
e) allergic rhinitis.

5. *The biopsy collected from the bronchial wall of a patient with chronic bronchitis revealed proliferations of the granulation tissue over mucosa; the granulation tissue is diffusely infiltrated by lymphocytes, histiocytes and plasmocytes, covered with glandular epithelium in some areas.*

Question:

Which type of bronchitis is in this case:

a) catarrhal–mucous chronic bronchitis;
b) purulent chronic bronchitis;
c) polypoid chronic bronchitis;
d) deformed chronic bronchitis;
e) mucopurulent chronic bronchitis.

IMMUNOPATHOLOGIC PROCESSES

Immunopathologic processes are determined by the function disorder of the immunocompetent (lymphoid) tissue. The immune reactions, which normally have a body defense function against various foreign antigens, can lead to alterations of own tissues, during these processes. Immune reactions exercise, in such conditions, a harmful action on tissues, more serious than the antigens themselves.

The organs of the immunocompetent system are subdivided into **central organs**: a) thymus and b) bone marrow and **peripheral organs**: a) lymph nodes, b) spleen, c) lymphoid tissue associated with the digestive tract mucosa – MALT (*mucosa-associated lymphoid tissue*): pharyngeal ring, lymphoid follicles from stomach mucosa, Peyer patches, vermicular appendix, solitary follicles of the large intestine; d) lymphoid tissue associated with bronchi and skin (BALT and SALT – *bronchi* and *skin – associated lymphoid tissue*), e) lymphoid tissue from exocrine glands (salivary glands, pancreas) and mammary gland.

Three cellular populations participate in the immune reactions: a) T lymphocytes (T-dependent), b) B lymphocytes (B-dependent) and c) macrophages.

The immune response may be of *cellular* or *humoral type* and it manifests itself morphologically by proliferation and differentiation of the cells of central or peripheral organs of the lymphoid system. Primarily, the character of the immune reaction depends on the peculiarities of the antigen, its quantity, the way of penetration into the organism, previous contacts with the respective immunogenic antigen.

The immune reaction of humoral type is triggered at the penetration into the body of different soluble (dissolved) antigenic substances, for example, of microbial toxins, extracellular pathogenic agent (bacteria). Its essence lies in antigen destruction by the specific antibody produced by plasmocytes, whose predecessors are B lymphocyte. The antigen-antibody complex is phagocytized by macrophages and eliminated from the organism; the process is called **immune phagocytosis**. Thus, the effector cell in humoral immune reaction is **plasmocyte** (Fig. 6–1a).

In case of penetration into the organism of some antigens of cellular (tissular) origin, for example foreign bodies, pathogenic agents which parasitize intracellularly (especially viruses and fungi), an immune reaction of cellu-

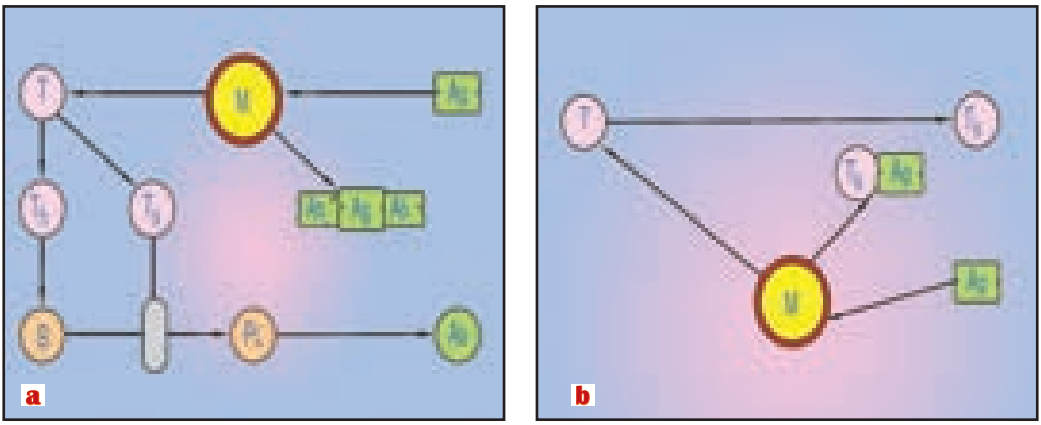


Fig. 6–1 a, b. Schematic representation of immune reactions: a) humoral, b) – cellular : B – B-lymphocyte, T – T-lymphocyte, Th – T-helper lymphocyte, Ts – T–suppressor lymphocyte, Tk – T–killer lymphocyte (cytotoxic), M – macrophage, Ag – antigen, Ab – antibody, Pl – plasmocyte.

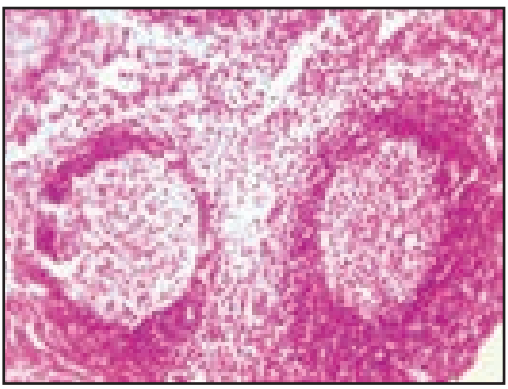


Fig. 6–2. Hyperplasia of lymph node follicles in antigenic stimulation (hematoxylin–eosin stain; ×70).

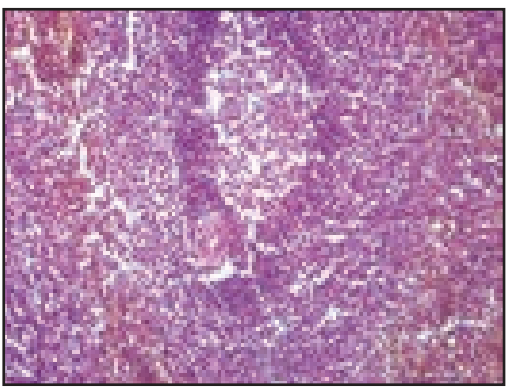


Fig. 6–3. Hyperplasia and plasmatization of lienal follicles in antigenic stimulation (hematoxylin–eosin stain; ×70).

lar type develops, whose essence lies in antigen destruction by sensitized T- killer lymphocyte with the help of macrophages, without participation of antibodies – **immune cytolysis** (cytolytic and cytopathic action of lymphocytes). The effector cells in the cellular immune reaction are the **T – killer lymphocytes and macrophages** (Fig.6–1b).

Each type of immune reaction includes 3 consecutive stages: *afferent stage* – information transmission to the specific reactive cells, *central stage* – proliferation and differentiation of the lymphatic system cells (blastic transformation of B or T-lymphocytes, the appearance of plasmocytes, T lymphocytes sensitization) and the *efferent stage* – the reaction of specific antibodies and T-lymphocytes sensitized with the antigen. Morphological changes, which occur in the lymph nodes and spleen at antigenic stimulation, are nonspecific, stereotyped. Macroscopically, these organs are increased in volume, edematous, hyperemic; microscopically, one notices a hyperplasia of immunocompetent cells, transformation of small lymphocytes in blastic cells (Fig. 6–2, 6–3).

Depending on the type of immune reaction, hyperplastic processes take place in different areas of lymphoid peripheral organs. The distribution of thymus-and bursa-dependent areas is presented in Table 6.1.

Table 6.1.

Distribution of thymus-and bursa-dependent areas

Organ	Bursa-dependent areas	Thymus-dependent areas
Lymph nodes	Cortical layer Medullar layer	Paracortical layer
Spleen	Peripheral areas of lymphatic follicles	Paraarterial area (around the centrofollicular artery)
Tonsils	Tonsil follicles	Interfollicular subepithelial lymphoid areas
Intestinal lymphoid tissue	Intestinal follicles	Interfollicular subepithelial lymphoid areas

The hyperplasia of B–lymphocytes and lymphoblasts, the plasmablastic and plasmocytic transformation of B-lymphocytes and proliferation of macrophages take place in bursa-dependent areas, at the onset of humoral immune reaction. The hyperplasia of T-lymphocytes (their activation or sensitization) and macrophages takes place in thymus-dependent areas, during the immune reaction of cellular type. These hyperplastic processes are more obvious in regional lymph nodes in relation with the place of antigen penetration. The induction of antibody development in humoral immune reaction associates with appearance of germinal centers (clear centers) in the follicles of the spleen and lymph nodes – the so-called secondary follicles (follicles with germinal centers), where the lymphoblastic proliferation takes place. These follicles are formed around the macrophages that contain antigen. The appearance of secondary follicles and the extent of their development reflect the intensity degree of immunity, the level of development of plasma cell antibodies, and, respectively, the antibody titer in blood plasma.

In the immune reaction of cellular type, the blastic transformation of small lymphocytes is not produced in the germinal centers of follicles, but in the paracortical areas of the lymph nodes and in the periarterial areas of splenic follicles. Macroscopically, the spleen is enlarged and has a mottled appearance with multiple whitish foci, which represent hyperplastic lymphatic follicles with germinal centers. In cases of massive and prolonged antigenic stimulation, these hyperplastic processes are more pronounced.

Immunopathies can be divided into four groups:

1) thymus lesions;
2) hypersensitivity (hypersensibility) reactions;
3) autoimmune diseases;
4) immunodeficiency syndromes.

6.1. LESIONS OF THE THYMUS

In some cases, they constitute the consequence, in others - the cause of immunological homeostasis disturbance.

The appearance of some immunodeficiency syndromes, autoimmune diseases and endocrine disturbances is related to thymus pathology.

Accidental or stress thymic involution

Macroscopically, a rapid decrease of thymus mass and volume is observed (8–10 times in several days). The histological examination reveals smaller thymus lobules, thinned and poor in lymphocytes cortical layer, as a consequence of their progressive destruction. Lymphocyte karyorrhexis, their active phagocytosis by macrophages, colabation (collapse) of reticular epithelium, dystrophic calcinosis and appearance of some cystic cavities in Hassal corpuscles take place. The characteristic sign – equivalence or even inversion of thymus lobule layers, according to lymphocyte content, the contrast between them disappears, as a result of cortical T-lymphocyte depletion; the content of lymphocytes in the medullar layer can turn higher than that of the cortical layer (Fig. 6–4).

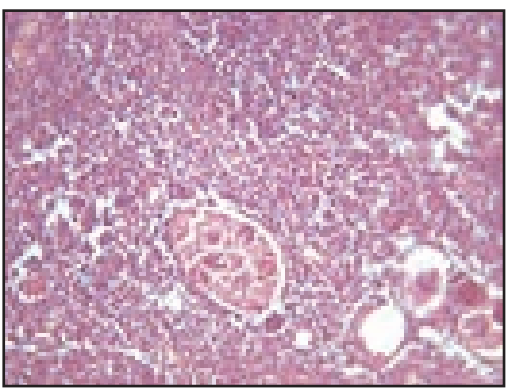


Fig. 6–4. Accidental thymic involution (hematoxylin–eosin stain; ×70).

It is observed in children in severe infectious diseases, malignant tumors with metastases, leukemias, traumatisms and different severe stressful situations, when rapid elimination of corticosteroids by the adrenals and massive antigenic stimulation of the immune system occur. The glucocorticoid hormones have the capacity to induce thymus apoptosis. The longer and more severe is the basic disease, the more evident is the involution extent of the thymus. If the disease evolution is not too long, the thymus can recover.

The possible consequences of thymus accidental involution:

a) regeneration of thymus;
b) atrophy of thymus.

The thymus accidental involution can be reversible, as the thymus has a high regenerative capacity, but in acute infectious diseases, bacterial and viral, purulent process infections or malignant tumors with metastases, it can lead to acquired thymus atrophy. The clinical–functional importance of thymus accidental involution lies in the decrease of intensity of cellular and humoral immunity, due to decrease of thymic hormone secretion.

The atrophy of the thymus – thymus decrease in mass and size. It is a consequence of accidental involution and represents the morphologic substratum of the acquired immunodeficiency.

The hyperplasia of the thymus – thymus enlargement, due to some hyperplastic processes. It develops as a Hodgkin's lymphoma chemotherapy complication, in massive thermal burnings, after corticosteroid treatment cease in children. The thymus structure

is kept. The morphologic substratum of immunity decrease in children is to be considered.

Thymic lymphoid hyperplasia is a particular form. It is increased in size, infiltrated with B-lymphocytes and plasmocytes; lymphoid follicles with germinal centers appear in the medullar layer of the thymic lobes, a fact that is not seen in normal conditions. It is observed in autoimmune diseases, for example, in myasthenia gravis, disseminated lupus erythematosus, rheumatoid arthritis, scleroderma, thyrotoxicosis etc.

Thymic agenesis (aplasia) - the thymus is absent or persists in the rudiment embryonic state.

Hypoplasia is incomplete thymus development. Macroscopically, the thymus is small, the lobules have diminished dimensions, the lymphocyte content is reduced considerably, the cortical layer is atrophied; an insignificant number of small Hassal corpuscles is observed in the medullar layer, lacking completely in some places; the interlobular connective tissue trabeculae are thickened (Fig. 6–5). The secretion of thymic hormones is decreased or abolished.

Dysplasia – the structure of the thymus is altered, the lymphocyte content is reduced.

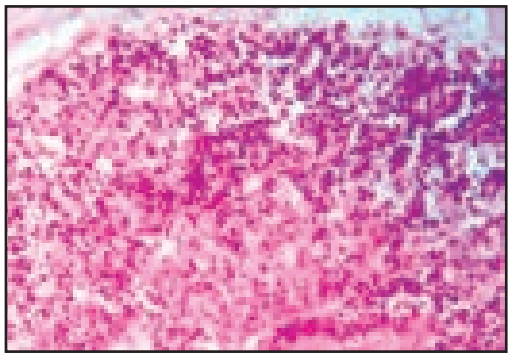


Fig. 6–5. Thymic hypoplasia in the combined immunodeficiency syndrome (hematoxylin–eosin stain; ×70).

These pathologic processes represent development vices, which often associate with congenital malformations and manifest themselves clinically as cellular or combined congenital immunodeficiency. It is usually associated with hypoplasia of the lymphoid tissue in the lymph nodes and spleen, where the preponderant atrophy of thymus-dependent areas is observed. It manifests itself clinically by organism's incapacity to trigger cellular and humoral immune reactions. Children are predisposed to infectious diseases that are recurrent and develop severe complications (pneumonia, septicemia). Concomitantly, malignant mesenchymal tumors are frequently observed.

6.2. HYPERSENSITIVITY REACTIONS

The humoral or cellular immune reaction to both endogenous and exogenous antigens can cause certain local lesions of the tissues. These reactions are called hypersensitivity reactions or diseases and appear in an already sensitized to a peculiar antigen organism.

The main pathogenic factors, which favor these reactions, are:

a) allergen' s prolonged (repeated) action;
b) allergen overcharge (high doses);
c) organism' s general hyperreactivity;
d) hereditary predisposition to allergy.

The hypersensitivity reactions are of 4 types:

1) hypersensitivity reaction of immediate type (anaphylactic);
2) cytotoxic and cytolytic reaction, mediated by antibodies. The inactivation, neutralization or stimulation reactions are a variant of this reaction;
3) hypersensitivity reaction mediated by immune complexes (immune complex diseases);
4) hypersensitivity reaction mediated by T-lymphocytes (cellular or delayed hypersensitivity); the granulomatous reaction is a variant of this reaction.

Pathogenetic mechanisms of hypersensitivity reactions

Immediate hypersensitivity reaction (type I or anaphylactic) (Fig. 6–6)

It is observed in patients that react to certain antigens (allergens) by abnormal IgE production, with affinity to mastocytes and basophiles. At the Ag's initial penetration, IgE is produced and fixed on the surface of mastocytes and basophils; at the repeated Ag's penetration, the Ag–Ac reaction determines mastocyte degranulation and sudden release of mediators (histamine, serotonin, heparin, enzymes, prostaglandins, eosinophilic chemotactic factor etc.), which provoke spasms of the smooth musculature of the bronchi, intestine, edema, mucus hypersecretion, vessels dilatation and hyperemia of vessels, increase of vascular permeability, proteolytic tissular destructions.

Morphologically, it manifests itself through acute immune inflammation with edema, fibrinoid intumescences

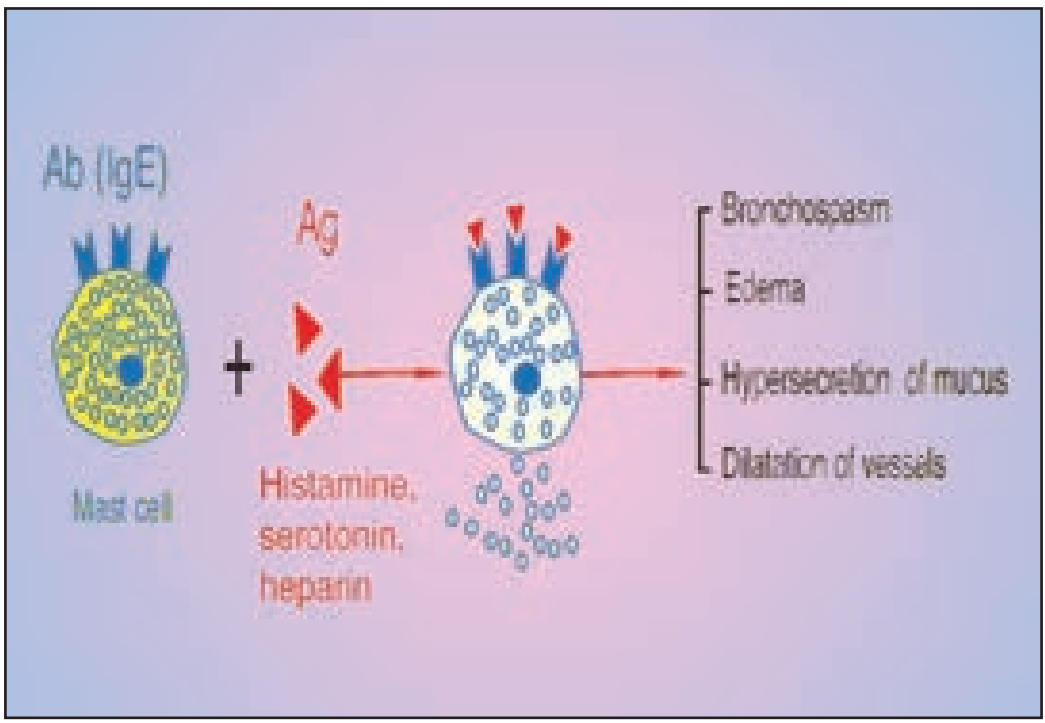


Fig. 6–6. Schematic representation of the immediate anaphylactic reaction: Ab - antibody, Ag - antigen.

and/or necrosis of the connective tissue and vessels, vessel thrombosis, formation of fibrinous or fibrinous–hemorrhagic exudate. These modifications appear in 5–20 min. and have the tendency to diminish gradually in 60 min. from the onset of the allergenic substance action.

It is observed in anaphylactic shock (due to medicins and insects venom), hives (Fig. 6–7), atopic bronchial asthma, allergic rhinitis (Fig. 6–8), hay fever, Quincke angioneurotic edema, food or drug allergy.

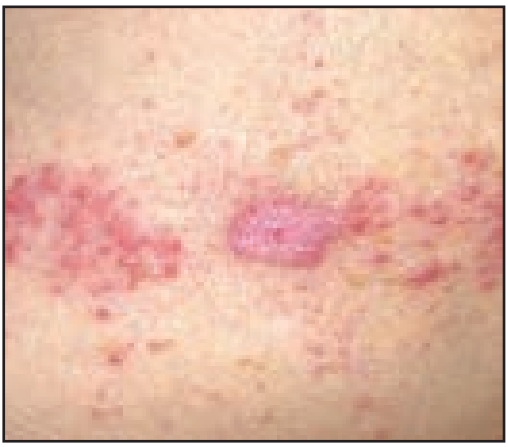


Fig. 6–7. Hives, allergic rash.

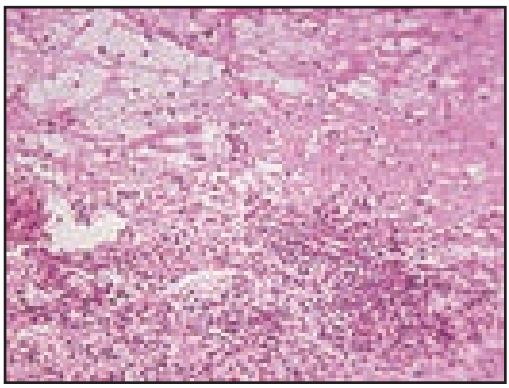


Fig. 6–8. Allergic rhinitis, edema, myxomatosis, inflammatory infiltration, predominantly eosinophilic of nasal mucosa (hematoxylin– eosin stain; ×70).

Cytotoxic /cytolytic hypersensitivity reaction (type II) (Fig. 6–9)

The antibodies develop against the superficial antigen components of the heterogenic cell membranes (transfused or own blood cells, transplant cells).There can be 2 variants:

➢ cytotoxicity mediated by anti-

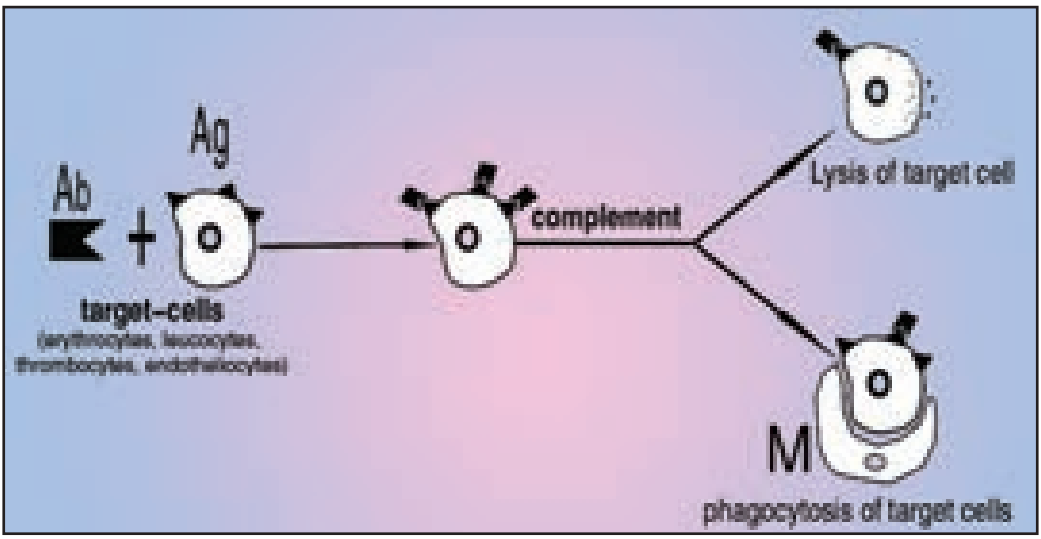


Fig. 6–9. Schematic representation of the cytolytic and cytotoxic reaction : Ab - antibody, Ag - antigen, M - macrophage.

bodies (antibody-dependent – the Ag–Ac reaction occurs on the surface of target cells, which are subsequently destroyed by the K-cells (killer) or NK (natural killer), or phagocytized by macrophages;

- cytotoxicity mediated by complement (cascade activation of the complement components causes elimination of mediators and lysis of the target cells).

It is observed in the hemolytic disease of the newborn, post transfusion reactions, autoimmune hemolytic anemia, medicinal cytopenia (agranulocytosis, thrombocytopenia), vascular purpura, graft (transplant) rejection reaction. Inactivation and neutralization or stimulation reactions are a variant of these reactions, where the development of antibodies against some biologically active substances or cell surface receptors occurs (Fig.6–10). Two development mechanisms of these reactions are known:

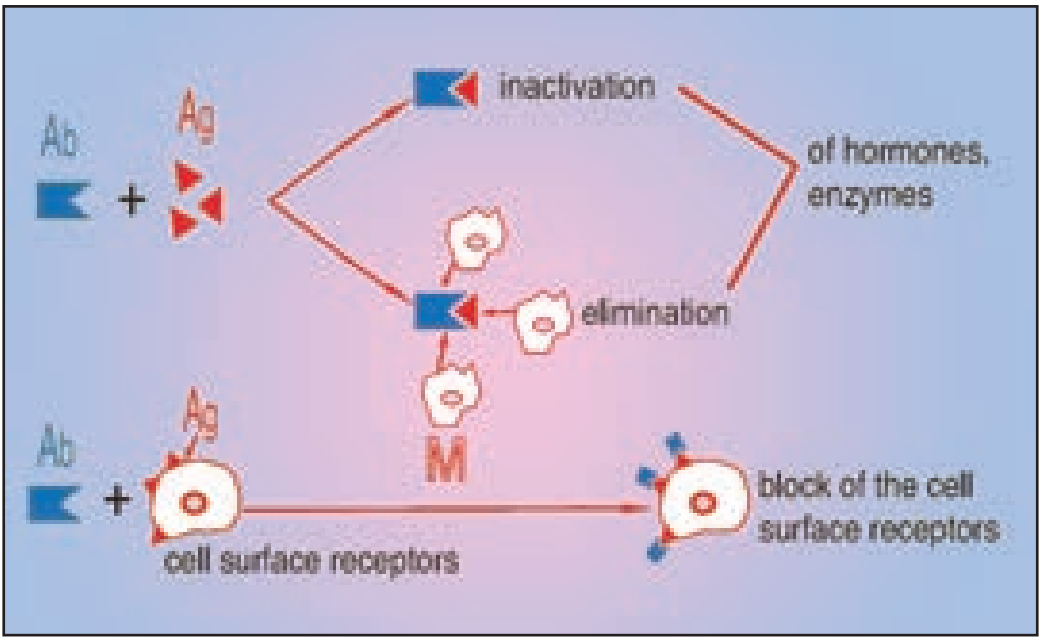


Fig. 6–10. Schematic representation of the neutralization and inactivation reaction : Ab - antibody, Ag - antigen, M - macrophage.

1) inactivation of hormones, enzymes (insulin, thyroglobulin, coagulation factors), toxins (in diphtheria, tetanus);

2) alteration of cellular function by antireceptor antibodies (antibodies against the receptors for insulin, acetylcholine, thyroid-stimulating hormone, thyroglobulin, against parietal cells of gastric mucosa); in some cases, the antireceptor antibodies block the functional activity of the cells and stimulate it in other cases.

Examples: insulin-dependent (type I) diabetes mellitus, *myasthenia gravis*, hypothyroidism, thyrotoxicosis, pernicious anemia, coagulopathy.

Hypersensitivity reaction mediated by toxic immune complexes (type III) or immune complex diseases (Fig. 6–11)

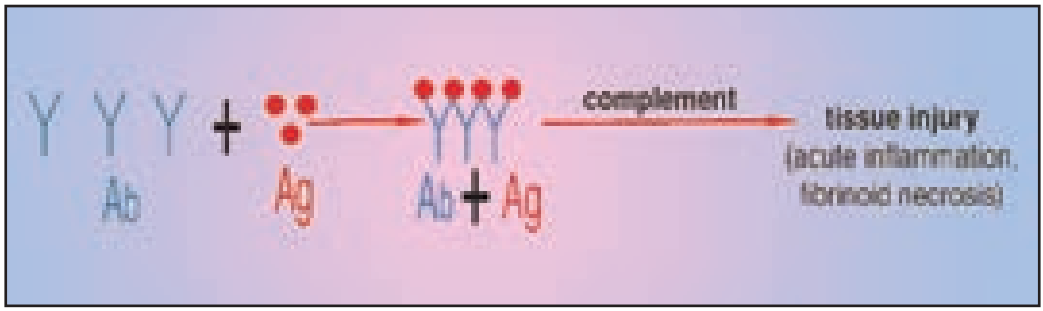


Fig. 6–11. Schematic representation of immune complex reaction : Ab - antibody, Ag - antigen.

The Ag–Ac immune complex induces the activation of complement components, basophilic and neutrophil leukocytes, elimination of inflammation mediators. The harmful action of toxic immune complexes can occur in case of:

a. excess of antibodies with inflammatory reaction in the place of antigen's introduction (Arthus reaction);
b. excess of antigen with generalized reaction and lodging of immune complexes in the basal membranes of kidney capillaries, joints, skin.

Examples: serum sickness, glomerulonephritis (Fig. 6–12), rheumatic diseases (disseminated lupus erythematosus, rheumatoid arthritis), allergic dermatitis, allergic alveolitis („farmer's" lung).

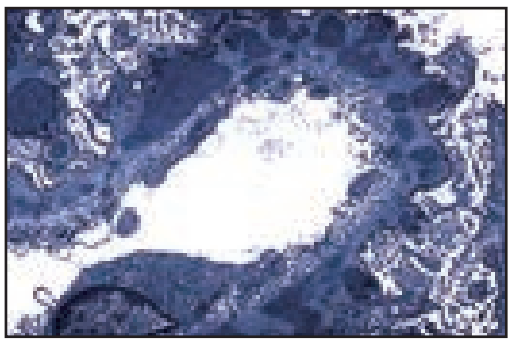


Fig. 6–12. Membranous glomerulonephritis, immune complex deposits on the basement membrane of the renal glomerulus capillary (electron microscopy; ×10000).

Hypersensitivity reaction mediated by T-cells (type IV or delayed hypersensitivity) (Fig. 6–13)

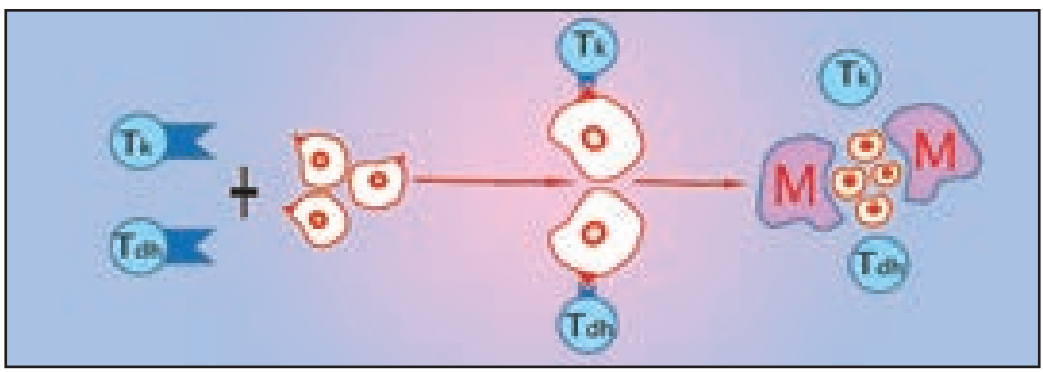


Fig. 6–13 Schematic representation of the hypersensitivity reaction mediated by T-cells: Tdh – delayed hypersensitivity T-lymphocytes, Tk - T-killer lymphocyte, M - macrophage.

The immune response appears in 24–72 hours or even in 1–2 weeks, related to T-lymphocytes and macrophages, which make the immune cytolytic - target-cell destruction. The morphological substratum is lymphocytic and macrophage infiltration. The granulomatous reactions constitute an alternative, when the isolation and delimitation of the pathogenic agent (allergen) take place. Main cellular components of granulomas are epithelioid cells and multinucleated giant Langhans cells (Fig. 6–14).

Examples: tuberculin type reaction, contact dermatitis, graft rejection, autoimmune diseases, tuberculosis, syphilis, helminthosis, mycosis. The classic example is the Mantoux reaction or tuberculin test: at intracutaneous injection of tuberculin in a person infected by the tuberculosis bacillus, there appears redness (erythema) and induration in 8–12 hours, reaching maximum size (1–2 cm in diameter) in 2–7 days. Histologically, perivascular (perivenular) infiltration with lymphocytes and monocytes occurs in the skin.

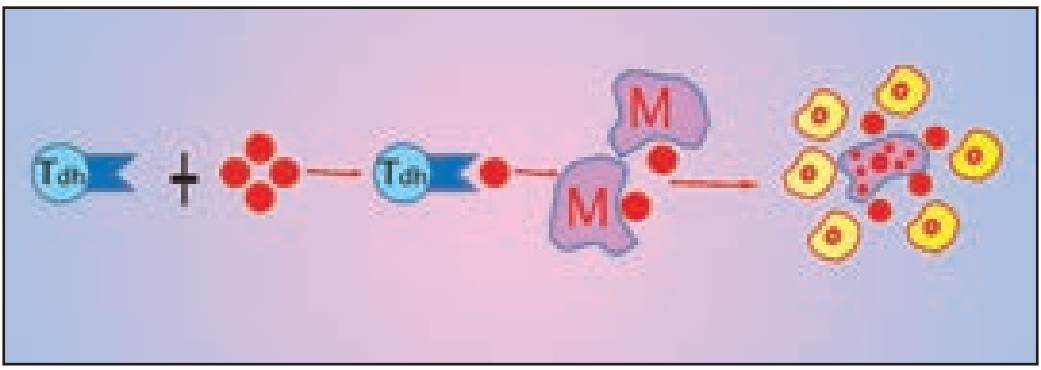


Fig. 6–14. Schematic representation of the hypersensitivity reaction, granulomatous type: Tdh – delayed hypersensitivity T-lymphocytes, M - macrophage.

6.3. AUTOIMMUNE DISEASES

Autoimmune diseases are a group of diseases based on the reaction of autoantibodies and sensitized lymphocytes against self-antigens, causing their structural and functional alterations. Among the most frequent etiologic factors of self immunization, the most important are chronic viral infections, radiation, certain chemical and physical actions, both on the immunocompetent organs and on the target organs.

According to the mechanism of autoimmunization development, three groups of autoimmune diseases are distinguished:

1) organ specific;
2) organ non-specific;
3) secondary autoimmune disorders.

