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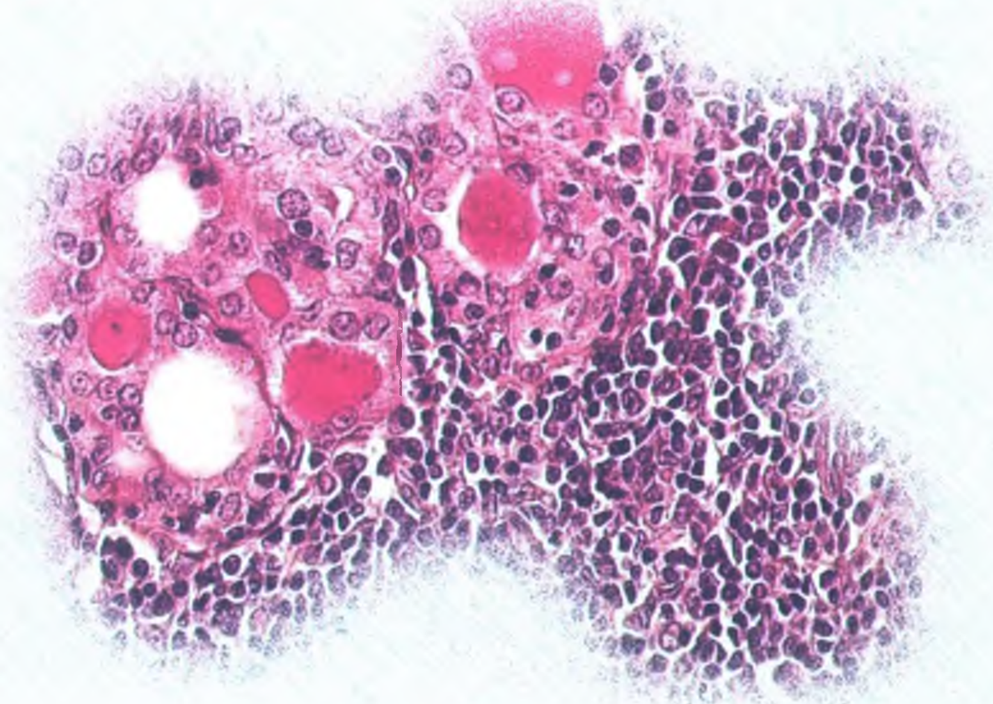
GENERAL MORPHOPATHOLOGY

A COMPENDIUM AND ATLAS

SECOND EDITION



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Redactor-chief *- Professor of Pathobiology, academician*

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GENERAL MORPHOPATHOLOGY

A compendium and atlas

Second edition

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GENERAL MORPHOPATHOLOGY

Compendium – atlas

Second edition

The book describes general pathological processes that represent the morphological substrate of all diseases as well as clinical elements necessary to understand the corresponding pathology. Each theme is well illustrated with images that reflect micro- macro- and electronomicroscopic manifestations of the pathological process.

The book is divided into the following chapters: Cell injury; Extracellular injury; Ireversible cell injury. Cell death: necrosis and apoptosis; Blood and lymph circulation disorders; Inflammation; Immunopathologic processes; Adaptive-compensatory processes; Tumors; Stomatopathology.

The value of the present compendium is increased by the slides that give it the status of an atlas.

It is addressed to medical students and will be used as didactic material in the course of general morphopathology and stomatopathology.

EDITOR'S FOREWORD

The publication of the present book written by Ieremia Zota, Vladimir Vataman and Ernest Jefferson Burkes, coordinated by academician Vasile Anestiade is the result of a successful cooperation between State Medical and Pharmaceutical University "Nicolae Testemitanu", Chisinau, Moldova and University of North Carolina, USA.

The work was conceived as compendium- atlas for medical students to study general elements of human pathology and stomatopathology.

To facilitate a more thorough and profound study, the authors have adopted a clear and concise style providing numerous tables and schemes. At the same time the authors have deliberately skipped a number of details, insisting upon basic elementary lesions absolutely necessary for the understanding of special morphopathology.

The small volume of the book includes a rich documentation thus turning the book into a compendium, recommended to be studied by medical practitioners such as morphopathologists, stomatologists, forensic specialists, and also by all practitioners in preparation for their residency exams.

The interdisciplinary character of morphopathology and its role in providing a scientific support to the explanation of the clinical symptomatology and the pathogenic mechanisms are permanently stressed in the book by correlating anatomic lesions with clinical consequences.

The value of this compendium is increased by the slides that give it the status of an atlas but also of a handbook for the macro-, micro or electronomicroscopical interpretation of pathological processes.

CONTENTS

Chapter 1
CELL INJURY

The concept of cell injury is at the core of the understanding of disease in pathology.

Injury refers to damage or pathologic alterations in molecules and structure that can occur in cells and extracellular components of tissue.

Cells composing tissues are normally under homeostatic conditions and are constantly adjusting structure and function to accommodate changing demands and extracellular stresses and maintain a constant intracellular environment.

In response to physiologic stresses and pathologic stimuli or injury cells can undergo:

1. Adaptation:

Changes in function and structure, that maintain a homeostatic state and cell viability.

Cells may revert to previous structure and function when the stress or injury is removed.

2. Reversible Injury:

Pathologic alterations in cell molecules and structure, that are associated with abnormal function and with loss of homeostatic state. Removal of stress or injury results in cell recovery and return to normal function.

3. Irreversible injury and cell death:

Damage to cells reaches magnitude or duration where the cells passes a point of no return. Despite removal of injury or stress, the cells can not recover and dies.

Morphologic and molecular events that occur after the cells is irreversibly injured allow identification of the cells as having undergone:

- ***Necrosis:***

  Pattern of cell death that often follows hypoxic, toxic and some microbial injuries.

- ***Apoptosis:***

  Receptor-mediated pattern of cell death that occurs in programmed cells death during development and following some endocrine-related, toxic and microbially mediated injuries and toxic.

Causes of cell Injury.

A. Hypoxia/hypoxemia:

Examples:

1. Cardio-respiratory failure and neuronal necrosis.
2. Renal vein thrombosis and renal tubular necrosis.

B. Physical Agents:

Examples:

1. Trauma (hit by car and organ rupture).
2. Thermal-induced skin necrosis.

C. Chemicals/Drugs:

Examples:

1. Lead toxicity and neuronal and renal tubular necrosis.
2. Glucocorticoid-induced lymphocyte apoptosis.

D. Infectious Agents:

Examples:

1. Adenovirus-induced epithelial cells necrosis.
2. Endotoxin-induced apoptosis of lymphocytes and hepatocytes in gram-negative bacteriemia.

E. Immunologic reactions:

Examples:

1. Complement-mediated hemolysis in autoimmune hemolytic anemia.
2. T-lymphocyte-induced cells apoptosis in viral infection.

F. Genetic defects:

Examples:

1. Congenital malformations due to the genetic disorders.
2. Lysosmal storage diseases caused by genetically determined enzymatic abnormalities.

G. Nutritional imbalances:

Examples:

1. Obesity in nutrirional excesses.
2. Anemia caused by low dietary iron intake.

Pathogenesis of cell injury.

- Intracellular systems are particularly vulnerable to the action of injurious agents:
  1/ intracellular aerobic respiration,
  2/ cell membranes,
  3/ enzymatic and structural protein synthesis, and
  4/ genetic apparatus.
- The structural changes of cell injury become apparent only after some critical biochemical derangement has occurred.
- The result of cell injury depends on the injury (i.e. the type, duration and severity of the injurious stimulus) and on the cells (i.e. the type, state and adaptability of the injured cell).

FORMS AND MORPHOLOGY OF THE CELL INJURY

A. Reversible cell injury:

- ***Degeneration*** (*cellular dystrophy*) refers to morphologic changes in cells caused by sublethal injury.
- The cells can revert to the former state of homeostasis if the noxious agent is removed.
- The changes are associated with the structural alterations in cell organelles or the cytoskeleton and with the intracellular accumulations of the various substances as a result of metabolic derangements in cells. The processes resulting in abnormal intracellular accumulations can be divided into three general types:
    a) storage in cells or/and in the interstitium of some physiologically common structural substances in excessive or decreased amounts;
    b) storage in cells or/and intercellular spaces of some substances that would not normally appear;
    c) appearance and storage in cells or/and in the interstitium of some substances that are not normally present in human body.

These quantitative and qualitative changes of different metabolic products are caused by enzymatic process disorders, and take place through four morphogenic stereotypes: infiltration, decomposition, transformation or pathological synthesis. They are briefly characterized in table 1.

Table 1

Morphogenic mechanisms of cell injury

Morphogenic mechanism	Characteristics	Examples
1	2	3
1) Infiltration	Excessive penetration in cells (intercellular spaces) of some metabolic products from blood, lymph, urine, and their further storage because of the insufficiency of the enzymatic systems which should normally metabolize them.	a) Infiltration of epithelial cells and renal tubules with glucose in diabetes mellitus. b) Infiltration with lipids of the hepatic lobules in obesity (lipemia).
2) Decomposition	The break down (decomposition) of some complex chemical substances and the storage of their components in cells or in the extracellular compartment.	a) Break down of lipoproteic complexes from the membrane structures in hypoxia, intoxications. b) The decomposition of the glicoproteic complexes from the fundamental substance of the connective tissue in rheumatic diseases.
3) Pathologic synthesis	The synthesis of some substances not normally seen in cells and tissues.	a) The synthesis of abnormal glycogen in some hereditary glycogenosis. b) The synthesis of abnormal protein in cells and of the abnormal proteoglucidic complexes in the intercellular space of the connective tissue in amyloidosis.

I. PROTEIC DEGENERATIONS.

1. Granular dystrophy.

It can be found in parenchymatous organs such as kidneys, myocardium, liver. Microscopically it manifests itself by the presence in the cells (nephrocytes, cardiomyocytes, 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, a flaccid consistency, and a whitish color, opaque and pale if sliced like boiled meat, therefore its name of dim intumescence.

Microspecimen "Granular dystrophy of the epithelium of contort renal tubules" (fig.1).

The epithelial cells of the contort renal tubules are bigger in size, tumefacted, indistinct, with unclear margins. The cytoplasm has a granular, reticulated aspect containing small proteic granules, uniformly spread, colored with eosin in pink. The lumen of the tubules is thinner than normal and some of them contain proteic masses (proteinuria).

The more frequent morphogenic mechanism of granular dystrophy is infiltration-penetration inside the cell of some chemical liquid substances, which are metabolic products of blood, lymph, urine, etc. The infiltration process can be easily seen using electronic microscopy.

Electronomicrography "Granular dystrophy of the epithelium of proximal renal tubules" (fig. 2).

The vesicles of the endoplasmatic reticulum are dilated, forming vacuoles which contain proteic masses; the mitochondria are somewhat tumefied.

A slight dysfunction of kidneys is observed in this type of dystrophy; in urine, proteic masses are present (proteinuria). This process is reversible if the cause is eliminated. In other cases, the changes can evolve to serious lesions, as found in the hyalincellular dystrophy, hydropic or lipidic dystrophy. The causes of the granular dystrophy are various: disorders of blood and lymph circulation (ischemia, venous stasis), infectious diseases (viral and bacterial), exogen and endogenous intoxication.

It must be mentioned that the appearance of proteic granules in the cytoplasm of cells can be seen also in physiological conditions, reflecting the morpho-functional peculiarities of the cell (e.g., the production of secretion granules in the endocrine cells, physiological resorption of proteins by the epithelium of proximal renal tubules, etc.), the increased function of protein synthesis (for example, in hepatocytes, secretory cells), hyperplasia and hypertrophy of cytoplasmic organelles caused by the overtaxing of the parenchymatous organs.

2. Intracellular hyaline dystrophy (intracellular hyalinosis).

It is manifest by the presence of large drops of proteic origin in the cells. This type of dystrophy is not macroscopically evident in the affected organs. Using electron microscopy, the tumefaction of cytoplasmatic organelles can be seen. The more frequently affected organs are the kidneys (the epithelium of renal tubules) and the liver (hepatocytes).

Electronomicrography "Intracellular hyaline dystrophy of the epithelium of proximal renal tubules" (fig. 3).

The destruction of mitochondrial crista as cause for their tumefaction and homogenisation, and their transforming into proteic hyalin structures, can be observed in the nephrocyte cytoplasm.

Using optic microscopy, these changes appear in the cytoplasm as acidophilic, confluent and homogeneous drops of proteic origin *(fig. 4)*.

Intracellular hyaline dystrophy in the kidneys is seen in such diseases as glomerulonephritis, renal amyloidosis, diabetic glomerulopathy, paraproteinemic nephrosis, intoxications, etc., when the permeability of the glomerular filter increases. This is an irreversible process that leads to focal coagulative necrosis of the cell. It is clinically manifested by severe disorders of organ function (e.g., the presence of proteins and cylinders in the urine).

Similar lesions appear in the cells of the liver in case of alcoholic hepatitis (alcoholic cirrhosis) – so called Mallory corpuscles or the alcoholic hyalin (hyaliniform inclusions situated around the nucleus).

Intracellular hyaline dystrophy is caused by such processes as the destruction of cellular organelles, cytoplasmic protein denaturation, resorption (infiltration) of some macrodispersive abnormal proteins or proteins pathologic synthesis (e.g. Mallory corpuscle).

3. Vacuolar dystrophy (cellular swelling, hydropic degeneration).

- Due to entry of excessive isotonic fluid into the cells as a result of functional derangements in the mitochondria and plasma membrane.
- The organ shows pallor, increased turgor and increased weight.
- Individual cells are swollen with accumulation of Na+ and water, and loss of glycogen.
- With progressive influx of water, clear vacuoles appear in the cytoplasm.

Microspecimen "Hydropic degeneration of the renal contort tubule epithelium" (fig.5).
A large number of optically empty vacuoles are present in nephrocytes of the renal contort tubules. These oval or round vacuoles are situated mostly along the basal membrane; the nucleus of these cells is pale and the lumen of the tubules is more narrow than in normal conditions.

Electronomicrography "Vacuolar swelling of the liver". In the altered hepatocyte ***(fig.6)*** a large number of dilated channels of the endoplasmatic reticulum are present; these all form cisterns containing cytoplasmatic liquid.

The basic mechanism of the vacuolar sweling is a disorder of the hydro-electrolyte and proteic metabolism. Modification of the intracellular coloid-osmotic pressure leads to the penetration of water into the cells, or to disorder of water elimination from cells while the redox processes take place. The excessive accumulation of water leads to destruction of cellular ultrastructures and the appearance of vacuoles containing cytoplasmatic liquid. This liquid accumulates in the cisterns of the endoplasmatic reticulum and in the mitochondria. The precise diagnosis of hydropic swelling can be made only after coloring the microspecimen for glycogen and lipids (the negative staining confirms the diagnosis). Vacuolar dystrophy is an irreversible process ending up with the colliquative necrosis of the cells. It can also end up with the swelling of cells as an aspect of focal colliquative necrosis. The affected organs suffer from severe functional disturbances. For example, the hydropic degeneration of the epithelium of contort renal tubules frequently seen in the nephrotic syndrom, is characterized by severe proteinuria (as a result of diminished of tubular resorption function), dysproteinaemia, hypoproteinaemia, hyperlipidaemia and edema. The vacuolar dystrophy of the myocardium manifests itself by a great reduction of the contractile function of the heart.

Hydropic accumulations is also present in some infectious diseases (mostly in variola and viral hepatitis), intoxications (with phosphor, arsen, carbon tetrachloride), inanition, avitaminosis and under the action of penetrating radiation, etc.

4. Keratinous dystrophy.

This type of dystrophy is mostly found in skin and mucous membranes covered by squamous and transitional epithelium. The excessive keratinization of the pluristratified squamous cornous epithelium of the skin (hyperkeratosis), or the presence of keratin in the mucous epithelium, which in normal condition is not cornous (leukoplakia).

Macro- and microspecimen "Hyperkeratosis of skin"

Macroscopically, in the sites of hyperkeratosis, the skin is thick, dry, and has a fish scaled appearance *(fig.7)*. Microscopically *(fig.8)*, the cornous stratum of the epidermis is considerably thickened as a result of the excessive keratin synthesis. Of great importance in the etiology of the lesions are chronic inflammation, viral infections, avitaminosis, especially the lack of vitamin A, chronic irritations, some skin developmental disorders (e.g. inborn hyperkeratosis or ichthyosis).

Macro- and microspecimen "Leukoplakia of the buccal cavity mucosa"

Macroscopically, *(fig.9)* it has a whitish color, with smooth or rough surfaces, and can reach several cm in size. Microscopically, the pluristratified squamous epithelium *(fig.10)* is thickened, the superficial layer consisting of keratinised anuclear cells and covered with a layer of keratin.

It is more frequently seen on the mucosa of the buccal cavity, tongue, lips, pharynx, larynx, vaginal surface of the uterine cervix, vagina and the bladder. The leukoplakia may appear also on the mucous surfaces covered with unistratified epithelium, following squamous metaplasia of the mucous membrane in bronchi, stomach, intestine, and endometrium. The most frequent causes of leukoplakia are chronic inflammation, chronic irritation, trauma, etc. It is considered to be a precancerous lesion.

The evolution of keratin dystrophy may lead to the rehabilitation of the affected tissue or to the necrosis of cells. The function of skin and mucous membranes in the affected regions is severely altered.

II. FATTY DEGENERATIONS

- Fatty change refers to any abnormal accumulation of fat within parenchymal cells.
- Liver cells, heart muscle cells and renal tubular cells are most commonly affected.
- The organ is large, pale and greasy.
- Individual cells contain in their cytoplasm membrane-bound fat droplets as clear vacuoles, may fuse, displace the nucleus to the periphery of the cell.

Macrospecimen "Fatty change of the myocardium (steatosis of myocardium)"

The heart is larger in all dimensions *(fig.11)*; the chambers are enlarged and dilated. The myocardium has a flaccid consistency, and broadens and stretches at necropsy; if sectioned, it is opaque, and pale yellow. Under the endocardium, especially close to the papillary muscles, alternating fatty yellowish striae and normal tissue can be observed, making the heart look like tiger skin ("tiger heart"). The tiger skin appearance of the myocardium is characteristic for focal fatty dystrophy, because the fat deposition is around the veins and venules.

Electronomicrography "Fatty change of the myocardium" (fig.12)

Drops of fat are found in the myocardial cells sarcoplasm, when electron microscopy is used; they are tightly bound to the membrane of the cytoplasmic organelles, especially of the mitochondria. At the contact zones with the lipidic inclusions, the intracellular membranes become structurally indistinct.

Fatty dystrophy is more frequently found in chronic cardiovascular insufficiency, severe anemia (pernicious anemia), severe infectious diseases (diphtheria), intoxications (with ethanol, phosphor), etc. The contractile function of the heart is decreased. The myocardic steatosis is considered to be morphologic substrate for the functional decompensation of the heart.

The predominant morphological mechanism of myocardic steatosis is decomposition, the degradation of the lipoproteic compounds of the intracellular membranes.

Macrospecimen "Fatty change of the liver (steatosis of liver)"

The liver is larger in weight and volume ***(fig.13)***. The fibrous capsule is weakened and smooth, with rounded margins, and soft and paste-like consistency. If sectioned it has a yellowish (clay) color, which can be either homogeneous or patchy. During necropsy, fat remains on the blade of the necropsy knife. The lobular aspect of the liver is either unchanged, in cases where the dystrophic changes take place only in some parts of the lobule, or is erased, in severe cases with diffuse steatosis of the hepatocytes. In the second case the liver is macroscopically like goose liver.

Microspecimen "Steatosis of liver"

The cytoplasm of hepatocytes ***(fig.14 and 15)***, may contain many lipidic drops of different dimensions, without a bordering membrane. These appear to be optically empty if prepared with paraffin (lipids are soluble in alcohol, chloroform, etc), and of a red-yellow (orange) color if the specimen has undergone cryosectioning (with the congelation microtom) and Sudan III staining (lipophilic colorant). The fat drops are larger at the lobule periphery and smaller in the central region. In some cells from the peripheral regions of the lobule, the fat drops undergo fusion and form one single drop which fill the entire cytoplasm. The nucleus appears to be flattened and pushed towards the cellular membrane.

Electronomicrography "Steatosis of the hepatocyte" (fig.16)

The cytoplasm of the hepatic cells contains numerous small lipidic inclusions, with black-white striations, situated mostly in the perinuclear region.

The most frequent causes of hepatic steatosis are lipidaemia (obesity, excess fats in alimentation, chronic alcoholism, diabetes mellitus, hormonal disturbances), hepatotropic intoxications (with phosphor, carbon tetrachloride, ethanol, chloroform, etc.), nutrition disorders (lack of proteins or lipotrop factors, avitaminosis, digestive tract affections, etc.), tissular hypoxia (cardiac insufficiency, severe anemia, pulmonary affections), etc.

The predominant morphogenic mechanism of peripheral zone steatosis of the hepatic lobules (peripheral or periportal steatosis) is infiltration which is observed in case of hyperlipidaemia (the fats reach the liver with the portal blood and infiltrate first in the peripheral zones of the lobules). The morphogenic mechanism of the central zone steatosis is decomposition, which occurs for example in case of progressive hypoxia of liver.

The function of the liver in case of fatty degeneration remains normal for a long time. If the action of the pathogenic factor persists, necrotic processes are associated and a portal type cirrhosis develops.

III. GLYCOGENIC DEGENERATION

It is manifested by the excessive accumulation of glycogen in the cytoplasm of cells, mostly found in diabetes mellitus.

Microspecimen "Glycogen infiltration of renal contort tubule epithelium in diabetes"

Glycogen granules of different dimensions staining red with Best carmin, are present in the epithelial cells of the renal tubules *(fig. 17)*. The most severely affected cells are the ones from the narrow segment and from the distal portion of the contort tubules. Glycogen granules can be observed also in the lumen of the tubules. The glomeruli suffer a thickening of the basal membrane of the capillaries and the depositing of polysacharides in the mesangium (intercapillar glomerulosclerosis). The main morphogenic mechanism of renal glycogenic dystrophy is infiltration.

The renal modifications in diabetes mellitus appear as a result of hyperglycemia and glucosuria. These are caused by the taking over and utilization of glucose by the tissues, associated with the insufficient secretion of insulin by the beta cells of the pancreatic isles (Langerhans). The process can be reversible.

IV. PIGMENTATIONS

A. Exogenous Pigments and Particulates.

Exogenous material often accumulate in the body that are not readily degraded by hydrolytic enzymes in the extracellular space or by macrophages. The most common example of this accumulations is pneumoconiosis.

1. Pneumoconioses:

Definition: Accumulation of particulate matter within the lung.

a. Small particles (1-5 microns in diameter) settle on the mucosa of the terminal airways (e.g., respiratory bronchioles) and are phagocytosed by alveolar and peribronchiolar macrophages.

Light microscopy reveals peri-bronchiolar cuffs of particle-laden macrophages (granular, brown-black, intracytoplasmic pigment).

b. Pathogenicity varies depending on the nature of the particulate material and amount of deposition. Particulates such as silica can cause pulmonary fibrosis, emphysema, and pulmonary inflammatory disease. Particulates such as asbestos can cause fibrosis and neoplasia.

c. Examples:

1. Anthracosis: called miners disease, carbon-rich particulates.
2. Silicosis: sand, flint, stone dust. Cause severe pulmonary fibrosis and pneumonia.
3. Asbestosis: asbestos fibers.

B. Endogenous cell pigments:

Substances produced by the organism/cells accumulate when they are produced in quantities that exceed the cells ability to metabolize or secrete them; or if the cell is lacking enzymatic capacity to metabolize them (example: hereditary storage diseases).

1. Lipofuscin/ceroid (latin: fuscus=brown, a brown lipid)

a. Composed of lipid-protein complexes derived from the peroxidation of lipid in cell membranes (free radical damage).
b. Lipofuscin accumulates in cells over time as a "wear and tear" pigment.
c. Conditions such as vitamin E deficiency lead to increased tissue deposition.
d. Most common tissue sites are heart, liver, and brain cells.
e. The cellular accumulation site are the lysosomes.
f. Lipofuscin is not toxic to cells except in large quantities.
g. Morphology:
   1) granular, brown pigment;
   2) autofluorescent and acid-fast;
   3) tissues look brown grossly when high accumulation occurs.

Macrospecimen "Brown atrophy of the heart"(fig. 18).

The heart is smaller in all dimensions, without adipose tissue under the epicardium. The coronary arteries have a meandering pattern; the myocardium is brown on surface and if sectioned.

Microspecimen "Lipofuscinosis of the liver" (fig. 19).

The hepatic trabeculae are thinner than normal because of atrophy of the hepatic cells. The cytoplasm of the hepatocytes in the central zones of the lobules contains granules of lipofuscin, which have a brown color. These granules are situated mainly around the nucleus. The spaces between the hepatic trabeculae are larger than normal.

The accumulation of lipofuscin in organs and tissues (acquired lipofuscinosis) takes place in cachectic conditions, senile atrophy, hypoxia, functional overtaxation (ex. lipofuscinosis of the myocardium in valvular lesions). Therefore lipofuscin is also called the "usage pigment".

The lipochromes produce the yellow color of the adipose tissue, the corpus luteus of the ovaries, the adrenocortical glands, the testicles, the blood serum, and the transudate.

2. Hemosiderin.

a. Derived from hemoglobin breakdown.
   - Erythrocyte phagocytosis leads to release of iron from hemoglobin.
   - Iron complexes with apoferritin form micelles that are seen as hemosiderin.
   - Usually locates in the lysosomes.
b. Normally observed in small amounts in mononuclear phagocytes in the bone marrow, spleen and liver.
c. Excessive tissue concentrations occur where there is hemorrhage, chronic congesion and diapedesis of erythrocytes into tissue, or excessive hemolysis (autoimmune hemolytic anemia, hemoparasitic diseases)
d. Morphology:
   1/ golden-yellow to brown, granular or crystalline, intracytoplasmic pigment;
   2/ prussian blue staining is blue-black.

Note: A tissue artifact that is sometimes mistaken for hemosiderin is acid hematin. Acid hematin has a similar brown appearance in tissue to hemosiderin. Acid hematin is formed when hemoglobin is precipitated in acid formalin fixatives. Use of neutral-buffered formalin avoids this problem.

e. Hemosiderin deposits are not usually toxic.
f. Pathologic accumulation of hemosiderin in parenchymal cells occurs in hemochromatosis, a disease characterized by excessive iron accumulation in cells. Iron builds up in cells such as hepatocytes, and cells injury results from free radical-induced lipid peroxidation and increased lysosomal membrane fragility.

Microspecimen "Hemosiderosis of kidneys" (fig. 20).
The epithelial cells of the renal contort tubules contain hemosiderin granules of brown color, which can be observed in some places in the lumen of the tubes.

Microspecimen "Pulmonary hemosiderosis (pulmonary chronic venous stasis)". In the alveolar lumen ***(fig. 21 and 22)***, in the thickness of the alveolar septum, and in the peribronchovascular connective tissue many macrophages are present. The cytoplasm of the macrophages contains hemosiderin granules of brown-black color, with hematoxylin-eosin and blue color in Pearls reaction. This reaction is a specific method for hemosiderin identification: by adding potassium ferrocyanide and hydrochloric acid on the unstained microspecimen, blue granules of iron ferricyanide form (also called Berlin blue or Prussia blue).

Pulmonary hemosiderosis appears in passive (venous), chronic congestion of the lungs, caused by heart diseases (valvulopathy, cardiosclerosis, myocarditis, etc.). Hemosiderin is synthesized in alveolocytes and histiocytes. The cells containing hemosiderin are eliminated with sputum and can be analyzed in a laboratory; these cells are called "cardiac cells". This pathological process is also called "brown induration (hardening) of the lungs" because of the increase of consistency as a result of the connective tissue proliferation under chronic venous hypoxy. Pulmonary hemosiderosis is an illustrative example of localized hemosiderosis resulting from exravascular erythrocyte hemolysis.

Macrospecimen "Cerebral hematoma" (fig. 23).
In the area of subcortical nuclei there can be observed a well delineated cavity filled with brownish clotted blood. The color is accounted for by hemosiderine

Microspecimen "Old cerebral hemorrhage" (cerebral hematoma) (fig. 24)
In the central part of the hematoma, hematoidin granules (crystals) can be observed, placed extracellularly in the necrotic masses (detritus). At the peripheral zones of the hematoma, in the surrounding cerebral tissue glial cells, hemosiderin (because of phagocytosis) can be seen.

3. Bilirubin

a. Bilirubin is a breakdown product from heme proteins derived from hemoglobin and from other heme groups such as cytochromes.
b. A major source is from erythrocyte breakdown in mononuclear phagocytes
   - Heme is converted to biliverdin by heme oxygenase.
   - Biliverdin is metabolized to bilirubin by biliverdin reductase.
c. Bilirubin is usually bound to albumin in plasma as the unconjugated form.
d. Unconjugated bilirubin is transported into hepatocytes, conjugated with glucuronic acid in the endoplasmic reticulum and excreted in bile.
e. **Jaundice (icterus)** is the yellow aspect of the skin, sclera, and mucous membranes due to elevated blood levels of bilirubin (>2-3 mg/dl)

f. Causes of hyperbilirubinemia (icterus) include:
1) Increased breakdown of heme proteins.
2) Decreased hepatic uptake of albumin-bound bilirubin.
3) Impaired conjugation of bilirubin.
4) Impaired intra-hepatic excretion of bilirubin into bile.
5) Bile duct obstruction.

g. Unconjugated bilirubin is highly toxic and is normally bound to proteins.
h. Conjugated bilirubin is not toxic at low concentrations. It can cause tubular necrosis when concentrated in urine.

Microspecimen "Biliary stasis in mechanical jaundice" (fig.25).

The biliary canaliculae and some interlobular canals are dilated, their lumen contains biliary coagulates of a brown color (biliary "thrombus"). The cytoplasm of some hepatocytes contains granules of biliary pigment. In the center of the hepatic lobules there can be observed necrotic foci of hepatocytes, which are imbued with bile.

Biliary stasis (mecanic jaundice) can be caused by biliary calculus, tumors of the biliary ducts, of the pancreatic head or of the duodenal papilla (Vater's ampulla), by malformations of the biliary ducts, by cancer metastasis in the lymph node of the hepatic hilus, by scar deformations of the biliary ducts, etc. The excess of conjugated bilirubine in blood leads to yellow-greenish coloring of the organs and tissues, including the skin and sclerae. Besides the intense coloring of the skin, the obstructive jaundice has other effects like general intoxication (with biliary acids), hemorragic syndrome, dystrophic lesions of the kidneys and hepato-renal insufficiency. The complication of biliary stasis is inflammation of the biliary ducts (cholangitis), but if the evolution of this process is chronic, it can lead to cholestatic biliary cirrhosis.

4. Melanin (*greek* melas=black)

a. Melanin is formed via oxidation of tyrosine to dihydroxyphenylalanine in melanocytes by tyrosinase.
b. Melanosis refers to excessive accumulation of melanin in tissue.

Macrospecimen "Pigmentary nevus" (fig. 26).

Two nodular structures with a papular appearance, having a diameter of several mm. can be observed on the skin. The structure is pigmented in brown or black-brown color and covered with hair. It has a smooth or verrucous surface and a soft consistency. The color of the nevus is a result of localized excess of melanin.

The pigmentary nevi represent circumscribed, congenital developmental disorders of the skin. They consist of nevus cells, which proceed from lemocytes (Schwann cells) and can synthesize melanin. They usually begin to grow in volume in puberty and during gestation, after which their growth slows down. They are an example of localized melanosis (hyperpigmentation). The pigmentary nevi can evolve into one of the most malignant tumors, the melanoma.

Macrospecimen "Metastasis of melanoma in bones" (fig. 27).

On the sectioned bones there can be observed multiple nodules of round or ovoid form, which are well limited from the surrounding tissue. They are black-brown in color due to the great quantity of melanin. The primary tumor can be localized on the skin, in the pigmentary tunica of the eye, and more rarely in leptomeninges and in the medulla of adrenal glands. The metastasis found in bones are spread hematogenous.

5. Calcification

A. Normal deposition of calcium salts occurs in bone and cartilage.

B. Abnormal (pathologic) deposition of calcium salts occurs in other tissues in either intra- or extracellular locations: deposits as calcium phosphate (similar to hydroxyapatite of bone) and deposits as calcium hydroxide in connective tissue: elastin and collagen.

C. **Morphology**:

1. Gross: calcified tissue is chalky white to grey, gritty to bone-hard when sectioned.
2. Microscopic: calcium deposits are usually deeply basophilic, granular and stain positively with Von Kossa stains (black) and alizarin red.

D. **Pathogenetic mechanisms**:

1. Dystrophic calcification
2. Metastatic calcification

E. **Dystrophic calcification:**

Abnormal calcium deposition in dead or degenerating tissues.

1. **Intracellular calcification**: initially accumulates in mitochondria of dying cells.
2. **Extracellular calcification**: calcium has a high affinity for phosphate-rich plasma membrane fragments and basement membrane (acid phospholipids accumulate due to phosphatase activity), calcified fragments usually present extracellularly in membrane-bound vesicles probably derived from degenerating cells.

Sequelae:

a. Persists and may result in tissue dysfunction (e.g. loss of tissue elastic properties).

b. Can serve as a focus for heterotopic bone formation (presence of bone in an abnormal location).

F. **Metastatic calcification**:

Abnormal calcium deposition in abnormal tissues secondary to hypercalcemia. This pathogenetic mechanism is complicated because high levels of calcium are capable of causing cells injury. In hypercalcemia, cells injury may underlie the cellular mineralization. Elevated serum calcium is present and abnormal calcium metabolism occurs.

Causes or examples include:

a. **Hypervitaminosis D.**

b. **Ingestion of toxic plants**, some plants such as *Solanum malacoxylon* and *Cestrum diurum*, contain agents identical to or similar to 1,25-dihydroxycholicalciferol (vitamin D_3).

c. **Primary Hyperparathyroidism**: increased levels of parathyroid hormone due to parathyroid neoplasia causes bone resorption and release of calcium into the circulation.

d. **Secondary (nutritional) hyperparathyroidism**: increased production of parathyroid hormone due to areal or relative decrease in serum calcium, which is the result of inadequate levels of calcium in the diet. Bone resorption occurs to maintain adequate calcium levels.

e. **Renal secondary hyperparathyroidism** occurs in chronic uremia, which results in phosphate retention by dysfunctional kidney and impaired uptake of calcium.

f. **Hypercalcemia of malignancy** (multiple myeloma, metastatic cancer, osteosarcoma, lymphosarcoma).

Common sites of metastatic calcification: Blood vessels (intima and media) and connective tissue of the kidney, lungs, and stomach.

Macrospecimen "Petrification in the lung" (fig. 28).

When the lung is sectioned, a focus of calcium salts in round form, whitish color and hard consistency can be seen. It has a chalklike appearance. This petrification has appeared as a result of dystrophic calcification of a caseous necrotic site in a case of pulmonary tuberculosis.

Microspecimen "Calcification (calcinosis) of the coronary artery in atherosclerosis" (fig. 29).

In the wall of the coronary artery there can be observed multiple focuses of calcinosis of a violet color, if the specimen is stained using hematoxylin-eosin. The accumulation of calcium salts takes place in the atherosclerotic plaque, a circumscribed, prominent thickening of the arterial intima. This leads to reduction in size of arterial lumen.

6. Nucleoproteic degenerations

The disorders of the nucleoproteic metabolism are manifest by the excessive formation of uric acid and of its salts, which can accumulate in tissues. It is seen in gout, urinary lithiasis and in the uratic infarct in newborn.

Microspecimen "Gout toph" (fig. 30).

Foci of crystalline or amorphous accumulations of sodium urates, surrounded by necrotic tissues, inflammatory infiltrates containing gigantic multinucleated cells of foreign bodies (which are responsible for the resorption of the uric salts). The proliferation of the connective tissue can be observed in the subcutaneous tissue. Macroscopically, these sites have the appearance of painful nodules in the region of the finger, knee and tibiotarsal articulations, etc.

7. Calculogenesis (*lithiasis*)

The classification, morphogenic mechanisms and the consequences of lithiasis are represented in table 2.

Macrospecimen "Biliary calculi" (fig. 31).

In the cavity of the gallbladder there can be observed multiple calculi of various forms and dimensions. They have a smooth, rough or granular surface, of a yellowish-white color and a hard consistency.

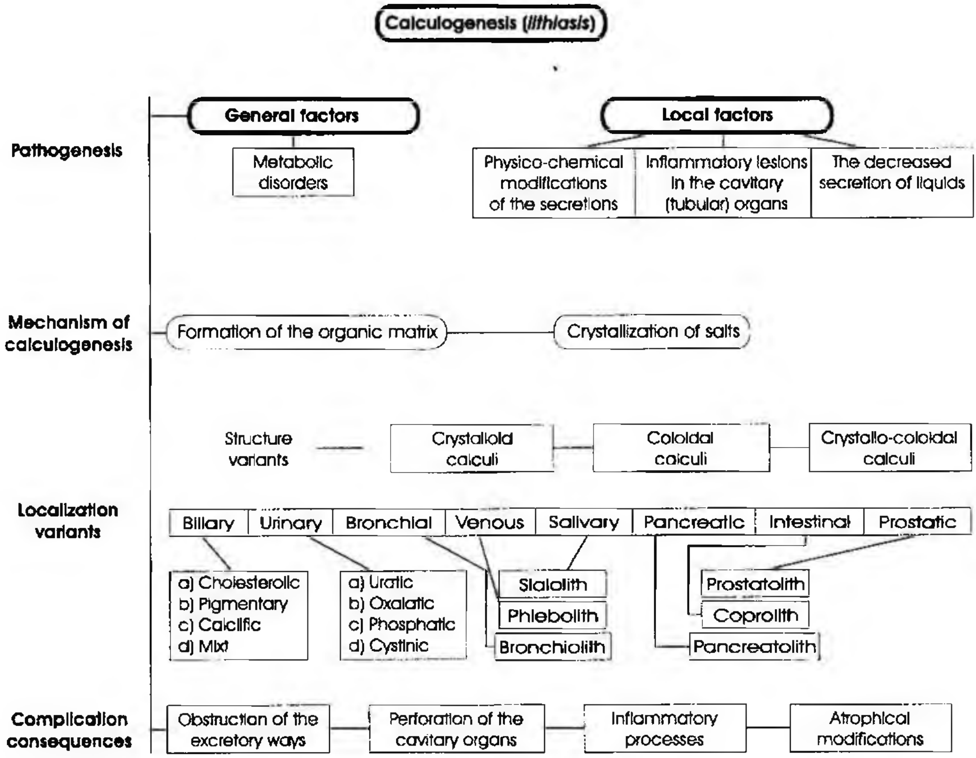
Considering their chemical structure the calculi can be cholesterolic, pigmentary, calcific or mixed. The biliary calculosis can evolve into obstruction of the cystic canal, retention of bile and the developing of hydropsy, mucocele or even of the vesicular empyema, the apparition of the acute or chronic inflammation of the vesicle, the perforation of the wall and the overflowing of bile into the peritoneal cavity, leading to consecutive biliary peritonitis.

Macrospecimen "Renal calculi" (fig. 32).

In the cavity of the renal pelvis there can be observed multiple calculi of irregular form, branchlike (corallike), with a rough surface and a whitish color. The cavities of the pelvis and of the calyces are dilated, and the renal parenchyma is atrophied.

Considering their chemical composition, the most frequent are the uratic calculi (consisting of uric acid and its salts), calcium oxalate and phosphate calculi. The pelvic calculi cause retention of the urine, distention of the pelvis and calyces, atrophy of the renal parenchyma, and repeated installation of hydronephrosis. It is associated with chronic pyelonephritis.

Table 2



Chapter 2
EXTRACELLULAR INJURY

In this type of degeneration the metabolic disorders are present in the connective tissue, particularly in the stroma of the organs and in the blood vessel walls (the basal membrane of the blood vessels consists of fundamental substance and reticuline fibers). They manifest themselves by the storing of some quantitative and qualitative modified metabolic products in the intercellular substance.

1. Fibrinoid degeneration (*fibrinoid intumescence*).

This is an irreversible process of disorganization of the connective tissue. It is manifest by the destruction of the fundamental substance and of collagen fibers. There is a considerable increase of vaso-tissular permeability, which leads to fibrinoid formation. Fibrinoid is a complex substance, consisting of proteins and polysacharides, which come from collagen and fundamental substance degradation, from plasma, as a result of an increased permeability of the blood vessels, and from cellular nucleoproteins. The obligatory component of the fibrinoid is fibrin. As a consequence, fibrinoid has tinctorial qualities to fibrin; that is where its name comes from.

Macroscopically, there are no characteristic changes. The function of the affected organs is severely altered.

Two kinds of fibrinoid degeneration can be distinguished: of the connective tissue and of the blood vessels.

Electronomicrography "Fibrinoid intumescence of the connective tissue" (fig. 33).

The collagen fibers are tumefacted, homogenized, without transversal striation, and have fibrin deposits between them.

The progress of the fibrinoid changes leads to fibrinoid necrosis of the connective tissue.

Microspecimen "Fibrinoid necrosis of the connective tissue in rheumatism"(fig. 34).

A site of complete destruction of the connective tissue is found in this specimen. The collagen fibers are tumefacted, dissociated, in some places disintegrated, and transformed into a homogeneous mass with eosin tinctoriality.

Macrophagic and lymphocytic infiltration is observed around this focus. As a consequence, in the places where the fibrinoid modifications take place, sclerotic processes and hyalinosis appear. In this case the function of the affected organ is severely disturbed. It is seen in some allergic and autoimune diseases (rheumatic diseases, glomerulonephritis), angioneurotical diseases (hypertensive disease), plasmorrhagic diseases (atherosclerosis), infecto-allergic diseases, etc.

2. Extracellular hyaline degeneration

Hyaline describes a non-specific, homogeneous glassy, pink appearance due to dystrophic alterations in the extracellular space.

Macrospecimen "Hyalinosis of the heart valves".

The cusps of the mitral valve *(fig. 35)* are thickened, deformed, and fused with a hard white non-transparent substance. The chorda tendineae are thickened and shortened; the left atrio-ventricular opening is reduced, stenosed. The function of the valve is severely affected, and the cardiac valvulopathy develops. There is stenosis or mitral insufficiency, or, more frequently, mitral valve disease with predominance of stenosis or valvular insufficiency. The complications are cardiac insufficiency, pulmonary edema, bronchopneumonia, intracardiac thrombosis, thromboembolia, infarct, etc. It is more frequently in rheumatism.

Macrospecimen "Hyalinosis of the spleen capsule".

The capsule of the spleen is thickened *(fig. 36)*, with a chondroid (like the hyalin cartilage) consistency, whitish color, and shiny and translucent appearance (hence its name "glazed spleen"). It is a local process which develops as a result of chronic inflammation and local sclerosis. Metabolic disorders from the connective tissue, for example, ascites-peritonitis in pacients with hepatic cirrhosis cause the condition. An analog mechanism is observed in hyalinosis of large, old scars, especially of those caused by burns (so called keloid scars).

The hyalinosis of the vessels appears especially in the small caliber arteries and arterioles, preceded by the increase of the vascular permeability and plasmatic imbibition (plasmorrhage) of the vessels wall. Vascular hyalin consists of plasmatic precursors, especially of plasma proteins; the fibrillar elements of the vascular walls are successively destroyed, undergoing imbibition with fibrin and with other plasmatic compounds.

Microspecimen "Hyalinosis of the splenic arteries" (fig. 37).

The lumen of the central arteries of the follicles are narrowed, and the walls are thickened because of the hyalin accumulation under the endothelium. The hyalin masses move to the exterior and destroy the elastic membrane. The media (muscular fibers) undergoes atrophy. Gradually, the arteriole transforms into a hyalin tube (like a glass tube) with a thickened wall and a narrow, sometimes even completely obstructed lumen. These modifications lead to the ischemia and hypoxia of the organ, the atrophy of the parenchyma, and the perivascular proliferation of the connective tissue. The hyalinosis of the splenic arteries is a physiological process determined by the morphofunctional peculiarities of the spleen as a blood depositing organ. Generalized hyalinosis of the arteries is characteristic in hypertensive disease, secondary hypertension, and diabetes mellitus. First of all are affected the arteries of the brain, heart, kidneys, endocrine glands, etc.

Hyalinosis is, usually, an irreversible process which can lead to functional disorders and severe complications (for example arteriolosclerotic nephrosclerosis with the shrivelling of the kidneys in the hypertensive disease, rheumatic cardiac valvulopathies, intercapillary glomerulosclerosis and diabetic retinopathy, etc).

3. Amyloidosis

A. Definition: Accumulation of abnormal proteinaceous substance between cells in various tissues and organs of the body. The predominant morphogenic mechanism of amyloidosis is the pathological synthesis. Amyloid is a glycoprotein in which the fibrillar proteins are conjugated with polysaccharides. It consists of two main components: the ***fibrillar (F)*** component, which is a fibrillar protein and the ***plasmatic (P)*** component - plasma proteins and polysaccharides. The proteopolysaccharidic components are tightly bound both with each other and with the elements of the tissue depositing the amyloid, especially with the chondroitinsulfats of the fundamental substance of the connective tissue. The proteins make up to 96-98%, while polysaccharides make up 2-4% of the whole mass of the amyloid.

B. Appearance:

1. Gross:

Organs may be enlarged in weight and volume, nodular or diffuse pale gray, somewhat firm, with a translucent waxy or lardy appearance.

2. Light microscopic:

Pink, amorphous to fibrillar material in hematoxylin-eosin stain.

Macrospecimens "Nodular and diffuse amyloidosis of the spleen".

In both specimens the spleen is enlarged and hardened. In the nodular type (initial stage) of amyloidosis, multiple whitish, translucent nodules disseminated in the white pulp can be observed in cross section ***(fig. 38)***.This gives the spleen a spotted appearance. The explanation of this is that amyloid accumulates in the walls of the centrofollicular arteries, extending after this into the entire follicle. The lymphatic follicles become larger, semitransparent, and have a glassy shine like sago beans. That is why such a spleen is also called "sago spleen" (Virchow).

In the diffuse type (second stage), the amyloid uniformly deposits in all the parenchyma along the reticular fibers. The spleen is much larger, it's weight can reach up to 1000g ***(fig. 39)***, it is of hard consistency, and has a translucent red-brown appearance, like smoked meat (spleen with smoked or lard meat appearance).

Macrospecimen "Amyloid dystrophy of the kidney"(fig. 40).

The kidney is larger in volume, of hard consistency and a whitish-pale translucent (lardy) appearance in cross section, especially in the cortical region ("big lardy kidney").

Using customary microscopic stain (hematoxyline and eosin, picrofuxine) the amyloid substance appears unstructured and homogeneous. For elective identification of amyloid, a series of histochemical methods are used (table 3).

Table 3

Specific methods of amyloid identification

Staining methods	Characteristics
1) Macroscopic Virchow reaction	At successive application, of Lugol solution and sulphuric acid (10%), the amyloid will be violet-blue or a dark shade of green on the cross section surface
2) With Congo red	Amyloid is stained a dark shade of red, while the rest of the tissue yellowish-pink
3) With methyl-violet or with gentian violet	Amyloid is stained red, while the rest of the tissular elements are stained violet (metachromatic staining)
4) With thioflavin-S or –T	At the luminescent microscope (ultraviolet light), amyloid appears to be of a yellowish-green color

Macroscopically the amyloid can be identified with the specific Virchow reaction: the amyloid depositions are stained with iodine (Lugol solution) in red-brown. This color changes into violet-blue or almost dark green after the application of sulphuric acid (10%) ***(fig. 41)***.

The localization of the amyloid deposits in organs and tissues is characteristic:

- in blood or lymph vessel walls (in the intima or adventitia);
- on the basal membranes of the glandular structures (tubules, channels, ducts);
- in the stroma of the organs, along the reticular or collagen fibers;
- in the stroma of the organs, along the reticular or collagen fibers.

Microspecimen "Renal amyloidosis" (fig. 42).

Selective depositions of dark red amyloid masses are observed in the mezangium and in the glomerular capillaries, under the endothelium of the small artery walls, under the basal membrane of the tubules and along the reticular fibers of the stroma. In the epithelial cells of the contort tubes there can be observed dystrophic modifications, while in some lumens there are hyalin cylinders. As the dystrophic process evolves, the glomeruli and the pyramids are completely replaced by amyloid masses. Subsequently the diffuse proliferation of the connective tissue with the amyloid shrivelling of the kidney takes place.

The fibrillar structure of the amyloid substance is clearly observed at electronomicroscopic examination.

Electronomicrography "Amyloidosis of myocardium" (fig. 43).

Filamentous structures with a chaotic arrangement, representing the fibrillar protein – (the main component of the amyloid substance), are observed on the surface of the sarcolemma of cardiomyocytes. It is observed that the amyloid deposits extracellularly. The mitochondria are slightly tumefacted, while the cristae are partially destroyed.

Amyloidosis is an irreversible process, which ends with progressive atrophy of the parenchyma and sclerosis of the affected organs. Severe insufficiency or the abolition of organ function results.

The effects of amyloid dystrophy on the parenchyma of the affected organs are clearly observed in the amyloidosis of the liver.

Microspecimen "Hepatic amyloidosis" (fig. 44).

Extensive zones, in the hepatic trabeculae which are atrophied. In some areas they are completely absent and substituted with amyloid masses, homogeneously stained with eosin. The function of the liver is severely altered in amyloidosis. Amyloid shrivelling develops in the liver as a result of parenchyma atrophy and sclerotic processes which take place as a consequence of the increased activity of fibroblasts, in hypoxia conditions.

C. Pathogenesis

Most forms of amyloidosis involve:

1. Induction and accumulation of a proteic excess in tissues.
2. Proteolytic cleavage to form orderly filaments that are arranged in β -pleated sheet configuration.
3. Abnormal accumulation in tissues is associated with abnormal tissue function.

D. Forms of Amyloidosis

1. **Primary amyloidosis** (immunocyte-associated amyloidosis): amyloid is composed of immunoglobulin light changes: **amyloid AL**, and is associated with B-cell (lymphocyte/plasma cell) proliferative diseases, such as multiple myeloma and monoclonal gammopathies. May be associated with defective degradation of light chains AL protein. Seen in plasma cells tumors.
2. **Secondary amyloidosis** (also known as reactive systemic amyloidosis): amyloid is composed of a unique, non-immunoglobulin protein called **Amyloid AA** (*amyloid-associated*). It is the most frequent and important form of amyloid in humans. It is also of great clinical importance.

   This form of amyloidosis develops on the background of other affections such as:
   a) some chronic infections (tuberculosis, syphilis, leprosy, dysentery, bacterial endocarditis, actinomycosis, etc.);
   b) diseases accompanied by chronic purulent processes (suppurative bronchiectasia, abscesses, osteomyelitis, suppurative wounds, empyema, chronic septicemia);
   c) rheumatismal diseases (especially rheumatoid arthritis and systemic lupus erythematosus);
   d) malignant tumors (chronic paraproteinemic leucosis, lymphogranulomatosis).
3. **Endocrine amyloid** in certain endocrine tumors (medullary carcinoma of thyroid, islet tumors of pancreas), in islet of pancreas in patients with type II diabetes mellitus; amyloid derived from hormones - procalcitonin, islet amyloid polypeptide, secreted by β-cells.
4. **Aging associated amyloidosis.**

   Amiloid is composed of:
   - the normal transthyretin molecule (TTR - protein which transports thyroxine and retinol) in senile systemic and senile cardiac amyloidosis;
   - the mutant form of transthyretin in familial amyloid polyneuropathies;
   - the β-amyloid protein in Alzheimer's disease cerebral plaques.
5. **Amyloidosis related to long-term hemodialysis**; amyloid content β_2-microglobulin (component of MHC class I molecule).

E. Tissue distribution of amyloid (predominant).

1. Immunocyte-associated amyloidosis: heart, gastrointestinal tract, lung, peripheral nerves, skin, tongue (occasionally the eye and skeletal muscle).
2. Reactive systemic amyloidosis: kidney, liver, spleen, intestine, adrenal glands, lymph nodes, thyroid and others tissues.
3. Organ dysfunction is the result of cells death subsequent to vascular occlusion and/or physical barrier due to progressive amyloid deposition.
4. Organ-specific lesions.

a. Kidney:

Amyloid accumulates in the glomerulus (capillary basement membranes, mesangium), as well as the peritubular interstitium and blood vessel walls. Glomerular barrier to protein (charge and molecular barrier) is altered to result in protein-loosing nephropathy.

b. Spleen: amyloid accumulations in the splenic follicles (a sago spleen on gross exam). Amyloid in the splenic sinuses form dense sheets (a lardaceous spleen).

c. **Liver:** amyloid accumulates in the spaces of Disse, squeeze out hepatocytes and obliterate the sinusoids, liver atrophy and failure may result in advanced cases in man.
d. **Pancreas:** amyloid accumulates in the islets, diabetes mellitus results.
e. **Heart:** usually in the coronary arteres of old man.
f. **Gastrointestinal tract:**
Can occur at all levels, and may accumulate in the mucosa, submucosa, or the muscular tunics. It causes defects in absorption of nutrients, interferes with secretion of locally active enzymes, and impairs motility.
g. **Lung:** nodular masses described in bronchi and trachea.

4. Lipidic extracellular degeneration.

The metabolic disorders of extracellular fats are found in adipose tissue; they are represented by excessive accumulation of fat (obesity), or their decrease (cachexia).

Obesity can be primary, determined by constitutional –hereditary factors (the necessity of a highly caloric alimentation, which is genetically determined) and secondary, which is symptomatic and can be observed in some cerebral, endocrine and hereditary diseases (table 4).

Morphologically, obesity is manifested by the increase of fat in the subcutaneous tissue, large omentum, mediastinum, mesentery, retroperitoneal tissue and in the stroma of some internal organs (heart, pancreas, kidneys, liver). The lipomatosis of the heart is present in all types of obesity.

Table 4

General characteristic of the secondary obesity

Type of obesity	The main etiopathogenic factors
a) Alimentary	Excessive nutrition, hypodynamia
b) Cerebral	Cerebral tumors, trauma, neurotrope infections
c) Endocrine	1) Hypercorticism (basophilic adenoma of the anterior lobe of the pituitary gland or hormonally active tumors of the adrenocortical glands; 2) Hypothyroidism; 3) Hypogonadism (inflammatory processes, tumors, castration, climax); 4) Hyperinsulinism (beta-cell adenoma of the pancreatic insulae)
d) Hereditary	Genetic defects (including hereditary enzymopathies)

Microspecimen "Lipomatosis of the heart" (fig. 45).

The specimen contains groups of adipose cells (adipocytes), which infiltrate the myocardium, dissociating the muscular fibers, most of which are atrophied.

Macroscopically ***(fig. 46)*** the heart is larger and contains fat accumulations under the epicardium which surround the heart as a muff.

These manifestations are more visible in the area of the right ventricle, which is about 1-2 cm thick (the normal thickness is of 2-3 mm).

The contraction force of the myocardium is decreased, leading to cardiac insufficiency. The rupture of the right ventricular wall is also possible, leading to heart tamponade and sudden death.

It must be mentioned that obesity (including the lipomatosis of the heart) is one of the risk factors of the cardiac ischemic disease (ischemic heart disease).

Chapter 3
IREVERSIBLE CELL INJURY. CELL DEATH: NECROSIS AND APOPTOSIS

NECROSIS

Necrosis is a localized death of the cells, tissue or an organ in a living organism. It can be determined by various causal agents: traumatic *(the physic or chemic factors)*, toxic *(the bacterial toxins, chemical toxic substances, drugs)*, neurotrophic *(disorders of the trophic function of the central and/or of the peripheral nervous system)*, vascular *(the decreased arterial blood flow in an organ or tissue)* and allergic *(the lytic action of the immune complexes, antibodies in a sensitized organism)*.

Microscopic characteristic of the necrosis

a. Nuclear changes:

- Karyopyknosis - the condensation of the chromatin and the shrinkage of the nucleus
- Karyorrhexis - fragmentation of nucleus (chromatin).
- Karyolysis *(syn – chromatolysis)* - dissolution of chromatin.

b. Modifications of the cytoplasm:

- Denaturation and coagulation of the cytoplasmatic proteins.
- Cytorrhexis (plasmorrhexis) – fragmentation of the cytoplasm.
- Cytolysis (plasmolysis) - liquefaction and hydrolysis of the cytoplasm.

The earlier structural modifications can be easily revealed using electronic microscopy. The precise moment of the cellular death can not be exactly established.

Electronomicrography "Necrosis of the cell, karyopyknosis" (fig. 47).

The nucleus is smaller in volume, its membrane is wrinkled and shriveled. The karyoplasm has an increased electronic density because of the chromatin condensation; the nucleolus is not differentiated. The cytoplasm contains many vacuoles, the mitochondria are tumefacted and homogeneous and the Golgy apparatus is smaller in dimensions.

Karyopyknosis can persist for a long time, after that the nucleus is fragmented into small granules (karyorrhexis) which are scattered into the cytoplasm. The desintegration and dissolution of the nucleus (karyolysis) follows, leaving only a small nuclear shadow. In a day or two the nucleus in the necrotic cell totally disappears.

The intracellular organelles are gradually destroyed. In later phases the cytoplasm is also fragmented and dissolved, forming a homogeneous mass of small granules of amorphous substance called *cellular detritus.*

Electronomicrography "Focal (partial) necrosis of the cardiomyocyte" (fig. 48).

The sarcoplasm of the cardiomyocyte contains a focus of intracellular organelle destruction and lysis leading to their disappearance and the formation of vacuoles of a low electron density.

Karyopyknosis, karyorrhexis, the destruction of mitochondria, of myofibrils, of the sarcolemma, etc., are all irreversible lesions. According to experimental data, the irreversible modifications in the cardiomyocytes begin after 20 min from the moment of alteration, while the cells of the liver and kidneys are affected after 25-40 min.

Morphologic patterns of necrosis

Several patterns of tissue necrosis may be distinguished, reflecting the peculiarities of the macroscopic appearance of the necrotic tissue.

1. Coagulative (or coagulation) necrosis

It is characterized by the predomination of the densification, denaturation and dehydration (drying) processes of the tissues. The necrotic masses are dry, dense, of a yellowish-white color and may be sharply demarcated from surrounding viable tissue; they do not undergo for an extended time hydrolytic decomposition. This type of necrosis takes place in tissues with relatively few lysosomes to bring about complete breardown of cellular proteins. The myocardial infarction is prime example.

Microscopically much of the cellular outlines and tissue architecture can be discerned, cells have a homogenously, compact eosinophilic cytoplasm with loss of cells detail and nuclear changes.

Microspecimen "Necrosis of the contort renal tubular epithelium" (fig. 49).

The epithelial cells of the proximal and distal contort tubules are tumefacted and do not contain nuclei (karyolysis). The cytoplasm is homogeneous, of a pink (eosinophilic) color; the lumen of the tubes is smaller, and even absent in some of the tubules because of the obstructing masses of cellular detritus (plasmorrhexis and plasmolysis). The blood vessels are dilated and hyperemic. The cellular structure of the glomerulus, Henle's loop and of the collector tubules is unchanged.

Necrotic nephrosis appears as a result of hemodynamic disorders (cortical ischemia of the kidneys) and of the toxic action upon the nephrocytes of chemical substances such as mercury bichloride, ethylenglycol, etc. Clinically it is manifest by acute renal insufficiency (oliguria or anuria). It is also seen in shock conditions (cardiogenic, traumatic, toxic, bacterial, hemorrhagic, posttransfusional, etc.).

The eventual consequences of necrotic nephrosis are convalescence (the regeneration of the renal tubules and the reestablishment of diuresis) or death as a result of uremia.

Microspecimen "Necrosis of the striated muscles (cerous or Zencker's necrosis)" (fig. 50).

Among the normal muscular fibers there can be observed necrotic fibers with a tumefacted cytoplasm, and without nuclei and transversal striation. Some of them are fragmented into homogeneous proteic blocks of irregular form and various dimensions (plasmorrhexis). Macroscopically necrotic areas have a waxy appearance. It is more frequently seen in skeletal muscles in typhoid fever, exanthematous typhus, especially in the rectus abdominis muscles.

2. Liquefactive (colliquative) necrosis

The prevalence of softening, liquefaction and the autolysis of the dead tissues is observed; the necrotic masses appear semi-liquid, have a soft, flaccid consistence as a result of dissolution of tissue by the action of hydrolytic enzymes. Occurs in tissues that is rich in water and have high lysosomal and lipid content and the processes of hydrolysis are intense. More frequently it is met in the infarcts of the brain and spinal cord (white or gray cerebral softening).

In the nervous tissue the huge lysosomal content in neurons and relative lack of extracellular structural proteins (collagen), leads to rapid liquefaction under action of the lysosomal enzymes.

Microscopically the cells loose their membrane envelope and become granular eosinophilic and basophilic debris. Tissue architecture is obliterated.

Macrospecimen "White cerebral softening" (fig . 51).

The left hemisphere of the brain is deformed. In the subcortical nuclei area and in the occipital region there can be observed necrotic foci of irregular form, soft consistency, composed of a yellowish-white gelatinous mass.

It is seen usually in atherosclerosis and in the hypertensive disease (cerebral ischemic infarct). Clinically, it is manifest by paralysis (monoplegia, hemiplegia, aphasia, etc.). The most frequent consequence of cerebral softening is the formation of a cystic cavity (cystic transformation). If the necrotic site has relatively small dimensions, organizing processes begin, leading to the formation of a glial-connective scar.

Macrospecimen "Cerebral cyst" (fig. 52).

On transverse section the brain contains a well delimited cystic cavity, filled with a gelatinous mass. It is formed after the softening and reabsorption of the liquefied necrotic masses in the central portion of the cerebral ischemic infarct site.

3. Caseous necrosis

Is a distinctive form of coagulative necrosis. The dead tissues is soft, has a white-yellow color and a "cheese-like" appearance on gross examination.

Occurs commonly in tuberculosis and some chronic diseases (syphilis, lymphogranulomatosis, leprosy).

Microscopically the necrotic area appears as amorphous homogenously pink granular debris with loss of cellular integrity. Tissue architecture is obliterated.

Macrospecimen "Caseous necrosis of the mesenteric lymph nodes" (fig. 53).

The mesenteric lymph nodes are larger, have a tight mutual adhesion forming packages and conglomerations of dense consistency. On section the lymphoid tissue has a whitish-gray color, resembling dry ewe's cheese.

Microspecimen "Caseous necrosis of the lymph node in tuberculosis" (fig. 54).

Necrotic foci can be observed in the lymph node, which show an amorphous, granular, intensively eosinophilic mass. At the periphery there can be observed nuclear fragments (karyorrhexis); the surrounding tissue contains tuberculous granulomas with Langhans polynucleated giant cells.

The most frequent consequences of caseous necrosis are calcification (petrifying) and encapsulation of the necrotic focus.

4. Gangrenous necrosis:

It represents the necrosis of those tissues that have contact with the outer environment (air, bacteria). It is characterized by the brown-gray or black color of the mortified tissues; the most frequent localization is: extremities, superficial soft tissues, digestive tract, lungs, uterus, urogenital tracts. There can be distinguished dry, liquefactive and gas (anaerobe) gangrene.

The prevalent processes of dry gangrene are drying, densification and shriveling of the mortified tissues.

Macrospecimen "Dry gangrene of the foot" (fig. 55).

The tissues affected by gangrene are dry, wrinkled, and mummified as a result of the evaporation or absorption of the water by the normal neighbouring tissues. They have a black color and a dense consistency. A well defined delimitation line can be observed between the normal and the affected tissues (demarking inflammation).

The most frequent causes of the extremity gangrene are: thrombosis or thromboembolism of arteries in atherosclerosis, diabetes mellitus, obliterating endarteritis, burns, freezing, vibration disease, etc. The black color is due to the iron sulphite, which is formed as a result of the interaction of the hemoglobinogenic pigments with the atmospheric air and the hydrogen sulfate produced by the bacteria found in the mortified tissues. During demarcation inflammation, a progressive erosion of the necrotic tissue can be observed which leads to its complete detachment or autoamputation.

Macrospecimen "Liquefactive gangrene of the foot" (fig. 56).

The affected tissues are tumefacted, imbued with liquid, of a soft consistency and a bluish-gray or blackish color. There is a smell of putrefaction, and there is no demarcation line.

It is mostly seen in the lower extremities (in diabetes mellitus), in the lungs (as a complication of pneumonia, pulmonary abscesses and infarcts), and in the intestines (in atherosclerosis). It evolves because of the action of putrefaction saprophyte bacteria (Bac. fusiformis, putrificans, proteus, etc.), which become pathogenic in the mortified tissues. Clinically, severe toxemia is observed as a result of toxic product absorption from the necrotic tissues. The liquefactive gangrene is encouraged by venous stasis.

In those cases where the affected tissues are contaminated by anaerobic bacteria (Clostridium perfringens, oedematiens, histolyticum, septicum, etc.), anaerobe or gas gangrene develops. The affected region gains a emphysematous aspect, which is bubbly at palpation due to the gas infiltration. It has a greenish-gray color and a putrefied smell *(fig.57)*.

The process extends extremely fast to the neighbouring tissues along the muscles, connective sheaths, vessels and other tissues leading to their necrosis. The respective microorganisms elaborate exotoxins which lead to severe intoxication and to the extension of the necrotic process. It represents a complication of the extended, open wounds produced in conditions of war, and road and work accidents which produce massive muscle and bone destruction. It is considered to be an independent infectious disease (primary gangrene).

Macrospecimen "Gangrene of the small intestine" (fig. 58).

The intestine wall is edematous and black, with an opaque serous tunica. It is covered with fibrin deposits.

It is usually seen in atherosclerosis of the aorta and of the mesenteric artery, thrombosis of the mesenteric veins, and the strangling of the intestine in a hernial sac. It can be complicated with diffuse peritonitis, perforation of the intestinal wall, etc.

Another variety of necrosis is the eschar or decubitus necrosis. It represents necrotic foci of a blue-black color in the soft superficial tissues, the skin being, in many cases, ulcerated *(fig. 59)*. It appears primarily in severe, cachectic patients with circulatory and neurotrophic disorders. It is severe in the regions that are exposed to long local mechanical compression (above the prominent parts of the bones) in sacral, trochanteric, scapular, calcanean regions, etc. It is observed especially in longtime immobilized bed patients in the same position (with malignant tumors, severe infectious diseases, cardiac insufficiency, etc.). The eschars gradually ulcerate, reaching the prominent parts of the bones.

5. Fat necrosis

Refers to the enzyme-mediated necrosis of adipose tissue, characterized by cleavage of neutral fat by lipase to triglycerides and fatty acids; the released fatty acids combine calcium and form insoluble salts that precipitate in necrotic foci. This necrosis result from liberation of powerful digestive enzymes into the substance of the pancreas and peritoneal cavity. It occurs in the acute pancreatitis and may be seen after trauma to fat.

6. Fibrinoid necrosis

Is manifested by the destruction of connective tissue (ground substance and collagen fibers) of the organ's stroma and of the vascular walls; the necrotic masses infiltrate with plasma proteins (fibrinogen). The fibrinoid necrosis is characteristic for the imuno-allergic diseases (rheumatism, systemic lupus erythematosus, rheumatoid arthritis) and malign hypertension.

The consequences of necrosis (table 5).

The substitution of the necrotic masses with connective tissue - organization (*cicatrization*) is one of the most frequent consequences of the necrosis of different organs. Other consequences are: a) encapsulation, calcification (*petrification*), ossification, sequestration – mostly seen in dry necrosis; b) the formation of cysts *(cystic transformation)*, purulent lysis – in liquefactive necrosis; c) autoamputation and mummification are frequent consequences of the dry gangrene.

Table 5

The consequences of necrosis

a) Organization *(cicatrization)*	The substitution of the necrotic site with connective tissue
b) Encapsulation	The formation of a membrane *(capsule)* of connective tissue around the necrotic site
c) Calcification *(petrification)*	The storing of insoluble calcium salts in the necrotic masses
d) Ossification	The substitution of the necrotic site with new formed bone tissue
e) Cyst formation *(cystic transformation)*	The appearance of some cavities after the lesion and reabsorption of the mortified tissue in liquefactive necrosis *(more frequently in the brain and the spinal cord)*
f) Sequestration	The detachment of the mortified tissue from the healthy tissue
g) Autoamputation	The total detachement from the body of some members or organs
h) Mummification	The drying of the mortified tissue in gangrene
i) Purulent lysis	The desintegration of the necrotic masses under the action of polymorphonucleated leukocytes in case of pyogenic overinfection.

APOPTOSIS

Apoptosis *(literally "falling off")* is a specialized, morphologically distinctive form of cell death, which should be differentiated from the common coagulative necrosis. It is a programmed and energy-dependent process of cell death designed to switch off and eliminate them *(so-called cell suicide)*. Apoptosis occurs both physiologically and pathologically.

The elimination of cells by apoptosis is the main mechanism of cell death in several important physiologic processes and diseases, for example:

- removal of excess cells during embryonic development, e.g. limb development;
- elimination of cells in developmental involution, e.g. involution of thymus;
- elimination of cells in hormone-dependent physiologic involution (e.g. involution of lactating mammary gland epithelium after weaning and cyclic changes in endometrium during the menstrual cycle);
- clonal selection of lymphocytes in the induction of self-tolerance in development (deletion of autoreactive T cells in the thymus);
- elimination of cells in tissues that require a high cell turnover (intestinal lining epithelial cells);
- elimination of cells with acquired DNA damage through viral infection, ultraviolet or ionizing irradiation, cytotoxic agents (drugs);
- elimination of neoplastic cells in tumors;
- killing of viral infected cells by cytotoxic T-cells (e.g. viral hepatitis);
- death of nerve cells in neurodegenerative diseases (Alzheimer`s disease).

Apoptosis usually involves single cell or clusters of cells. Initially the apoptotic cell lose surface specializations and junctions, shrinking in size, the nuclear chromatin condenses beneath the nuclear membrane. After that there is spitting of the cell into several fragments – apoptotic bodies. Apoptotic body is recognized in tissue sections as rounded or oval masses of intensely eosinophilic cytoplasm, containing some dense nuclear chromatin fragments and viable mitochondria and intact organelles. In final phase apoptotic bodies is recognized and phagocitosed by adjacent cells for destruction ***(fig. 60)***. The process takes a few minutes only, therefore this type of cell death is often hard to observe in vivo. This phagocytosis is clearly different from that seen in inflammation, when activated macrophages are recruited from outside the immediate area of death.

Apoptotic death can be triggered by a wide variety of stimuli, and not all cells necessarily will die in response to the same stimulus. Among the more important death stimuli is DNA damage (by irradiation or drugs used for cancer chemotherapy and by viruses).

Pathologic inhibition of apoptosis is observed in many neoplastic diseases and in several viral diseases.

Chapter 4
BLOOD AND LYMPH CIRCULATION DISORDERS

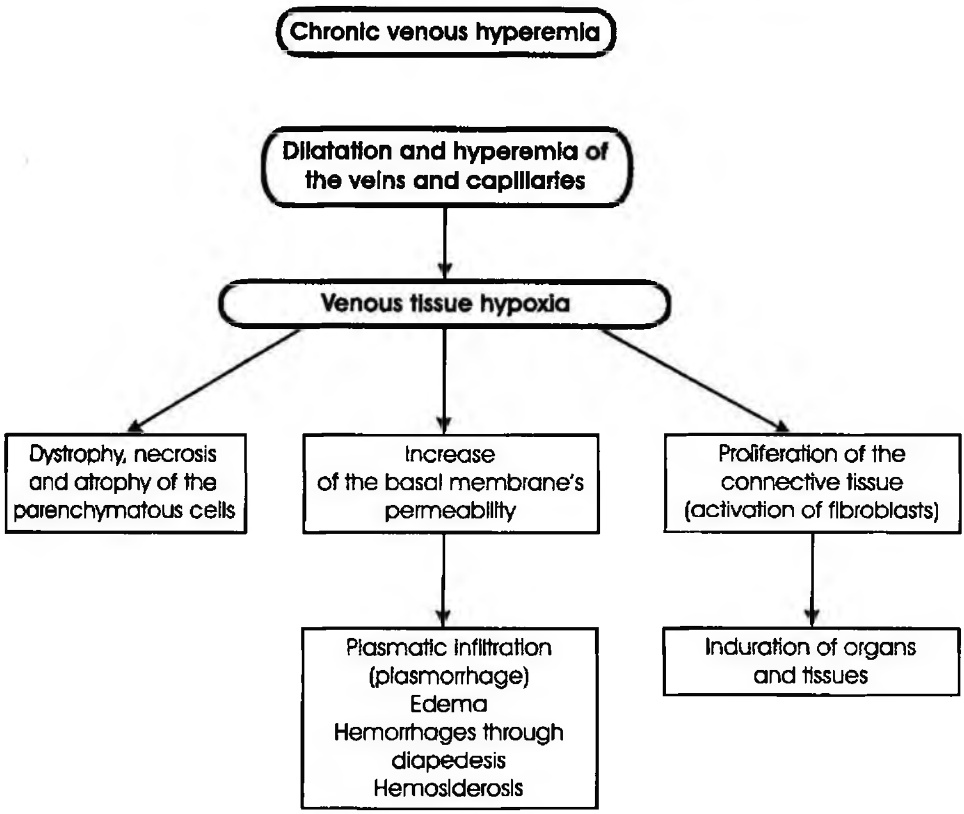
4.1. THE VENOUS HYPEREMIA (VENOUS CONGESTION)

Venous hyperemia is caused by the slowing (decrease) of venous blood flow in normal arterial flow conditions. It is manifest by a passive dilatation of veins and capillaries with an excess of blood in these vessels. It can be localized or generalized, acute or chronic.

Generalized venous hyperemia is due to the acute or chronic cardiac insufficiency, being based on the failure of cardiac activity (decompensation of the heart). Acute cardiac insufficiency is seen in myocardial infarction, acute myocarditis, acute endocarditis with valvular rupture, hypertonic crisis, etc. It is manifest by generalized acute venous hyperemia: the appearance of hyperemia and dilatation of veins and capillaries, plasmatic infiltration (plasmorrhagia) and edema, multiple perivascular hemorrhage through diapedesis, dystrophic and necrotic lesions of the parenchymatous elements can be observed in organs and tissues. Chronic cardiac insufficiency is seen in some chronic cardiac diseases such as valvulopathy, cardiosclerosis, rhythm and conduction disorders, chronic myocarditis, constrictive pericarditis, etc. and leads to atrophy, hemosiderosis and sclerosis of organs and tissues. These modifications are stereotypical and are seen both in generalized and localized venous hyperemia (they are schematically represented in table 6).

Table 6

Morphogenesis of the stasis (cyanotic) induration of the organs



The main pathogenic mechanism of the morphologic changes in venous hyperemia is the tissue hypoxia (venous hypoxia or due to passive congestion).

The characteristic macroscopic aspects of the organs affected by chronic venous hyperemia can be divided in the following way:

a) the increased dimensions and weight;
b) the organ's capsule is smooth, spread (under tension);
c) increased consistency (density);
d) the color of the organ, if sectioned is dark red – purple – the color of unoxygenized venous blood;
e) if sectioned, a great quantity of dark colored blood drains out.

The modifications of various organs and tissues in chronic venous congestion have many common features and are named "stasis or cyanotic induration". Some specific symptoms in various organs can be observed because of their vessel structures, especially in liver and lungs (table 7).

Table 7

The morphologic manifestations of the chronic generalized venous stasis (of the chronic cardiac insufficiency)

Organ	Morphologic modifications
1	2
Skin	Cyanosis (acrocyanosis)
Subcutaneus cellular adipose tissue	Edema (anasarca)
Liver	Hyperemia – atrophy – nutmeg fibrosis or cirrhosis (cirrhosis cardiac)
Lungs	Brown induration, edema
Spleen, kidneys	Cyanotic induration
Serous cavities	Hydropsy: hydrothorax, hydropericardium, ascites (hydroperitoneum)

Macrospecimen "Cyanotic induration of the kidney (stasis kidney)".

The kidney is larger in weight and volume ***(fig.61)***, the capsule is under tension, the consistency is dense, if sectioned the color is dark-purple-red (cyanotic), the limit between the cortical and medullar layers is unclear, erased.

At microscopic examination, there is dilatation and hyperemia of the glomerular and peritubular capillaries, dystrophic lesions of the contort tubulae epithelium and the excessive proliferation of connective tissue is observed in the stasis kidney.

The most frequent causes of the stasis kidney are cardiac insufficiency, thrombosis or the renal vein compression (tumors, metastasis, aortic aneurism, adherences).

Macrospecimen "Venous hyperemia of the skin".

Macroscopically, the skin and the mucous membranes have a bluish (cyanotic) color and a decreased temperature ***(fig.62)***. The veins and capillaries of the dermis are dilated, filled with blood; in some places perivascular hemorrhages through diapedesis, and proliferation of connective tissue are present. The tissular elements are dissociated due to edema liquid accumulation.

On the background of longtime stasis, edema and sclerosis, inflammatory processes and trophic ulcers can appear in the skin.

It is a doubtless symptom of the cardiac insufficiency.

Macrospecimen "Chronic venous hyperemia of the liver (nutmeg liver)"(fig.63).

The liver is larger in size and weight, has a spread smooth capsule, increased consistency, and a rounded anterior margin. On section a very accentuated lobular aspect is observed, a variegated characteristic aspect, which resembles the American nut kernel (nutmeg), this is due to the alternation of some small, punctiform foci of dark red color (central lobular zones of the hepatic lobules), mixed with others of a brown-yellow color (peripheral zones of the lobules). This variegated aspect of the liver is due to the particularities of the liver blood circulation and of the organ's angioarchitecture. It is most frequently seen in right cardiac insufficiency (greater circulation stasis). An analogy can evolve in the thrombosis of the hepatic veins (Budd-Chiary syndrome).

Microspecimen "Chronic venous hyperemia of the liver (nutmeg liver)"(fig.64).

The central veins of the hepatic lobule and the adjacent portions of the sinusoid capillaries are dilated, filled with blood. In the center of the lobules diapedetic hemorrhages can be observed ("blood lakes"), the hepatocytes are atrophied, the central portions of the hepatic trabecles are thin almost liniar (macroscopically, these pericentrolobular zones have a dark red color). In the intermediary zones of the lobules, fat dystrophy of the hepatocytes can be observed (macroscopically, they have a brown-yellow color). In the peripheral zones, the sinusoidal capillaries and the hepatocytes are not modified, and the trabecular structure is unchanged (macroscopically the color of these zones is brown-red – the normal appearance of the hepatic parenchyma).

Selective hyperemia of the central zones of the lobules is explained by the fact that venous stasis involve firstly the hepatic veins then at lobular level – the centrolobular veins and the neighboring portions of the sinusoid capillaries. The stasis does not extend to the lobular periphery, due to the greater blood speed and pressure in the peripheral zones of the sinusoid capillaries where the arterial capillaries of the hepatic artery system penetrate (at the border of the external and intermediary third of the hepatic lobules). Because of this, the center of the hepatic lobule is hyperemiated, while periphery is not affected by hyperemia. These facts produce the variegated appearance of the stasis (nutmeg) liver. The mechanism of development of the nutmeg liver is illustrated schematically in fig.65. Chronic venous hyperemia leads to stasis cirrhosis (cardiac) of the liver.

Macrospecimen "Chronic venous hyperemia of the lung (brown induration of the lung)" (fig.66).

The lung is larger in weight and volume, has a dense consistency, and the section surface has a brown color. The porosity of the parenchyma is decreased.

The increased consistency of the lung is due to the excessive proliferation of the connective tissue in the alveolar walls, its color – to the accumulation of hemosiderin pigment. The decreased porosity is due to the thickening of the alveolar septa because of hyperemia and the sclerosis of the vessels.

Microspecimen "Chronic venous hyperemia of the lung (stasis lung, brown induration of the lung)" (fig.21).

The interalveolar septa are thickened, affected by sclerosis. The veins and capillaries are dilated, and hyperemic, with thickened walls. The alveolar spaces contain phagocyte cells filled with hemosiderin granules (sideroblasts and siderophages); some alveoli contain edema liquid, the whole erythrocytes or parts of desintegrated erythrocytes.

Stasis hyperemia of the lungs is seen most frequently in cardiac insufficiency, especially in mitral stenosis (due to this fact it is also called "cardiac lung"). Macrophages with hemosiderin granules in their cytoplasm can be found in the sputa of patients with cardiac insufficiency and are called "cardiac cells". Diapedetic hemorrhages, hemosiderosis and the proliferation of connective tissue are linked to venous tissular hypoxia which determines the increase of vascular permeability and of the synthetic activity of the alveolar septa fibroblasts.

4.2. ISCHEMIA

Ischemia is the decrease or suppression of the arterial blood flow in a tissue, organ or part of the organ. The most frequent causes of this phenomenon are thrombosis, embolism and angiospasm (table 8). Macroscopically, the organ is reduced in size, has a decreased temperature, and pale color. The effects of ischemia depend on many factors. Among them the main factors are:

a) the rapidity of obstruction onset (sudden or slow, gradual);
b) the step of obstruction (partial or complete);
c) the level of obstruction (the major or minor branches of arteries);
d) causative factor peculiarities (spasm, thrombus, embolus);
e) the state of collateral circulation;
f) duration of obstruction (of ischemia);
g) the tissue sensitivity towards the lack of oxygen;
h) the state of tissular metabolism;
i) the functional state of the organ at the moment of ischemia onset (work state or rest state).

Dystrophic and necrotic lesions appear in acute ischemia, due to the absence of oxygen and nutritive substances in the tissue and to the accumulation of metabolic products. These lesions are preceded by certain histochemic and ultrastructural modifications: the disappearance of glycogen from the tissue affected by ischemia, the decreased (absent) activity of the oxidoreduction ferments, the tumefaction and destruction of the mitochondria. Longstanding obstructive ischemia can cause ischemic necrosis and infarct.

Table 8

General characteristics of ischemia

Variants of ischemia	Mechanisms of development	Examples of diseases in which it is seen
a) Angiospastic	The spasm of artery due to the action of various vasoconstrictive factors	Hypertensive disease, atherosclerosis, Raynaud's disease
b) By obstruction	Thrombosis, embolism, inflammation of the arterial wall, proliferation of connective tissue	Artery atherosclerosis, obliterative endarteritis, productive vasculitis
c) By compression	External compression of the arteries	Tumors, liquid accumulations, ligatures, exostosis
d) By blood redistribution	The penetration of a zone being preliminary affected by ischemia by a great quantity of blood	Ischemia of the brain after the rapid elimination of ascites liquid from the abdominal cavity in patients with hepatic cirrhosis

4.3. INFARCTION

Infarction is the necrosis of a portion of an organ or of a whole organ due to the interruption of the blood flow, as a consequence of ischemia (vascular or ischemic necrosis).

The direct causes of the infarct can be: longtime vascular spasm, thrombosis, embolism or the functional overtaxation of an organ with insufficient blood flow conditions. In the infarct evolution two successive stages can be observed: ischemic (prenecrotic) and necrotic.

For the diagnosis of the ischemic stage of infarct, electron microscopy, luminescent microscopy and histochemic methods are used (table 9).

Table 9

Morphologic identification methods of early ischemic lesions

Investigation methods	Investigation methods	Ischemia's criteria
1	2	3
a) Electron microscopy	Usual methods of electron microscopy	Tumefaction and destruction of the mitochondria; the lesions appear after 10-20 min, evolving until the rupture of the mitochondrial membrane in 1-2 hours after the onset of ischemia
b) Histochemical methods	I –Glycogen identification: PAS reaction with amylases or the Best reaction with carmin – the glycogen granules are stained in red (after treating with amylases the glycogen disappears)	The decrease and disappearance of glycogen from cells (begins after 5-15 min of ischemia)
	II – The determining of the activity of oxidoreduction ferments (SDH-ase, NAD-diaphorase); The reaction products – phormasan granules stained in violet-blue	The decrease and stopping of the activity of oxidoreduction ferments
c) Luminescent microscopy	I – The staining of the specimens with acridin orange	The ischemic zones have a greenish-yellow luminescence which is more intense than in normal tissues
	II – The photochemical fluorochroming (the treating of the specimens with short wave UV rays)	The intensity of the ischemic site luminescence is greater comparing to the intact zones

Electronomicrography "The ischemic stage of the myocardial infarction"(fig.67).

During infarction the mitochondria are tumefacted, the cristae are partially disintegrated, the glycogen granules are absent and the intracellular structures are dissociated due to the accumulation of the edema fluid. In the nucleus, marginal localization (under the membrane) of the chromatin can be observed. The rapid disappearance of glycogen from the sarcoplasm of the cardiomyocytes (in the first 5-15 min) is one of the early signs of the myocardial ischemia. The mitochondrial modifications and the margination of the nuclear chromatin begins after 10-20 min from the ischemic onset.

Histotopographical microspecimen "Myocardial infarction: the decrease of the succinatdehydrogenase activity".

In the ischemic zone of the myocardium *(fig.68)* the decrease or disappearance of the SDH-ase activity (colorless zones) can be observed while in the normal zones the activity of the enzyme is normal. In the intermediary zone the color intensity is lower, indicating the diminishing of the enzyme activity. The mechanism of the reaction consists in the reduction of the tetrazolium salts under the action of SDH-ase and their sedimentation as blue-violet granules. The reaction to SDH-ase and to other oxidoreduction ferments disappears 12 hours after the ischemic onset.

Microspecimen "The ischemic stage of the myocardial infarction: luminescent microscopy with acridine orange" (fig.69).

The ischemic zones have a greenish colored fluorescence of a greater intensity than the intact zones, which have a much lower luminosity.

The fluorescence modification of cardiomyocyte sarcoplasm is due to the physico-chemical disorders of the myofibrillar proteins, especially of myosin, in ischemic conditions. These modifications determine a more intense fixation of acridine orange by myosin and the increase of luminescence intensity of the ischemic cells.

The duration of the ischemic stage of the infarct is of about 18-24 hours. After this period of time the necrotic stage of the infarct begins. It is characterized by the autolysis of the mortified tissue and all the macro- and microscopic signs of necrosis; the infarct zone becomes microscopically visible.

By the external appearance (color) and by the morphogenetic mechanism three varieties of infarct can be distinguished: white (ischemic), red (hemorrhagic) and white with a red border (ischemic with a hemorrhagic belt).

The classification of infarcts is represented in table 10.

Table 10

Classification of infarcts

Classification criteria	Variant of infarct	Morphogenetic mechanism	Most frequent localization
I – By morphogenetic mechanism and color	1) White (ischemic)	Insufficient collateral circulation	Spleen
	2) Red (hemorrhagic)	a) Double vascularisation of the organ b) Venous stasis	Lungs, intestine
	3) White with red border (ischemic with hemorrhagic belt)	The spasm of the infarct peripheral zone vessels is followed by their dilatation, hyperemia and diapedetic hemorrhages	Myocardium, kidneys
I – By the geometrical shape	1) Triangular (conical)	Magistral type of organ vascularisation	Spleen, lungs, kidneys
	2) Irregular	Rich anastomotic circulation of the organ	Myocardium, brain, intestines
III – By the type of necrosis	1) Dry (coagulation) necrosis		Myocardium, spleen, kidneys
	2) Liquifactive (coliquation) necrosis		Brain, intestine

Macrospecimen "White (ischemic) infarct in the spleen" (fig.70).

The infarct zones are well delimited, have a triangular (conical) shape with the tip of it pointed towards the hilum of the organ and with its base – towards the capsule. It has a white color, and increased consistency (coagulation necrosis). In the zones where the infarct reaches the surface of the spleen the capsule is rough, and covered with fibrin deposits (reactive fibrinous perispleenitis). This causes pain in the left hypochondric area. The most frequent causes of the splenic infarct are thrombosis or embolism of the splenic artery. It is seen in verrucose rheumatismal or infective endocarditis, leucosis, ischemic heart disease, hypertensive disease, etc. The conic shape and the white color are determined by the magistral type of vascularisation of the spleen and by the poor collateral circulation, which excludes the possibility of alternative blood flow in the infarct zone.

Microspecimen "Ischemic infarct in the spleen" (fig.71).

The specimen contains an amorphous, homogeneous, eosinophilic, necrotic zone. The cells do not contain nuclei (karyolysis). The trabecular and vascular outline is unchanged. At the peripheral zones of the infarct polymorphonucleated leukocyte infiltration is observed as a manifestation of the demarcational inflammation, which delimits the necrotic zone. This zone is determined by the harmful influence upon the tissue of the toxic substances eliminated from the necrotic masses.

The splenic infarct has usually a benign evolution, but in some cases rupture of the spleen with hemorrhage into the abdominal cavity, abscess and total necrosis of the spleen is possible. The most frequent consequence is the organization and cicatrization of the infarct, with the deformation of the spleen *(fig.72)*. The perifocal inflammation of the capsule leads often to adhesions between the splenic capsule and the diaphragm muscle, parietal peritoneum, intestinal loops.

Red infarct with massive hemorrhage in the necrotic tissue is rarely observed in the spleen. It is seen in thrombosis or compression of the splenic artery, because of splenic venous stasis (hemorrhagic venous infarct).

Macrospecimen "Renal infarct" (fig.73).

The kidney contains a well delimited zone of a yellowish-white color surrounded by a red belt (white infarct with a red belt).This zone has a triangular shape, with the tip pointed towards the renal pelvis and the base towards the capsule, and there is increased consistency (coagulation necrosis). On the surface of the capsule fibrinous deposits can be observed. The necrotic process affects both layers of renal parenchyma.

The most frequent causes of the renal infarct are thromboembolism or thrombosis of the renal artery. It is seen in rheumatismal and infective endocarditis, atherosclerosis, hypertensive disease, ischemic heart disease etc.

Microspecimen "White infarct with hemorrhagic belt in kidneys" (fig.74).

The specimen contains a necrotic zone with decreased nuclei. The tissue is homogeneously eosinophilic, but the histologic architecture of the renal tissue is unchanged. The outline of the glomeruli and of the tubules can be recognized, while in the peripheral zones the hyperemia of glomerular and peritubular capillaries and hemorrhages (the hemorrhagic belt) are observed. The appearance of this belt is explained by the fact that the vascular spasm from the infarct periphery is followed by dilatation, hyperemia and hemorrhages. Leukocyte infiltration as a sign of demarcational perifocal inflammation is observed in this zone.

As a result of the hemorrhagic belt, renal infarct is clinically manifest by hematuria, while inflammation of the capsule determines the presence of pain in the lumbar region.

The red (venous) infarct rarely develops in the kidneys due to renal vein thrombosis.

The most frequent consequence of the renal infarct is cicatrization (organization).

Macrospecimen "Hemorrhagic pulmonary infarct" (fig.75).

The infarct zone has a conical shape with its base toward the pleura, the color is dark red; the consistency of the tissue is increased. The surface of pleura contains fibrinous deposits.

The cause of pulmonary infarct is the obstruction of the pulmonary artery by a thrombus or embolus (with a starting point in the peripheral venous system, especially in the veins of the lower extremities). The hemorrhagic appearance of the infarct is due to the double circulation in pulmonary tissue: from the pulmonary artery (small circulation) and the bronchial artery (great circulation). These arteries contain multiple anastomosis between them, which do not function in physiological conditions. The obstruction of the pulmonary artery is followed by the reflex opening of the anastomosis with the penetration of blood under pressure from the great circulation (bronchial artery) in the ischemic territory. This leads to the wall rupture of pulmonary capillaries and venules and to the blood regurgitation with the flooding of the infarct zone (of the interalveolar septa and of the alveolar spaces).

The second factor that determines the hemorrhagic character of the lung infarct is the venous stasis, because it supports the retrograde circulation of blood through veins, flooding the ischemic zone. Venous congestion is seen in left cardiac insufficiency, especially in mitral stenosis. Clinically, pulmonary infarct is manifest by hemoptysis (the presence of blood in the sputa) and pleural friction (frottage) at auscultation.

Microspecimen "Pulmonary hemorrhagic infarct"(fig.76).

In the necrotic site, signs of the pulmonary tissue necrosis are observed: destruction of the interalveolar septa, the absence of nuclei in the septal cells and in the epitheliocytes (alveolocytes), infiltration with agglutinated and hemolysed erythrocytes which are collected in the alveolar lumen and interstitial tissue. The blood vessels are dilated and hyperemic. The erythrocytes can also be seen in the lumen of the bronchi, explaining hemoptysis. In the peripheral zones of the infarct there can be observed a perifocal inflammatory reaction (polynucleated leukocyte infiltration) and collections of siderophages.

The usual consequence of the pulmonary infarct is cicatrization. The possible complications are: postinfarct pneumonia, pulmonary abscess, pleural empyema, pneumothorax, pulmonary gangrene; in the posinfarct scar pulmonary cancer can appear.

White (ischemic) pulmonary infarct is very rare, seen in cases of obstruction of the bronchial artery by sclerosis and obliteration.

Macrospecimen "White cerebral infarct (white cerebral softening)".

In the subcortical nuclei and in the right occipital zone *(fig.50)* sites of softening cerebral tissue which have a white-gray color (coliquative necrosis), and an irregular form can be observed. It is most frequently found in atherosclerosis of the cerebral arteries or of the major arteries of the head (carotid and vertebral) and in hypertensive disease. The direct causes are spasm, thrombosis or embolism of the arteries. It is also observed in cases of intracardiac thrombosis (for example, in acute transmural myocardial infarct, cardiac aneurysm) and verrucose rheumatic endocarditis. Clinically, it is manifest by psychic or neurological disorders, depending on the localization of the necrotic process. For example the affection of the subcortical nuclei with the lesion of the conduction ways leads to paralysis. As a consequence of a small cerebral ischemic infarct a connective-glial scar is formed, while the softened area suffers a cystic transformation (the formation of a cystic cavity *(fig. 51)*).

In conclusion, analysis of the described specimens demonstrates that the clinical importance and the effects of the infarction depend on its localization and spreading. In some cases the infarction can evolve without any symptoms or functional significance. In case of vital organ lesion, it can lead to severe complications and even to death (myocardial, cerebral infarct). The general events of the infarct are manifest by fever and leukocytosis.

The possible consequences of a different localization infarction are:

a) autolysis, reabsorption of the necrotic tissue and the reestablishment of the preexisting tissue;
b) organization (cicatrization);
c) incapsulation;
d) petrification (calcification);
e) formation of cysts (cystic transformation);
f) hemosiderosis;
g) purulent lysis (festering).

4.4.1. HEMORRHAGE. PLASMORRHAGE

Hemorrhage represents the exiting of blood from the lumen of the vessels or from the heart chambers. It can be external, when the blood drains out of the body (table 11) and internal, when the blood accumulates in the tissues, organs or preexisting cavities (table 12).

Table 11

Varieties of the external hemorrhages

Term	Significance
1	2
Epistaxis (rhinorrhagia)	- nasal hemorrhage
Haemoptysia	- bronchopulmonar hemorrhage with elimination of blood with the sputum
Haematemesis	- gastric or esophagal hemorrhage manifest by blood vomiting
Melaena	- the elimination of blood with fecal masses (fecal masses with tarry appearance , black color)
Metrorrhagia	-intermenstrual uterine bleeding (between menstrual periods)
Menorrhagia	- abundant and prolonged menstruation
Hematuria	- the elimination of blood with urine
Otorrhagia	- bleeding from the ear
Stomatorrhagia	- the bleeding from the bucal mucousa

Table 12

Varieties of hemorrhages into the serous cavities and cavitary organs

Term	Significance
Haemopericardium	- bleeding into the pericardial sac
Haemothorax	- bleeding into the pleural cavity
Haemoperitoneum	- accumulation of blood in the peritoneal cavity
Haemarthrosis	- bleeding into the cavity of an articulation
Haematocoele	- bleeding into the tunica vaginalis of the testicle or into the scrotal tissue
Haemosalpinx	- bleeding into the lumen of the uterine tubes
Haemobilia	- bleeding into the gallbladder
Haemamnion	- bleeding into the amniotic liquid due to the rupture of the umbilical cord vessels
Haemocephaly	- bleeding into the cerebral ventricles
Haematometrum	- accumulation of blood in the uterine cavity

The hemorrhage can be produced by:

a) rupture of the vascular or cardiac wall;
b) the erosion of the vascular wall;
c) diapedesis, caused by the increased permeability of the venular and capillary walls (table 13).

The interstitial hemorrhage (in tissues) can be manifest as a hemorrhagic infiltration and hematoma (table 14).

Table 13

The morphogenic mechanisms of the hemorrhage

The mechanism of hemorrhage	Examples of diseases in which it is seen
1	2
a) By the rupture of the vessels (per rhexis)	Hypertensive disease, atherosclerosis, arterial aneurysm, cardiac aneurysm, myocardial infarction, varicose veins, trauma, leukosis
b) By the erosion of the vascular wall (per diabrosis)	Ulcer diseases, typhoid fever, dysentery, tuberculosis, abscess, malignant tumor (cancer, sarcoma), tubal pregnancy
b) By diapedesis: - the increase of vascular permeability (per diapedesis)	Hypertensive disease, systemic vasculitis, infectious diseases (flu, smallpox, anthrax, septicemia), anemia, leukosis, tissue hypoxia, C avitaminosis.

Table 14

Interstitial (tissue) hemorrhage varieties

Term	Signification
Petechiae	- small, pin-point hemorrhage, of capillary origin
Ecchymosis	- Hemorrhage in the skin, mucous membranes, manifest by spots of thumb-nail dimensions or a little larger, which do not manifest surface elevation
Hemorhagic suffusion	- flat hemorrhage under a covering layer (skin, mucous membranes, serous membranes), which can reach large size
Hemorhagic infiltration	- tissue hemorrhage with the blood spreading between the tissue elements
Hematoma	- interstitial hemorrhage with a circumscribed accumulation of blood and the formation of a cavity due to the compression and destruction of the adjacent tissue; the blood can be liquid or coagulated
Apoplexy	- massive, acute hemorrhage in an organ causing more or less the total functional loss (cerebral a., ovarian a.., suprarenal a.)
Cephalohematoma	- cranial subperiosteal hematoma in newborn as a result of the obstetrical trauma; it can be internal and external (between dura mater and periosteum)
Purpura	- syndrom characterized by the appearance of multiple hemorrhages in the skin and mucous membranes manifest by petechiae and ecchymosis

Macrospecimen "Cerebral hemorrhage" (fig.23).

The cerebral tissue contains an accumulation of dark red colored clotted blood; in the hemorrhagic site the cerebral substance is desintegrated (cerebral hematoma). The mechanism of the hemorrhage in this case is the rupture of the artery wall. It is most frequently seen in hypertensive disease and the atherosclerosis of the cerebral arteries. Clinically, it is accompanied by cerebral coma, and paralysis. Subsequently the blood from the hemorrhagic site is gradually reabsorbed with the formation of a cystic cavity with brown walls (due to the accumulation of hemosiderin).

The most frequent consequences of internal hemorrhages (interstitial and in serous cavities) are:

a) synthesis of hemoglobin pigments (hemosiderin, hematoidin, bilirubin) with the modification of the hemorrhagic site color;
b) resorption of blood;
c) organization;
d) encapsulation;
e) cystic cavity formation (in the brain);
f) supuration.

Macrospecimen "Tubal pregnancy with rupture of tube" (fig. 77).

The uterine tube is dilated, distended up to 3-4 cm by a contained mass of freshly clotted blood, in which may be seen bits of gray placental tissue and fetus. The tubal pregnancy result more frequently from chronic inflammation of tube (salpingitis), which may lead to the deformation of tube and appearance of hindrance that retards passage of the ovum along its course through the oviducts to the uterus.

Macrospecimen "Chronic gastric ulcer: the erosion of an artery from the bottom of the ulcer" (fig.78).

The gastric wall contains an oval shaped ulcer with smooth margins which are raised, with a hard consistency, with thickened folds of the surrounding mucousa which converge towards the ulcer. The bottom of the ulcer contains a eroded vessel, which is opened, with thickened walls affected by sclerosis and brown-black masses of blood.

Gastric hemorrhage due to the erosion of the ulcer vessels under the action of pepsin and hydrochloric acid from the gastric juice is clinically manifest by hematemesis and melena.

Microspecimen "Diapedesis hemorrhages in the brain" (fig.79).

The cerebral tissue contains small hemorrhagic sites, which have in some places a muff around the small vessels; the integrity of the vessel walls is not affected.

Hemorrhage by diapedesis of erythrocyte is caused by increased vascular permeability and is seen in hypertensive disease, infectious diseases, scurvy (C avitaminosis), venous stasis, etc.

Plasmorrhage is the exiting of plasma from the lumen of the vessels leading to the imbibition of the vascular wall and of the surrounding tissue.

Microspecimen "The plasmatic infiltration of the cerebral arteries" (fig.80).

The walls of the arteries are tumefacted , thickened as a result of their infiltration with homogeneous-eosinophile blood plasma; plasmatic accumulations around the vessels and severe pericellular edema can be observed.

Plasmorrhage is determined by the increase of vascular permeability and is frequently seen in the hypertensive disease and atherosclerosis, cardiac insufficiency, infectious diseases, diabetes mellitus. Plasmatic infiltration leads to subsequent hyalinosis of the arterial walls.

4.4. THROMBOSIS

Thrombosis represents the coagulation process which takes place in the lumen of vessels or in the heart chambers in the course of life. The clot (coagulum) is formed of normal constituents of the blood and is called thrombus.

The morphogenetic mechanism of the thrombus consists both of local and general factors. The most important of them are:

a) local modifications of vascular and cardiac walls (arteritis, flebitis, atherosclerosis, hypertensive disease, trauma, rheumatic or infective endocarditis);
b) blood circulation disorders (the slowing or turbulent, whirly flow of the blood in arterial or cardiac aneurysms, varicose veins, cardiac insufficiency, venous stasis);
c) blood clotting disorders (modifications between coagulation and anticoagulation systems relations, increased number of thrombocytes, increase of blood viscousity, increased amount of macrodisperse proteins and of lipids in the blood plasma, etc.).

Among the local conditions of thrombus formation the most important is vascular endothelium lesions, while among the general factors – the disturbance of the correlation (interaction) between the clotting and anticlotting systems of the blood.

The morphogenetic mechanism of the thrombus has four evolving stages:

a) thrombocyte agregation;
b) the transformation of fibrinogen into fibrin;
c) erythrocyte agglutination;
d) the precipitation of plasma proteins.

Electronomicrographies "Stages I, II and III of thrombus formation" (fig. 81, 82, 83, 84).

Stage I: thrombocyte agregation *(fig.81 and 82)*. The first figure shows the place of vascular endothelium lesion (indicted by an arrow). The mitochondria of the endotheliocytes are tumefacted and homogenized, the subendothelial layer is edematous, the collagen fibers are dissociated and chaotically displaced; the unmodified thrombocyte approaches the place of endothelial lesion.

Fig.82 shows an agglomeration of thrombocytes which are adhering one to another.

Stage II: the transformation of fibrinogen into fibrin *(fig.83)*.

The zone of endothelial lesion contains degranulated thrombocytes and agglomerations of fibrin filaments, which adhere to the wall.

Stage III: erythrocyte agglutination *(fig.84)*. The lumen of the vessel contains degranulated thrombocytes, while between them there are fibrin filaments and agglutinated erythrocytes.

Like the erythrocytes, the initial thrombus attracts circulating leukocytes and plasma proteins. When the blood platelet desintegrates, retractozim – ferment with retractile activity, and serotonin which promotes vascular constriction (narrowing) are produced. Retractozim and serotonin cause thrombus retraction and its densification.

The definitive thrombus has a hard consistency, dry appearance and is friable; the older is the thrombus, the more compact and hard it is.

Macrospecimen "Parietal thrombus in the abdominal aorta (in atherosclerosis)".

The intima of the aorta *(fig.85)* is rough, with multiple ulcerations and with a parietal thrombus which adheres to the vascular wall (head of the thrombus). The thrombus has a red-gray color, hard consistency, irregular surface, dry opaque appearance, is friable. The body and the tail of the thrombus are free in the lumen of the vessel.

The bands from the surface of the thrombus (Zahn lines) are composed of agglutinated thrombocytes and leukocytes and are formed due to the blood waves, reminding the bands of sand from the sea shore. This is an evident sign that the blood clotting took place in life conditions.

By these characteristics the thrombus can be differentiated from the cadaver clot (table 15). The differential diagnosis of the thrombus as an intravital process and of the cadaver clots, which appear post mortem due to the stopping of the heart and blood circulation, is made during the autopsy of cadavers at the necropsy table.

Table 15

The main characteristics of the thrombus and of the cadaver clots

Thrombus	Cadaver clots
a) Adherence to the vascular wall	No adherence to the vascular wall
b) After thrombus detachment a endothelial defect remains	After detachment of the clot, the endothelium remains smooth and shiny
c) Has an irregular, rough surface	Has a smooth surface
d) Has an opaque, mat-like, dry appearance	Has a wet, shiny appearance
e) An increased, hard consistency	The consistency is soft, flaccid
f) Is friable	Is elastic

Most frequently the thrombus is formed in veins (especially in the lower extremity veins, hemorrhoid, mesenteric, portal vein), and less frequently in arteries (coronary, cerebral, mesenteric, renal, pulmonary, aorta, etc.) especially in atherosclerosis. They can also be found in heart chambers, on the surface of the mitral and aortic valvulae (in infective or rheumatic endocarditis), in the left auricle (for example in mitral stenosis) or on the walls of the heart chambers (parietal thrombosis in myocardial infarction, rheumatism, cardiomyopathies, etc).

Macrospecimen "Parietal thrombi in the lower extremity veins with varicose dilatations"(fig.86).

The lumen of the veins is obliterated by dry, mat-like thrombotic masses of a dark red color, which have an intimate adherence to the vascular walls; the veins have a meandering appearance, with multiple nodular varicose dilatations.

Venous thrombosis is more often seen in the varicose disease of the lower extremity veins, in the chronic cardiovascular insufficiency, in hemorrhoids, etc.

Macrospecimen "Spherical thrombus in the left atrium in the stenosis of the left atrioventricular orifice (mitral stenosis)".

The thrombus has a round, spherical shape ***(fig.87)***, with its diameter of about 3-4 cm, and smooth surface. It is situated freely in the atrial chamber. It is formed due to the turbulent flow of blood in conditions of left atrioventricular orifice stenosis and the distention of the left atrium.

Macrospecimen "Chronic cardiac aneurysm with thrombosis" (fig.88).

The lateral wall of the left ventricle has a bulging area, forming a saclike dilatation of the ventricular cavity – aneurysm (from greek aneuryno – to distend); if sectioned, the wall of the aneurysm is thinner, composed of cicatricial tissue, the cavity of the aneurysm is filled with thrombotic masses.

The cardiac aneurysm evolves as a result of expanded myocardial infarct cicatrization. The main cause of the thrombus formation is the turbulent flow of the blood in the area of the aneurysmal sac; the thrombosis process is favored by the microtraumas of the aneurysmal wall, which appear due to hemodynamic disorders.

According to the way of formation and structure, 4 types of thrombi can be distinguished:

a) white thrombus (gray or agglutinative) is composed of thrombocyte collections, which form coral-like structures, leukocytes and a meshwork of fibrin filaments. It most frequently has a parietal positioning, and is found in arteries and on the heart valves;
b) red thrombus (coagulative); is composed of a meshwork of fibrin, with erythrocytes, thrombocytes and a small amount of neutrophiles; it is more often found in veins and is obstructive;
c) mixed thrombus (variegated, stratified); it is composed of both white thrombus and red thrombus elements. The localization of the mixed thrombus can be diverse. It has three portions: the head, body and tail. The head of the obstructive thrombus is orientated towards the heart (right ventricle) in veins and in an opposite direction in arteries. The parietal thrombus in veins, the same as in arteries, can grow both in the blood flow direction and against blood flow direction;

d) hyalin thrombus; usually they are multiple and are localized in the vessels of the microcirculatory system. They are seen in some extreme conditions: shock, burns, massive tissue destruction. The hyalin thrombi have an amorphous, homogeneous, unstructured appearance due to the destruction of the cellular structures and precipitation of plasma proteins.

Microscopically, every thrombus is composed of agregated thrombocytes and fibrin filaments, and among them trapped erythrocytes and leukocytes.

Microspecimen "Recent mixed vascular thrombus" (fig .89).

The vascular lumen contains an obstructive thrombus, composed of fibrin filaments, and blood elements (thrombocytes, erythrocytes, leukocytes).

The consequences of thrombi can be favorable and unfavorable (table 16).

Table 16

The consequences of thrombi

I – Favorable consequences	a) Reabsorption of the thrombus b) Aseptic autolysis (softening) c) Connective tissue organization d) Vascularisation e) Canalization (recanalization) f) Calcification (petrification)
II –Unfavorable consequences	a) Septic autolysis (purulent softening) b) The rupture of the thrombus and its transformation into a thromboembolus

Microspecimen "Thrombus in course of organization" (fig.90).

In the peripheral zone of the thrombus, which adheres to the vascular wall, the proliferation of young connective tissue (granulation tissue), rich in cells (fibroblasts) and new formed capillaries, which invade and replace the thrombotic masses can be observed. The process of thrombi organization contributes to their consolidation at the place of formation. This excludes the possibility of thromboembolus apparition.

4.5. EMBOLISM

Embolism represents a pathologic process characterized by the circulation in the cardiovascular (lymphatic) system of some particles that are not normally seen in blood (lymph) and which cause the complete or partial blockage of the blood (lymphatic) vessels. These particles circulated through blood (lymph) are called emboli. They can be of exogenous or endogenous origin, while according to their physical proprieties they can be: solid (thrombi, tissue fragments, cell groups, foreign bodies, bacterial colonies), liquid (amniotic liquid, liquid fats) and gaseous (air, nitrogen, oxygen). The classification of emboli is given in tables 17 and 18.

Table 17

Types of embolism according to the composition (structure) of emboli

Type of embolism	Characteristic	Diseases in which it is seen	Consequences, diagnostic methods
Thrombo-embolism	Embolism with thrombi or fragments of detached thrombi: the starting place can be in veins, arteries, heart chambers	Thromboflebitis, varicose disease of the lower extremity veins, hemorrhoids, arterial atherosclerosis, arterial and cardiac aneurysms, bacterial or rheumatic thromboendocarditis, myocardial infarction	Infarct; gangrene; sudden death in pulmonary artery thromboembolism
Fat embolism	With adipose tissue, endogenous or exogenous fats	Bone fractures (especially of the femur and tibia), contusions of the adipose tissue (subcutaneous, pelvic cellular adipose tissue at the time of birth), the intravenous introduction of some oily substances	Embolism of the pulmonary capillaries with acute asphyxiation, embolism of the cerebral vessels; the identification at autopsy is made using colorants for lipids
Air embolism	Produced when air invades the venous or arterial system	Trauma or surgical intervention in the region of the neck (jugular vein), thorax, lungs, heart surgery, laparoscopy, pneumothorax, pleural puncture, atony of the uterus after birth, injections or transfusions with technical defections	The small circulation vessel embolism, the accumulation of air in the right chambers of the heart; for diagnostic identification at autopsy the right chambers of the heart are opened under the water (preventively water is poured into the pericardial sac); the blood has a foamy appearance
Gaseous embolism	Obstruction of the vessels with bubbles of gas (nitrogen)	It is seen at divers, caisson assemblers, pilots due to the rapid passing of the body from low or high atmospheric pressure to normal pressure	Capillary obstruction in the brain, spinal cord and other organs, with ischemic and necrotic lesions, punctiform hemorrhages and thrombi (decompression or caisson disease)
Tissue (cellular) embolism	Embolism with isolated cells or tissue fragments	Malignant tumors, infective endocarditis (rupture of the cardiac valves), cerebral and hepatic trauma, amniotic liquid embolism (squamous cells, hair, vernix caseosa, meconium) in lying-in women in case of incomplete detachment of the placenta, in foetus and newborn in obstetric trauma	Apparition of ischemic and necrotic hotbeds, malignant tumor metastasis (cancer, sarcoma, melanoma)

Microbial embolism	The embolus is composed of microorganisms (microbe colonies, fungi or parasites) detached from a septic site	In sepsis (septicopyemia), infective endocarditis	The appearance of ischemic and necrotic modifications and of purulent lesions (metastatic abscesses) in organs
g) Foreign bodies embolism	With ashes, bullets, splinters, catheter fragments, cholesterol crystals, calcium salts, etc.	In trauma, catheterization of the heart and vessels, in atherosclerosis	The appearance of ischemic and necrotic lesions

Table 18

Types of embolism according to the direction of embolus circulation

Embolism	Characteristic
1	2
I – Direct (forward) *(fig.91)*	The embolus circulates in blood flow direction: a) from the veins of the great circulation – to the right compartments of the heart and to small circulation vessels; b) from the pulmonary veins, the left compartments of the heart, aorta and the major arteries - to the arteries of the great circulation (coronary, cerebral, renal, lienal, mesenteric, of the lower extremities); c) from the branches of the portal system - into the trunk of the portal vein and into the liver
II – Paradoxical (crossed) *(fig.92)*	When the embolus from the great circulation veins reaches directly the left compartments of the heart and the arteries of the great circulation, avoiding the small circulation system (the pulmonary capillary system); it is seen in congenital cardiac diseases: the persistence of foramen ovale (interatrial communication), interventricular sepal defect and arteriovenous bypasses (communications)
III – Retrograde *(fig.93)*	The circulation of the embolus against the blood flow direction; for example, the embolism of the hepatic or renal veins, when the thromboembolus comes from vena cava inferior at the moment of sudden increase of intraabdominal or intrathoracic pressure (couth access)

The most clinically important is the thromboembolism of the pulmonary artery.

Macrospecimen "Thromboembolism of the pulmonary artery" (fig.94).

In the area of the pulmonary artery bifurcation there can be observed a thromboembolus freely situated in the vessel, alike the "rider in its saddle". It does not adhere to the vascular wall, but obliterates the orifices of both pulmonary arteries. The starting point of the pulmonary thromboembolus can be in the veins of the lower extremities (in the varicose disease), pelvic veins (hemorrhoids) and intraabdominal veins, venae cavae, right heart chambers. Thromboembolism of the small intrapulmonary branches leads to pulmonary hemorrhagic infarct, while the embolism of the common trunk and of the major branches of the pulmonary artery leads to sudden death. This embolus blocks pulmonary circulation leading to asphyxia and acute pulmonary heart. In some cases, sudden death can occur even due to thromboemboli of small dimensions as a cause of pulmocoronarian reflex with spasm of the branches of the pulmonary artery, bronchi, coronary arteries and cardiac arrest.

Macrospecimen "Congenital cardiac abnormality: interventricular septum defect" (fig.95).

The interventricular septum contains an orifice. Through this defect the embolus can pass from the right ventricle to the left ventricle and vice versa, avoiding the small circulation – paradoxical embolism, for example, the thrombus from the hemorrhoid veins can arrive to the cerebral arteries.

Microspecimen "The fat embolism of the pulmonary blood vessels" (fig.96).

The vessels of the interalveolar septa are filled with fat drops of different dimensions, stained yellow-red with Sudan III. The fat embolism is seen in the subcutaneous adipose tissue traumas, fractures of the long tubular bones with injury of the bone marrow, after birth (lesions of the pelvic cellular adipose tissue). The drops of fat obliterate the pulmonary capillaries, which can lead to acute asphyxia (if more than 2/3 of the pulmonary capillaries are blocked).

Microspecimen "Cancerous embolism of the pulmonary lymphatic vessels" (fig.97).

The lymphatic vessels are dilated, the lumen is obliterated by collections of cancerous cells (cellular, tissue emboli).

The process of transportation in the body of some pathologic elements from one place to another leading to the appearance of secondary pathologic lesions at a distance from the primary site is called metastasizing. The secondary lesion is called metastasis.

Cancerous embolism of the pulmonary lymphatic vessels is seen in lung, mammary, esophagal and gastric cancer, etc.

Macrospecimen "Carcinoma metastasis in lungs" (fig.98).

The sectioned lung contains multiple round or oval tumor nodules of white-gray color, under the visceral pleura. They have a diameter of 3-5 cm, and are well delimited from the surrounding tissue.

Microspecimen "Bacterial embolism of the glomerular capillaries (purulent embolic nephritis)" (fig.99).

The lumen of the glomerular capillaries, afferent arterioles and veins contain collections of bacteria. The colonies of microbes stain intensively with hematoxylin, like ink stains. Necrotic modifications and focal collections of neutrophile leukocytes (sites of purulent inflammation, metastatic abscesses) can be observed around the bacterial emboli.

It can be seen in sepsis, infective endocarditis, septic autolysis of the thrombi, etc.

Macrospecimen "Purulent embolic nephritis (metastatic abscesses in kidneys)".

The kidney is larger in all dimensions ***(fig.100)***. On the surface, under the capsule, multiple foci of purulent inflammation of a yellowish color – abscesses, can be observed. Some of them can be surrounded by a red border, a zone of hyperemia and hemorrhages.

The exposed specimens demonstrate that the consequences of embolism depend on the nature (structure), spreading and localization of the emboli. The most frequent and severe effect of the embolism is the ischemia which leads to infarct or gangrene developing. The consequences of vascular obstruction can be very dangerous in the embolism of cerebral arteries (ischemic infarct, white cerebral softening), coronary arteries (myocardial infarction) and pulmonary arteries (pulmonary infarct or sudden death in thromboembolism of the pulmonary artery). The air, gaseous and fat emboli can undergo reabsorption, but if the embolism is massive, severe complications may occur. The bacterial (septic) embolism can lead to metastatic abscesses, which can be of vital importance depending on their localization, and to the generalized dissemination of the infection. The cellular (tissue) embolism in malignant tumors (cancer, sarcoma) is the main rout of metastasis and generalized spread of the tumor process.

4.6. STASIS (HEMOSTASIS)

Stasis represents the stopping of blood in the capillaries and venules with a dilated lumen, accompanied by the aggregation (sticking) of the erythrocytes in homogeneous columns due to the modifications of physico-chemical proprieties of the erythrocytes. Stasis does not involve hemolysis and blood clotting. It is a non specific process which is seen in circulatory disorders (cardiac valvulopathies, myocardial infarction), infectious diseases (malaria, typhus exanthematous), intoxications, under the actions of some physical factors (increased temperature, cold).

Microspecimen "Stasis in the myocardial capillaries".

The myocardial capillaries ***(fig.101)*** are dilated, containing erythrocyte aggregations in their lumens. These erythrocytes are sticking one to another and are positioned in columns. The collections of erythrocytes obliterate the small caliber vessels. The myocardial stasis is more often seen in myocardial infarction. On the background of stasis hyalin thrombi may appear.

The longtime stasis leads to the hypoxia of the respective zone, dystrophic and necrotic lesions.

4.7. EDEMA

Edema is manifest by the increased quantity of fluids in tissues and serous cavities. In tissues the edema fluid accumulates in the extracellular compartment (interstitium). The edema fluid or the transudate is transparent, contains up to 1-2% serum proteins, which are weakly associated with the proteins and glycosaminoglycans of the ground substance of the interstitial tissue. Edema can be localized or generalized, chronic or acute. The main factors which cause the appearance of edema can be <u>vascular</u>: a) the increase of hydrostatic pressure of the blood in the small vessels; b) the decrease of colloid-osmotic pressure of the plasma; c) the increased permeability of the capillary and venular walls; d) lymph stasis, and <u>tissular</u>: a) the retention of electrolytes in tissues, especially of sodium and water; b) the increased colloid-osmotic pressure of the interstitial fluids.

Macroscopically, the tissues (organs) affected by edema are increased in volume, and tumefacted, the consistency of the lax tissues becomes paste-like, and gelatinous. Under digital pressure a depression remains. In the extremities the bony contours are erased.

The parenchymatous organs are increased in volume, with a weakened capsule, increased consistency. When sectioned they have a wet, shiny appearance , decreased temperature and a pale color due to the capillary compression. A colorless or pale-yellow liquid drains from the surface when sectioned.

Microscopically, there can be observed a dissociation of the fibrillar and cellular structures by the edema fluid. This fluid has a colorless or weakly eosinophilic (pink) color and homogeneous appearance in hematoxylin and eosin stain. The fluid accumulates especially perivascular, and the lymphatic vessels are dilated.