General characteristic of autoimmune diseases

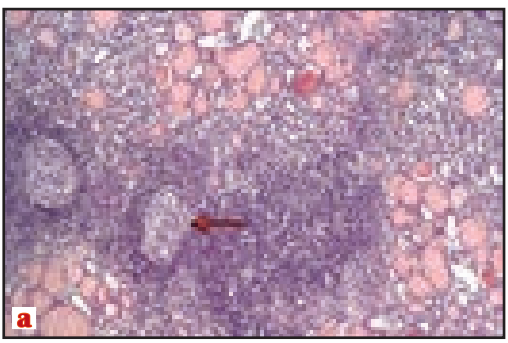
Organ specific (true) autoimmune diseases

The pathogenetic mechanism consists in impairment of physiological isolation of organs and tissues towards which there is no immunological tolerance, alteration of their histohematic barriers; the unmodified antigens of these tissues, which are isolated (sequestered) immunologically, cause develop-

ment of antibodies and/or sensitization of T-lymphocytes. The causative factors are chronic viral infection, trauma, radiation, sunstroke.

It can be found in the Hashimoto's thyroiditis (goiter), disseminated sclerosis, autoimmune encephalomyelitis, sympathetic ophthalmia, autoimmune orchitis, idiopathic Addison's disease.

The most classic example of autoimmune true disease is Hashimoto autoimmune thyroiditis or goiter. A diffuse stroma infiltration with lymphocytes and plasma cells is revealed in the thyroid gland, sometimes forming lymphoid follicles with germinal clear centers (Fig. 6–15a). These infiltrations substitute gradually the glandular parenchyma. The thyroid follicles are atrophied; they contain poorly colored or vacuolated colloid, some of them lack the lumen, sclerosis processes develop. Macroscopically, the thyroid gland is enlarged, painless; it has an elastic consistency and does not adhere to adjacent tissues (Fig. 6–15b). Clinically, the evolution is accompanied by hypothyroidism and advances towards myxedema. It is found almost exclusively in women aged between 40–50 years.



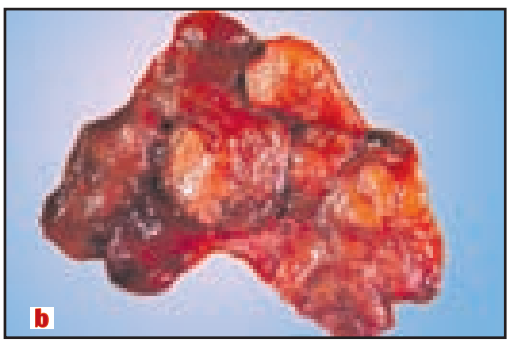


Fig. 6–15 a, b. Autoimmune Hashimoto thyroiditis: a – microscopic pattern (hematoxylin–eosin stain; ×70); b – macroscopic aspect.

Organ nonspecific (systemic) autoimmune diseases

It is a group of diseases with primary disorders of immunocompetent system function. There is loss of lymphocytes capacity to distinguish the foreign antigens from own ones. Morphological lesions have a general, systemic character. The most important causative factors are: mutations, lymphotropic virus infections, ultraviolet radiation, drugs etc. It is observed primarily in the systemic diseases of the connective tissue: disseminated lupus erythematosus, rheumatoid arthritis, systemic scleroderma, dermatomyositis, ankylosing spondyloarthritis, polyarteritis nodosa, Sjogren syndrome. Development of antibodies against various structural elements of organs and tissues occurs in these diseases.

Examples:

- **in disseminated lupus erythematosus** – antinuclear, antinucleolar, antimitochondrial, anti-erythrocyte, anti-thrombocyte, anti- lymphocyte autoantibodies etc; the most important for diagnosis are the antinuclear antibodies against the double–stranded DNA. The nuclei of altered cells react with antinuclear auto antibodies and convert into homogeneous corpuscles, which are stained with he-

matoxylin - hematoxylin bodies (Fig. 6–16). Such nuclei are phagocytized by neutrophil leukocytes and macrophages, forming lupus erithematosus cells (LE–cells) (Fig. 6–17). The immune complexes lodge in the skin (erythema, butterfly-shaped rash on the face), kidneys (glomerulonephritis), blood vessels (vasculitis) (Fig. 6–18), heart valves (Libman–Sacks endocarditis), synovial membranes of joints;

- **in rheumatoid arthritis** – autoantibodies against Fc fragments of IgG; immune complex, called *rheumatoid factor*, represents "Ig–anti–Ig", found in blood serum and synovial fluid.

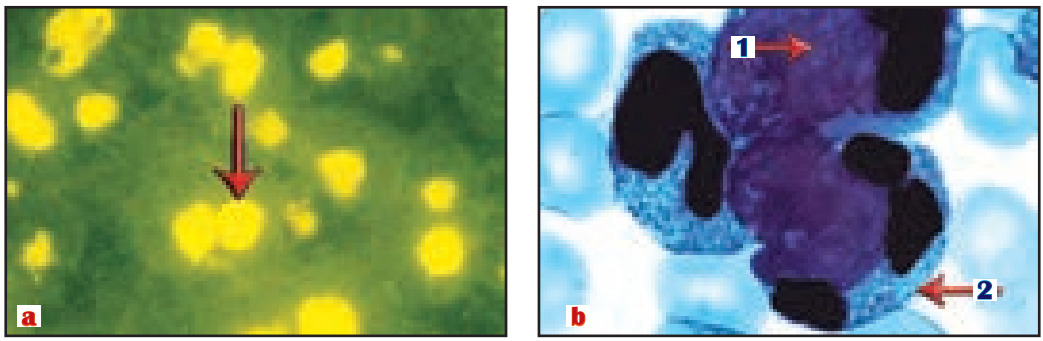


Fig. 6–16. Hematoxylin bodies: a – antinuclear antibodies (immunofluorescent reaction); b – blood smear (azure–eosin stain).

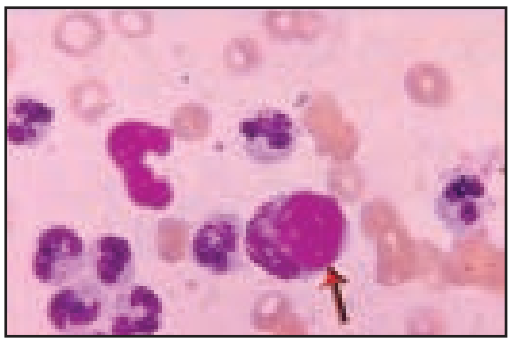


Fig. 6–17. Lupus erithematosus cell, blood smear (azure–eosin stain).

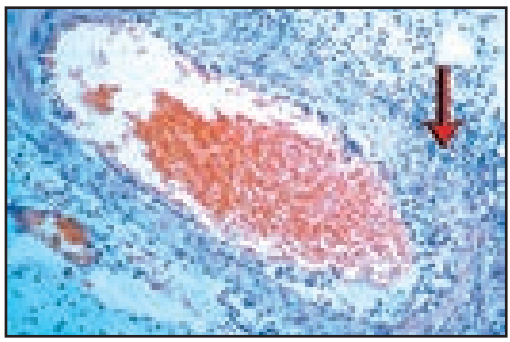


Fig. 6–18. Allergic vasculitis, fibrinoid intumescence and cellular infiltration of vascular wall (hematoxylin–eosin stain; ×70).

Mainly, it affects small and medium size joints;

- **in systemic sclerosis** – antinucleolar autoantibodies are more characteristic; it affects the skin and visceral organs;
- **in Sjogren syndrome** – autoantibodies against salivary duct cells; it is manifested by inflammation, atrophy and sclerosis of salivary and tear glands.

Secondary autoimmune diseases

The secondary autoimmunization occurs in the appearance of new, heterogeneous antigens in the body, which may lead to suppression of natural tolerance.

The ethiopathogenetic mechanisms:

- protein distortion in burns, irradiation, cold injury, chronic inflammation, viral infections;
- cross–reaction: the appearance of

some bacterial antigens, whose structure is identical with the structure of body tissue (e.g. serological Y type – *cardial* – of beta–hemolytic streptococcus has antigenic community with cardiomyocyte sarcolemma, and the XII serotype – *nephritogenic* – with basement membranes of renal glomeruli, *klebsiella* – with the lung tissue;

- haptenic mechanism - the necrotic products, drugs, toxins acting as haptens.

Examples: glomerulonephritis, rheumatism, myocardial infarction, chronic gastritis, ulcerative colitis, liver cirrhosis, drug disease, allergic anemia, etc.

Group III disorders are not independent autoimmune diseases, the autoimmune conflict being only a complication of basic morbid process. Secondary autoimmune disorders result in chronization and aggravation of the respective diseases.

Morphologically, the autoimmune conflict is manifested through target- organ infiltration with immunocompetent cells (lymphocytes, plasma cells and macrophages), the appearance of lymphatic follicles with germinal centers, dystrophic and necrotic parenchyma lesions, proliferation of connective tissue stroma.

Amyloidosis

The disease is characterized by deposition of a complex protein substance, called amyloid, in various tissues and organs. The name is due to its tinctorial properties, similar to starch (Rudolf Virchow). The amyloid substance is a glycoprotein, where fibrillar proteins are conjugated with polysaccharides. It contains two main components: the fibrillar component (F), which is a fibrillar protein, synthesized by amyloidoblasts (macrophages, fibroblasts, plasmocytes, endotheliocytes etc., which were subject to the action of some mutagenic factors) and the plasmatic component (P) – blood plasma proteins and polysaccharides. The proteo–polysaccharide components are closely related to each other and to elements of the tissue where the amyloid is deposited, particularly with chondroitin sulfates of the ground substance of the connective tissue (heparan sulfate and dermatan sulfate). Fibrillar proteins constitute 90%, and polysaccharides – 10% of the total mass of amyloid.

Today, the classification of amyloidosis is adopted according to the biochemical composition of the amyloid substance. There are more than 20 biochemical variants of amyloidosis. The most common and important are the following:

1) **AL–amyloidosis** (*amyloid light chain*); the amyloid is composed of light chains of immunoglobulins, synthesized by plasma cells. It is found in cases of monoclonal proliferation of B-lymphocytes, most frequently in multiple myeloma, which is a malignant tumor of plasma cells (plasmocytoma). This form of amyloidosis is considered *primary*, because it is not preceded by other illnesses. It develops in 10–15% of patients with multiple myeloma, but it is also found in other B-cell lymphomas. The lesions have a systemic character, affecting mainly the cardiovascular system, muscles, nerves, skin.

2) AA – amyloidosis associated with protein synthesis in the liver –serum precursors of amyloid substance (*SAA – serum amyloid associated protein*). The production of this protein is increased in different inflammatory processes. This form of amyloidosis is considered *secondary (reactive),* since it is preceded

by other chronic inflammatory diseases, for example, in some chronic infections (tuberculosis, syphilis, leprosy, dysentery, infective endocarditis, actinomycosis, etc.), in diseases accompanied by chronic purulent processes (suppurative bronchiectasis, abscesses, osteomyelitis, suppurated wounds, empyema, chronic septicemia), in rheumatic diseases (rheumatoid arthritis and systemic lupus erythematosus), in Hodgkin's disease. It is a generalized form of amyloidosis, with predominant damage of the spleen, liver, kidneys, adrenals and intestine.

3) Aβ amyloidosis is found in brain lesions in Alzheimer disease. The Aβ protein comes from transmembrane glycoproteins, called amyloid precursor proteins (*Aβ PP – amyloid β precursor protein*). The Aβ amyloid constitutes the main component of senile plaques, which are found in Alzheimer disease both in the brain substance and in cerebral blood vessels.

Morphological characteristics. Macroscopically, the affected organs are enlarged, have a yellow color, dense consistency, lardy or waxy appearance (Fig. 6–19). Initially, the spleen in amyloidosis has a mottled appearance due to the focal amyloid deposits in lymph follicles, reminding of sago beans (it is called *sago spleen*, Fig. 6–20) and later, as the lesions progress, the process becomes diffuse, homogeneous, the spleen gains a lardy aspect (*lardy spleen*, Fig. 6–21 a). At optical microscopy, the amyloid is an amorphous, non-structured substance of a homogeneous eosinophilic color, which lodges extracel-

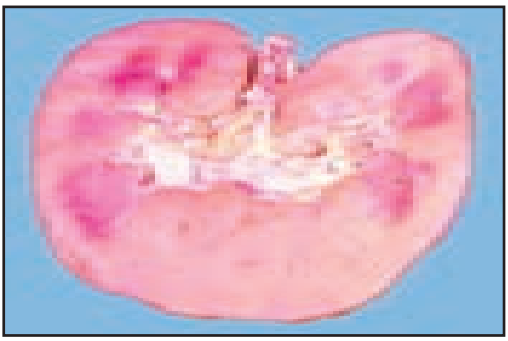


Fig. 6–19. Renal amyloidosis.

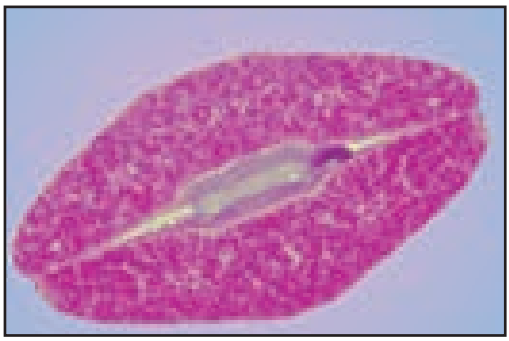


Fig. 6–20. Focal amyloidosis of the spleen (sago spleen).

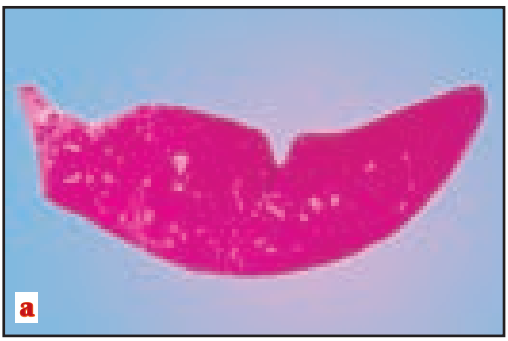


Fig. 6–21 a, b. Diffuse amyloidosis of the spleen: a – lardy spleen; b– macroscopic Virchow reaction for amyloid identification.

lularly (Fig. 6–22), and with a fibrillar structure at electron microscopy (Fig. 6–23). The amyloid substance does not cause inflammatory reaction. The predominant places for amyloid deposits in various organs are:

- walls of blood and lymph vessels (in intima or adventitia);
- basement membranes of glandular structures (tubes, channels, ducts);
- organ stroma, along reticular or collagen fibers.

The main morphogenetic mechanism of amyloidosis is pathological synthesis.

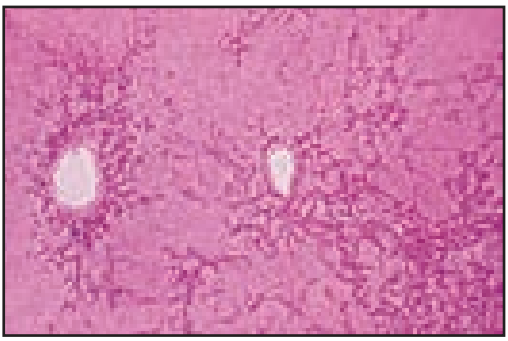


Fig. 6–22. Hepatic amyloidosis (hematoxylin–eosin stain; ×70).

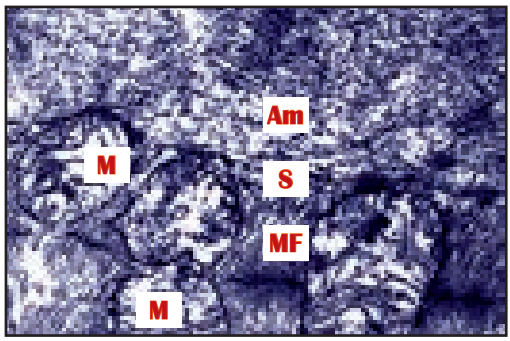


Fig. 6–23. Amyloidosis of myocardium (electron microscopy; ×23000): Am - amyloid, MF - myofibrils, M - mitochondria, S - sarcolema.

To identify the amyloid substance, specific methods are used:

- ✧ Virchow macroscopic reaction – the successive application of Lugol solution and sulfuric acid (10%) on sectional area colors the amyloid into blue–purple or dark green (Fig. 6–21b).
- ✧ with Congo red, the amyloid stains into dark red and the remaining tissue - into pink-yellow (Fig. 6–24).
- ✧ with methyl–violet or gentian violet, amyloid turns red, and the other tissular elements turn violet (metachromatic stain).
- ✧ with S or T thioflavin - the amyloid appears green-yellow at the luminescent microscope (ultraviolet light).

To make a diagnosis, the aspiration biopsy of the subcutaneous adipose tissue or the biopsies of the rectal or oral cavity mucosa are used.

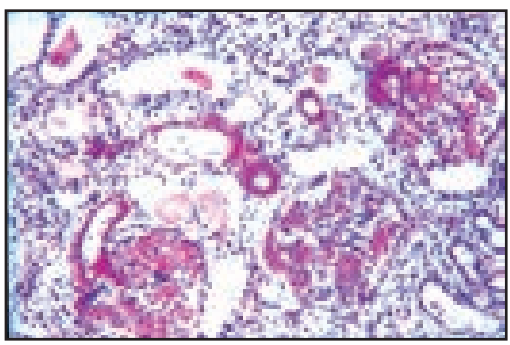


Fig. 6–24. Renal amyloidosis (Congo red stain; ×70).

The consequences of amyloidosis. It is an irreversible process resulting in progressive parenchyma atrophy and sclerosis of damaged organs, and, under the functional aspect, in severe impairment or abolition of their function.

6.4. IMMUNODEFICIENCY SYNDROMES

The immunodeficiency syndromes represent a manifestation of immune system failure, which can be primary (congenital) or secondary (acquired).

Primary immunodeficiency syndromes

They are caused by development disorders of the immune system. They are subdivided into: a) primary combined immunodeficiencies (cellular and humoral); b) primary cellular immunodeficiencies; c) primary humoral immunodeficiency.

Primary combined immunodeficiency syndromes are observed in children and neonates, being transmitted in the autosomal recessive way. Morphologically, thymus and peripheral lymphoid tissue hypoplasia is observed, which leads to functional failure of cellular and humoral immunity. In children, there is a high frequency of infectious diseases and complications that have a recurrent evolution and severe complications (pneumonia, meningitis and septicemia). There are also records malignant mesenchymal tumors, different developmental vices.

Examples: Swiss-type agammaglobulinemia (Glanzmann-Riniker syndrome) and Louis–Bar ataxia telangiectasia).

Primary cellular immunodeficiency syndromes. In children, there is a selective T-cell deficiency due to agenesis or hypoplasia of the thymus (Fig. 6–5, 6–25) and thymus dependent areas of peripheral lymphoid tissue. The hypoplasia of periarterial areas of lienal follicles and paracortical layers of lymph nodes occurs. Clinically, there is a severe deficiency of cellular immunity but the synthesis of immunoglobulin is normal. Concomitantly, there are multiple developmental vices, particularly agenesis of parathyroid glands and severe infectious diseases.

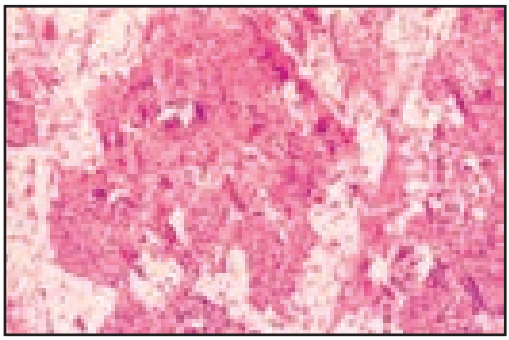


Fig. 6–25. Atrophy, fibrosis and lipomatosis of thymus in cellular immunodeficiency (hematoxylin–eosin stain; ×70).

Examples: DiGeorge syndrome (thymic hypoplasia or agenesis).

Primary humoral immunodeficiency syndromes. In children, the bursa-dependent areas of the peripheral lymphoid tissue are absent. The lymph follicles lack or they are much reduced in size in lymph nodes, spleen, tonsils, intestine; they do not contain germinal centers and plasmocytes (Fig. 6–26, 6–27).

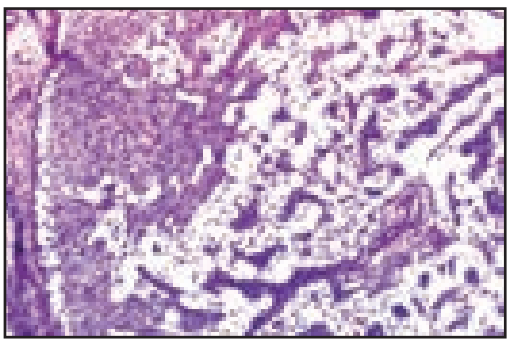


Fig. 6–26. Atrophy, fibrosis and lipomatosis of the lymph node in humoral immunodeficiency (hematoxylin–eosin stain; ×70).

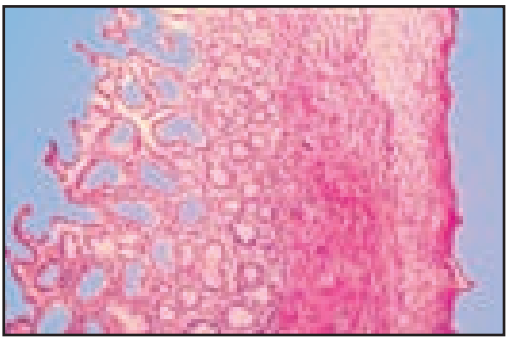


Fig. 6–27. Absence of lymphoid tissue in the vermicular appendix wall (hematoxylin–eosin stain; ×70).

The paracortical layer of the lymph nodes, which is a thymus dependent area, persists. An absence or significant decrease of the content of all immunoglobulins or only of certain classes of immunoglobulins is recorded. There is a high frequency of infectious diseases in children (bronchitis, otitis, skin infections).

Examples: Bruton agammaglobulinemia related to X chromosome (X–linked), selective deficiency of A immunoglobulin (West syndrome).

Secondary immunodeficiency syndromes

Secondary immunodeficiency occurs more frequently as a complication of various diseases or treatment; the morphofunctional lesions of the immune system develop in a secondary way.

Examples:

- ✧ secondary immunodeficiency in leukemias, malignant lymphomas, thymic tumors (thymoma), sarcoidosis;
- ✧ secondary immunodeficiency in plasmacytoma (multiple myeloma), Waldenstrom macroglobulinemia as a result of pathological immunoglobulin secretion;
- ✧ secondary immunodeficiency after the treatment with corticosteroids, immunosuppressants, antilymphocyte serum, radiotherapy, in thymectomy;
- ✧ secondary immunodeficiency is the main manifestation of AIDS - (acquired immunodeficiency syndrome, which has a viral etiology, being caused by retrovirus with tropism for T–helper lymphocytes). There is a severe depression of cellular immunity. Morphologically, it is characterized primarily by generalized lymphadenopathy, opportunistic infections and neoplastic processes. The most common infections are with mycobacteria (mycobacterium tuberculosis), viruses (cytomegalovirus, herpes, hepatitis B, etc.), protozoa (Pneumocystis carinii, toxoplasma) and fungi (Candida, hystoplasma and cryptococcus). Kaposi's sarcoma, non-Hodgkin lymphomas, Hodgkin lymphoma, carcinomas are characteristic among tumors.

ESSENTIAL TERMS
on the subject "IMMUNOPATHOLOGIC PROCESSES"

AA amyloidosis	cytotoxic/cytolytic reaction	immune cytolysis
Aβ amyloidosis	delayed–type allergic reaction	immune phagocytosis
accidental thymus involution	disseminated lupus erythematosus	inactivation reaction
agenesis	Hashimoto autoimmune thyroiditis	lupus erythematosus cells
AL amyloidosis	hematoxylin body	organ nonspecific autoimmune diseases
amyloidosis	humoral immunodeficiency	organ specific autoimmune diseases
aplasia	humoral-type immunity	primary amyloidosis
atrophy	hyperplasia	rheumatoid arthritis
autoimmune disease	hypersensitivity	rheumatoid factor
cellular immunodeficiency	hypersensitivity reaction	secondary amyloidosis (reactive)
cellular-type hypersensitivity	hypoplasia	Sjogren's syndrome
cellular-type immunity	immediate anaphylactic reaction	systemic sclerosis
combined immunodeficiency	immediate-type allergic reaction	Virchow reaction
cross immune reaction	immune complexes reaction	

TESTS
on the subject "IMMUNOPATHOLOGIC PROCESSES"

SET I.

Multiple-choice questions with one correct answer

1) *Which immune reaction manifests itself morphologically by expanding germinal centers and increasing the number of plasmablasts and plasmocytes:*
   a) cellular-type immune reaction;
   b) mixed immune reaction;
   c) autoimmune reaction;
   d) immunodeficiency reaction;
   e) humoral-type immune reaction.
2) *All the listed signs characterize the immediate-type allergic reactions, with the exception of:*
   a) it develops in several minutes;
   b) lymphocytes and macrophages prevail;
   c) sero–hemorrhagic inflammation;
   d) fibrinoid necrosis of vascular walls;
   e) vessels thrombosis.
3) *All the listed signs characterize the delayed-type allergic reactions, with the exception of:*

a) it develops in 24 – 72 hours;
b) lymphocytes and macrophages prevail;
c) neutrophil leukocytes prevail;
d) granulomatosis;
e) interstitial infiltrate.

4) *Which of the listed autoimmune diseases have a local, organ-specific character:*
a) disseminated lupus erythematosus;
b) rheumatoid arthritis;
c) scleroderma;
d) Hashimoto thyroiditis;
e) polymyositis.

5) *Which of the listed autoimmune diseases are characterized by antinuclear autoantibodies?*
a) polymyositis;
b) scleroderma;
c) Hashimoto thyroiditis;
d) systemic lupus erythematosus;
e) autoimmune hemolytic anemia.

SET II.

Multiple-choice questions with 2, 3 or more correct answers.

1. *In which of the listed diseases does the immediate–type hypersensitivity reaction occur*:
a) atopic bronchial asthma;
b) anaphylactic shock;
c) tuberculin-type reaction;
d) contact dermatitis;
e) hemolytic disease of the newborn.

2. *What macroscopic changes of the organs are observed in amyloidosis:*
a) reduced size;
b) increased size;
c) dense consistency;
d) flaccid consistency;
e) wax or bacon appearance.

3. *Which of the listed signs are typical for AA amyloidosis?*
a) the absence of previous disease;
b) generalized character of lesions;
c) predominant damage of the brain, pancreas, arteries;
d) presence of previous disease;
e) predominant impairment of the spleen, kidneys, liver, adrenals, intestine.

4. *Which of the listed signs characterize the humoral immunodeficiency syndrome*:
a) thymic hypoplasia;
b) absence of immunoglobulins in the blood;
c) absence of germinal centers in lymph nodes;
d) the number of plasma cells is normal;
e) high frequency of severe infections and septicemia.

5. *Which of the listed malignant tumors are observed in AIDS more frequently:*
a) skin cancer;
b) Kaposi`s sarcoma;
c) nephroblastoma;
d) non-Hodgkin lymphoma;
e) multiple myeloma.

SET III.

The classification tests include 2–4 subjects and a series of answers. Indicate which answers are correct for each separate subject.

1. *Which of the listed signs characterize the immune reactions:*
I – of humoral type;
II – of cellular type;
a) the antigen is destroyed by immune cytolysis mechanism;
b) B lymphocyte participation;
c) T lymphocyte participation;
d) the antigen is destroyed by immune phagocytosis mechanism;

e) the plasmocyte is the effector cell;
f) T–killer lymphocytes and macrophages are the effector cells.

2. What are the areas of distribution of:
I – B lymphocytes;
II – T lymphocytes;
a) the cortical layer of the lymph nodes;
b) the paracortical layer of the lymph nodes;
c) the medullar layer of the lymph nodes;
d) the centrofollicular (periarterial) area of lienal lymph follicles;
e) the peripheral area of lienal lymph follicles.

3. Which of the listed diseases are parts of:
I – organ-specific autoimmune diseases;
II – systemic autoimmune diseases;
a) disseminated lupus erythematosus;
b) rheumatoid arthritis;
c) Hashimoto thyroiditis;
d) autoimmune orchitis;
e) scleroderma.

4. Which of the listed diseases are characterized by the following auto antibodies:
I – antinuclear;
II – against IgG;
III – antinucleolar;
IV – anti–basement membrane;
a) glomerulonephritis;
b) systemic lupus erythematosus;
c) systemic sclerosis;
d) rheumatoid arthritis.

5. In which of the listed diseases may develop:
I – AL amyloidosis;
II – AA amyloidosis;
a) syphilis;
b) plasmacytic dyscrasia;
c) Crohn disease;
d) Hodgkin lymphoma;
e) chronic osteomyelitis.

SET IV. SITUATIONAL PROBLEMS

Daily practice cases are presented with clinical and morphological data from clinical histories and/or from necropsy protocols. Each subject includes simple or multiple – answer questions, with 1, 2 or more correct answers.

1. After eating certain foods, a 30-year-old patient develops rash, redness and edema of the skin.

Questions:

A) What is the correct name of this pathological process:
a) hyperkeratosis;
b) dermatitis;
c) erysipelas;
d) hives;
e) ichthyosis.

B) Which of the listed hypersensitivity mechanism are involved in this case?
a) local anaphylactic reaction (type I);
b) systemic anaphylactic reaction (type I);
c) cytotoxic hypersensitivity (type II);
d) reaction with toxic immune complexes (type III);
e) T-cell–mediated hypersensitivity (type IV).

2. A man, who was bitten by a stray dog was prescribed a course of antirabic vaccination. A fever up to 38° appeared in 30 minutes after the IV injection, as well as redness and swelling in the vaccine site.

Questions:

A) Which hypersensitivity reaction, from those listed, is involved in this case:
a) atopic;
b) idiosyncratic;
c) Arthus phenomenon type;

d) serum disease type reaction;
e) contact dermatitis.

B) Which is, in the majority of cases, the organ that is impaired and that can cause death:

a) brain;
b) kidneys;
c) heart;
d) ovaries;
e) lungs.

3. *After a wasp's bite, a patient developed Quincke allergic edema, localized in the lax subcutaneous tissues of the face, buccal mucosa and upper respiratory tract.*

Questions:

A) Which complication is the most life threatening for a patient:

a) spastic abdomen pains;
b) larynx edema;
c) mucus hypersecretion;
d) eyelids edema;
e) bronchi spasm.

B) Which pathogenic mechanism is involved in edema occurrence:

a) T-lymphocyte action on the smooth muscular cells;
b) IgA from the surface of basophils and mastocytes;
c) IgA from the surface of lymphocytes and eosinophils;
d) IgE from the surface of basophils and mastocytes;
e) IgE from the surface of lymphocytes and eosinophils.

4. *A 1,5-year-old child died from acute pneumonia. The necropsy and the histopathological examination of the corpse assays revealed: incomplete development of thymus, its small dimensions, unclear structure; the paracortical layer lacks in lymph nodes; lienal and lymph nodes lymphatic follicles have an ordinary structure. The blood analyses from the medical chart show a lack of T-lymphocytes and the number of B lymphocytes is unchanged.*

Questions:

A) What is the correct definition for thymic modifications:

a) thymic aplasia;
b) thymic agenesis;
c) thymic dysplasia;
d) thymic hypoplasia;
e) thymic hyperplasia.

B) What immunodeficiency syndrome develops in this case:

a) agammaglobulinemia;
b) severe combined immunodeficiency syndrome;
c) IgA selective deficiency;
d) DiGeorge syndrome;
e) secondary immunodeficiency.

5. *A 45- year-old patient has been suffering from chronic pulmonary fibrocavitary tuberculosis for several years. Some weeks ago, signs of nephrotic syndrome with proteinuria and edema appeared.*

Questions:

A. What renal complication developed in this patient:

a) glomerulonephritis;
b) pyelonephritis;
c) renal calculosis;
d) reactive amyloidosis;
e) renal carcinoma.

B. Which of the listed staining should be applied in renal biopsy to establish diagnosis:

a) Sudan III;
b) carmine;
c) Congo red;
d) PAS reaction;
e) T or S thioflavin.

ADAPTIVE–COMPENSATORY PROCESSES

The elements of adaptation of cellular (tissular) structures to certain new conditions, modified by functional activity, prevail in the **adaptive processes**. It is a manifestation of the organism's interrelation with the external environment and can reflect different functional conditions, for example, functional overstrain, hypofunction or denaturation of the tissue (organ) function. The main adaptive processes are the following: **1) atrophy; 2) adaptive hypertrophy (hyperplasia); organization (encapsulation); 4) tissue morphological restructuration; 5) metaplasia; 6) dysplasia.**

Compensatory processes develop due to organ (tissue) alteration, under the action of harmful factors. It is oriented towards correction of functional disturbances, which appeared during diseases. This group includes: a) **regeneration; b) compensatory hypertrophy (hyperplasia).**

7.1. ADAPTIVE PROCESSES

7.1.1. ATROPHY

Atrophy is reduction in size of cells, tissues, organs, with a decrease of their functional activity. It can be physiologic and pathologic, general and local.

Physiologic atrophy is observed in different age groups, for example, atrophy of umbilical vessels in the newborn, of arterial canal (Botallo duct) in the first three months of extra uterine life, atrophy of sexual glands, skin, bones and other tissues (organs) in old people.

Pathologic atrophy can has a general or local character.