The main types of edema according to the morphogenetic mechanisms are represented in table 19, while the terminology – in table 20.

Table 19

Classification of edemas

Type of edemas	Main morphogenic factors	Morphologic particularities	Examples of diseases
1	2	3	4
I – Generalized edemas			
a) Cardiac	- Increased hydrostatic pressure in veins as a result of contractile insufficiency of the heart (decompensation of the heart); - Sodium retention due to the increased aldosteron secretion	The predominant localization of the edema is in the region of the lower extremities (due to the gravitational force); the teguments have a cyanotic appearance (cyanotic edema)	Cardiac valvulopathies, infectious endocarditis, diffuse myocarditis, pericarditis, diffuse cardiosclerosis, severe chronic cardiac arrhythmia, cardiomyopathies, etc.
b) Renal	- Decreased colloid-osmotic pressure as a result of proteinuria; - Sodium retention	Initially the edema appears in the connective tissue in the region of the face (palpebral region), subsequently – on the dorsal surfaces of hands and feet, in the region of the scrotum; gradually the edema becomes generalized; the integument has a pale appearance (white edema)	Nephritis, nephrotic syndrome, acute renal insufficiency
c) Dystrophic (cachectic, starvational, nutritional)	- Decreased colloid-osmotic pressure of the blood due to the protein insufficiency in the blood (hypoproteinemia); - Increased vascular permeability due to the decrease of the intratissular tension (the disappearance of cellular adipose tissue, muscular atrophy)	The edematous tissues have a whitish appearance, the localization of the edema being especially in the region of the lower extremities, abdominal cavity (ascites)	Malnutrition, the deficiency of proteins in alimentation, malabsorption diseases (chronic enterocolitis), hypovitaminosis, cachexia
II – localized edemas			
a) Due to stasis	Increase of pressure in veins or in the lymphatic vessels	Edema is localized in the zone of the vascular obstruction, and has a cyanotic appearance	Thromboflebitis, the compression of a vein or of a lymphatic vessel (by tumors, adherence, ligatures)

b) Inflammatory	Hemodynamic disorders in the microcirculatory system and the increase of capillary permeability under the action of inflammatory mediators (histamine, serotonin)	Edema is localized around the inflammatory site	Various inflammatory processes, especially exudative
c) Angioneurotic (anaphylactic)	Increase of vascular permeability due to the action of histamine and other analogue to histamine substances, eliminated by labrocytes in course of the allergic reactions (hypersensibility) of immediate type.	Edema appears suddenly, more often in the region of the face (palpebrae and lips), larynx, glottis, trachea, bronchi, genital organs; has a white appearance	Quincke's edema, rash

Table 20

Terminology of edema

Hydropsy (lat. hydrops)	Generalized edema, accumulation of edema fluid (transudate) in the tissues and cavities of the body, especially in the subcutaneous tissue, serous cavities and parenchymatous organs – more frequently used to name the accumulation of liquid in serous cavities
Anasarca (lat. anasarca)	Accumulation of edema fluid in the entire subcutaneous adipose tissue (generalized edema of the subcutaneous tissue)
Ascites or hydroperitoneum (lat. ascites s. hydroperitoneum)	Accumulation of edema fluid in the abdominal (peritoneal) cavity
Hydrothorax (lat. hydrothorax)	Edema in the pleural cavity (uni- or bilateral)
Hydropericardium (lat. hydropericardium)	Pericardic hydropsy, accumulation of edema fluid in the pericardial sac
Hydrocele (lat. hydrocele)	Accumulation of liquid in tunica vaginalis of the testicle (testicular hydropsy)
Hydrocephaly (lat. hydrocephalia)	Excessive accumulation of cerebrospinal fluid in the cranial cavity. It can be internal (in the cavities of the cerebral ventricles) or external (in the subarachnoid space)
Hydrarthrosis (lat. hydrarthrosis)	Accumulation of edema fluid in the cavity of an articulation

The microscopic appearance of edema can be clearly observed in the pulmonary and cerebral edema.

Microspecimen "Pulmonary edema" (fig.102).

The pulmonary alveoli are filled with a homogeneous eosinophilic fluid which replaces air. Some alveoli contain small bubbles of remaining air; in some places there can be observed solitary alveolocytes which are detached from the alveolar wall and flow in the edema fluid. The interalveolar septa are thickened, tumefacted, and hyperemic. The fibrocellular elements are dissociated, distanced one from another by the edema fluid.

Macroscopically, the lungs have an increased volume, and are crepitant at palpation. They have a paste-like consistency; when sectioned a great quantity of foamy pink liquid, (mixed with air) drains from its surface.

Clinically, pulmonary edema is manifest by labored respiration (dyspnea). It is usually seen in acute insufficiency of the left chambers of the heart (myocardial infarction, mitral stenosis, hypertensive crisis, severe myocarditis, cardiomyopathies, etc.). It can lead to the patient death due to acute respiratory insufficiency. In case of favorable evolution, the edema fluid is reabsorbed. Persistent chronic edema is associated with the excessive proliferation of the connective tissue, sclerosis and the induration of the lungs.

Microspecimen "Cerebral edema" (fig.103).

The cerebral tissue is rarefied, and contains edema fluid, which is localized around the blood vessels and cells (the colorless spaces) – perivascular and pericellular edema.

Macroscopically, there can be observed an increased volume of the brain, thickened, flatted circumvolutions, diminished sulci, dilated meningeal vessels, and paste-like consistency. When sectioned, the cerebral tissue has a wet, shiny, pale appearance, the cortex being not well delimited from the white substance.

It is seen in hypoxia (severe pneumonia, bronchial asthma), meningitis, cerebral abscesses, intoxications, and severe infectious diseases. Clinically, it is manifest by intracranial hypertension. Complications include the penetration of the cerebellar amigdala into the great occipital foramen, the compression of the medulla oblongata and sudden death.

4.8. LYMPHATIC CIRCULATION DISORDERS

Lymphatic circulation disorders can be of mechanical, dynamic and resorptional character.

The mechanical insufficiency of the lymphatic circulation is caused by the increase of general, local or regional venous pressure, lymphatic vessel compression (tumors, cicatrix, adherence, ligatures), their obliteration (parasites, thrombi, tumor emboli), the interruption of the lymphatic vessels (surgical excision of the lymphatic vessels and ganglions, for example in malignant tumors, and the insufficiency of lymphatic vessel valves, etc.

Dynamic insufficiency is determined by the discrepancy between excess tissue fluid and its elimination efficiency. The main causal factor is the excessive filtration of fluid in the blood capillaries, leading to the accumulation of a great quantity of interstitial fluid, which the lymphatic system is unable to eliminate.

The resorption insufficiency is determined by the decreased permeability of the lymphatic capillaries or the modification of the tissue protein composition, which causes the retention of water in the tissues.

Lymphatic stasis is morphologically manifest by the dilatation of the lymphatic vessels, the appearance of collateral circulation, and of lymphangiectasia (persistent dilatation of lymphatic vessels). As a consequence lymphedema (lymphatic edema), lymphorrhage or lymphorrhea (the exit, drainage of lymph from the vessels) can occur. Lymphatic or lymphovenous fistulae and lymphogenic sclerosis of tissues are also observed. Lymphatic stasis causes sclerosis, because it causes tissue hypoxia and the excessive proliferation of the connective tissue (fibroblast activation). The edematous tissues have an increased volume. The outlines of the organs become erased, the skin is hard, thickened. These modifications are named elephantiasis and are frequently seen in regions of the extremities and genital organs. Lymphorrhage can lead to chylons ascites (lymph accumulation in the peritoneal cavity) or to chylothorax (lymph accumulation in the pleural cavities).

Microspecimen "Lymph stasis in the small intestine wall".

The intestinal wall contains dilated lymphatic vessels ***(fig.104)*** filled with eosinophilic colored lymph; the fibrillar and cellular elements are dissociated, distanced one from another by the edema fluid.

Macroscopically, the intestine wall is thickened, tumefacted, with a whitish appearance, and a milky-white liquid drains from the surface of section.

It can evolve as a result of lymphatic vessel compression by tumors, tumor metastasis, adherence, cicatrix, etc.

Chapter 5
INFLAMMATION

5.1. GENERAL ASPECTS

Inflammation is a complex local vaso-mesenchymal reaction of the body to alteration of tissue by various pathogenic factors. It is aimed to eliminate or inactivate and also to delimit the pathogenic agent with the subsequent structure and function reestablishment of the altered tissue. The causes of inflammation can be various physical, chemical and biological factors of exogenous or endogenous origin, which have a harmful action upon the tissues. Morphologically, the inflammatory process is manifest by alterative, exudative and proliferative modifications. In the first, alterative phase of inflammation, in the lesion site, dystrophic and necrotic modifications of the cellular and interstitial elements are observed. As a result of these modifications, chemical mediators of inflammation – biologically active substances are produced, which act upon the blood vessels, determining the evolution of the inflammatory process and encouraging the exudative reactions. According to their origin, the inflammatory mediators may be cellular (tissular) and plasmatic. The cellular mediators are eliminated by labrocytes, neutrophil and basophil leukocytes, thrombocytes, lymphocytes and monocytes (histamine, serotonon, heparin, acid lipids, lymphokines, monokines, etc.). Among the plasmatic mediators of greater importance are kinins (bradykinin and kalikrein) and some components of the complement and clotting / anticlotting systems of the blood. The cellular mediators can be eliminated from the cells via 2 pathways: a) exocytosis – process that reminds sectretion and is observed in leukocytes and b) degranulation, characterized by the elimination of granules from the cytoplasm and their subsequent desintegration in the extracellular space – processes that are observed in labrocytes.

Electromicrography "Degranulation of labrocytes" (fig.105).
The left side (a) of the image contains the normal ultrastructure of the labrocyte. The cytoplasm contains multiple specific electronodense granules, which contain active amines: histamine, serotonin and heparin. The right side (b) of the image represents the elimination of the granules from the cytoplasm of the labrocyte by ruptures of the cellular membrane.

The second, exudative phase of the inflammation is determined by the chemical mediators (especially by histamine and serotonin) and is manifest by three important processes:

a) dilatation of the microcirculatory system vessels and the disturbance of the blood circulation (modification of the rheologic proprieties of the blood);
b) exudation (extravasation) of plasma
c) migration of blood cells.

The dilatation of the microcirculatory bed vessels, especially of the postcapillaries and venules under the action of histamine, causes an increased blood flow and active inflammatory hyperemia in the lesion site. This clinically is manifest by redness and local fever.

Microspecimen "Inflammatory hyperemia of the skin in phlegmon".

In the dermis *(fig.106)* the dilatation and marked hyperemia of the vessels, edema with the dissociation of cellular and fibrillar elements, predominantly perivascular diffuse infiltration with neutrophil leukocytes. Macroscopically, the inflamed area of the skin is red and has a locally increased temperature.

Phlegmon is a purulent inflammation with no precise delimitation. It is characterized by the diffuse spreading of the exudate among tissular elements. It is more often localized in the cellular adipose tissue. In skin, the phlegmon can be caused by cutaneous wound supuration as a result of pyogenic bacteria (staphilococus, streptococus) invasion.

Exudation (extravasation) of the fluid components of blood with the formation of inflammatory edema and of local tumefaction of tissues represents an essential aspect of inflammation. The extravasation of plasma is determined by the increased permeability of the microcirculatory system vessels and is morphologically manifest by the intensification of pinocytosis processes.

Electronomicrography "Pinocitosis in the capillary endothelium in inflammation" (fig.107).

The cytoplasm of endotheliocytes contains multiple pinocytotic vesicles of small dimensions filled with plasmatic liquid. At the inner surface level of the endothelial cells there can be observed the inclusion of plasma by membrane invagination causing the formation of vacuoles. These vacuoles cross the cytoplasm of the endotheliocytes and eliminate their fluid content into the extracellular (extravascular) space.

Subsequently, plasma pass the basal membrane, which has an increased permeability due to the influence of chemical mediators. The mediators (especially histamine, bradykinin, hyaluronidase and other proteolythic enzymes) determine polysacharide depolymerisation of the ground substance, leading to the increased laxity and permeability of the capillary basal membrane. As a consequence, a transendothelial active transport of the blood plasma with the accumulation of fluid in tissues (extravascular spaces) and the appearance of inflammatory edema is observed. The liquid component of the exudate contains water, plasmatic proteins, electrolytes, salts, metabolic products, chemical mediators, antibacterial and antitoxical substances, etc. The quantity and quality of the inflammatory fluid depend on: pathogene agent peculiarities, the level of vasotissular permeability, and the localization of the process.

The migration of the blood cells represents the main aspect of the cellular phase of the inflammation. This process begins with the migration of the neutrophil leukocytes, when they detach from the axial zone of the blood column. The cellular elements move towards the vascular wall. Subsequently, the neutrophils adhere to the endothelial cells, give out cytoplasmic expansions (pseudopodes), and actively strain through the interendotheliocyte junctions into the subendothelial and interendothelial space. After this the neutrophils penetrate the basal membrane, due to the tixotropic phenomenon (the basal membrane ground substance colloidal state modification) and reach the perivascular connective tissue. The leukocytic diapedesis takes place predominantly in the postcapillaries and venules.

Electronomicrography "Neutrophil leukocyte migration in inflammation" (fig.108 and 109).

Figure 108, a contains neutrophil leukocytes which are attached to the vascular wall; the leukocyte from the lower part of the image penetrated partially into the subendothelial space of the wall, with the help of pseudopodes at the level of interendothelial junctions. On the surface of the endotheliocyte there can be observed a pseudopod belonging to a third neutrophil leukocyte.

Fig.108 represents some polymorphonucleated neutrophils, which are situated in the capillary wall, between the endothelium and the basal membrane. Exterior to the basal membrane, collagen fiber fascicles are observed.

Fig.109 represents two neutrophil leukocytes, which have penetrated the basal membrane and have exited the lumen of the capillary into the perivascular connective tissue. The endothelial layer is unchanged, the contact zones of the endotheliocytes are observed. The lumen of the capillary contains a leukocyte ready to migrate.

Similar to this is the active migration mechanism of monocytes and eosinophils, while the lymphocytes cross the vascular wall through the cytoplasm of the endothelial cells (transendothelial); the erythrocytes cross the vascular wall passively, through the same holes as neutrophils do. After cell migration, the integrity of basal membrane is reestablished.

The polymorphonucleated neutrophils that have reached the perivascular spaces propel themselves actively towards the pathogenic agent through amoeboid movements of cytoplasmic expansions, whose length may be up to 10 times greater than the leukocyte diameter. The propulsion speed of the neutrophil is of about 0.02 mm per minute. This oriented (directioned) movement is due to the substances with positive chemotactic activity – so called attracting substances (immune complexes, some complement fractions, bacterial exotoxines, nucleic acid derivatives and other products from the lesion site).

The main function of polymorphonucleated leukocytes and monocytes in the lesion is phagocytosis – the engulfing of microorganisms, tissular remnants, foreign particles or other substances, with their subsequent intracellular digestion (destruction). Neutrophils are specialized cells, that have the ability to phagocyte small bodies, especially microorganisms (microphages). Monocytes and histiocytes phagocyte large, sizable particles, for example foreign bodies (macrophages). The phagocytosis process includes two main stages: I – the adhesion of the particles or microorganisms to the phagocyte membrane, the invagination of the membrane and their penetration into the cytoplasm; II – the forming of phagocyte vacuoles (digestion vacuoles) around the engulfed particles and their intracellular digestion under the influence of lysosomal enzymes.

Electronomicrography "Phagocytosis" (fig.110).

The neutrophil leukocyte cytoplasm contains vacuoles with phagocytosed staphilococi, which are in different phases of desintegration.

Phagocytosis can be either complete or incomplete. Incomplete desintegration can encourage the dissemination and generalizing of the infection.

After the phagocytic activity, the neutrophil leukocytes suffer dystrophic modifications, especially fat dystrophy, and die. Monocytes survive for a long time due to their ability of producing new lysosomes and new lysosomal enzymes.

As a consequence of these processes, especially of the plasma extravasation and of blood cells migration, the exudate (the inflammatory fluid) is formed in tissues as a final product of the inflammation.

The main components of the exudate are: a) the liquid part – water with proteins (albumin, globulin, fibrinogen; the liquid composition in proteins is more than 1-2%); b) cells of hematogenic (especially leukocytes and mononuclaer phagocytes) and histogenic (local connective, epithelial and parenchymatous cells) origin; c) tissue destruction products (tissular detritus). The consistency, appearance, color and character of the exudate depend on the ratio between its components. The accumulation of exudate in the inflammatory site leads to local tumefaction of the tissue (tumor) and pain (dolor) as a result of nerve termination compression with tissular tension (related to the inflammatory edema) and their excitement by the chemical mediators (kinins, histamine, various metabolites). The pain and local tumefaction lead to the functional disorder of the organ (tissue) affected by inflammation (functio laesa). The clinical (macroscopic) signs of the inflammation are schematically represented in *fig.111*.

The *proliferative* phase (III) of the inflammatory process is manifest by cellular elements multiplication in the inflammatory site. Vascular hyperemia, extravasation of plasma and the migration of cells in tissues is gradually decreases, thus delimiting the altered zone from the adjacent tissues. The collection of cells in the inflammatory site is called inflammatory infiltrate.

Microspecimen "Cellular infiltrate in the inflammatory site (interstitial productive myocarditis)" (fig.112).

In the inflammatory site of the myocardial stroma there can be observed a localized collection of polymorphic cellular elements: lymphocytes, plasmocytes, macrophages. Leukocytes are rare; the vascular and exudative phenomena are insignificant.

The character of the inflammation depends on:

I) peculiarities of the causal factor (for example, in the lungs the pneumococus causes fibrinous inflammation frequently, Staphylococcus aureus – purulent inflammation; flu virus – hemorrhagic inflamation);

II) the localization of the inflammatory process (the structural and functional peculiarities of the organ; for example, the lungs have a lax structure, while the bones have a hard, compact structure);

III) macroorganism reactivity (for example, in case of immune deficiency, the inflammatory reaction is more severe and extensive, tending to generalize the morbid process).

The morphologic particularities of the inflammatory process are determined by the relation between three major processes: necrosis of tissues under the action of pathogenic agents, the exudation of plasma and the proliferation of cells.

According to the morphologic criteria, inflammatory reactions are subdivided into exudative and productive.

5.2. EXUDATIVE INFLAMMATION

Exudative inflammation is characterized by the prevalence of microcirculatory bed vascular reaction and the formation of the exudate in tissues and in body cavities.

According to the peculiarities of the exudate the following varieties of exudative infalammation can be distinguished: serous, fibrinous , purulent, putrid, hemorrhagic, catarrhal and mixed. Their general characteristics are represented in table 21.

Serous inflammation *(from lat. serum).*

In this case, the exudate is a lemon-yellow, opalescent liquid. It contains 1-3% proteins (albumin), like the blood serum, being poor in cells. The localization of serous inflammation is various, the exudate can accumulate in the serous cavities, mucous membranes, meninx, skin and interstitial spaces of the parenchymatous organs (myocardium, liver, kidneys).

Microspecimen "Epidermal vesicle containing serous exudate".

The specimen *(fig.113)* contains a peripheral portion of a cutaneous vesicle formed as a result of epidermal detachment from the dermis by a serous exudates. It has a light eosinophilic color due to the presence of proteins and a reduced number of cells; the superficial zones of the dermis contain a relatively unexpressed cellular infiltration and edema.

Macroscopically, the skin displays swelling filled with yellowish, opalescent fluid; the adjacent zones are edematous and hyperemic *(fig.114)*.

Serous inflammation of the skin is seen in erysipelas (infectious disease caused by the hemolytic streptococcus – *Streptococcus pyogenes*), burns (in second degree burns the cutaneous vesicles contain serous exudate), allergic dermatitis, etc.

Microspecimen "Serous focal pneumonia" (fig. 115).

The alveolar lumen contains a pink (eosinophilic) fluid with rare polymorphonucleated leukocytes and desquamated alveolar cells. Clinically, wet rales are heard accompanying the normal respiratory sounds on auscultation of the chest. The most frequent etiology of focal pneumonia is infectious.

Consequently the serous exudate is reabsorbed and the altered tissue is completely reestablished. Serous inflammation evolves usually acutely (1-2-3 weeks), or even overacutely (2-3 days), having a light clinical evolution. Sometimes the serous inflammation can have major clinical manifestations by compression of parenchymatous organs (in pericarditis, serous pleurisy) or by their function disturbances (for example in myocarditis, hepatitis, serous glomerulonephritis).

Fibrinous inflammation

Fibrinous inflammation is characterized by the formation of an exudate rich in fibrin. It is more often localized on mucous and serous membranes, but it is also seen in some parenchymatous organs, for example in lungs (lobar pneumonia), kidneys (fibrinous glomerulonephritis), etc. It appears in cases when the pathogenic agent causes a significant increase of vascular permeability, which causes the extravasation of fibrinogen. After its extravasation fibrinogen coagulates into fibrin under the action of thromboplastin, which is eliminated as a result of tissular 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 is represented by whitish or yellowish membranes, localized on the surface of mucous and serous membranes, or by dense masses formed of fibrin meshwork localized in the respective parenchymatous organs.

Two forms of fibrinous inflammation my be distinguished: croupous and diphtheroid. In the croupous inflammation, the fibrin membrane is thin, weakly adhering to the adjacent tissue and can be easily detached. This is due to the fact that the necrosis of the underlying layers of the mucous and serous membranes is superficial.

Macrospecimen "Croupous tracheitis in diphtheria (diphtheric croup)".

The mucous membrane of the trachea *(fig.116)* is covered with a whitish-yellowish-gray membrane, which has a weak adherence to the underlying tissue. In some places the membrane detaches from the mucous membrane, causing superficial ulcerations.

It is more often seen in diphtheria, but can be also met in cases when some inhaled chemical substances or the cold air, etc. act harmfully upon the mucous membranes of the respiratory ways.

In croupous tracheitis, as a result of easy detachment of the fibrin membrane, stenosis or even obstruction of the respiratory ways and death due to asphyxia can occur.

Macrospecimen "Lobar pneumonia (stage of gray hepatization)".

The affected lobe is larger in size ***(fig.117)***, of an increased consistency (reminds the consistency of the liver) and without air. When sectioned has a gray color due to the storage in the alveoli of fibrinous exudate, rich in neutrophil leukocytes. On the pleural surface there can be observed fine depositions of fibrin (fibrinous parapneumonic pleuritis).

The most frequent causal factor of the lobar pneumonia is the pneumococcus.

In the evolution of the inflammatory process liquefaction of exudate under the action of leukocyte enzymes, elimination by expectoration, reabsorption by lymph drainage pneumatization of the altered lobe is involved. The pleural fibrinous exudate is usually organized with the formation of fibrous adherences in the pleural cavity.

Table 21

Varieties and general characteristic of the exudative inflammation

Type of inflammation	Characteristics of the exudates	Macroscopic aspects of the organs (tissues)	Consequences	Examples
1	2	3	4	5
a) Serous	The exudate is a yellowish opalescent fluid, containing 3-8% proteins (albumin) and a reduced number of cells (leukocytes, lymphocytes); the exudate reminds the blood serum	The tissue is tumefacted, hyperemic, without its characteristic shine, is warm at palpation, the serous cavities contain an accumulation of serous fluid	The process is usually reversible, the exudate is being reabsorbed	Serous – pneumonia, myocarditis, hepatitis, pancreatitis, peritonitis, etc.
b) Fibrinous	The exudate is rich in fibrin, has a whitish, opaque, dense appearance	The mucous and serous membranes are covered by whitish or yellowish membranes, which have a weak (*croupous infl.*) or strong (*diphtheroid infl.*) adherence to the underlying tissue; the affected zones loose their characteristic shine, and have a husk-like or sawdust-like aspect	On the mucous membranes – the detachment of the membranes with the formation of superficial or profound ulcerations, which subsequently undergo cicatrization. On serous membranes the organization of fibrin with the appearance of adherences in the serous cavities leading to their partial or total obliteration	Fibrinous tracheitis, bronchitis in diphtheria; lobar pneumonia, fibrinous colitis in dysentery; and fibrinous pericarditis, pleuritis, peritonitis in uremia

c) Purulent	Pus is a viscous, dim fluid, of a yellowish- green color, composed of numerous disintegrated neutrophil leukocytes, tissular detritus and microbes	The affected zone represents a cavity in the parenchymatous organs or in the walls of cavitary and tubular organs; it is well delimited from the adjacent tissues and is filled with pus (*abscess*), or is tumefacted, with an opaque aspect imbued with pus; the pus fluid diffusely spreading among the tissular elements, without precise delimitation (*phlegmon*); the inflamed tissue undergoes necrosis and lysis (*melting*); the cavitary and tubular organs contain accumulations of pus in the respective anatomical cavities (*empyema*)	Organization, petrification (calcification) or fistulation of the abscess; sclerosis of tissues in the phlegmonous inflammation	Pulmonary, hepatic, renal, cerebral, subcutaneous, etc. – abscess; phlegmonous tonsillitis, appendicitis, gastritis, cholecystitis; phlegmon of the cellular adipose subcutaneous tissue; empyema of the vermicular appendix, bladder, pleural cavity, pericardial cavity. etc.
d) Putrid (gangrenous)	The exudate is a green-gray mass, composed of necrotic, liquefied tissue	The inflamed tissue has a putrid dirty-gray color, with a ugly (*fetid*) smell	Sclerosis of the altered tissue	Gangrenous – pneumonia, appendicitis, cholecystitis, endometritis, cystitis
e)Hemorrhagic	The exudate is rich in erythrocytes, like a hemorrhagic fluid	The inflamed tissue is opaque and has a reddish color	The reabsorption of the exudate, sclerosis of the altered tissue	Focal hemorrhagic pneumonia in flu, plague; hemorrhagic meningitis in anthrax; pustular hemorrhagic dermatitis in variola
f) Catarrhal	Initially, the exudate has a serous, lemon-opalescent appearance which gradually gets thicker, becoming sero-mucous (mucous), subsequently becoming muco-purulent	The mucous membranes are tumefacted, hyperemic, covered with a serous (*serous catarrh*), mucous (*mucous catarrh*) or purulent (*purulent catarrh*) fluid, which drains on their surface	The reabsorption of the exudate; in chronic forms – sclerosis of the mucous membranes	Catarrhal – rhinitis (cold), tracheitis, bronchitis, cholecystitis, endometritis

Macrospecimen "Fibrinous pericarditis (villous heart)".

The epicardium is opaque ***(fig.118)***, has an irregular surface, and is covered with villose -like yellowish-white deposits of fibrin, due to the movements of the heart. The heart gains a hairy or "cat tongue" appearance (villous heart). The fibrin deposits are flaccid and can be easily detached (croupous inflammation).

At clinical examination (auscultation) it is manifest by pericardial frottage.

It is seen in rheumatism, tuberculosis, transmural myocardial infarction, uremia, etc.

Microspecimen " Fibrinous pericarditis".

On the epicardium surface ***(fig.119)*** there can be observed fibrin deposits of a eosinophilic color. In the underlying layer - vascular hyperemia, edema, inflammatory infiltrate with neutrophil leukocytes, lymphocytes, macrophages are present.

Fibrinous pericarditis ends up more often with the organization of the fibrinous exudate and the formation of some adherences inside the pericardial sac, subsequently obliterating it.

With time, calcium salts are deposited in the serous membranes affected by sclerosis. These salts petrify or undergo ossification ("heart in cuirass"), leading to a progressive chronic cardiac insufficiency.

In diphtheroid inflammation, the fibrin membrane is thicker, having a strong adherence to the underlying tissue. It can be hardly be detached because the necrosis in these regions is much more profound. Fibrin and the necrotic masses form a common compact membrane. If this membrane is detached, sometimes bleeding ulcerations occur.

The croupous or diphtheroid character of the fibrinous inflammation depends not only on the profoundness of the necrosis, but also on the type of the mucous membrane epithelium. Diphtheroid inflammation usually affects the membranes covered with squamous epithelium (buccal cavity, tonsills, vocal plicae, esophagus, cervix uteri), while the mucous membranes covered with simple glandular epithelium and the serous membranes (mesothelium) are more often affected by croupous inflammation (superior respiratory ways, gastrointestinal tract, endometrum, pleura, peritoneum, pericardium).

Macrospecimen "Diphtheroid fibrinous colitis"(fig.120).

The large intestine wall is thickened and edematous. The mucousa is covered with a rough membrane of a yellowish-white membrane, which adheres to the underlying layer. At its detachment profound bleeding ulcerations remain.

It is frequently seen in severe, toxic forms of dysentery, it can also appear in uremia. The healing process of the ulcerations inside the intestine may result in stenosing and deforming fibrous scars, causing severe functional disorders (constipation, intestinal occlusion, etc.).

The consequences of the fibrinous inflammation can be various: in some cases the complete reabsorption of the exudate occurs due to the fibrinolytic action of the leukocytic enzymes. In other cases the fibrin is not reabsorbed, but organized causing mucous membrane scars or adhesions (also called symphysis or synechia). In the serous cavities (pericardial, pleural, peritoneal) causing their partial or total obstruction and the functional disturbance of the respective organs.

Purulent inflammation

Purulent inflammation is characterized by the predominance in the exudate of neutrophil leukocytes, by tissular necrosis and lysis (histolysis).

Pus is a viscous, dim, greenish-yellow fluid, composed of polymorphonucleated neutrophil leukocytes, which suffer dystrophic modifications (especially fat dystrophy) and are gradually desintegrated (so called *pus globules or pyocytes*), tissular detritus, and microbes. Purulent inflammation is most frequently caused by pyogenic bacteria (staphylococcus, streptococcus, meningococcus, coli bacillus, etc.).

Tissular necrosis in purulent inflammation is due to direct injurious action of pyogenic bacteria toxins on tissues, and to circulatory disorders (linked with vascular thrombosis or with their compression by the inflammatory edema). Histolysis (proteolysis) is produced by proteolytic enzymes (protease), which are eliminated by neutrophil leukocytes; a viscous semifluid mass appears as a result of lysis of the altered and necrotic tissues.

Two morphological variants are met: abscess and phlegmon.

Abscess is a circumscribed purulent inflammation, manifest by lysis of tissues and the formation of a cavity filled with pus.

Macrospecimen "Hepatic absecesses"(fig.121).

The liver contains multiple cavities of various dimensions, which are well delimited from the surrounding tissue. These cavities contain pus which has a yellowish color.

It most frequently appears after the spread of infection into the liver by the hematogenic way through the portal system (for example, pilephlebitic abscesses in destructive appendicitis), as a complication of severe purulent cholangitis (cholangitic abscesses) or of purulent pancreatitis (infection propagation by lymph vessels), etc. Besides these, liver can be infected by the blood stream through the hepatic artery system in cases of septicemia (pyemic abscesses).

The hepatic abscess can be complicated by fistulization, causing the exiting of pus into the abdominal cavity leading to the appearance of diffuse purulent peritonitis; this process is encouraged by the increased osmotic pressure in the abscess cavity due to the proteolytic processes and to the water absorption from the surrounding tissues. In cases of benign evolution of the abscess, the pus becomes more dense, then subsequently substituted by connective tissue or undergoes calcification (petrification).

Macrospecimen "Metastatic abscesses in kidneys" (fig. 100).

The surface, cortical and medullary layers of the kidney contain multiple small foci, with a yellowish-gray color, filled with pus (abscesses).

Microspecimen "Metastatic abscesses in kidneys (purulent embolic nephritis)".

The renal cortex and medulla ***(fig.122)*** contain multiple foci of purulent inflammation or abscesses. These are represented by neutrophil leukocyte collections. The renal tissue is destroyed. In the center there are bacterial colonies (bacterial embolus). The tubules and the adjacent glomerules are necrosed, the vessels are dilated and hyperemic. Metastatic abscesses in kidneys appear more often as a result of bacterial embolism seen in septicopyemia (a form of sepsis).

Microspecimen "Acute cerebral abscess" (fig.123).

The cerebral tissue contains a well outlined focal collection of desintegrating neutrophil leukocytes; the encephalic substance in the purulent site is necrosed and liquefied. In the surrounding tissue dystrophic modifications and pericellular edema is observed.

The cerebral abscess is a complication of purulent leptomeningitis, pneumonia, purulent otitis and mastoiditis or of septicopyemia. Clinically, it is manifest by paresis or paralysis. Small cerebral abscesses can heal resulting a fibroglial cicatrix, while larger abscesses form a cystic cavity.

Acute abscesses are delimitated from the adjacent tissue by a fibrinoleukocytic exudate or by granulation tissue. The chronic abscess is delimited by a pyogenic membrane, consisting of granulation tissue rich in capillaries from which an intense migration of leukocytes takes place. On the outer side, the membrane consists of fibrous connective tissue.

According to its clinical evolution, the abscess can be either acute or chronic. The consequences of abscesses can be:

a) Organization (cicatrization);
b) Petrification (condensation and calcification of the pus);
c) Fistulization – formation of fistulas, through which the pus drains to the exterior or into a preformed bodily cavity. The pathologic channel through which the pus drains from the abscess cavity to the exterior or onto the surface of the organ, or can penetrate into a neighboring organ is called a *fistula*. If the purulent site contains tissue fragments, which can not undergo autolysis or organization, or are unable to exit the cavity due to their excessive dimensions, then this substance is called sequestrum (for example, bony sequestrum in fistulized purulent chronic osteomyelitis).

Phlegmon (phlegmonous inflammation). It is characterized by a diffuse spreading of pus, with no delimitation among tissular elements, along intermuscular spaces, adipose tissue and neuro-vascular trunks, etc. It is more often caused by streptococcus hemolyticus, which produces great amounts of hyaluronidase and fibrinolysin. These alter the ground (intercellular) substance, encouraging the spreading of the inflammatory process. It is seen in adipose tissue (subcutaneous, mediastinal, retroperitoneal), in muscles, in the walls of cavitary and tubular organs (vermicular appendix, gall bladder, stomach, intestine, etc.) and in leptomeningitis, etc.

Macrospecimen "Purulent leptomeningitis" (fig.124).

The leptomeninge from the convex surface of the brain, especially from the frontal, temporal and parietal zones, is thickened, edematous, imbued with a yellowish-gray purulent exudate. The inflamed zone does not have a precise outline. Most frequently the cause of purulent leptomeningitis is the meningococcus. In consequence, either the reabsorption of the exudate and the complete resolution, or the thickening of membranes and the formation of some adhesion between the membranes can occur on the brain surface, encourage the appearance of cystic cavities in the leptomeninges or internal hydrocephaly due to the stenosis or obstruction of Magendie and Luschka orifices.

Macrospecimen "Acute phlegmonous appendicitis" (fig.125).

The vermiform appendix is thickened, especially its distal portion, dilated, filled with pus (empyema). The serous membrane is opaque, hyperemic and covered with fibrinous deposits of a whitish-gray color (periappendicitis). The wall of the appendix is thickened, imbued diffusely with pus; the mesentery is thickened, edematous, hyperemic. The most severe complications of acute phlegmonous appendicitis can be: perforation of the wall causing peritonitis, gangrene of the appendix with its autoamputation, metastatic abscesses in the liver, etc.

Microspecimen "Phlegmonous inflammation of the adipose tissue (phlegmonous cellulitis)" (fig.126).

In this specimen there can be observed a diffuse infiltration of the adipose tissue with neutrophil leukocytes, most of which are in state of desintegration. The blood vessels are dilated and hyperemic.

Macroscopically, the inflamed zone is tumefacted, warm at palpation and imbued with pus. On section, it has a dim, yellowish-gray color. It can have either a hard, wood-like consistency (*hard phlegmon*) or a flaccid one (*soft phlegmon*), depending on the spreading and gravity of the tissular necrosis processes in the respective zone (in cases of diffuse tissular necrosis the consistency is harder).

Phlegmon of the subcutaneous adipose tissue (dermal phlegmon) of diverse localization can occur as a complication of purulent wounds, furunculosis, carbuncle, dental caries, lymphadenitis, hydradenitis, osteomyelitis, etc.

According to its clinical evolution, the phlegmonous inflammation can be either acute or chronic. The acute phlegmon can be complicated with septicemia (when the inflammation spreads along veins and lymphatic vessels with the installation of thrombophlebitis and purulent lymphangitis). Secondary amyloidosis can occur as a complication of chronic forms of abscesses and phlegmons.

The site of purulent inflammation can be infected with putrefaction bacteria (*colibacili, proteus vulgaris*, etc.), which cause putrid desintegration of the inflamed tissues, accompanied by gas formation having an unpleasant (putrid) smell. Such an inflammation is called a **putrid (gangrenous) inflammation**. It is localized in tissues that are in contact with the external environment (gangrenous - tonsillitis, stomatitis, pneumonia, appendicitis, colitis, endometritis, etc.).

Hemorrhagic inflammation

Hemorrhagic inflammation is characterized by the presence of a great number of erythrocytes in the exudate. It is seen in flu, plague, streptococcic infection, anthrax, variola, especially in patients with hemorrhagic diathesis or cachexy.

Microspecimen "Influenzal hemorrhagic bronchopneumonia".

The lung is diffusely hyperemic ***(fig.127)***, the alveolar and bronchiolar lumen contains an exudate composed mainly of erythrocytes. In some places there can be observed a serous eosinophilic fluid and a reduced number of macrophages and leukocytes. Macroscopically the sites of hemorrhagic pneumonia have a reddish color.

The hemorrhagic exudate usually is associated with another type of inflammation. It has to do with a significant increase of vascular permeability and/or with a negative chemotaxis towards leukocytes.

Catarrhal inflammation

It affects the mucous membranes of the respiratory ways (rhinitis, bronchitis), digestive tract (gastritis, enteritis, colitis, cholecystitis), urogenital ways (endometritis, salpingitis, cystitis). First the catarrhal exudate has a serous character, and yellow color when the mucous membranes drains an abundant liquid exudates. The exudate gradually gets thicker, gaining a mucous (seromucous) character, due to the excessive secretion of mucus, desquamation of epithelial cells and migration of neutrophil leukocytes. In the end the exudate may become purulent (mucopurulent).

Macro – and microspecimen "Catarrhal tracheitis".

The inferior portion of the trachea contains a yellowish-white viscous exudate, which drains on the surface of the mucous membrane ***(fig.128)***. Microscopically, the exudate consists of mucus, serous liquid, desquamated epithelial cells and a reduced number of neutrophil leukocytes; the mucosecretory glands are larger in size, filled with mucus.

According to its clinical evolution, the catarrhal inflammation can be either acute or chronic. The acute catarrhal inflammation can heal in 1-2-3 weeks. Chronic catarrhal inflammation can lead to the atrophy or hypertrophy of the mucous membranes, causing function disorders in the respective organs (for example, the hypertrophic chronic rhinitis is manifest by nasal talking, while the atrophic rhinitis– by resonant voice). The most frequent causes of the catarrhal inflammation are: viral and bacterial infections, irritant gases, toxic substances (uremia), thermal factors, etc.

5.3. PRODUCTIVE INFLAMMATION

5.3.1. General aspects

Productive (proliferative) inflammation is characterized by the predominance of cell multiplication and transformation in the inflammatory site. The alteration and exudative modifications are insignificant. As a result of the proliferation processes, in the inflammation zone, diffuse or focal collections of cells appear, which are called *inflammatory infiltrate*. The cellular composition of these infiltrates can be various, but more often the predominance of 3 cell types can be observed: monocellular phagocytes (macrophages, epithelioid and gigantic cells), lymphoid cells (lymphocytes, plasmocytes, immunoblasts) and fibroblasts, and very rarely – leukocytes, especially eosinophils (in allergic inflammations). The predominance of different cell populations can vary depending on the stage of the inflammatory process. Most important are the macrophages and their derivations: epithelioid and polynucleated gigantic cells, which have the function of phagocytosis, which encourages the healing and regeneration processes.

Productive inflammation is usually chronic in nature, evolving for several months or even years. The chronic character of the inflammatory process is caused by the persistence of the pathogenic agent (infection or foreign body) in the lesion site. The inflammation persists as long as the irritant factor maintains its action. With elimination of the irritant, repair (regeneration) processes begin. The cellular composition of the inflammatory infiltrate gradually becomes homogeneous, and the predominance of only one cell is observed – the fibroblast. This cell participates at fibrillogenesis processes making the inflammation end with the neoformation of connective tissue (fibrosis, sclerosis and cirrhosis of the organs), (table 22).

Table 22

Characteristic of connective tissue proliferation processes

The name of the process	Characteristic	Examples
Fibrosis	The proliferation of connective tissue without the hardening of the organ	Pneumofibrosis, myofibrosis
Sclerosis	Pathological process, which leads to diffuse (microfocal) or local hardening of the internal organs, vessels, tissues, due to the excessive proliferation of the connective tissue	Cardiosclerosis, pneumosclerosis, nephrosclerosis, arteriosclerosis, phlebosclerosis
Cirrhosis	Sclerotic process, which leads to significant deformations of the organs	Hepatic, pulmonary, renal - cirrhosis

Chronic inflammation occurs in cases of:

a) reduced pathogenicity (virulence) of the infection (for example, mycobacterium tuberculosis);
b) physical factors, which can not be phagocytized (sand, talc, foreign bodies);
c) small concentrations of chemical substances;
d) repeated and prolonged action of harmful agents (for example of professional factors);
e) circulatory disorders in the tissue that is affected by the action of the pathogenic agent.

Rarely the productive inflammation may have an acute evolution (for example in typhus fever).

So, the most frequent consequence of the productive inflammation is the neoformation of connective tissue in the place of the lesion site, causing the appearance of some more or less extended cicatrix, adherences, synechia, etc. More rarely the reabsorption of the inflammatory infiltrate can occur in productive inflammation, leading to the complete reestablishment of the altered tissue.

There can be distinguished 3 types of proliferative inflammation:

a) interstitial;
b) granulomatous;
c) with the formation of the polypus and condyloma accuminatum.

5.3.2. INTERSTITIAL INFLAMMATION

The inflammatory process is localized in the stroma of the parenchymatous organs (myocardium, kidneys, lungs, liver).

Microspecimen "Interstitial myocarditis".

The interstitial tissue of the myocardium ***(fig.112)*** contains infiltrates consisting of lymphocytes, monocytes, macrophages, plasmocytes, fibroblasts. The cellular infiltration is more prominent around the vessels (perivascular), especially in the subendocardial and subepicardial zones. In the sarcoplasm of the cardiomyocyte dystrophic lesions is observed. It is seen in viral infections (measles, rubella, influenza), bacterial infections (scarlet fever, typhus exanthematicus, meningococcic infection, typhoid fever, brucellosis, septicemia, etc.), mycotic and parasite infections. Clinically, it is manifest by signs of cardiac insufficiency, rhythm and conduction disorders, etc. As a consequence of interstitial myocarditis, either the complete rehabilitation of the myocardium or cardiosclerosis can occur.

Microspecimen "Interstitial pneumonia" (fig.129).
The inflammatory process is localized in the pulmonary interstitium, the interalveolar septa are thickened, edematous, hyperemic and infiltrated with mononuclear cells (lymphocytes, monocytes, macrophages). The alveolar lumen contains an insignificant number of desquamated alveolar cells.

Interstitial pneumonia is more often seen in viral infections. Clinically, it is manifest by gas diffusion processes disorders (alveolo-capillary block). The severe forms can cause diffuse pneumofibrosis.

Microspecimen "Productive vasculitis in periarteritis nodosa" (fig.130).
The coronary artery wall is considerably thickened due to the diffuse inflammatory infiltration (lymphocytes, macrophages, plasmocytes), localized especially in the adventitia. In the stroma there can be observed a slight tendency towards basophilia and edema. The arterial lumen is thinner than normal. As a consequence, either acute coronary insufficiency, with the necrosis of the myocardium, or the chronic coronary insufficiency, with the beginning of cardiosclerosis can occur.

The periarteritis nodosa belongs to the rheumatic diseases group (collagenosis). Though the name of the disease indicates the localization of the inflammatory process in the adventitia, all the tunics of the arterial wall are affected, thus this is a panarteritis.

5.3.3. GRANULOMATOUS INFLAMMATION

Granulomatous inflammation is characterized by the formation of granulomas in the inflammatory site. The granuloma represents a circumscribed focal inflammatory infiltrate, which appears as a result of proliferation and transformation of phagocyte and lymphocyte cells of bone marrow origin. Usually a granuloma has a diameter of about 1-2 mm, but it can reach up to 3-5 cm. A tissular detritus (with a possible localization of the pathogenic agent) can be observed in the center of the granuloma; it is surrounded by cellular elements, especially by monocytes, lymphocytes and their derivations (macrophages, epithelioid and gigantic cells, plasmocytes).

According to their cellular composition, the following types of granulomas can be distinguished:

a) macrophagic granuloma (simple granuloma or phagocytoma);
b) epithelioidocellular granuloma (epitelioidocytoma);
c) gigantocellular granuloma (gigantocytoma).

Typical macrophagic granulomas are formed in rheumatism, especially in the tunics of the heart.

Microspecimen "Granulomatous inflammation of the endo- and myocardium in rheumatism" (fig.131).
The stroma of the endo- and myocardium contains multiple foci of productive inflammation. These are round or oval shaped granulomas, composed of polymorphous macrophages with big nuclei, intensively stained with hematoxyline, and having a basophilic cytoplasm. Among the granuloma cells there can be observed connective tissue desintegration

products, fibrinoid masses (fibrinoid intumescence) and tissular detritus (fibrinoid necrosis). In some granulomas the cellular elements have a palisade or fan disposition around the fibrinoid central masses ***(fig.132)***.

The rheumatic granuloma appears as a disorganizing inflammatory reaction of the connective tissue. It is produced under the action of streptococcus- β hemolyticus from group A (the main causal agent of rheumatism). Macrophages posses a high phagocytic activity and are capable of fibrinoid mass reabsorption. Dynamically, as the fibrinoid masses are gradually absorbed, the prevalence of fibroblasts is becoming evident in the granuloma, as the collagen production increases and the granuloma undergoes cicatrization (substitution with connective tissue). The evolution in time of the ganuloma from its debut until cicatrization lasts for about 3-4 months.

Granulomas appear in cases when the pathogenic agent is relatively resistant to phagocytosis, and can not be rapidly digested so that it persists for a long time in the inflammatory site. By granuloma formation, the harmful factor is isolated, outlined from the rest of the body, thus the pathological process being localized. Under the action of the granuloma cells, degradation and gradual destruction of the pathogenic agent occurs. Besides this, the cells of the granuloma possess the function of secreting various biologically active substances, which regulate the local tissular medium and contribute to the regeneration of the altered tissues.

Granulomatous inflammation reflects the reduced intensity of phagocytosis processes, and the body ability to outline and localize the pathogenic agent. It has been experimentally demonstrated that it is impossible for the inflammatory site that contains macrophages to get secondary local infection.

The formation of granulomas begins with a focal accumulation in tissues of young, unactive monocytes from the vascular bed. When these become mature, they transform into macrophages – cells with a pronounced phagocytic ability (so called "sweeping cells" or "scavenger").

Those macrophages that can not phagocytize or the ones that have already engulfed particles, completely digested and eliminated them, transform gradually into epithelioid cells. The life duration of these cells is of 1-4 weeks. These cells can divide leading to the formation of new typical macrophages. If the phagocytized material can not be immediately digested or is hard to digest, the macrophages transform into gigantic polynucleated cells (macrophages suffering from "indigestion"). The gigantic cells subdivide into "foreign body" cells and Langhans type cells; they are formed as a result of incomplete fusion or division of epithelioid or macrophage cells. These are seen in tuberculosis, syphilis, mycosis, in cases of insoluble substances (ligatures, sutures, foreign bodies, talc, sodium urate crystals in gout, etc.). The gigantic cells can have a diameter of about 150μ and can contain up to 200 nuclei. In the gigantic cells of foreign bodies the nuclei have a chaotic distribution in the cytoplasm, while in the Langhans cells – a uniform distribution along the cellular membrane, in crown-like or horseshoe-like shapes occur.

Microspecimen "Foreign body granuloma in gout (gout tophus)".

The subcutaneous tissue ***(fig.30)*** contains deposits of sodium urate salts, surrounded by necrotic foci and perifocal inflammatory infiltrates with polynucleated gigantic cells – foreign body cells. These cells have the function of uric salts reabsorption. These macrophages surround the salt deposits, outlining and isolating them from the healthy adjacent tissues. The peripheral zones of the granuloma contain fibrous connective tissue fascicles. Macroscopically, these productive granulomatous have the appearance of painful nodules in articulation regions.

The granulomatous inflammation is seen in more than 70 diseases (granulomatous diseases). Usually, it appears in cases of: a) resistance to phagocytosis of the pathogen agent (incomplete phagocytosis); b) significant concentrations of the pathogen agent; c) the presence of factors that stimulate the maturation activity of the macrophages, for example, of corpuscular substances. The classification and most frequent etiology of the granulomatous inflammation is represented in table 23.

Table 23

Classification of the granulomatous inflammation after etiologic criteria

Granuloma group	**Examples of granulomatous diseases**	**The most frequent localization of Granulomas**
1	2	3
I) Nonspecific infectious granulomas	Typhus fever	Lymphoid structures from the small intestine, mesenteric lymph ganglions, spleen, bone marrow
	Exanthematic typhus	Brain, skin and other organs (excluding the liver, spleen, lymph nodes and bone marrow)
	Tularemia	Skin, lymphatic ganglions
	Brucellosis	Liver, heart, brain, meninx, kidneys, spleen
	Rabies	Brain (medulla oblongata, Sylvian aqueduct zone, the wall of the third ventricle, Ammon's horn)
	Polyomyelitis	Spinal cord (anterior horns)
	Cat scratch disease	Lymphatic ganglions - satellites of the pathogenic agent inoculation zone
	Various mycosis:	
	- actinomycosis	Cervico-facial region, digestive tract, lungs
	- candidosis	Digestive tract, urinary ways, lungs
	Parasitic diseases:	
	- echinococcosis	Liver, lungs
	- trichinellosis	Skeletal muscles
	- cysticercosis	Brain, eyes, skeletal muscles
	- toxoplasmosis	Brain, eyes
II) Specific infectious granulomas	Tuberculosis Syphilis Leprosy Rhinoscleroma	Characteristics given in table 24
III) Rheumatic diseases granulomas	Rheumatism	Tunics of the heart
	Rheumatoid arthritis	Periarticular tissues
	Nodose periarteritis	Small and medium caliber arteries
IV) Noninfectious granulomas	Pneumoconiosis:	
	- anthracosis	Lungs
	- silicosis	Lungs
	Foreign bodies	Various localization
	Suture material	Various localization
	Oily substances (drugs)	Cellular adipose tissue
V) Granulomas of an unclear genesis	Sarcoidosis	Lymphatic ganglions, skin, lungs, liver, spleen
		Gastrointestinal tract
	Crohn disease	Temporal artery (temporal gegantocellular arteritis)
	Horton disease	

The macro- and microscopic aspects of the granulomatous inflammation of different origin are illustrated in the anatomical and microscopic specimens described below.

Macro- and microspecimen "Granulomatous productive inflammation in hepatic echinococcosis".

Macroscopically *(fig.133)*, the liver contains a cavity, (unicameral echinococcus or hydatid cyst) outlined by a whitish membrane – so called chytinic membrane – filled with multiple daughter-vesicles. A fibrous capsule is formed around the echinococcic cyst, while the adjacent hepatic tissue is compressed and undergoes atrophy.

Microscopically *(fig.134)*, the specimen contains small cavities delimited by chytinic membranes, stained homogeneously with eosin (pink). Outside the chytinic membrane, the hepatic tissue contains necrotic foci, and a zone of productive inflammation with a polymorphous cellular infiltrate. This infiltrate contains numerous eosinophil leukocytes. On the periphery the proliferation of fibrous connective tissue is observed; in the adjacent hepatocytes dystrophic and atrophic modifications are revealed. The infiltrate may contain unique gigantic cells (foreign body cells). These cells have the function of chytinic and necrotic masses reabsorption. The presence of eosinophils indicates sensibility to the toxic substances eliminated by the parasite. The fibrous capsule that is formed around the echinococcic cyst during the productive inflammation delimits the parasite, protecting the neighboring tissues from harmful action. If the echinococcus dies, the altered zone infiltrates with calcium salts (calcification and petrification).

Microspecimen "Foreign body granuloma (suture granuloma)" (fig.135).

The specimen contains unreabsorbed catgut sutures surrounded by a productive inflammatory reaction having great number of polynucleated foreign body gigantic cells (reabsorption cells). The inflammatory reaction leads to the gradual reabsorption of the suture material. If this does not happen, than the incapsulation with fibrous connective (cicatricial) tissue and the isolation from the rest of the organ occurs, with the formation of a pseudotumoral nodule of a hard consistency.

Microspecimen "Actinomycotic granuloma in the lung" (fig.136).

The specimen contains an inflammatory focus with a central zone containing an actinomycotic druse (colony of actinomycetes, intensly stained with hematoxylin, surrounded immediately by a neutrophil leukocyte collection (abscess). The next zone constitutes a inflammatory infiltrate made out of macrophages, plasmocites, epithelioid cells, xanthomatous cells (these contain lipids, have a clear foamy cytoplasm, due to the fat being dissolved in alcohol), neoformed vessels, and young connective tissue cells. At periphery there is fibrous connective tissue.

Macroscopically, the actinomycotic sites are hard, yellow on section, with multiple small confluent abscesses. The affected zone looks like a honeycomb. It is most frequently seen in the cervico-facial region (buccal cavity, tonsils, cervical subcutaneous tissue). It often produces external fistulae, while in chronic forms secondary amyloidosis may occur.

The most frequent consequences of the granulomas are:

a) the resorbtion of the cellular infiltrate;
b) organization;
c) incapsulation;
d) calcification (petrification);
e) ossification;
f) secondary necrosis.

5.3.3.1. SPECIFIC GRANULOMATOUS INFLAMMATION

The specific inflammation differs from common (nonspecific) inflammation by characteristics of the granuloma, that make possible the morphological diagnosis of the respective disease without identifying the pathogenic agent. Most frequently specific granulomatous inflammation is seen in tuberculosis, syphilis, leprosy and rhinoscleroma. The productive inflammation in these diseases has usually an undulate chronic evolution and is accompanied by primary or secondary caseous necrosis of the altered tissue (primary necrosis appears at initial penetration of the pathogenic agent, while secondary necrosis is preceded by exudative or proliferative reactions). It must be mentioned that in these diseases, alterative, exudative and proliferative inflammatory lesions are observed. Productive inflammation characterizes the particular disease, a granuloma being the most eloquent morphologic sign of the specificity and of great significance for diagnosis.

The general characteristic of the specific granulomatous inflammation is summarized in table 24.

Tuberculous granulomatous inflammation

The macroscopic appearance of the tuberculous granulomas is clearly seen in the miliary tuberculosis of the lungs.

Macrospecimen "Miliary pulmonary tuberculosis".

The sectioned surface of the lung *(fig.137)* contains multiple whitish-gray lesions of a hard consistency. They are the size of a millet grain (lat. milium), 1-2 mm in diameter, uniformly spread through the lung parenchyma. These lesions represent tuberculous granulomas, which appear due to the spreading (generalizing) of the infection via hematogenous pathways.

Microspecimen "Tuberculous granuloma in the lungs"

The pulmonary parenchyma contains tuberculous granulomas *(fig.138)* that have a central zone of caseous necrosis (macroscopically, the necrotic masses has a "cheese-like" appearance), which is eosinophilic, amorphous (astructural) and anuclear. They are surrounded by a crown of cells placed in the following order: immediately surrounding the necrosis are the epithelioid cells, with enlarged, pale nuclei which have a radial distribution; they remind the cells from stratum spinosum of the epidermis (that is why they are called so), though they are of mesenchymal origin. Among these there can be observed the Langhans gigantic polynucleated cells, with eosinophilic cytoplasm and the nuclei placed in a horseshoe or crown-like pattern *(fig.139)*. The Langhans cells are typical of tuberculosis.

Their cytoplasm may contain phagocytosed Koch bacilli. At the periphery of the granuloma there can be seen a belt of lymphoid cells (small lymphocytes, macrophages and lymphocytes).

The absence of blood capillaries and the persistence of reticulin fibers are typical. Depending on the prevalence of specific cellular elements, tuberculous granulomas can be gigantocellular, epithelioid and lymphoid ones.

The tuberculous nodules can be of various dimensions, from the size of a pin head (in miliary tuberculosis) up to structures of several cm in diameter.

The consequences of the tuberculous granuloma can be various. In cases of favorable evolution (tuberculostatic treatment, increased body resistence) resorption, organization, incapsulation or petrification and ossification of the lesion can occur. Unfavorable evolution can lead to secondary caseous necrosis and the softening of the granuloma.

Syphilitic (luetic) granulomatous inflammation

The inflammatory lesions characteristic of syphilis appear in the tertiary phase of the disease, which appear 3-6 years after contamination. They can have a nodular or diffuse character and are morphologically manifest by the formation of granulomas in organs and tissues. These are called syphilitic gummas or gummous (gumma type) infiltrates. Syphilitic gummas can be solitary or multiple. Their localization can be very diverse: in visceral organs (liver, heart, brain, kidneys), tegument, soft tissues, bones, cartilage, nasal septum, etc. The diameter of the gummas can vary from 1 cm to 5-6 cm (from the size of a pea to that of a hen egg).

Macrospecimen "Syphilitic gumma in the liver" (fig.140).

The liver section contains a well delimited node of affected tissue, having a pink-gray color and elastic consistency. With time the central zones of the gumma suffer necrotic modifications and the softening of the preexisting tissue. This zone is reminiscent of the arabic gum (that is where the name comes from: gr.kommi – gumma, rubber).

Microscopically *(fig.141)*, the syphilitic gumma represents a necrotic site in the center, in which preexistent tissular structures can be seen (unlike in tuberculosis, where the caseous necrotic zone is amorphous, astructural). It is surrounded by a cellular wreath, consisting predominantly of lymphocytes and plasmocytes, though epitelioid and somee Langhans type giant cells can also be seen, but are not characteristic of luetic inflammation. Blood vessels persistence is typically seen, with a productive inflammation (phlebitis and arteritis), leading to their narrowing and lumen obliteration. This obliteration explains in some degree the appearance of necrotic lesions.

The syphilitic gumma evolves more frequently into sclerosis and connective tissue cicatrization, with the formation of some retractile and deforming cicatrix in parenchymatous, cavitary and tubular organs. For example the deforming of the nose ("saddle nose"), liver (*hepar lobatum* – "rope-tied liver"), and lungs (*pulmo lobatus*), strictures of larynx, trachea, stomach, etc.

The syphilitic gumma-type inflammation has a more or less diffuse character; the infiltrate consisting of lymphocytes and plasmocytes mostly located perivascularly. It can be seen in aorta, liver, stomach, bronchi, intestines, etc.

Microspecimen "Syphilitic mesaortitis" (fig.142).

The medium layer of the aorta contains lymphoplasmocytic infiltrates surrounding the vasa-vasorum. There is fragmentation of elastic fibers. The ascending portion of the aorta including the semilunar valves are most seriously affected. Gummatous inflammation can evolve into sclerosis and cirrhosis of the affected organs and tissues. Syphilitic mesaortitis leads to the installing of ascendent aorta aneurysm. Rupture of the aneurism is one of the frequent causes of death in syphilitic patients.

Leprous granulomatous inflammation

In leprosy the inflammatory lesions are more frequently localized in skin, subcutaneous tissue, superior respiratory ways, peripheral nerves, etc.

The specific granuloma – leproma, appears in the lepromatous form of leprosy. It represents a inflammatory focus in the dermis of the skin. It is separated from the epidermis by a clear zone of connective tissue poor in cellular elements. The granuloma is made out of macrophages, lymphocytes, plasmocytes and giant cells with a foamy (vacuolar) cytoplasm due to the lipidic inclusions – so called leprous cells (leprous globes or Virchow cells). The latter are typical of leprosy and represent some macrophages, whose cytoplasm contains huge numbers of Hansen bacilli (leprous mycobacteriae), closely packed like cigarettes in a box, which are made prominent by staining in the Ziehl-Nielson test ***(fig.143)***.

Macroscopically ***(fig.144)***, the lepromas look like nodes of various shape and size located in the skin. The leprous granulomas can become necrotic, subsequently organizing and forming mutilating scars, which distort the facial features ("leonine face"). As the disease evolves, trophic changes, cutaneous ulcerations, finger distortion, phalange mutilation, etc. may occur. The trophic disorders are due to the involvement of nervous trunks in the inflammatory process (demyelinization and lysis of neurofibrilles takes place).

Granulomatous inflammation in rhinoscleroma

The inflammatory process is located in the mucous membrane of the superior respiratory ways, particularly in the nasal cavity. It can also extend to the larynx and trachea. Macroscopically, it is manifest by a pseudotumoral proliferation of hard granulation tissue, leading to the narrowing or obliteration of the respiratory tract. The inflammatory process can infiltrate the adjacent tissues of the upper lip. Clinically, it is manifest by chronic catarrh; it can produce respiratory disorders (asphyxia).

The microspecimen ***(fig.145)*** shows a productive inflammation zone with granulomas consisting of plasmocytes, epithelioid cells and lymphocytes. Typical of the lesion is the presence of large macrophages, with clear foamy cytoplasm – Mikulicz cells. These cells contain a large number of Frisch bacilli, as well as fuxinophilic corpuscles (Russel hyalin spheres). They are caused by dystrophic lesions of the plasmocytes (containing γ-globulines – plasmocytes secretion product). The inflammatory process evolves into sclerosis and to the hyalinosis of the granulomatous tissues.

5.3.4. PRODUCTIVE INFLAMMATION WITH THE FORMATION OF POLYPS AND CONDYLOMA ACUMINATUM

Polyps. They represent pseudotumoral formations at mucous membranes level. They have a smooth or papillary surface, vary from 1-2 mm to several cm in size; they can be solitary or multiple. They are covered with glandular epithelium and are seen in the stomach, intestine, uterus, nasal meatus, bronchi and trachea. The appearance of polyps is determined by the productive inflammation of the mucous membranes accompanied by the proliferation of glandular epithelium and underlying connective tissue.

Macrospecimen "Gastric polyposis" (fig.146).

On the gastric mucous membrane multiple polyps of various dimensions can be seen. They have a broad or narrow base (pedicle), many of them having a cauliflower –like appearance.

Gastric polyposis can cause hemorrhage, secondary inflammation, circulatory disorders, stenosis of pylorus or cardia (depending on its location and dimensions).

Macrospecimen "Endometric polyp" (fig.147).

The bottom region of the uterus contains a polyp of relatively big dimensions, prominent into the uterine cavity. The color of the polyp is violet-brown due to the circulatory disorders.

Microscopically, the endometric polyp is made from glands of various shapes and dimensions, some of them with cystic dilatations. The covering epithelium is cylindrical, the stroma contains a lymphoplasmocytic infiltration ***(fig.148)***. Clinically, it is manifest by uterine hemorrhage (metrorrhagia), endometritis, etc.

Macrospecimen "Tracheal polyp" (fig.149).

The inferior portion of the trachea contains a polyp which obliterates the main bronchus, causing atelectasis of the respective lung. It can produce pulmonary hemorrhage and inflammatory processes.

The glandular polyps of various organs are considered precancerous conditions because they can undergo malignant transformation (from this background a cancerous tumor can evolve).

Condyloma acuminatum (gr. *kondylos* – prominence, lat. *acumen* – peak). These are papillary formations (sometimes with a cauliflower-like appearance), covered with pluristratified squamous epithelium ***(fig.150)***. Hyperkeratosis, acanthosis, parakeratosis and koilocytosis of the epidermis is observed (koilocytes – cells with perinuclear cytoplasmic vacuolization and angulated nucleus). They are located on the skin from the perineal region, on the mucous membrane of the uterine cervix or of the urethra. Pathogenetically they depend on the irritant action of the genital tract secretions in gonorrhea, syphilis and other sexually contagious diseases. In the connective stroma of the condylomas a chronic inflammatory infiltration occurs (productive inflammation). Actually is proved that in majority of cases the anogenital condyloma acuminata is caused by human papilloma virus infection.

Table 24

General characteristic of the specific granulomatous inflammation

Disease	Pathogenic agent. The name of the granuloma	Most frequent location	Morphologic characteristics (structure of the granuloma)	Consequences
1	2	3	4	5
Tuberculosis	Mycobacteria tuberculosis (Koch bacillus) Tuberculous granuloma (nodule, tubercle)	Can be located in all the organs and tissues	The center of the granuloma contains a focus of caseous necrosis, surrounded by a wreath of cells, composed of (from the center to the periphery): - epithelioid cells with a radial disposition, - giant polynuc-leated cells of Langhans type, - lymphoid cells	Reabsorption, organization (encapsulation, petrification, secondary necrosis, the softening of the granuloma leading to the formation of ulcerations or cavities)
Syphilis	Treponema pallidum Syphilitic gumma	Subcutaneous tissue, liver, myocardium, brain, bones	The central zone contains a necrotic focus of a glue-like consistency, surrounded by lymphocytes, plasmocytes, epithelioid and solitary giant Langhans type cells	Organization, petrification
Leprosy	Mycobacterium leprae (*Hansen bacillus*) Leproma	Skin, subcutaneous tissue, respiratory ways, digestive tract, nervous system	Nodular agglomerations of lymphoid cells, plasmocytes, macrophages, and Virchow cells	Necrosis, organization
Rhinoscle-roma	Frisch bacillus (Klebsiella rinoscleromatis) Rhinoscleromatous granuloma	Nasal mucous membrane, larynx, trachea	Granulomas composed of lymphocytes, plasmocytes, epithelioid cells and Mikulicz cells	Sclerosis, hyalinosis

Chapter 6
IMMUNOPATHOLOGIC PROCESSES

Immunopathologic processes occur because of functional disorder of the immunocompetent (lymphoid) tissue. During these processes, the immune reactions, which normally have the defense function of the body against various foreign antigen substances, can cause the alteration of the self tissues. The immune reactions, in these conditions, act more harmfully upon the tissues than the antigens themselves.

The immune response can be of cellular or humoral types, and are morphologically manifest by cellular proliferation and differentiation in the central and peripheral organs of the lymphoid system. The character of the immune reaction depends especially on: antigen peculiarities, its quantity, the way of access into the body, and previous contacts with the respective immunogenic antigen. When various soluble antigenic substances, for example microbial toxins or extracellular pathogenic agents (bacteria) penetrate into the body, a humoral type immune reaction is unleashed. Its essence consists in the destruction of the antigen by the specific antibody, produced by plasmocytes, whose predecessors are the B lymphocytes. The antigen-antibody complex is phagocitized and eliminated from the body by macrophages – immune phagocytosis ***(fig.151)***. Thus, the effector cell in the humoral immune reaction is the plasmocyte.

In cases when cellular (tissular) antigens penetrate into the body, for example foreign cells or some pathogenic agents which parasitize intracellularly (especially viruses and fungi) cellular type immune reaction is stimulated. The essence of it is in the destruction of the antigen by the sensitized T (killer) lymphocytes, with the help of macrophages, without the participation of antibodies the immune cytolysis (cytolytic ant cytopathic action of the lymphocytes). The effector cells from the cellular immune reaction are the T - killer lymphocytes and the macrophages ***(fig.152)***.

Each type of immune reaction includes 3 consecutive stages: afferent stage – information transmission from specific reactive cells, central stage – cellular proliferation and differentiation from the lymphoid system (blastic transformation of B or T lymphocytes, the appearance of plasmocytes, the sensitizing of T lymphocytes) and the efferent stage – the reaction of specific antibody and sensitized T lymphocytes with the antigen.

The morphologic manifestations of the immunopathologic processes can be divided into 2 groups: immunogenesis disorders and local immune reactions (allergic or hypersensitivity reactions).

Immunological disorders

Immunological disorders are seen in cases of massive (long time) antigenic stimulation, in immunodeficiency states (immunodeficient syndromes) and autoimmune diseases. They are manifest by characteristic lesions of the central lymphoid organs (thymus) and peripheral lymphoid organs (lymphatic ganglions, spleen, lymphoid formations of the digestive tract: tonsils, Peyer's patches, vermiform appendix, solitary follicles of the large intestine).

The lesions of thymus, which can be observed in immune disturbances are represented in table 25. These lesions are the result of, and in some cases, the cause of immunologic homeostasis disturbances. Thymus disease can lead to a number of immunodificient syndromes, autoimmune diseases and endocrine disturbances.

Table 25

The modifications of thymus in immunological disturbances

Type of lesion	Morphologic characteristic	Causes	Consequences, functional importance
Accidental involution	Macroscopically – the rapid decrease of thymus weight and volume (8-10 times); microscopically – the progressive destruction of lymphocytes, collapse of the reticuloepithelium, dystrophy of the Hassall corpuscles; the characteristic sign –reversal of the thymic lobule layers	Severe infectious diseases, malignant tumors with metastasis, leukosis	a) Thymus regeneration b) Thymus atrophy
Atrophy	The decrease in weight and volume of the thymus	It is a consequence of accidental involution	Acquired immunodeficiency
Thymomegaly	Thymus has an increased weight and volume, the histologic structure is normal	Can be a congenital or acquired malformation (in chronic insufficiency of the adrenal glands)	Functional insufficiency of the thymus, immune deficiency of cell – medioted reactions
Thymus hyperplasia with lymphoid follicles	Thymus is increased in size, is infiltrated with B lymphocytes and plasmocytes; the thymic lobules contain lymphoid follicles with germinative centers, which are not normally present	Immunocompetent system functional disorders	The appearance of autoimmune processes
Agenesis (aplasia) Hypoplasia Dysplasia	Thymus is either absent or persists as a embryonic rudiment The incomplete development of the thymus The structure of the thymus is altered , the number of lymphocytes is reduced	Congenital malformations	Congenital cellular or mixed immunodeficiency

Microspecimen "Accidental involution of the thymus".

The thymic lobules *(fig.153)* are smaller in size, the cortical layer is thinner and poor in lymphocytes as a result of progressive destruction and phagocytosis by macrophages. The medullary layer gets equal or even richer in lymphocytes than the cortical layer (the reversing of thymic lobule layers). The thymic corpuscles are also of smaller dimensions, and present as homogeneous eosinophilic masses. Some of the corpuscles undergo fusion and cystic formation. Dystrophic calcification sites (of an intensed eosinophilic color) also occur; the reticuloepithelium is collapsed, the interlobular connective tissue septa are thickened.

Macroscopically, the dimensions and weight of the thymus decrease rapidly (by about 8-10 times).

Involution is seen in many childhood diseases with intoxication, especially in severe infectious diseases, trauma, overcooling or overheating, malignant tumors, leukosis, etc.

The degree of thymus involution depends on the duration and severity of the respective disease. If the disease evolution has a short course, the thymus can be rehabilitated. The main cause of thymus involution in these cases is the hypersecretion of glucocorticoid hormones in stress conditions, as well as long time massive antigenic stimulation.

The accidental involution of the thymus can be reversible, due to the high regenerative capacity. In cases of severe infectious diseases, (bacterial or viral) infections with purulent processes or malignant tumors with metastasis, aquired atrophy of the thymus may result.

The clinico-functional importance of thymic accidental involution depends on the degree of decrease of cellular and humoral immunity, due to the diminished thymic hormonal secretion.

Macrospecimen "Thymomegaly".

The thymus has considerably increased in size *(fig.154)*, leading to the compression of the neighboring organs, especially the trachea, causing respiratory disorders. It is usually seen in children, and represents a congenital condition. The histologic structure of the thymus is unchanged. As a rule, it is associated with developmental disturbances of the cardiovascular system (aorta and major arteries), disfunction of adrenal and sexual glands. In the same patients, despite thymomegaly, thymic disfunction with its hormonal secretion and cellular immunity disorders is observed. These patients are very sensitive to antigenic stimulation (to immunization, in infectious and infectoallergic diseases, surgery, narcosis, drugs). Sudden death frequently occurs at the action of various stress factors (for example, during surgical interventions). The sudden death is caused not only by thymus disfunction, but also by adrenocortical functional insufficiency. It is also seen in adults in cases of chronic adrenal insufficiency (the thymus is a effector organ of the adrenal glands). The causes of death are usually infectious and infectoallergic diseases, whose evolution is aggravated by the disorders of the immune system.

Microspecimen "Thymic hypoplasia in the mixed immunodeficient syndrome".

The thymic lobules *(fig.155)* are smaller in size, the number of lymphocytes is considerably reduced, the cortical layer is atrophic, the medullary layer contains an insignificant number of small Hassall corpuscles, which can be totally absent in some regions. The interlobular connective tissue septa are thickened.

Thymic hypoplasia is a congenital development disturbance. Macroscopically, the thymus is incompletely developed, the thymic hormonal secretion is decreased or completely abolished. It is associated with hypoplasia of the lymphoid tissue from the lymph nodes and spleen, the atrophy affects mainly the thymodependent zones. It is clinically manifest by the body inability to unleash cellular and humoral reactions. Children are predisposed to infectious diseases, which have a relapsing course with severe complications (pneumonia, septicemia). Thymic hypoplasia is frequently associated with other congenital anomalies and malignant mesenchymal tumors.

The modifications which occur in the lymphatic ganglions and in the spleen as a result of antigenic stimulation are unspecific and stereotypical. Macroscopically, these organs have an increased volume, are affected by edema and hyperemia. Microscopically, hyperplasia of the immunocompetent cells, especially the transformation of small lymphocytes into blastic cells is observed.

Depending on the type of the immune reaction, the hyperplastic processes take place in different zones of the peripheral lymphoid organs. The repartition of thymodependent and bursodependent zones is given in table 26.

Table 26

Repartition of burso- and thymodependent zones

Organ	Bursodependent zones	Thymodependent zones
Lymphatic ganglions	Cortical layer Medullar layer	Paracortical layer
Spleen	The peripheral zones of the lymphatic follicles	Paraarterial zone (around the centrofollicular artery)
Tonsils	Tonsillar follicles	Interfollicular subepithelial lymphoid zones
Intestinal lymphoid tissue	Intestinal follicles	Interfollicular subepithelial lymphoid zones

When the humoral immune reaction is stimulated in the bursodependent zones, B lymphocytic, lymphoblastic hyperplasia, plasmoblastic and placmocytic transformation of the B lymphocytes and the proliferation of macrophages occur. During cellular type immune reaction in thymodependent zones, T lymphocytic activation and sensitizing and macrophagic hyperplasia occur. These hyperplastic processes are more evident in the regional lymph nodes in immediate proximity of the site of antigen entrance into the body. The induction of antibody elaboration during the humoral immune reaction is associated with the appearance of germintive centers in the follicles of the lymph nodes and spleen, the so called secondary follicles (follicles with germinative centers). The proliferation of limphoblasts takes place in the germinative centers. These follicles are formed around the macrophages which contain the antigen. During the cellular type immune reaction the blastic transformation takes place not in the germinative centers of the follicles but in the paracortical zones of the lymph nodes and in the periarterial zones of the splenic follicles.

Microspecimen"Hyperplasia of the lymph node follicles as a result of antigenic stimulation".

The lymph node *(fig.156)* contains multiple secondary follicles with clear germinative centers, in which the proliferation of lymphoblasts takes place. The appearance of secondary follicles and its increased development reflects the degree of the immune reaction intensity and of the plasmocyte antibody secretion. These hyperplastic processes are more intense in the lymph nodes which are located near the place of antigen entrance into the body.

Microspecimen "Hyperplasia and the plasmatisation of the lienal follicles in antigenic stimulation".

In the lymph nodes *(fig.157)* hyperplasia of the lymphoid follicles and the appearance of germinative centers can be observed. The T lymphocytes of the periarterial zone (of an intense basophilic color) move toward the periphery, while at the periphery of the follicles there can be observed the proliferation of plasmoblasts and plasmocytes. This shows the intensity of humoral type immune reaction. Macroscopically, the spleen is larger in size, has a variegated appearance. There are multiple whitish foci, which represent hyperplastic lymphatic follicles with germinative centers.

In case of hereditary humoral immunodeficiency , the spleen suffers follicle decrease, and absence of germinative centers and of plasmocytes. In the lymph nodes the lymph follicles and the cortical layer (bursodependent zones) are absent, while the paracortical layer (thymodependent zones) persists. In cellular immunodeficiency syndromes, hypoplasia of paraarterial zones of the lienal follicles and also hypoplasia of paracortical layers of the lymph nodes is observed. In mixed immunodeficiency there is total hypoplasia of the peripheral lymphoid tissue.

The local allergic reactions or the hypersensitivity reactions

These reactions appear in a sensitized body and are characterized by the local alteration of tissues.

The main etiologic factors that encourage these reactions are: a) prolonged (repeated) action of the allergen; b) allergenic overtaxation (big doses); c) general hyperreactivity of the body; d) hereditary predisposition for allergy.

The hypersensitivity reactions can be: a) immediate type; b) late or delayed type; c) transplantation immune manifestations (graft rejection reaction).

The general characteristics of the hypersensitivity reactions are summarized in table 27.

The mechanisms of achievement (effector mechanisms) of the allergic processes are:

a) inactivation or neutralization reaction; b) immediate anaphylactic reaction; c) cytotoxic and cytolytic reaction; d) toxic immune complexes reaction; e) cellular type sensitization (delayed hypersensitivity); f) granulomatous reaction.

Table 27

Characteristics of allergic reactions (hypersensitivity reactions)

Criteria	Immediate type	Delayed type
1	2	3
Term of appearance	15-20 min after the contact of the specific allergen with the sensitized tissues	24-72 hours after the introduction of the allergen unleashing dose
Which type of immune reaction it is linked with	With humoral immune reaction	With cellular immune reaction
Factors that alter the tissues	Complement, circulating immune complexes, circulating antibodies	Sensitized T (killer) lymphocytes and macrophages

Morphologic manifestations	Acute immune inflammation with tissular edema, intumescence and/or fibrinoid nec-rosis of the connective tissue and vessels, vascular thrombosis, the formation of fib-rinous or fibrino-hemorrhagic exudate	Chronic immune inflammation with the infiltration of the immune conflict site with lymphocytes and macrophages or the formation of granulomas
Effector mechanisms	Anaphylactic reaction Cytotoxic (cytolytic) reaction Toxic immune complex reaction	Cellular type hypersensitivity Granulomatous reaction
Examples of allergic diseases	Anaphylactic shock Arthus phenomenon Atopic bronchial asthma Urticaria Frank lobar pneumonia Quincke edema Serum disease	Tuberculin type reaction Autoimmune diseases Contact dermatitis Some bacterial or viral diseases (tuberculosis, leprosy, brucellosis, tularemia)

The characteristic of these immunopathologic mechanisms is given in table 28 and in ***fig.158-163***.

Morphologically, the allergic processes are manifest by classic inflammatory reactions (acute or chronic immune inflammation).

Table 28

Characteristic of the immunopathologic proceses (fig.158-163)

Reaction type	General characteristic	Examples
Inactivation and neutralization reaction	The elaboration of antibodies against some bio-logically active substances or cellular surface receptors: - inactivation of hormones, enzymes (insulin, thyroglobulin, clotting factors), toxins (in diph-theria, tetanus); - cell function alteration due to the antireceptor antibodies (antibodies against insulin, acety-lcholine, thyroid stimulating hormone, thyroglobulin receptors, against parietal cells of the gastric mu-cous membrane); the antireceptor antibodies in some cases are bloc-king, in other cases are stimulating the functional activity of the cells	Insulinodependent diabetes mellitus, myasthenia gravis, hypothyroidism, thyreotoxicosis, pernicious anemia, coagulopathies
Anaphylactic reaction of immediate type	At first antigen (Ag) penetration, IgE are elaborated, which stick to the surface of mast cells and basophil leukocytes; at repeated administration of the same Ag, the antigen-antibody reaction causes the degranulation of mast cells and the sudden release of mediators (histamine, serotonin, heparin), which cause spasms of the smooth muscles of the bronchi and intestine, edema, mucus hypersecretion, vascular dilatation and hyperemia	Anaphylactic shock (to drugs, insect venom), urticaria, atopic bronchial asthma, allergic rhinitis, hay fever, Quincke edema, alimentary or medi-camentous allergy

Cytotoxic (cytolytic) reaction	The antibodies are elaborated against the super-ficial antigenic components of the heterogeneous cellular membrane (the cells of the transfused or self blood, transplant). There can be two variants: - the cytotoxicity mediated by the complement (activation of the complement causes the secretion of mediators and the lesion of the target cell); - the cytotoxicity mediated by antibodies (anti-bodydependence – Ag-Ab reaction) takes place on the surface of the target cells, which subsequently are destroyed by K (killer) cells or NK (natural killer) cells, or phagocytized by macrophages	The hemolytic disease of the newborn, posttransfusional reactions, au-toimmune hemo-lytic anemia, medicamentous cytopenia (agranulocytosis, thrombocytopenia), vascular purpura, graft (transplant) rejection reactions
The reaction of toxic immune complexes	The antigen-antibody immune complex leads to the activation of complement components, basophil and neutrophil leukocytes, to the elimination of the inflammatory mediators. The lytic action of the toxic immune complexes can be produced by: a) excess of antibodies with inflammatory re-action in the site of antigen entrance (Arthus reaction); b) excess of antigen with generalized reaction and the depositing of the immune complexes in the basal membranes of the capillaries from the kidneys, articulations, skin (serum disease)	Serum sickness disease, glomerulonephritis, rheumatic diseases (disseminated lupus erythematosus, rheomatoid arthritis), allergic dermatitis, farmer's lungs
Cellular type allergic reaction (cellular sensitizing)	The immune response appears after 24-72 hours, depending on the T lymphocytes and macrophages, which are responsible for the im-mune cytolysis – the destruction of target cells, which contain antigens; the morphologic substrate – lymphocytic and macrophagic infiltration	Tuberculin type reaction, contact dermatitis, graft rejection, autoim-mune diseases, tuberculosis, syphilis, helminthosis, mycosis
Granulomatous reaction	Appears in case of long time(or unlimited) antigenic persistence; the granulomatous reaction leads to the isolation and delimitation of the pathogenic antigen (allergen). The main cellular components of the granulomas are the epithelioid and giant cells	Tuberculosis, syphilis, rheumatism, sarcoidosis, Crohn disease, berylliosis

Microspecimen "Allergic rhinitis".

In the specimen *(fig.164)* there is proliferation of glandular epithelium. The mucous membrane is strongly edematous and hyperemic. An inflammatory infiltrate is located predominantly perivascularly, with a large number of lymphocytes, plasmocytes and eosinophil leukocytes. Clinically, it is manifest by abundant seromucous secretion. It appears as a reaction to allergens of vegetal (pollen) or bacterial origin. It can complicate with the appearance of nasal polyps.

6.1. AUTOIMMUNE DISEASES

The autoimmune diseases represent a group of diseases which are based on the autoantibody and sensitized limphocytes reaction against the antigens of the self tissues, causing their functional and structural alteration. Among the most frequent etiologic factors of autoimmunization, of a great importance are the chronic viral infections, radiation, and some physical and chemical agents. These act upon the organs of the immunocompetent system as well as target-organs. Three groups of autoimmune diseases may be distinguished depending on autoimmunization development mechanism: I) organ-specific; II) organ-non-specific; III) affections with secondary autoimmune disorders.

The general characteristic of these groups are represented in table 29.

Table 29

General characteristic of autoimmune diseases

Autoimmune disease group	Mechanisms of producing and the most important causal factors	Examples
1	2	3
Organ-specific autoimmune diseases (genuine)	Affection of the physiologic isolation of organs and tissues, which are deprived of the immune tolerance, and the alteration of the histo-hematic barriers; the unmodified antigens of these tissues, which are immunologically isolated (sequestered) cause the elaboration of antibodies and/or T lymphocyte sensitization; the causal factors: chronic viral infection, trauma, radiation, sunstroke	Hashimoto's thyroiditis, encephalomyelitis, disseminated sclerosis, polyneuritis, sympathetic ophthalmia, aspermia, idiopathic Addison's disease
Organ-non-specific autoimmune diseases (systemic)	Primary functional disorders of the immunocompetent system, the lymphocytes loose the ability to distinguish between self and nonself antigens; the lesions have a generalized (systemic) character; causative factors: mutations, lymphotropic viral infections	Disseminated lupus erythematosus, rheumatoid arthritis, systemic sclerodermia, dermatomyositis, thrombocytopenic hemolytic purpura
Diseases with secondary auto-immune disorders	Secondary autoimmunization, the appearance in the body of some new heterogeneous antigens, which can lead to the suppressing of natural tolerance. Etiopathogenic mechanisms: - protein denaturing in burns, irradiation, cold trauma, chronic inflammation, viral infections; - cross reaction: the appearance of some bacterial antigens, whose structure is identical to the one of some bodily tissues (for example, the cardiac serotype Y of the beta-hemolytic streptococcus has antigenic commonality with cardiomyocyte sarcolemma, while the nephritogenic serotype XII – with the basal membranes of the renal glomeruli, klebsiella – with the pulmonary tissue; - the haptenic mechanism; the role of haptenes play the necrotic products, drugs, toxins	Glomerulonephritis, rheumatism, myocardial infarction, chronic gastritis, ulcerous colitis, hepatic cirrhosis, medicamentous disease, allergic anemia, etc.

It must be mentioned that the group III affections are not independent autoimmune diseases, the immune conflict is only a complication of the main morbid process. Secondary autoimmune disorders lead to the chronicity and aggravation of the respective disease.

Morphologically, the autoimmune conflict is manifest by the infiltration of the target- organ with immunocompetent cells (lymphocytes, plasmocytes, macrophages), the appearance of lymphoid follicles with germinative centers, dystrophic and necrotic lesions of the parenchyma and the proliferation of connective tissue.

Autoimmune or the Hashimoto's thyroiditis can serve as an example of a true autoimmune disease. In the microscopic specimen ***(fig.165 and 166)*** the stroma of the thyroid gland is diffusely infiltrated with lymphocytes and plasmocytes. Some places contain lymphoid follicles with clear germinative centers. These infiltrates gradually replace the glandular parenchyma. The thyroidian follicles are atrophic, containing weakly stained or vacuolated colloid, some of them without a lumen and with sclerotic foci. Macroscopically, the thyroid gland is larger, harder, with an elastic consistency and without adherences to the neighboring tissues. Clinically, it is accompanied by hypothyroidism and it evolves toward mixedema. It is seen almost exclusively in women 40-50 years of age.

Chapter 7
ADAPTIVE – COMPENSATORY PROCESSES

The adaptive – compensatory processes are subdivided conventionally into 2 groups:

I) The adaptive processes, in which cellular (tissular) structure adaptation for a particular functional activity prevails: a) atrophy; b) morphological restructuring of the tissue; c) metaplasia d) organization;

II) The compensatory processes, which are developed when an organ (tissue) is altered because of the action of some lesion factors: a) regeneration; b) hypertrophy; c) hyperplasia. The prevalence of compensation and rehabilitation of altered structures and functions are observed in these processes.

7.1. REGENERATION

Regeneration is the process of restoration (renewal) of an organ (tissue) structural elements in place of the altered ones. During regeneration, the rehabilitation of both structure and function of the altered tissue (cells) is observed.

Regeneration is produced via two forms:

a) the cellular form, when the cells multiply by mitosis (indirectly) or amitotically (directly);
b) the intracellular form, which is manifest by the multiplication and the increase in size (hypertrophy) of the cytoplasmic organelles (nuclei, mitochondria, ribosome, etc.). The last form of regeneration is represented in ***fig.167***.

The evolution of the regenerative process has two phases: 1) proliferation; 2) differentiation. In the first phase the multiplication of young (immature) undifferentiated cells – so called stem or precursor cells, and of intracellular organelles takes place. In the second phase the immature cells become mature, gaining specific structural and functional proprieties. The immature intracellular organelles undergo the same process of maturation and differentiation.

Three varieties of regeneration can be distinguished: a) physiologic; b) reparatory; c) pathologic.

Physiologic regeneration

Ensures a normal functioning of all organs and tissues. The basis of all the functions are the decomposition and synthesis processes at molecular level, thus the vital necessity of constant intracellular renewal. Physiologic regeneration is permanent, during all life and is characterized by the continuous renewal of the cells, fibrillar elements and ground substance from the connective tissue. Biochemical regeneration is produced at subcellular level, which is the structural equivalent for the bodily functions.

Reparatory regeneration

This is the kind of regeneration that takes place in various morbid processes accompanied by cellular and tissular alteration. It is manifest by the same morphological mechanisms as the physiologic regeneration, thus representing a physiological regeneration in an affected body. It starts at the same time as the disease starts.

Reparatory regeneration can be either complete or *restitution* and incomplete or *substitution.*

Complete regeneration is characterized by substituting the defect with tissue which is identical to the altered (preexistent) one. It is observed in tissues with cellular type of regeneration, for example, in the connective tissue, bones, skin (epidermis), mucous membrane of the digestive tract, respiratory and urogenital tracts, vascular endothelium, mesothelium of the serous membranes, and hematopoietic system.

Incomplete reparatory regeneration is characterized by substituting the defect with cicatricial connective tissue. The rehabilitation of the functional parenchyma is produced by hypertrophy of the remaining part of the organ called *regenerative hypertrophy.* This can evolve via two ways: 1) cellular hyperplasia; 2) hyperplasia and hypertrophy of the cellular ultrastructures, that is cellular hypertrophy.

An organ function and mass rehabilitation by cellular hyperplasia is more frequently seen in the regenerative hypertrophy of the liver, kidneys, pancreas, lungs, adrenal glands, etc. In these organs regeneration of the epithelium can take place either by cellular hyperplasia or by the association of cellular hyperplasia with their hypertrophy, which takes place by hyperplasia of subcellular (cytoplasmic) elements.

In the myocardium and brain (ganglionar cells), the regenerative hypertrophy takes place exclusively by hypertrophy of the remaining cells, due to hyperplasia and/or hypertrophy of the intracellular structures.

Microscopic specimens representing regeneration peculiarities of various organs and tissues

Microspecimen "Granulation tissue".

The specimen ***(fig.168)*** contains many newformed blood vessels, including capillaries, among which are numerous young autochtoneus and allochthonous cellular elements of the connective tissue: mesenchymal cells, epithelioid cells, fibroblasts, labrocytes, histocytes, lymphocytes, polymorphonucleate leukocytes, plasmocytes. The cells are surrounded by loose ground substance, while the vessels are of small caliber, with thin walls.

Macroscopically, it represents a thin, juicy tissue of a reddish color, with granular surface (thus the origin of its name), the granules being composed of newformed vessels. Granulation tissue bleeds easily due to the great number of capillaries.

Granulation tissue is the first phase of connective tissue regeneration, being young connective tissue, rich in cells and blood vessels and poor in collagen fibers. It is a typical example of complete cellular regeneration.

The formation of granulation tissue begins with the proliferation (division) of young mesenchymal cells and the neoformation of blood microvessels. The regeneration of microvessels takes place by:

a) the budding of the existent capillaries; lateral prominences appear in their walls due to the intensive proliferation of the endothelial cells leading to the formation of some cellular columns; these subsequently gain a lumen, that continues the "maternal" capillary;
b) autogenic neoformation of the capillaries; collections of undifferentiated cells which are transformed into endothelial cells appear in the connective tissue; fissures then appear in these collections, which unite with the preexistent capillaries.

Dynamically, as the inflammatory process attenuates, the number of cells and blood vessels gradually is reduced, while the mesenchymal cells (precursor of the all connective tissue cells) are transformed into epithelioid cells, and then into fibroblasts. During the maturation period of the granulation tissue the predomination of fibroblasts is observed, while the number of vessels is progressively reduced ***(fig.169)***. At the same time, the increase of fibroblast activity and the intensive synthesis of collagen fibers is observed and the vessels transform into arteries and veins. The maturation process of the granulation tissue ends up with the formation of fibrous (cicatricial) connective tissue, which contains an insignificant number of fibrocytes and vessels ***(fig.170)***.

The neoformation of granulation tissue takes place not only in case of connective tissue regeneration, but also in cases of incomplete regeneration in other organs (when the defect is replaced with connective tissue), as well as in organization, encapsulation, wound healing and in productive inflammation processes.

Microspecimen "The regeneration of the striated skeletal muscle" (fig.171).

In the site of striated muscle destruction bizarre, polynucleated cells – myoblasts, can be seen. These represent cells that appeared during the regeneration of altered muscular fibers if their sarcolemma remains unaltered. The myoblasts are formed as a result of regeneration of the sarcoplasma and its organelles. This fulfills the tube delimited by the unaltered sarcolemma. The myoblasts subsequently stretch. Myofibrilles with transverse striation appear in them leading to the restoring of the muscular fiber. In cases when the sarcolemma is altered, the defect is replaced with a connective cicatrix (muscular callus). At the ends of the discontinuous muscular fibers prominences (expansions) appear with many nuclei, which are called muscular buds, while the continuity of the muscular fiber remains unaltered.

Microspecimen "The regeneration of liver in cirrhosis" (fig.172).

The liver contains sites of connective tissue proliferation, while between them trabecules of hepatic cells with regenerative phenomena, manifest by the appearance of binucleated cells and increased mitosis persist.

The liver is a typical organ where the regeneration takes place both via cellular and intracellular (regenerative hypertrophy) ways. The defect, for example the necrotic focus, is replaced with connective tissue, while the rest of the organ becomes hypertrophied by hypertrophy and hyperplasia of the cells leading to the subsequent remodeling in the hepatic lobules which have a normal histological structure.

Macro – and microspecimen "Macrofocal cardiosclerosis postinfarction (myocardial cicatrix after infarction)".

The left ventricle ***(fig.173)*** contains multiple extended scars which appeared as a result of necrotic (infarction) foci replacement with connective tissue. The ventricular wall around the scars is hypertrophied. Microscopically, ***(fig.174)*** an extended site of cicatricial connective tissue, composed of collagen fiber fascicles with an insignificant number of cellular elements and blood vessels can be observed. The striated muscle fibers surrounding the cicatricial site are larger. Their nuclei are enlarged, irregular in shape, and intense stained with hematoxylin (nuclear hyperchromatosis).

In the cardiac muscle the neoformation of cardiac cells does not take place; the regeneration is incomplete. The lesion site (necrotic zone) is replaced with cicatricial connective tissue, while the structural rehabilitation is produced by hypertrophy of the remaining myocardial fibers, especially of those which are situated near the postinfarction cicatrix (regenerative hypertrophy). This takes place by hypertrophy and/or by hyperplasia of the cytoplasmic ultrastructures (schematically represented in ***fig.175***).

Electronomicrography "Regenerative hypertrophy of the myocardium".

The myocardial cell contains an increased number of mitochondria and myofibrilles – hyperplasia of the intracellular organelles ***(fig.176)*** and gigantic mitochondria ***(fig.177)*** as a result of cytoplasmic organelle hypertrophy. This electronomicroscopical picture shows that the activity of the heart after infarction is assured by hypertrophy of the remaining part of the myocardium.

Pathologic regeneration

Pathologic regeneration is an abnormal, atypical, disturbed regeneration, characterized either by quantity or quality changes of the regenerative process. It is seen in disorders of local and general factors, which may influence the regeneration: such as innervation and circulatory disorders, protein and vitamin deficiency, and chronic inflammation.

It can be manifest by:

a) *hyperregeneration* (overregeneration) – exaggerated neoformation of regenerative tissue. For example, there may be an excess of cicatricial connective tissue (keloid cicatrix as a result of wound, burn healing), exuberant (hypertrophic) callus of the bone or exostosis (bony prominences) in fractures, amputational neuroma, etc.;
b) *hyporegeneration* - insufficient formation of regenerative tissue. For example, there may be vicious (deficient) bony callus in fractures, with the appearance of pathologic mobility of the bone fragments or the development of pseudoarthrosis, atonic ulcerations of the skin, etc. ***(fig.178)***;
c) *metaplasia*, the transforming of unistratified epithelium from mucous membrane of the bronchi, trachea, cervical canal, endometrium etc., into squamous epithelium (epidermoid metaplasia) in cases of chronic inflammations (chronic bronchitis, tracheitis, cervicitis or endometritis).

Macrospecimen "Vicious callus in femoral fracture".

In uncomplicated fractures (closed, uninfected, without fragment misplacements), regeneration has five stages:

1) the formation of a hematoma between the two fractured ends of the bone as a result of vascular lesion;
2) the organization of the hematoma, its replacement with connective tissue leading to the formation of the connective (fibrous) callus;
3) ossification of the fibrous callus with the formation of the preliminary bony callus by the activation and proliferation of the osteoblasts in the periosteum and endosteum (periosteal and endosteal callus). In the osteogenic fibroreticular tissue poorly calcified bony trabecles appear;

4) the formation of the final bony callus, which takes place by the maturation of the preliminary bony callus; this callus transforms into mature, dens bone with low vascularization and chaotically disposed trabeculi;
5) functional reconstruction, architectonic remodeling of the newly formed tissue, according to the functional stimulus of the respective bone. As a result the location of the bone fracture can not be identified neither clinically nor radiologically over time.

The abnormal regeneration of bone can be manifest by the excessive formation of bone tissue with the appearance of single or multiple prominences (exostosis) on the surface of the bone in the zone of the healed fracture (hyperregeneration –*fig.179*). The regenerative process may slow due to association of purulent inflammation or disturbances of differentiation of osteocartilaginous callus into bony callus. This process leads to the deformation of the fractured bone (hyporegeneration); the interposition of soft tissues (especially muscles) between the ends of the fractured bone leads to the formation of pseudoarthrosis and pathologic mobility of the bone in the respective zone.

The specimen ***(fig.180)*** shows an incorrect coalescence of the femoral bone fracture fragments, with longitudinal dislocation of the fractured bone ends. As a result a periosteal callus has formed, which strengthens the displaced fractured segments. This formation leads to the thickening, shortening and deformation of the leg.

Microspecimen "Keloid cicatrix".

The keloid is a linear thickening of the skin of a pink color and hard consistence. Microscopically, it is composed of chaotically disposed fascicles of collagen fibers, which are intensively hyalinized, and an insignificant number of vessels and cellular elements ***(fig.181)***. The keloid cicatrix is formed more frequently in some burns or supurative wounds.

7.2. HYPERTROPHY AND HYPERPLASIA

Hypertrophy represents the increase of weight and volume of the cell, tissue or organ. Hyperplasia is the numeric increase of the structural elements of the tissue or cell. Hypertrophy can appear by the increase of functionally active cells (cellular hyperplasia), or by their increase in volume (intracellular hyperplasia), or by the association of both processes.

The next specimen can be a demonstrative example of hyperplasia.

Microspecimen "Hyperplasia of the elastic membrane in arterial hypertension" (fig.182).

The specimen contains two medium caliber arteries (of muscular-elastic type) with a considerably narrowed lumen and a thickened wall due to hyperplasia of the internal elastic membrane and the proliferation of connective tissue between the dissociated elastic elements. It is seen as a compensatory reaction of the arterial wall to the increased intravascular pressure. It occurs both in hypertensive disease and in the symptomatic (secondary) hypertensions.

In the organs and tissues with intracellular type regeneration, hypertrophy and hyperplasia of the cytoplasmic organelles takes place (myocardium, cerebral neurons). In the organs with cellular type regeneration hypertrophy occurs by cellular hyperplasia (connective tissue, bones, hemopoietic tissue, etc.).

True hypertrophy is determined by the increase in volume of the structures that have the specialized function of the organ. False hypertrophy (pseudohypertrophy) occurs when the increase in volume (mass) of the organ is conditioned by the excessive proliferation of the connective and adipose tissue.

Depending on the mechanism of its appearance, three varieties of veritable hypertrophy can be distinguished:

a) work (compensatory) hypertrophy;
b) vicarious hypertrophy;
c) neurohormonal hypertrophy.

Work (compensatory) hypertrophy occurs as a result of excessive functional activity of the organ.

Vicarious hypertrophy is the hypertrophy of one of the pair organs (lungs, kidneys, adrenal glands) as a result of nonfunction of the contra-lateral organ. An example is the hypertrophy of the remaining lung after the surgical extirpation of the other one in cases of tuberculosis, abscess, bronchiectatic disease, cancer, etc.

The neurohormonal hypertrophy has an adaptive character (non compensatory); it occurs as a result of neurohormonal disorders with the modification of the hormonal balance which has a stimulatory action upon the organ and tissue growth. Examples:

a) hypertrophy of uterus and of mammary glands during gestation and lactation under the action of the placental and ovarian corpus luteum hormones;
b) acromegaly – hypertrophy and unproportional growth of arms, legs, facial prominences (mandible, ear, nose, lips), affecting both the skeleton and the soft parts.The growth is produced by the hypersecretion of the somatotropic (growth) hormone in eosinophilic cell tumors (adenoma) of the pituitary gland;
c) glandular hypertrophy of the endometrium as a result of estrogen hormone hypersecretion;
d) gynecomastia – hypertrophy of mammary glands in men due to the sexual glands hypofunction which can be of diverse etiology (in conditions of eunuchoidism, congenital abnormalies, genetic deseases, testicular tumors, some adrenocortical tumors, hepatic cirrhosis, etc. or in case of prostate cancer treatment with excessive doses of estrogens).

The most clinically important is the compensational (work) hypertrophy.

Macrospecimen "Hypertrophy of the heart left ventricle" (fig.183 and 184).

The size and weight of the heart are increased, the wall of the left ventricle is considerably thickened, its thickness can reach up to 2.5-3 cm (the normal thickness is 1.0-1.2 cm), while the heart weigh – 600-1000 g (the normal weight 260-280 g). The trabecular and papillary muscles of the left ventricle are also increased in volume. It is seen in the essential arterial hypertension (hypertensive disease), secondary (symptomatic) hypertension, cardiac valvulopathies, especially in aortic stenosis (the narrowing of orifice through which the blood passes from the left ventricle into the aorta). The hypertrophy of the left ventricle from the mentioned pathologic processes occur as a result of functional overtaxation of the heart due to the presence of an obstacle in the greater circulation (in arterial hypertension) or at the aortic valve level.

Macrospecimen "Hypertrophy of the heart right ventricle" (fig.185).

The size and weight of the heart are increased, the right ventricle wall is thickened. Its thickness can reach up to 1-1.5 cm (in normal condition – 0.2-0.3 cm), and the papillary and trabecular muscles are larger in volume. It is seen in the hypertension of the small circulation, during various chronic pulmonary affections: pulmonary emphysema, pneumosclerosis, chronic tuberculosis, bronchiectatic disease, etc. (this is why it is also called pulmonary heart), as well as in cardiac valve lesions.

The heart chambers are hypertrophied and can be narrowed. The cardiac muscle tonus is increased and there is concentric hypertrophy (hypertrophy in compensation stage) or dilated - excentric hypertrophy (hypertrophy in decompensation stage). In the last case the consistence of the myocardium becomes flaccid, having, if sectioned, an opaque appearance due to the dystrophic lesions. In some cases the heart gains a specific character of a "tiger-like heart" ***(fig.11)*** as a manifestation of the myocardial fat dystrophy. This represents the morphological substrate of the heart decompensation. The heart distention in the compensation stage is called active or tonogenic, while in decompensation – it is passive or myogenic.

Microspecimen "Heart hypertrophy".

The cardiomyocytes ***(fig.186)*** are considerably thickened, the nuclei are larger, and intensively basophilic (hyperchromatosis). Their shape is irregular; the stroma quantity and vessel number are also larger. The cardiac muscle hypertrophy occurs only by intracellular hyperplasia with the hypertrophy of the preexistent muscular cells, and not by cellular hyperplasia. This mechanism becomes more evident at electronooptic examination (see ***fig. 176 and 177***).

Macrospecimen "Hypertrophy of the bladder wall in prostate adenoma" (fig. 187).

The wall of the bladder, the muscular trabeclae are considerably thickened, and the cavity is distended. The prostate is larger, with a dense consistency, and irregular, nodular surface. Inside of the prostate a tumoral process can be observed, a nodular adenomatous hyperplasia (adenoma – benign tumor of glandular epithelium). The tumoral nodules press on the urethra, causing urine stasis in the bladder and the compensatory hypertrophy of its wall. The recesses formed between the hypertrophied muscular trabeclae can store urinary salts subsequently forming calculi. Because of urinary stasis, inflammatory processes of the bladder mucous membrane (cystitis) can occur.

An example of hormonal hypertrophy, which does not have a compensatory character, can be the glandular hyperplasia of the endometrium.

Microspecimen "Glandular (glandulocystic) hyperplasia of the endometrium".

The endometrium is thickened ***(fig.188)***, corresponding to the proliferative phase of the menstrual cycle. It contains multiple glands of unequal volume and irregular shapes, some of them are small, others elongated, having a meandering appearance or cystic distention. The glandular epithelial cells are of cylindrical shapes, with elongated hyperchromic nuclei. The endometrial stroma is rich in fibroblasts (cellular hyperplasia).

Glandular hyperplasia of the endometrium is a manifestation of hormonal disorders and occurs in cases of estrogen hormone hypersecretion in some ovarian disturbances, especially in the pre- and menopausal period. It is clinically manifest by irregular and persistent uterine hemorrhages. It is considered to be a precancerous stage of the uterus.

7.3. ATROPHY

Atrophy is the process of cellular, tissular or organ volume decrease accompanied by the diminishing or loss of their functional activity. It can be either physiologic or pathologic, general or local.

The etiopathogenetic variants of the general pathologic atrophy and their characteristics are represented in table 30.

Table 30

Variants of the general pathologic atrophy (cachexy)

Cachexy variants	**The predominant etiopathogenic mechanisms**
a) Alimentary	Subnutrition or assimilation disturbances
b) Cancerous	In malignant tumors (cancer, sarcoma, melanoma) as a result of nutrition disorders, enzymatic system disorders and digestive glands secretion disorders, intoxications
c)Endocrine	Function disorders of the internal secretion glands (pituitary, thyroid glands)
d) Cerebral	Inflammatory or tumoral processes in the hypothalamus area
e) In some chronic infectious diseases	Tuberculosis, chronic dysentery, AIDS, brucellosis, etc.

In physiologic or pathologic general atrophy reduction, the volume and weigh of all organs and tissues takes place, accompanied by their functional decrease. Lipofuscin (wear pigment) accumulates in organs, especially in the myocardium, liver, striated muscles. Due to this pigment the respective organs and tissues gain a brown color.

Macro- and microspecimen "The brown atrophy of the heart".

The heart is smaller in size and weight ***(fig.18)***, the epicardium does not contain adipose tissue, the coronary arteries manifest prominences under the epicardum, having a meandering appearance, while the muscle has a brown aspect.

Microscopically ***(fig.189)***, the myocardial fibers are thinner, and atrophic. Their cytoplasm contains accumulations of lipofuscin brown granules, localized at the poles of the cellular nuclei.

Such modifications of the heart are seen in some cachectic diseases as an expression of general atrophy.

The general characteristic of the local pathologic atrophy is represented in table 31.

Table 31

The local pathologic atrophy

Atrophy type	**Pathogenetic mechanism**	**Examples**
1	2	3
1. Dysfunctional (by inactivity)	The decrease or abolition of the organ, tissue functional activity (decrease of metabolic processes, blood supply)	Muscular atrophy in bone fractures, arthritis, arthrosis, etc., the atrophy of the gall bladder in the obturation of the cystic duct by calculi
2. Neurotic	Trophic innervation disorders	Trauma with motor nerve lesions, nervous tumors, inflammations, for example in poliomyelitis (alteration of the motor nerves from the anterior horns of the spinal cord)

3. Ischemic (vascular)	Arterial blood supply disturbances (circulatory hypoxia)	Atherosclerosis of the cerebral arteries (brain atrophy), coronary arteries (heart atrophy), renal arteries (atrophy of the kidneys)
4. By compression	The compression of the functional parenchyma of the organ, which leads to its ischemia and hypoxia	In tumors, aneurysms, fluid accumulations (hydronephrosis, hydrocephaly)
5. At the action of physical and chemical factors	The inhibition of regenerative processes	The atrophy of hemopoietic tissue and sexual glands due to penetrating radiation, the atrophy of endocrine glands caused by the administration for a long time of hormonal substances

Macrospecimen "The ischemic atrophy of the brain hemisphere" (fig.190).
It can be observed that the left hemisphere of the brain is uniformly smaller in size, while the circumvolutions are thinner. Such a process called also "hemiatrophy of the brain", is more frequently caused by the atherosclerosis of the carotid arteries. Obliteration of the internal carotid artery with fibrous plaques, causing chronic ischemia and atrophy of the respective brain hemisphere.

Macrospecimen "Internal hydrocephaly with atrophy by compression of the cerebral tissue".
The lateral ventricles are considerably dilated *(fig.191)*, overfilled with cerebrospinal fluid. The cerebral tissue of the great hemispheres is atrophic due to its long term compression. The disorders of cerebrospinal fluid circulation is caused by the appearance of some obstacles in the Sylvius aqueduct or in the Monroe orifice, as consequences of meningitis or brain tumors. Clinically, it is characterized by cephalalgia (head aches), nausea, vomiting.

Microspecimen "Atrophy of renal parenchyma by compression in hydronephrosis" (fig.192).
The renal parenchyma is thinner, and the majority of glomeruli are smaller in size, affected by sclerosis (replaced with connective tissue) and hyalinosis. The diffuse proliferation of connective tissue takes place, the blood vessels are affected by sclerosis. The remaining few renal tubules with narrowed lumens can be observed. It is seen when obstacles appear in the urinary tract (ureters), especially urinary calculi in case of nephrolithiasis. The retention of urine in the renal pelvis leads to its distention and the compression of the renal parenchyma. This causes functional insufficiency of the respective kidney.

7.4. MORPHOLOGIC RESTRUCTURING OF TISSUES

Restructuring is an expression of adaptive reactions. It is morphologically manifest by hyperplastic and regenerative processes in the specialized elements of the organs and tissues.

Examples:

a) In cases of collateral circulation, the respective blood vessels become distended, the walls get thicker by hypertrophy of the muscular fibers and hyperplasia of the elastic elements;
b) The transforming of the pulmonary alveolar epithelium into cubic epithelium in cases of atelectasis (the epithelial cells produce prominences in the alveolar lumen);
c) The modification of nephrothelial cells from the parietal layer of the Bowmann's capsule, in case of renal glomeruli function loss (the cells become cuboidal), etc.
d) The thickening of cranial bones in case of uni- or bilateral atrophy of the brain (it is also called *hypertrophy ex vacuo*).

These processes are also named *histological accommodation*, representing an expression of the tissular accommodation to some new conditions of life.

7.5. METAPLASIA

Metaplasia is the transforming of a differentiated adult tissue into another type tissue. It represents a process of tissue adaptation toward modified functioning conditions. The transforming of one tissue into another takes place in the same embryonic layer, by proliferation of young cells. It is more frequently seen in the covering epithelium layers as well as in the connective tissue. The metaplasia of the epithelium is manifest by the transforming of the prismatic or cylindrical epithelium into pluristratified squamous epithelium with keratinization. For example, the epidermoid metaplasia of the tracheal or bronchial mucous membrane during various chronic inflammatory processes, and metaplasia of the glandular epithelium from the endocervical mucous membrane (the cervical canal of the uterus) in chronic inflammations (chronic endocervicitis), cervical polips, etc. Metaplasia of the connective tissue is manifested by formation of the cartilaginous or osseus tissue (for example in scars, in the tumor stroma, during caseous necrotic lesions ossification in tuberculosis, etc.).

Microspecimen "Squamous metaplasia of the bronchial mucous membrane epithelium" (fig.193).

In an area of the bronchial wall the replacement of cilliary epithelium of the mucous membrane with pluristratified squamous epithelium can be observed. The underlying layer contains hyaline cartilage of the bronchial wall. It is seen in chronic bronchitis, bronchiectasis, etc. With the background of squamous metaplasia of the bronchial mucous membrane, the epidermoid cancer of the bronchi can occur.

7.6. ORGANIZATION

Organization represents the process of replacement with connective tissue of some necrotic sites, exudates, thrombi, hematomas, tissular defects, parasites and foreign bodies. First the proliferation of young tissue takes place – granulation tissue, which is then transformed into fibrous connective tissue, thus a cicatrix, adherence, synechia, etc. appears in the respective place. Sometimes only the delimitation (encapsulation) of the necrotic site takes place.

Microspecimen "The organization of a necrotic lesion in the striated muscle".

The specimen *(fig.194)* contains a granulation tissue proliferation focus, which contains desintegrated muscular cells (cellular detritus). A cicatrix is subsequently formed .

During the organization process, the elimination of necrotic masses, fibrin, exudates and tissue desintegration products takes place with their subsequent replacement by granulation tissue.

Microspecimen "The encapsulation of a caseous necrotic lesion in tuberculosis".

The specimen *(fig.195)* contains an unstructured eosinophilic focus of caseous necrosis, without nuclei (karyolysis). It is delimited by a dense fibrillar connective tissue zone, which passes gradually into the adjacent pulmonary tissue with thickened, affected by sclerosis alveolar septa.

7.7. HEALING OF WOUNDS

It is a particular form of organization and connective tissue regeneration. It evolves differently depending on the shape, expending, depth of the wound, its character, the absence or presence of infection, the general condition of the body (nutrition state, the condition of the immunocompetent, nervous, cardiovascular systems) and local structural peculiarities of the tissue (vascularization, innervation, regeneration capacity).

The *per primam intentionem* healing is seen in wounds with straight margins, whose edges are contacting, aseptic (uninfected) and without significant tissular destructions (usually in surgical incisions). There can be distinguished the following consecutive processes:

a) the formation of the blood clot (fibrin), which fills the tissular defect, joining the wound margins (the first 24 hours);
b) the replacement of the clot with granulation tissue rich in blood vessels and cellular elements (first 4-5 days);
c) maturation of the granulation tissue, its transforming into fibrous connective tissue, with the subsequent epithelialization of the defect (epithelial regeneration), without the restructuring of sweat glands and pilosebaceous adnexa (2-3 weeks). The suturing of wounds increases the per primam intentionem healing, because it reduces the margin dehiscence, encouraging the regenerative processes. The process ends up with a thin cicatrix.

Another variant of *per primam intentionem* healing is the under crust healing, which is seen in small superficial defects, on the surface of which a crust appears, composed of coagulated blood and lymph. This crust protects the wound from the influence of the ambient environment factors, encouraging the regeneration. After the recovering of epithelium, the crust comes off.

Microspecimen "The healing of a cutaneous wound".

The specimen *(fig.196)* is a cutaneous wound covered by regenerated epidermis. Proliferation of epithelial cells from the basal layer of the epidermis, beginning with the wound margins, can be seen. The cells subsequently stretch on the surface of the wound, forming initially an unistratified epithelium, which afterwards transforms into pluristratified epithelium. The pilosebaceous and sweat adnexa are absent (do not regenerate). The dermis contains a new formed cicatricial connective tissue rich in collagen fibers and poor in vessels and cellular elements.

The *per secundam intentionem* healing is seen in extended, opened wounds with infected massive tissular destruction and necrosis which contain foreign bodies. It is associated with the purulent inflammation, during which the elimination of necrotic masses and tissular remains (secondary cleaning of the wound) takes place. It ends up with the abundant formation of granulation tissue and the appearance of a maimed cicatrix accompanied by the retracting and deformation of tissues. The regeneration process takes much longer than the *per primam intentionem* healing.

The pathologic regeneration of wounds can be manifest by the slowing down of regeneration processes (hyporegeneration) or by the appearance of keloid scars (hyperregeneration).

Chapter 8
TUMORS

8.1. GENERAL ASPECTS

The tumor (syn: neoplasm or blastoma) represents a pathologic process characterized by the unlimited and irrepressible proliferation of cells. The cellular proliferation in tumors is uncontrollable, uncoordinated and does not respond to any regulatory actions of the body, being relatively autonomous. Another major feature of the neoplasms is the fact that the proliferation process does not have an adaptive – compensatory character.

Tumors are subdivided into benign, malignant and locally destructive tumors.

Their general characteristics are given in table 32. The histogenetic classification (depending on the origin tissues) of tumors is the following:

1) epithelial tumors without specific localization (organ-non-specific);
2) epithelial tumors with specific localization (organ-specific – of the endo- and exocrine glands and epithelial covering layers);
3) mesenchymal tumors;
4) tumors of the melanopoietic tissue;
5) tumors of the nervous tissue and of the meningeal membranes;
6) tumors of the hemopoietic and lymphoid tissues;
7) teratomas;
8) tumors of unknown origin.

Table 32

General characteristics of benign, malignant and local destructive tumors

Criteria	Benign tumors	Malignant tumors	Tumors with local destructive proliferation
1	2	3	4
Growth rhythm	Slow	Fast	Slow
Tumor cell differentiation degree	Mature, differentiated cells	Immature, undifferentiated cells	Mature, differentiated cells
Atypism	Tissular	Tissular, cellular (ultrastructural, biochemical, histochemical, antigenic)	Tissular
Growth character in relation with adjacent tissues	Expansive	Invasive (infiltrative)	Invasive (infiltrative)

Tumor borders	Clear, precise (are encapsulated)	Erased, unclear	Erased, unclear
Metastasizing	No metastasizing	Metastasizing	No metastasizing
Relapsing	Does not relapse	Relapses	Relapses
Clinico-morphologic evolution	Can become malignant	Can not become benign	Can become malignant

8.1.1. MACROSCOPIC CHARACTERISTICS OF TUMORS

The macroscopic aspect of tumors is variable. In most cases the tumors have round or ovoid nodular appearance. This nodule may be localized inside an organ or on its surface; in the cavitary and tubular organs it may be in the wall thickness or in the organ's lumen. The surface of the tumor nodules can be either smooth or with an irregular shape, rough, sometimes like cauliflower. Their dimensions and consistency are also various: from microscopic dimensions up to an adult's head size or even bigger. Their consistency may vary from soft, flaccid to hard, and rocky. The color varies depending on the structural and functional peculiarities of the origin tissue and the secondary modifications which occur in the tumor tissue (dystrophic or necrotic lesions, circulatory disorders, inflammatory processes, etc.). The tumors can be circumscribed, encapsulated, and well delimited or can invade, and infiltrate the adjacent tissues. Depending on their number, tumors can be unicentric or multicentric.

Macrospecimens:

"Pulmonary chondroma" (fig.197).

The lung contains a tumor nodule that has a round shape, significant size, whitish color, and lobular appearance. It is delimited from the adjacent pulmonary parenchyma and has a hard consistency. It is a benign tumour from cartilaginous tissue, which is found in the pulmonary bronchial walls. Microscopically, it is composed of hyaline type cartilage tumor tissue.

"Neurofibromatosis of skin" (fig.198).

The skin contains multiple tumor nodules of various dimensions (up to several cm), round shape, and flaccid consistency; the nodules are prominent on the skin surface. The tumor originates from the nerve fiber sheaths (from the perineurium), is composed of connective tissue, and contains nerve cells and fibers. Usually it has a systemic character, generalized neurofibromatosis (Recklinghausen disease).

"Myxoma of the heart" (fig.199).

The cavity of the right ventricle contains a localized tumor situated at the level of the tricuspid valves. The dimensions are of about 9 - 10 cm, with an irregular lobular surface, soft consistency, and whitish color. It protrudes into the cavity, causing stenosis of the right atrioventricular orifice, explaining the hypertrophy of the right ventricle. The tumor is composed of connective tissue which has a mucoid, gelatinous appearance and originates from pluripotental embryonic mesenchymal elements.

8.1.2. MICROSCOPIC APPEARANCES OF TUMORS

Microscopically, tumors are composed of two tissular components: the stroma and the parenchyma. The stroma is composed of connective tissue, and contains blood and lymph vessels as well as nerve fibers. The parenchyma is composed of tumor cells. The relation between stroma and parenchyma can be varied; in some tumors the predominance of stroma is observed (fibrous tumors), while in others the parenchyma (histoid tumors) is greater. In some cases the stroma and parenchyma have a uniform relationship (organoid tumors).

The tumor differs from normal tissue by morphological, biochemical, histochemical and immunological atypism. The morphologic atypism can be tissular, cellular and ultrastructural.

Tissular atypism is manifest by the modification of the original tissue architecture, of structural element arrangement, and of the relation between them. For example there are modifications of the stroma-parenchyma relations, variations of number, shape and dimensions of the epithelial structures in epithelial tumors and diversity of distribution of fibrillar, cellular, vascular, etc. structures in mesenchymal tumors.

Microspecimen "Tissular atypism in fibroadenoma of the breast" (fig.200).