General pathologic atrophy or cachexia (Greek *kakos* – bad and *hexis* - condition) can be conditioned by different causal factors. The following cachexia variants are distinguished:

1) **alimentary cachexia** – caused by subnutrition or disturbed assimilation;
2) **cancerous cachexia** – is observed in malignant tumors, as a result of nutritional disorders, enzymatic system and digestive gland secretion disturbances, cancerous intoxication;
3) **endocrine cachexia** – appears as a consequence of endocrine glands function disturbance (pituitary, thyroid gland);
4) **cerebral cachexia** – caused by in-

flammatory or tumor processes in the hypothalamus area;

5) **cachexia in some chronic infectious diseases**, e.g. in tuberculosis, chronic dysentery, AIDS.

One observes the disappearance of the subcutaneous adipose tissue in general atrophy, as well as size and mass decrease of all organs and tissues, with decrease of their function. In organs, especially in the myocardium and liver, the lipofuscin pigment accumulates and stains them with brown color (*brown atrophy*) (Fig.7–1).

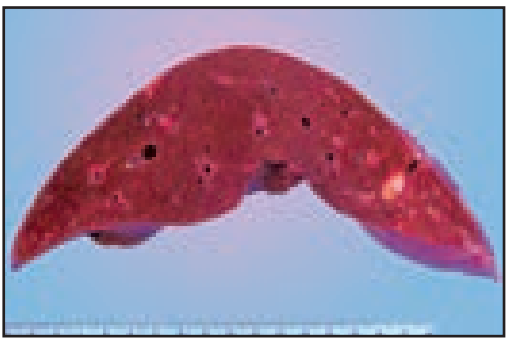


Fig. 7–1. Brown atrophy of the liver.

Local pathological atrophy may be caused by various etiologic factors. The following varieties of local atrophy are distinguished:

1) **dysfunctional atrophy** is caused by inactivity, decrease or suspension of functional activity of the organ, for example, muscle atrophy in bone fractures, gallbladder atrophy in the cystic duct obstruction by gallstones, atrophy of the teeth ridge after tooth removal;
2) **neurotic atrophy** – it appears after trophic innervation disturbance, for example, in traumas with motor nerve injury, nervous tumors, poliomyelitis; it is more demonstrative in the skeletal muscles (Fig.7–2);
3) **ischemic** (vascular) **atrophy** is caused by decreased arterial blood supply, for example, in atherosclerosis of cerebral arteries (brain atrophy, Fig. 7–3), renal arteries (kidney atrophy);

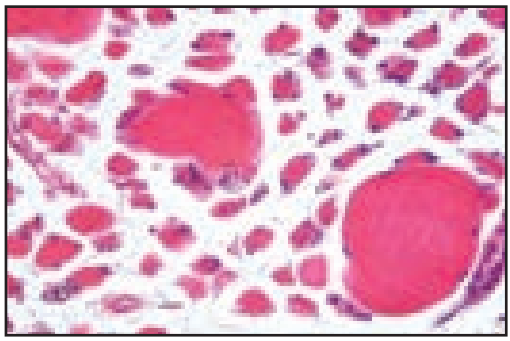


Fig. 7–2. Neurogenic atrophy of striated muscle (hematoxylin–eosin stain; ×70).

4) **compression atrophy** – as a consequence of mechanical compression of the functional organ parenchyma, leading to its ischemia, for example, in benign or malignant tumors, fluid accumulations (in *hydronephrosis* – dilatation of renal pelvis and calyces by aseptic urine accumulation, *hydrocephalus* – accumulation of cerebrospinal fluid in the cranial cavity (Fig.7–4));

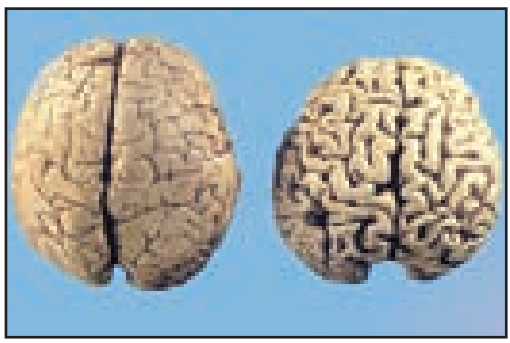


Fig. 7–3. Bilateral ischemic atrophy of the brain (on the left – normal brain).

5) **atrophy caused by physical and**

chemical factors, for example, inhibition of regenerative processes

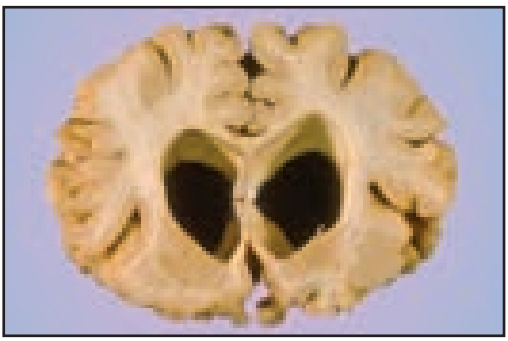


Fig. 7–4. Compression atrophy of the cerebral tissue in internal hydrocephalus.

and atrophy of hematopoietic tissues and sexual glands, due to the penetrating radiation, atrophy of endocrine glands after a long use of hormonal drugs.

Atrophy consequences depend on the degree of organ's reduction and the decrease of its function. Pathological atrophy is a reversible process. After removing the cause of the atrophy, it is possible to restore the structure and the function of the affected organ completely, for example, restore muscles after bone fracture healing.

7.1.2. ADAPTIVE HYPERTROPHY (HYPERPLASIA)

Hypertrophy is the increase in size and mass of cells, tissues, organs, and **hyperplasia** is the increase of the number of the structural elements of tissue and cells. Hypertrophy of an organ (tissue) can be produced by multiplication of cells, by increasing the number and size of intracellular elements or by combination of both these processes. There are two varieties of hypertrophy/hyperplasia of adaptive nature: 1) neurohormonal hypertrophy and 2) hypertrophic proliferations.

Neurohormonal (neurohumoral) **hypertrophy** is an adaptive process (not compensatory) that occurs as a result of neurohormonal disorders with alteration of hormone balance, which exercises a stimulating action on the growth of organs and tissues. Examples:

- ✧ hypertrophy of uterus and mammary glands during pregnancy and lactation, under the action of ovarian corpus luteum and placental hormones;
- ✧ acromegaly – hypertrophy and disproportionate growth of arms, legs, jaw, ears, nose; it is caused by hypersecretion of the somatotropic hormone in the eosinophilic adenoma of the pituitary gland; **gigantism** develops in children and adolescents;
- ✧ glandular endometrial hyperplasia, resulting from hypersecretion of estrogen hormones (Fig. 7–5);
- ✧ gynecomastia – hypertrophy of the

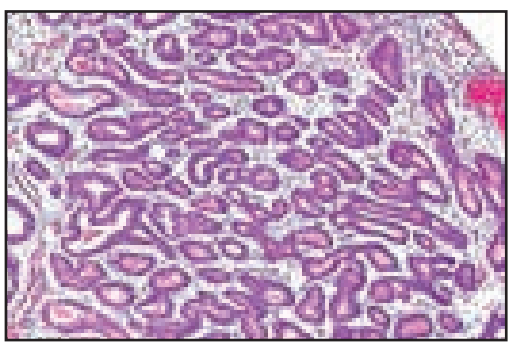


Fig. 7–5. Glandular hyperplasia of endometrium (hematoxylin–eosin stain; ×70).

mammary glands in males, caused by testicular hypofunction (testosterone hyposecretion);
- ✧ nodular hyperplasia of the prostate in elderly men, caused by androgen hormones hyposecretion and androgen/estrogen balance shift.

Hypertrophic proliferations lead to size increase of tissues and organs and have a diverse origin. Examples:
- ✧ development of hyperplastic polyps on the mucous membranes in chronic inflammation;
- ✧ development of elephantiasis in chronic lymphostasis;
- ✧ adipose and connective tissue proliferation in cases of partial or total organ atrophy (pseudohypertrophy or false hypertrophy), for example, in atrophy of kidneys, skeletal muscles;
- ✧ blood vessel intimae proliferation in blood pressure decrease.

7.1.3. ORGANIZATION AND ENCAPSULATION

The organization is the substitution with connective tissue of some necrosis foci, exudates (Fig.7–6), thrombi, hematomas, tissular defects, parasites, foreign bodies. The removal of necrotic masses, fibrin, exudates, products of tissue disintegration and their replacement by granulation tissue occur during the process of organization.

Encapsulation is the delimitation of necrotic focus, infarction, foreign body, parasite, etc. by a fibrous connective tissue membrane (Fig. 7–7).

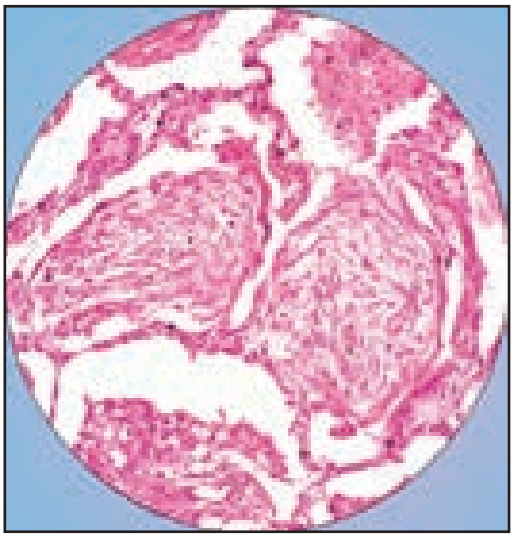


Fig. 7–6. Organization of pulmonary alveoli exudate in unresolved pneumonia (pneumonia in course of organization or carnification) (hematoxylin–eosin stain; ×70).

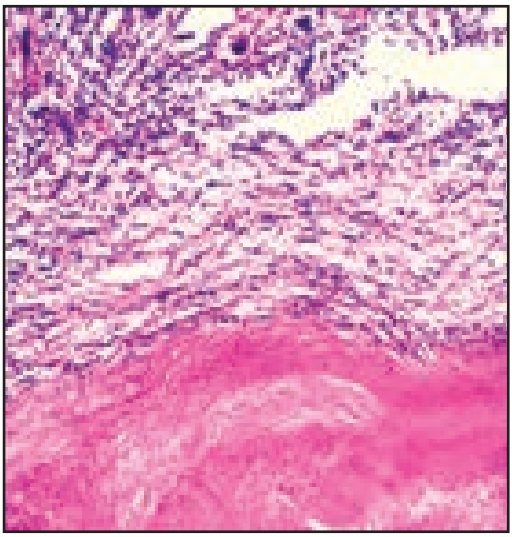


Fig. 7–7. Encapsulation of caseous necrotic focus in tuberculosis (hematoxylin–eosin stain; ×70).

7.1.4. MORPHOLOGICAL RESTRUCTURATION OF TISSUES

It is an adaptation reaction of tissues to new functioning conditions, being also called ***histological accommodation***. Examples:

- ✧ dilatation and hypertrophy of collateral blood vessel walls, in case of blood circulation disorder occurring in the magistral vessels (hypertrophy of smooth muscle cells and neoformation of elastic fibers occur, the small vessel structure becomes identical to the structure of large vessels);
- ✧ transformation of flat alveolar epithelium in cubic epithelium in atelectases;
- ✧ transformation of the nephrothelium of the renal glomerular capsule in cubic epithelium, in case of glomerulus sclerosis and hyalinosis;
- ✧ thickening of cranial bones in case of brain atrophy (also called ex *vacuo hypertrophy*).

7.1.5. METAPLASIA

Metaplasia is transformation of a differentiated adult tissue into another type of adult tissue, differentiated as well. It is a process of tissue adaptation to modified functioning conditions. The transformation of a tissue into another occurs only within one and the same germ layer, by proliferation of young cells. It is observed more frequently in the coating epithelium and connective tissues. Metaplasia is a reversible process and it usually occurs as a response to chronic irritation and inflammation, avitaminosis A (vitamin A deficiency induces epithelial metaplasia and its excess stops the keratinization). The biological role of metaplasia is to replace more sensitive and vulnerable cells with others, more resistant and able to survive under certain unfavorable environmental conditions. The squamous (epidermoid) metaplasia of the glandular epithelium is observed most frequently, when the respective epithelium is substituted with stratified squamous epithelium with or without cornification.

Examples: squamous metaplasia of trachea or bronchi epithelium in smokers (Fig. 7–8), of uterus cervical canal epithelium in chronic endocervicitis, of the epithelium of excretory ducts, salivary glands, pancreas, biliary tract, which is observed more frequently in calculosis. In all these cases, the denser and more compact stratified squamous epithelium is more resistant to the action of harmful factors, which can alter the specialized and more fragile columnar epithelium. It should be noted that the stratified squamous epithelium is not functional in these cases. One also observes intestinal metaplasia of gastric mucosa epithelium, gastric or intestinal type metaplasia of stratified squamous epithelium lining the esophagus mucosa (Barrett esophagus), squamous metapla-

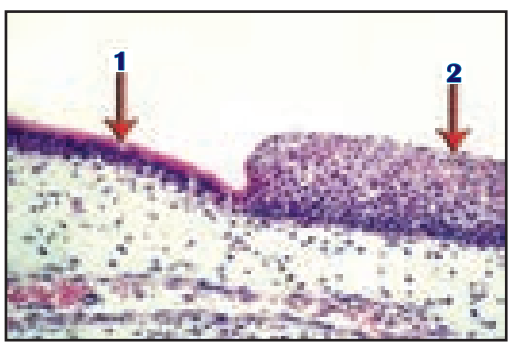


Fig. 7–8. Squamous metaplasia (2) of glandular respiratory epithelium (1) (hematoxylin–eosin coloration; ×70).

sia of the transitocellular epithelium of urinary tract. The process of metaplasia does not imply a direct transformation of one epithelium into another: the transformation occurs by multiplication of cambial cells, which are not differentiated in the glandular epithelium, but in the stratified squamous epithelium.

Metaplasia is not considered directly carcinogenic. It can induce malignant transformation of metaplastic epithelium, only in cases where the causative factor persists for a long time. For example, the squamous lung cancer begins in the squamous metaplasia foci of the bronchial epithelium.

Connective tissue metaplasia with appearance of cartilaginous, bony or adipose tissue is observed in sclerosis foci, scars, adhesions, in the stroma of tumors, in the capsule of healed foci of caseous necrosis in tuberculosis etc. Metaplastic tissue formation starts with proliferation of young connective tissue cells, which are subdivided in chondroblasts, osteoblasts, lipoblasts.

7.1.6. DYSPLASIA

Dysplasia is a pathological process manifested by marked disorders of epithelium proliferation and differentiation, with development of cellular atypism and disturbance of its hystoarchitectonics. *Atypical hyperplasia* is a synonym to dysplasia.

Main characteristics:

- epithelial stratification is preserved, but the orientation of cells within the layers is changed; epitheliocyte polarity and sometimes of features specific for the given tissue or organ are lost;
- changes of cellular nuclei, their size and hyperchromatism increase;
- variability of cell size and shape;
- increase of mitotic activity, number of mitoses and their appearance in all epithelial layers;
- intact, unaltered basement membrane of epithelium.

The listed characteristics demonstrate clearly that dysplasia is more a tissular concept than a cellular one.

Dysplasia occurs in inflammatory and regenerative processes, as a manifestation of abnormal cell proliferation and differentiation. It is also observed in epitheliums in metaplasia.

There are three stages of dysplasia: I – mild, II – moderate (Fig. 7 – 9) and III – severe. Sometimes, it is difficult to establish the boundary between them. If nuclear immaturity is observed in all epithelial layers, including the superficial ones, the lesion is classified as severe. If nuclear immaturity is located only in basal layers of epithelium, the injury is considered mild. It is often very difficult or even impossible to make a clear differentiation between III grade dysplasia and carcinoma "in situ". The early I and II stages of dysplasia are often reversible; the III stage is considered a precancerous condition.

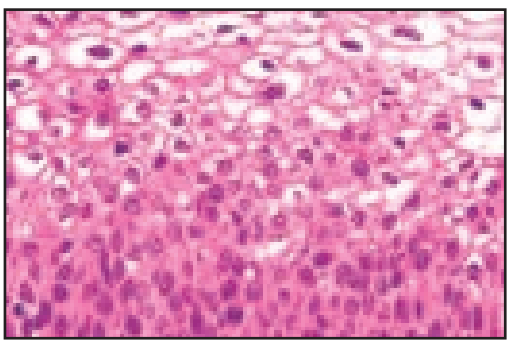


Fig. 7–9. Moderate dysplasia of ectocervical epithelium: thickening of basal layer, hyperchromatosis of nuclei, mitotic figures (hematoxylin–eosin stain; ×70).

7.2. COMPENSATORY PROCESSES

7.2.1. REGENERATION

Regeneration is the process of recovery (renewal) of the structural elements of tissue (organ) instead of those destroyed. Both restoration of structure and function of altered tissues (cells) occur during regeneration.

Regeneration can occur in two morphological forms:

- ✧ **cellular form** – multiplication of cells, their mitotic (indirect) or amitotic (direct) division;
- ✧ **intracellular form** – manifested by multiplication and size increase of cytoplasmic organelles (nuclei, mitochondria, ribosomes, etc). This form of regeneration is shown schematically in the Fig. 7–10: in case of partial necrosis of the cell (Fig.7–10 b), its function is compensated by hyperplasia of cytoplasmic organelles from the preserved portions of the same cell.

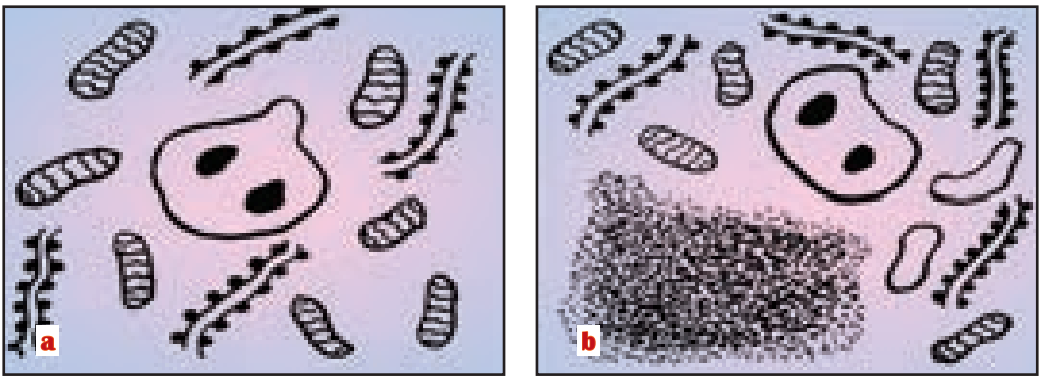


Fig. 7–10. Schematic presentation of the intracellular regeneration: a – normal cell; b – partial cell necrosis and hyperplasia of the remaining cytoplasmic organelles with reestablishment of their number.

Two distinct stages are distinguished in the regenerative process evolution: 1) *proliferation* and 2) *differentiation*. The first stage includes the multiplication of young, immature, undifferentiated cells – the so-called cambial, stem or precursor cells and of intracellular organelles. The immature cells become mature in the second stage and acquire some specific functional, structural features. The immature intracellular organelles undergo the same process of maturation and differentiation.

7.2.1.1. VARIETIES OF REGENERATION

There are three varieties of regeneration: **a) physiological; b) reparative; c) pathological.**

Physiological regeneration. It ensures the normal function of all organs and tissues, because each function is based on decomposition and synthesis processes at the molecular level, hence the vital need of constant intracellular renewal. Physiological regeneration is carried out continuously throughout life and is characterized by continuous renewal of cells, fibrillar elements and ground substance of connective tissue. It

occurs at the subcellular level; the biochemical (molecular) permanent regeneration, which is the structural equivalent of body functions, occurs.

Reparative regeneration is regeneration from different pathological processes, when alteration of cells and tissues takes place. It manifests itself through the same morphological mechanisms as the physiological regeneration, representing, in fact, *physiological regeneration in the sick body*; it starts concomitantly with the action of the harmful factor. Reparative regeneration may be complete ***(restitution)*** and incomplete ***(substitution)***.

Complete regeneration is characterized by the replacement of the defect with a tissue identical to the destroyed (preexisting) one. It is observed in tissues where the cellular form of regeneration prevails, for example, in connective tissue, bones, skin, digestive, respiratory and urogenital tract mucosa, vessel endothelium, serous membrane mesothelium, hematopoietic tissue.

Incomplete reparative regeneration is characterized by replacement of defect with cicatricial connective tissue, and functional parenchyma restoration occurs through hypertrophy of the remaining part of the organ, known as ***regenerative hypertrophy***. The latter can be done in two ways: 1) cell hyperplasia (observed in liver, kidney, pancreas, lungs, etc.); 2) hyperplasia and hypertrophy of intracellular organelles, i.e. cell hypertrophy (observed in myocardium and brain).

The regeneration of altered tissues takes place in accordance with the same mechanisms that regulate tissue growth and differentiation during normal conditions of development. These mechanisms provide the ability to restore tissue defects, both full restoration of previous tissue and incomplete restoration through scarring of the affected area. Growth factors have an important role: to regulate the regeneration and repair processes. They originate from epithelial altered cells, platelets and macrophages. The main growth factors are:

- ✧ epidermal growth factor, EGF (*epidermal growth factor*) that stimulates the regeneration of specialized epithelial cells;
- ✧ factor that activates the fibroblasts – TGFβ (*transforming growth factor beta*);
- ✧ angiogenetic factor, which stimulates the formation of new capillaries – VEGF (*vascular endothelial growth factor*).

The nature and intensity of the regeneration process depend on many local and general factors, for example:

- ✧ age (regeneration intensity in the elderly is much lower compared to the childhood period);
- ✧ nutritional status (regeneration is much slower in obese and cachectic people);
- ✧ metabolic condition, such as protein deficiency and avitaminoses, which influence negatively the regeneration processes;
- ✧ blood and lymph circulation condition (ischemia, venous and lymphatic stasis endanger the regeneration process);
- ✧ hematopoiesis condition (the intensity of regeneration decreases considerably in anemia, leukopenia and lymphopenia);
- ✧ innervation condition (regeneration is disturbed in denervated areas or in patients with paralysis);

- ✧ particularities of the pathological process, firstly, type and size of tissular injury, for instance, burn wounds are healing more difficult;
- ✧ regenerative potential of tissue/organ.

The Pathological regeneration is the abnormal, atypical regeneration, characterized by quantitative or qualitative changes of the regenerative process. It is caused by innervation and circulatory disorders, protein and vitamin deficiency, chronic inflammation.

It may manifest itself through:

- ✧ **hyperregeneration** – exaggerated neoformation of regenerative tissue, for example, excess of granulations (exuberant granulations) or cicatricial connective tissue (keloid scars) after healing of wounds, burns (Fig. 7–30), exostoses (bony growths), bone thickening and deformation in fractures (Fig. 7–16), amputation neuroma (Fig. 7–22);
- ✧ **hyporegeneration** – insufficient formation of regenerative tissue, e.g. deficient bone callus in fractures with occurrence of pathological mobility of bone fragments or pseudoarthrosis, in trophic skin ulcers (Fig. 7–29);
- ✧ **metaplasic regeneration** – appearance in the regenerative process of a different tissue compared to the previous one, for example, stratified squamous epithelium foci in the bronchi, trachea mucosae (Fig. 7-8), cervical canal, endometrium, etc., which, under normal physiological conditions, are covered with glandular epithelium (squamous metaplasia).

7.2.1.2. REGENERATION OF VARIOUS TISSUES AND ORGANS

According to the regeneration potential, the cells can be divided into three categories:

Labile cells, which multiply throughout life, with a continuous turnover, both in physiological and pathological conditions. Such features are observed in skin epithelial cells (epidermis), mucous membranes of gastrointestinal, respiratory and urogenital tracts, hematopoietic system cells, endothelium, mesothelium, bone, lax connective tissue cells. The regenerative potential is very high and injury cure is complete in most cases.

Stable cells, with a low intensity of physiological regeneration, but a high potential of reparative regeneration. In pathological conditions, when tissue lesion occurs, the remaining cells regenerate intensely, both by cellular and intracellular ways, providing structural and functional restoration of the altered organ. This group includes liver, kidneys, lungs, exocrine parenchyma of pancreas, skeletal and smooth muscles, endocrine system, including pancreatic insular apparatus, glial cells. In these organs, the epithelium regeneration can be made both by cell hyperplasia and association of cell hyperplasia with their hypertrophy, which is produced by hyperplasia of subcellular (cytoplasmatic) elements.

Permanent cells that do not possess proliferation capacity in the postnatal period and regenerate only intracellularly. The regenerative and hyperplastic intracellular processes provide the material substrate for the compensation of the altered functions during patho-

logical processes. This phenomenon is observed in cardiomyocytes and nerve cells, where the regenerative hypertrophy is conducted exclusively by hypertrophy of remaining cells, which, in its turn, is produced by hyperplasia and/or hypertrophy of intracellular structures.

The structural–functional peculiarities of the altered tissue/organ and the expansion of the lesion have an important role in regenerative processes.

✧ ***Connective tissue regeneration***. It occurs in two stages: 1) granulation tissue and 2) mature connective tissue.

Granulation tissue is the initial stage of the connective tissue regeneration, being, actually, a young connective tissue, rich in cells and blood vessels and poor in collagen fibers. It is a typical example of complete, cellular regeneration. Granulation tissue formation starts with proliferation (division) of young mesenchymal cells and neoformation of blood microvessels. Macroscopically, it is a soft, juicy tissue, of a reddish color, with granular surface (hence the name), the granules being composed from new formed vessels. It bleeds easily because of the large number of capillaries (Fig. 7–11). Microscopically, numerous blood vessels are observed, including capillaries, among which there are many young cells (polymorphonuclear leukocytes, macrophages, lymphocytes, plasma cells, fibroblasts). There are small caliber vessels, with thin walls (Fig. 7–12). In dynamics, with the attenuation of the inflammatory process, the number of cells and

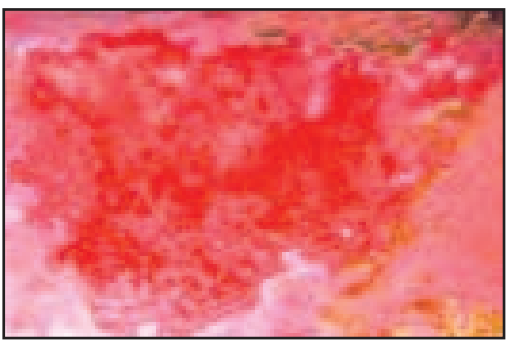


Fig. 7–11. Granulation tissue – macroscopic aspect.

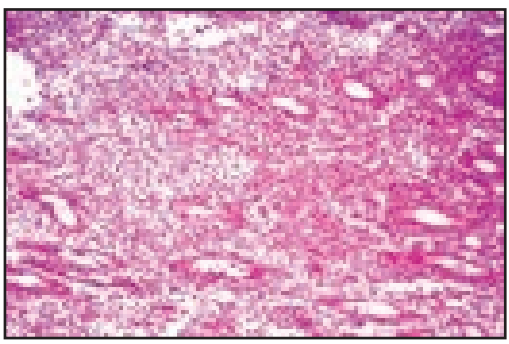


Fig. 7–12. Granulation tissue (hematoxylin–eosin stain; ×70).

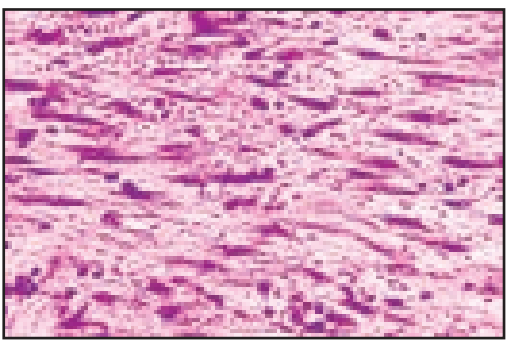


Fig. 7–13. Granulation tissue during maturation (hematoxylin–eosin stain; ×70).

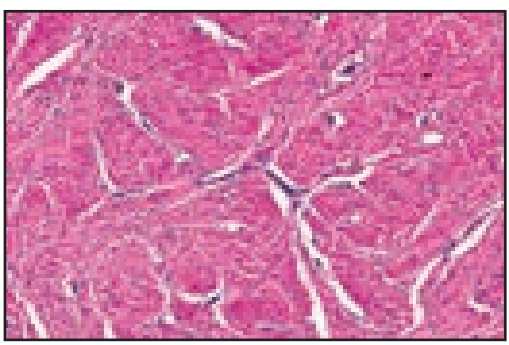


Fig. 7–14. Fibrous cicatricial connective tissue (hematoxylin–eosin stain; ×70).

blood vessels is reduced gradually; mesenchymal cells (stem cells of connective tissue) are transformed into epithelioid cells and latter - in fibroblasts. Fibroblasts prevail in the granulation tissue under maturation and the number of vessels reduces progressively (Fig.7–13). The increase of fibroblast activity and the intense production of collagen fibers occur simultaneously, vessels turn into arteries and veins. The process of granulation tissue maturation ends with a **fibrous (cicatricial) connective tissue formation**, where a small number of fibrocytes and vessels is met (Fig. 7–14). The neoformation of granulation tissue occurs not only in connective tissue regeneration, but also in cases of incomplete regeneration of other organs (when the defect is replaced by connective tissue), and in organization processes, encapsulation, wound healing and productive inflammation.

✧ ***Regeneration of blood and lymphatic vessels*** differs according to their caliber.

Microvessel regeneration can occur in two ways:

a) **budding** of existing capillaries, when lateral protrusions appear in their wall, due to the intense proliferation of endothelial cells with formation of cellular cords, where lumens appear later, continuing the original capillary;

b) **autogenous** neoformation of capillaries, when clusters of undifferentiated cells that transform into endothelial cells appear in the connective tissue; subsequently, fissures appear in these clusters and merge with preexisting capillaries.

Complete restoration just of the internal tunic – of endothelium – occurs in the regeneration of large blood and lymphatic vessels, and the middle and external tunic defects are replaced by fibrous connective tissue, which can result in deformity and narrowing of the vascular lumen.

✧ ***Bone tissue regeneration in bone fractures.*** The evolution of fracture healing process depends largely on the degree of destruction of bone tissue, nature of fracture (with or without splinters), movement of the broken bone ends under the action of adjacent muscles, correctness of bone fragment reposition, age and general condition of the patient, local conditions (state of blood circulation, inflammation, presence of infection etc.).

Regeneration undergoes the following stages in uncomplicated (closed, uninfected, without displacement of fragments) fractures:

I) formation of a **hematoma** between fractured bone ends;

II) hematoma organization and **fibrous callus** formation;

III) fibrous callus ossification by the temporary **bony callus formation** through proliferation of osteoblasts in the periosteum and endosteum; poorly calcified bone trabeculas appear in the new formed tissue; bone regeneration is impossible without the presence of periosteum;

IV) formation of **definitive bone callus** through maturation of temporary bone callus; it turns into a mature, dense, less vascularized and less bulky bone, which differs from normal bone tissue only by the cha-

otic disposition of bone trabeculas (Fig. 7–15);

V) functional reconstruction, **remodeling** of neoformed tissue with bone trabecula restructuring, according to the functional requirements of the respective bone. As a result, the fracture area returns to normal and the bone fracture site can be observed neither clinically nor radiologically, over a period of time.

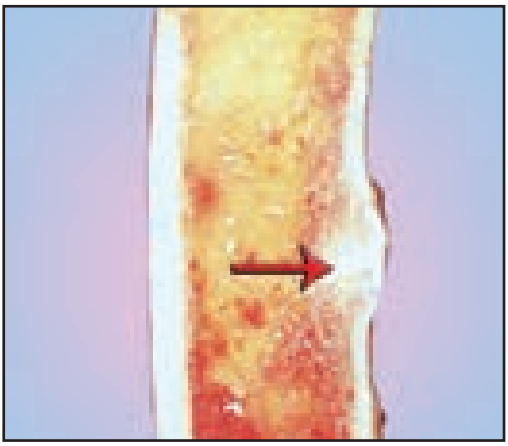


Fig. 7–15. Bone callus on the fracture site.

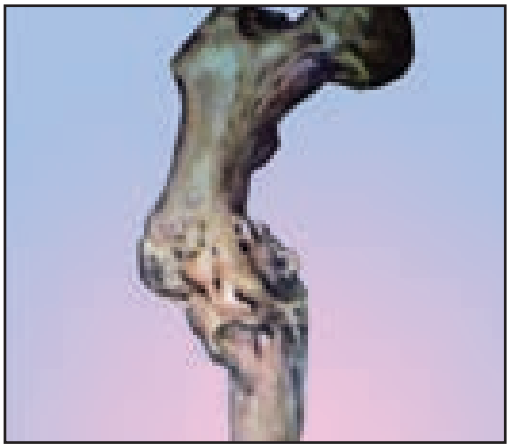


Fig. 7–16. Vicious bone callus in femoral fracture.

In case of unfavorable local conditions, for example, in rib fractures, when immobilization is practically impossible, a cartilaginous tissue appears initially between the broken bone fragments, a *preliminary osteocartilaginous callus*, which subsequently turns into mature bone tissue. This way of fracture healing is frequently met and lasts longer.

The correcteness of reposition and immobilization of bone ends, infection penetration, blood supply condition and nutrition in general (proteins, calcium, vitamins D and C), age have a key role in the healing process of bone fractures.

The disorders of bone fracture healing process manifest themselves by appearance of pseudoarthroses, bone excrescences, exostoses, bone deformity in the fracture site (Fig. 7–16).

Regeneration of muscle tissue. It occurs differently, depending on the type of tissue.