The fibroadenoma is a benign tumor, which originates from glandular epithelium and is associated with an excessive proliferation of connective tissue. It can be seen that the tumor nodule is composed of proliferative glandular formations, which are chaotically disposed and have varied shapes and dimensions. Simultaneously there can be observed an abundant proliferation of compact dense connective tissue disposed concentrically around the tubular structures; the canaliculi are carpeted with regular unistratified epithelium, reminiscent of the normal epithelium.

Microspecimen "Tissular atypism in leiomyoma".

Leiomyoma is a benign tumor, which originates from smooth muscular tissue; usually it is associated with the fibroconnective tumoral proliferation, named fibroleiomyoma. It is seen most frequently in the uterus and digestive tract. The specimen ***(fig.201)*** contains a tumor of smooth muscle fiber fascicles, disposed chaotically, without any order. In some places whirls of varied thickness and orientation are interspersed with collagen fiber fascicles; the tumor muscular cells are well differentiated, like normal smooth myocytes from the original tissue.

The tissular atypism is characteristic for mature benign tumors.

The cellular atypism is manifest by the unevenness of shape, volume and size of cells, nuclei, and cytoplasmic organelles. There is a different ratio between the nucleus and the cytoplasm, an increase of mitotic activity, and the appearance of pathological mitosis, etc.

Microspecimens "Cellular atypism in undifferentiated cancer and in rabdomyosarcoma".

Cancer is a malignant tumor of epithelial origin without any specific localization.

The rabdomyosarcoma is a malignant tumor which originates from striated muscular tissue; it is seen in skeletal muscles, myocardium, tongue, etc.

In the respective specimens ***(fig.202 and 203)*** a significant cellular and nuclear atypism and polymorphism can be observed. The tumor cells have varied shapes and size; some of them are giant, polynuclear, with uneven nuclei, some of them are very large, with many monstrosities.

Their staining intensity is also varied (hyper- or hypochromatosis of the nuclei), and the number of mitosis is considerably increased, including abnormal mitosis. The original tissue architectural disruption and the chaotic arrangement of the tumor cells must be mentioned.

Microspecimen "Cellular atypism in hepatocellular carcinoma".
In the center of the specimen ***(fig.204)*** there can be seen a site of cancerous transformation (malignization) with characteristic signs of cellular atypism and polymorphism. It is composed of tumor cells of varied shapes and sizes, with large, giant and hyperchromic nuclei. The cytoplasm is more basophilic compared to the surrounding hepatocytes. The mitosis are aberrant; the arrangement of tumor cells is chaotic, with no order. Gradual transformation of the normal hepatic tissue into a tumor is taking place.

The cellular atypism is common for the malignant immature tumors.
The ultrastructural atypism includes ribosome number increase, shape and volume diversity of mitochondria, nuclei, mitosis atypism, and the appearance of some hybrid or chimaera-cells (cells that possess the function of two different types of cells).
The histochemical atypism reflects the biochemical and metabolic peculiarities of the tumor tissue which distinguish it from the origin tissue, for example the predominance of anaerobic glycolytic metabolism and the increased content of nucleic acids, etc.

8.1.3. METASTASIZING AND RELAPSE OF TUMORS

Metastasis is the process of transferring the tumor cells, their dissemination and multiplication at some distance from the primary tumor, leading to the formation of secondary tumor nodules or metastases. It is characteristic for malignant tumors (cancer, sarcoma, melanoma).
It can evolve via the following ways: a) through blood (hematogenous metastasizing); b) lymphatic (lymphogenic metastasizing); c) by continuance (for example perineurally) and d) by contiguity (implantation or contact metastasizing), which are more frequently seen on the serous membranes (for example, the carcinomatosis of peritoneum, pleura). The metastasizing in the brain can take place through the cerebrospinal fluid (fluid metastasizing).

Microspecimen "Tumor embolus in a blood vessel".
The vascular (vein) lumen contains a collection of tumor cells (cellular embolus), which adhere to the intima, implanting partially into the vascular wall ***(fig.205)***. Subsequently the extravasation of tumor cells takes place leading to the occurrence of secondary tumor lesions, or metastases. The tumor embolism is mostly seen in veins and capillaries, more rarely in arteries. Hematogenous (venous) metastasizing is characteristic especially for sarcomas, melanomas, chorioncarcinomas, etc.

Microspecimen "Cancerous embolism of the pulmonary lymphatic vessels".
The specimen ***(fig. 97)*** contains lymphatic vessels, which are obliterated by collections of tumor cells (cellular tumor emboli). The lymphatic metastasizing is typical for cancerous tumors, the first metastases being found in the regional lymph nodes (satellite nodes of the respective region). After the taking over the regional lymph nodes, the tumor cells invade the blood circulation and varied organs and tissues.

Microspecimen "The perineural spreading of glandular carcinoma".

The specimen ***(fig.206)*** contains glandular cancerous structures (adenocarcinoma), which spread by continuance along the nervous trunk sheath (perineurally). The primary tumor is located in the pancreas (pancreatic adenocarcinoma).

Macrospecimens "Cancer metastases in liver (fig.207) and lung (fig.98), and ocular melanoma metastases in bones (fig. 208)".

The respective organs contain multiple secondary metastatic tumor nodules, disposed without any order. They are more or less well delimited, and of variable sizes.

The hematogenous metastases in the liver are more frequently seen in gastric, pancreatic, colon, etc. carcinomas. In lungs, mammary gland, and stomach cancer metastases, are more frequently seen. Melanoma metastases contain melanin pigment, the primary tumor being located in the eye (in the enucleated ocular globe there can be seen a tumoral lesion of a brown-black color).

Microspecimen "Gastric adenocarcinoma metastases in the liver".

In the focus, ***(fig.209)*** two zones can be seen: cancerous atypical glandular structures and adjacent compressed hepatic tissue, with dystrophic changes.

Relapse of the tumor represents its reappearance in the same place after surgical excision or after radiotherapy. It grows from the cells that can remain at the tumor site or from the near by lymphatic metastases. It is characteristic for the malignant tumors. It is also seen in tumors with local destructive growth (intermediary type), for example in basalioma or a basal-cell carcinoma (a tumor localized more frequently on the skin of the face), desmoid (connective tissue tumor localized usually in the anterior abdominal wall), in ameloblastoma (odontogenic epithelial tumor located in the mandible).

8.1.4. MORPHOGENESIS AND GROWTH OF TUMORS

The evolution of tumors can begin de novo, but more frequently it begins with the background of some pretumoral (precancerous, preneoplastic) lesions. These lesions represent pathologic processes, which create a high risk for tumor occurrence. The pretumor lesions are subdivided into obligatory (they end up with cancer in the majority of cases) and optional (they rarely lead to cancer). The most eloquent examples of obligatory precancer are the congenital polyposis of the large intestine and xeroderma pigmentosum; both diseases are hereditary in nature. The optional pretumor conditions include some hyperplastic, dysplastic and dysembryoplastic processes, accompanied by morphologic restructuring of tissues and functional disorders. Examples are leukoplakia, squamous metaplasia and inflammatory polyposis of the mucous membrane, dysplasia of mucosal epithelium, endocervicosis of the uterine cervix, glandulo-cystic hyperplasia of the endometrium, hepatic cirrhosis, chronic gastric ulcer, chronic atrophic gastritis, senile keratosis, etc.

Depending on the degree of tumor differentiation and the relation with adjacent tissues, there can be distinguished the following variants of tumor growth:

a) expansive – the tumor grows slowly, "by itself", eliminating and compressing the surrounding tissues which gradually form a fibroconnective capsule around the tumor nodule (the parenchymatous elements undergo atrophy). The tumor has precise limits and can be easily eliminated (enucleated); it is common for benign tumors;

b) appositional – the tumor evolves by tumoral transformation of the surrounding normal cells and their subsequent proliferation no further than the tumor field;
c) invasive (infiltrative) – the tumor cells infiltrate and destroy the adjacent normal tissues (destructive growth); the invasion can evolve along nerve fibers, blood and lymph vessels, intertissular spaces, etc. The tumor nodule does not have precise limits; it is characteristic for malignant tumors.

Depending on the number of initial tumor growth sites, the tumors can be unicentric (with a single site) and multicentric (with multiple sites). In the cavitary and tubular organs the tumor can grow exophytic – expansive growth in the cavity of the organ and endophytic – the tumor is localized in the wall of the respective cavity.

8.2. ORGANO-NON-SPECIFIC EPITHELIAL TUMORS

This group of tumors evolve from the squamous, transitional and glandular epithelium which do not have specific functions. They can be benign or malignant. Their classification is given in table 33.

Table 33

Epithelial tumors without specific localization

Origin tissue	Benign tumors	Malignant tumors
Pluristratified squamous epithelium Transitional epithelium	Papilloma	Carcinoma in situ Squamous carcinoma (epidermoid) Transitional carcinoma
Monostratified cuboidal, cylindrical or prismatic epithelium of the glandular organ mucous membranes	Adenoma (acinic, tubular, trabecular, papillary, fibroadenoma, adenomatous polyp)	Carcinoma in situ, adenocarcinoma, muciparous carcinoma (colloidal)
Stem cells or predecessor cells of the epithelium	—	Fibrous carcinoma (scirrhous) Trabecular carcinoma (solid) Parenchymatous carcinoma (medullary) Undifferentiated carcinoma (anaplasic)

The benign epithelial tumors without specific localization are papilloma and adenoma.

Papilloma. A papilloma arises from pluristratified squamous and transitional type epithelium. It is seen in skin and on the mucous membranes covered by the respective epithelium: buccal cavity, pharynx, larynx (vocal plicae), esophagus, bladder, uterine cervix.

Macro- and microspecimen "Papilloma of the skin".

Macroscopically ***(fig.210)***, the surface of the skin contains a tumor structure of spherical shape, with a rough surface, dense consistency, having a large implantation base. The size can vary from 1-2 mm up to 1-2 cm.

Microscopically ***(fig.211)***, the papilloma is composed of parenchyma and stroma, the parenchyma being represented by proliferating pluristratified squamous epithelium. The tumor epithelium is unevenly thickened, forming prominent papillary projections on the surface of the skin; the corneous layer is thickened (hyperkeratosis), as well as the malpighian layer (acanthosis). The stroma is abundant; the blood vessels are chaotically disposed. All these modifications show a tissular atypism in papilloma. The integrity of the basal membrane and the morphological polarity (the localization of varied cytoplasmic organelles either at the basal or apical pole of the cell) of the epithelium are unaffected; facts that are characteristic for the benign tumors.

The clinical manifestations and evolution depend on the localization, and can be complicated with ulcerations and secondary inflammation. Papillomas can be single or multiple (papillomatosis). Sometime after excision they relapse (especially the papilloma of the vocal plicae and bladder). In cases of long mechanical irritation the papilloma can become malignant (squamous cancer occurs).

Adenoma. Adenoma evolves from glandular epithelium. It is seen in glandular organs (prostate, pancreas, liver, salivary, sudoriferous glands, mammary gland, endocrine glands, etc.) and in mucous membranes covered by glandular cylindrical-cuboidal epithelium (gastrointestinal, tracheobroncheal, uterine, of billiary tract and gall bladder mucous membranes). In compact organs the adenoma appears as a well delimited, encapsulated nodule (expansive growth), having the same color and consistency as the origin tissue. On the mucous membranes it has either a pediculated polyp appearance or a large implantation base. The adenoma can become malignant, transforming into adenocarcinoma (glandular cancer).

Macrospecimen "Prostate adenoma" (fig.187).

The prostate is bigger in volume, has a rough surface, and hard consistency. It consists of gray or yellowish nodules of varied size, composed of glandular and tubular structures, covered with regular cylindrical-cuboidal epithelium. It can be complicated with the urine stasis in the bladder, hypertrophy of the bladder wall, and the association of inflammatory processes in the urinary tract (cystitis, urethritis, ascending pyelonephritis).

Macrospecimen "Adenomatous polyps of the colon" (fig.212).

The mucous membrane of the large intestine contains multiple pediculated polyps of varied sizes, irregular surface and cauliflower-like appearance. They can be complicated with intestinal hemorrhage and secondary inflammation. Colon polyposis is a hereditary, familial disease and is considered to be an absolute precancerous condition, because very often the adenomatous polyps of the large intestine can become malignant, transforming into adenocarcinoma.

Microscopically, the following adenoma varieties can be distinguished: 1) acinic (alveolar); 2)tubular; 3) trabecular; 4) papillary. In cases when the connective stroma predominates over the glandular parenchyma, the tumor is called fibroadenoma or adenofibroma.

Microspecimen "Adenoma (adenomatous polyp) of the large intestine".

Macroscopically, it has a pediculated polyp appearance (adenomatous polyp), a spherical shape and a smooth surface.

Microscopically *(fig.213)*, the tumor consists of glandular structures. These structures *have varied shapes and sizes. Some of them are cystically distended. with mucus hypersecretion, and intact basal membrane. The complications are ulceration, hemorrhage,* and secondary inflammation; it can become malignant.

8.2.1. CARCINOMA

Carcinoma is a malignant tumor of epithelial origin without a specific localization. Term "cancer" is more genetic, refered to all malignant tumors. The microscopic classification of cancer is given in table 34.

It can arise in pluristratified squamous, transitional or glandular epithelium. It is characterized by cellular and tissular atypism, invasive (infiltrative) growth, metastases (predominantly lymphatic) and recurreance.

Macroscopically, it has a nodular appearance, without precise limits, infiltrates the neighboring tissues (invasive growth), and has a flaccid or dense consistency. It has a whitish color on section. It may be localized in the depth of the compact organs or on their surface, while in the cavitary and tubular organs it may be on the surface (exophytic growth) or in the thickness of the walls (endophytic growth).

Table 34

Classification and general characteristics of carcinoma

Type of cancer	Characteristics
1	2
1. Carcinoma in situ (preinvasive, intraepithelial)	The cellular atypism and polymorphism is observed no further than the epithelial layer; the tumor invasion does not pass across the basal membrane, which remains intact; dynamically it becomes invasive (infiltrative); it is seen in squamous, transitional or glandular epithelium
2. Squamous carcinoma (epidermoid)	Arise in squamous (skin, buccal cavity, esophagus, pharynx, larynx, uterine cervix, vagina), transitional (renal pelvis, ureters, bladder) or glandular epithelium which has suffered epidermoid metaplasia (bronchi, endometrium, gall bladder, etc.); it is composed of fascicles of atypical epithelial cells, which invade the adjacent tissue. In epidermoid keratinizing carcinoma, the cornification ability is maintained, forming "keratin pearls"
3. Glandular (adenocarcinoma), tubular, alveolar or papillary carcinoma	Derives from the prismatic, cylindrical or cuboidal epithelium from the mucous membranes and from glandular organs (stomach, intestine, uterus, lungs, liver, pancreas, prostate, salivary, sudorife-rous, mammary, endocrine glands, etc.).
4. Muciparous (colloidal) carcinoma	Derives from glandular epithelium, the tumor cells are producing great amounts of mucus; macroscopically it has a mucinous or colloid appearance; the cells can gain the shape of a "sealed ring".
5. Undifferentiated carcinoma a) with small cells b) with large cells c) with giant cells	The tumor cells are monomorphous. They do not form specific structures. The quantity of stroma is small; it is a very malignant form of carcinoma, which metastasizes widely in the body.
6. Parenchymatous (medullary) carcinoma	Parenchyma predominates in this tumor; the amount of stroma is small. It is an undifferentiated form of carcinoma, giving off multiple widespread metastases
7. Fibrous (scirrhous) carcinoma	Stroma predominates in this tumor. Among the abundant fascicles of connective tissue, thin strings of atypical hyperchromatic tumor cells are observed. It has a high malignancy, with widespread metastases.
8. Trabecular (solid) carcinoma	The stroma and parenchyma are uniformly disposed; the tumor cell fascicles alternate with fibroconnective fascicles; it is a undifferentiated form of carcinoma with rapid growth and widespread metastases.
9. Dimorphous carcinoma	This is a mixed type of carcinoma, in which there can be observed both glandular and epidermoid structures

Macrospecimens:

"Laryngeal carcinoma" (fig. 214).

In the laryngeal cavity there can be observed a tumoral nodule with exophytic growth, prominent on the mucous membrane surface. It has a hard consistency, a necrotic center and a ulceration zone. It can be complicated by mechanical asphyxia, hemorrhage, secondary inflammation, superinfection, and metastases, especially in the regional lymph nodes. In most cases it occurs at vocal plicae level. The most frequent histologic form is the epidermoid (squamous) carcinoma with or without cornification. It appears often with the background of chronic inflammation, leukoplakia and dysplasia of the laryngeal mucous membrane, etc.

"Fungiform gastric carcinoma" (fig. 215).

In the stomach there can be observed a voluminous tumor with exophytic growth, irregular surface, hemorrhagic foci, flaccid consistency, and a mushroom-like (fungiform) appearance. It is more often localized in the region of the smaller curve and pylorus. It can be complicated with hemorrhage, perforation, inflammation of the gastric wall (phlegmon), invasion of the neighboring organs (pancreas, transverse colon, etc.), and metastasizes firstly in the regional lymph nodes, liver. Histologically, in most cases the glandular type of gastric cancer is observed (adenocarcinoma). It is most frequently preceded by precancerous conditions like the chronic gastric ulcer, chronic gastritis (especially achylia) and gastric poliposis.

"Peripheral pulmonary carcinoma" (fig. 216).

In the peripheral subpleural zone of the lung there can be observed a tumor nodule of large size, which almost entirely occupies the inferior lobe of the lung. It has a dense consistency, unaired, whitish color, with destruction and necrotic lesions. It derives from bronchiolar or small bronchi epithelium, usually having a glandular structure (adenocarcinoma). It frequently causes obliterative atelectasis, hemorrhage, abscess, gangrene, fibrinohemorrhagic pleuritis, pleural carcinomatosis, and metastases in the bronchial, bifurcational and distant lymph nodes. It usually appears following chronic bronchitis, chronic abscess, bronchiectatic disease, pneumosclerosis, chronic pneumonia, chronic tuberculosis, pneumoconiosis and other precancerous conditions.

"Diffuse gastric carcinoma" (fig. 217).

The stomach wall is thickened, indurated, immobile and of a whitish color on section. The layers of the stomach wall are erased and the mucous membrane is uneven, with massive thick pliae. These modifications are due to the infiltrative cancerous process, which spreads diffusely through the gastric wall (endophytic growth). Histologically, it usually has a scirrhous or trabecular carcinoma appearance.

"Carcinoma of the cervix" (fig. 177).

The uterine cervix is deformed, caused by a tumoral mass without precise limits. It has a cauliflower-like papillary surface, with destructive and necrotic areas, infiltrating the inferior portion of the uterine cervix. Microscopically, it can have a glandular or squamous carcinoma structure. It frequently invades the bladder and rectum, metastasizing to the regional lymph nodes and widely from the primary tumor. Clinically it is manifest by uterine hemorrhage (metrorrhagia). The precancerous conditions are endocervicosis of the uterine cervix, polyps, leukoplakia, dysplasia and chronic inflammation.

Microscopic specimens:

"Carcinoma in situ".

The squamous epithelium *(fig. 219)* is thickened, with a pronounced cellular atypism. There is polymorphism of cells and nuclei, some of the nuclei being very large and hyperchromic, with monstrosities and pathological mitosis in the superficial layers. The nuclear-cytoplasmic ratio is increased, and the cells are unevenly arranged, without polarity. Vertical stratifying, characteristic for the normal pluristratified squamous epithelium is erased. The basal membrane appears to be intact, continuous, without the tumor cells penetrating it.

It is a preinvasive form of carcinoma (syn. preinvasive or intraepithelial carcinoma). The carcinoma in situ becomes invasive (infiltrative) if given enough time.

"Epidermoid (squamous) keratinizing carcinoma".

The tumor consists of columns of atypical and polymorphous cancerous cells *(fig. 220)*. The basal membrane is altered (torn) so that the tumor proliferation infiltrates the underlying tissue. The neoplastic cells keep their capacity to keratinize. Keratin masses accumulate in the center of some neoplastic cell islands, forming so called "keratin pearls", the characteristic sign of the epidermoid keratinizing carcinoma *(fig. 221)*.

"Epidermoid non-keratinizing carcinoma".

The tumor masses *(fig. 222)* are composed of atypical, polymorphous cancerous cells, with large monstrous and hyperchromatic nuclei and numerous pathological mitosis. The loss of epithelial stratification is observed. The tendency towards keratinization and keratin pearl formation is lost. The degree of malignancy of this form of carcinoma is greater than that of epidermoid keratinizing carcinoma.

Epidermoid carcinoma is seen on the skin and on mucous membranes covered with pluristratified squamous epithelium or on mucous membranes covered with glandular epithelium, which has undergone squamous (epidermoid) metaplasia.

"Glandular carcinoma (adenocarcinoma)".

The tumor consists of atypical tubular *(fig. 223)* or papillary *(fig. 224)* glandular structures of varied shape and sizes, which infiltrate the adjacent tissues. The basal membrane is absent; the tumor cells are atypical, polymorphous and in some places disposed in several rows. The adenocarcinoma can be acinic, tubular or papillary. It derives from prismatic, cylindrical and cuboidal epithelium of the mucous membranes and glandular organs. It is more frequently located in the stomach, large intestine, uterus, lungs, biliary tract, pancreas, etc.

"Muciparous carcinoma" (fig. 225).

The cancerous cells secrete large quantities of mucus, and due to this fact they have a characteristic appearance, that of "sealed ring cells". The nucleus is moved toward the cell membrane and flattened by the mucus masses. Macroscopically, the tumor has a gelatinous appearance. It is a form of undifferentiated carcinoma of adenogenic (glandular) origin. It is seen in the stomach, intestines, lungs, endometrium, etc.

"Scirrhous (fibrous) carcinoma".

The tumor consists of great quantities of mature, fibrillary connective tissue, whose fascicles contain chaotically disposed, highly atypical cancerous cells, with large, hyperchromatic nuclei *(fig. 226)*. It is an undifferentiated, adenogenic tumor, with an increased degree of malignancy. The main characteristic is the prevalence of connective tissue stroma over the cellular parenchyma. Microscopically, the scirrhous carcinoma has a hard, wood-like consistency, deforming the respective organ; it has an endophytic growth pattern in the cavitary and tubular organs *(fig. 217)*.

"Carcinoma with small cells".

The cancerous tumor consists of small, monomorphous, round, lymphocyte-like cells, disposed unevenly, diffusely, in a poor stroma *(fig. 227)*. Macroscopically, it has a flaccid consistency. It is a undifferentiated form of carcinoma with increased malignancy, which metastasizes early. In some cases it is difficult to determine the histogenesis of the tumor (anaplastic carcinoma).

The cancerous tumors are usually accompanied by dystrophic, necrotic, circulatory and secondary inflammatory lesions. These lesions are stronger and earlier in tumors with an increased degree of malignancy. As mentioned, the carcinoma metastasizes more often by lymphatic system, the first metastases being localized, usually in the regional lymph nodes.

8.3. MESENCHYMAL TUMORS

The mesenchymal group of tumors includes the tumors which originate in mesenchymal tissues, loose and dense connective tissue, smooth and skeletal striated muscles (including the cardiac muscle), cartilaginous and osseous tissues, serous and synovial membranes. They usually have a histoid structure, composed with a prevalence of parenchymatous elements. The stroma is poorly developed. They may be subdivided into benign and malignant mesenchymal tumors (table 35).

Table 35

Mesenchymal tumors

Origin tissue	Benign tumors	Malignant tumors
1	2	3
Connective tissue	Fibroma (soft, hard) Dermatofibroma (histiocytoma) Elastofibroma Desmoid tumor Myxoma	Fibrosarcoma Malignant histiocytoma - - Myxosarcoma
Adipose tissue	Lipoma Hibernoma	Liposarcoma Malignant hibernoma
Muscular tissue	Leiomyoma Rhabdomyoma Tumor with granular cells (myoblastoma)	Leiomyosarcoma Rhabdomyosarcoma Malignant myoblastoma
Blood vessels	Hemangioma (capillary, venous, cavernous, arterial) Hemangioendothelioma Hemangiopericytoma Glomangioma	Hemangiosarcoma (malignant hemangioendothelioma or hemangiopericytoma)
Lymphatic vessels	Lymphangioma	Lymphangiosarcoma

Osseous tissue	Osteoma (compact, spongious) 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)

8.3.1. BENIGN MESENCHYMAL TUMORS

The benign tumors of mesenchymal origin, like all benign tumors, have a slow, expansive growth, are well delimited, and encapsulated. They are composed, microscopically, of mature differentiated cells, being characterized only by the tissular atypism.

Macro- and microspecimens:

"Fibroma" (macro- and microspecimen).

Fibroma is a benign tumor which derives from connective tissue. Macroscopically *(fig. 228)*, it is a well delimited tumor nodule, which is encapsulated (expansive growth) with the diameter reaching up to several cm. It is whitish in color, with varying consistency: soft (soft fibroma, with the predominating cellular elements) or dense (dense fibroma, predominantly composed of collagen fibers). On section it has a fibrillar structure, an evident tissular atypism, the connective fascicles being disposed chaotically, and in some places forming whirls.

Microscopically *(fig. 229)*, the tumor consists of connective tissue cells (fibroblasts and fibrocytes) and collagen fibers, arranged without any orientation order in unevenly thick fascicles. The relation of cells and vessels is also uneven. Small sites of hyalinosis can be seen.

The location of fibroma is most variable, but is more often seen in skin, uterus, mammary gland, fascias, tendons, orbit, cranial basis. The clinical importance and manifestations depend on the localization of the tumor.

"Desmoid tumor" (microspecimen).

The desmoid tumor (desmoma) is a variety of fibroma. It is a tumor with local destructive character. The difference is that it has an infiltrative growth, though histologically the tumor is mature (the cellular atypism and polymorphism are absent, and so are the mitoses). It is more frequently seen in the anterior abdominal wall of females, especially in the rectus abdominis muscles, but it can be also located extraabdominaly.

It can be seen in the specimen *(fig. 230)* that the tumor tissue consists of fibroblast type cells and collagen fibers, like the hard fibroma. The tumor nodule does not have precise limits, infiltrating and dissociating the adjacent muscular fibers, which undergo dystrophic changes. Due to its invasive character, the desmoma can recur after surgical excision.

"Lipoma" (macro- and microspecimen).

Lipoma is a benign tumor of adipose tissue.

Macroscopically *(fig. 231)*, in the thickness of the skeletal muscle a tumoral nodule can be observed. It has an oval shape (particularly it is a smaller one, of a round shape), soft consistency, well delimited, encapsulated and lobulated. When sectioned it has a yellowish color.

Microscopically *(fig. 232)*, the tumor consists of adipose cells (adipocytes) of varied sizes, with the nuclei moved to the cell periphery. The cytoplasm contains a large lipidic vacuole. The stroma is poor, forming thin fibrous septa, which contain blood vessels.

The lipoma can be very large (several kg). It is more frequently seen in the subcutaneous cellular adipose tissue, mediastinum, retroperitoneal space, mesentery, epiploon, mammary gland, soft tissues (skeletal muscles), etc.

"Hibernoma" (microspecimen).

Hibernoma is a benign tumor, which derives from the brown adipose tissue (brown lipoma). It is composed of *(fig. 233)* polyhedral cells containing vacuolized cytoplasm (fat multiocular cells), the nucleus being situated in the center of the cell. The vacuoles are small fat drops, containing lipochrome. Small cells, containing homogeneous eosinophilic cytoplasm with a decreased quantity of fat can be seen. Macroscopically, the tumor nodule has a yellowish-brown color. The tumor can be localized in the interscapular region, mediastinum and neck region, places where brown adipose tissue is usually present. This tissue is more abundant in infants, while in adults it is exceptional.

"Uterine fibroleiomyoma" (macro- and microspecimen).

Leiomyoma is a benign tumor of smooth muscle tissue. It is most frequently seen in the uterus, but can also be found in the digestive tract, bladder, prostate, etc. It originate from smooth muscles, or from the walls of blood vessels. Due to the fact that muscular parenchyma proliferation is accompanied by fibroconnective tissue stroma proliferation, the name fibroleiomyoma is more fitting.

Macroscopically *(fig. 234)*, the uterine wall contains three tumor nodules of varied size, two of them are in an intramural position, partially endocavitary, well delimited, encapsulated, with a yellowish- white color. A pediculated nodule is situated in the cervical canal undergoing expulsion from the uterine cavity. The consistency of the nodules is usually hard; in cases where secondary modifications occur (hemorrhages, edema, necrotic foci, myxomatosis), the consistency can be more soft. The uterine fibroleiomyoma is usually multiple, the tumor nodules being localized under the mucous membrane, intramural or subserous and can reach giant sizes. On section, they have a fibrillar structure, the muscular and connective fascicles being chaotically disposed, and whirled.

Microscopically *(fig. 201)*, the leimyomatous tumor nodule consists of smooth muscle fiber fascicles, arranged unevenly without any order. They are interspersed with collagen fiber fascicles and connective tissue cells which are being also chaotically arranged (tissular atypism).

Uterine fibroleiomyoma can frequently be complicated with uterine hemorrhage (metrorrhage). The leiomyoma can transform into leiomyosarcoma.

"Myocardial rhabdomyoma" (macrospecimen).

Rhabdomyoma is a benign tumor derived from striated muscles. It is predominantly seen in the myocardium, skeletal muscles and tongue. It is a relatively rare tumor.

The specimen *(fig. 235)* contains multiple tumor nodules (multicentric growth), situated in the thickness of the left ventricle wall. These nodules are well delimited, of a whitish-pink color and with a diameter up to 2-3 cm. The cardiac rhabdomyoma is usually associated with developmental anomalies.

"Rhabdomyoma" (microspecimen).

The tumor nodule is composed of striated muscle cells of varied shapes and sizes *(fig.236)*. The diagnosis can be made with the help of those techniques that highlight the transverse striation of the myocyte sarcoplasm.

"Capillary hemangioma" (microspecimen).

Hemangioma is a benign tumor of the blood vessels, originating from all elements of the vascular wall. The following variants of hemangioma can be distinguished: capillary, venous, cavernous and arterial.

The capillary hemangioma *(fig. 237)* consists of capillary type vessels of varied size. Their walls are covered with endothelial cells. It is more frequently seen in children, being localized in the skin, mucous membrane of the digestive tract and in the liver. It is nodular with a red or cyanotic color and smooth or papillary surface.

"Cavernous hemangioma of the liver" (macro- and microspecimen).

The tumor nodule is well delimited from the adjacent tissue *(fig. 238)*, having a bluish-red color, flaccid consistency and a spongy structure.

Microscopically *(fig. 239)*, the tumor is represented by small, distended, interconnected vascular cavities, of varied size, covered with endothelial cells and are filled with blood. These cavities have thin walls made of fibrous connective tissue.

Besides the liver, cavernous hemangioma is also seen in skin, spongy bones, skeletal muscles, etc.

"Chondroma"(macro- and microspecimen).

Chondroma is a benign tumor of cartilaginous tissue. It is more frequently seen in bones of the extremities (phalanx of the hands and feet), pelvis, ribs and vertebrae. It can also be seen in extraosseous locations, especially in lungs. Macroscopically, it is a well delimited nodule, of dense consistency and bluish-white color, like hyalin cartilage *(fig. 197)*. In bones, it can be localized on the surface (ecchondroma) or intraosseously (enchondroma).

Microscopically *(fig. 240)*, the tumor is composed of chondrocytes. They are disposed unevenly, chaotically, and have unequal shapes and sizes. Between the cells, the homogeneous basophilic ground substance can be seen.

All the benign mesenchymal tumors can be accompanied by dystrophic, necrotic lesions, circulatory disorders, edema, myxomatosis, calcification, etc.

8.3.2. MALIGNANT MESENCHYMAL TUMORS

The malignant tumors of mesenchymal origin are called 'sarcomas' (table 35). They are characterized by cellular and tissular atypism, rapid and invasive (infiltrative) growth. They do not have precise limits, are not encapsuled and weakly delimited from the surrounding tissues. The tumor mass has a fish meat- like appearance macroscopically. These tumors metastasize and relapse.

Macrospecimens:

"Fibrosarcoma" (fig. 241, general and section appearance).
"Chondrosarcoma" (of the spinal column, fig. 242).
"Osteosarcoma" (fig. 243).

Fibrosarcoma is a malignant tumor of the connective tissue, localized more frequently in the subcutaneous tissue and in the deep soft tissues of the extremities and trunk. It is rare in the internal organs.

Chondrosarcoma is a malignant tumor of cartilaginous tissue. It is more frequently seen in the long bones of the extremities (the upper extremities of the femur and humerus), ribs, scapulae, pelvic bones, vertebral column. In bones it can be localized in the medullary or periosteal zones.

Osteosarcoma is the most frequent malignant tumor of the osseous tissue and can have two variants: osteoblastic and osteoclastic. It is localized predominantly in the femur, humerus, tibia, scapular and pelvic bones.

In all three macrospecimens an irregular shape of the tumor can be seen. There are unprecise limits, the absence of capsules, whitish color, flaccid consistency, and a fish meat –like appearance on section. Some of these tumors can be accompanied by dystrophic lesions and hemorrhage.

Microspecimens:

"Fibrosarcoma" (fig. 244).
"Leiomyosarcoma"(fig.245).
"Liposarcoma" (fig. 246).

In the microscopic specimens the specific histological characteristics of sarcomas, especially the cellular atypism and polymorphism, can be seen.

Fibrosarcoma consists of immature, fibroblast type cells and an insignificant quantity of collagen fibers. The tumor has a histioid structure (predominance of cellular elements), relatively uniform, though there can be seen some large, hyperchromatic nuclei with few atypical mitoses. The neoplastic cells are arranged in fascicles, which are without orientation or order. It is a form of fibrosarcoma with medium malignancy.

Leiomyosarcoma is a malignant tumor of smooth muscle tissue, localized more frequently in the uterus and digestive tract. It can occur by malignant transformation of the benign muscular tumor (leiomyoma) or it can evolve as a malignant tumor from the very beginning. It consists of poorly differentiated muscle cells with an evident cellular and nuclear polymorphism. Some of the nuclei being large, monstrous, hyperchromatic, with pathological mitoses; the connective stroma is poorly developed.

Liposarcoma is a malignant tumor derived from adipose tissue. It consists of poorly differentiated adipose cells, with unequal fat content. Cells with a homogeneous eosinophilic cytoplasm, with or without a reduced quantity of fat, and bizarre, monstrous, hyperchromatic nuclei can be seen. It is more frequently seen in the subcutaneous, retroperitoneal and mediastinal cellular adipose tissue.

All sarcomas are accompanied by circulatory disorders (hemorrhages), edema, dystrophic and necrotic lesions, myxomatosis, and cystic cavities. Sarcomas metastasize predominantly by the hematogenous way, the first metastases being produced in the lungs or liver.

8.4. TUMORS OF THE MELANIN-FORMING TISSUE

The tumors of the melanin-formung tissue are called melanomas. They can be either benign or malignant.

The benign melanomas are also called nevi. The nevi are seen predominantly on skin, especially on the skin of the face, neck and trunk. The classification of cutaneous nevi is given in table 36.

Table 36

Classification and general characteristics of the cutaneous nevi

Nevus type	Most frequent localization	Macroscopic appearances	Microscopic characteristic	Evolution
1	2	3	4	5
Junctional nevus	On every part of the body	Macule or papule, of a brown color, several mm in diameter	Consists of nevic cell collections, with or without pigment, at the epidermis-dermis junction	Can become malignant
Intradermal nevus	In the region of the head, neck and trunk	Prominence with a narrow or large base, of brown-black color, with smooth or rough surface, up to several mm in diameter	Consists of nests and fascicles of nevus cells, with or without pigment, situated in the dermis; the epidermis is intact, atrophic	Has a benign evolution; becomes malignant extremely rarely
Mixed (compound) nevus	On every part of the body	The association of junctional and intradermal nevi	The proliferation of nevus cells is localized both in the basal layer of the epidermis and in the thickness of the dermis	Malignant transformation can take place
Nevus with epithelioid or fusiform cells	In the region of the face, especially in children and teenagers (syn. juvenile nevus)	The nodule has a narrow or large base, of reddish-brown color, with smooth or irregular surface, having up to 1-2 cm in diameted	Consists of fusiform or/and epithelioid fascicles of cells with a clear cytoplasm and a decreased melanin content, localized both in the junctional zone and intradermally; there can be seen giant polynuclear cells of Langhans or Touton type	Has a benign evolution
Blue nevus	In the gluteal and extremity region	Nodule of a bluish color, up to 1-1,5 cm in diameter; it has a smooth surface	Consists of melanocyte nests, which penetrate deeply in the dermis to the subcutaneous adipose tissue layer	Has a benign evolution; can relapse

Macroscopically, nevi are prominent structures on the skin, with smooth or rough surface, brown to black color (can even have a bluish shade), and a diameter from 1-2 mm to 1-2 cm *(fig. 26)*.

Histologically, the nevus consists of so called nevus cells of neuroectodermal origin.

Microspecimen "Intradermal nevus".

Intradermal nevus is the most frequently seen form of cutaneous nevi.

The dermis *(fig. 247)* contains collections of small cells, of elongated shape, which contain melanic pigment at the surface. They do not contain melanin deep in the cytoplasm. The epidermis is intact. The intradermal nevi very rarely become malignant.

The malignant melanoma is one of the most malignant tumors of the human body. It can begin by malignant transformation of nevi. It is more frequently localized in the skin, eye, meninges, adrenal glands, and mucous membranes.

Macroscopically, it can have a macular, plaque or pigmentary nodular shape, have a blue-black color, and a flaccid consistency *(fig. 248)*; the pigmentation persists in the metastases *(fig. 208)*.

Microscopically *(fig. 249)*, the tumor consists of polymorphous cells, some of them are monstrous. The majority of cells contain melanin granules of brown color; multiple mitoses can be also observed.

The malignant melanoma is characterized by rapid growth, and early polyvisceral (pulmonary, hepatic, cerebral, osseous, etc.) hematogenous metastases. In the tumor tissue necrotic and hemorragic lesions occur, accompanied by melaninuria. Less often the malignant melanoma can be achromic (amelanotic).

8.5. TUMORS OF THE NERVOUS TISSUE AND OF THE MENINX

The tumors of nervous system can arise from varied elements of the central, peripheral and vegetative nervous system. They are subdivided into benign and malignant tumors, though all the intracranial tumors have a malignant clinical evolution due to the compression of some nervous centers of vital importance.

The histogenetic classification of the nervous system tumors is given in table 37.

The tumors of the central nervous system can be either of neuroectodermal or meningovascular origin. The neuroectodermal tumors can arise from nervous, neuroepithelial and glial cells.

Among the neuroectodermal tumors derived from nerve cells, ganglioneuroma (gangliocytoma) is the most frequently met tumor.

Microspecimen "Ganglioneuroma (gangliocytoma)" (fig. 250).

The tumor consists of ganglion cells of mature type, disposed chaotically, without any order. They are interspersed with glial fiber fascicles. Macroscopically, it has the appearance of an encapsulated tumor nodule. It is situated more frequently in the third ventricle region, and rarely in the hemispheres of the brain.

Ganglioneuroma is also seen in the vegetative peripheral system.

The malignant analogue of ganglioneuroma is the ganglioneuroblastoma or the malignant ganglioneuroma, characterized by significant cellular polymorphism *(fig. 251)*. It is often located extracerebrally, in the sympathetic ganglions.

Among the tumors of glial origin, most frequent is the astrocytoma.

Table 37

Tumors of the nervous tissue

Origin tissue	Benign tumors	Malignant tumors
1	2	3
I. Neuroectodermal tumors		
A. Glial elements 1) Astrocytes 2) Oligodendrogliocytes	 Astrocytoma Oligodendroglioma	 Malignant astrocytoma (astroblastoma) Malignant oligodendroglioma (oligodendroblastoma)
B. Ependymal cells	Ependymoma	Malignant ependymoma
C. Choroid plexus epithelium	Choroidpapilloma (choroid plexus papilloma)	Choroidcarcinoma (choroid plexus carcinoma)
D. Nerve cells	Ganglioneuroma (gangliocytoma)	Ganglioneuroblastoma Neuroblastoma
E. Undifferentiated and embryonic cells	-	Medulloblastoma Glioblastoma
II. Meningovascular tumors		
Meningothelium	Meningioma	Meningeal sarcoma
III. Tumors of the autonomous nervous system		
Sympathogonia Ganglion cells Cells of the non chromaffin paraganglions (glomus)	- Ganglioneuroma Benign paraganglioma (chemodectoma, glomus tumor)	Sympathogonioma Ganglioneuroblastoma Malignant paraganglioma (malignant chemodectoma)
IV. Tumors of peripheral nerves (cranial and rachidian (spinal))		
Schwann cells	Neurilemoma (schwannoma, neurinoma) Neurofibroma Neurofibromatosis (Recklinghausen disease)	Malignant neurilemoma (neurogenic sarcoma)

Macro- and microspecimens "Astrocytoma".

Astrocytoma is a benign tumor, which arises from the astrocytic glia. Macroscopically ***(fig. 252)***, the tumor has the appearance of a nodule localized in the white matter, well or less delimited from the adjacent tissue. It can reach up to 5-10 cm in diameter. It has a flesh-like, homogeneous, whitish, dense appearance on section. In the central part a cystic cavity is formed; the gray matter from the tumor site is atrophic.

Microscopically ***(fig. 253)***, the tumor consists of glial fiber fascicles and a relatively small number of well differentiated astrocytic cells. Histologically, the astrocytoma can be either protoplasmatic or fibrillar, depending on the predominance of cells or glial fibers. The astrocytoma is clinically characterized by slow growth. It can be seen at all ages.

Of all the neuroepithelial tumors, derived from cells that cover the cavities of the brain and spinal cord, the most common are the ependymoma and the choroid plexus papilloma (benign tumors), and the ependymoblastoma as well as choroid plexus carcinoma (malignant tumors).

Microspecimen "Ependymoma".

The ependymoma can be located either intra- or extraventricular. The specimen ***(fig. 254)*** contains a prominent tumor nodule with irregular surface and circulation disorders, situated in the left lateral ventricle. Microscopically, the ependymoma is characterized by rosette-like arrangement of the tumor cells around the vessels.

Microspecimen "Choroid plexus papilloma".

This tumor is a benign tumor derived from the epithelium of the choroid plexus. It is seen in the lateral ventricles and in the IV-th ventricle. Macroscopically, it has a rough, cauliflower-like surface. Microscopically ***(fig.255)*** the tumor consists of papillary branches, covered with 1-2 layers of prismatic or cuboidal epithelial cells. The choroid plexus papilloma grows in the lumen of the respective ventricle, and can associate with hydrocephaly due to the hypersecretion of cerebrospinal fluid.

Of the poorly differentiated and embryonic tumors the most frequent are the glioblastoma and medulloblastoma.

Macro- and microspecimens "Glioblastoma".

Glioblastoma is a malignant tumor that arises from undifferentiated glial elements of the brain. It is one of the most frequent tumors that are localized in the white matter of the brain hemispheres. Macroscopically ***(fig. 256)***, the occipital zone contains a tumor nodule of an irregular shape, without precise limits, infiltrating the adjacent zones of the encephalic substance. On section it has multiple necrotic and hemorrhagic sites, which explain the variegated appearance and uneven consistency of the tumor; the peritumoral zones are edematous. Clinically, it is manifest by intracranial hypertension, and varied functional disorders, depending on the tumor location.

Microscopically ***(fig.257)***, the tumor is characterized by a strong cellular polymorphism, being composed of atypical cells, of various shapes and sizes. Some of them are monstrous, giant cells, with hyperchromatic nuclei (that is why it is also called multiforme glioblastoma). Necrotic and hemorrhagic sites are also characteristic. Glioblastomas metastasize more often by the cerebrospinal fluid, but can also metastasize extracranially.

Microspecimen "Medulloblastoma".

Medulloblastoma is highly malignant tumor, arising from the most immature, undifferentiated cellular elements of the brain, the medulloblasts. These embryonic neuro-ectodermal cells can differentiate into neuroblasts and spongioblasts (glioblasts). It is usually seen in cerebellum in children, being situated in the vermis. The tumor invades the IV-th ventricle, cerebral trunk and the leptomeninges, the excision of the tumor is impossible. Microscopically ***(fig.258)***, it consists of small, uniform cells, with round or oval, hyperchromatic nuclei and limited cytoplasm. The cells are arranged densely, compactly, often in rhythmic or rosette-like structures. The medulloblastoma metastasizes by the cerebrospinal fluid.

The most frequent meningovascular tumor is the meningioma, which arises from the cellular elements of the meninges. It can be situated in the dura mater, arachnoid or pia mater, usually parasagital, on the convexity and in the spinal channel. The histological variants: meningothelial (endotheliomatous), fibromatous and angiomatous.

Microspecimen "Fibromatous meningioma".

The tumor nodule ***(fig. 259)*** consists of fibroblastic cell fascicles and chaotically arranged connective tissue fibers. In some places whirls are formed, like the fibroma from other organs.

The meningioma is a benign tumor that grows slowly, compressing the brain. Macroscopically, it can have the appearance of a nodule, with a smooth, irregular or flat shaped surface, extending on the meningeal membrane surface. The tumor can cause atrophy by compression of the neighboring cranial bone. The malignant variant of the meningioma looks like fibrosarcoma and is called meningeal sarcoma.

The tumors of the peripheral nerves arise from the elements of their sheaths. The most frequent are the neurilemoma (neurinoma) and the neurofibroma.

Microspecimen "Neurinoma".

Neurinoma is a tumor derived from the Schwann cells of the peripheral nerves, being situated along these nerves (syn. schwannoma). Microscopically ***(fig. 260)***, the tumor consists of prolonged cell fascicles, with stick-like, parallel arranged nuclei (these cell collections are called Verocay bodies). These fascicles alternate with the collagen fibers, forming rhythmic structures, the characteristic sign of neurinoma.

The malignant homologue of this tumor is the malignant neurinoma, characterized by cellular density, atypism, polymorphism and rhythmic structures ***(fig. 261)***.

Microspecimen "Neurofibroma".

The tumor arises from the connective elements of the nervous sheaths. Microscopically ***(fig. 262)***, it consists of collagen and nerve fiber fascicles disposed chaotically, and also a number of nervous cells. It is more frequently seen in skin and subcutaneous cellular adipose tissue. It can be single or multiple ***(fig. 198)***, and is often seen in Recklinghausen disease (multiple neurofibromatosis).

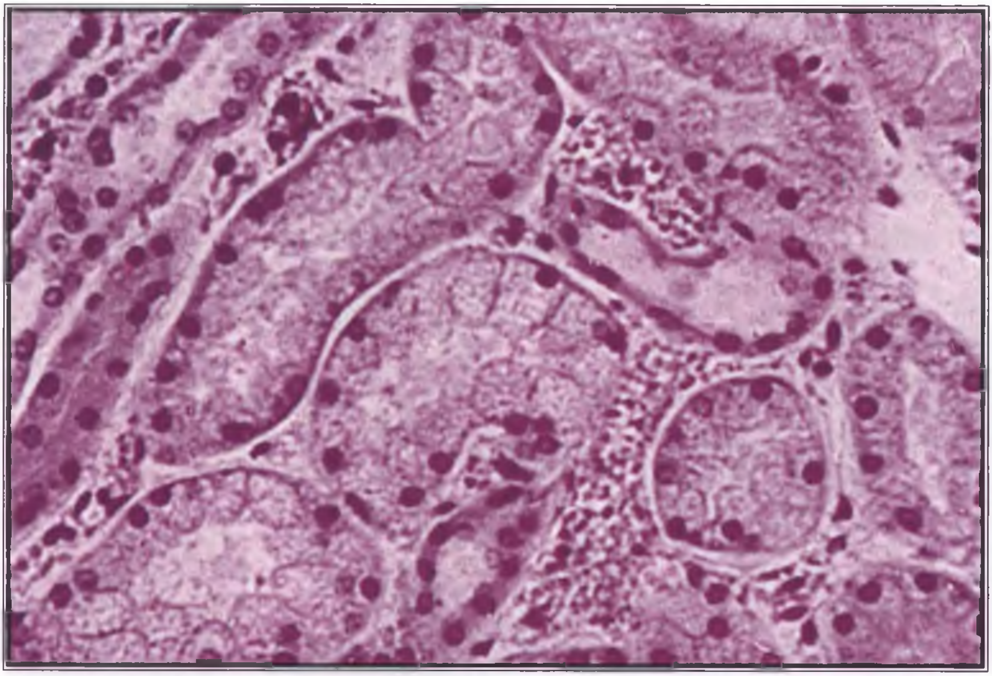


Fig. 1. Granular dystrophy of the contort renal tubule epithelium, microscopic view (H.E. stain, × 70).

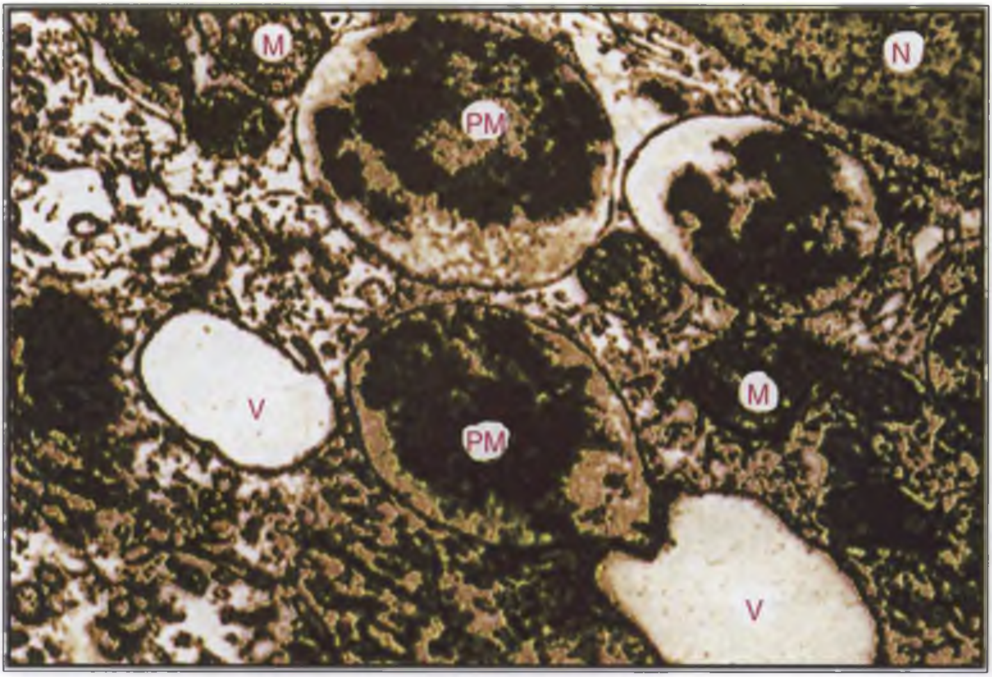


Fig. 2. Granular dystrophy of the contort renal tubule epithelium, electronomicroscopic image (× 16000): N - Nucleus; M – mitochondria; V - vacuoles (dilated endoplasmatic reticulum); PM - proteic masses.

Fig. 3. Hyalin cellular dystrophy of the contort renal tubule epithelium, electronomicroscopic image (× 18000): M - mitochondria; HM - hyalinized mitochondria.

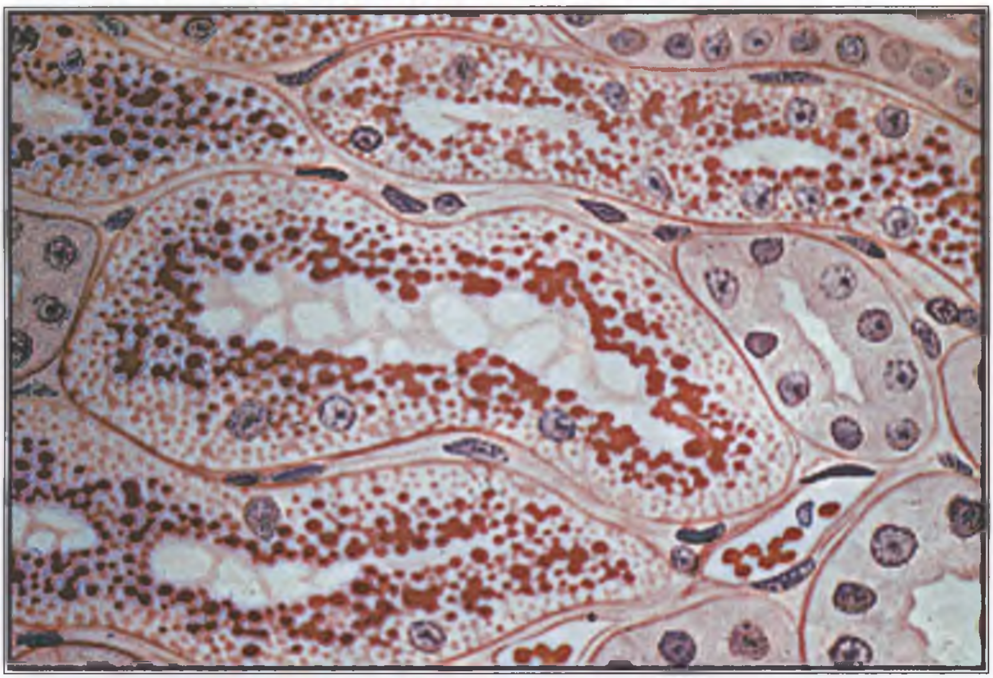


Fig. 4. Hyalin cellular dystrophy of the contort renal tubule epithelium, microscopic aspect (H.E. stain, × 140)

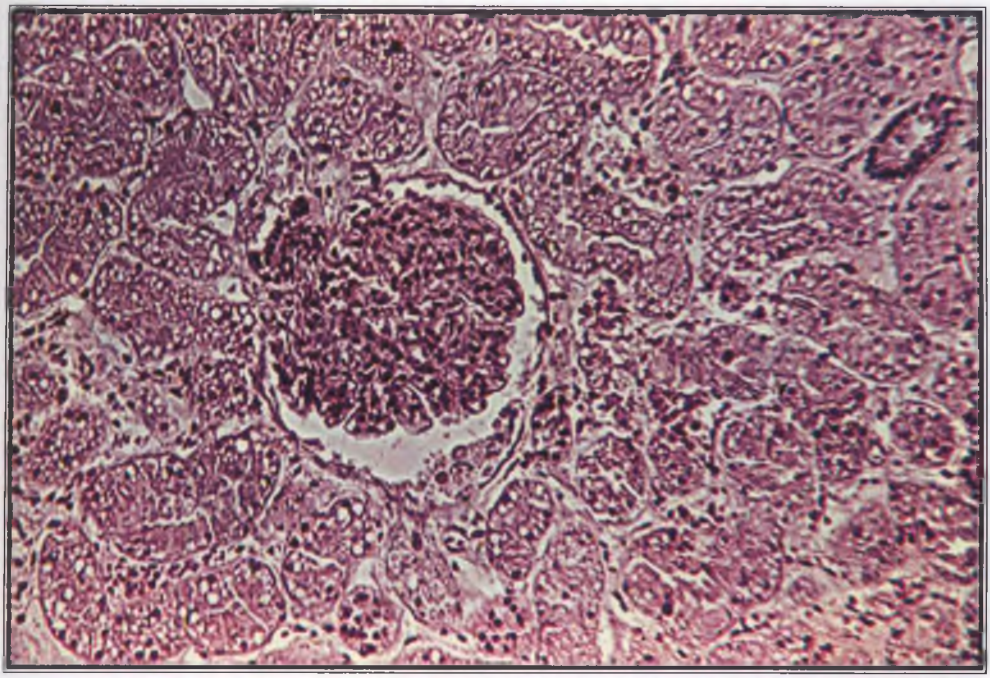


Fig. 5. Hydropic dystrophy of the contort renal tubule epithelium (H.E. stain, × 70).

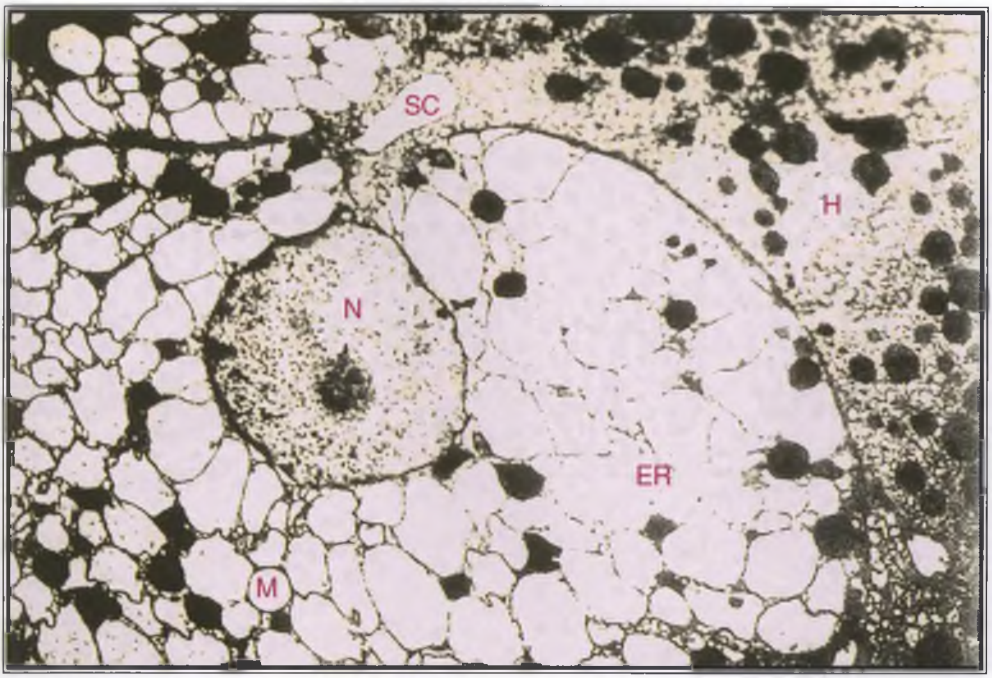


Fig. 6. Hydropic (vacuolar) dystrophy of the liver, electron microscopy, × 7000: N – nucleus; M – mitochondria; ER - endoplasmatic reticulum; H - normal hepatocyte; SC - sinusoidal capillary.

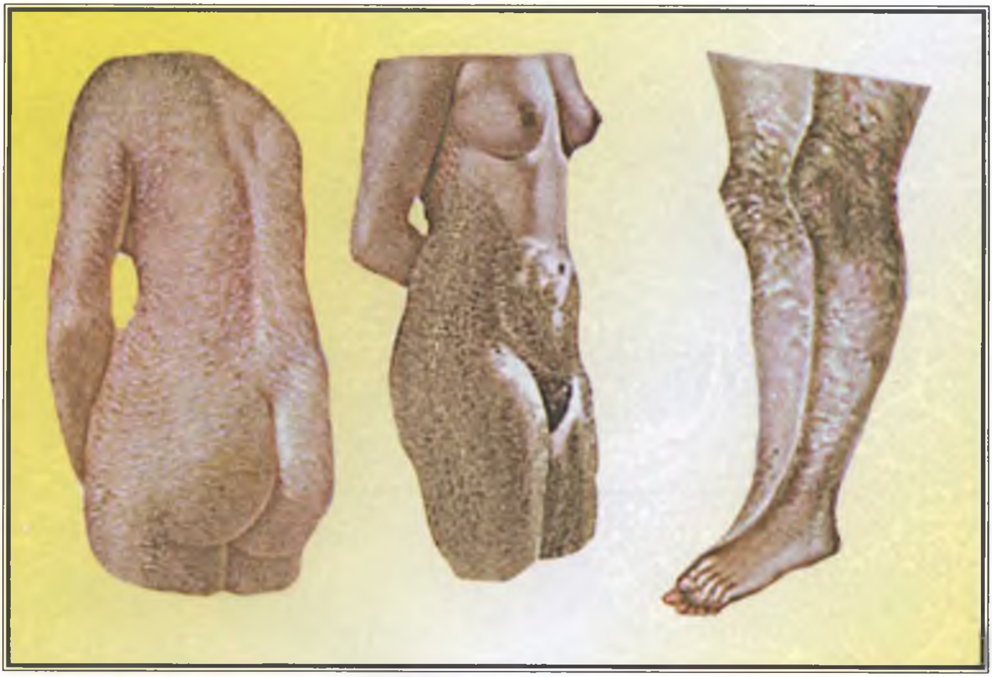


Fig. 7. Hyperkeratosis of skin, macroscopic aspect.

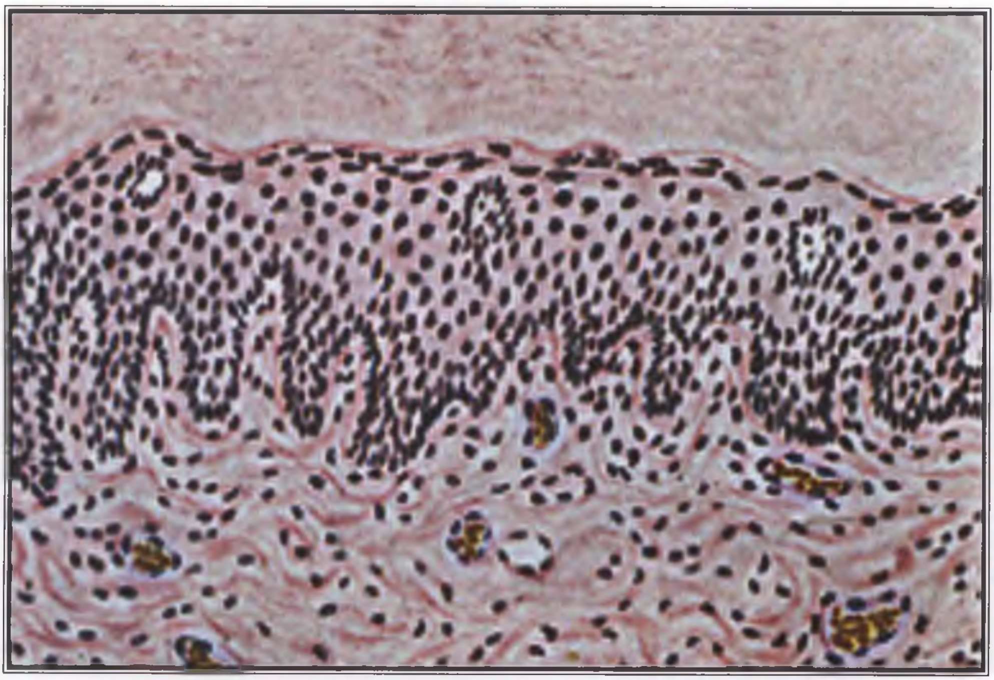


Fig. 8. Hyperkeratosis of skin, microscopic aspect (H.E. stain, × 70).

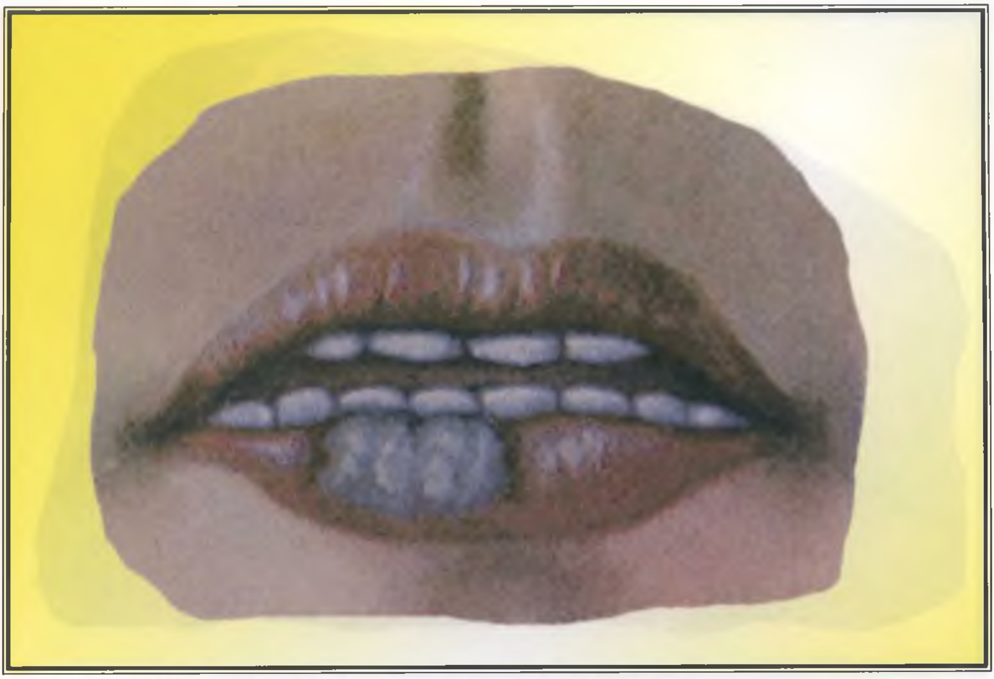


Fig. 9. Leukoplakia of the buccal mucosa, macroscopic aspect.

Fig. 10. Leukoplakia of the buccal mucosa, microscopic aspect (H.E. stain, × 70).

Fig. 11. Fatty dystrophy of the myocardium (steatosis of myocardium), macroscopic aspect.

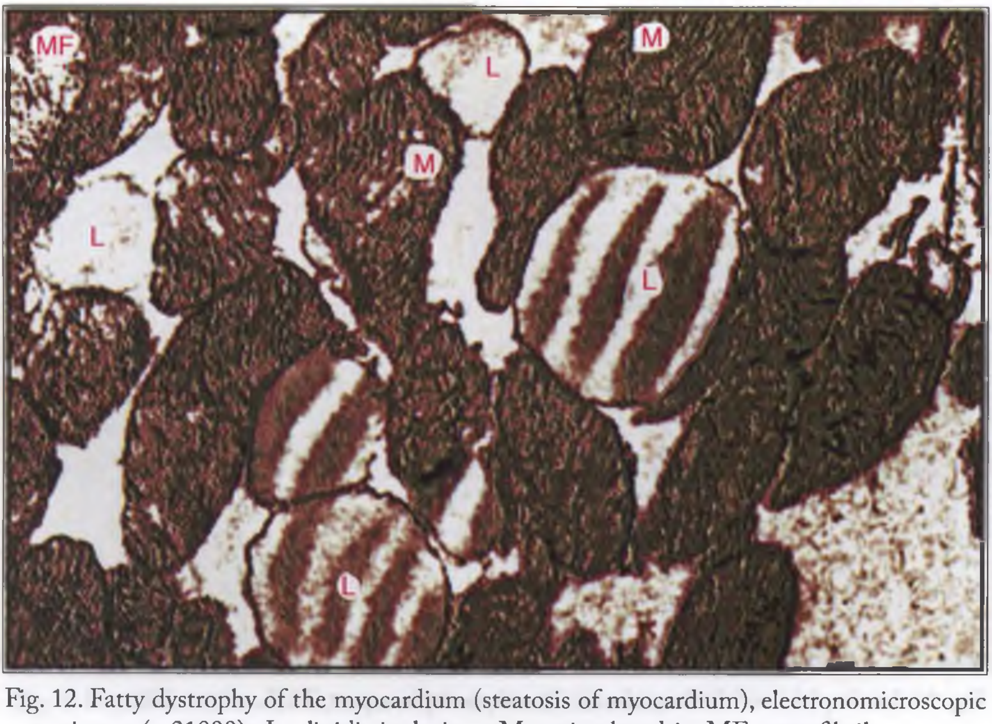


Fig. 12. Fatty dystrophy of the myocardium (steatosis of myocardium), electronomicroscopic image (× 21000): L - lipidic inclusions; M - mitochondria; MF - myofibrils.

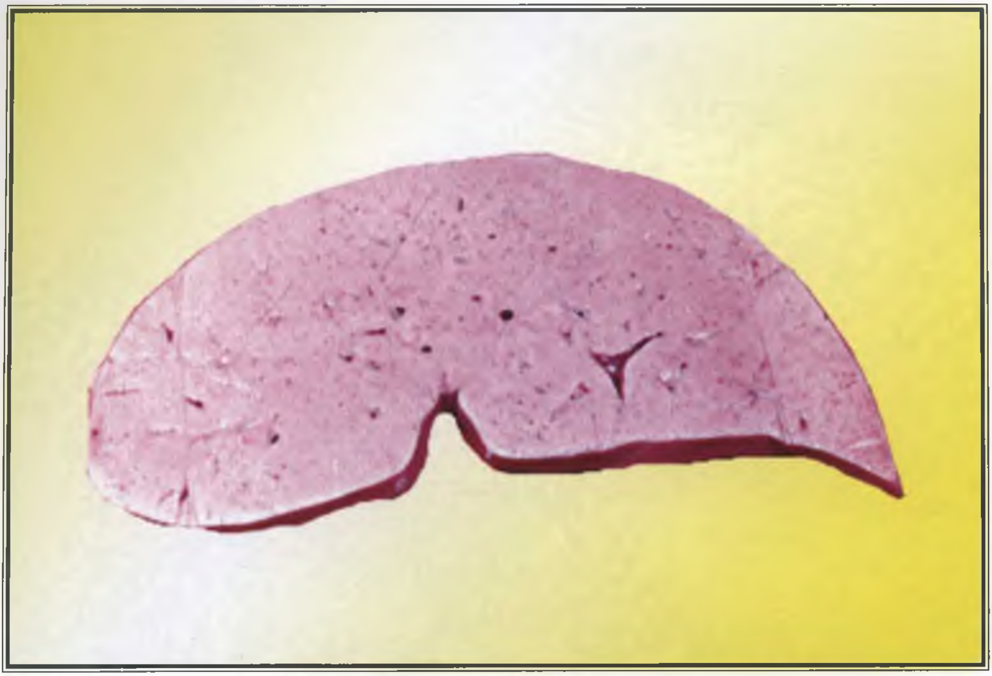


Fig. 13. Fatty dystrophy of the liver (steatosis of liver), macroscopic aspect.

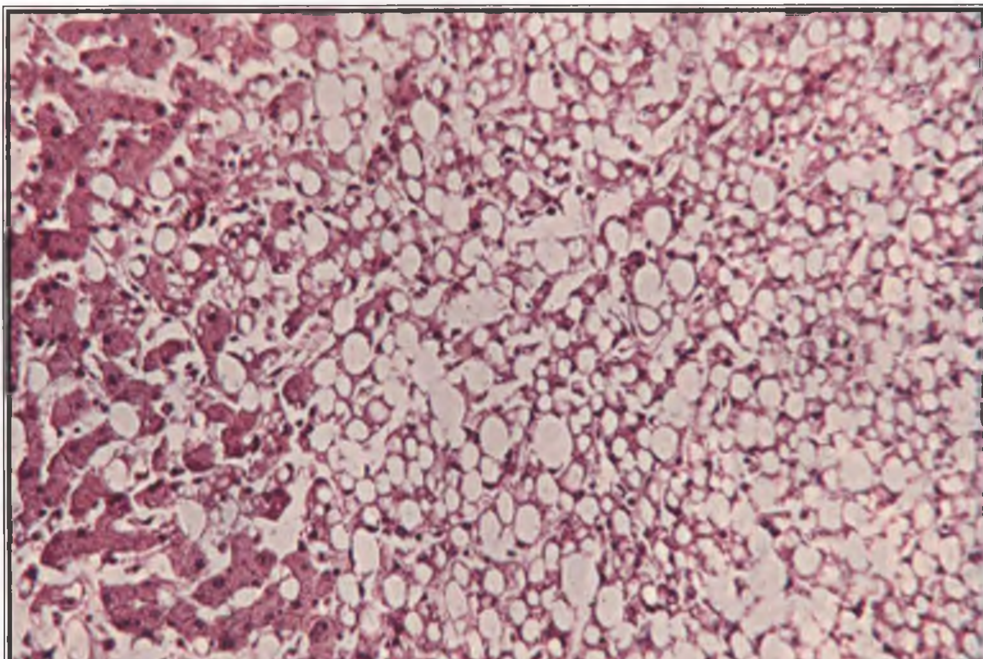


Fig. 14. Fatty dystrophy of the liver, microscopic aspect (H.E. stain, × 70).

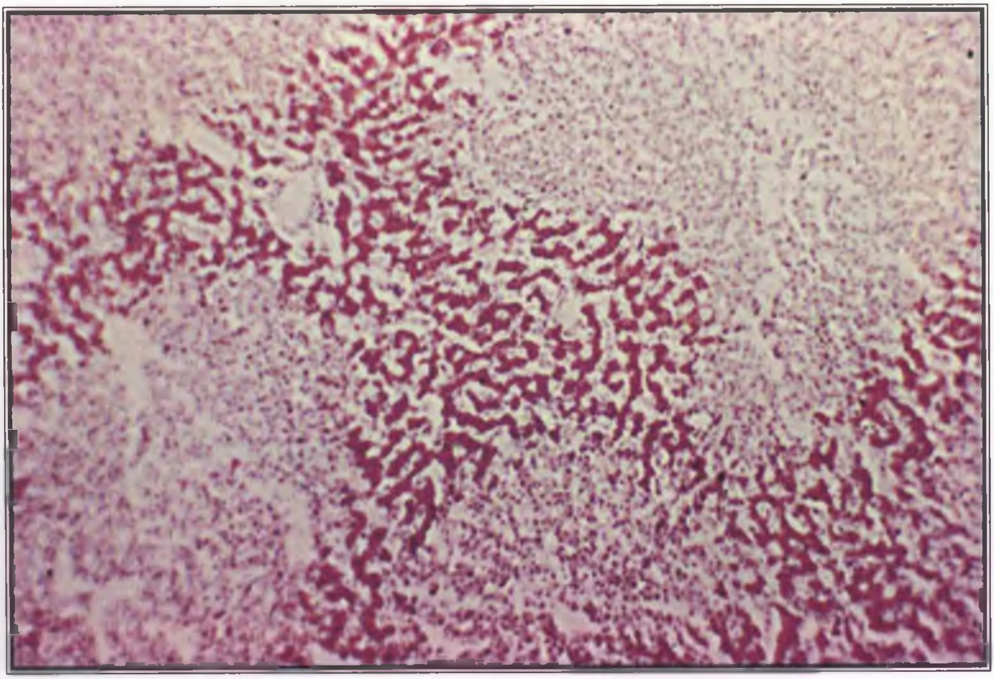


Fig. 15. Fatty dystrophy of the liver, Sudan III stain (× 50).

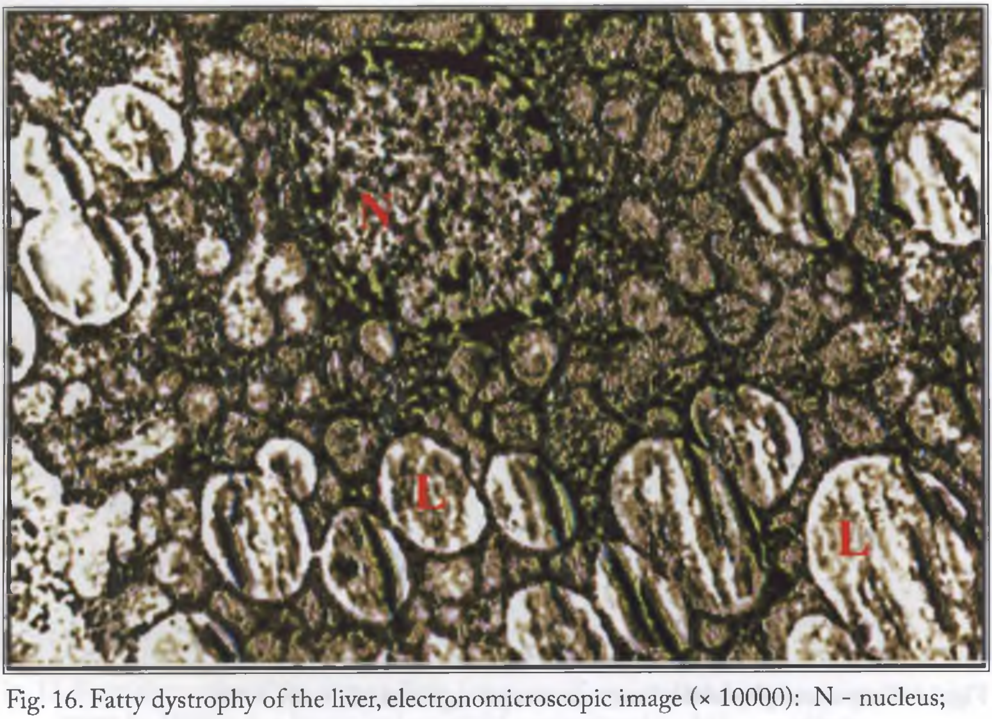


Fig. 16. Fatty dystrophy of the liver, electronomicroscopic image (× 10000): N - nucleus; L - lipid drops.

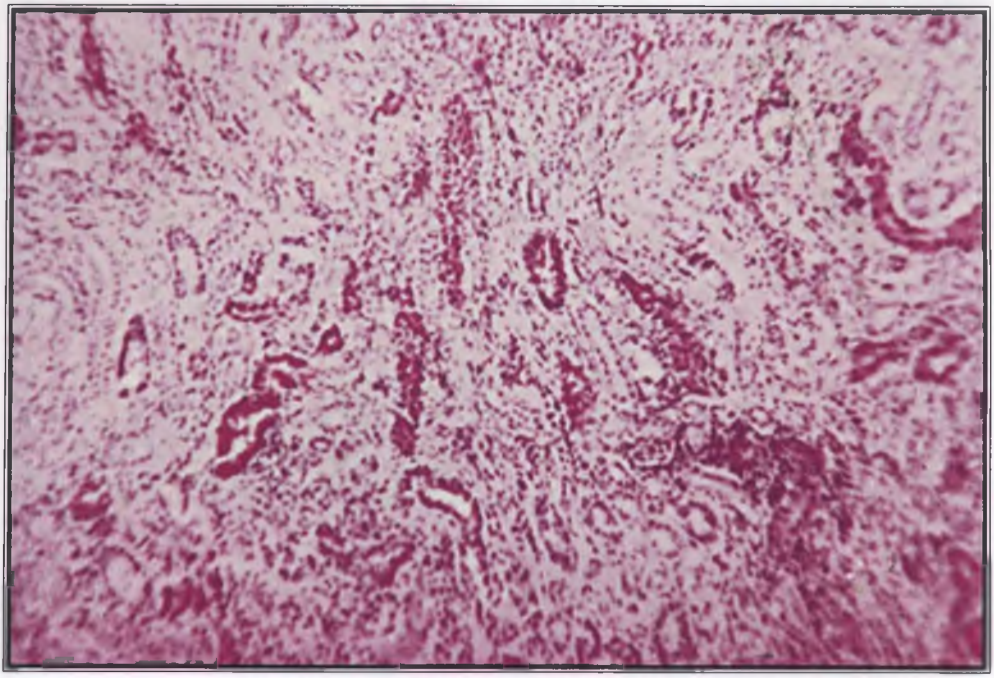


Fig. 17. Glycogen infiltration of renal contort tubule epithelium in diabetes mellitus (Best carmin stain, × 70).

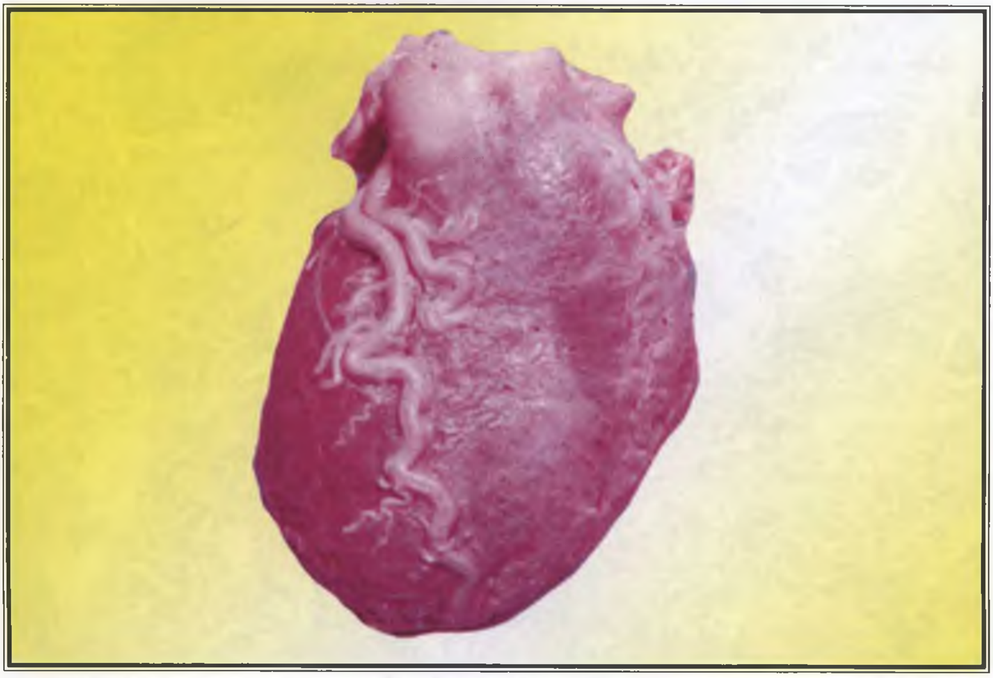


Fig. 18. Brown atrophy of the heart.

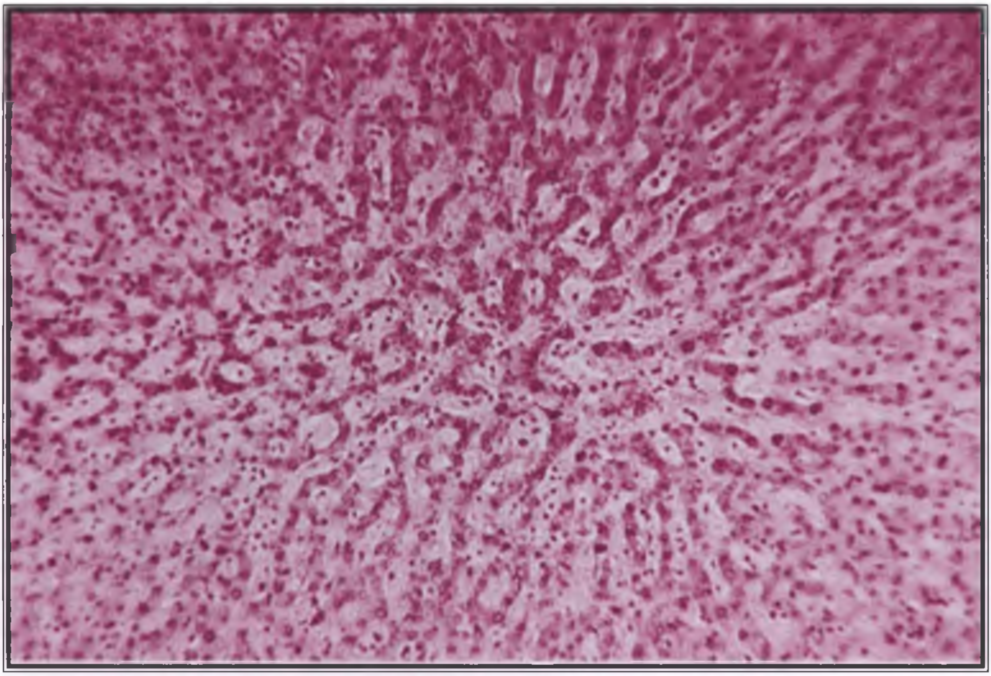


Fig. 19. Lipofuscinosis of the liver (H.E. stain, × 70).

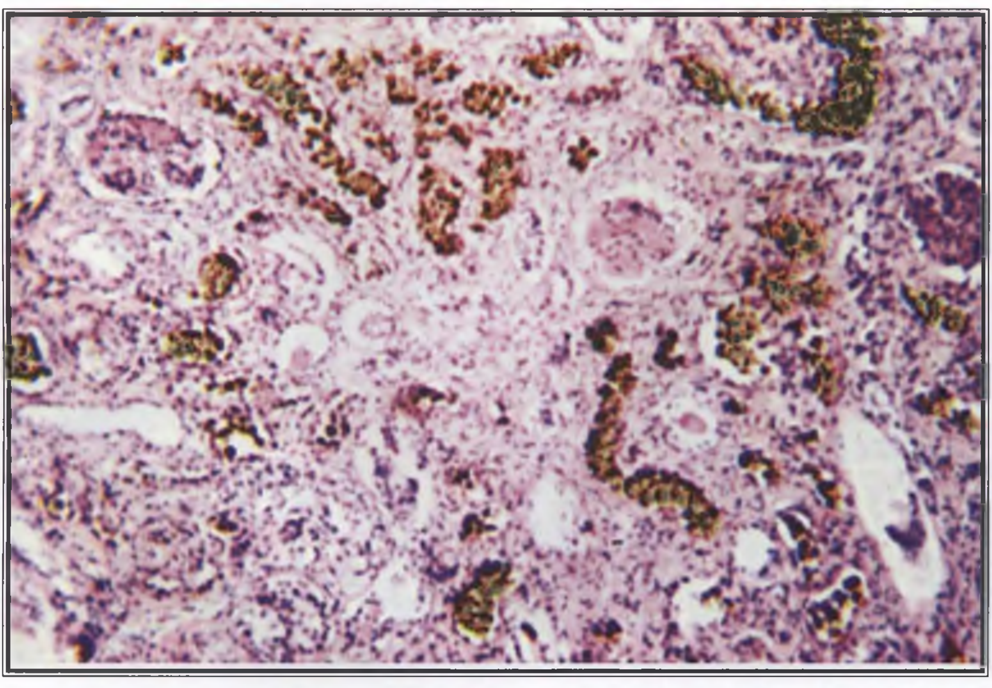


Fig. 20. Hemosiderosis of kidneys (H.E. stain, × 70).

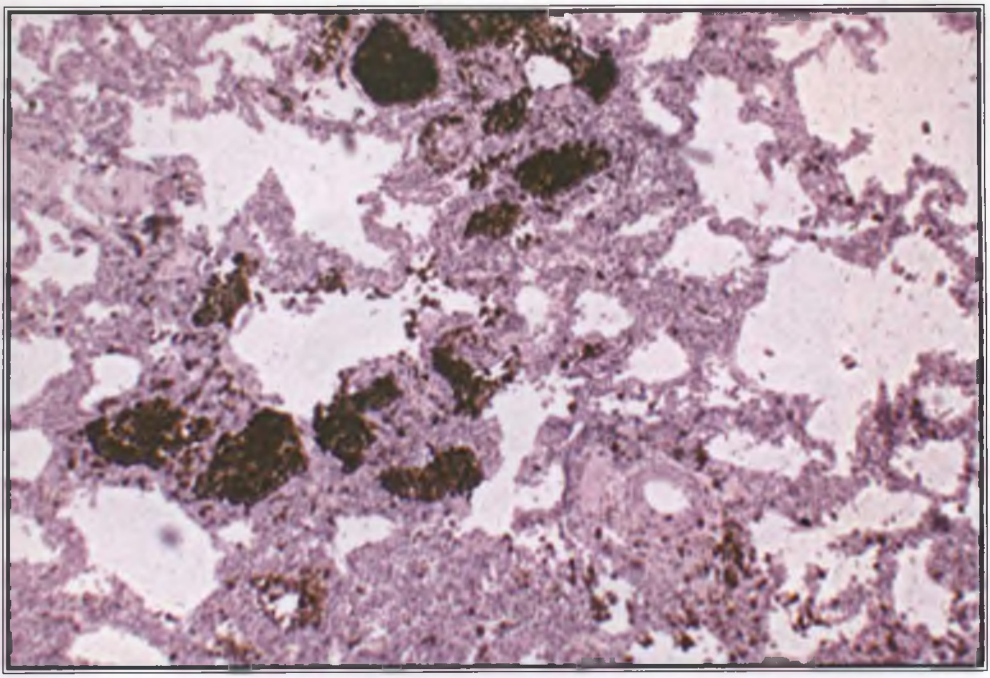


Fig. 21. Pulmonary hemosiderosis (H.E. stain, × 70).

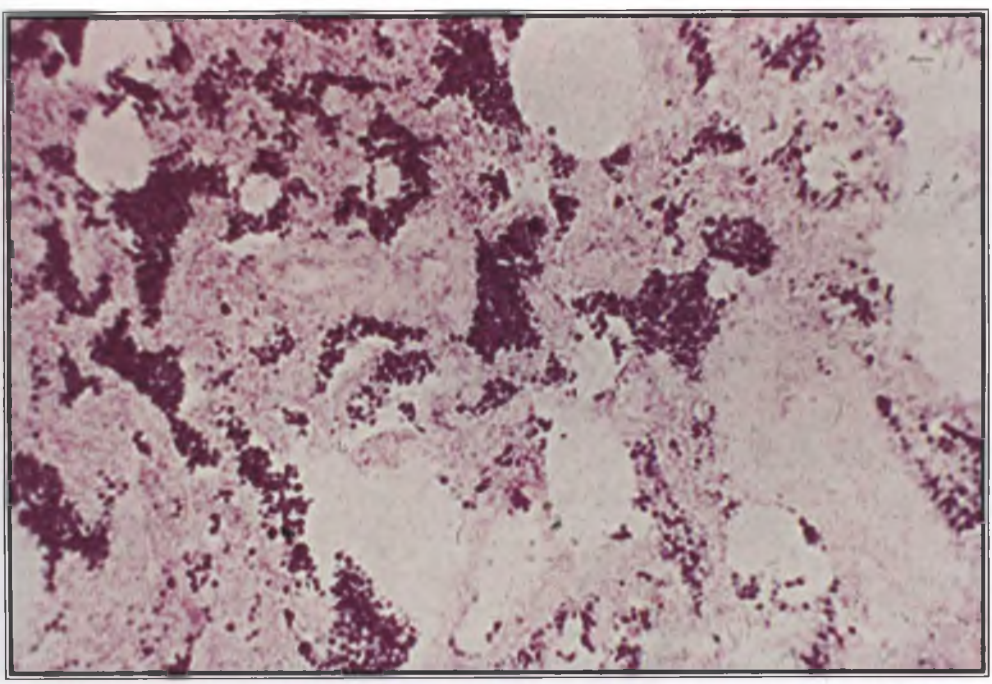


Fig. 22. Pulmonary hemosiderosis (Pearls reaction, × 70).

Fig. 23. Cerebral hematoma.

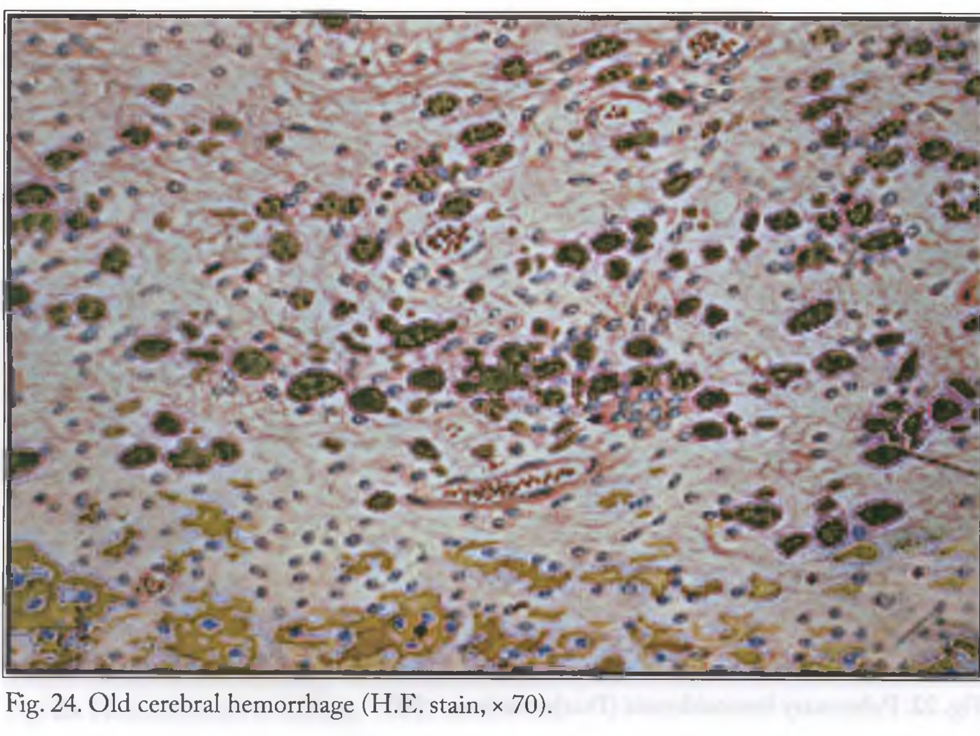


Fig. 24. Old cerebral hemorrhage (H.E. stain, × 70).

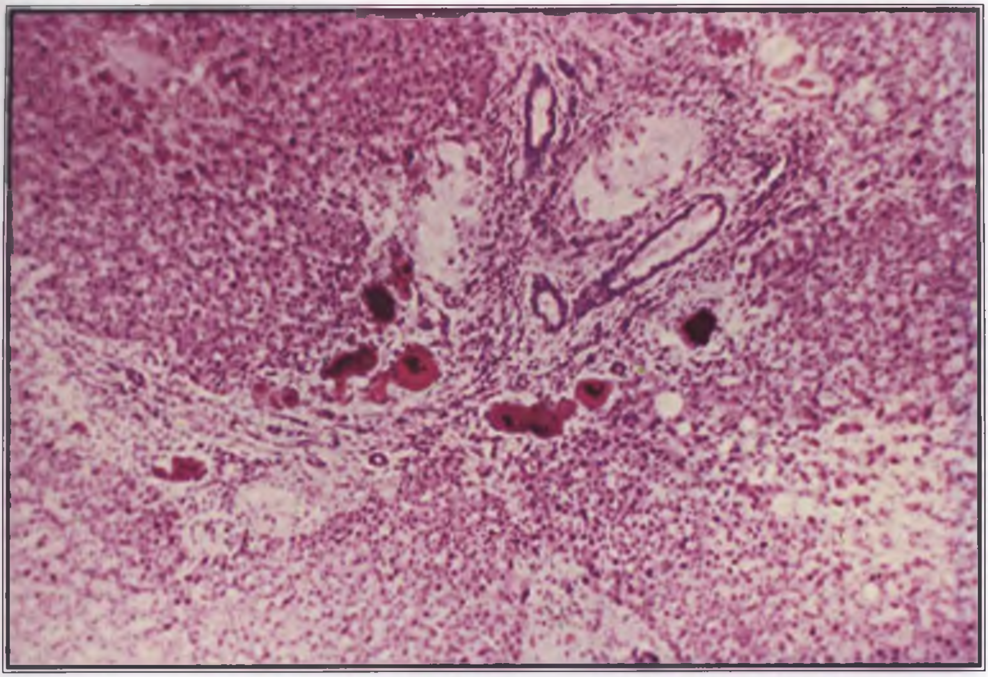


Fig. 25. Biliary stasis in mechanical jaundice (H.E. stain, × 70).

Fig. 26. Pigmentary nevus.

Fig. 27. Metastasis of melanoma in bones.

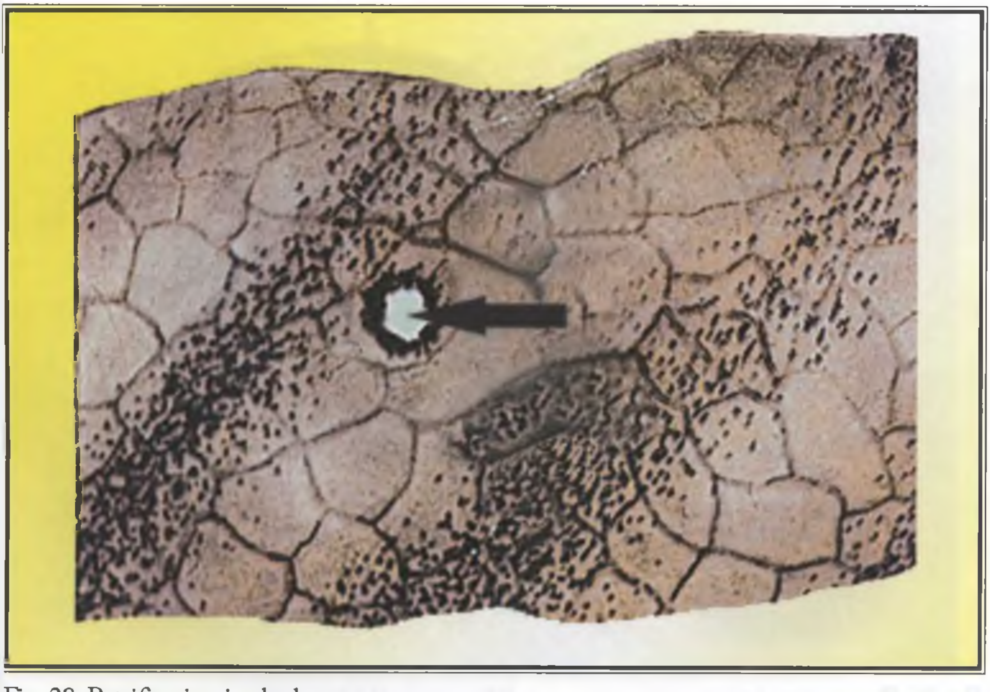


Fig. 28. Petrification in the lung.

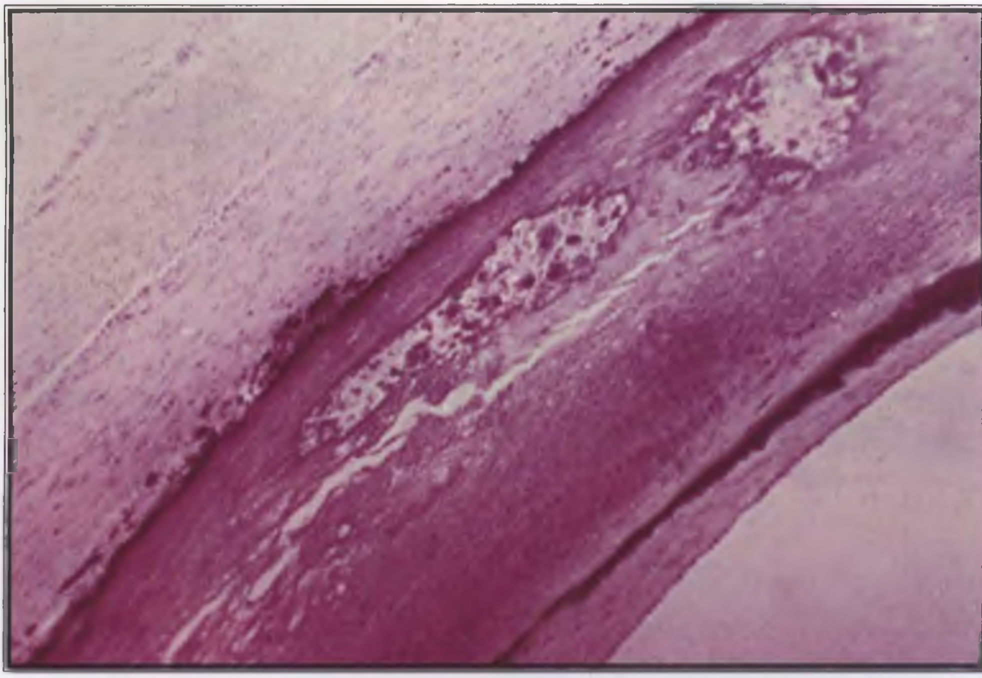


Fig. 29. Dystrophic calcification (calcinosis) of the coronary artery in atherosclerosis (H.E. stain, × 70).

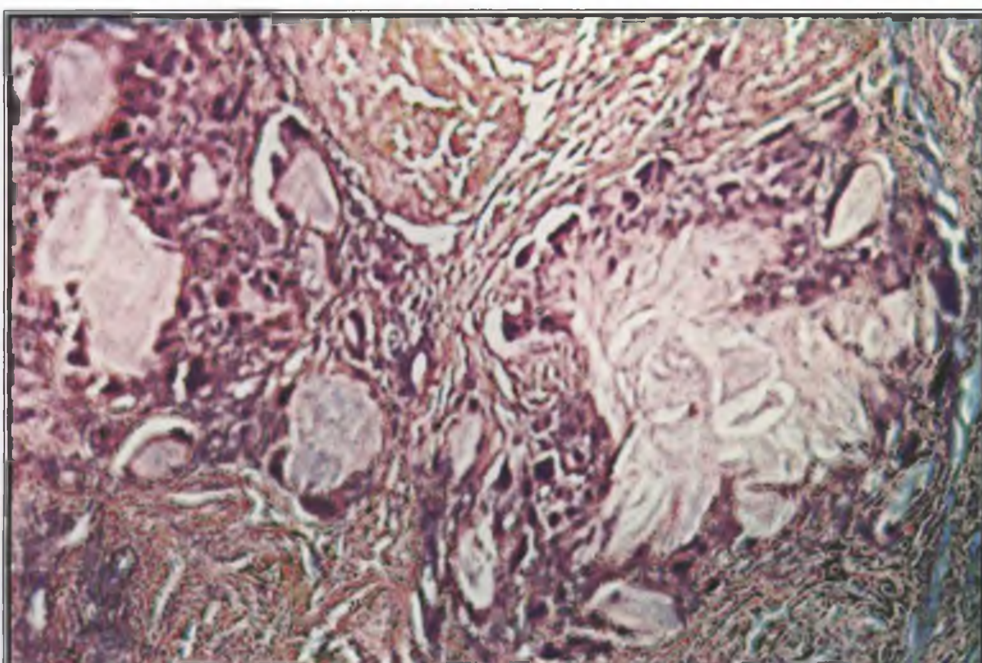


Fig. 30. Gout tophi (H.E. stain, × 70).

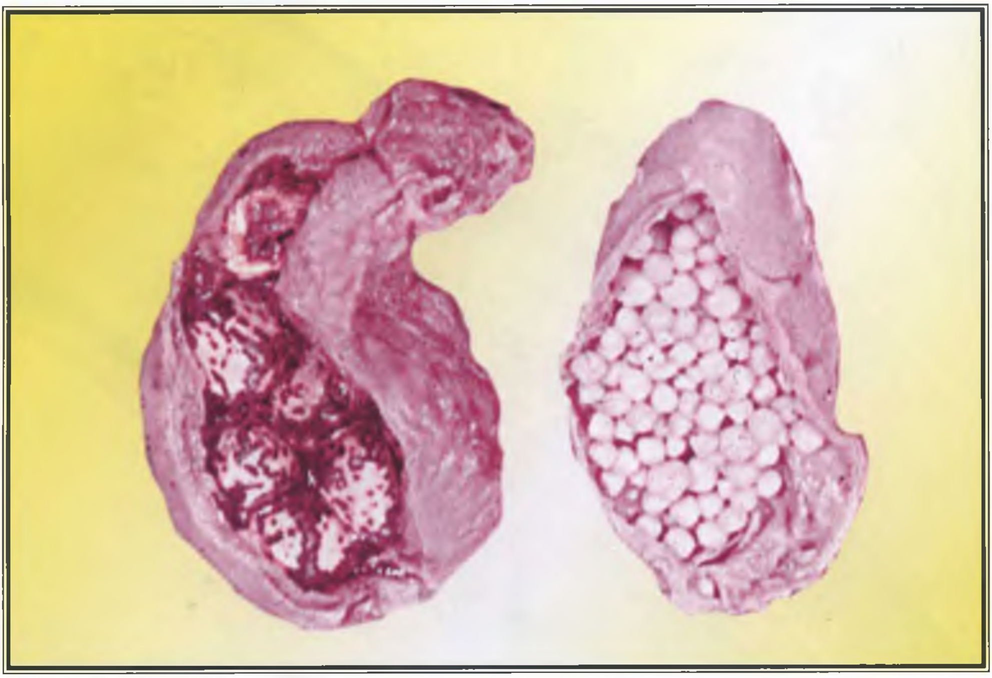


Fig. 31. Biliary calculi.

Fig. 32. Renal calculi.

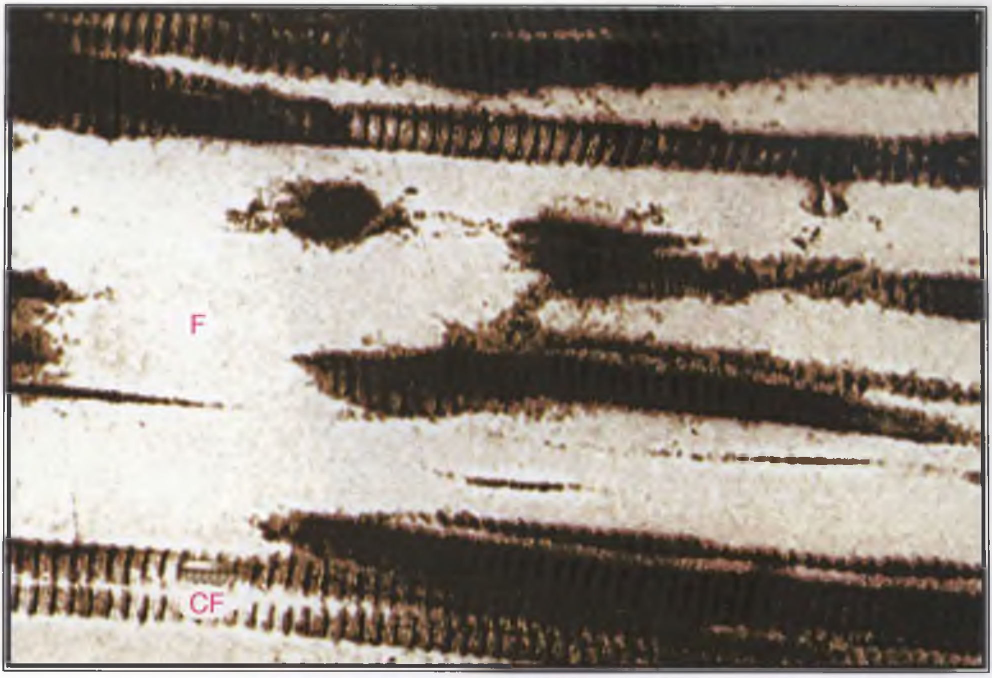


Fig. 33. Fibrinoid intumescence of the connective tissue (electron microscopy, × 35000): CF – collagen fibers; F – fibrin.

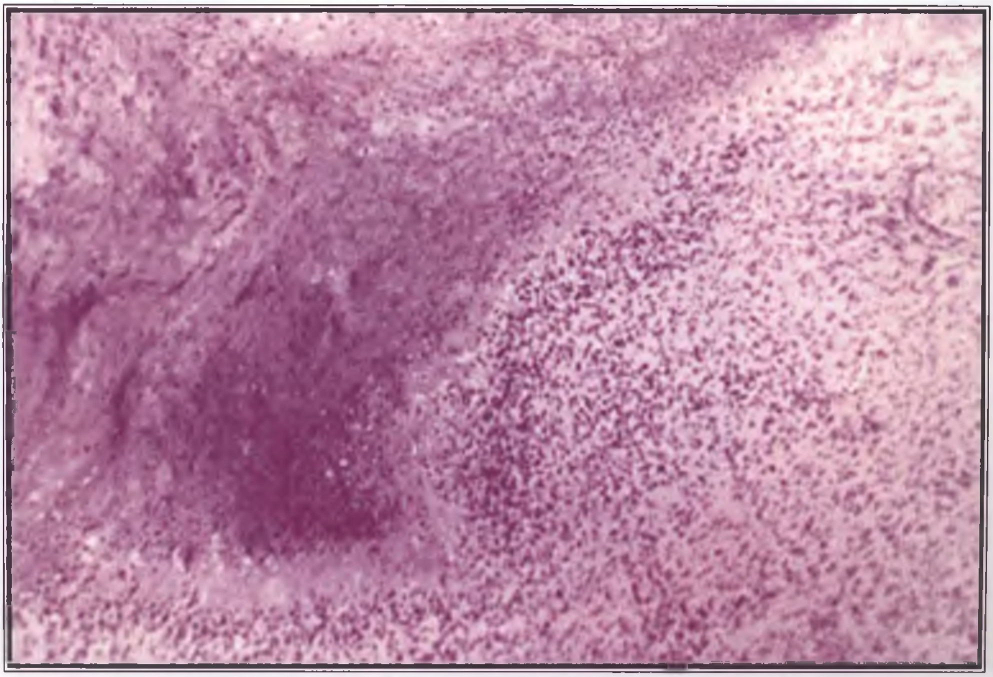


Fig. 34. Fibrinoid necrosis of the connective tissue in rheumatism (H.E. stain, × 70).

Fig. 35. Hyalinosis of the heart valves.

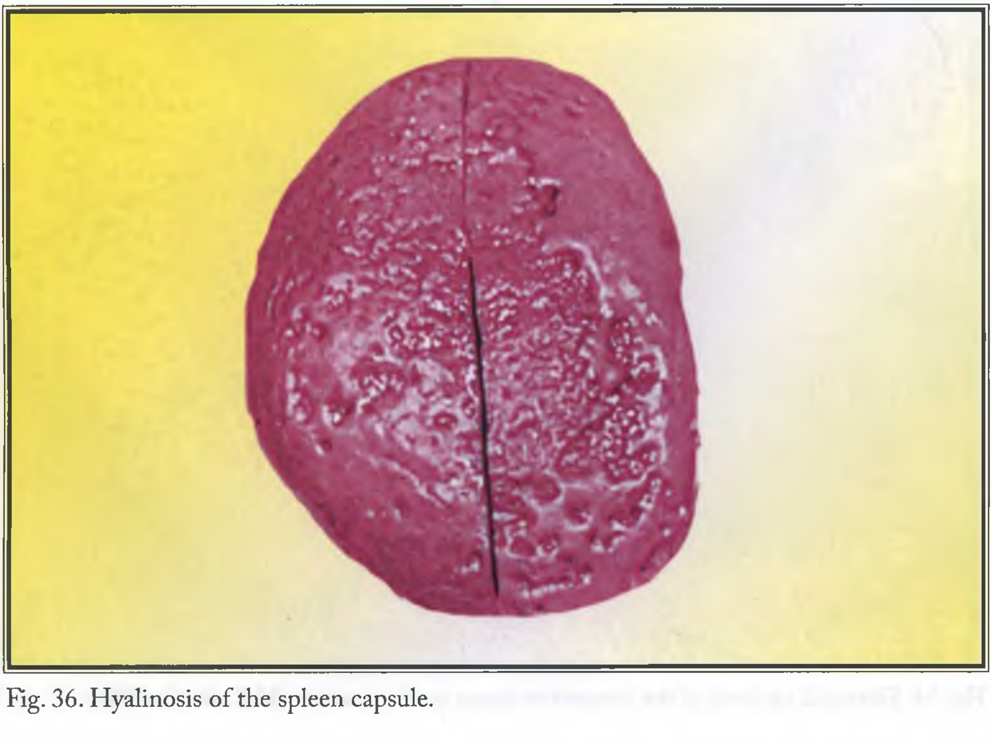


Fig. 36. Hyalinosis of the spleen capsule.

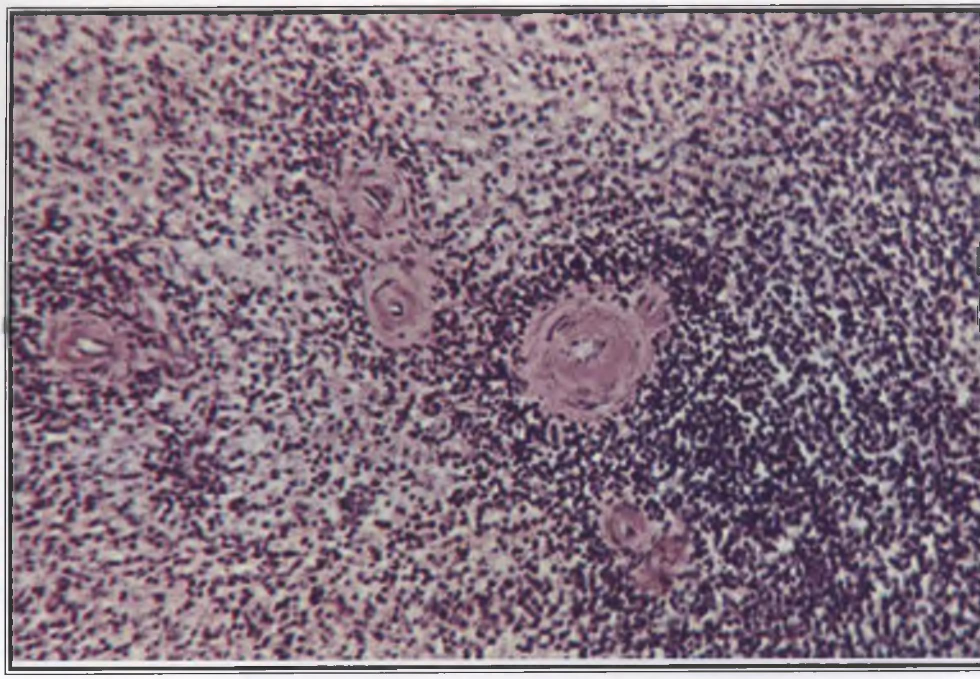


Fig. 37. Hyalinosis of the splenic arteries (H.E. stain, × 70).

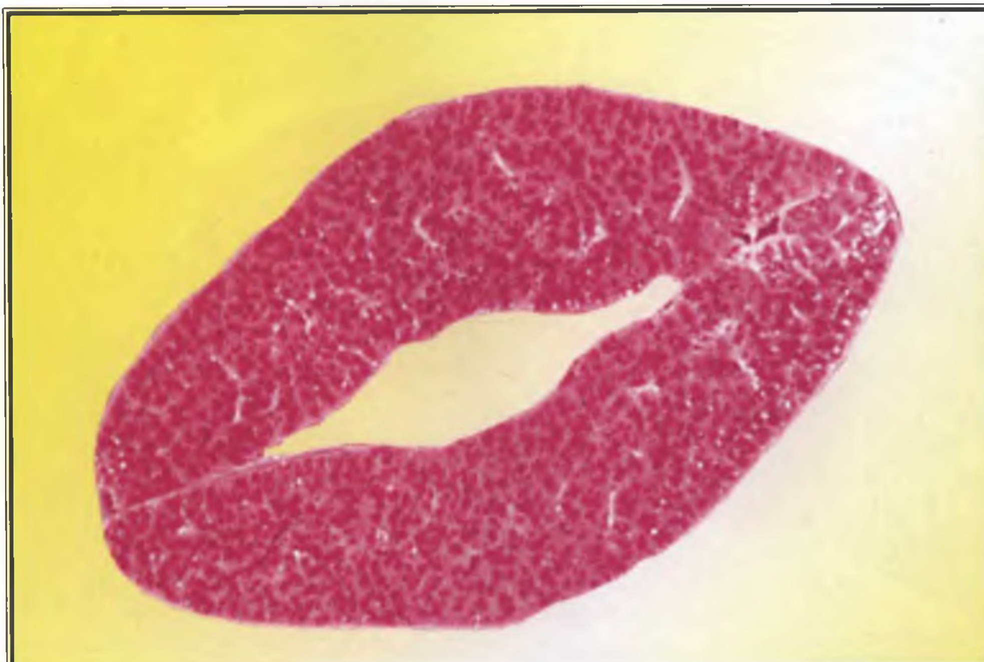


Fig. 38. Nodular amyloidosis of the spleen.

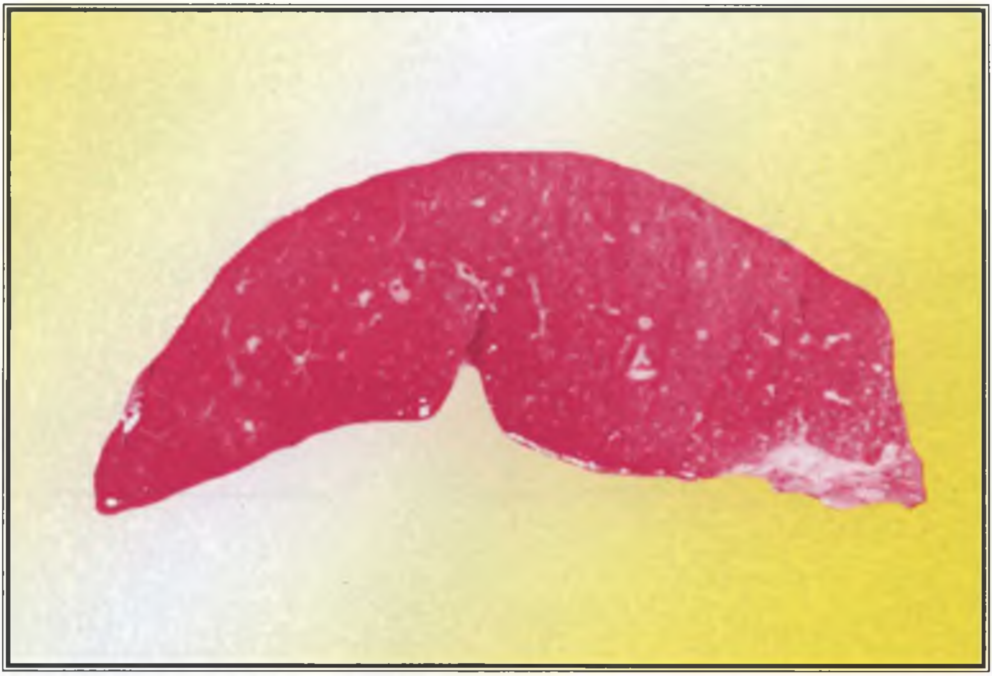


Fig. 39. Diffuse amyloidosis of the spleen

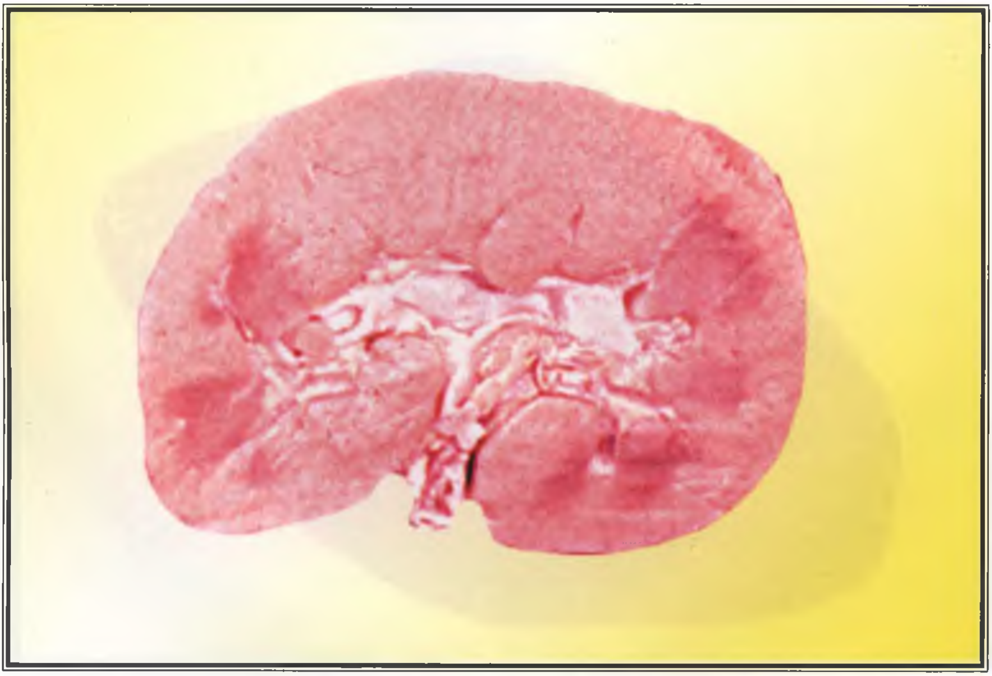


Fig. 40. Amyloid dystrophy of the kidney.

Fig. 41. Histochemical reaction for macroscopic amyloid identification (Virchow reaction).