The small defects in smooth muscles are restored completely by multiplication of adjacent leiomyocytes or by metaplasia of connective tissue cellular elements. The large defects of the smooth muscle, e.g. in the gastric or intestinal walls, are replaced by fibrous scars and persistent muscle fibers are subjected to regenerative hypertrophy.

Complete regeneration occurs in skeletal striated muscles only in cases, when myocyte sarcolemma is preserved. Multiplication of cambial or satellite cells, located in sarcolemma thickness, between the basement membrane and plasmalemma, occurs inside the muscle tube. In symplast destruction, after removal of muscle debris by macrophages, intense activation and division of satellite cells (myoblasts) take place, which fill the delimited sarcolemma sheath, forming chains. Later on, their myogenic differentiation, contractile protein synthesis, myofiber assembly, sarcomeres

formation and muscle fiber restoration occur. In cases when sarcolemma is injured, the defect is replaced by connective tissue scar (muscle callus); some protrusions (expansions) with many nuclei appear at the broken ends of interrupted muscle fibers, called muscle buds and the muscle fiber continuity is not restored. Myofibrils disappear in these buds, cytoplasm becomes basophilic, they can detach from the original fiber and transform into giant multinucleated cells of myogenic origin (Fig.7–17).

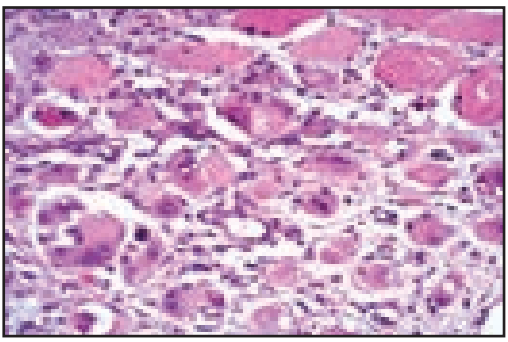


Fig. 7–17. Regeneration of striated muscle (hematoxylin–eosin stain; ×70).

✧ ***Epithelial regeneration***. The epithelial regenerative potential is very high, especially of skin epithelia. Usually, large defects of the skin regenerate completely. Initially, an intense multiplication of the germinal layer cells occurs at the edges of the defect, covering it in one layer, then, the neoformed epithelium becomes stratified, gains polarity and other features of normal epithelium. Restoring the skin epithelium becomes possible only after filling the defect with granulation tissue. Also, the mucosal epithelium regenerates actively through proliferation of cells, which cover the crypts and excretion ducts of glands.

Regeneration of specialized epithelium of parenchymatous organs (liver, kidneys, pancreas, lung alveoli and endocrine glands) is produced by injured tissue cicatrization and regenerative hypertrophy of the remaining parenchyma. It is very important, if the support tissue (stroma) is preserved. Epithelial cells proliferate and move along the reticulin network during regeneration. Concomitant damage to parenchyma and fibrous connective tissue stroma leads to organization and scarring of altered areas.

The liver has a remarkable regenerative capacity. The organ's weight is restored, even after a resection of 2/3, already in two weeks. Complete regeneration (restitution) of the liver occurs in cases of small necroses and after resection. The remaining portions of the organ undergo hypertrophy by cellular hypertrophy and hyperplasia with subsequent remodeling in the liver lobules with normal histological structure. The massive necroses and injuries caused by long-term action of harmful factors lead to incomplete regeneration (substitution) of the liver. Hyperplasia and hypertrophy of hepatocytes are observed in the persistent hepatic parenchyma. Regenerative nodules, penetrated by fibroconnective septa, appear and are called pseudo– lobules, because they lack radial orientation of liver trabeculas and the vessels are placed incorrectly (central veins are missing or are located eccentrically, triads are not always detected).

The regenerative process is manifested by appearance of bi– and polynucleic hepatocytes, increased number of mitoses and hyperchromic nuclei. Simultaneously, proliferation of biliary

epithelium takes place, with neoformation of genuine biliary ducts (with lumen) or pseudo-ducts (without lumen) (Fig. 7–18 a, b).

✧ ***Myocardium regeneration.*** Neoformation of muscular cells does not take place in myocardium and the regeneration is incomplete. The lesion

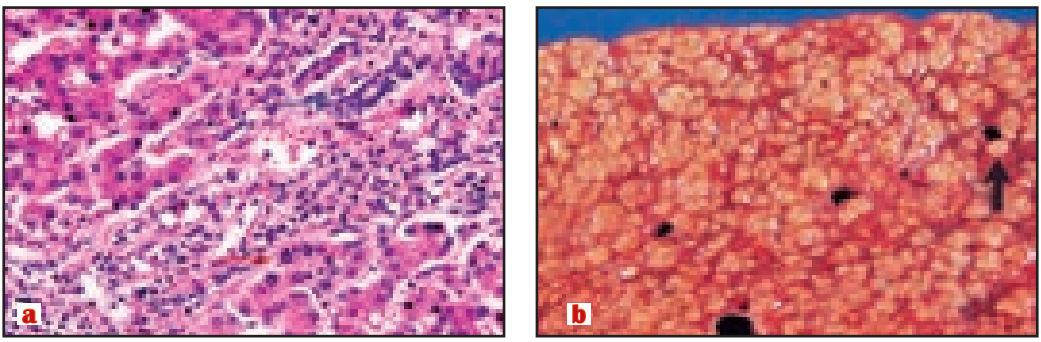


Fig. 7–18 a, b. Regeneration of liver in cirrhosis: a – microscopic aspect (hematoxylin–eosin stain; ×70); b – macroscopic aspect.

focus (infarct area) is replaced by cicatricial fibroconnective tissue (postinfarction macrofocal cardiosclerosis, Fig. 7–19 a, b), but structural reestablishment is realized through the hypertrophy of the remaining myocardial fibers, primarily those in the immediate vicinity with the postinfarction scar

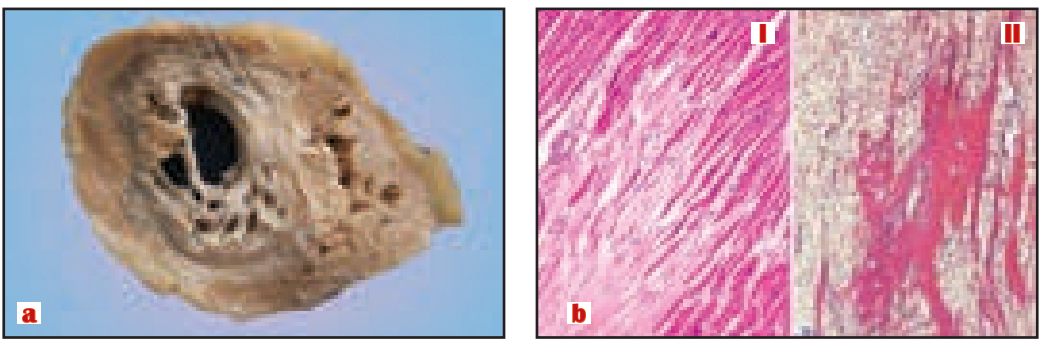


Fig. 7–19 a, b. Postinfarction macrofocal cardiosclerosis: a – macroscopic aspect (circular postinfarction scar in the left ventricle wall); b – microscopic aspect (I – hematoxylin–eosin stain and II – picrofuchsin van Gieson; ×70).

(regenerative hypertrophy). The latter is made through hypertrophy and/or hyperplasia of cytoplasmic ultrastructures (Fig. 7–20). The contractile activity of the heart after infarction is provided through hypertrophy of the remaining portions of the heart muscle. The Fig. 7–21 shows schematically the mechanism of the regenerative myocardial hypertrophy (intracellular regeneration). The ovals with septa indicate conventionally the functional ultrastructures (for example, mitochondria), and those colorless – the altered ultra structures (Fig. 7–21 I a). Structure reestablishment of the altered elements or their neoformation is observed during the intracellular re-

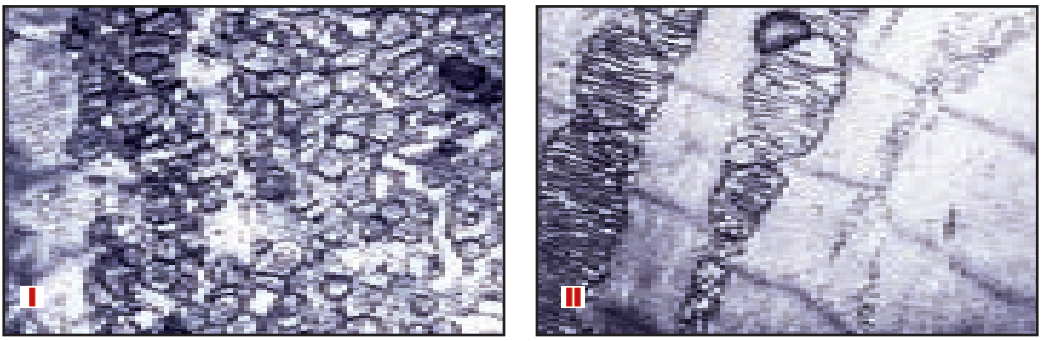


Fig. 7–20. Regenerative hypertrophy of myocardium: I – hyperplasia of mitochondria, II – hypertrophy of mitochondria (electron microscopy, ×16000)

parative regeneration (Fig. 7–21 I b). In case of compensatory intracellular hyperplasia, when a cell is necrotized (Fig. 7–21 II a), the number of cytoplasm ultrastructural elements is increased in the persistent cell (II b). The function is restored because the number of functional elements remains unchanged; they are not located in two cells, but only in one. This ensures the appropriate number of functional structures, no matter how many cells are arranged (D. S. Sarkisov, 1990).

✧ ***Regeneration of nervous system.*** Brain and spinal cord neurons do not divide, so the restoration of damaged cells

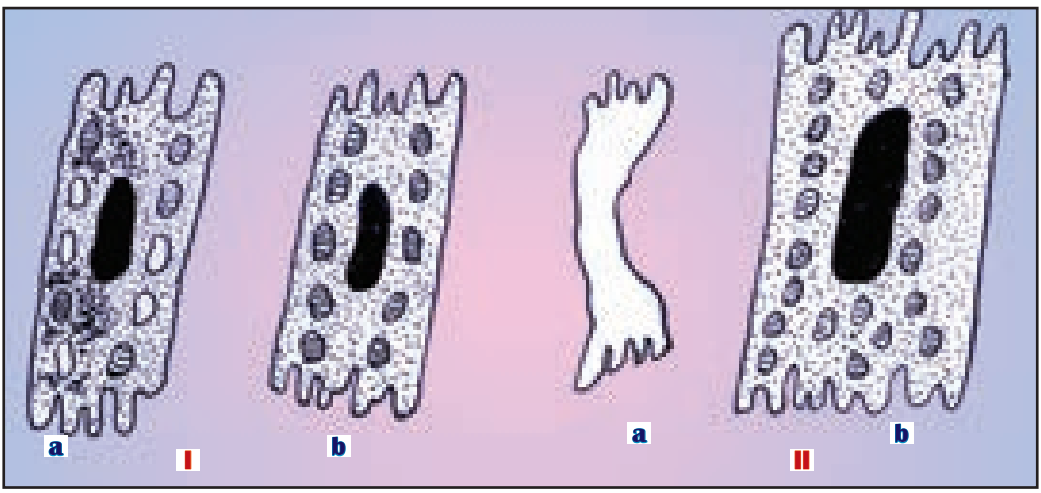


Fig. 7–21. Schematic representation of the intracellular regeneration of the myocardium: I a, b – intracellular regeneration, II a, b – intracellular regeneration with compensatory hyperplasia of cytoplasmic organelles and regenerative hypertrophy of the remaining cardiomyocyte.

is impossible. The normalization of the altered functions of the nervous system after an injury is produced only through hypertrophy of persistent brain cells; hypertrophy and hyperplasia of cytoplasm elements occur.

The neuroglia regenerates in a cellular or a mixed cellular and intracellular way. Small necrotic foci are replaced with glial tissue (fibro–glial scar).

If a peripheral nerve is dissected, regeneration takes place due to the prox-

imal segment, which remains in contact with the cell, but the distal segment dies. Phagocytosis of axon and myelin occurs in the peripheral blunt, as well as proliferation of Schwann cells, which are placed along the nerve, forming a tube, where the regenerative axons of the central segment penetrate. Nerve fibers, from which one or more enter the neural tube, appear at the peripheral end of the viable axon. Later, one of these fibers is myelinated and turns into a new functional axon. When the regenerative process is disturbed due to considerable movement of sectioned nerve ends, tissue interposition between the section heads or proximal segment inflammation, intense proliferation of connective tissue occurs and a scar appears where the nerve fibers are arranged chaotically. These proliferations composed of nerve fibers and fibrous tissue are called "amputation neuromas" (more correctly pseudoneuromas) (Fig. 7–22). They are met at the sectioned nerve ends in limb blunt after their amputation.

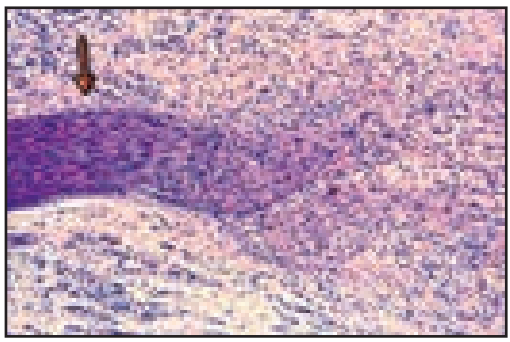


Fig. 7–22. Amputation neuroma (hematoxylin–eosin stain; ×70).

7.2.2. HYPERTROPHY AND HYPERPLASIA

Hypertrophy may occur by increase of the number of cells (cell hyperplasia) or by increase of their volume (intracellular hyperplasia), or by combination of both processes.

There exists **true** hypertrophy, due to increased volume of specialized structures of the organ, and **false** hypertrophy (pseudohypertrophy), when the increase in volume and mass of the organ is caused by excessive proliferation of connective and fat tissue.

According to the appearance mechanism, there are two varieties of true hypertrophy:

1) **work** (compensatory) hypertrophy;
2) **vicarious** hypertrophy (from Lat. *vicarius* – substitute).

Work (compensatory) hypertrophy occurs as a consequence of excessive functional activity of the organ. Functional overuse of an organ may occur both in physiological conditions (muscle and heart hypertrophy in athletes, workers performing physical work) and in diseases.

Examples:

- left ventricle hypertrophy in hypertension, valvular heart disease, primarily in aortic stenosis. Heart mass can reach 600–1000g (normal weight is 260–280 g), the left ventricle wall thickens considerably, its thickness can reach 2,5–3,0 cm (nor-

mal thickness is 1,0–1,2 cm); of the trabeculae and papillary muscles of the left ventricle are enlarged (Fig.7–23 a, b).

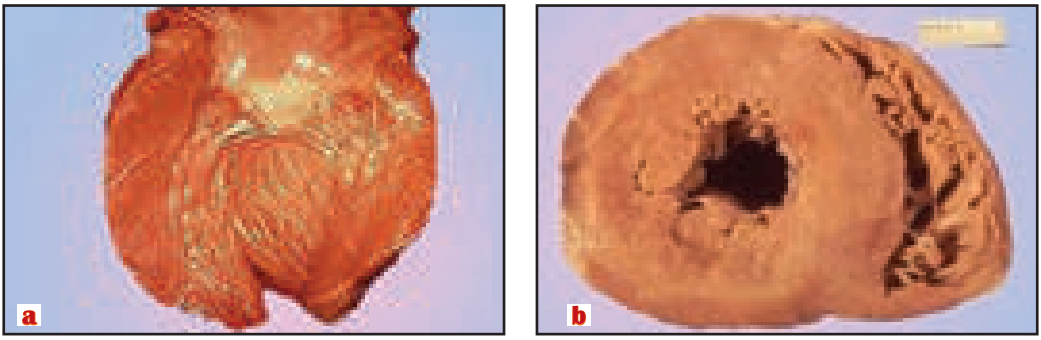


Fig. 7–23 a, b. Hypertrophy of the left ventricle: a – longitudinal section, b – transverse section.

➢ Right ventricle hypertrophy is observed in small circulation hypertension in different chronic lung diseases: emphysema, pneumosclerosis, chronic tuberculosis, bronchiectasis, interstitial pulmonary fibrosis etc. (hence the name of cor pulmonale or pulmonary cardiomyopathy), as well as in cardiac valvular lesions, for example, in stenosis or valvular insufficiency of the pulmonary artery (Fig. 7–24).

Concentric hypertrophy of the heart is observed in the compensation period, when its cavities are narrowed and the heart muscle tonus is increased. Microscopically, cardiomyocytes are enlarged; the nucleus is also increased, irregularly shaped, intensely colored, basophilic (Fig. 7–25). Electron optically, sarcoplasm mass increase is detected, as well as cardiomyocyte nuclei size increase, hyperplasia and hypertrophy of cytoplasmic organelles. Simultaneously, prolifer-

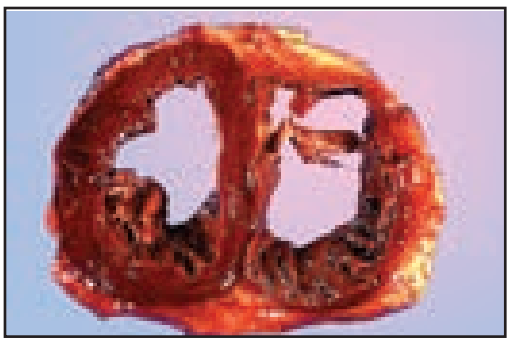


Fig. 7–24. Hypertrophy of right ventricle.

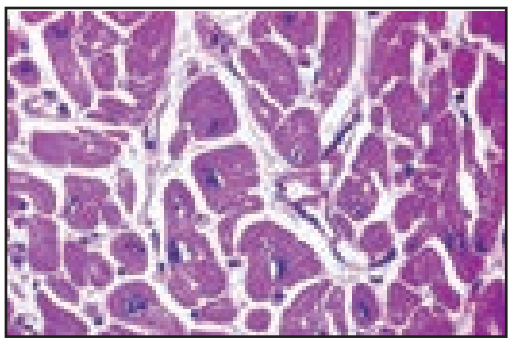


Fig. 7–25. Hypertrophy of myocardium (hematoxylin–eosin stain; ×70).

ation of fibrillar structures of the stroma, intramyocardial vascular branches and intramural nervous system elements of the heart occur. **Eccentric** hypertrophy takes place in the decompensation period, when the heart cavities are dilated, heart consistency is flaccid, with opaque appearance as a result of dystrophic le-

sions; myocardium steatosis is observed ("tiger heart"). Hypertrophy reaches a level, when the hypertrophied heart muscle cannot compensate the increased functional demands anymore and heart failure develops. Heart dilatation at the compensatory stage is called active or **tonogenic** and in decompensation – passive or **myogenic**.

Other examples: urinary bladder wall hypertrophy in nodular hyperplasia of prostate (Fig. 7–26), hypertrophy of intestinal wall in stenosing tumors, stomach hypertrophy in pyloric stenosis etc.

Vicarious hypertrophy is the hypertrophy of one of the paired organs (lungs, kidneys, adrenals) after failure of the contralateral organ and increased effort of the remaining organ.

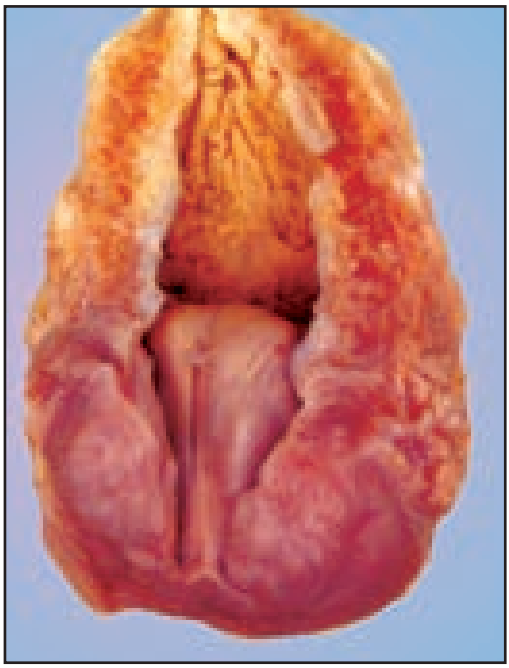


Fig. 7–26. Hypertrophy of urinary bladder wall in nodular hyperplasia of prostate.

7.3. WOUND HEALING

Wound healing evolves differently depending on the form, extent, depth of the wound, its character, absence or presence of infection, foreign bodies, overall condition of the body (age, nutritional status, immunity, circulatory, endocrine and nervous systems etc.), local structural features of the tissue (vascularization, innervation, regeneration capacity).

The following variants of wound healing are distinguished: 1) immediate closure of the defect, 2) healing under the crust, 3) wound healing by primary intention (primary union or *per primam intentionem*), 4) wound healing by second intention (secondary union or *per secundam intentionem*).

Immediate closure of epithelial cover defect. It is observed in superficial epithelial defects. The epithelium extends over the defect and closes it.

Healing under the crust. It is observed in small defects of cornea and mucous membranes. A crust formed of coagulated blood and lymph appears on the surface of the defects; this crust protects the wound from the influence of external environment factors and detaches independently after epidermis restoration (in 3–5 days after trauma).

Healing per primam intentionem. It is met in non-infected wounds, with straight edges, the distance between them does not exceed 1cm, usually in surgical incisions. Initially, a blood clot forms between the edges of the wound, which contains fibrin and blood cells. The fibrin clot binds the wound edges,

fills the space between them and thereby protects the wound from dehydration and possible infection. An inflammatory reaction with sero–fibrinous exudate and neutrophil leukocytes appears in the wound edges, in the first 24 hours. Lysis of fibrin clot and tissue debris takes place, under the action of leukocytic proteolytic enzymes. In 2–3 days, leukocytes are replaced by macrophages, which continue the phagocytosis of cellular debris and fibrin. Simultaneously, the basal cells of the neighborhood epidermis proliferate, forming a continuous, epithelial monolayer gradually. Proliferating keratinocytes elaborate basement membrane components. By the 5th day, the space between the edges of the wound is filled with granulation tissue. There is an intense neoformation process of capillaries and collagen fibers, which, initially, are arranged vertically and then horizontally, forming bridges that connect the edges of the wound. Epithelium proliferation continues: it gradually thickens through stratification and differentiation, reaching a normal thickness of epidermis (Fig. 7–27). In 10–15 days, the granulation tissue matures completely, the wound defect is epithelialized definitely and the wound heals to a fine scar. Skin annexes in the scar area are not restored (Fig. 7–28). In surgical wounds, healing by primary intention is accelerated by suture of wound edges. Scar remodeling process lasts several months, the scar tissue gradually gains density and strength adequate to the functional requirements.

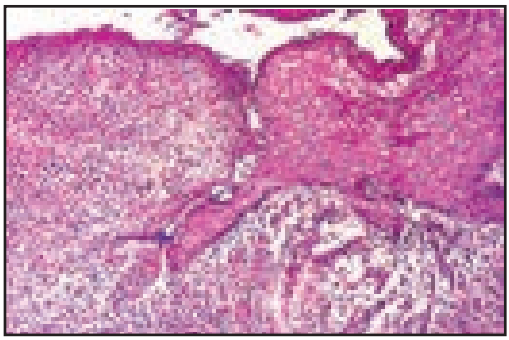


Fig. 7–27. Wound healing, proliferation of stratified squamous epithelium under the crust of fibrin and necrotic masses (hematoxylin–eosin stain; ×70).

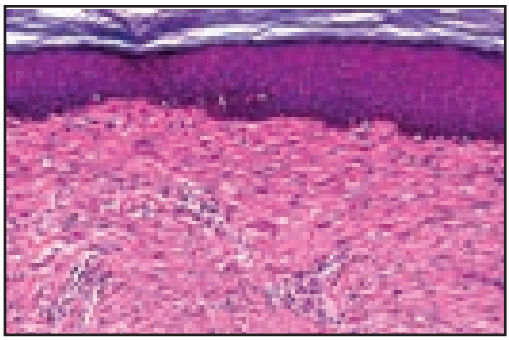


Fig. 7–28. Skin wound healing, neoformed scar tissue in subepidermal skin layer (no hair follicles, sebaceous and sudoriferous glands) (hematoxylin–eosin stain; ×70).

Healing per secundam intentionem occurs in large wounds (the distance between the edges is more than 1 cm), which are dehiscent, unsutured, irregularly shaped, infected, accompanied by larger tissue damage, penetration of foreign bodies in the wound. It is favored by nutritional disorders, excess of corticosteroids, diabetes mellitus, circulatory and innervation disorders. The main factor is the presence of infection, accompanied usually by purulent inflammation, which promotes the expansion of tissue necrosis in the wound edges, vessel thrombosis, circulatory disorders, exudate and granulation tissue abundance. Wound healing by secondary intention is distinguished by the following characteristics:

1) extensive tissue defects, with large amounts of necrotic debris and

fibrin, which produce an intense inflammatory reaction;
2) large amounts of granulation tissue (Fig. 7–11);
3) wound contraction, observed in large size wounds, due to the appearance of myofibroblasts – altered fibroblasts, which contain elements of smooth muscle cells and have contractile features, favoring the retraction of wound surface and the reduction of its size;
4) the process of wound healing by secondary intention is longer compared with primary healing.

Finally, a formation of a large scar, with tissue retraction and deformation, occurs. Mutilating scars may form in the case of large, irregularly-shaped wounds. Scar remodeling lasts several months, e.g. in 3 months, the scar regains 80% of the initial density and strength parameters.

Wound healing disorders manifest themselves through the appearance of atonic chronic ulcerations of the skin (Fig. 7–29), which may lead to development of skin carcinoma, exuberant granulations and keloid scars (Fig. 7–30).

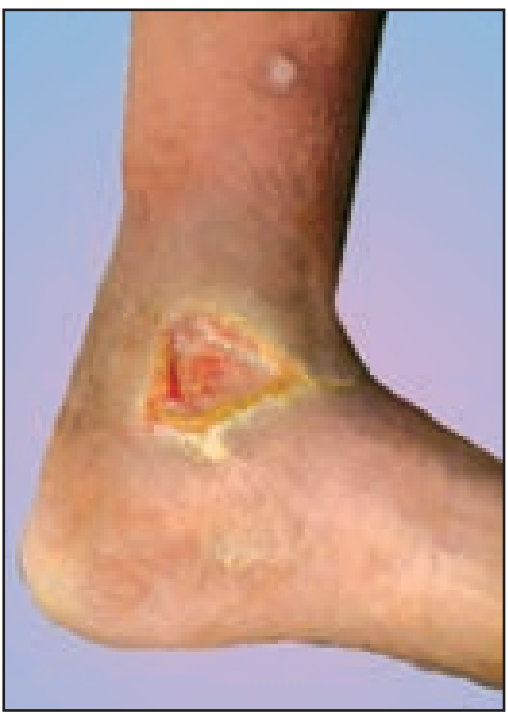


Fig. 7–29. Atonic (trophic) skin ulceration – macroscopic aspect.

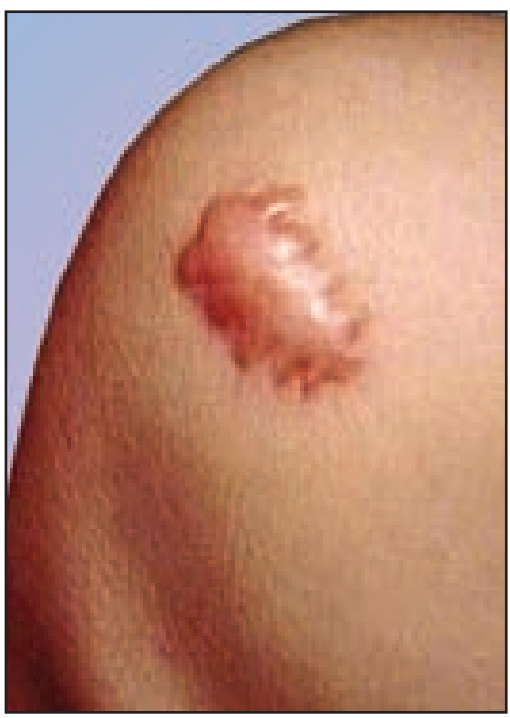


Fig. 7–30. Keloid scar – macroscopic aspect.

ESSENTIAL TERMS
on the subject "ADAPTATIVE–COMPENSATORY PROCESSES"

acromegaly	glandular hyperplasia of endometrium	pathological regeneration
atrophy	gynecomastia	physiological regeneration
bone callus	histological accommodation	pseudoarthrosis
cachexia	hyperplasia	regeneration
compensatory hypertrophy	hyperregeneration	regenerative hypertrophy
compression atrophy	hypertrophy	reparative regeneration
dysfunctional atrophy	hyporegeneration	restitution
encapsulation	ischemic atrophy	substitution
exostosis	keloid	vicarious hypertrophy
ex vacuo hypertrophy	local atrophy	wound healing *per primam intentionem*
false hypertrophy	metaplasia	wound healing *per secundam intentionem*
general atrophy	organization	wound healing under crust
gigantism	neurotic atrophy	

TESTS
on the subject "ADAPTATIVE–COMPENSATORY PROCESSES"

SET I.

Multiple-choice questions with one correct answer.

1. What is the correct definition of regenerative hypertrophy:

a) substitution of pathologic focus with connective tissue;
b) complete restoration of previous tissue;
c) partial restoration of previous tissue;
d) disturbance of regenerative process;
e) hypertrophy of the remaining portion of the organ (tissue).

2. Which of the listed statements characterize the pathological regeneration;

a) regeneration of injured tissues in various pathological processes;
b) substitution of the tissue defect with a tissue similar to the destroyed one;
c) permanent renewal of the structural elements of the organ (tissue);
d) quantitative or qualitative changes in the regenerative process;
e) substitution of defect with scar connective tissue.

3. *What is the correct definition of hypertrophy:*
   a) substitution of a pathologic focus with connective tissue;
   b) increase of the number of structural elements;
   c) size and mass increase of cells, tissue, organ;
   d) delimitation of the pathologic focus through the fibroconnective capsule;
   e) size and mass decrease of an organ (tissue).
4. *All the listed pathological processes are manifestations of local atrophy, with the exception of:*
   a) bone wear in the tumor area;
   b) leg atrophy in femoral artery atherosclerosis;
   c) muscle atrophy after bone fracture;
   d) tissue atrophy in case of denervation;
   e) cachexia.
5. *All the listed conditions promote wound healing per primam intentionem, except for:*
   a) unsutured wounds;
   b) sutured surgical wounds;
   c) wounds without bacterial infection;
   d) wounds with linear aspect of edges;
   e) small wounds up to 1 cm.

SET II.

Multiple-choice questions with 2, 3 or more correct answers.

1. *Which of listed morphological processes characterize the reparative regeneration;*
   a) the appearance of multi-layered squamous epithelium during bronchial epithelium regeneration;
   b) regenerative hypertrophy of myocardium;
   c) false joint appearance after bone fracture;
   d) renewal of epidermal cells;
   e) restoration of liver parenchyma after massive necrosis of liver, in intoxication with poisonous mushrooms.
2. *In which of the listed organs does the reparative regeneration through cell hyperplasia occur:*
   a) myocardium;
   b) liver;
   c) skin;
   d) hematopoietic tissue;
   e) digestive tract epithelium.
3. *In which of the listed organs does the reparative regeneration through hyperplasia and hypertrophy of intracellular organelles occur;*
   a) bones;
   b) pancreas;
   c) endometrium;
   d) nerve cells;
   e) myocardium.
4. *Which of the listed morphological processes characterize the pathological regeneration?*
   a) the appearance of gastric or intestinal type epithelium in the esophageal mucosa;
   b) regenerative hypertrophy of nerve cells;
   c) exostoses occurrence;
   d) wound healing per primam intentionem;
   e) keloid scar formation.
5. *Which of the listed signs are typical for the decompensation stage of the work hypertrophy of myocardium:*
   a) eccentric hypertrophy;
   b) heart muscle flaccid consistency;
   c) myocardial steatosis;
   d) passive dilation of heart cavities;
   e) active dilation of heart cavities.

SET III.

The classification tests include 2–4 subjects and a series of answers. Indicate which answers are correct for each separate subject.

1. *Which of the listed morphological processes characterize:*
   I – complete regeneration;
   II – incomplete regeneration;
   a) regenerative hypertrophy of myocardium;
   b) regeneration of blood after hemorrhage;
   c) formation of postinfarction cicatrix in the spleen;
   d) restoration of intestinal mucosa in the site of superficial ulcer;
   e) restoration of the broken bone.

2. *Which of the examples below characterize:*
   I – reparative regeneration;
   II – pathological regeneration;
   a) keloid scar formation;
   b) formation of a fine scar after surgical incision;
   c) appearance of multi-layered squamous epithelium in the cervical canal mucosa;
   d) complete healing of skin wounds;
   e) restoration of liver mass after resection.

3. *Which variant of atrophy do the pathological processes listed below refer to:*
   I – dysfunctional atrophy;
   II – compression atrophy;
   III – neurotic atrophy;
   a) atrophy of peritumoral tissues;
   b) atrophy of sternum in the aneurysm of the thoracic aorta;
   c) muscle atrophy in cases of paralysis in patients with cerebral infarction;
   d) muscle atrophy in ankylosis of joints in patients with rheumatoid arthritis;
   e) maxillary bone atrophy after extraction of teeth;
   f) atrophy of the gallbladder wall in obstruction of the cystic duct with calculi.

4. *Which of the listed pathological processes can cause:*
   I – kidney atrophy through compression;
   II – ischemic atrophy of the kidney;
   a) renal artery stenosis in atherosclerosis;
   b) ureteral stricture;
   c) basin calculi;
   d) nodular hyperplasia of prostate;
   e) sclerosis and hyalinosis of renal arterioles in arterial hypertension.

5. *Which of the listed wounds will heal*:
   I – per primam intentionem;
   II – per secundam intentionem;
   a) a wound with dehiscence of edges larger than 1 cm;
   b) a cut wound, with straight edges, without dehiscence;
   c) large burn-caused wound;
   d) overinfected wound;
   e) surgical wound.

SET IV. SITUATIONAL PROBLEMS

Daily practice cases are presented with clinical and morphological data from clinical histories and/or from necropsy protocols. Each subject includes simple or multiple - answer questions, with 1, 2 or more correct answers.

1. *A 70–year–old patient, with diabetes mellitus type II for more than 20 years, came up with a cut wound on the right leg, which does not heal for a long time, gradually turning into an ulcerous defect (atonic ulceration).*

Questions:

A) Which regeneration variant occurs in the given case:

a) reparative;
b) physiological;
c) pathological;
d) complete;
e) incomplete.

B) Which variant of this form of regeneration occurs in the given patient?

a) metaplasia;
b) hyporegeneration;
c) hyperregeneration;
d) dysplasia;
e) organization.

2. A patient had liver resection due to a large-size tumor, diagnosed histologically as benign tumor of vascular origin – cavernous hemangioma. A year later, the laparoscopic examination showed that the surface of the surgical wound was cicatrized and the liver mass was restored through hypertrophy of the remaining part of the organ.

Questions:

A) Which regeneration variant occurs in the given case:

1) reparative;
2) physiological;
3) pathological;
4) complete;
5) incomplete.

B) Which morphological form of this regeneration prevailed in this patient:

1) hyperplasia of cytoplasmic organelles;
2) cell hyperplasia;
3) hypertrophy of remaining cells;
4) hypertrophy of cytoplasmic organelles;
5) cellular anaplasia.

3. A patient with frequent hemorrhages from peptic gastric ulcer and signs of chronic posthemorrhagic anemia died from acute ischemic cerebral infarction. The necropsy revealed that the bone marrow in the femur diaphysis is juicy, red (normally, in diaphysis, the bone marrow is yellow, constituted from adipose tissue).

Question:

Which is the regeneration variant in this case:

1) work hypertrophy;
2) compensatory hyperplasia;
3) vicarious hypertrophy;
4) dyshormonal hypertrophy;
5) neurogenic hypertrophy.

4. A patient died suddenly of acute myocardial infarction. The necropsy confirmed the diagnosis of myocardial infarction; concomitantly, it revealed that the right lung had a considerably increased size and the left lung was absent. He had had left pneumonectomy few years ago, due to a lung cyst.

Question:

What morphological changes occurred in the right lung of this patient:

a) neurohormonal hypertrophy;
b) physiological hypertrophy;
c) interstitial pneumonitis;
d) vicarious hypertrophy;
e) diffuse pneumosclerosis.

5. A patient, who had a myocardial infarction, shows signs of cardiac insufficiency during physical activities: cyanosis and edema in legs, dyspnea.

Questions:

A) What morphological changes developed in the site of the old myocardial infarction in this patient:

a) intracellular regeneration;
b) interstitial myocarditis;
c) myocardial atrophy;
d) cardiomyocyte proliferation (neoformation);
e) focal cardiosclerosis.

B) What morphological changes can be detected in the periinfarct area of the myocardium:

a) cardiomyocyte atrophy;
b) cardiomyocyte proliferation;
c) proliferation of connective tissue;
d) cardiomyocyte hypertrophy;
e) blood vessel neoformation.

TUMORS

Tumor *(synonyms: neoplasm or blastoma)* – pathological process characterized by unlimited proliferation of cells. The cell proliferation in tumors is uncontrolled, autonomous; it is not subject to the regulatory systems of the body and continues after cessation of the causative stimulus. Other important feature of neoplasms is that the proliferative process does not have a compensatory–adaptive character.

Tumor pathology ranks on the 2nd place in the lethality structure from all the countries (after cardiovascular pathology).

8.1. ETIOLOGY AND PATHOGENESIS OF TUMORS

The factors that can cause tumor development are called *cancerogenic or carcinogenic factors*. At present, it is established that the transformation of a normal cell into a cancer cell is based on the occurrence of a mutation, under the mutagenic action of some agents from the external environment. Epidemiological studies have shown that 80–90% of human cancers result from environmental factors.

The main theories, which tackle the etiological and pathogenetic aspects of the tumorigenesis, are:

a) theory of chemical carcinogenesis;
b) theory of physical (radiation) carcinogenesis;
c) theory of viral (infectious) carcinogenesis.

8.1.1. THEORY OF CHEMICAL CARCINOGENESIS

Numerous experimental studies on animals have identified several chemical substances with carcinogenic effect. The most important are: polycyclic aromatic hydrocarbons, azo dyes (aniline), aromatic amines and amides (naphthylamine), some metals (cobalt, nickel, lead) and natural substances produced by plants and fungi. Cases of professional tumors (cancers) are also in favor of this theory.

The following factors are important in chemical carcinogenesis: a) dosage and duration of action of the chemical

substance; b) way of entering the body; c) physical–chemical nature of the respective substances; d) animal species, etc.

The primary and most important target of carcinogens is the nuclear DNA.

Carcinogens induce proto-oncogene mutations, transforming them into active oncogenes, mutations in cancer–suppressor genes, mutations in genes that regulate apoptosis.

Examples of chemical carcinogens:

4) alkylating agents, e.g. cyclophosphamide – immunosuppressant in cancer treatment. Patients, who are treated with this drug for a long time, face an increased risk of other cancers.
5) aromatic hydrocarbons are contained in cigarette smoke and have a major role in the development of lung cancer.
6) azo dyes, aniline (rubber industry) for example, causes urinary bladder cancer.
7) aflatoxin Bl, produced by the *Aspergillus flavus* fungus, causes liver cancer (through food contaminated by mould, for example peanuts).
8) nitrosamines and amides synthesized in the body from nitrates, which are in the food, contribute to the development of gastric cancer.

Other carcinogens:

- ✧ asbestos – induces lung cancer, pleural mesothelioma;
- ✧ arsenic - generates skin cancer;
- ✧ hormones, for example, estrogens have an important role in endometrial cancer, the reduction of testosterone secretion has a beneficial effect in patients with prostate cancer.

8.1.2. THEORY OF PHYSICAL CARCINOGENESIS

Radiant energy in the form of ultraviolet rays or ionizing radiation can also cause cancer development. Solar ultraviolet radiation causes skin cancer or malignant melanoma localized particularly on the open body parts, exposed to the sunstroke. The risk of these tumors is especially high in white population from geographic areas with long annual sunlight duration. The predisposition to skin cancer in patients, who suffer from albinism, is well known.

Also, the electromagnetic and corpuscular radiations have a carcinogenic effect, confirmed by many examples:

- ✧ high incidence of lung cancer in miners working in radioactive ore mines;
- ✧ very high incidence of leukemia among survivors of atomic explosions at Hiroshima and Nagasaki;
- ✧ high incidence of thyroid gland cancer in areas contaminated by radiation from the Chernobyl nuclear accident;
- ✧ cancer cases in patients undergoing treatment with radioactive isotopes.

The carcinogenic effect of radiant energy depends on the way of action of the radiation, dosage and duration of exposure, for example:

- ✧ direct, repeated action of X–rays on a certain body area predisposes to malignant tumors of the skin and bones in that area;
- ✧ inhaling gas or radioactive dust – lung cancer;

- ingestion of radioactive iodine – thyroid cancer;
- radioactive metals, which penetrate the body and store in bones – tumors of bone marrow and bones.

The carcinogenic effect of radiation is related to its action on the cellular DNA and the emergence of mutations. The cells that proliferate extensively in physiological conditions, primarily the hematopoietic marrow, gastrointestinal mucosa epithelium, are particularly vulnerable. Mutations occur by direct action of radiant energy or indirect effect of free radicals from water and oxygen. Corpuscular radiation is much more carcinogenic than electromagnetic radiation (e.g. X– or gamma rays).

8.1.3. THEORY OF VIRAL CARCINOGENESIS

Experimental studies have shown that, in animals, many tumors have a viral origin. Viruses have a less important role in human cancer. However, there exists a range of tumors, in which virus participation is confirmed.

Oncoviruses may contain DNA or RNA.

The following **DNA viruses** are observed in the genesis of human tumors:

- *Human Papilloma Virus (HPV)*. The role of this virus in the etiology of cancer is confirmed by many examples:
  a) the cells contain HPV type 16 or 18 in more than 90% of cervical cancer ;
  b) genital warts (condyloma acuminata) are caused by HPV types 6 and 11;
  c) molecular research of cervical carcinoma associated with HPV showed viral genome integration into host cell's DNA.
- *Epstein–Barr virus* belongs to the herpes–virus group. It is associated with:
  *a) Burkitt lymphoma, which occurs in children and adolescents in some countries in Equat*orial Africa;
  b) nasopharyngeal carcinoma, spread endemically in some regions of China; Epstein-Barr virus genome is detected in cancer cells in all cases;
  c) B–cell lymphoma in patients with immunosuppression, especially in AIDS;
  d) some forms of Hodgkin lymphoma.
- *Hepatitis B and C viruses* are associated with liver carcinoma. The risk of hepatic carcinoma is very high in some geographical regions (China, South Africa), where viral hepatitis B and C are endemic. The carcinogenic potential of hepatitis virus is determined by its ability to cause cell necrosis, chronic inflammation and regenerative hyperplasia of hepatocytes.

Among **RNA viruses**, the most prominent example is the human T-cell lymphotropic virus type 1 (HTLV–1),

associated with leukemia/lymphoma from T-lymphocytes with a strict tropism for T-CD4 lymphocytes. This form of leukemia/lymphoma is an endemic pathology in Japan, etc.

The mechanism of action of blastomogenic viruses is complex. For example, the DNA virus enters the cell, is incorporated directly into the cell nucleus, but the RNA virus produces a new DNA by means of the reverse transcriptase, which also is incorporated into the host cell nucleus, activating cellular proto–oncogenes. Thus, normal cells are transformed into tumor cells.

In cancer cells, the balance between stimulating factors and cell division inhibitors is disturbed and this induces intensification of proliferative processes. Proto-oncogene activation, inhibition of tumor–suppressor genes and apoptosis occur simultaneously in many malignant tumors.

The immune system status has a significant importance in tumor occurrence. Some types of cancers are observed more frequently in patients with immunosuppression, e.g. the patients, receiving immunosuppressants for kidney transplantation face a high risk of squamous skin cancer.

8.1.4. PROTO–ONCOGENES AND CELLULAR ONCOGENES

At the molecular level, the carcinogenesis process is determined by nonlethal lesions of the genetic material of the cell, which manifest themselves through mutations of genes or cellular genome. The targets of mutagenic factors are: a) proto-oncogenes, b) cancer–suppressor genes and c) genes that regulate apoptosis.

Cellular proto–oncogenes are genes present in the genome of every normal cell. They regulate and stimulate cell division and differentiation, being, usually, non–active in mature tissues. Initially, they were discovered in viruses (viral oncogenes) and, later, homologous human genes were identified. The active forms of the proto–oncogenes are called *cellular oncogenes*. They have the ability to induce tumor growth. The name of cellular oncogenes is formed from 3–letter abbreviations, such as *src* (from sarcoma), plus prefix *c* – or *v* –, depending on cellular or viral origin (*c–src, v-src*). Oncogenes encode the synthesis of proteins=oncoproteins, which, according to their functional characteristics, are subdivided into: a) homologous oncoproteins of growth factors (*c–sis*), b) homologous oncoproteins of growth factor receptors (*c–erbA, c–erbB*), c) oncoproteins involved in the functioning of receptors through protein kinases and G protein (*c–src, c–abl, c–ras*) and d) oncoproteins – nuclear transcription factors (*c–fos, c–myc*).

Activation of proto–oncogenes occurs through different mechanisms: a) point mutations; b) translocation of chromosome fragments containing proto-oncogenes; c) amplification of proto-oncogenes (increase of the number of copies); d) insertion of viral genes into the cell genome, which can be oncogenes or can act as an activator (enhancer) of proto–oncogenes.

Examples: 1) *c–ras* proto–oncogene mutation occurs in urinary bladder cancer, *c– rasK* proto–oncogene mutation occurs in colon cancer; 2) mutual translocation of *c–myc* gene from chromosome 8 to chromosome 14 is observed in Burkitt lymphoma; 3) Philadelphia chromosome appears in chronic myeloid leukemia, as a result of *c–abl* proto–oncogene mutual translocation between chromosomes 9 and 22; 4) amplification of oncogenes is detected in glioblastoma (*c–erbB*), lung, colon and pancreatic cancer (*c–myc*, *c–ras*), breast cancer (*c–neu*).

Genes that inhibit cell proliferation and have antitumor action were detected in the cellular genome. P53 and Rb are the main antioncogenes or tumor–suppressor genes. P53 gene produces a protein of 53 kilodaltons (hence the name), which plays an important role in protecting against cancer. It is called the "guardian angel of cell genome". If the injury of cellular DNA is insignificant, the p53 protein stops cell division until the defect is removed, but if the injury is major, it initiates the cell death ("suicide") by apoptosis. More than a half of human cancers are based on p53 gene mutations and p53 protein inactivity. Rb gene alteration is detected in ocular retinoblastoma in children, which may be sporadic or hereditary.

Besides the p53 gene, cellular oncogenes from *c–bcl2* and *c–myc* families are regulatory factors of apoptosis. The *c–bcl2* hyperexpression in tumor cells protects them from apoptosis and thus ensures tumor growth and progression. Such gene alterations occur in B–cell follicular lymphoma and in the small cell lung cancer.

Experimental and clinical data show that the activation of proto– oncogenes and the inactivation of tumor–suppressor genes are the main mechanism of evolution of normal cells to malignancy. These genes are the main targets of the action of various chemical, physical or viral carcinogens. The evolution of malignant tumors has a multistage character with initiation, promotion and progression as its stages. Gradual accumulation of lesions of genes in control of cell proliferation, differentiation and apoptosis occurs, and the malignant tumor progresses, i.e. the degree of malignancy increases.

8.2. STRUCTURE OF TUMORS

8.2.1. MACROSCOPIC CHARACTERISTICS OF TUMORS

The **macroscopic** aspect of tumors may be different. In most cases, they have the aspect of a round or ovoid nodule, lodged in the organ's thickness or on its surface. They are lodged in wall thickness or protrude into the respective lumen in hollow and tubular organs.

The surface of the nodules may be smooth or rough, sometimes resembling a cauliflower.

Tumors' size and consistency vary: from microscopic to very large; from soft, flaccid to hard. The color varies depending on the structural-functional features of the original tissue and on the secondary changes that occur in the tumoral tissue (dystrophic, necrotic lesions, circulatory disorders, inflammatory processes, etc.).

Tumors can be encapsulated, circumscribed and well-defined or can infiltrate adjacent tissues. Numerically, they can be unicentric or multicentric (Fig. 8–1, 8–2, 8–3).

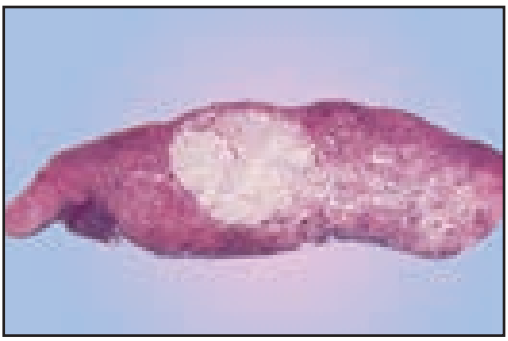


Fig. 8–1. Pulmonary chondroma – benign tumor of hyaline cartilage of bronchi.

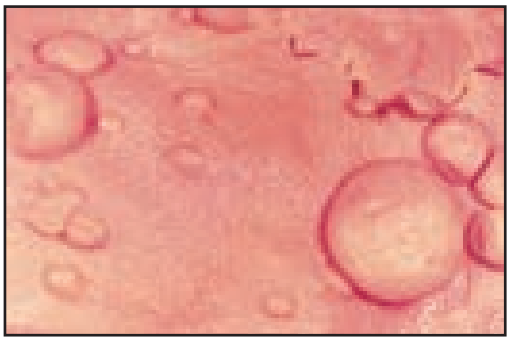


Fig. 8–2. Neurofibromatosis of skin – multicentric tumor, which originates from the sheath of nerve fibers (from the perineurium).

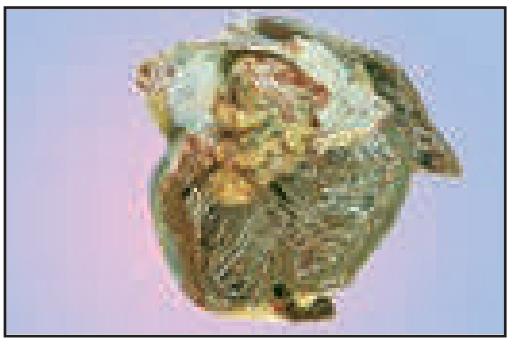


Fig. 8–3. Cardiac myxoma with exophytic growth; it develops from pluripotent embryonic mesenchymal elements.

8.2.2. MICROSCOPIC ASPECTS OF TUMORS

Microscopically, tumors are composed of two tissular components: **parenchyma** and **stroma**. Parenchyma is the tumor cells themselves. Stroma is formed of connective tissue, contains blood and lymphatic vessels, nerve fibers.

The ratio between the stroma and parenchyma may be different; stroma predominates in some tumors (*fibrous* tumors), parenchyma - in others (*histioid* tumors). In some cases, the stroma and parenchyma are developed evenly (*organoid* tumors).

The tumor differs from the normal tissue by **atypism** and **polymorphism**. The atypism can be: a) morphological, b) biochemical, c) histochemical and d) antigenic.

The morphological atypism can be tissular, cellular and ultrastructural. **Tissue atypism** manifests itself by changing the structure of original tissue, the arrangement of structural elements, the ratio between them, for example, the change of the ratio between parenchyma and stroma, variations of number, shape and size of epithelial structures, chaotic distribution of fibrillar, cellular, vascular structures etc. Tissue atypism is characteristic for mature, benign tumors. For example, in breast fibroadenoma – a benign tumor of glandular epithelium - the tissue atypism is manifested by presence of proliferating, unevenly distributed glandular formations of various shapes and sizes (Fig. 8–4), in leiomyoma – a benign tumor of smooth muscle tissue – the atypism is characterized by chaotic, unordered position of fascicles of muscle fibers, sometimes in whirlwinds, with varying thickness and orientation, interspersed with collagen fiber fascicles. The tumor cells are well differentiated, reminding the original tissue cells (Fig. 8–5).

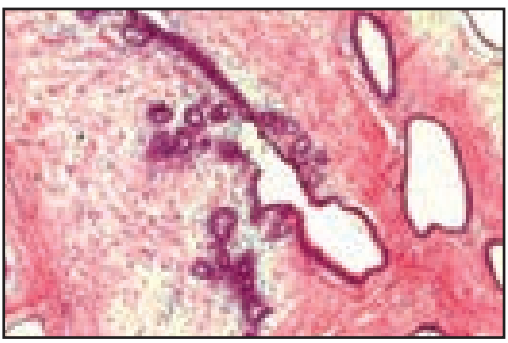


Fig. 8–4. Tissue atypism in breast fibroadenoma (hematoxylin–eosin stain; ×70).

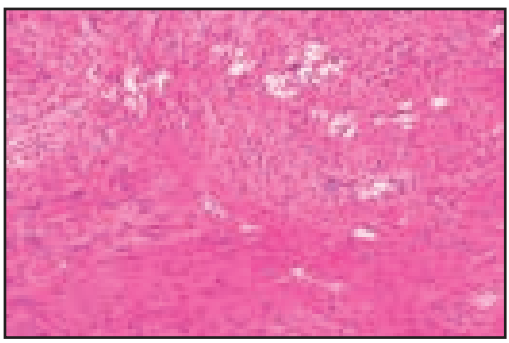


Fig. 8–5. Tissue atypism in leiomyoma (hematoxylin–eosin stain; ×70).

Cellular atypism manifests itself by inegalities in the shape, volume and size of the tumor cells and nuclei, cytoplasmic organelles, different ratio between nucleus and cytoplasm, increased mitotic activity, appearance of pathological mitosis, multinucleated giant cells. The intensity of nucleus staining is different (nuclear hyper– or hypochromatosis); the arrangement of tumoral cells is cha-

otic, unordered etc. (Fig. 8–6, 8–7, 8–8). Cellular atypism is observed in immature, malignant tumors.

Ultrastructural atypism reflects increase of the number of ribosomes, diversity of form, volume and location of mitochondria, nuclei, atypical mitosis.

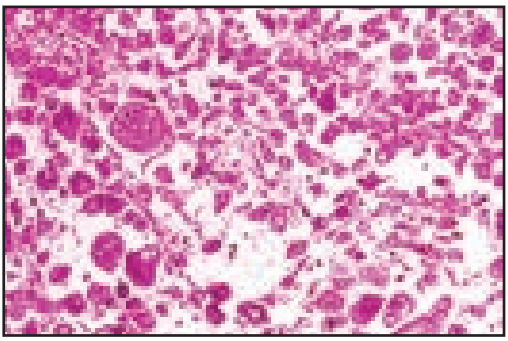


Fig. 8–6. Cellular atypism in undifferentiated cancer (hematoxylin–eosin stain; ×70).

Histochemical atypism reflects biochemical and metabolic characteristics of the tumor tissue that distinguish it from the original tissue, for example, prevalence of glycolytic, anaerobic metabolism enzymes and increased content of nucleic acids etc.

Antigenic atypism – specific (viral, embryonic, etc.) tumor antigens appear in some tumors, characteristic only to this tumor.

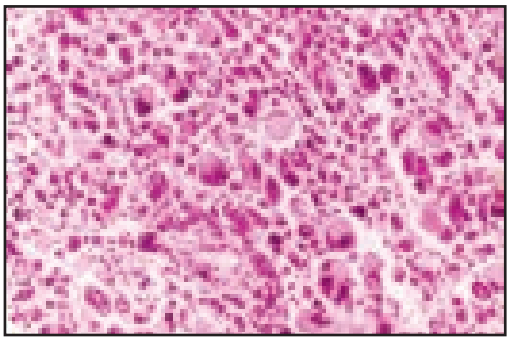


Fig. 8–7. Cellular atypism in rhabdomyosarcoma – malignant tumor of striated muscle tissue (hematoxylin–eosin stain; ×70).

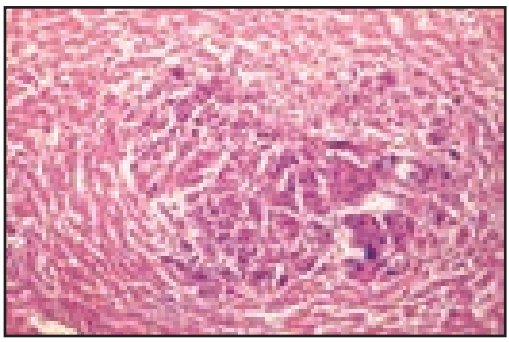


Fig. 8–8. Cellular atypism in hepatocellular carcinoma (hematoxylin– eosin stain; ×70).

8.2.3. METASTASIS AND RELAPSE OF TUMORS

Metastasis – the process of tumor cell moving in the body, their seeding and multiplication at distance from the primary tumor, forming secondary tumoral nodules or metastases (Fig. 8–9 a, b and 8–10). It is characteristic for malignant tumors (cancer, sarcoma and melanoma).

Varieties of tumor metastasis:

a) Blood (hematogenous) **metastasis** is a cell embolism process, which is

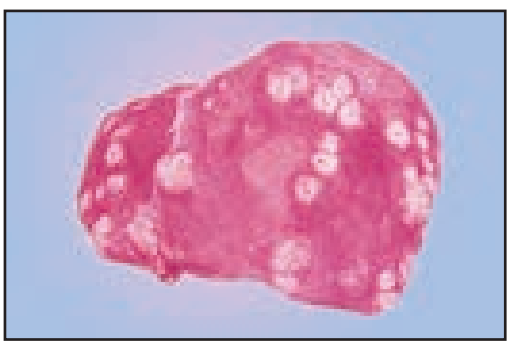


Fig. 8–9 a. Cancer metastases in liver – macroscopic aspect.

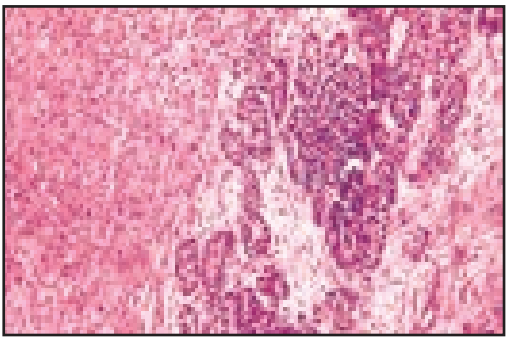


Fig. 8–9 b. Cancer metastases in liver: – microscopic aspect (hematoxylin–eosin stain; ×70).

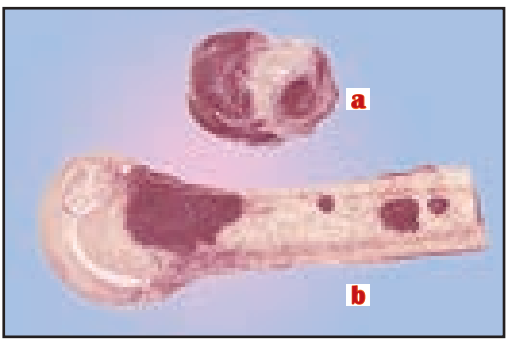


Fig. 8-10. Ocular melanoma (a) with metastases in femoral bone (b).

found predominantly in veins and capillaries, rarely in arteries (Fig. 8–11). One can follow three consecutive stages

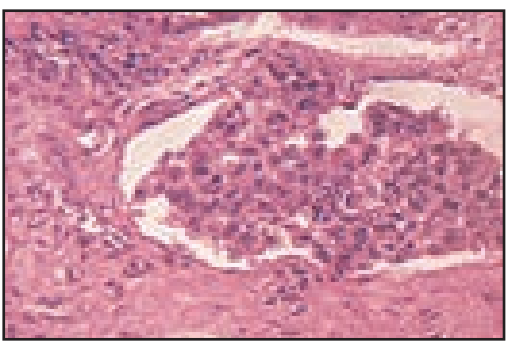


Fig. 8–11. Tumor embolus in a blood vessel (hematoxylin–eosin stain; ×70).

in the evolution of this process: 1) *invasion stage* – tumor cells penetrate the lymphatic vessels and later - the bloodstream, where most are killed within 24 hours, 2) *embolic stage* – the tumor cells form aggregates, surrounded by a layer of fibrin; the cell embolus stops at the level of precapillary arterioles and 3) *implantation stage* – individual tumor cells detach from the embolus, cross postcapillary venule wall, implant in the perivascular tissue and form secondary metastatic nodules. Depending on the primary location of tumors and characteristics of the venous drainage of the affected organ, there are several variants of hematogenous metastasis: a) *pulmonary variant* – the primary tumor is localized in the lungs; the tumor cells fall in the left heart through the pulmonary veins, and then – in the large circulation vessels, 2) *liver variant* – the primary tumor is located in the liver; liver tumor cells fall into inferior vena cava, the right heart and lungs through the hepatic veins, and then – in the left heart and great circulation vessels, 3) *vena cava variant* – the primary tumor is lodged in different areas of the body, from which venous blood flows into the vena cava; tumor cells penetrate the right heart, lungs, and then can reach the left heart and great circulation vessels, 4*) portal vein variant* – the primary tumor is lodged in an intraabdominal organ (stomach, intestine, pancreas, etc.); firstly, tumor cells metastasize to the liver through the portal vein and then reach the right heart, lungs, left heart and great circulation vessels. Blood metastasis is characteristic especially for sarcomas, melanomas, choriocarcinoma etc.

b) **Lymphatic** (lymphogenous) **metastasis** is characteristic for carcinomas. The first metastases are lodged in regional lymph nodes (satellite-lymph nodes of the affected area). After overcoming regional lymph nodes, tumor

cells enter the systemic circulation and various organs and tissues.

c) **Metastasis by implantation or by contact** can be observed more frequently in serous membranes (e.g. peritoneal, pleural carcinomatosis), in the brain (through the cerebrospinal fluid), along the nerve trunks (perineural spread of tumors, Fig. 8–12). One can also meet **intracanalicular** spread of malignant tumors through epithelial ducts, e.g. spread of breast cancer through lactiferous breast ducts, spread of gallbladder cancer – through billiary ducts, urinary bladder cancer – through ureters.

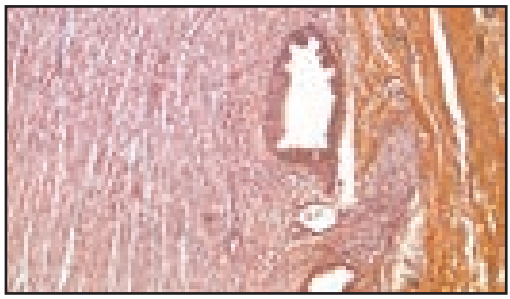


Fig. 8–12. Perineural spread, by contact, of glandular carcinoma (hematoxylin–eosin stain; ×70).

8.2.4. MORPHOGENESIS OF TUMORS

Relapse – reappearance of tumor *in the same site* after surgical removal or after radiotherapy. It develops from cells that may remain in the tumor site or from the closest lymphatic metastases. It is characteristic for malignant tumors (*e.g. in carcinoma, sarcoma, melanoma*). It is also met in tumors with locally destructive growing *(for example, in basalioma, desmoid tumor, ameloblastoma)*.

Tumor development can begin *de novo*, but, more frequently, it emerges on the background of some pre-tumoral (precancerous or premalignant) lesions. These lesions show some pathological processes, which create a high risk for tumor development. Pretumoral lesions are subdivided into **obligatory** (turn into cancer in most cases) and **optional** (turn rarely into cancer). The best examples of obligatory precancer are the congenital polyposis of the large intestine and the xeroderma pigmentosum, both of hereditary nature. Optional pretumoral conditions include some processes of hyperplasias, dysplasias and dysembrioplasias, accompanied by morphological restructuring of tissues and functional disorders. Examples: leukoplakia, squamous metaplasia and mucosal polyposis, chronic gastric ulcer, liver cirrhosis, dysplasia of mucosal epitheliums, glandular cystic hyperplasia of endometrium, chronic atrophic gastritis, etc.

8.2.5. GROWTH OF TUMORS

According to the differentiation degree of tumors and the report towards the adjacent tissues, the following tumor growth variants are observed:

a) expansive – tumor grows slowly "from itself", removing and compressing the nearby tissues, which gradually form a fibroconnective capsule around the tumoral node (parenchymatous elements atrophy); the tumor has precise limits and can be easily removed (enucleated); it is characteristic for benign tumors;

b) infiltrative (invasive) – tumor cells infiltrate and destroy adjacent normal tissue (destructive growth); invasion occurs along nerve fibers, blood and lymphatic vessels, intertissular spaces etc; the tumoral node does not have

precise boundaries; it is characteristic for malignant tumors.

According to the number of initial tumoral growth foci, tumors can be unicentric (one focus) and multicentric (with multiple foci).

In hollow and tubular organs, tumors can have an **exophytic** growth – expansive growth in the organ's cavity, and **endophytic** growth– the tumor lodges in the wall thickness of the respective cavity.

Terminology of tumors: in most cases, the tumor name is formed from the root of the injured tissue or organ's name, plus the suffix "oma" ("oma" – swelling, tumefaction), for example, *nephroma, hepatoma, fibroma, angioma, myoma, osteoma* etc. This principle is mainly used to designate benign tumors. As to malignant tumors, the terms **cancer or carcinoma**, introduced by Hippocrates (Greek "*karkinos*" = sea crab) are used for tumors of epithelial origin; **sarcoma** - for tumors of mesenchymal origin (Greek "*sarcos*" = fish meat). The suffix **blastoma** (Greek "*blastos*" = germ+oma) is used for malignant tumors of nervous origin, for example, neuroblastoma, glioblastoma, medulloblastoma. The term *cancer* is sometimes used as a generic name of all malignant tumors.

8.2.6. CLASSIFICATION OF TUMORS

I. Clinical and morphological classification of tumors: a) benign, b) malignant, c) with locally destructive growth *(intermediate type)*. Their general characteristic is presented in the Table 8.1.

Table 8.1.

General characteristic of tumors

Criterion	Benign tumors	Malignant tumors	Tumors with locally destructive growth
Growth rate	Slow	Rapid	Slow
Degree of differentiation of tumor cells	Mature, differentiated cells	Immature, undifferentiated cells	Mature, differentiated cells
Atypism	Tissular	Tissue, cellular (ultrastructural, biochemical, histochemical, antigenic)	Tissular
Growth character towards adjacent tissues	Expansive	Infiltrative (invasive)	Infiltrative
Tumor boundaries	Clear, precise (encapsulated)	Blurred, unclear	Blurred, unclear
Metastasis	No metastasis	Metastasis	No metastasis
Recurrence	No relapse	Relapse	Relapse
Clinical, morphological evolution	Can turn malignant	Cannot turn benign	Can turn malignant

Benign tumors have a slow development, remain localized, grow expansively, compressing the adjacent tissues; they do not exert a general action on the body. These tumors are composed of mature, differentiated cells, so their histogenetic origin can always be established. They differ only by tissular atypism and, usually, do not recur after surgery and do not metastasize. In some cases, benign tumors may have major clinical effects, depending on location, such as intracranial or intracardiac tumors, hormonal active tumors of endocrine glands.