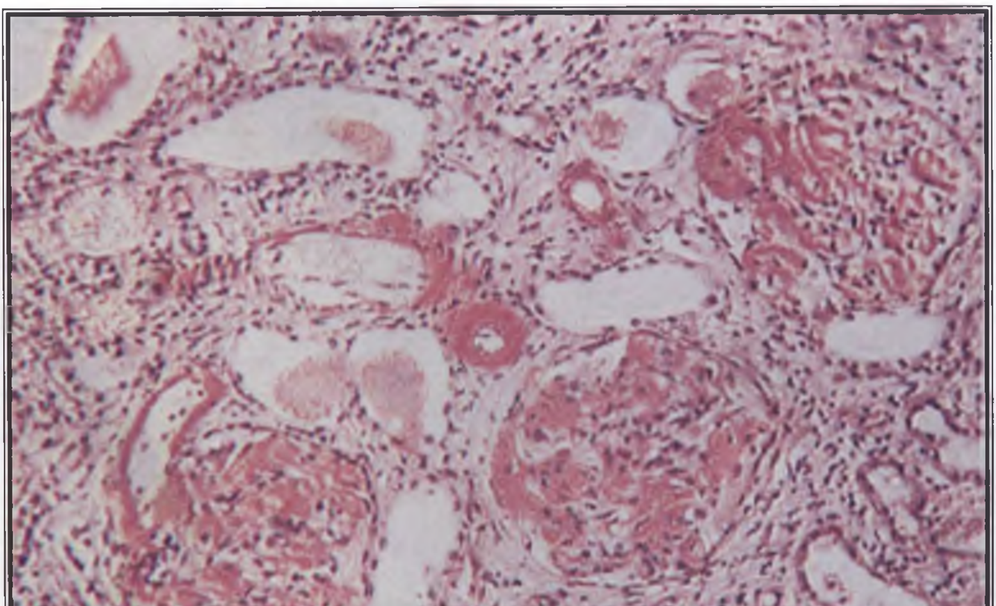


Fig. 42. Renal amyloidosis (Congo red stain, × 112).

Fig. 43. Amyloidosis of myocardium (electron microscopy, × 23000): M - mitochondria; MF - myofibrils; Am - fibrillar component of the amyloid substance; S – sarcolemma of the cardiomyocite.

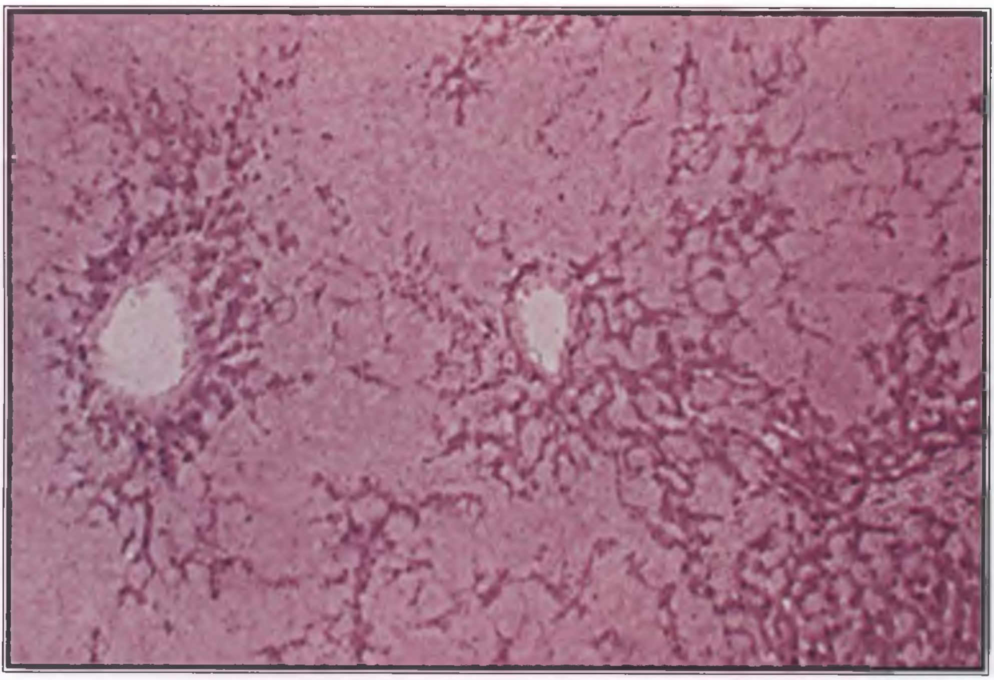


Fig. 44. Hepatic amyloidosis (H.E. stain, × 70).

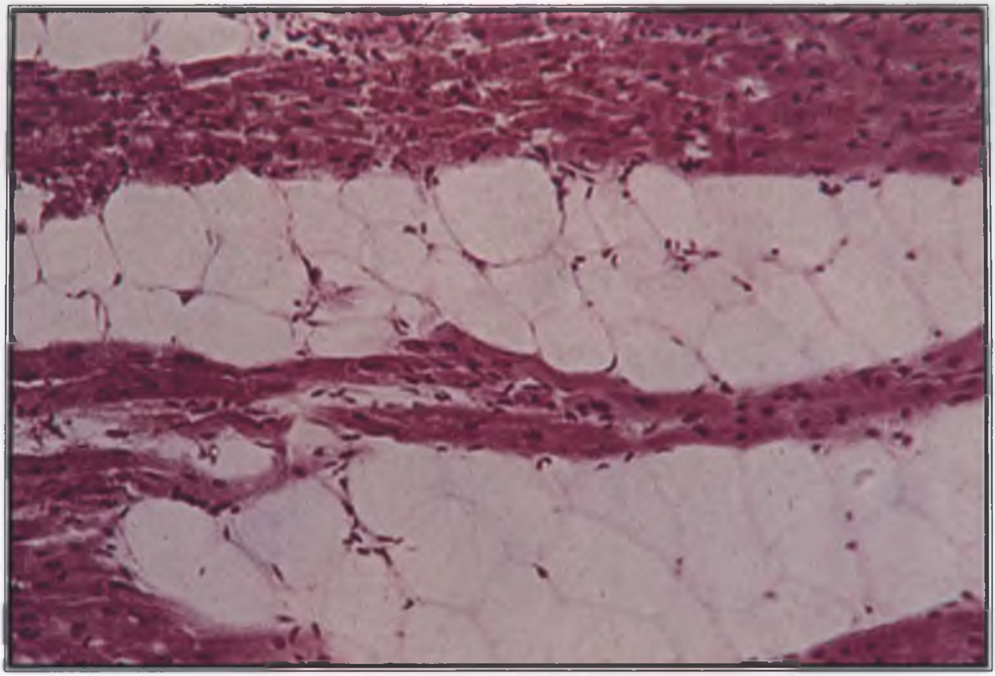


Fig. 45. Lipomatosis of the heart (H.E. stain, × 70).

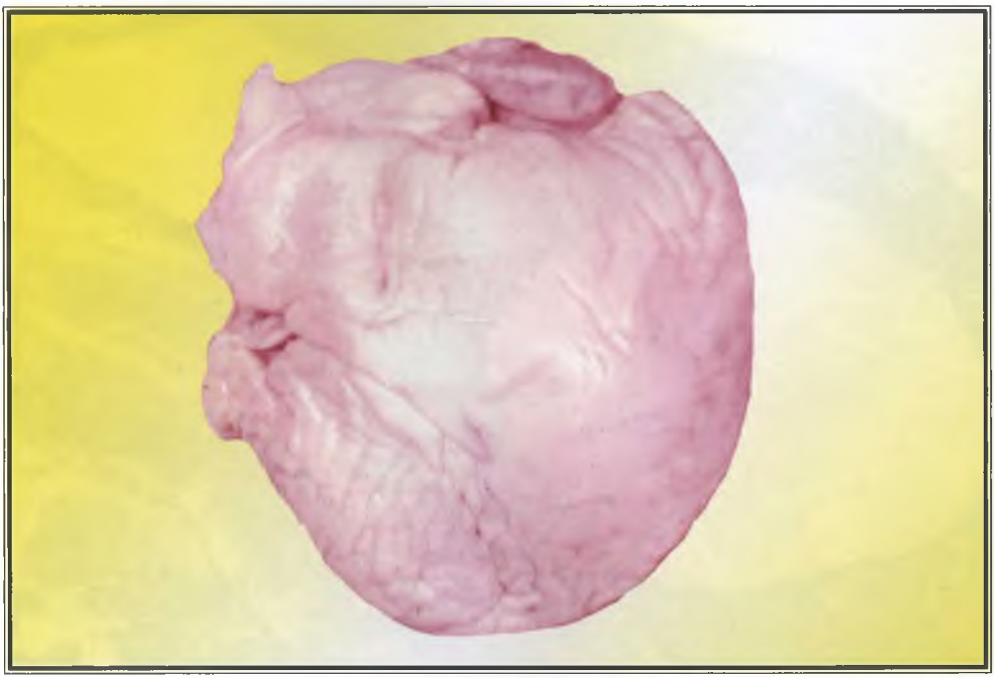


Fig. 46. Lipomatosis of the heart, macroscopic aspect.

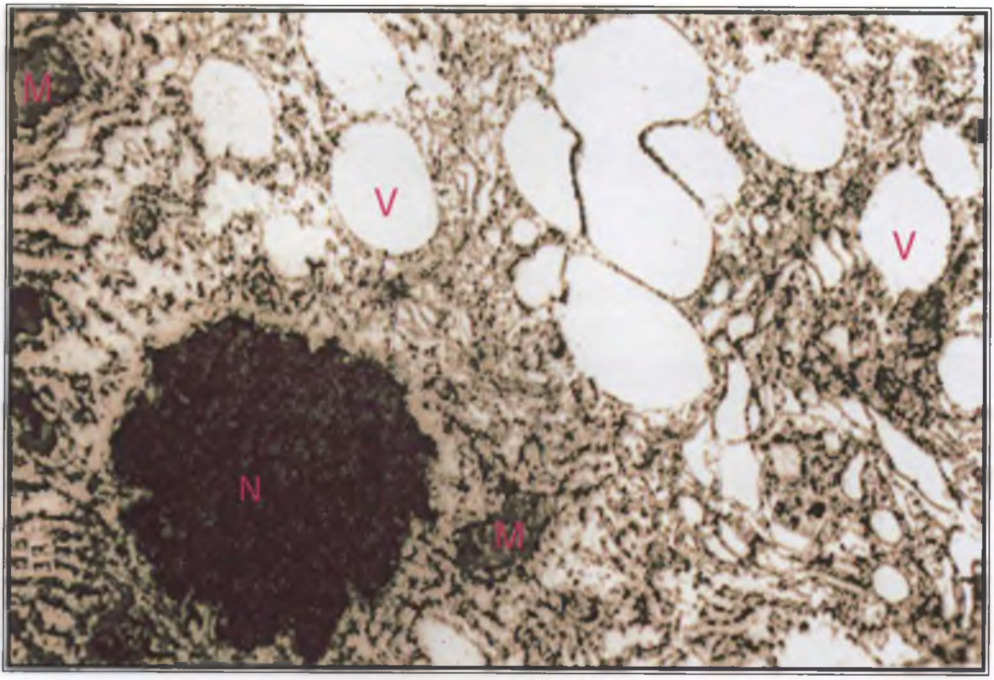


Fig. 47. Necrosis of the cell, karyopyknosis (electron microscopy, × 17500): N - nucleus; V - vacuoles; M - mitochondria.

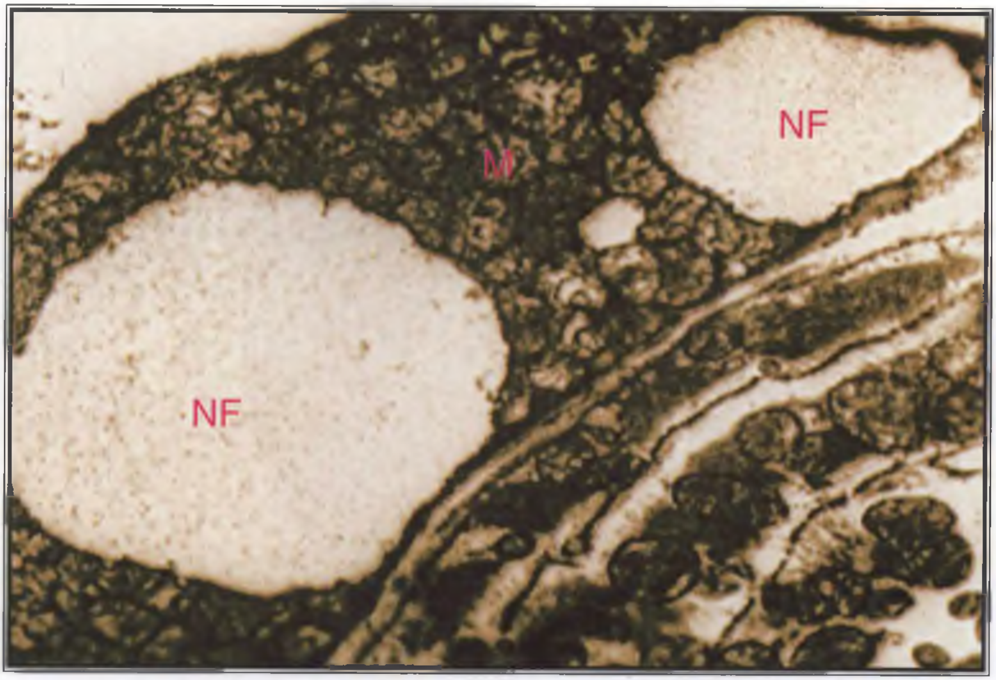


Fig. 48. Focal (partial) necrosis of the cardiomyocyte (electron microscopy, × 10000): M - mitochondria; NF - necrotic focus.

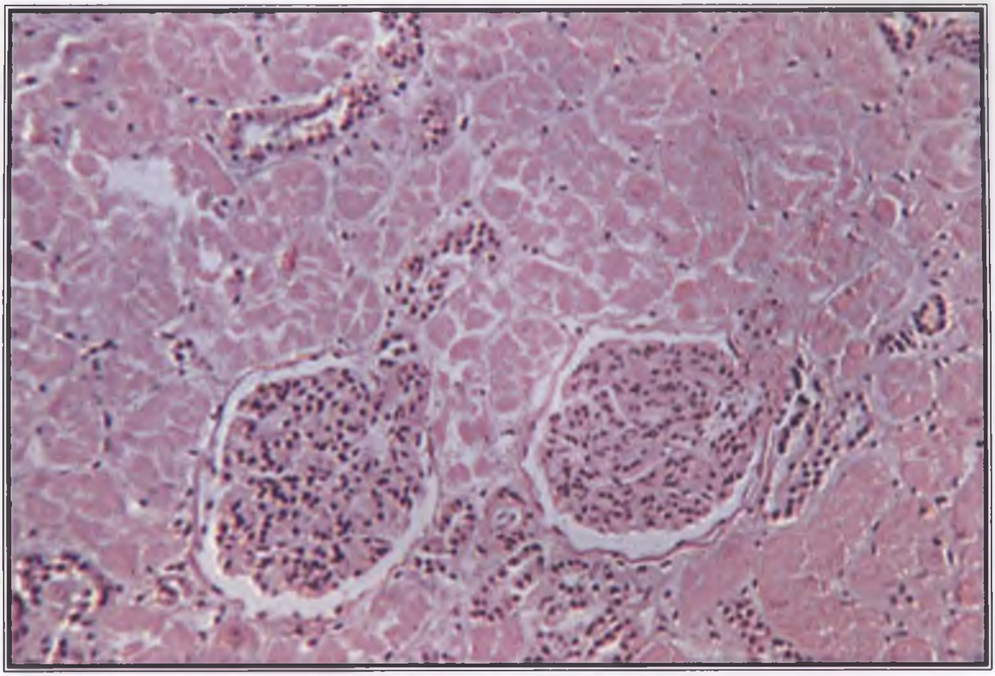


Fig. 49. Necrosis of the contort renal tubule epithelium (H.E. stain, × 70).

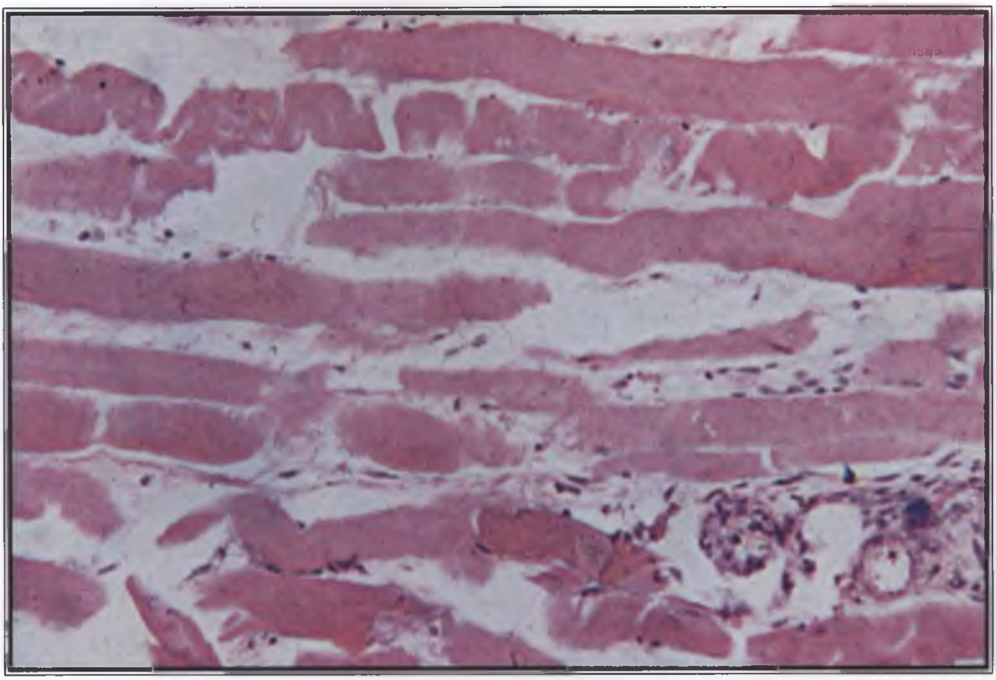


Fig. 50. Necrosis of the striated muscles (cerous or Zencker`s necrosis) (H.E. stain, × 70).

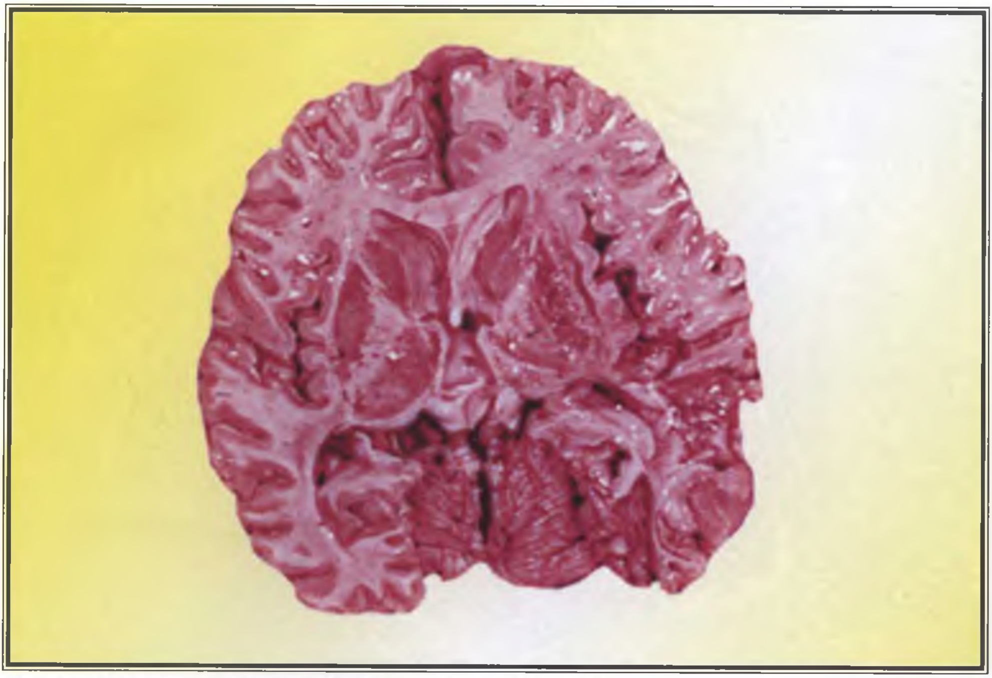


Fig. 51. White cerebral infarct (white cerebral softening).

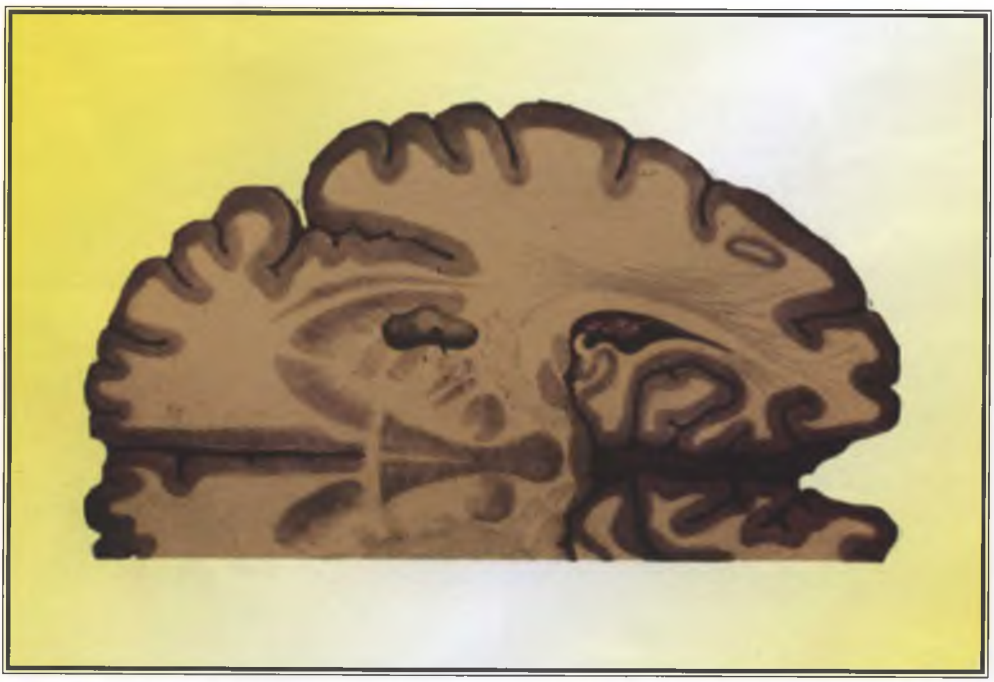


Fig. 52. Cerebral cyst.

Fig. 53. Caseous necrosis of the mesenteric lymph nodes in tuberculosis, macroscopic aspect.

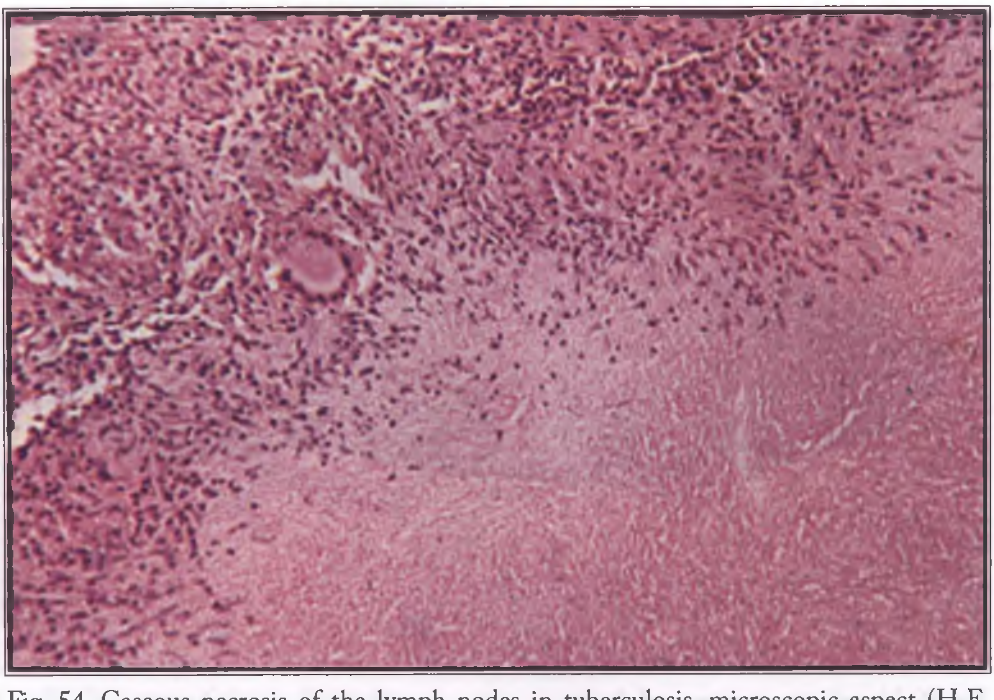


Fig. 54. Caseous necrosis of the lymph nodes in tuberculosis, microscopic aspect (H.E. stain, × 70).

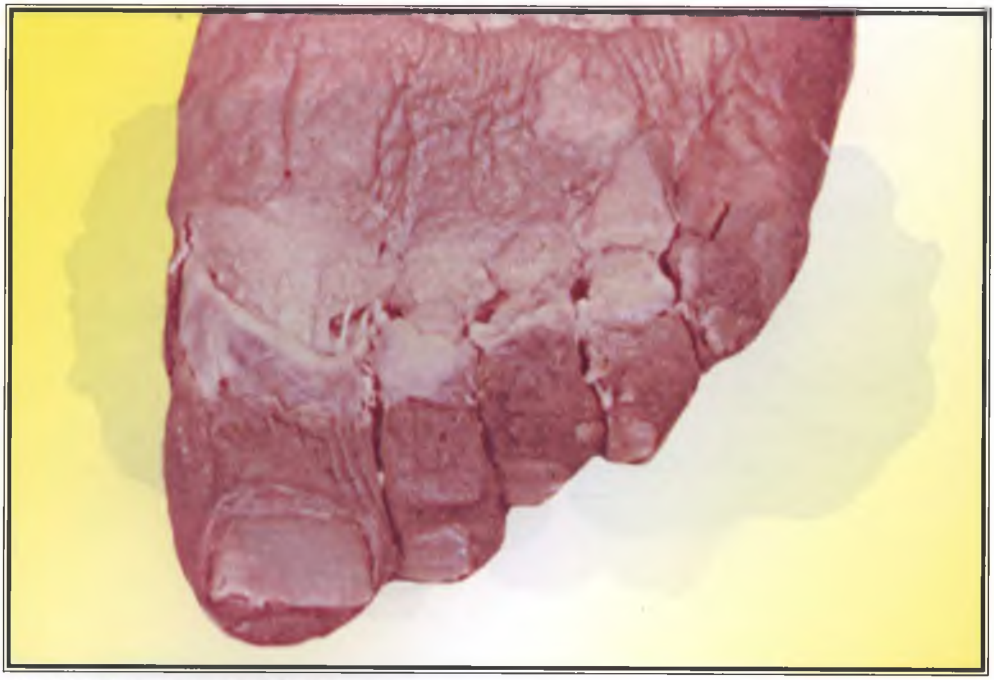


Fig. 55. Dry gangrene of the leg.

Fig. 56. Liquefactive gangrene of the leg.

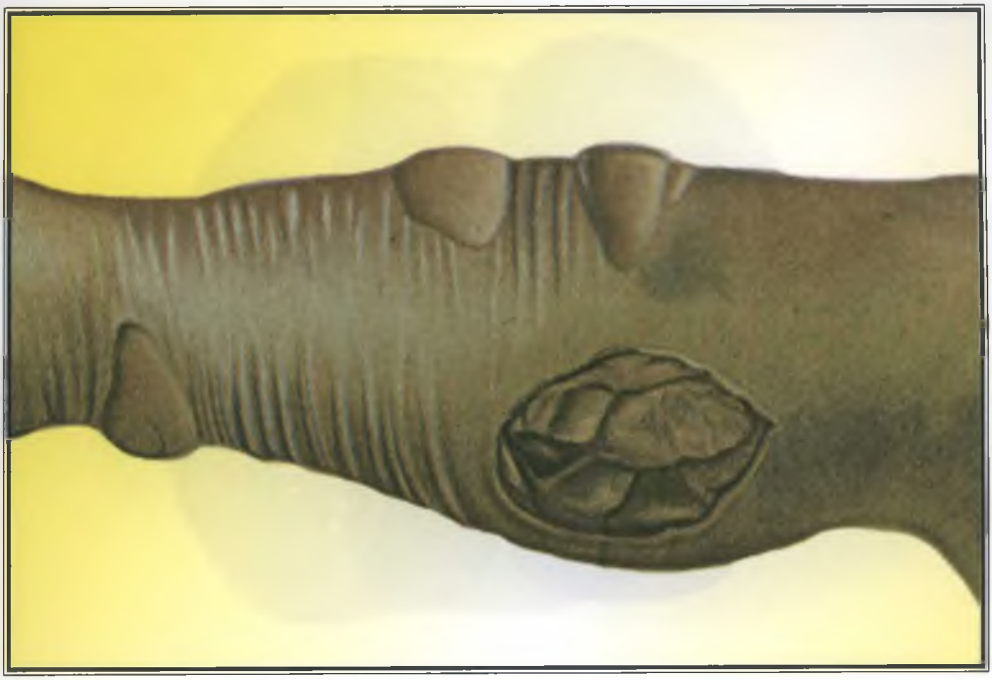


Fig. 57. Gaseous gangrene of the leg.

Fig. 58. Gangrene of the small intestine.

Fig. 59. Decubitus (eschar).

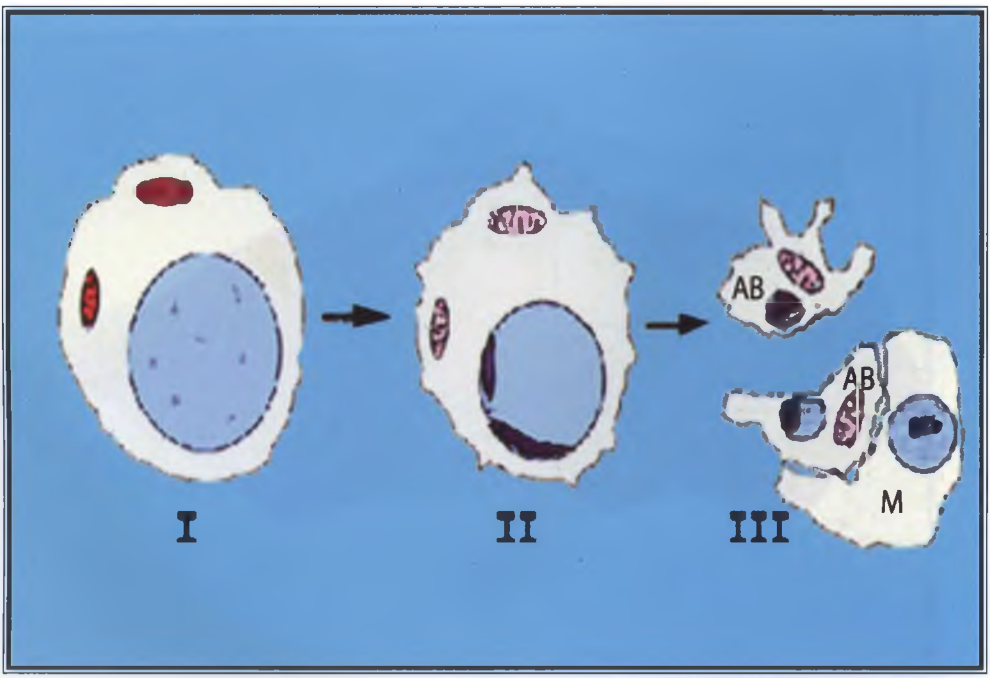


Fig. 60. Apoptosis: I – the normal cell; II – the apoptotic cell shrinking in size, the chromatin condenses beneath the nuclear membrane; III – phagocytosis of the apoptotic bodies (AB – apoptotic bodies, M– macrophage).

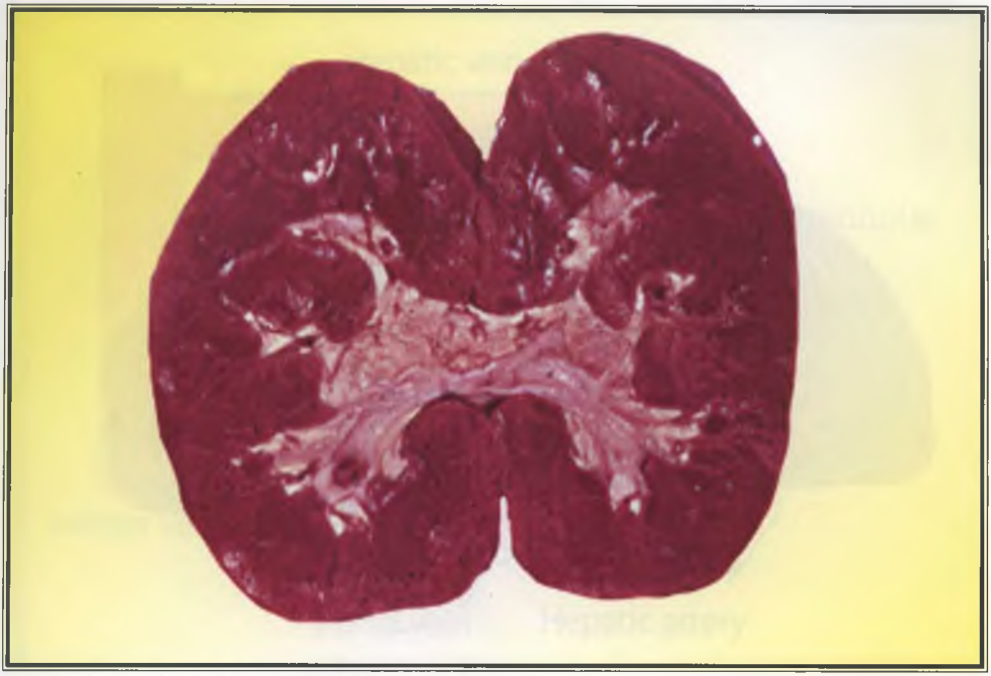


Fig. 61. Cyanotic induration of the kidney.

Fig. 62. Cyanosis of facial skin and of the mucosa of the lips.

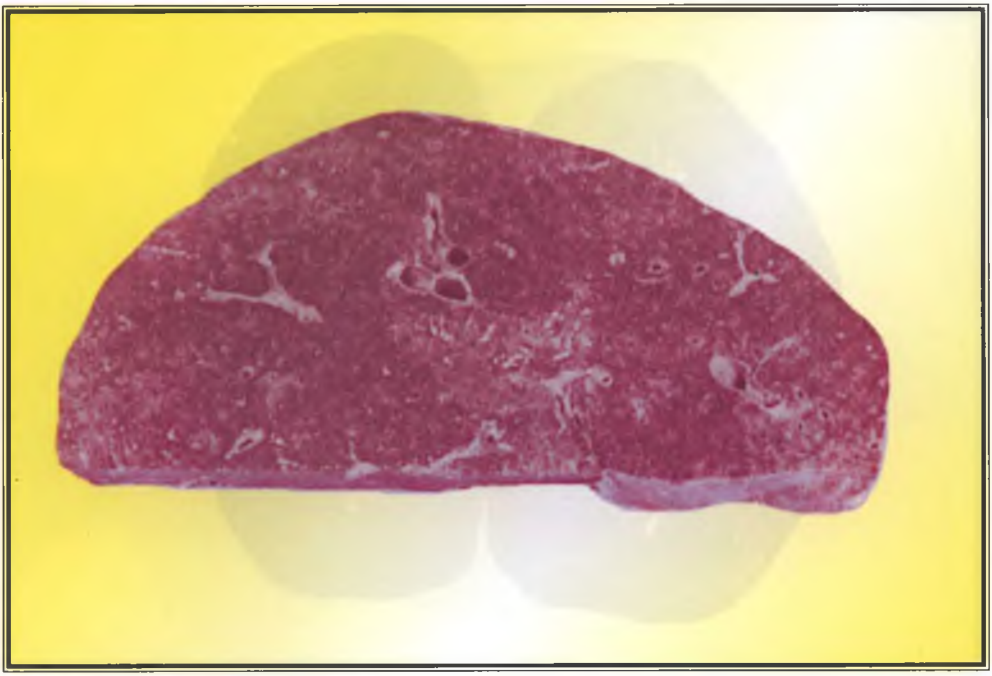


Fig. 63. Chronic venous hyperemia of the liver (nutmeg liver), macroscopic aspect.

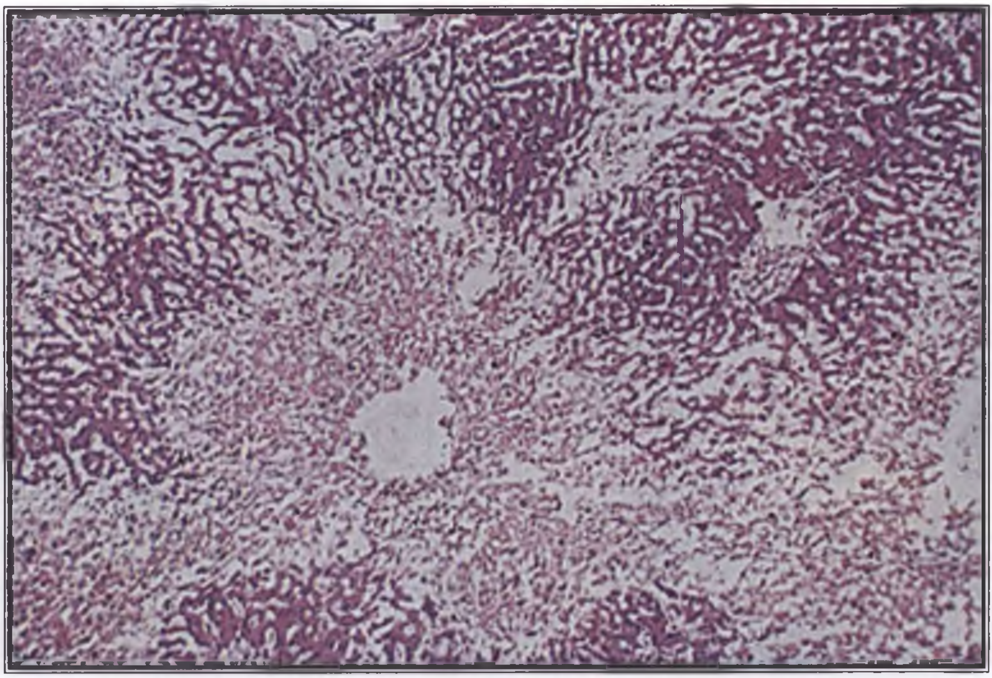


Fig. 64. Chronic venous hyperemia of the liver (nutmeg liver), microscopic aspect (H.E. stain, × 70).

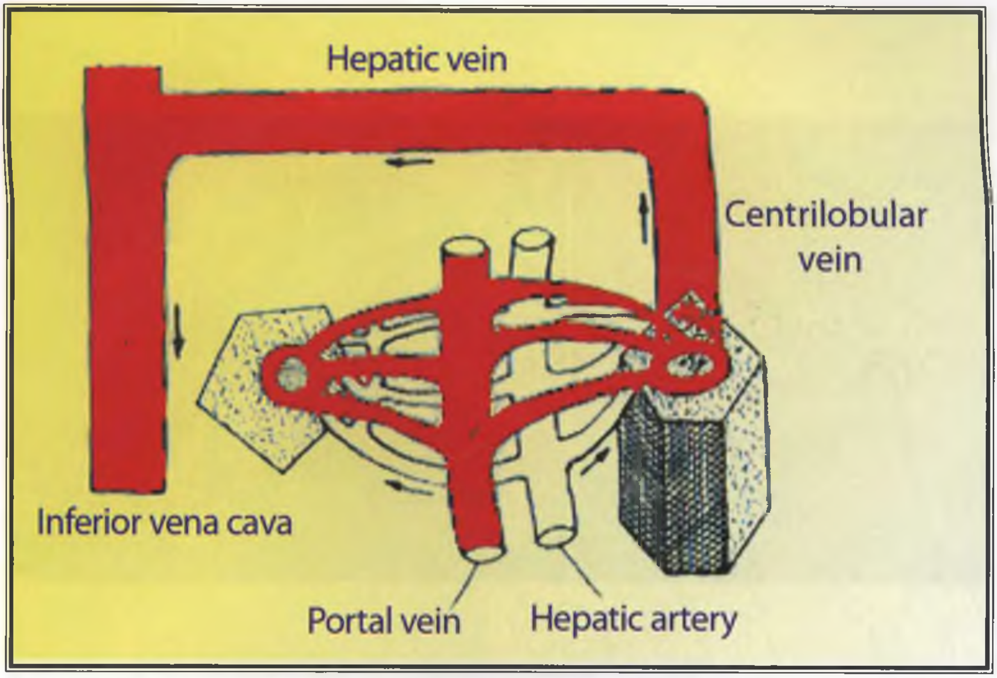


Fig. 65. Nutmeg liver development scheme.

Fig. 66. Brown induration of the lung.

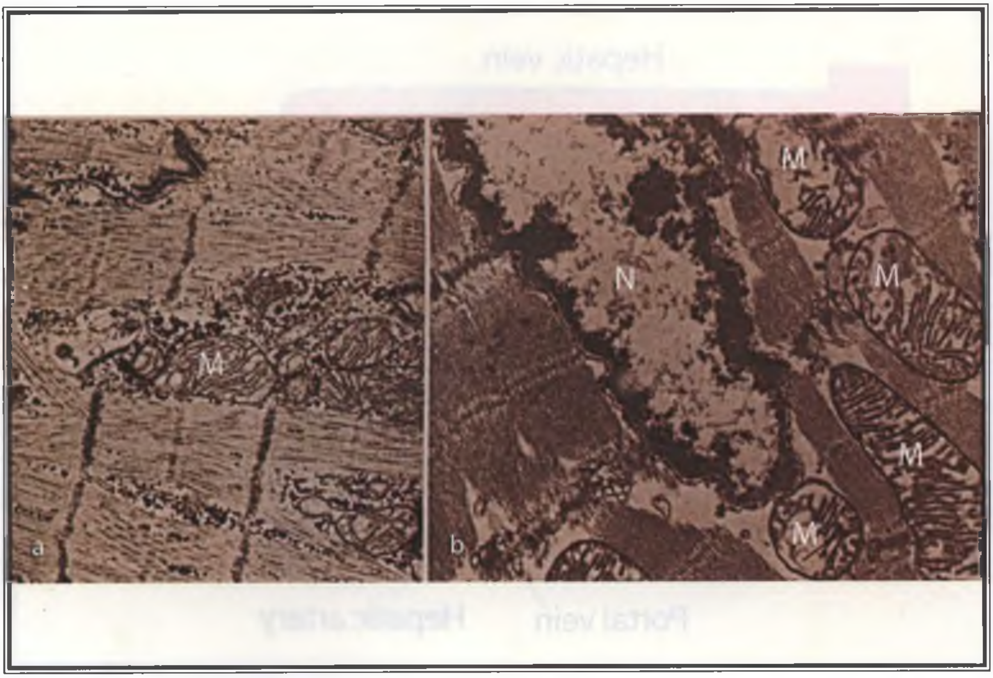


Fig. 67. Ischemic stage of myocardial infarction (electron microscopy): a - normal cardiomyocyte (× 10000); b - cardiomyocyte affected by ischemia (× 15000); N- nucleus; M- mitochondria).

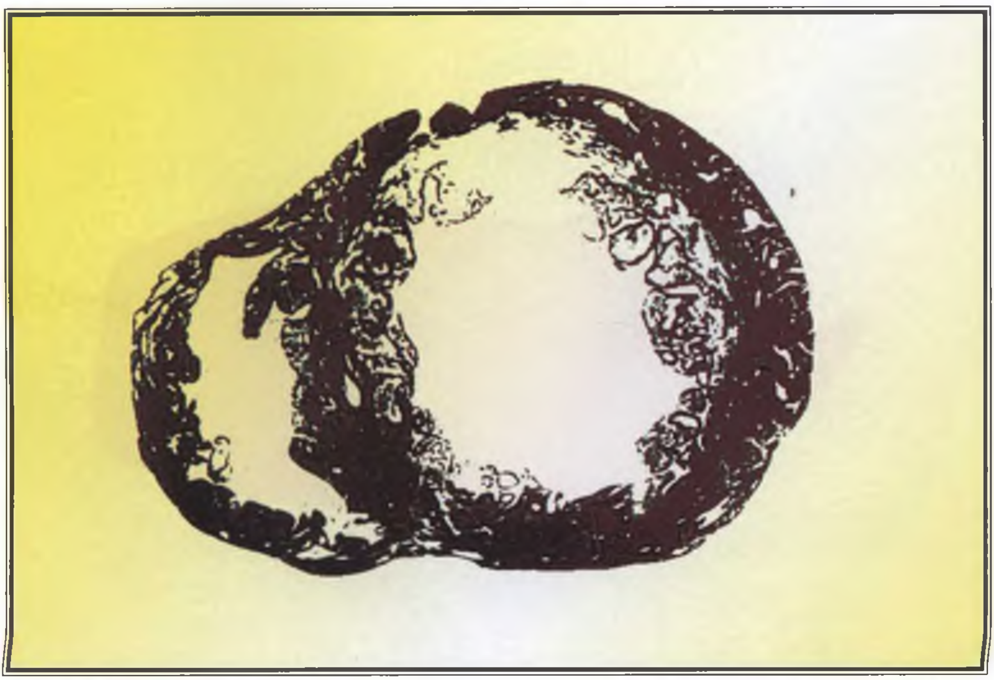


Fig. 68. Myocardial infarction: succinatdehydrogenase activity identification histotopographic reaction using tetrazolium nitrate blue; the decrease (disappearance) of the enzyme's activity in the ischemic region.

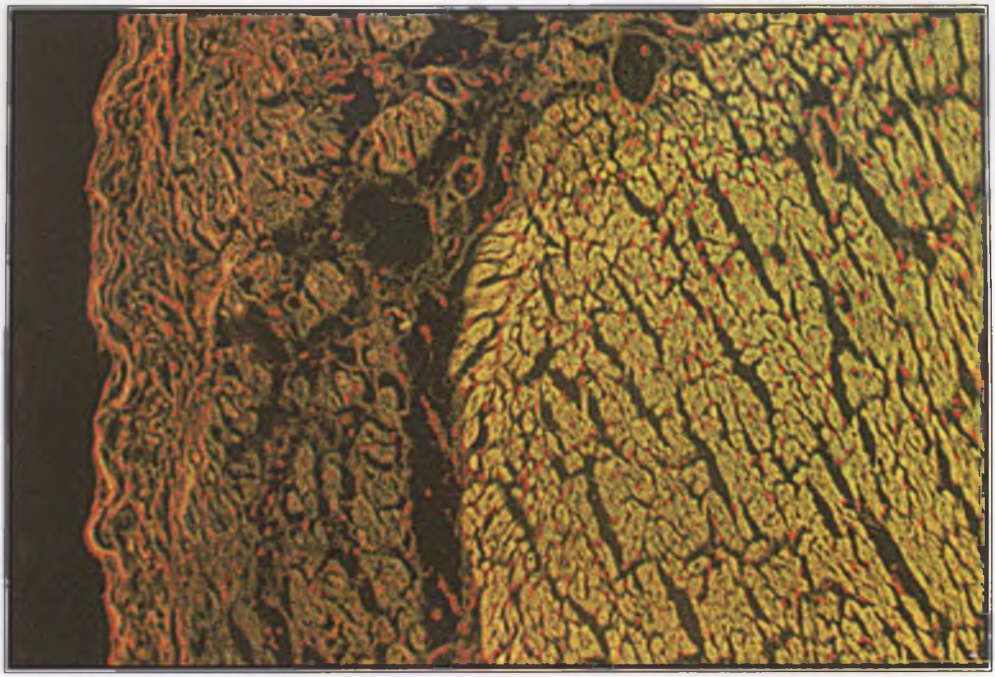


Fig. 69. Myocardial infarction: luminescent microscopy with acridin orange.

Fig. 70. Ischemic infarct of the spleen, macroscopic aspect.

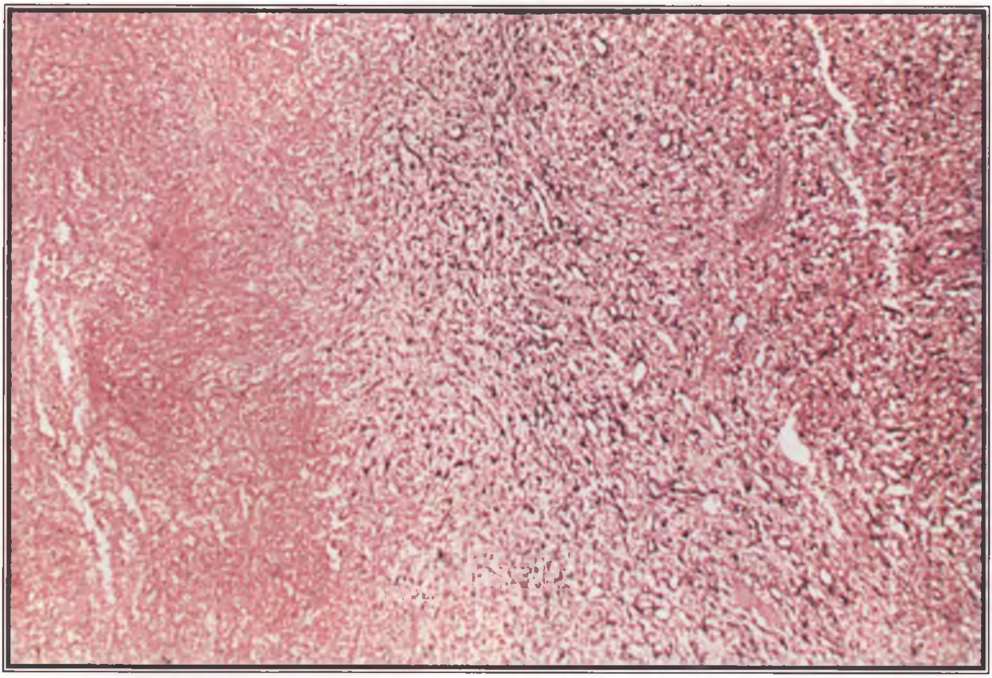


Fig. 71. Ischemic infarct of the spleen, microscopic aspect (H.E. stain, × 70).

Fig. 72. Postinfarction cicatrix in spleen.

Fig. 73. Renal infarct, macroscopic aspect: 1- infarct zone; 2- hemorrhagic belt; 3- thrombosed vessel.

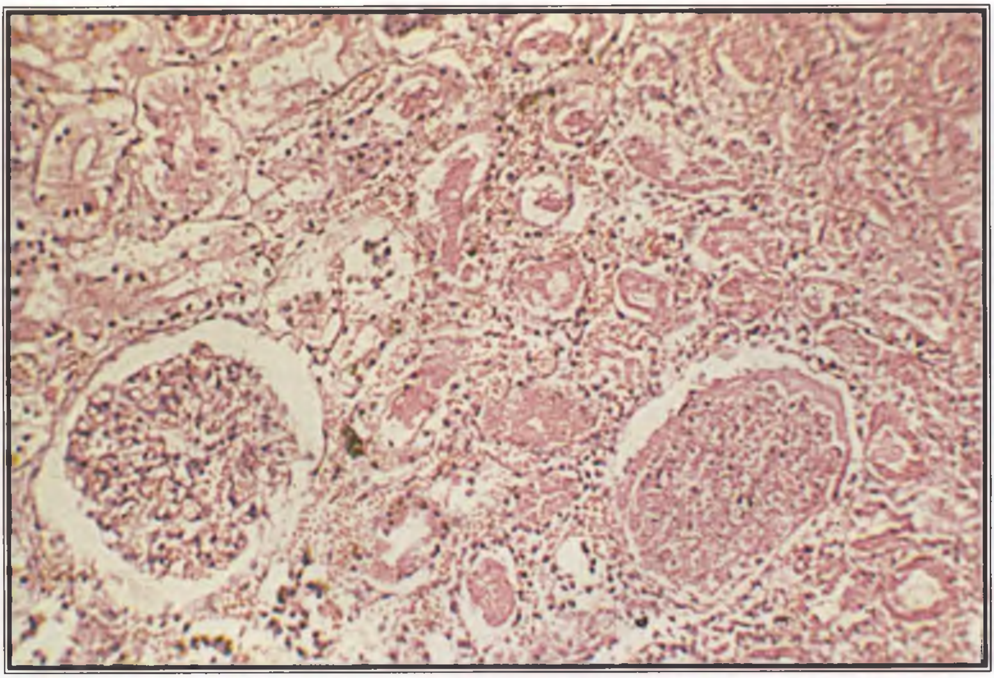


Fig. 74. Renal infarct, microscopic aspect (H.E. stain, × 70).

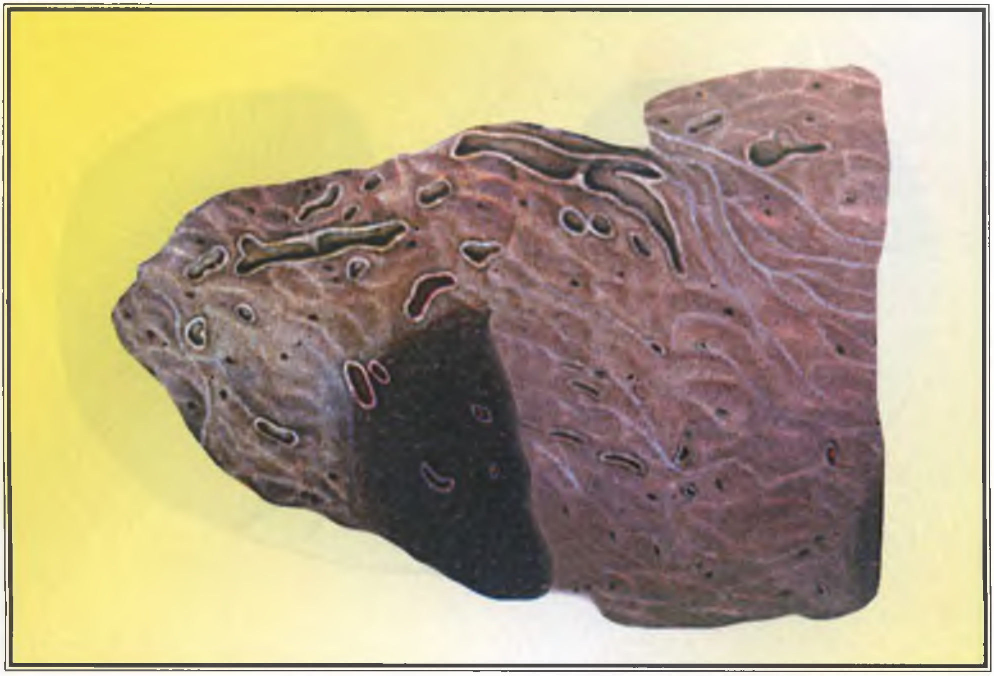


Fig. 75. Pulmonary hemorrhagic infarct, macroscopic aspect.

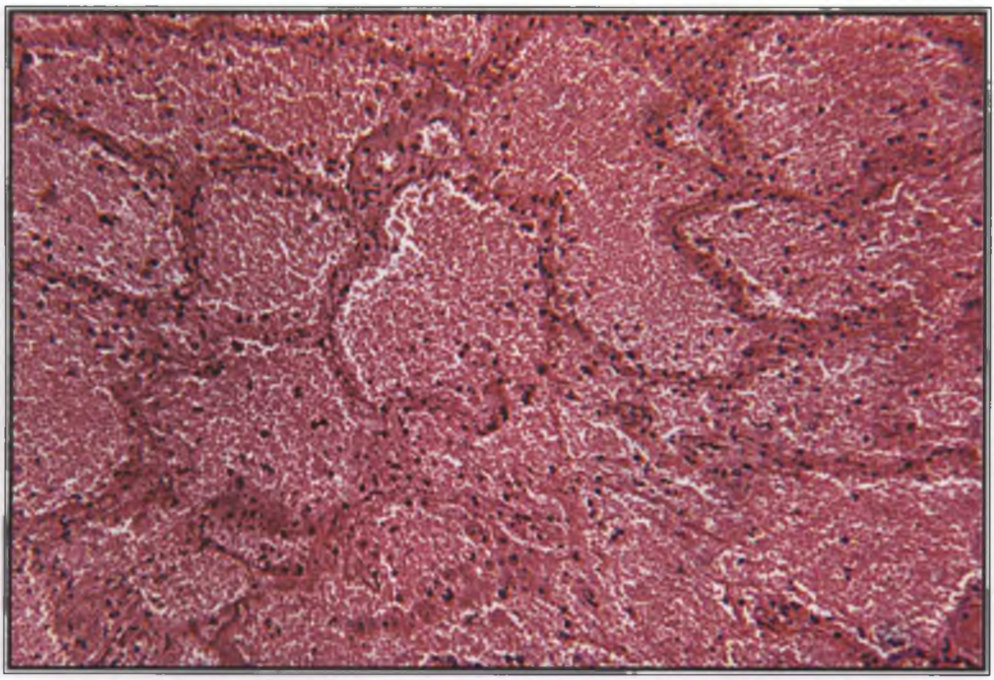


Fig. 76. Pulmonary hemorrhagic infarct, microscopic aspect (H.E. stain, × 70).

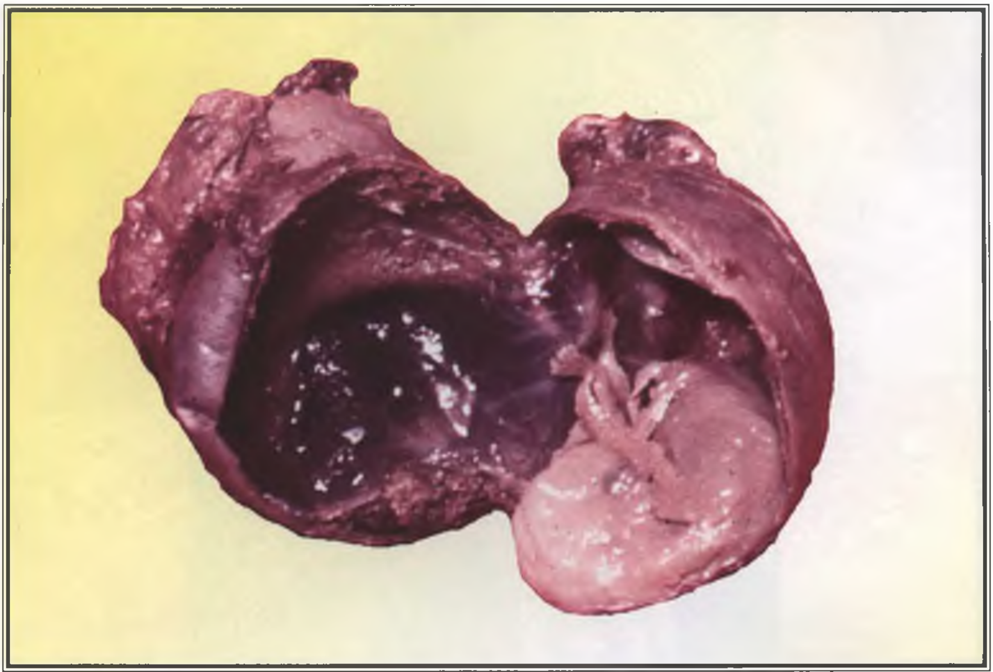


Fig. 77. Tubal pregnancy with rupture of tube.

Fig. 78. Chronic gastric ulcer, the erosion of an artery from the bottom of the ulcer.