Benign tumors in parenchymatous organs have the appearance of encapsulated, well-defined nodules, which can be easily enucleated; they have the color of the original tissue, when sectioned. On the surface of the skin and mucous membranes, benign tumors are polyp-shaped, with smooth or rough surface (cauliflower aspect) or nodule-shaped, with a broader (sessile) or narrower (pedunculated) implantation base.

Malignant tumors have a fast growth, infiltrative towards neighboring tissues and characterized by cellular atypism. They are formed of immature, undifferentiated cells; sometimes, their tissular origin cannot be identified. Malignant tumors recur and metastasize, exerting local and general effects on the body. In parenchymatous organs, malignant tumors have the form of single or multiple nodules with imprecise, unclear boundaries or no boundary at all, infiltrating and destroying the surrounding tissues. Frequently, secondary changes, like necrosis foci, hemorrhage, inflammation, myxomatosis, cystic cavities occur in malignant tumors.

Tumors with locally destructive (invasive) growth occupy the intermediate position of semi-malignant tumors. They are formed of mature, differentiated cells, with infiltrative growth, therefore they may relapse, but do not metastasize. The desmoid, ameloblastoma, craniopharyngioma can be examples of such tumors.

II. Histogenetic classification (according to the original tissue) of tumors:

1) epithelial tumors with no specific location (non organ-specific);
2) epithelial tumors with specific location (organ-specific);
3) mesenchymal tumors;
4) melanopoietic tissue tumors;
5) nervous system and meningeal membranes tumors;
6) hematopoietic and lymphoid tissue tumors;
7) teratomas (*disontogenetic tumors*).

III. TNM classification of tumors:

The TNM system (*tumor, nodus, metastasis)* was developed by the **Union for International Cancer Control (UICC),** in order to assess the stage of cancer. The TNM system has two classifications: TNM – pre-therapeutic clinical and radiological classification, and pTNM - postoperative histopathological classification, based on additional findings made during surgery and macro-microscopic examination of the removed part. This staging classification is based on 3 categories: T – primary tumor extension, N –absence or presence and extent of metastases in regional lymph nodes, M – absence or presence of distant metastases. These three components are added numbers from 0 to 4 in each category and the tumor stage is assessed, for example:

1) **T** – primary tumor characteristic: T0 – no histological signs of primary tumor; Tis – carcinoma in

situ; T1, T2, T3, T4 – size and/or local extension of primary tumor;

2) **N** – condition of regional lymph nodes: N0 – microscopically, there are no metastases in the regional lymph nodes, N1, N2, N3 – number and size of metastases in regional lymph nodes (metastases in other than the regional lymph nodes are assessed as distant metastases);
3) **M** – absence (M0) or presence of distant metastases (M1).

For example, **TNM classification of gastric cancer: T – primary tumor:** T0 – no evidence of tumor at histopathological examination, Tis – intraepithelial carcinoma (in situ), T1 – tumor invasion of mucosa or submucosa, T2 – tumor invasion of the muscular layer or subserous membrane, T3 – tumor invasion of subserous membrane, but without invasion of adjacent structures, T4 – tumor invasion of adjacent structures (spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal glands, kidneys, small intestine and retroperitoneal space); **N – regional lymph nodes** (regional lymph nodes of the stomach are located on the large and small curvature, along the left gastric, common hepatic, lienal and celiac arteries and hepatoduodenal nodes): N0 – no metastases in regional lymph nodes, N1 - metastases in 1–6 regional lymph nodes, N2 – metastases in 7–15 regional lymph nodes, N3 – metastases in more than 15 regional lymph nodes (involvement of other intraabdominal lymph nodes is classified as distant metastases); **M – distant metastases**: M0 – no evidence of distant metastases, M1 – presence of distant metastases (in liver, lungs, bones, brain, ovaries, supraclavicular lymph nodes etc).

A decisive criterion of tumor malignancy is the condition of lymph nodes. The presence of lymph node metastases requires a more aggressive, more radical therapeutic conduct towards the cases when such metastases lack. The presence of distant metastases is generally a contraindication for other surgeries than the palliative ones.

IV. Classification of tumors according to the histopathological degree of differentiation:

All types of tumors must be histologically confirmed by biopsy. At microscopic examination, the degree of similarity of tumor cells with their normal tissue prototype (tissue of origin) is assessed, based on the general histoarchitectonics, cell atypism, number of mitoses, presence of atypical mitoses, nuclear pleomorphism, etc. Each parameter is assigned a score from 1 to 4, allowing the inclusion in one of the following degrees of differentiation:

Gx – the degree of differentiation cannot be established;
G1 – high degree of differentiation (low malignancy)
G2 – moderate degree of differentiation (moderate malignancy)
G3 – low degree of differentiation (high malignancy)
G4 – undifferentiation (very high malignancy, indicating anaplastic tumor).

In some cases, degrees 3 and 4 can be merged (G3–4). The histopathological degree of differentiation is important in the estimation of the clinical severity of malignant tumors and in the evaluation of the therapeutic act. Less differentiated tumors have a higher malignancy, grow faster and are more sensitive to radiotherapy. Generally, higher degree tu-

mors (G3 and G4) are more aggressive than the lower grade tumors; the G1 tumors have the most favorable prognosis. Sarcomas can show a high and a low degree of differentiation. This gradation is, however, imperfect, because the histopathological degree of differentiation may vary in different areas of the tumor and the tumor degree can change with its growth.

8.2.7. GENERAL AND LOCAL COMPLICATIONS OF TUMORS

Local effects:

- deformation of organs, for example, breast deformation in cancer;
- tumor compressive action on adjacent tissues, for example, atrophy of brain tissue by compression, in case of meningioma or osteoma of cranial bones;
- stenosis of tubular and hollow organs through endophytic or exophytic growth of tumors, e.g. intestinal obstruction in colon cancer, mechanical jaundice in encephalic pancreatic cancer, pyloric stenosis in gastric cancer;
- pains caused by nerve compression or perineural expansion of cancer cells;
- destruction of normal adjacent tissues, e.g. bone fracture in myeloma or in cancer metastases in bones, perforation of hollow organs (stomach, colon) in cancer;
- necrotic lesions, ulcers, infarcts, caused by compression or thrombosis of vessels;
- bleeding through the erosion of blood vessels, for example, in uterine, lung and gastric cancers.

General effects:

- **non–specific symptoms**: fever, loss of appetite, fatigability, general weakness, due to absorption of tumor tissue destruction products and bacterial toxins, in case of infected tumors;
- **cancer cachexia**, determined by several factors, e.g. digestive disorders caused by tumors themselves (in esophageal, gastric, pancreatic cancer), secretion of tumor necrosis factor (TNF–α), which enhances catabolic processes in the body, leading to reduction of adipose and muscle tissue, intensification of protein and energy metabolism in tumoral tissue, etc.
- **paraneoplastic syndromes** – general clinical manifestations that cannot be directly related to local effects of tumor or to metastasis; they disappear after tumor removal and reappear, if it recurs. It is observed in 10–15% of oncologic patients.

The most important paraneoplasic syndromes:

1) **endocrinopathies** – ectopic secretion of hormones or hormone– like substances in malignant tumors of some organs (tissues) that do not have endocrine function in normal conditions, for example, **Cushing's syndrome** in small cell lung cancer (adrenocorticotropic hormone secretion), **hypercalcemia and osteoporosis** in squamous lung cancer, renal cell carcinoma (secretion of parathormone–like proteins), **hypoglycemia** in uterine leiomyosarcoma, retroperitoneal fibrosarcoma, liver cancer (secretion of insulin-like

factors), **carcinoid syndrome** in carcinoid tumors of bronchi, ileum (secretion of serotonin, which causes facial erythema, diarrhea, bronchial and bowel spasm);

2) **hematologic manifestations – phlebothrombosis (venous thrombosis),** often migratory or Trousseaux syndrome in pancreatic cancer (tumor cells synthesize thromboplastic substances), **DIC syndrome** – in leukemia, prostate, lung, stomach cancers (tumor cells synthesize thromboplastic substances and consume the clotting factors); **anemia** – in various malignancies (caused by chronic hemorrhage, appearance of anti-erythrocyte autoantibodies, substitution of hematopoietic bone marrow with tumor infiltrates, reduction of hematopoietic function after chemotherapeutic or radiotherapy treatments); **erythrocytosis** (*increase of the number of red blood cells*) in renal cell carcinoma (excessive secretion of erythropoietin), **thrombocytopenia** etc.;
3) **cutaneous manifestations – acanthosis nigra** (skin hyperpigmentation in the axillary, neck, perianal, inguinal areas) in gastric cancer, squamous bronchogenic cancer;
4) **neurological manifestations – myasthenia gravis** in thymus tumors, **peripheral neuropathy**, **cortical cerebellar degeneration** in small cell bronchogenic cancer, breast and ovarian cancer.

8.3. EPITHELIAL TUMORS WITH NO SPECIFIC LOCATION *(NON- ORGAN-SPECIFIC)*

This group of tumors develops from squamous, transitional and glandular epithelia, which do not perform specific functions. They can be benign and malignant.

8.3.1. BENIGN EPITHELIAL TUMORS

Papilloma and **adenoma** are benign epithelial tumors with out specific location.

Papilloma develops from squamous, stratified and transitional epithelium. It is met on the skin and mucosa covered with respective epithelia: oral cavity, nasopharynx, larynx (vocal folds), esophagus, urinary bladder, cervix. Papilloma is also observed in the excretory ducts of exocrine glands and mammary gland.

Macroscopically, papilloma is a spherical tumoral formation with rough surface, dense consistency, wide or narrow implantation base and sizes from 1–2 mm to 1–2 cm (Fig. 8–13 a).

Microscopically, papilloma consists of stratified squamous epithelium, proliferated unevenly (parenchyma) and

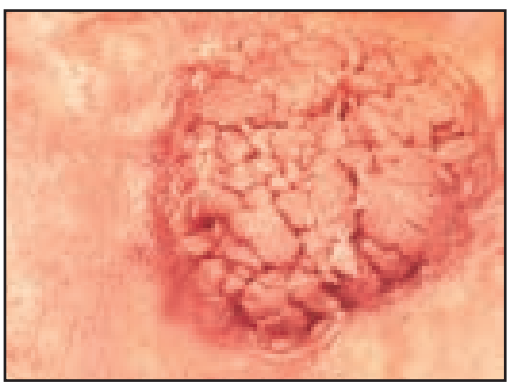


Fig. 8–13 a. Skin papilloma, macroscopic aspect.

subepithelial connective tissue, rich in blood vessels (stroma), distributed chaotically. The epithelium forms protruding papilliform proliferations on the skin surface. The basement membrane is preserved, as well as the complexity and polarity of epithelial cells (localization of different cytoplasmic organelles in the apical and basal poles of the cell), which is characteristic for benign tumors (Fig. 8–13 b). The corneal layer is thickened (hyperkeratosis), as well as the malpighian one (acanthosis). All

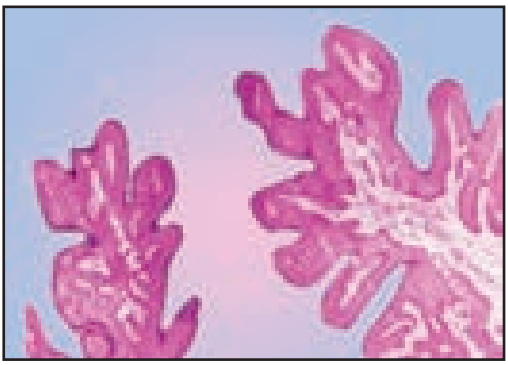


Fig. 8–13 b. Skin papilloma, microscopic aspect (hematoxylin–eosin stain; ×70).

these changes reflect the tissular atypism in papilloma.

In cases of prolonged mechanical irritation, the papilloma may become malignant, squamous carcinoma appears. Clinical manifestations depend on the location (vocal folds, urinary bladder, nasal cavities, cervix, etc.). Papillomas of excretory ducts, larynx and urinary tract are considered potential precancerous lesions.

Adenoma. It develops from glandular epithelium. It can be found in glandular organs (prostate, pancreas, liver, salivary, sweat glands, mammary gland, adrenal glands, ovaries, etc.) and at the level of mucosas covered with glandular epithelium (gastrointestinal, tracheal–bronchial, uterine, gallbladder and biliary tract mucosas etc.). In compact organs, adenoma appears as well- delimited, encapsulated (expansive growth) nodules, with the color and consistency of the original tissue. On mucosal membranes, it has the aspect of a pedunculated or with a large implantation base polyp (Fig. 8–14a, b). Adenoma may become

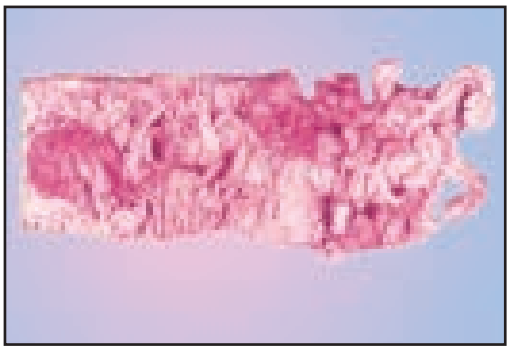


Fig. 8–14 a. Colon adenomatous polyps (adenomas), macroscopic aspect.

malignant and transform into adenocarcinoma (glandular carcinoma).

Microscopically, the tumor shows glandular structures of various shapes and sizes, some are cystically dilated; tumor cells are well differentiated, mature, reminding the original glandular epithelium. The basement membrane is intact, polarity and complexity of the epithelium is preserved (Fig. 8–14b). The following varieties of adenoma can

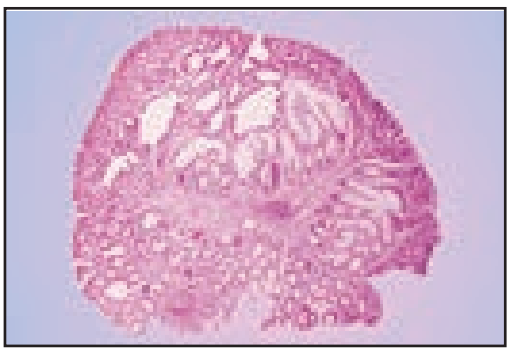


Fig. 8–14 b. Colon adenomatous polyps (adenomas), microscopic aspect (hematoxylin–eosin stain; ×70)

be distinguished: **1) acinar** *(alveolar);* **2) tubular; 3) trabecular; 4) papillary** *(villous adenoma)*. The last variant is more common in the colon, it is often associated with epithelial dysplasia and 30% of cases become malignant. The tumor is called **fibroadenoma** or **adenofibroma,** in cases when the connective stroma prevails over the glandular parenchyma in the adenoma. The fibroadenoma is the most common benign tumor of the mammary glands and can have two histological variants: intracanalicular, when the connective tissue proliferates, distorting and compressing the glandular ducts, and pericanalicular, when the connective stroma proliferates around the ducts. Adenomas of endocrine glands can be hormonally active. In such cases, different clinical syndromes, caused by excess of the respective hormones, develop in patients, e.g. acromegaly appears in somatotropic pituitary adenoma, Cushing's syndrome appears in cortical adenoma of adrenals with ACTH hyper secretion, hyperglycemic syndrome - in pancreatic insulinoma derived from beta cells with secretion of insulin etc.

8.3.2. MALIGNANT EPITHELIAL TUMORS

The general name of malignant epithelial tumors without specific location is **cancer** or **carcinoma.**

Cancer is met more frequently than other malignancies. It can develop from squamous stratified epithelia of transitional or glandular type. It is characterized by cellular and tissue atypism, infiltrative (invasive) growth, predominantly metastasis and relapse. The first lymphogenous cancer metastases emerge in regional lymph nodes, but, as tumor progresses, hematogenic and implantation metastases may also develop. Cancer often appears on the background of precancerous processes, usually of epithelium dysplasia, that evolves into cancer.

Macroscopically, it usually has the aspect of a tumor node with no precise limits, infiltrating the surrounding tissues *(invasive growth)*. It has a flaccid or dense consistency; it is whitish on section, located in the depth or on the surface of compact organs, on the surface (exophytic growth) or wall thickness (endophytic growth) – in hollow and tubular organs (Fig. 8–15, 8–16,8–17, 8–18, 8–19). Cytokeratins, a marker of epithelial tumors (cytokeratins are present in the cytoskeleton of all true epithelia), stand out in cancer cells.

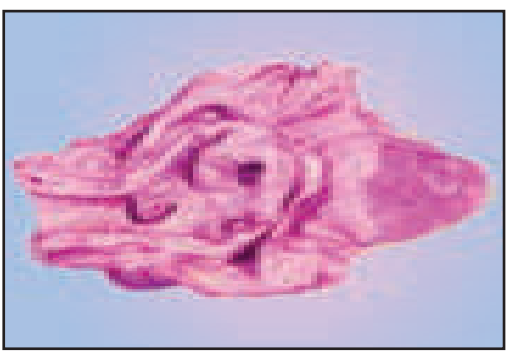


Fig. 8–15. Laryngeal carcinoma.

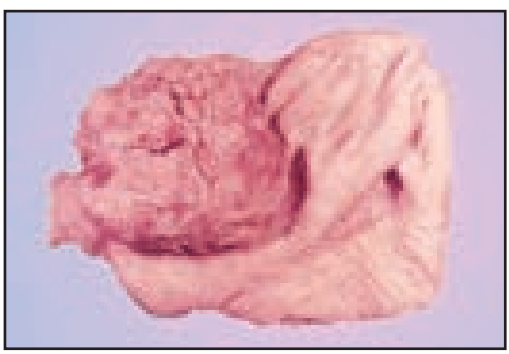


Fig. 8–16. Fungoid gastric carcinoma (mushroom aspect).

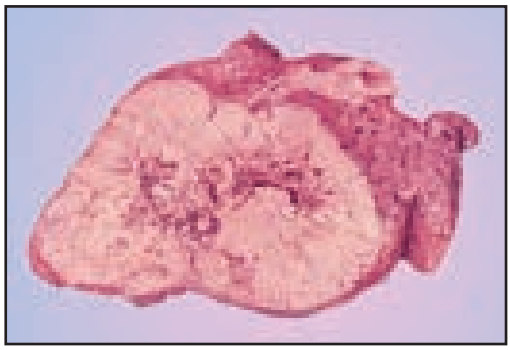


Fig. 8–17. Peripheral lung cancer – macroscopic aspect.

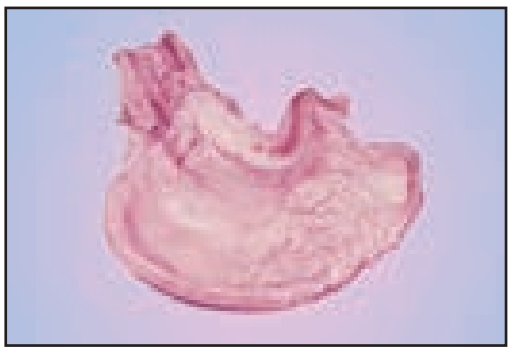


Fig. 8–18. Diffuse gastric cancer with endophytic growth – macroscopic aspect.

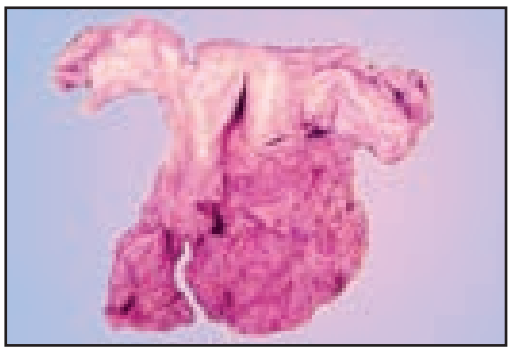


Fig. 8–19. Cervical cancer – macroscopic aspect.

Classification and general characteristics of cancer

The following cancer forms are distinguished: 1) in situ (pre–invasive), 2) squamous cell (epidermoid) cornified and non-cornified, 3) glandular (adenocarcinoma) 4) muciparous (colloid), 5) undifferentiated (anaplastic), 6) parenchymatous (medullary), 7) fibrous (scirrhous), 8) trabecular (solid), 9) dimorphic.

1) **Carcinoma *in situ* (pre-invasive, intraepithelial):** cellular atypism and polymorphism, pathological mitoses are observed only in the epithelial layer; the vertical stratification, which is characteristic for the normal squamous stratified epithelium, is blurred, unclear and the tumor invasion does not exceed the basement membrane, it remains intact (Fig. 8–20); it turns invasive (infiltrative) in dynamics.

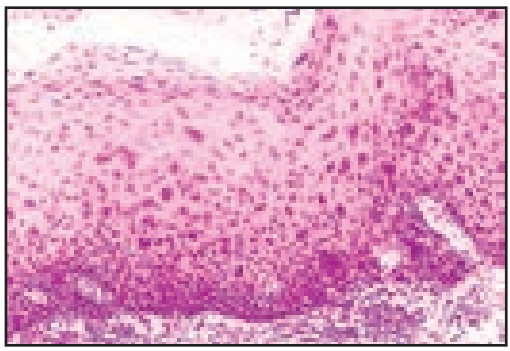


Fig. 8–20. Carcinoma in situ (hematoxylin–eosin stain; ×70).

2) **Squamous (epidermoid or squamous cell) carcinoma** originates from squamous (skin, oral cavity, esophagus, pharynx, larynx, cervix, vagina) or transitional epithelium (renal pelvis, ureters, urinary bladder), as well as from glandular epithelium with previous squamous metaplasia (bronchi, endometrium, gallbladder, etc.). The squamous carcinoma is made up of fascicles of atypical epithelial cells, which invade the adjacent tissue; it has two variants: with and without cornification (or keratinization); "keratin pearls" – an accumulation of keratin masses in the center of tumor cell islands, reflecting the keratinization ability of the epithelium, are observed in

cornified squamous cancer (Fig. 8–21a, b and 8–22); the mitosis rate is higher in non-cornified cancer; urothelial epithelium carcinomas have a papillary, villous or mushroom aspect, usually, with ulcerations; the proliferative transitional epithelium is not less than 7 cell layers thick.

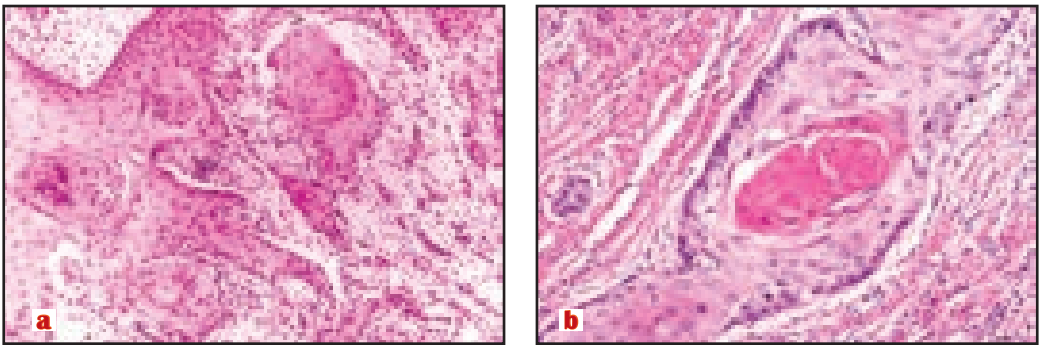


Fig. 8–21 a, b. Squamous (epidermoid) keratinizing carcinoma with keratin pearls (hematoxylin–eosin stain; ×70).

3) **Glandular carcinoma (adenocarcinoma)** derives from the prismatic, cylindrical or cubic epithelium of the mucous membranes and of glandular organs (stomach, intestine, uterus, lungs, liver, pancreas, prostate, salivary, sudoriferous, mammary and endocrine glands etc.). It can adopt the following histological forms: tubular (Fig. 8–23a), alveolar or papillary (Fig. 23b). According to the degree of differentiation, adenocarcinoma can be highly, moderately and low differentiated. The gland forming ability decreases considerably in low dif-

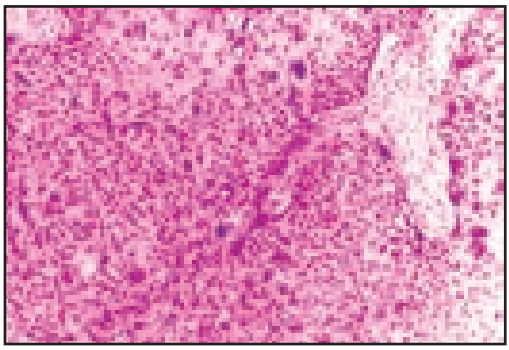


Fig. 8–22. Squamous (epidermoid) non-keratinizing carcinoma (hematoxylin–eosin stain; ×70).

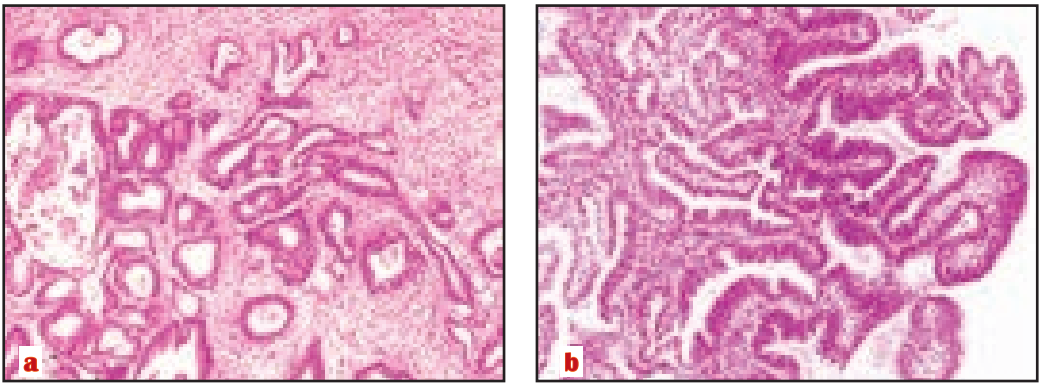


Fig. 8–23. Glandular carcinoma (adenocarcinoma): tubular (a) and papillary (b) (hematoxylin–eosin stain; ×70).

ferentiated tumors and it is difficult to detect glandular structures at the microscopic examination.

4) **Muciparous carcinoma *(colloid)*** originates from glandular epithelium; tumor cells produce large amounts of mucus. Macroscopically, it has the aspect of a mucinous or colloid mass (gelatinous appearance). Cancer cells accumulate vacuoles of mucin and may take the shape of "a signet ring" (Fig. 8–24). This form of cancer is most common in the stomach, but it can also be met in other organs.

5) **Undifferentiated (anaplastic) carcinoma** - the origin of the tumor cannot be identified. Histological variants: a) small cells, b) large cells, c) giant cells. Tumor cells are monomorphic and do not form any structures, stroma is poor (Fig. 8–25); it is a highly malignant form of cancer that develops early metastases.

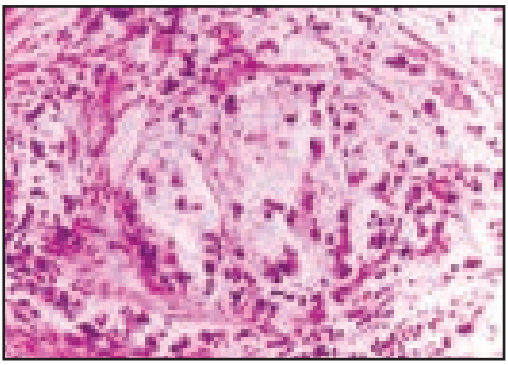


Fig. 8–24. Muciparous carcinoma (hematoxylin–eosin stain; ×70).

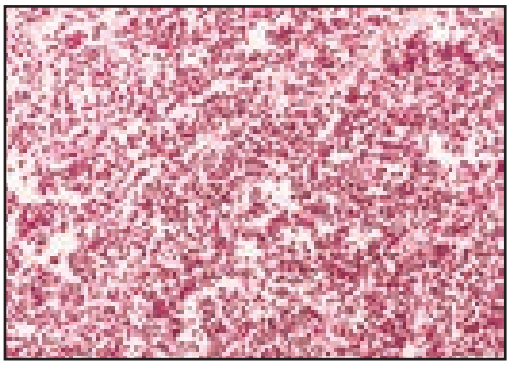


Fig. 8–25. Undifferentiated cancer with small cells (hematoxylin–eosin stain; ×70).

6) **Parenchymatous (medullary) carcinoma**: parenchyma prevails in the tumor, the stroma is poor; it has soft consistency and reminds the cerebral tissue or the bone marrow; it is a form of undifferentiated adenogenic cancer, which develops early multiple metastases (Fig. 8–26 a, b).

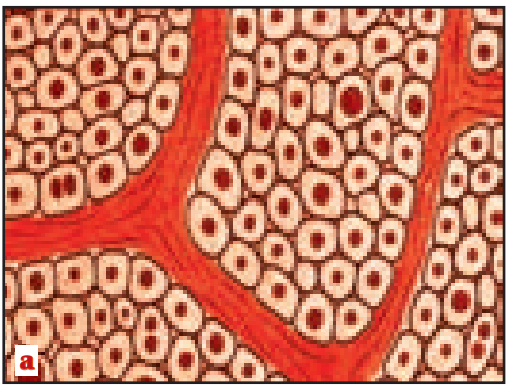


Fig. 8–26 a, b. Parenchymatous (medullary) carcinoma: a-schematic representation, b-microscopic pattern (hematoxylin–eosin stain; ×70).

7) Fibrous (*scirrhous*) carcinoma: stroma prevails in the tumor; thin cords of atypical, hyperchromic tumor cells are observed among the abundant fascicles of connective tissue (Fig. 8–27a, b); the tumor has a thick consistency; it is distinguished by high malignancy and early metastases.

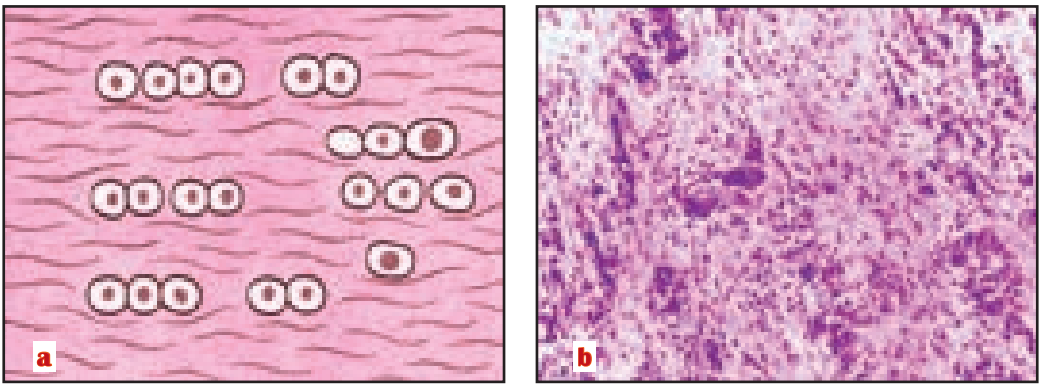


Fig. 8–27 a, b. Fibrous (scirrhous) carcinoma: a-schematic representation, b-microscopic pattern (hematoxylin–eosin stain; ×70).

8) Trabecular *(solid)* carcinoma: stroma and parenchyma are represented uniformly; fascicles of tumor cells alternate with fibroconnective fascicles (Fig. 8–28 a, b); it is a form of undifferentiated cancer, with rapid growth and early metastases.

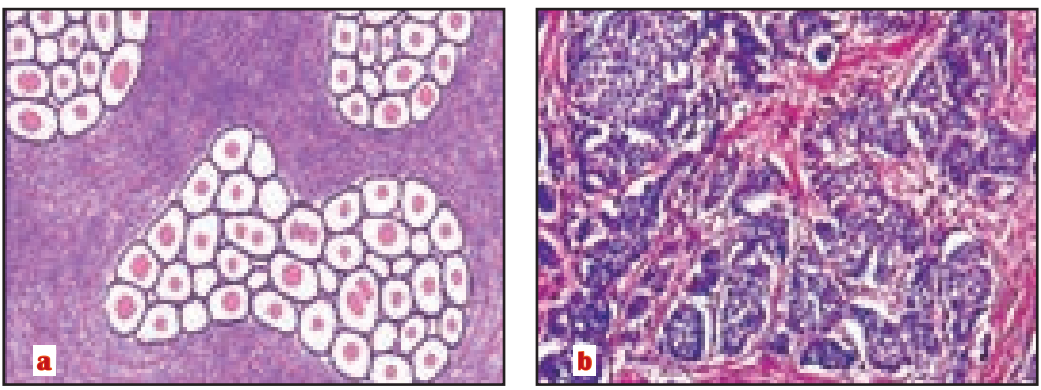


Fig. 8–28 a, b. Trabecular (solid) carcinoma: a-schematic representation, b-microscopic pattern (hematoxylin–eosin stain; ×70).

9) Dimorphic carcinoma: it is a mixed form of cancer, where glandular and squamous structures are observed. Usually, secondary dystrophic, necrotic, circulatory and inflammatory lesions appear in cancerous tumors. These lesions are more marked and appear earlier in tumors with higher malignancy.

ESSENTIAL TERMS

on the subject "NON-ORGAN-SPECIFIC EPITHELIAL TUMORS"

adenocarcinoma	expansive growth	papilloma
adenoma	glandular cancer	paraneoplastic syndrome
atypism	invasive growth	relapse
blastoma	keratin pearl	scirrhous cancer
cancer	medullary cancer	solid cancer
cancer in situ	metastasis	squamous cancer
carcinoma	muciparous (colloid) cancer	TNM classification
dimorphic cancer	neoplasm	tumor
endophytic growth	obligatory pre-cancer	undifferentiated cancer
exophytic growth	optional pre-cancer	

TESTS

on the subject "NON-ORGAN-SPECIFIC EPITHELIAL TUMORS"

SET I.

Multiple-choice questions with one correct answer.

1. *Which of the listed signs is typical for benign tumors:*
   a) expansive growth;
   b) growth with formation of secondary nodules;
   c) diffuse growth;
   d) invasive growth;
   e) metastasis.
2. *Which of the listed pathological processes is characterized by disturbance of the epithelium proliferation and differentiation processes, with appearance of cellular atypism and without alteration of basement membrane;*
   a) metaplasia;
   b) aplasia;
   c) hyperplasia;
   d) dysplasia;
   e) anaplasia.
3. *Lymphogenic metastases are a manifestation of all the below-listed processes, except for:*
   a) tissue embolism;
   b) malignant tumors;
   c) cancer;
   d) invasive growth;
   e) benign tumors.
4. *Which tissues does cancer develop from:*
   a) connective tissue;
   b) adipose tissue;
   c) striated muscular tissue;
   d) bony tissue;
   e) epithelial tissues.
5. *Which of the listed signs is characteristic for scirrhous cancer:*
   a) prevalence of parenchyma over stroma;
   b) prevalence of stroma over parenchyma;
   c) homogeneous development of stroma and parenchyma.

SET II.

Multiple-choice questions with 2, 3 or more correct answers.

1. Which of the listed signs are typical for benign tumors:
a) tissue atypism, rapid, infiltrative growth;
b) expansive, slow growth;
c) tissue atypism, slow growth;
d) tissue atypism, invasive growth;
e) slow growth, metastasis.

2. Which of the listed signs characterize tumor metastasis:
a) circulation of cells by blood and lymphatic stream;
b) emergence of new node on the extirpation site;
c) infiltrative growth;
d) implantation of tumor cells;
e) transformation of parenchymatous cells in tumoral ones.

3. Which of the listed tumors develop from glandular epithelium:
a) adenoma;
b) fibroma;
c) papilloma;
d) adenocarcinoma;
e) squamous cancer.

4. Which of the listed signs characterize adenoma:
a) develops from stratified squamous epithelium;
b) develops from glandular epithelium;
c) is a benign tumor;
d) recurs frequently;
e) metastasizes hematogenously.

5. Which of the listed signs are typical for cancer:
a) it is a malignant tumor of mesenchymal origin;
b) metastasizes more frequently by lymphogenous way;
c) develops from epithelial tissue;
d) has an expansive growth;
e) cellular atypism.

SET III.

The classification tests include 2–4 subjects and a series of answers. Indicate which answers are correct for each separate subject.

1. Which of the listed signs are characteristic for:
I – benign tumors;
II – malignant tumors;
a) frequent relapse after tumor's removal;
b) the tumor, usually, does not recur after removal;
c) marked cellular atypism;
d) tumor consists of mature, differentiated cells;
e) tumoral cachexia is characteristic;
f) tumor metastasis is typical;
g) compression and atrophy of adjacent tissues.

2. Which of the morphological manifestations of tumor characterize:
I – tissue atypism;
II – cellular atypism;
a) presence of pathological mitosis;
b) chaotic location of fibrillar structures in tumors;
c) tumor cells are mature, differentiated, form structures that are unusual for the respective tissue (organ);
d) change of the connection between stroma and parenchyma of tumor;
e) tumor cells differ significantly from the original tissue cells;
f) tumor cell anaplasia.

3. Which of the listed morphological processes characterize:

I – expansive growth of tumors;
II – invasive growth of tumors;
a) tumor cells invade adjacent tissues;
b) tumor does not have clear limits;
c) tumor node can be removed (enucleated) easily;
d) tumor cells destroy blood and lymphatic vessel walls;
e) the tumor has usually a well–defined, node-like form;
f) compressed adjacent tissues form a pseudocapsule.

4. Which of the listed morphological signs are characteristic for:
I – squamous cancer;
II – adenocarcinoma;
a) typical location – gastrointestinal mucosa;
b) typical location – skin;
c) tumor cells preserve the ability of mucus secretion;
d) it is preceded by squamous metaplasia of epithelium on the mucosas covered by prismatic epithelium;
e) tumor cells preserve the cornification ability;
f) develops from glandular epithelium;
g) develops from stratified squamous epithelium.

5. Which version of tumor growth towards the lumen of hollow organs is listed in the examples below:
I – endophytic growth;
II – exophytic growth;
a) urinary bladder papilloma;
b) adenomatous polyp of the colon;
c) scirrhous gastric cancer;
d) peribronchial lung cancer;
e) intrabronchial lung cancer;
f) polypoid or fungoid gastric cancer;
g) cardiac myxoma with growth in left atrium cavity;
h) cardiac rhabdomyoma with growth in left ventricle wall thickness.

SET IV. SITUATIONAL PROBLEMS

Daily practice cases are presented with clinical and morphological data from clinical histories and/or from necropsy protocols. Each subject includes simple or multiple - answer questions, with 1, 2 or more correct answers.

1. The biopsy of a tumoral formation with a diameter of 0,8 cm, papillary surface, resembling cauliflower, was collected at the endoscopic examination of the urinary bladder. Microscopically, the tumor consists of branched papillae, covered with several layers of transitional-type epithelial cells; the basement membrane is unaltered.

Question:

What kind of tumor has developed in this case:
a) adenoma;
b) papilloma from transitional epithelium;
c) cancer in situ;
d) cancer from transitional epithelium;
e) squamous cancer.

2. The histological examination of an endoscopic biopsy from the stomach revealed signs of cellular and tissue atypism and cancer diagnosis was established.

Question:

Which of the listed signs play a decisive role in the respective diagnosis:

a) gastric mucosa glands vary in shape and size;
b) gastric glands are arranged chaotically;
c) gastric glands are covered by polymorphic cells with large, hyperchromic nuclei and an increased number of nucleoli, atypical mitoses;
d) gastric glands are located very close to each other;
e) sometimes, epithelial cells are arranged in several rows.

3. *The histological examination of a malignant tumor of the mammary gland revealed that the tumor consists of undifferentiated, atypical cells of epithelial origin, which form trabeculas, separated by fibroconnective fascicles; the correlation between cells and stroma is 1:1.*

Question:

Which histological variant of cancer is in this case:

a) adenocarcinoma;
b) squamous cancer;
c) scirrhous cancer;
d) solid cancer;
e) medullary cancer.

4. *Biopsy was collected from a 47-year-old patient, with erosion of the vaginal portion of the cervix. The microscopic examination of biopsy revealed thickening of the stratified squamous epithelium, basal cells proliferation, marked atypism and polymorphism of epithelial cells, hyperchromatosis of nuclei, numerous pathological mitoses; the basement membrane is not crossed by neoplastic cells.*

Question:

What diagnosis should be made in this case:

a) cancer in situ;
b) noncornified squamous cancer;
c) scirrhous cancer;
d) adenocarcinoma;
e) epithelial dysplasia.

5. *Biopsy was collected from a suspect site of bronchial mucosa, of a 67-year-old patient with the clinical diagnosis of chronic bronchitis, pneumosclerosis and cardiopulmonary failure. Histologically, cellular and tissue atypism, "keratin pearls" structures were revealed.*

Question:

What pathological process develops in the given patient:

a) polypoid chronic bronchitis;
b) cancer in situ;
c) squamous metaplasia of bronchial epithelium;
d) cornified squamous cancer;
e) noncornified squamous cancer.

8.4. MESENCHYMAL TUMORS

Mesenchymal tumors are the tumors that develop from tissues of mesenchymal origin: lax and dense connective tissue, white and brown adipose tissue, blood and lymph vessels, smooth and striated (the cardiac one included) muscular tissue, cartilaginous, bony tissue, synovial and serous membranes. The pluripotent mesenchymal cell is the development source of these tumors. Generally, the mesenchymal tumors are more infrequent than the tumors of epithelial origin; they have no specific location and can be found in any organ. Mostly, they have a monophasic structure, formed from a single tissue, but they also may be polyphasic with more tissular components (*called* **mesenchymal**). Mesenchymal tumors may be heterotopic, consisting of a tissue, which is not characteristic for the given organ, for example, lung osteoma, retroperitoneal synovioma etc. Usually, they have a histioid structure, with prevalence of parenchymatous elements in their composition; the stroma is weakly developed.

Mesenchymal tumors are subdivided into benign and malignant *(Table 8.2)*.

Table 8.2.

Classification of mesenchymal tumors

Tissue of origin	Benign tumors	Malignant tumors
Connective tissue	Fibroma (soft, hard) Dermatofibroma (histiocytoma) Elastofibroma Fibromatosis (desmoid tumor)	Fibrosarcoma Malignant histiocytoma
Adipose tissue	Lipoma Hibernoma	Liposarcoma Malignant hibernoma
Muscular tissue	Leiomyoma Rhabdomyoma	Leiomyosarcoma Rhabdomyosarcoma
Blood vessels	Hemangioma (capillary, venous, cavernous, arterial) Hemangiopericytoma Glomangioma	Hemangiosarcoma (malignant hemangioendothelioma or hemangiopericytoma)
Lymphatic vessels	Lymphangioma	Lymphangiosarcoma
Bone tissue	Osteoma (compact, spongy) Osteoid osteoma (benign osteoblastoma)	Osteosarcoma (osteoblastic or osteolytic)
Cartilaginous tissue	Chondroma (ecchondroma, enchondroma) Benign chondroblastoma	Chondrosarcoma
Mesothelial tissue	Benign mesothelioma	Malignant mesothelioma
Synovial membranes	Benign synovioma	Synovial sarcoma (malignant synovioma)

8.4.1. BENIGN MESENCHYMAL TUMORS

Benign tumors of mesenchymal origin, like all benign tumors, have a slow, expansive growth, they are well defined, encapsulated, microscopically composed of mature, differentiated cells, similar to the tissue of origin; they are characterized only by tissue atypism. These tumors grow slowly, can reach large dimensions, do not recur, nor metastasize. Dystrophic, necrotic lesions, circulatory disorders, edema, myxomatosis, dystrophic calcinosis etc. can occur in all the benign mesenchymal tumors. Also, mesenchymal tumors subdivide in soft tissue tumors (nonskeletal) and hard tissue tumors (osteocartilaginous).

Fibroma is a benign tumor that derives from connective tissue. Macroscopically, it is a well–defined, encapsulated (expansive growth) tumor nodule, of few mm to 10–15 cm of diameter, whitish, soft or hard consistency. One distinguishes *soft* fibroma, where cellular elements prevail and *hard* fibroma, formed predominantly of collagen fibers. On section, it has a fibrillar structure, an obvious tissue atypism; the connective fascicles are arranged chaotically, sometimes in eddies (Fig. 8–29 a). Microscopically, the tumor consists of connective tissue cells (fibroblasts and fibrocytes) and collagen fibers, arranged in unevenly thick and disorderly oriented fascicles (Fig. 8–29 b).

Fibroma location may be the most diverse, but it is found more frequently in skin, uterus, mammary gland, fascias, tendons. Manifestations and clinical importance depend on the localization.

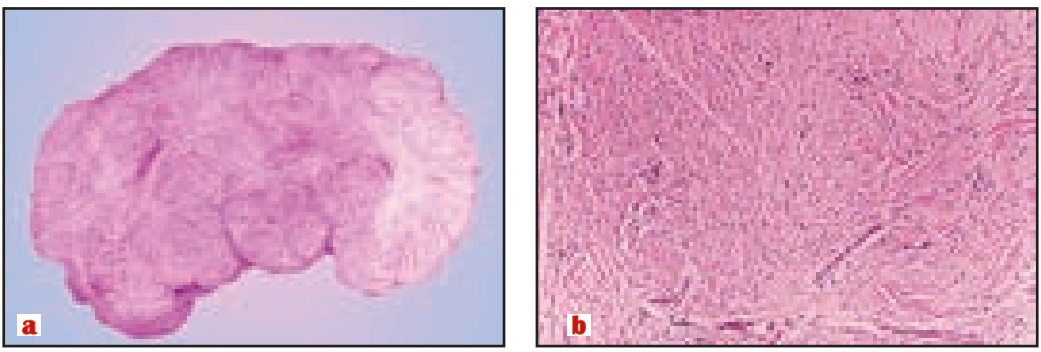


Fig. 8–29 a, b. Fibroma: a – macroscopic aspect, b – microscopic pattern (hematoxylin–eosin stain; ×70).

Elastofibroma is a nodular tumor, which can reach 10–15 cm in diameter, and is usually located in the subscapular and interscapular regions. It is found in older people, frequently women. Microscopically, it consists of fibrous tissue, where the elastic fibers prevail (stained with orcein).

Histiocytoma (dermatofibroma) is located in the skin, subcutaneous tissue, most commonly on the level of lower extremities. Macroscopically, it has the form of a small dimension, brown colored tumoral node, with a diameter up to 1 cm, which protrudes above the skin. Microscopically, it consists of two cell types (fibroblasts and histiocytes), fascicles of collagen fibers and a large number of blood capillaries. Histiocytic cells contain lipid inclusions (xanthomatous cells), hemosiderin granules (siderophages), which stain brown

the tumor; giant multinucleated cells (Touton cells) are met. The Pearls reaction (highlights hemosiderin) is used for the purpose of a differential diagnosis.

Fibromatoses are tumors of fibroconnective origin, with locally invasive growth. They are met in fascias, aponeuroses. The microscopic structure is identical to the fibromas one, but does not have a capsule and infiltrates the adjacent tissues. Variants: desmoid, palmar, plantar, penile fibromatosis.

Desmoid tumor (desmoid) is the most common variant of fibromatosis and is a part of the group of locally destructive tumors. It is distinguished by infiltrative growth, although, by its histological structure, the tumor is mature (cellular atypism, polymorphism and mitoses are missing). According to the location, there are three varieties of desmoid: abdominal, intra-abdominal and extra-abdominal. More frequently, abdominal desmoid is met in women, in the anterior abdominal wall, especially in striated muscles, during pregnancy and postpartum. The tumoral node does not have precise limits, infiltrating and dissociating adjacent muscle fibers, where dystrophic changes occur (Fig. 8– 30). Desmoid recurs frequently after surgical removal, due to the invasive nature. The intra-abdominal desmoid is observed in mesentery, pelvis, and the extra-abdominal desmoid - in the humerus, chest wall, femur, spine region.

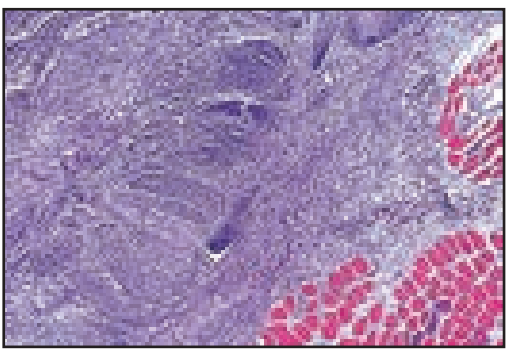


Fig. 8–30. Desmoid tumor (Masson's trichrome stain; ×70).

Lipoma is a benign tumor composed of adipose tissue. Macroscopically, it is an oval tumoral nodule of soft consistency, well–defined, encapsulated and yellow on section, lobulated (Fig. 8–31a).

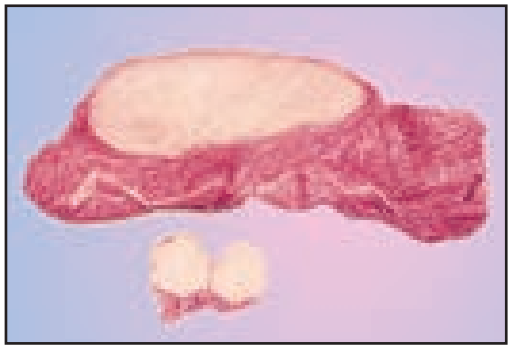


Fig. 8–31 a. Lipoma – macroscopic aspect.

Microscopically, the tumor is composed of fat cells (adipocytes) of different sizes, their nucleus is shifted to the cell periphery; the cytoplasm is a massive lipid vacuole; the stroma is usually poor and forms thin fibrous septa, containing blood vessels (Fig. 8–31b). In some cases, the tumor has a rich stromal, fibroconnective component (fibrolipoma), in others – a vascular component (angiolipoma).

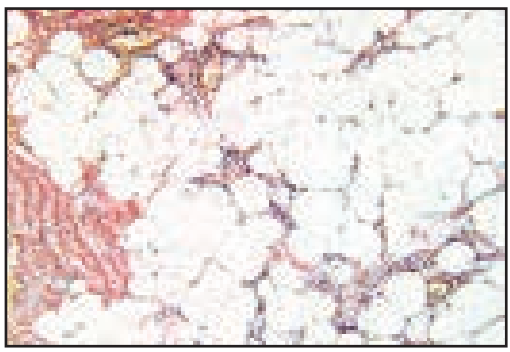


Fig. 8–31 b. Lipoma – microscopic aspect (hematoxylin–eosin stain; ×70).

Lipoma can reach very large dimensions (several kilograms). It is met, more

frequently, in subcutaneous adipose tissue, mediastinum, retroperitoneal space, mesentery, epiploon, mammary gland; it can also be located intramuscularly.

Hibernoma is a benign tumor, which is derived from brown adipose tissue (it is also called brown lipoma). It consists of cells with vacuolated cytoplasm (multilocular adipocytes); the nucleus is in the centre of the cell; vacuoles are fat droplets rich in lipochromes (Fig. 8–32). Macroscopically, the tumor nodule has a brown-yellowish color. The tumor can

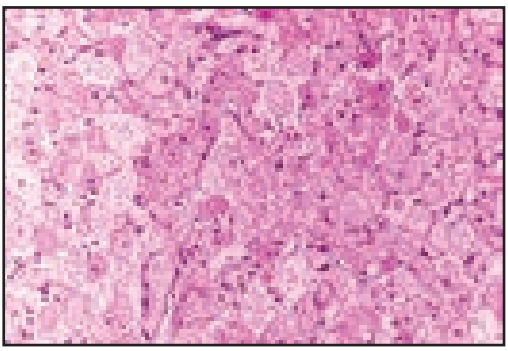


Fig. 8–32. Hibernoma (hematoxylin–eosin stain; ×70).

be localized in the interscapular region, mediastinum and neck area – the regular sites of brown adipose tissue in humans. This tissue is more abundant in infants and is observed exceptionally in the adults. Hibernoma is observed more frequently in women of advanced age, in the interscapular region.

Myomas are benign tumors of muscular origin, which subdivide in leiomyomas and rhabdomyomas.

Leiomyoma is a benign tumor of smooth muscle tissue. Most frequently, it is found in the uterus, but it is also observed in the digestive tract, urinary bladder, prostate, etc. It develops from smooth muscle itself or from blood vessel walls. The name of *fibroleiomyoma* is more correct, as the proliferation of muscular parenchyma takes place at the same time with the proliferation of the fibroconnective stroma. Leiomyoma is the most common uterine tumor, which usually increases during pregnancy and decreases in the menopause, due to the fact that it is sensitive to estrogens.

Macroscopically, the nodules are well-defined, encapsulated, of yellowish– whitish color. The consistency of nodules is usually hard, but it can be lax in case of secondary changes - hemorrhages, edema, necrosis foci and myxomatosis. The uterine fibromyoma is usually multiple, the tumor nodules are located submucously, intramurally or subserously and can reach giant sizes. On section, they have a fibrillar structure, muscular and connective fascicles are distributed chaotically, in eddies (Fig. 8–33). Microscopically, the leiomyomatous tumor nodule consists of fascicles of smooth muscular fibers, arranged disorderly and unevenly, interspersed with

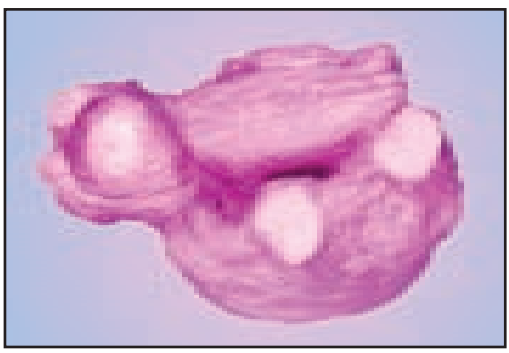


Fig. 8–33. Uterine leiomyoma– macroscopic aspect.

collagen fiber fascicles and connective tissue cells, also distributed chaotically (tissue atypism). In order to differentiate fibroleiomyoma from fibroma, picrofucsin stain (van Gieson's method) is applied: the collagen fibers stain red and the leiomiocytes – yellow; collagen fibers only are detected in fibroma. One of the more commonly observed uterus fibroleiomyoma complications is the uterine

bleeding (metrorrhagia). Leiomyoma can transform into leiomyosarcoma.

Rhabdomyoma is a benign tumor that derives from striated muscles and is found predominantly in the myocardium (Fig. 8–34), skeletal musculature and tongue. It is a relatively rare tumor.

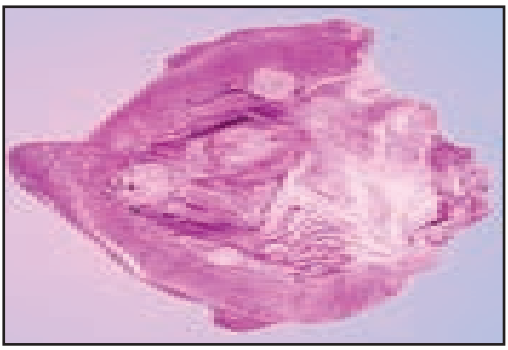


Fig. 8–34. Myocardial rhabdomyoma– macroscopic aspect.

Hemangiomas are benign tumors that derive from blood vessels. All the vascular wall elements can participate in the formation of hemangioma. These tumors occupy an intermediate position between hamartoma (congenital malformations) and true tumors. The following variants of hemangioma are distinguished: *capillary, venous, cavernous and arterial, glomangioma, benign hemangiopericytoma*. Capillary hemangioma is composed of capillary–type vessels of various sizes; their wall is lined by endothelial cells (Fig. 8–36). It is met, more frequently, in children's skin, mucosa of the digestive tract, liver. The tumor nodule is red or cyanotic, with smooth or papillary surface. *Cavernous hemangioma* has a spongy structure and is composed of large vascular, dilated cavities of different sizes, interconnected, filled with blood, lined by endothelial cells (Fig. 8–37). It can be found in the liver (Fig. 8–38 a and 8–38 b), skin, spongy bones, skeletal muscles etc.

Glomangioma (glomus tumor) is observed more frequently at the fingers' level, especially in the nail area. Macroscopically, it is a small, bluish,

Microscopically, it consists of striated muscle cells of various shapes and sizes (Fig. 8–35), with vacuolated sarcoplasm, due to high content of glycogen. The diagnosis is confirmed using techniques that highlight the transversal striation of myocyte sarcoplasm.

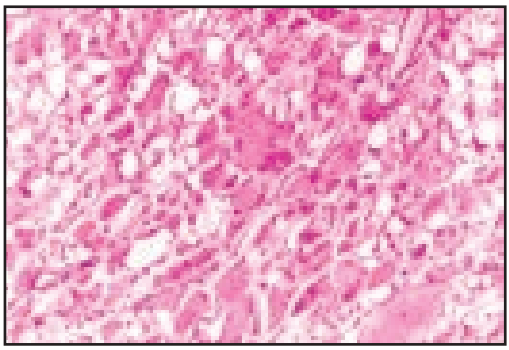


Fig. 8–35. Rhabdomyoma (hematoxylin–eosin stain; ×70).

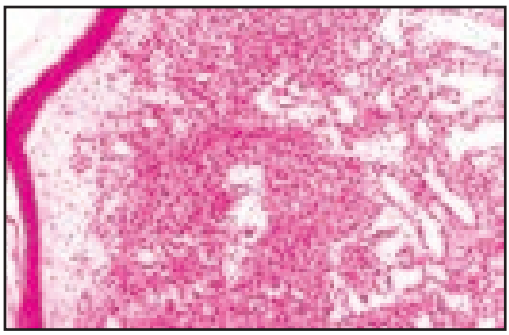


Fig. 8–36. Capillary hemangioma (hematoxylin–eosin stain; ×70).

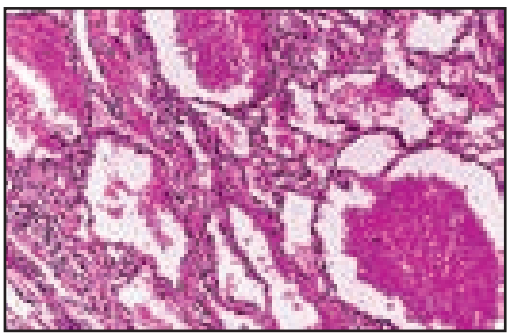


Fig. 8–37. Cavernous hemangioma (hematoxylin–eosin stain; ×70).

often painful nodule. Microscopically, it is formed of anastomosed vessels, in

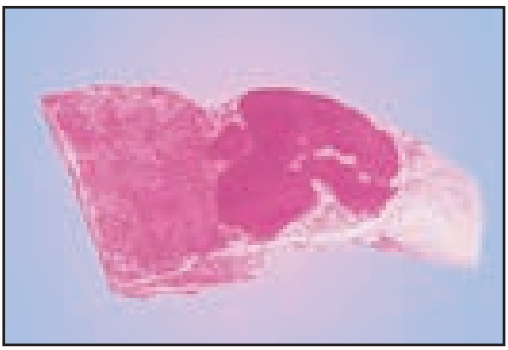


Fig. 8–38 a. Cavernous hemangioma of liver–macroscopic aspect.

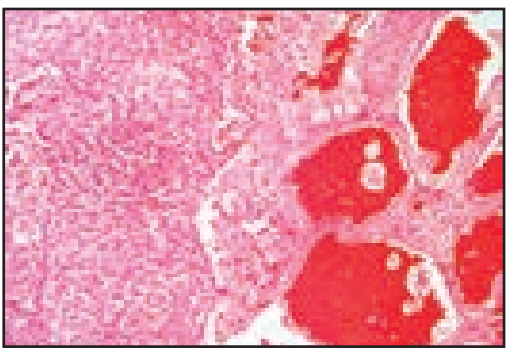


Fig. 8–38 b. Cavernous hemangioma of liver–microscopic aspect (hematoxylin–eosin stain; x50).

the form of slits lined with endothelium, surrounded by epithelioid cell sheaths, reminding the glomic cells; the tumor is richly innervated.

Benign hemangiopericytoma lodges more frequently in the skin, rarely – in soft tissues of the limbs, trunk and in omentum. Macroscopically, the reddish nodule has dense consistency and is well–defined. Microscopically, it is formed of capillaries and sinusoids, lined by endothelium and surrounded by sheaths of elongated cells, called pericytes; cellular sheaths, in their turn, are interwoven by a network of argyrophilic fibers. Argyrophilic fiber impregnation and PAS reaction for carbohydrates are applied for differential diagnosis with capillary hemangioma. These tumors can recur and therefore, according to some views, are considered malignant.

Lymphangioma is a tumor derived from lymphatic vessels and found especially in children. It is analogous to hemangioma. It lodges in the cervical area, buccal mucosa, tongue and mesentery. The most common variant is the cavernous or cystic lymphangioma, where cavities of different sizes, filled with lymph and lined with endothelium, are observed. Macroscopically, it has the form of a nodule or of diffuse thickening of an organ. It can manifest itself by increased size of tongue or lips – macroglossia and macrocheilia.

Chondroma is a benign tumor from cartilaginous tissue (Fig. 8– 39). It is met more frequently in the limb bones (phalanges of hands and feet), pelvis, ribs, vertebrae, but it may also be lodged extraosseously, especially in lungs. Macroscopically, it is a whitish-bluish, well–defined tumor nodule of dense consistency, reminding the hyaline cartilage. In the bones, it may be located on the surface of bone (ecchondroma) or intraosseously (enchondroma). Micro-

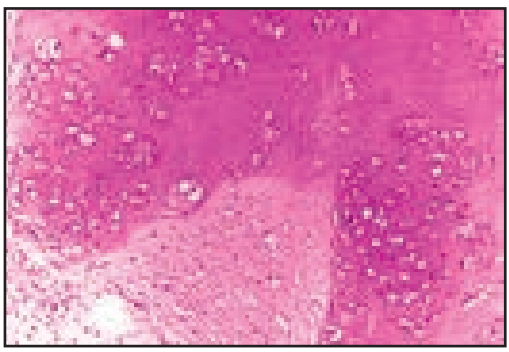


Fig. 8–39. Chondroma (hematoxylin–eosin stain; ×70).

scopically, it consists of hyaline cartilage; cells are arranged chaotically in the ground substance.

Benign chondroblastoma is a benign chondrogenic tumor, located more frequently in the humerus, tibia and femur. It is usually found in young people, in the second decade of life, when skeletal growth is not finished yet. Microscopically, it contains cellular masses composed of chondroblasts with varying degrees of differentiation, arranged in the intercellular matrix, formed of chondroid tissue.

Osteoma is a benign tumor from osseous tissue. It is found in flat, tubular bones and, more frequently, in the cranial bones, paranasal sinuses. The extraosseous location may be in the tongue, mammary gland. Microscopically, it has a structure of spongy or compact bone tissue; the osseous trabeculas are arranged disorderly. It may have an exophytic growth on the surface of the bone (exostosis) or endophytic, intraosseous growth (enostosis).

Benign osteoblastoma or osteoid osteoma is met, more frequently, in children, adolescents and young adults. It has small dimensions up to 1 cm. Location may be the most diverse, but more frequently - in the femoral bone, humerus, tibia, vertebrae. Microscopically, it consists of osteoid anastomosed trabeculas, surrounded by reactive bone tissue at the periphery.

Benign synovioma is a benign tumor that develops from synovial elements of tendon sheaths and tendons. It is met, more frequently, in the knee joint area. Its microscopic structure is polymorphic, with elongated cells, similar to fibroblasts, synovial cells, forming pseudoadenomatous structures, and giant multinucleated cells. The tumors can relapse.

Benign mesothelioma is a benign tumor from mesothelium. It affects the serous membranes, especially the pleura. Macroscopically, it has the aspect of a tumor nodule, of whitish color and thick consistency. Microscopically, it is identical to soft (cellular) fibroma. The mesothelial origin of tumor cells can be demonstrated only in cell cultures.

8.4.2. MALIGNANT MESENCHYMAL TUMORS

Malignant tumors of mesenchymal origin are called **sarcomas**.

They are characterized by cellular and tissue atypism, rapid, infiltrative growth, so they do not have precise boundaries, are not delimited by surrounding tissues, are not encapsulated; macroscopically, the appearance of the tumor mass is of fish meat (*hence the name in Greek sarcos – meat*), of whitish color and flaccid consistency. Microscopically, it is characterized by cellular, marked polymorphism and atypism. Sarcoma's malignancy amplifies along with the similarity decrease of tumor cells with the original ones and is in direct proportion to the rate of mitosis (10 and more mitoses in a visual field of 40-lens). Early circulatory disorders (hemorrhages), edema, dystrophic and necrotic lesions, myxomatosis, cystic cavities develop in all sarcomas. Sarcomas recur and metastasize more frequently through the blood; the first metastases emerge in the lung or liver. Sarcomas are

relatively rare tumors and constitute 1% of all malignant tumors. More than two thirds of sarcomas are localized in the femoral area, scapular girdle and retroperitoneal space. The forecast (prognosis) of sarcomas depends primarily on the histopathological degree of differentiation and the tumor stage, but also on the size and depth of the tumor process (the prognosis is worse in larger dimensions and deeper location in the tissue).

Fibrosarcoma is a malignant tumor of the connective tissue, more frequently located in the subcutaneous tissue and in the depth of soft tissues of the limbs and trunk, more rarely – in the internal organs (Fig. 8–40 a, b). Microscopically, it consists of polymorphic, fusiform, fibroblastic-type immature cells and an insignificant quantity of collagen fibers; the tumor has a histioid structure (cellular elements prevail), relatively uniform, although increased, hyperchromic nuclei and single atypical mitoses are observed; neoplastic cells are usually arranged in disorderly-oriented fascicles. Vimentin is detected in the tumor cells, at immunohistochemical examination. The prognosis depends on the tumor stage and its extension at the moment it was detected.

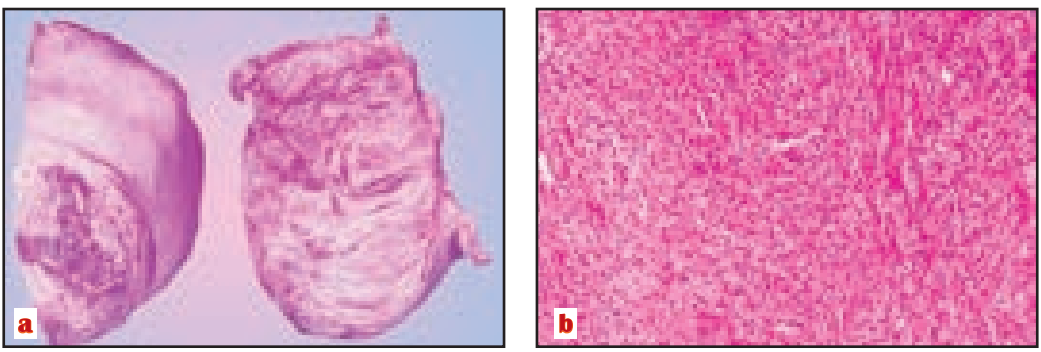


Fig. 8–40 a, b. Fibrosarcoma: a – macroscopic aspect, b – microscopic pattern (hematoxylin – eosin stain; ×70).

Malignant histiocytoma lodges more frequently in lower limbs and retroperitoneal tissue, where it can reach large sizes (10–15 cm). It is currently considered the most common malignant tumor of soft tissues in adults. Microscopically, it is formed from histiocytic and fibroblastic cells, xanthomatous cells and Touton-type giant multinucleated cells; cellular and nuclear marked atypism and polymorphism, multiple mitoses, including atypical ones, are observed. The most common histological form is fibrous histiocytoma with dimorphic cellular component – elements of fibroblastic and histiocytic type. Metastases are observed in 40–50% of cases, more frequently in lungs (up to 87%) and lymph nodes (30%).

Liposarcoma is a malignant tumor derived from adipose tissue, from precursor cells of adipocytes. It consists of poorly differentiated fat cells, with uneven fat content; cells with homogeneous eosinophilic cytoplasm, without lipids or with a small amount of them, bizarre, monster, hyperchromic nuclei are observed (Fig. 8–41). More frequently, it is met in subcutaneous adipose, retroperitoneal, mediastinal tissues. Necrotic lesions, myxoid degeneration of tumor stroma are characteristic. Histological variants of liposarcoma: predominantly highly-differentiated, predominant-

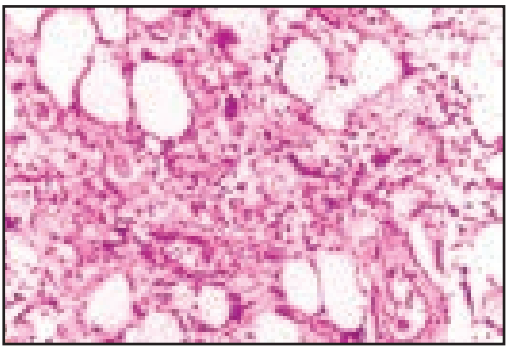


Fig. 8–41. Liposarcoma (hematoxylin–eosin stain; ×70).

ly myxoid (embryonic), predominantly round cell and predominantly polymorphocellular. Differentiated liposarcoma presents slow growth and late metastasis; the undifferentiated liposarcoma develops early metastases.

Malignant hibernoma (fetal lipoma) has the same location as the benign hibernoma. Histologically, a marked polymorphism of multilocular lipocytes is observed. Metastases are rare. It is considered a variant of polymorphocellular liposarcoma.

Leiomyosarcoma is a malignant tumor of smooth muscular tissue, with a more frequent location in the uterus, gastrointestinal tract and retroperitoneal space (Fig. 8–42). By frequency, it ranks 3rd in the retroperitoneal tissue, preceded by malignant fibrous histiocytoma and liposarcoma. It can develop by malignant transformation of benign muscle tumor (leiomyoma) or as a malignant tumor from the start. It is composed of muscle cells with a little differentiation, with an obvious cellular and nuclear polymorphism, some big, monstrous, hyperchromic nuclei, pathological mitoses; the connective stroma is weakly developed. An important criterion of the degree of malignancy is the number of mitosis. Immunohistochemically, actin is detected in tumor cells.

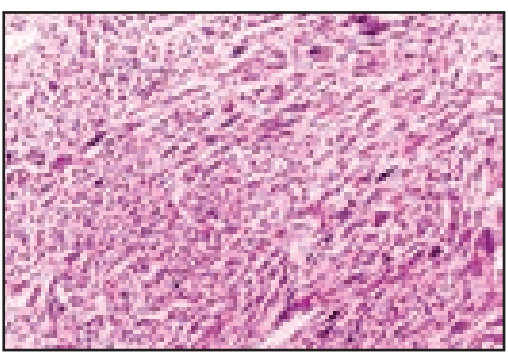


Fig. 8–42. Leiomyosarcoma (hematoxylin–eosin stain; ×70).

Rhabdomyosarcoma is a rare malignant tumor that originates from striated muscular tissue. It is met in children on the head, neck, retroperitoneal tissue, in adults – in the limbs. Microscopically, it consists of stellate and polymorphic fusiform cells, some of them with transversal striation. The certain diagnosis can be established by desmin and myosin highlighting in the tumor cells, on application of immunohistochemical reactions.

Hemangiosarcoma is a malignant, relatively rare tumor of vascular origin, lodged in the skin, skeletal muscle and liver. Microscopically, it consists of atypical endothelial and pericyte cells - *malignant hemangioendothelioma and malignant hemangiopericytoma*. Malignant hemangioendothelioma is considered one of the most malignant tumors with rapid growth and multiple, abundant and early metastases.

Lymphangiosarcoma (malignant lymphangioendothelioma) appears due to chronic lymphostasis after mastectomy. Histologically, it consists of fissured lymphatic vessels, lined with atypical and polymorphous endothelial cells; it resembles the hemangioendothelioma.

Chondrosarcoma is a malignant tumor of cartilaginous tissue, originating

in the precursor cells of chondrocytes; it is found more frequently in the long limb bones (femur and humerus upper end), ribs, scapula, pelvic bones, vertebral column (Fig. 8–43). It may be located in the medullary or periosteum area, in the bones. It is characterized by slow growth and late metastases.

Osteosarcoma (osteogenic sarcoma) is the most frequent malignant tumor of the bone tissue and derives from pluripotent precursor cells of osteocytes. Most frequently, it is located in the femur, humerus (Fig. 8–44), tibia, pelvic and scapular bones. Microscopically, atypical and polymorphic tumor cells are observed. The cells secrete various cytokines and growth factors, which stimulate the proliferation of osteoblasts (*osteoblastic osteosarcoma*), osteoclasts (*osteolytic os-*

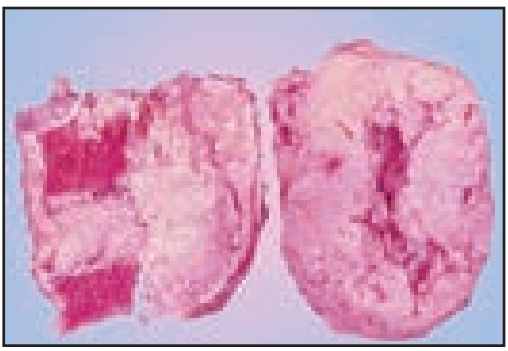


Fig. 8–43. Chondrosarcoma– macroscopic aspect..

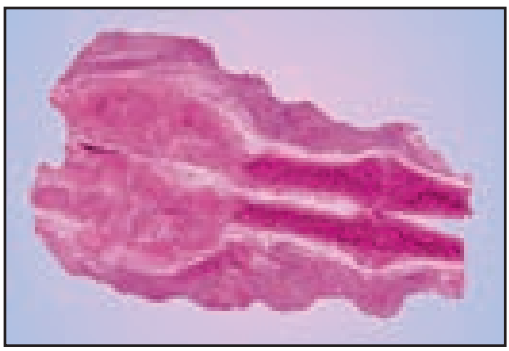


Fig. 8–44. Osteosarcoma– macroscopic aspect.

teosarcoma) or capillaries (*teleangiectatic osteosarcoma*).

Malignant synovioma (synovial sarcoma) is found in large joints, but can develop extraarticularly, in soft tissues and retroperitoneal space. It can have monophasic or biphasic histological structure and be composed of gland-like epithelioid structures, in cells where cytokeratin, a marker of epithelium, and atypical cells resembling fibroblasts, are determined. It has a rapid growth and early metastases.

Malignant mesothelioma is observed in the peritoneum, pleura and pericardium. It tends to early expand and disseminate through lymphatic vessels; "tumor lymphangitis" develops and leads to appearance of multiple nodules on the serous membrane surface. Often, the tumor infiltrates the underlying tissues. Typical metastases appear in regional lymph nodes.

8.5. TUMORS OF MELANIN-FORMING TISSUES

The melanocytes of neuroectodermal origin are the development source of these tumors. They are localized in the basal layer of the epidermis, hair follicles, most mucous membranes, covered with stratified squamous epithelium, leptomeniges, retina, vascular membrane of the eye. ***Pigmented nevi and malignant melanomas*** may develop from melanocytes. The melanocytic cells express S–100 and HMB–45 antigens. Their immunohistochemical identification in tumor cells allows the correct diagnosis.

Pigmented nevi are benign tumors that are most frequently met on the skin of the face and trunk. Histologically, they

are agglomerations of melanocytic cells, called nevus cells or nevocytes (cells that derive from Schwann cells of cutaneous nerves and can synthesize melanin). The nevus cell groups can be located at the level of dermo–epidermic junction, intradermally or an association of junctional and intradermic locations. The following varieties of nevi are distinguished:

1) **junctional nevus** – macroscopically, it has the aspect of a slightly prominent brown spot or plaque, with smooth surface and hairless, several millimeters in diameter. Microscopically, it consists of nests of nevus cells, located at the level of dermo-epidermal junction, especially at the top of epithelial ridges (Fig. 8–45 a, b). The basal layer of the epidermis has a normal structure and may contain a greater number of melanocytes. The junctional nevi, located on the palms, soles and mucous membranes have a high malignancy potential.

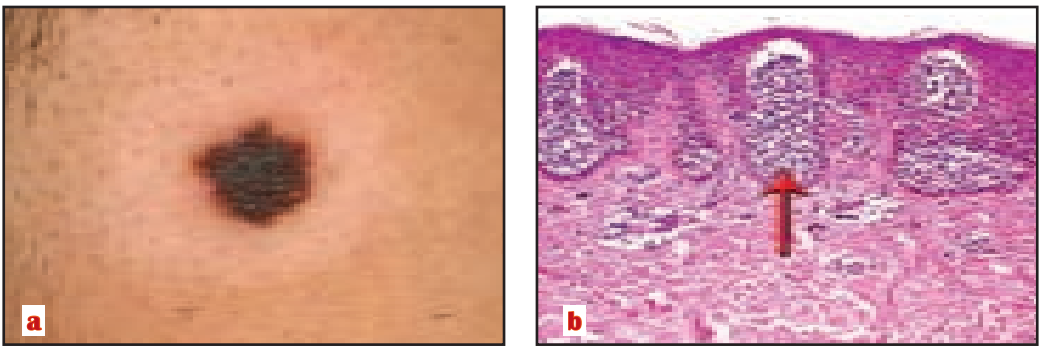


Fig. 8–45 a, b. Junctional nevus: a – macroscopic aspect, b – microscopic pattern (hematoxylin–eosin stain; ×70).

2) **dermal nevus** – the most commonly met, especially on the head, neck, trunk. Macroscopically, it has the form of brown–black warts, with a sessile or pedunculated base, smooth or rough surface, often covered with hair, down to a few mm size. Microscopically, it is formed from nests and cords of nevus cells located only in dermis, usually, in the upper areas of the dermis, around the pilosebaceous elements, without being in contact with the epidermis (Fig. 8–46). Nevocytes contain a lot of melanin, giant multinucleated cells are met.

3) **compound or mixed nevus** combines features of junctional and dermal nevus and is formed of junctional nevus cells and nests of nevocytes lodged deeply in the dermis; it is rich in melanin.

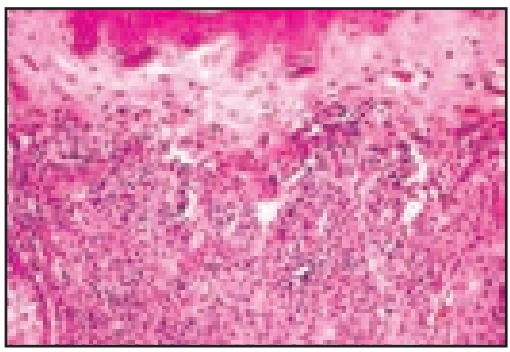


Fig. 8–46. Dermal nevus (hematoxylin–eosin stain; ×70).

4) **juvenile or epithelioid cellular nevus** is composed of epithelioid and fusiform cells with little melanin; giant multinucleated cells of Langhans or Tou-

ton type may be found. It lodges both at the level of dermo-epidermal junction and in the dermis, more frequently in the face and leg area, being observed mainly in children and adolescents.

5) **blue nevus** is composed of proliferating melanocytes, deeply lodged in the thickness of the dermis, at the level of reticular layer; it may invade the subcutaneous adipose tissue. It is met more frequently in the extremities and buttock region. At macroscopic examination, it has the aspect of a 10–15 mm nodule of dark blue color (Fig. 8–47).

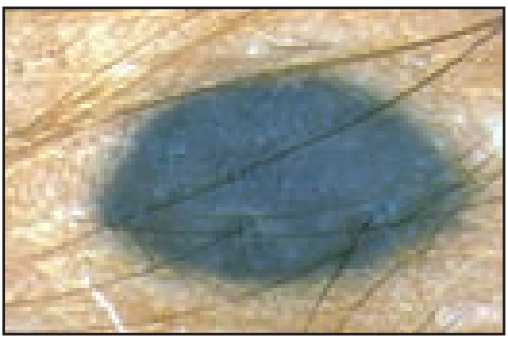
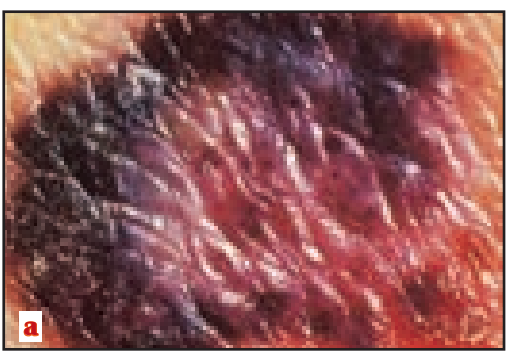


Fig. 8–47. Blue nevus– macroscopic aspect..

Generally, pigmented nevi are considered congenital or acquired skin hamartomas (*hamartoma – pseudo-tumoral formation, composed of cells and tissues, normal components of the given organ*). Congenital nevi are observed on average in 1% of the newborn, the acquired ones appear usually during puberty, pregnancy, and later, their growth becomes slower. Congenital nevocellular nevi rarely become malignant, but the acquired ones can turn into malignant melanomas. Various factors of local chronic irritation, such as repeated trauma, present favorable conditions for transformation into malignant melanoma.

Malignant melanoma or melanoblastoma is a highly malignant tumor, very severe prognosis and propensity to hematogenous and lymphogenous metastasis. A more common location is the skin of the face, extremities and external genitalia. It constitutes 1,2% of malignant tumors and 4% of all skin tumors. As extracutaneous locations, the impairment of eyeball (retina and choroid), meningeal membranes and adrenal medullary layer can be observed, more rarely – the oral cavity and gastrointestinal mucosa etc. It is seen more frequently in women aged 30–50 years, on the skin, legs, head and neck. The melanoma is associated with chronic, solar radiation (UV), which plays an important role in the tumor development. It frequently develops de novo, but, sometimes, it appears through malignization of pre–existing nevi. Macroscopically, on the skin, it has the aspect of a spot, plaque (Fig. 8–48 a) or a brown–black nodule with



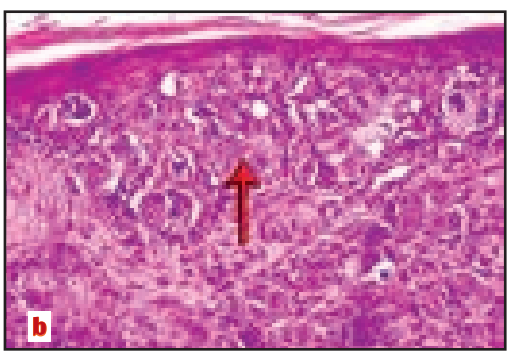


Fig. 8–48 a, b. Malignant melanoma with superficial extension: a – macroscopic aspect, b – microscopic pattern (hematoxylin–eosin stain; ×70).

a tendency to ulceration (Fig. 8–49 a); there are cases of amelanotic melanoma (non-pigmented). The most common clinical morphological forms are the forms with superficial and nodular extension. Microscopically, in the first version, the tumor consists of proliferating atypical melanocytes, which form nests and cords along the dermo–epidermal junction or in the basal layer of the epidermis (Fig. 8–48 b), and, in the second version – in the thickness of the dermis (Fig. 8–49 b).

The tumor cells are very diverse, polymorphous, with epithelioid or fusiform aspect, voluminous, hyperchromic nuclei, multiple mitoses, including atypical ones, well–defined eosinophilic nucleoli, melanin granules in the cytoplasm. Necrosis, hemorrhage and calcification foci are observed in tumor. The destructive lesions in melanoma

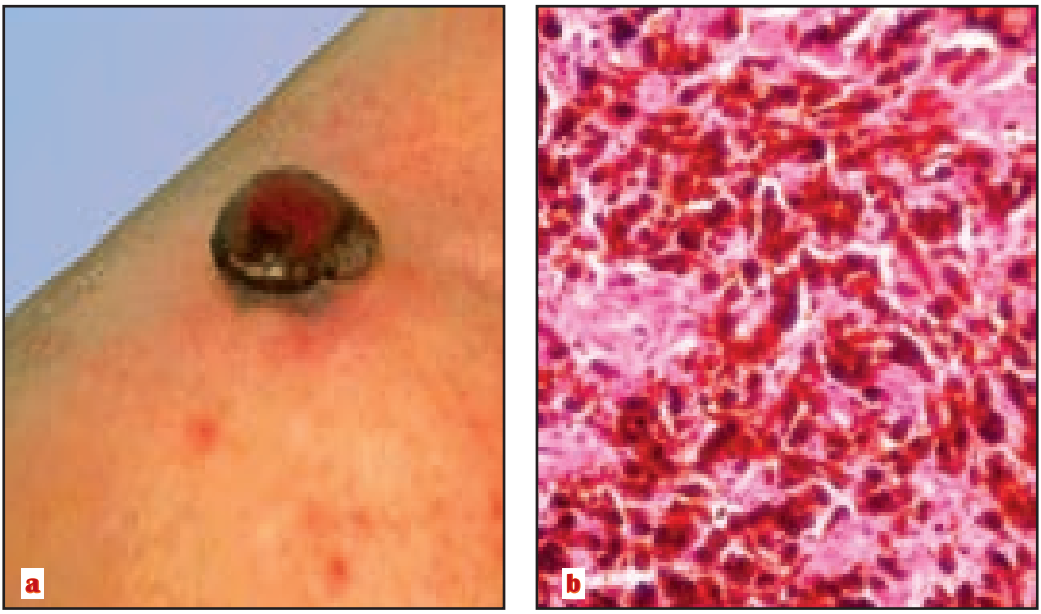


Fig. 8–49 a, b. Malignant melanoma, nodular form: a – macroscopic aspect, b – microscopic pattern (hematoxylin–eosin stain; ×70).

may lead to higher levels of melanin in the blood and urine – melanemia and melanuria. The prognosis depends on the level of tumor invasion in the depth, vertically. According to Klark, the following levels of melanoma invasion are distinguished:

I – intraepidermal tumor (*in situ*);
II – invasion of dermis along hair follicles;
III – damage of the whole papillary layer of the dermis up to the reticular layer;
IV – invasion of the reticular layer of the dermis;
V – invasion of subcutaneous adipose tissue (of the hypodermis).

The 5–year survival prognosis of patients in I and II invasion levels is 100%, in III level - 88%, in IV level - 66% and 15% - in V level. The prognosis also depends on tumor thickness.

Melanoma develops early, multiple metastases by hematogenous and lymphogenous ways. Melanin is contained in metastases.

ESSENTIAL TERMS
on the subject "MESENCHYMAL TUMORS"

benign chondroblastoma	hemangiopericytoma	malignant myoblastoma
benign osteoblastoma	hemangiosarcoma	melanoma
blue nevus	hibernoma	mesothelioma
chondroma	histiocytoma	myoblastoma
chondrosarcoma	junctional nevus	myxoma
compound (mixed) nevus	juvenile nevus	myxosarcoma
dermal nevus	leiomyoma	nevus
dermatofibroma	leiomyosarcoma	osteoid osteoma
desmoid	lymphangioma	osteoma
elastofibroma	lymphangiosarcoma	osteosarcoma
fibroma	lipoma	rhabdomyoma
fibrosarcoma	liposarcoma	rhabdomyosarcoma
glomangioma	malignant hibernoma	sarcoma
hemangioendothelioma	malignant histiocytoma	synovial sarcoma
hemangioma	malignant mesothelioma	synovioma

TESTS
on the subject "MESENCHYMAL TUMORS"

SET I.

Multiple-choice questions with one correct answer

1. What growth variant is characteristic for benign mesenchymal tumors:
a) invasive;
b) infiltrative;
c) destructive;
d) by implantation;
e) expansive.

2. Which stain is used to differentiate fibroma from leiomyoma:
a) carmine;
b) toluidine blue;
c) Congo red;
d) picrofuchsin;
e) thioflavin.

3. What is the location of the first hematogenic metastases of femur sarcoma:
a) lymph nodes;
b) liver;
c) lungs;
d) kidneys;
e) brain.

4. All the listed signs characterize the uterine leiomyoma, with the exception of:
a) collagen stroma is well-developed in many cases;
b) fascicles of smooth muscular cells are arranged chaotically;
c) tumor cells are homogenous in form and structure;
d) mitotic activity is high;
e) muscular cells have oval nuclei.

5. All the statements, regarding hematogenous metastases, are correct, except for:
a) they are a consequence of invasive growth of tumors;

b) they are a consequence of tissue embolism;
c) they are characteristic for sarcomas;
d) they are a criterion of malignant tumor evolution;
e) they are a manifestation of benign tumor growth.

SET II.

Multiple-choice questions with 2, 3 or more correct answers

1. *What signs from those listed bellow characterize the benign mesenchymal tumor:*
   a) tumors grow expansively, compressing neighboring tissues;
   b) tumor cells are mature, differentiated;
   c) multiple typical and atypical mitoses are observed;
   d) metastasize limphogenously;
   e) as a rule, it does not recur after tumor removal.
2. *Which statements related to sarcoma are correct:*
   a) the tumor is well-defined and compresses the neighboring tissues;
   b) it is brown or black on section;
   c) tumor cells are immature, atypical;
   d) tumor cells infiltrate the adjacent tissues;
   e) it may recur after tumor removal.
3. *Which of the listed malignant tumors derive from adipose tissue:*
   a) lipoblastic lipoma;
   b) liposarcoma;
   c) infiltrative lipoma;
   d) malignant hibernoma;
   e) malignant histiocytoma.
4. *Which of the listed signs characterize the leiomyoma:*
   a) it is the most frequent benign tumor of the uterus;
   b) tissular atypism;
   c) multiple pathological mitoses;
   d) it is frequently multicentric;
   e) tumor nodules are well-defined.
5. *Which of the listed signs characterize liver cavernous hemangioma:*
   a) tissular atypism;
   b) it has the form of a well-defined nodule;
   c) it is constituted from large vascular cavities, filled with blood;
   d) it is constituted from capillary-type vessels;
   e) expansive growth.

SET III.

The classification tests include 2–4 subjects and a series of answers. Indicate which answers are correct for each separate subject.

1. *Which of the listed signs are characteristic for:*
   I – benign mesenchymal tumors;
   II – malignant mesenchymal tumors;
   a) relapse after tumor removal;
   b) the tumor does not recur, as a rule;
   c) polymorphism and marked cellular atypism;
   d) infiltrative tumor growth;
   e) tumor cells are mature, differentiated;
   f) hematogenous metastases of tumors is typical;
   g) compression and atrophy of adjacent tissues.

2. *What morphologic manifestations of mesenchymal tumors characterize:*
   I – tissular atypism;
   II – cellular atypism;
   a) presence of pathologic mitoses;
   b) chaotic arrangement of structural elements in the tumor;
   c) tumor cells are mature, differentiated;
   d) ratio between tumor stroma and parenchyma is modified;
   e) tumor cells differ significantly from original tissue cells;
3. *Which of the listed morphological processes characterize:*
   I – tumor expansive growth;
   II – invasive growth;
   a) tumor cells invade the adjacent tissues;
   b) the tumor does not have clear limits;
   c) the tumor nodule can be easily removed;
   d) tumor cells destroy blood and lymph vessel walls;
   e) usually, the tumor has the form of a well-defined nodule.
4. *Which of the listed statements refer to:*
   I – cancer (carcinoma);
   II – sarcoma;
   a) it derives from mesenchymal tissues;
   b) it metastasizes more frequently by lymphogenous way;
   c) it metastasizes more frequently by hematogenous way;
   d) it derives from epithelial tissues;
   e) the first metastases are observed in regional lymph nodes;
   f) the first metastases are observed in lungs and liver;
   g) on section, it has the aspect of fish meat.
5. *Which of the listed statements are correct for:*
   I – desmoid;
   II – fibrosarcoma;
   a) it is formed from mature connective tissue, with infiltrative growth;
   b) it is formed from immature, non-differentiated connective tissue;
   c) it does not develop metastases;
   d) it is lodged more frequently in the anterior abdominal wall;
   e) it metastasizes hematogenously;
   f) numerous typical and atypical mitoses are observed in the tumor nodule;
   g) it is met more frequently in women.

SET IV. SITUATIONAL PROBLEMS

Daily practice cases are presented with clinical and morphological data from clinical histories and/or from necropsy protocols. Each subject includes simple or multiple – answer questions, with 1, 2 or more correct answers.

1. *A tumor nodule of 1,5 cm in diameter was detected and removed from the forearm of an 18-year-old patient. The nodule was mobile, well-defined and dense. The microscopic examination revealed that the tumor was formed from fascicles of collagen fibers, arranged chaotically, and an insignificant number of fibroblasts cells.*

Question:

What kind of tumor is in this case:

a) leiomyoma;

b) lipoma;
c) melanoma;
d) hemangioma;
e) hard fibroma.

2. *A red-colored nodule, which became pale when pressed with a blade, appeared in the cervical area of a 2-year-old child.*

Question:

What kind of tumor can be suspected in this case:

a) pigmented nevus;
b) intradermal nevus;
c) leiomyoma;
d) capillary hemangioma;
e) lymphangioma.

3. *A well-delimited, whitish-colored (on section) tumor nodule of 2,0 cm in diameter was found in the small intestine wall. The microscopic examination showed that it was formed from fascicles of smooth muscular fibers, with signs of tissue atypism.*

Question:

The presumptive diagnosis of which tumor from those listed below can be established in this case:

a) fibroma;
b) lipoma;
c) hemangioma;
d) leiomyoma;
e) desmoid.

4. *A tumor formation in the anterior abdominal wall, without precise limits, appeared in a 34-year-old patient, postpartum. The histological examination revealed that the formation consists of fascicles of fibroblastic-type cells, without signs of atypism; tumor cells infiltrate the adjacent muscular tissue.*

Question:

What is the presumptive diagnosis in this case:

a) leiomyoma;
b) mixed nevus;
c) histiocytoma;
d) desmoid;
e) fibroma.

5. *In a 12-year-old child, a tumor formation without precise limits appeared in the epiphysis of the humeral bone, due to an elbow contusion trauma. The histological examination of biopsy revealed a large number of osteoblastic-type polymorph cells, with a large number of pathologic mitoses.*

Question:

What is the presumptive diagnosis in this case:

a) chondrosarcoma;
b) osteosarcoma;
c) melanoma;
d) fibrosarcoma;
e) synovial sarcoma.

ANSWERS TO THE TESTS

CHAPTER 2. REVERSIBLE CELLULAR AND EXTRACELLULAR LESIONS

REVERSIBLE CELLULAR AND EXTRACELLULAR LESIONS

Set I	Set II	Set III	Situational problems
1c	1 a, c, d	1 – I a, d; II b, c	1 – Ac; B 1b, 2a
2 e	2 a, b, e	2 – I b, d, e; II a, c	2 – c d
3 b	3 b, d, f	3 – I a, b, c, d, e; II f	3 – A b; B b
4 b	4 b, d	4 – I a, e, f, g; II b, c, d	4 – e
5 b	5 a, c, d, e	5 – I a, d, e, f; II b, c	5 – e

MIXED EXTRA AND INTRACELLULAR LESIONS (MIXED DYSTROPHIES)

Set I	Set II	Set III	Situational problems
1 c	1 a, c, d	1 – I b, d, e; II a, c, f	1 – a, c, e
2 b	2 b, c, d	2 – I b, c, e, g; II a, d, f	2 - d
3 d	3 a, e	3 – I b, e, f; II a, c, d	3 – A b; B b
4 c	4 c, d, e, f	4 – I a, c; II b, d	4 – A a; B a, b, d
5 c	5 b, c, d,	5 – I a, b, c, d; II e	5 – A a, b, d, e; B b

CHAPTER3. IRREVERSIBLE CELLULAR LESIONS. NECROSIS AND APOPTOSIS

Set I	Set II	Set III	Situational problems
1 d	1 a, c, d	1 – I c, d, f, h; II a, b, e, g	1 – b
2 d	2 a, b, e	2 – I a, b, c, e, f; II d, g	2 – a
3 b	3 a, b, d, e	3 – I a, b, e, f; II c, d	3 – d
4 e	4 b, c, e	4 – I b; II e; III f; IV d; V a; VI c	4 – d
5 b	5 c, d	5 – I c, d, e, f, g, j; II a, b, h, i	5 – a

CHAPTER 4. DISTURBANCES OF BLOOD AND LYMPHATIC CIRCULATION

HYPEREMIA, DISORDERS, ISCHEMIA, INFARCTION, HEMORRHAGE

Set I	Set II	Set III	Situational problems
1 e	1 b, c, f	1 – I b, e; II a, c, d, f, g	1 – A b, c; B c
2 a	2 a, d, e, g	2 – I a, b, d, g; II c, e, f, h	2 – A a; Bb; C d
3 c	3 a, b, e	3 – I b, c, d, e; II a	3 – Ad; B d
4 c	4 a, b, c, d	4 – I a, e; II d, f; III b, c	4 – A e; B c
5 e	5 b, e, f	5 – a, d; II b, c, e	5 – A b

THROMBOSIS, EMBOLISM, EDEMA, SHOCK

Set I	Set II	Set III	Situational problems
1 a	1 a, d	1 – I a; II b, c, d, e, f; III a; IV f	1 – A b; B c
2 c	2 b, c, d	2 – I a, b, d, f; II c, e	2 – A e; B c; C b
3 b	3 a, d	3 – I a, b, e; II c, f; III d	3 – A a; B c; C d, e
4 b	4 a, b, c, e	4 – I c, e, f, g; II a; III d; IV b	4 – Ad; B d
5 c	5 b	5 – I b, d, e; II a, c, f	5 – Ac; B a, d, f; C d

CHAPTER 5. INFLAMMATION

ACUTE (EXUDATIVE) INFLAMMATION

Set I	Set II	Set III	Situational problems
1 d	1 b, d, e	1 – I a, e, f; II b, c, d	1 - c
2 c	2 a, d	2 – I a, c, d; II b, e, f, g	2 - a
3 d	3 b, d	3 – I c, f, g; II a, b, d, e	3 – Ac; B c; C b
4 c	4 d, e	4 – I a, c, d; II b, e	4 – Ad; B b, c, d, e
5 c	5 a, d, e	5 – I b, d, f, h; II a, c, e, g	5 – A e; B c

CHRONIC INFLAMMATION (PROLIFERATIVE)

Set I	Set II	Set III	Situational problems
1 c	1 a, b, c	1 – I b, e, f, h; II a, c, d, g	1 – A e; B a; C b, c, e
2 b	2 b, c, d	2 – I b, c; II a, d, e, f	2 – c
3 a	3 c, d, e	3 – b, c; II a, d, e	3 – c
4 d	4 a, b, e	4 – I a, c, e, f; II b, d, g	4 – c
5 d	5 a, b, e	5 – I b; II c; III a; IV e; V d	5 – c

CHAPTER 6. IMMUNOPATHOLOGIC PROCESSES

Set I	Set II	Set III	Situational problems
1 e	1 a, b	1 – I b, d, e; II a, c, f	1 – Ad; Bb
2 b	2 b, c, e	2 – I a, c, e; II b, d	2 – Ad; Bb
3 c	3 b, d, e	3 – I c, d; II a, b, e	3 – Ab; Bd
4 d	4 b, c, e	4 – I b; II d; III c; IV a	4 – Ad; Bd
5 d	5 b, d	5 – I b; II a, c, d, e	5 – Ad; B c, e

CHAPTER 7. ADAPTIVE–COMPENSATORY PROCESSES

Set I	Set II	Set III	Situational problems
1 e	1 b, d, e	1 – I b, d, e; II a, c	1 – Ac; Bb
2 d	2 b, c, d, e	2 – I b, d, e; II a, c	2 – A a, e; B a, b, c, d
3 c	3 d, e	3 – I d, e; II a, b, f; III c	3 – b
4 e	4 a, c, e	4 – I b, c, d; II a, e	4 – d
5 a	5 a, b, c, d	5 – I b, e; II a, c, d	5 – A e; B d

CHAPTER 8. TUMORS

NON ORGAN-SPECIFIC EPITHELIAL TUMORS

Set I	Set II	Set III	Situational problems
1 a	1 b, c	1 – I b, d, g; II a, c, e, f	1 – b
2 d	2 a, d	2 – I b, c, d; II a, e, f	2 – a, b, c, e
3 e	3 a, d	3 – I c, e, f; II a, b, d	3 – d
4 e	4 b, c	4 – I b, d, e, g; II a, c, f	4 – a
5 b	5 b, c, e	5 – I c, d, h; II a, b, e, f, g	5 – d

MESENCHYMAL TUMORS

Set I	Set II	Set III	Situational problems
1 e	1 a, b, e	1 – I b, d, g; II a, c, e, f	1 – e
2 d	2 c, d, e	2 – I b, c, d; II a, e	2 – d
3 c	3 a, b, c, d	3 – I c, e; II a, b, d	3 – d
4 d	4 a, b, d, e	4 – I b, d, e; II a, c, f, g	4 – d
5 e	5 a, b, c, e	5 – I a, c, d, g; II b, e, f	5 – b

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