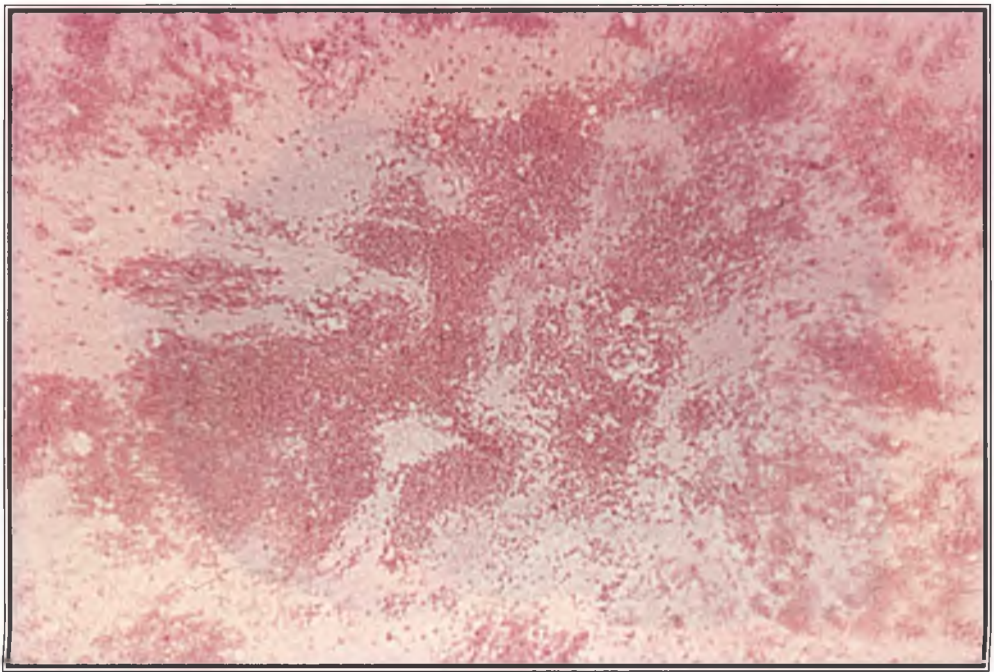


Fig. 79. Cerebral diapedetic hemorrhage (H.E. stain, × 70).

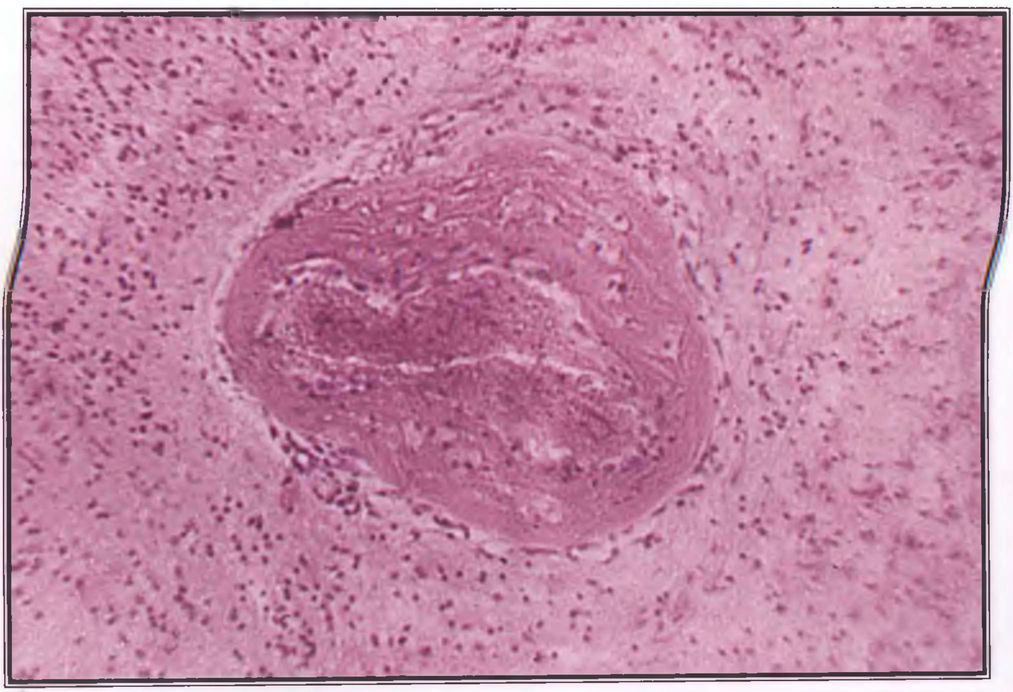


Fig. 80. Plasmatic infiltration of cerebral artery (H.E. stain, × 70).

Fig. 81. Stage I of thrombus formation (electron microscopy, × 9000): En- endothelium, T- thrombocytes, M-mitochondria, EF- elastic fibers, CF- collagen fibers.

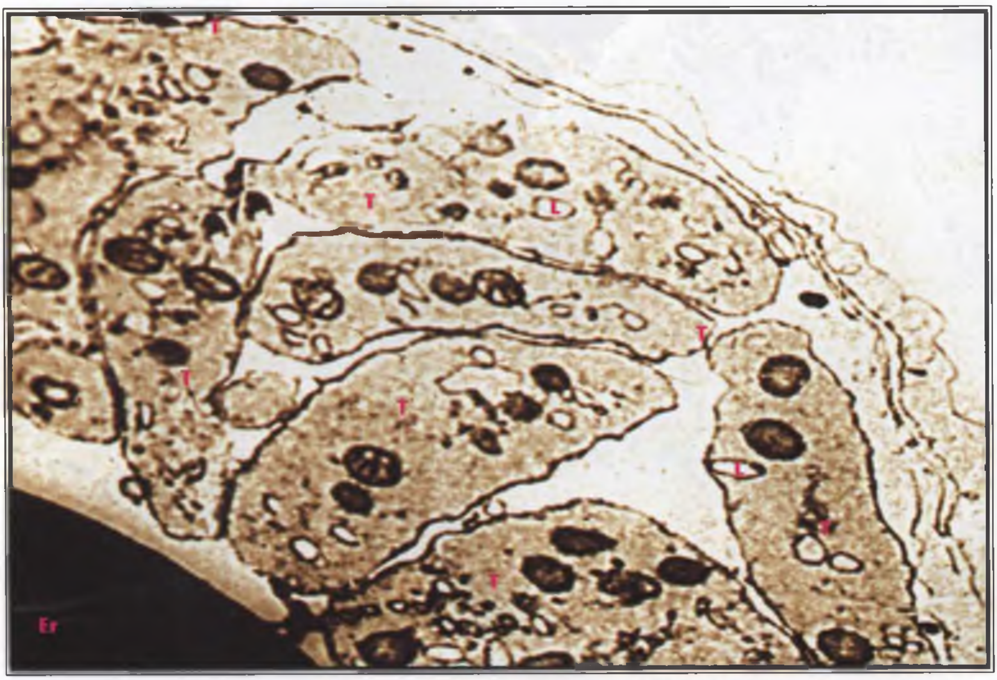


Fig. 82. Stage I of thrombus formation, agregation of thrombocytes (electron microscopy, × 56000): T- thrombocytes, Er- erythrocytes, L- lipids of the lipoproteic complexes from the peripheral zones of the thrombocytes, which encourage their agregation.

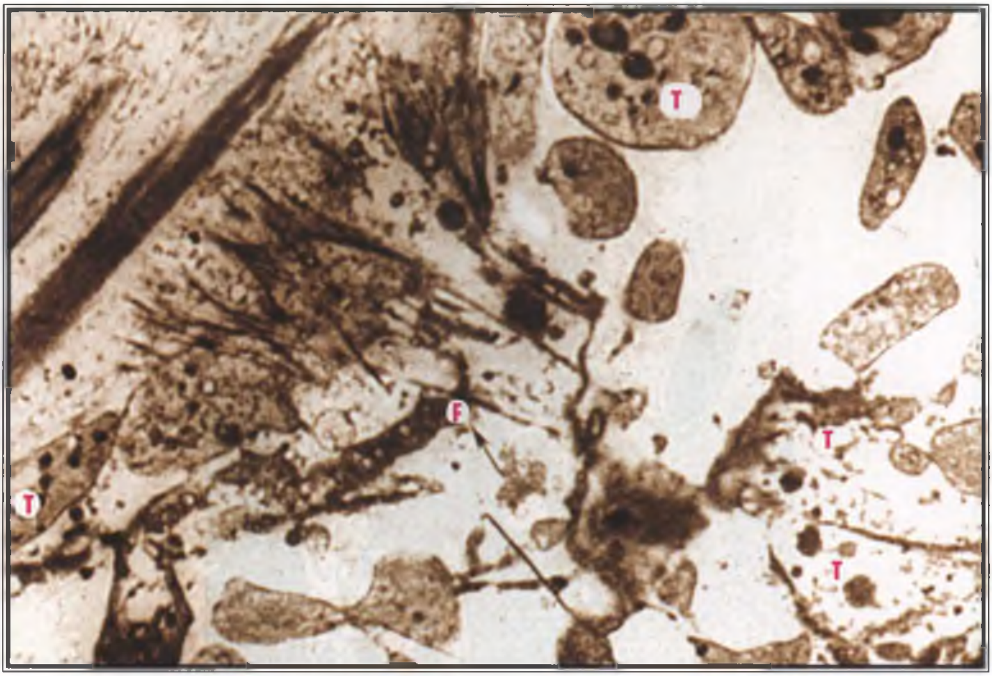


Fig. 83. Stage II of thrombus formation (electron microscopy, × 7750): T- thrombocytes, F- fibrin filaments.

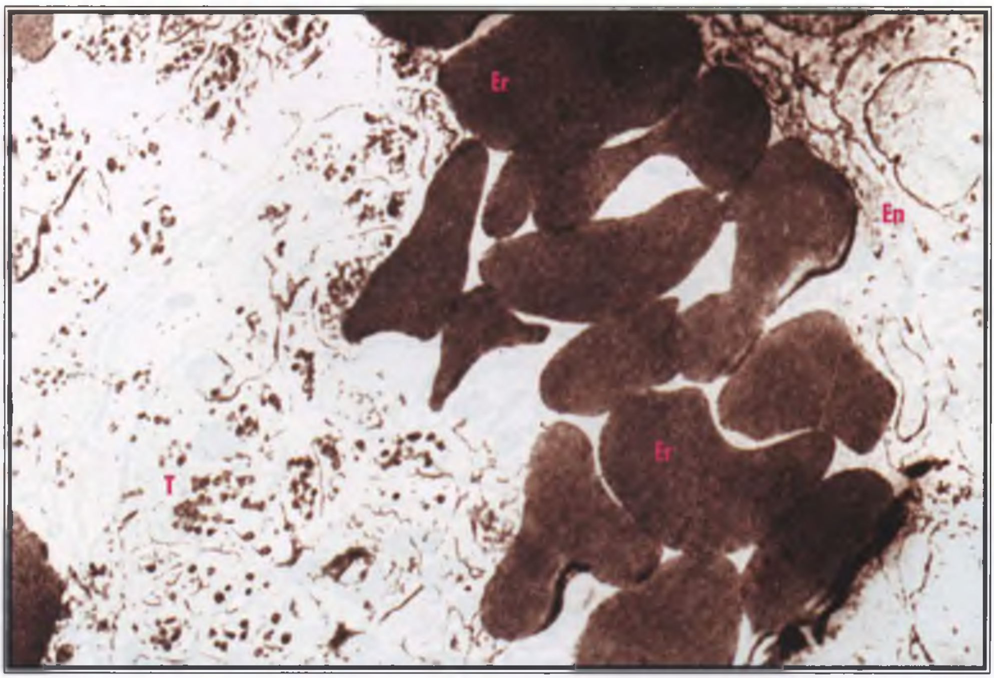


Fig. 84. Stage III of thrombus formation (electron microscopy, × 58000): En- endothelium, T- thrombocytes, Er-erythrocytes.

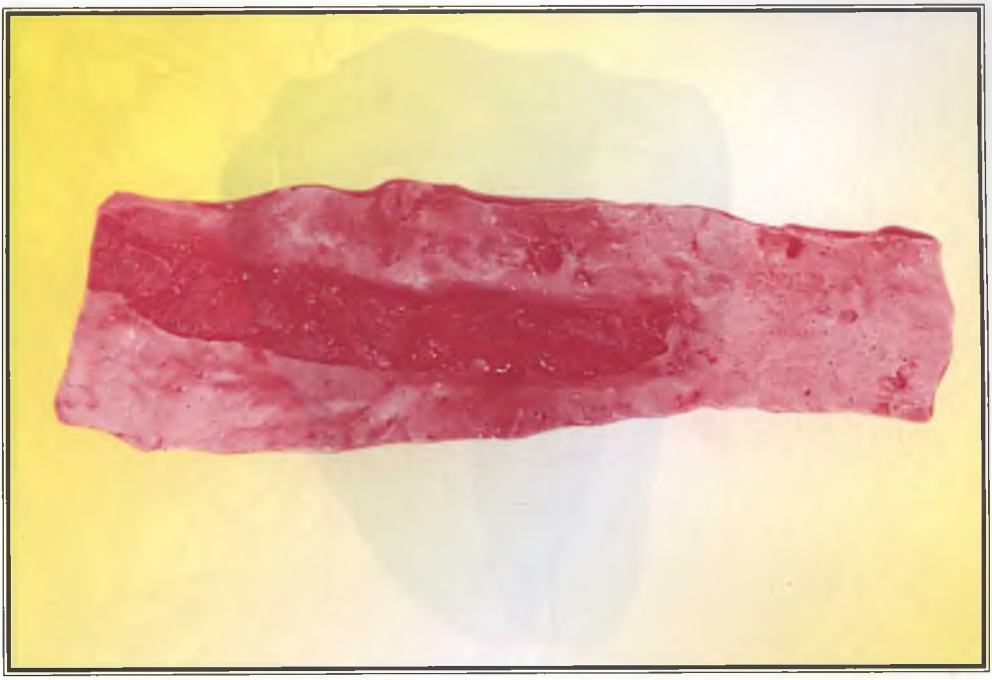


Fig. 85. Parietal thrombus in the abdominal aorta in atherosclerosis.

Fig. 86. Thrombi in the lower extremity veins with varicose dilatations.

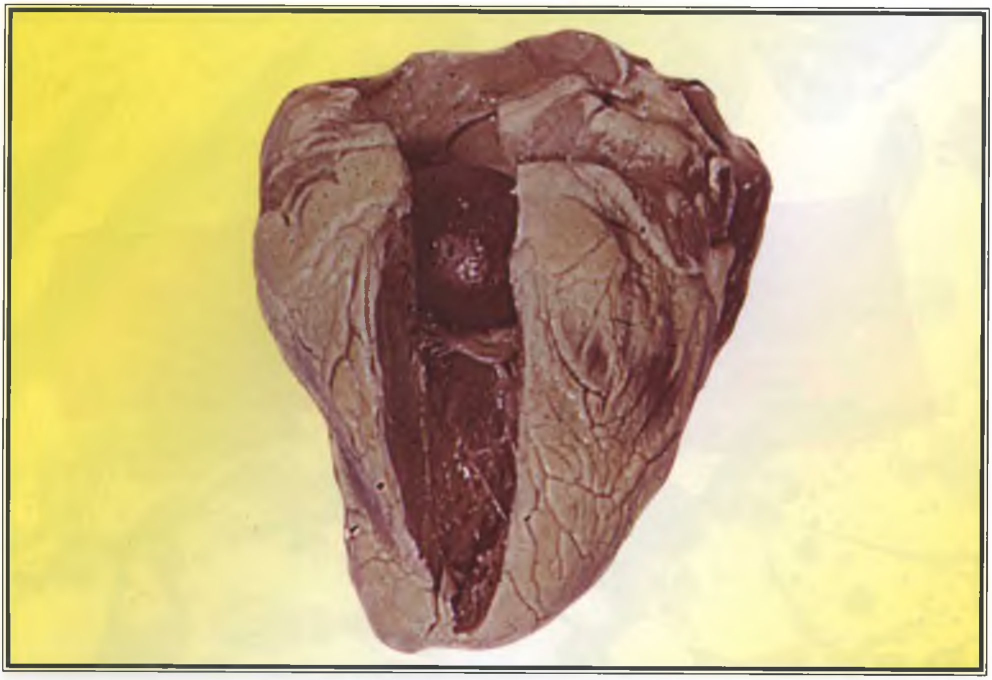


Fig. 87. Spherical thrombus in the left atrium in the stenosis of the left atrioventricular orifice.

Fig. 88. Chronic cardiac aneurysm with thrombosis.

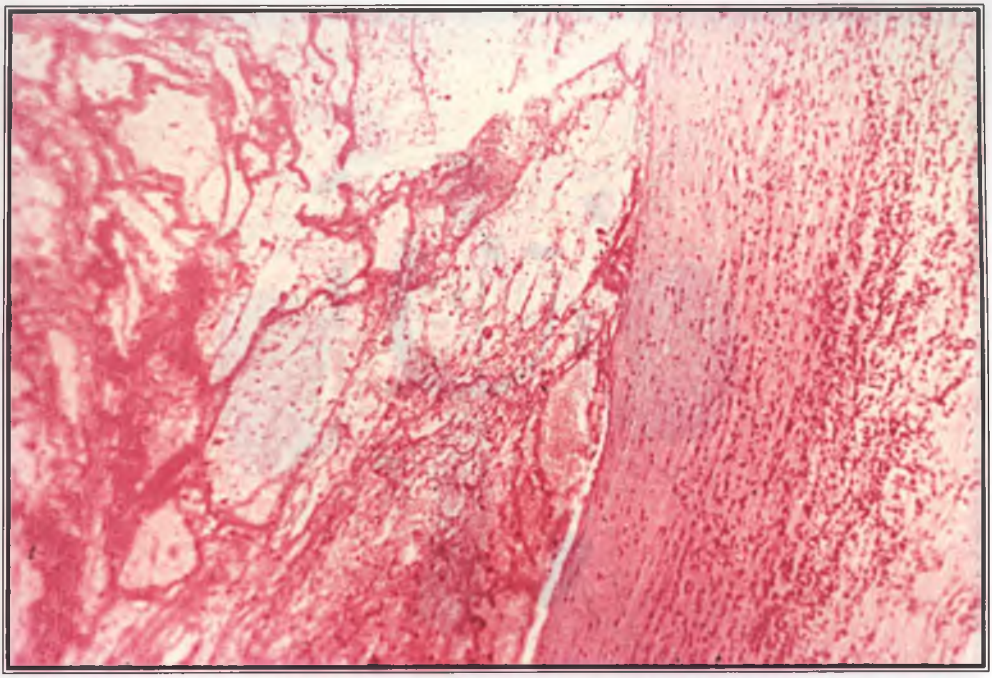


Fig. 89. Recent mixed vascular thrombus (H.E. stain, × 70).

Fig. 90. Thrombus in course of organization (H.E. stain, × 70).

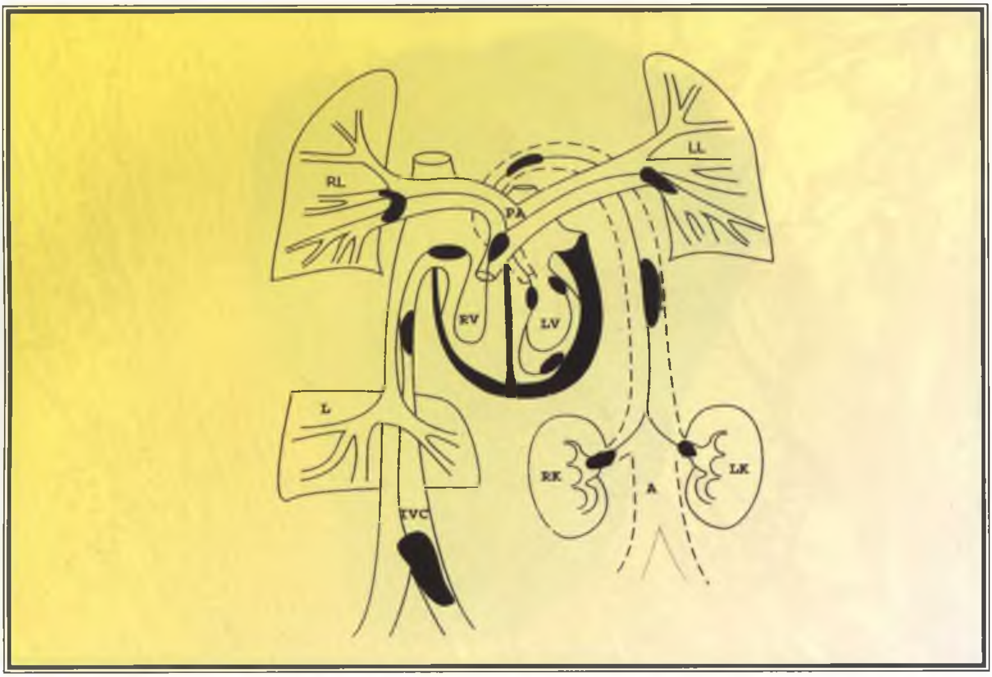


Fig. 91. Direct (ortograde) embolism scheme (PS – left lung, PD – right lung, AP – pulmonary artery, VS – left ventricle, VD – right ventricle, F – liver, VCI – inferior vena cava, RS – left kidney, RD – right kidney, A - aorta).

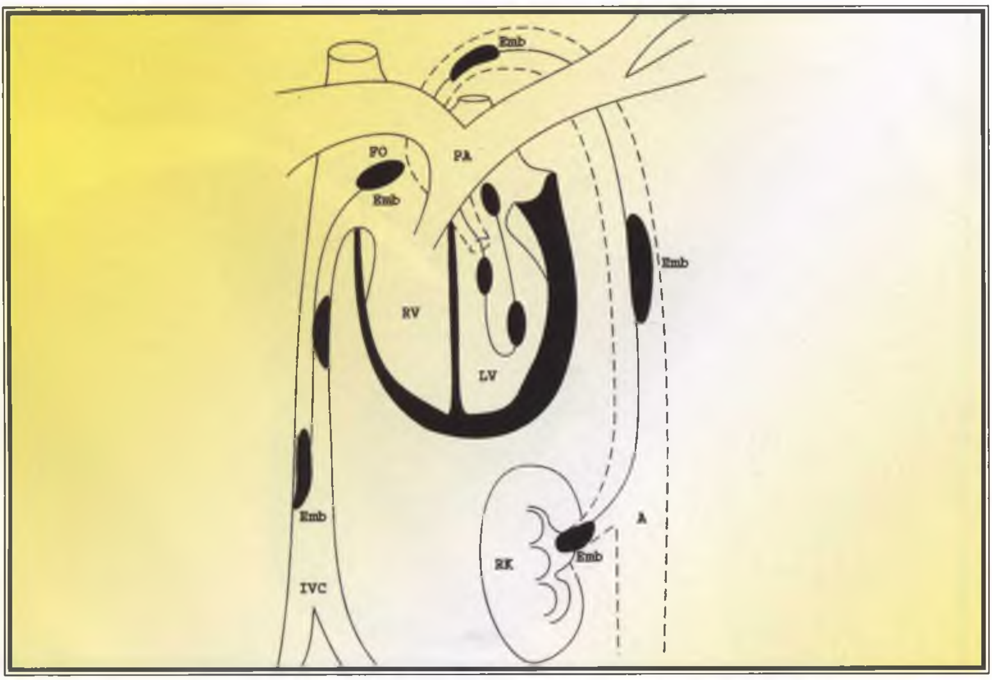


Fig. 92. Paradoxal embolism scheme (GO - foramen ovale, AP - pulmonary artery, Emb – embolus, VS – left ventricle, VD – right ventricle, VCI – inferior vena cava, RD – right kidney, A - aorta).

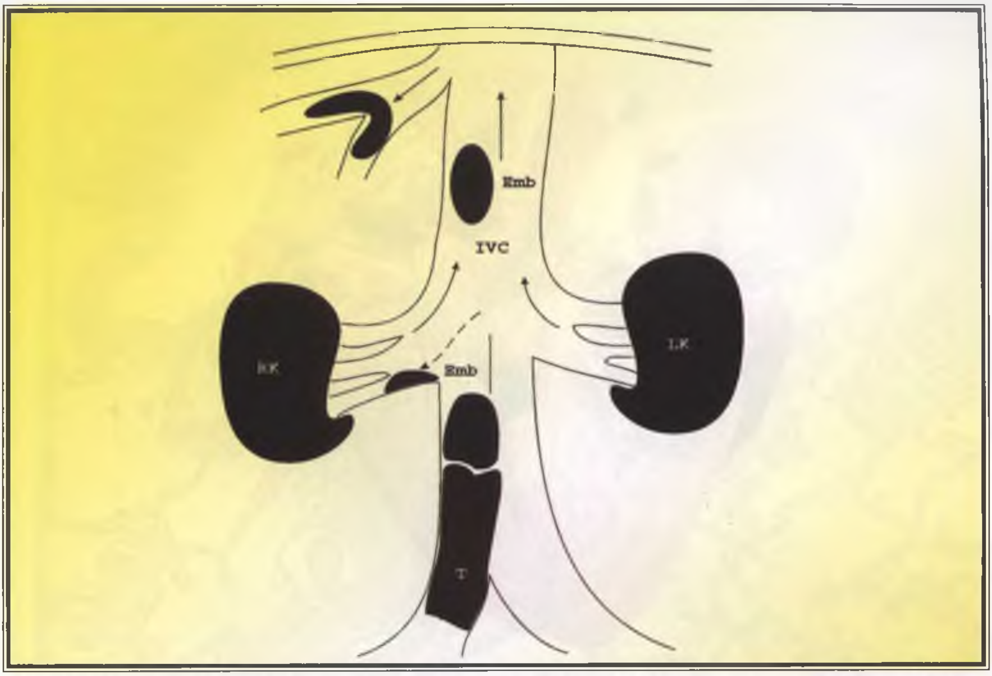


Fig. 93. Retrograde embolism scheme (T – thrombus, VCI – inferior vena cava, Emb – embolus, RD – right kidney, RS – left kidney).


Fig. 94. Thromboembolism of the pulmonary artery.

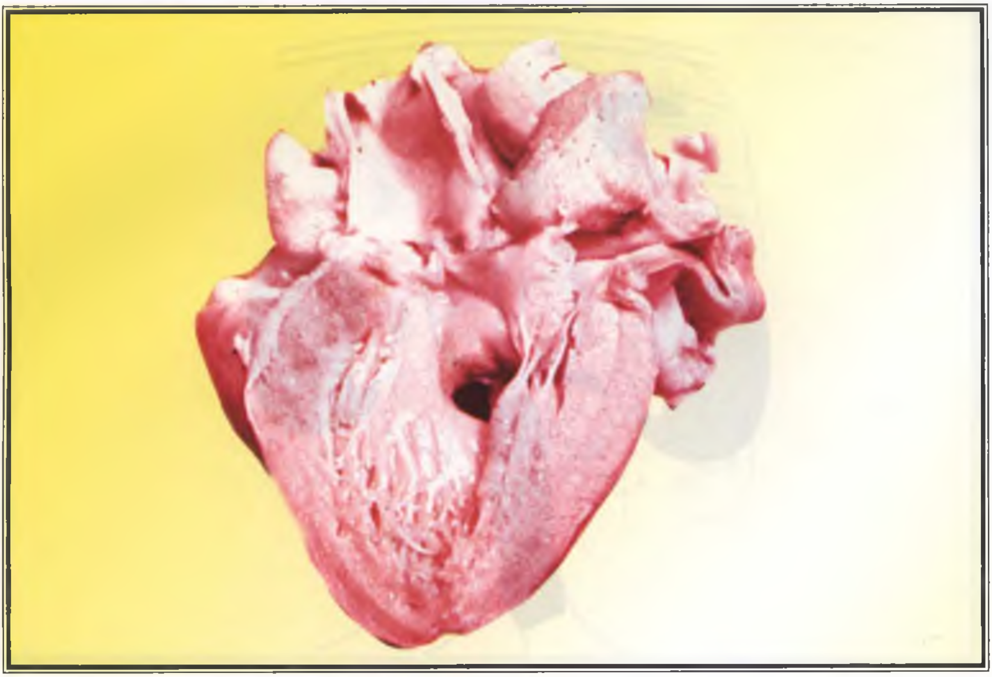


Fig. 95. Congenital cardiac abnormality: interventricular septum defect.

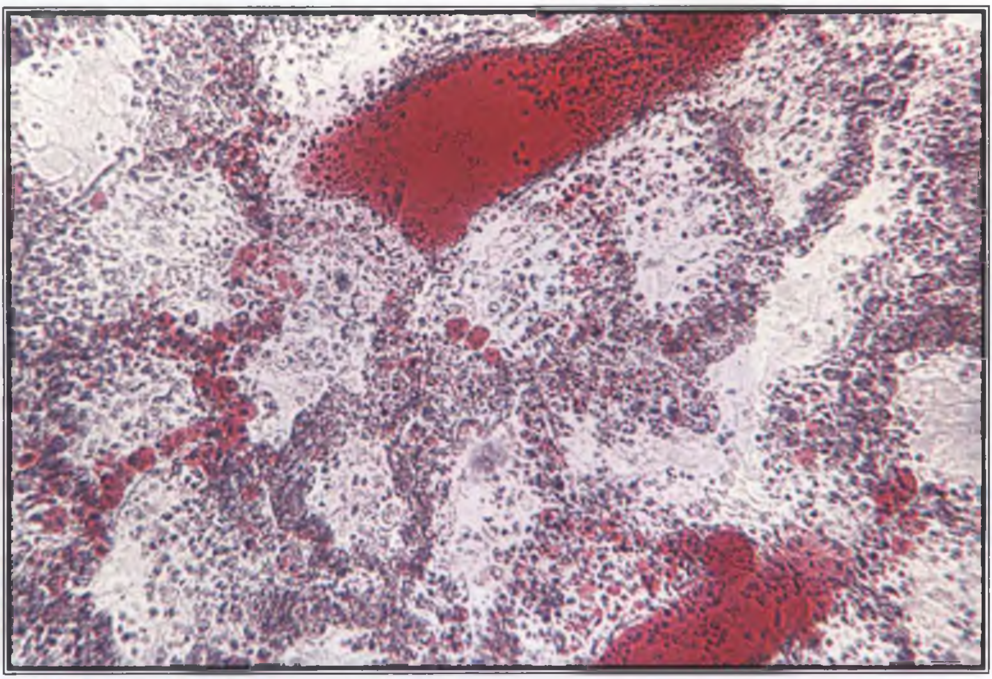


Fig. 96. Fat embolism of the pulmonary blood vessels (H.E. stain, × 70).

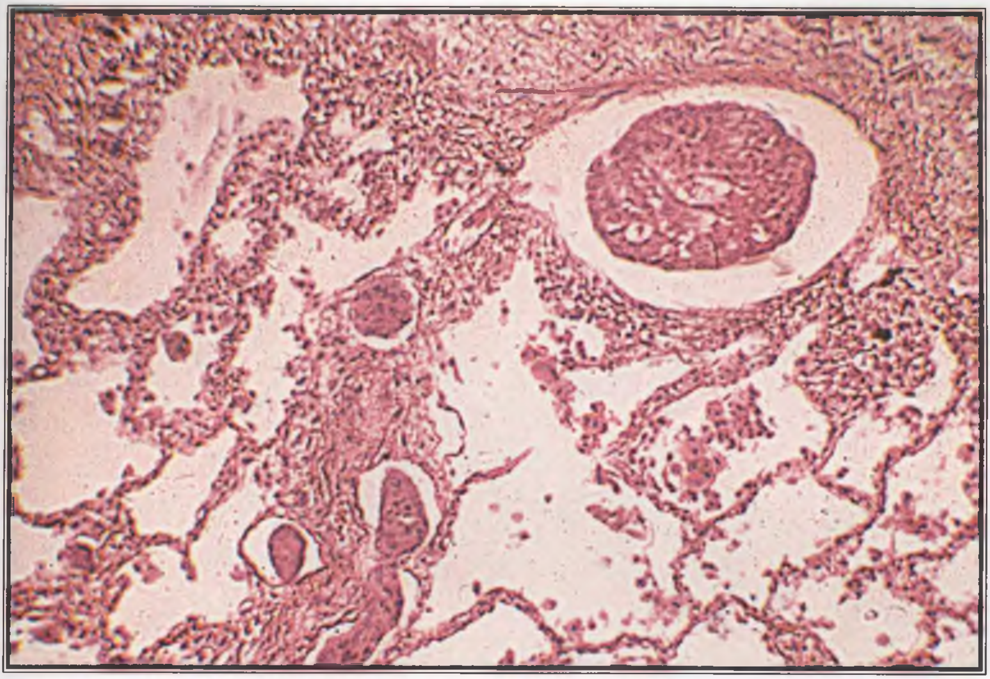


Fig. 97. Carcinomatous embolism of the pulmonary lymphatic vessels (H.E. stain, × 70).

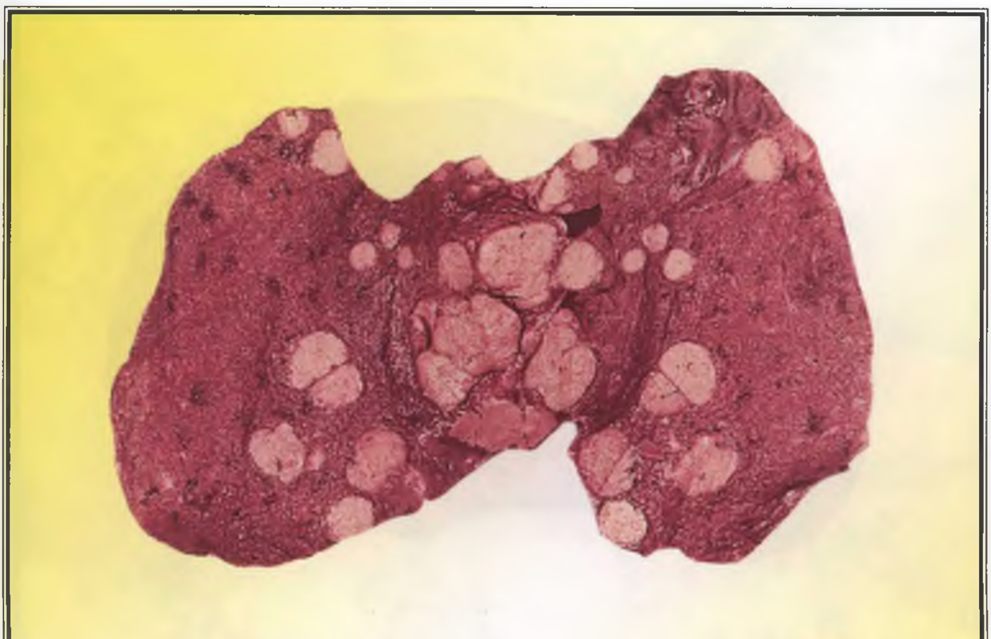


Fig. 98. Carcinoma metastasis in lungs.

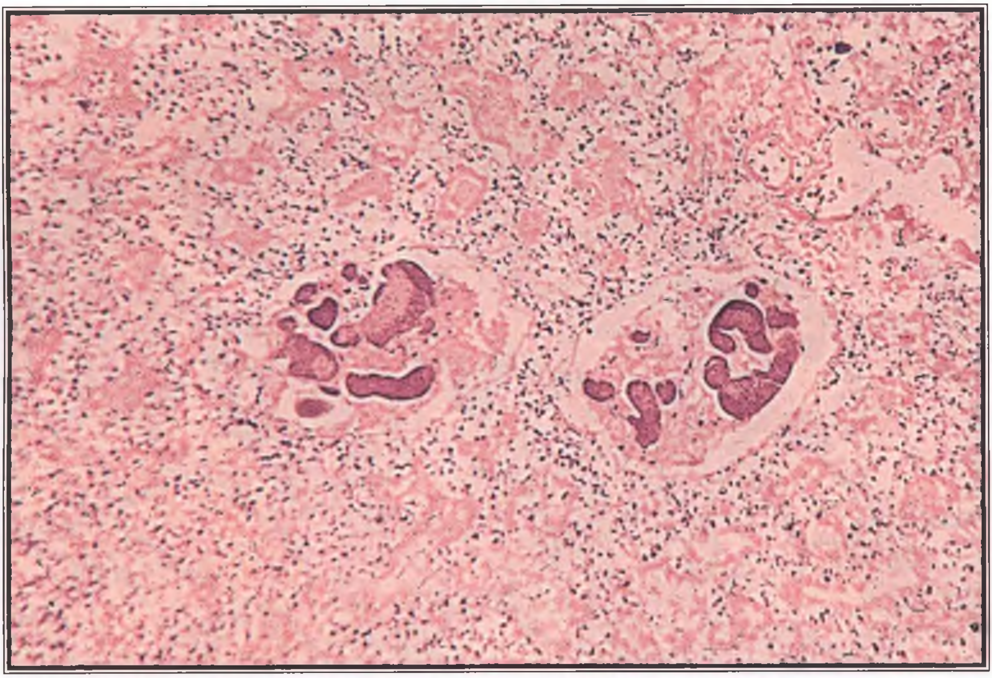


Fig. 99. Bacterial embolism of the glomerular capillaries (H.E. stain, × 70).

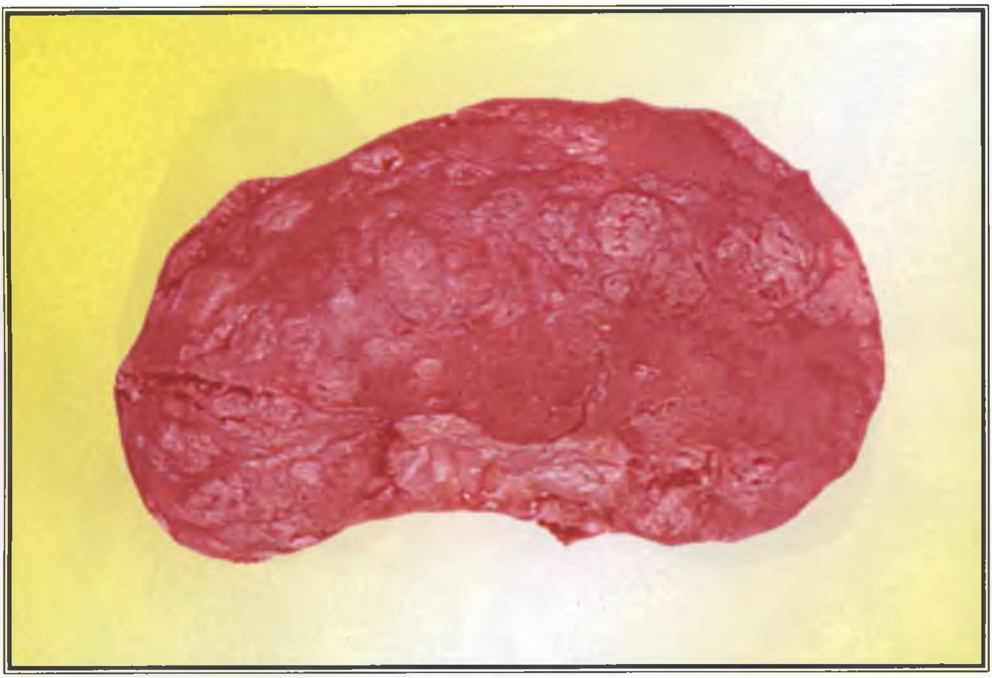


Fig. 100. Purulent embolic nephritis (metastatic abscesses in kidneys).

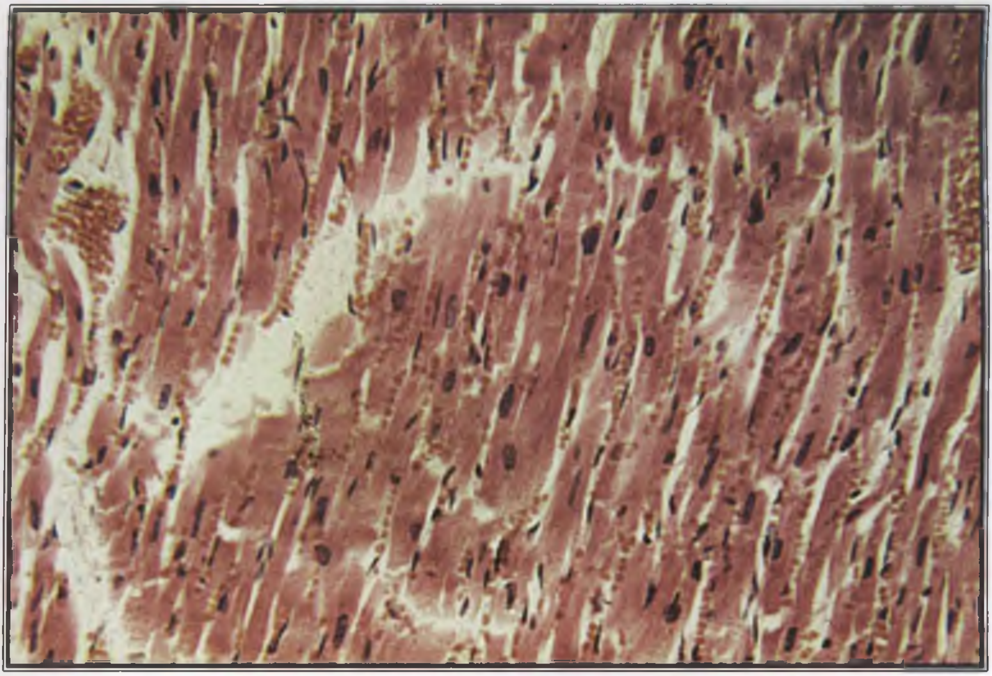


Fig. 101. Stasis in the myocardial capillaries (H.E. stain, × 70).

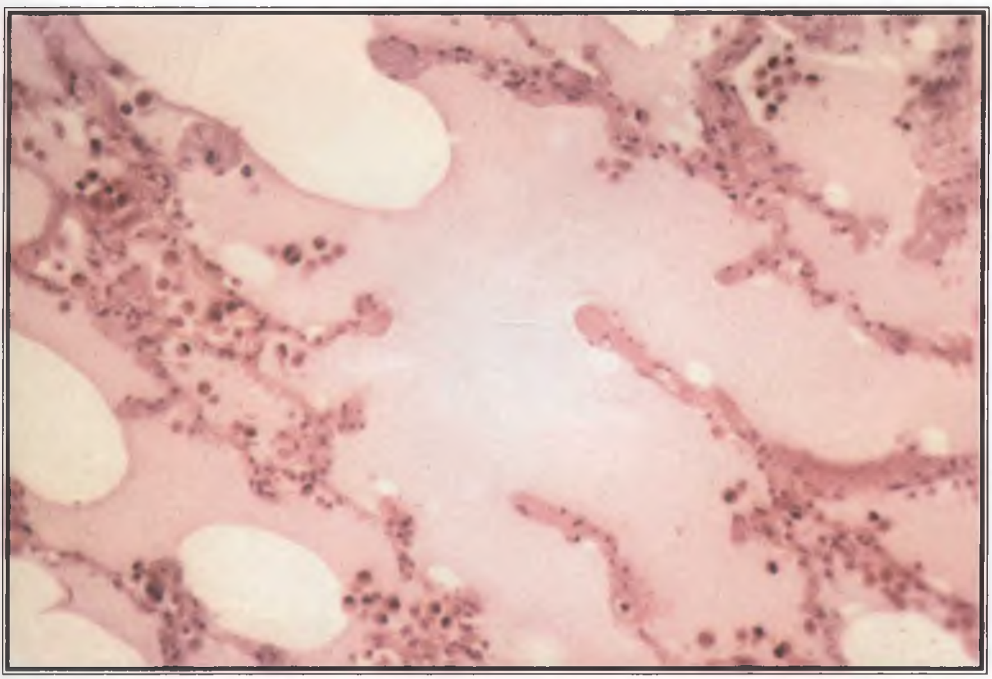


Fig. 102. Pulmonary edema (H.E. stain, × 70).

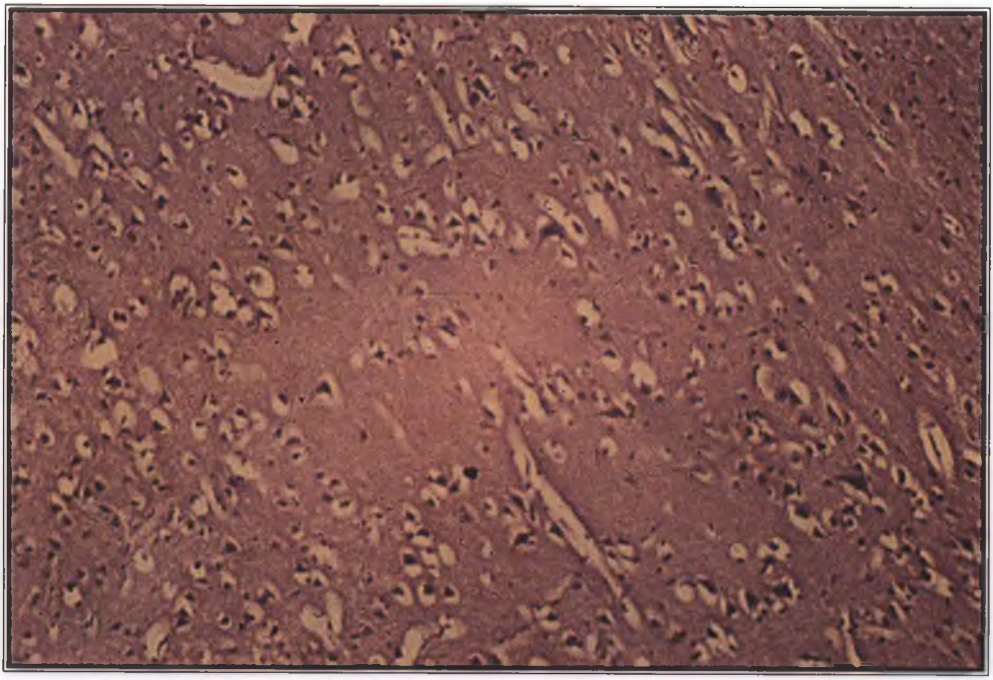


Fig. 103. Cerebral edema (H.E. stain, × 70).

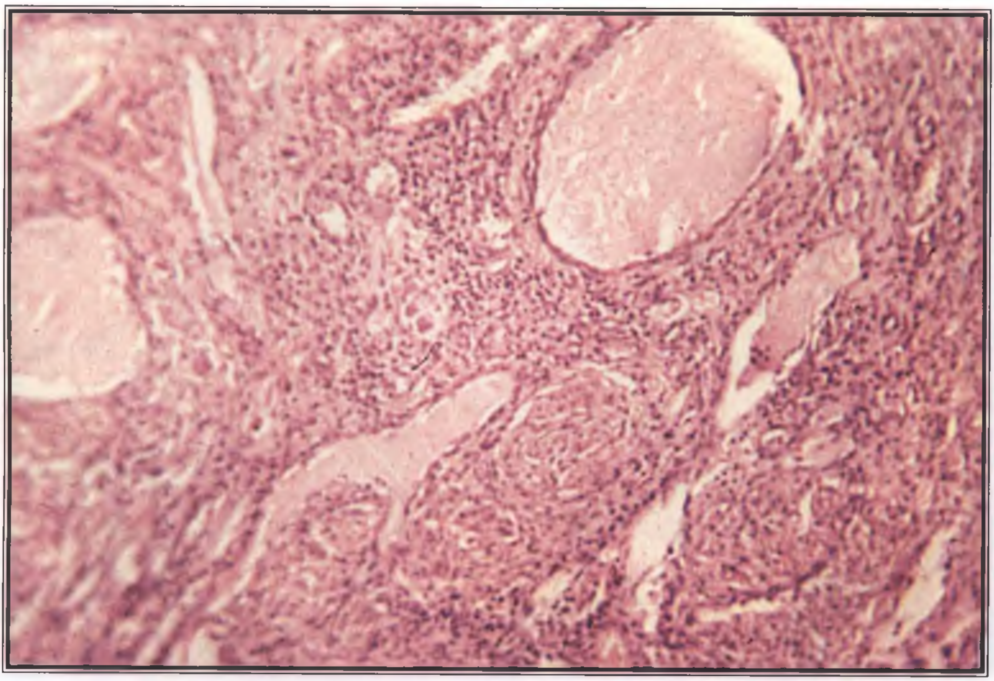


Fig. 104. Lymph stasis in the small intestine wall (H.E. stain, × 70).

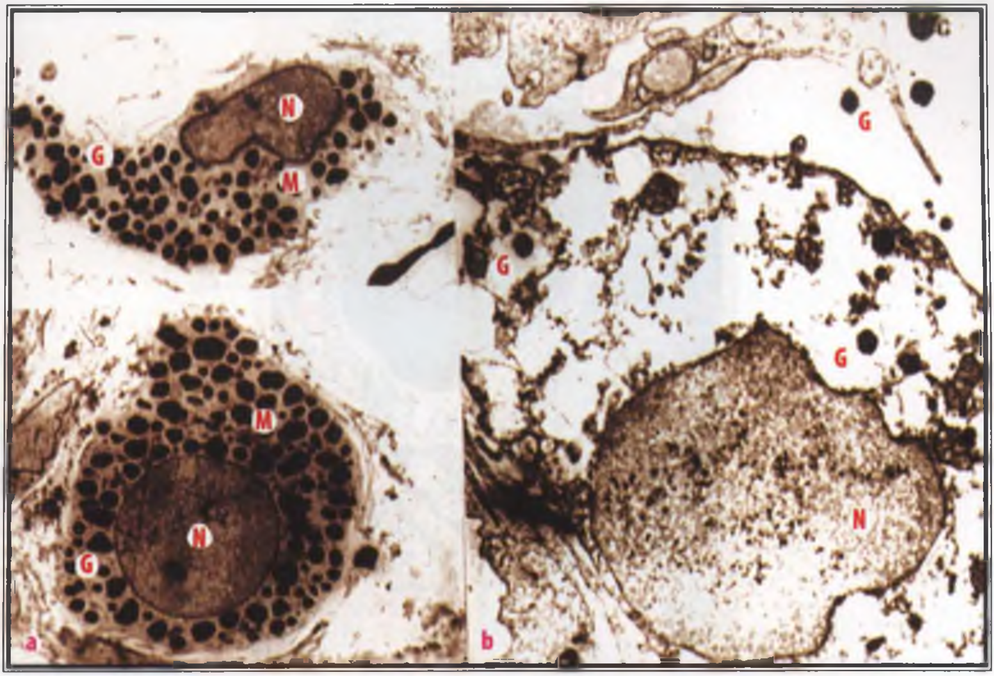


Fig. 105. Degranulation of labrocytes (electron microscopy): a - normal ultrastructure of the labrocyte (× 8000); b- granule expelling from the labrocyte cytoplasm by cellular membrane rupture (× 20000): N- nucleus; M- mitochondria; G- specific granules of the labrocytes.

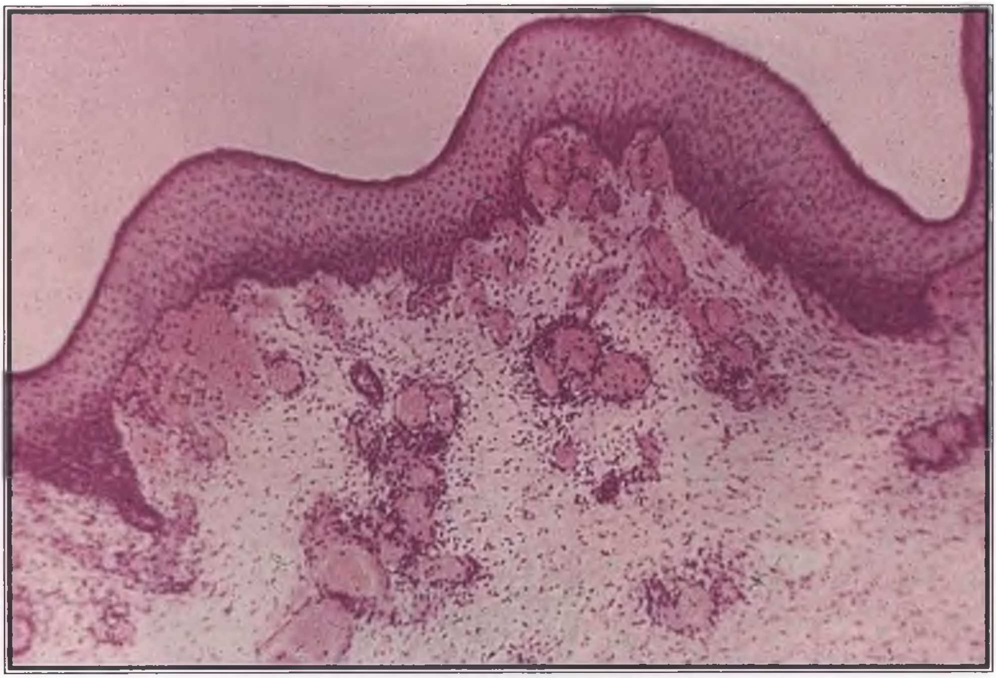


Fig. 106. Inflammatory hyperemia of the skin in phlegmon (H.E. stain, × 70).

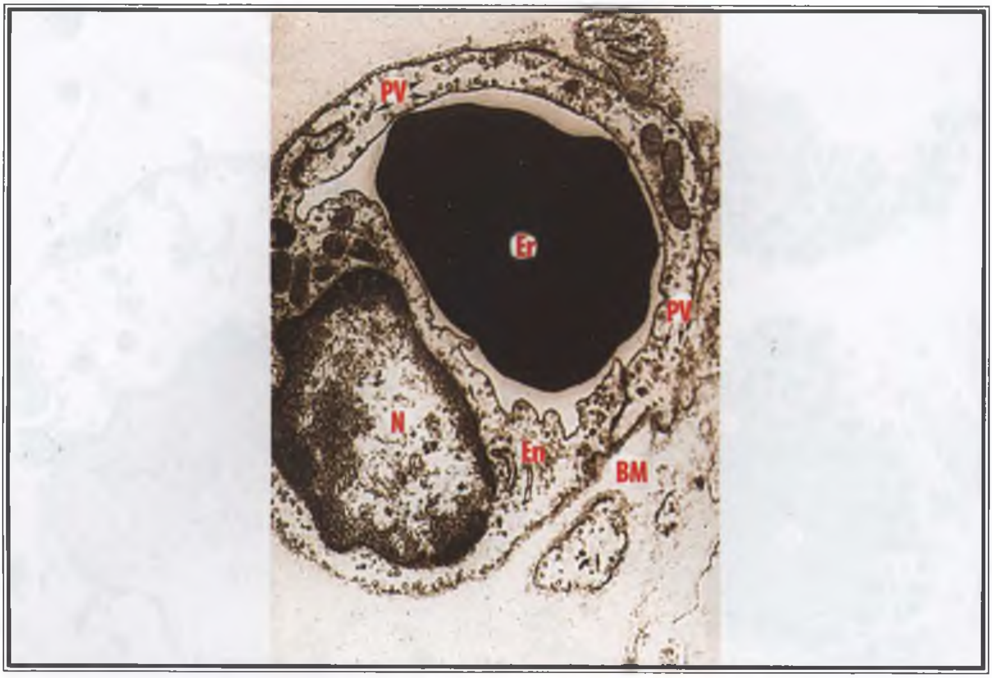


Fig. 107. Pinocytosis in the capillary endothelium (electron microscopy, × 11000): N- nucleus; Er- erythrocyte; En- endothelium; BM- basal membrane; PV- pinocytic vesicles..

Fig. 108. Neutrophil leukocyte migration in inflammation (electron microscopy, × 20000; NL - neutrophil leukocytes; En - endothelium; J - junctions between the endothelial cells; CL - capillary's lumen; N - nucleus of the leukocyte; BM - basale membrane; CF - collagen fibers

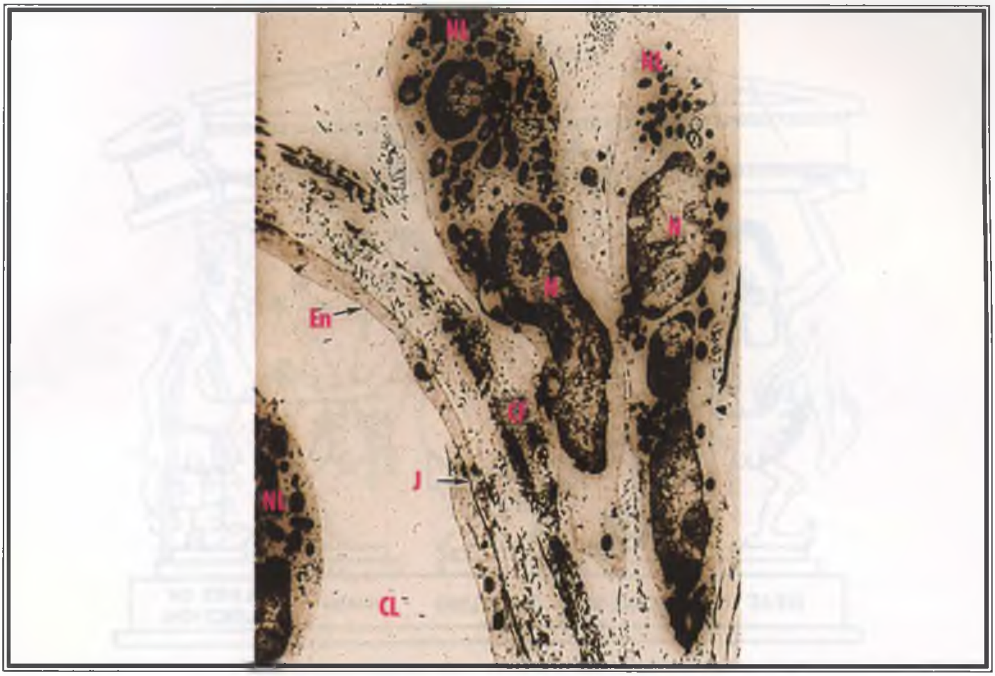


Fig. 109. Emigration of neutrophil leukocyte in the perivascular space (electron microscopy, × 12000): NL – neutrophil leukocytes; En – endothelium; J - junctions between the endothelial cells; CL - capillary's lumen; N - nucleus of the leukocyte; CF - collagen fibers.

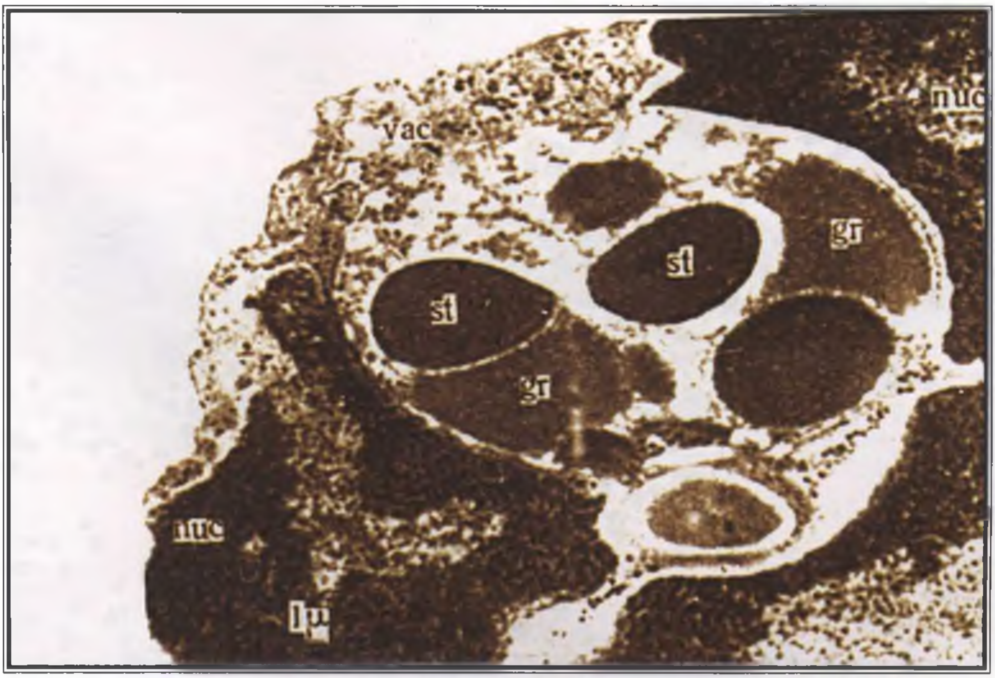


Fig. 110. Phagocytosis (electron microscopy, × 15000): nuc- nucleus; vac- digestion vacuole; gr- cytoplasmic granulations, which contain hydrolytic enzymes; st- staphylococcus).

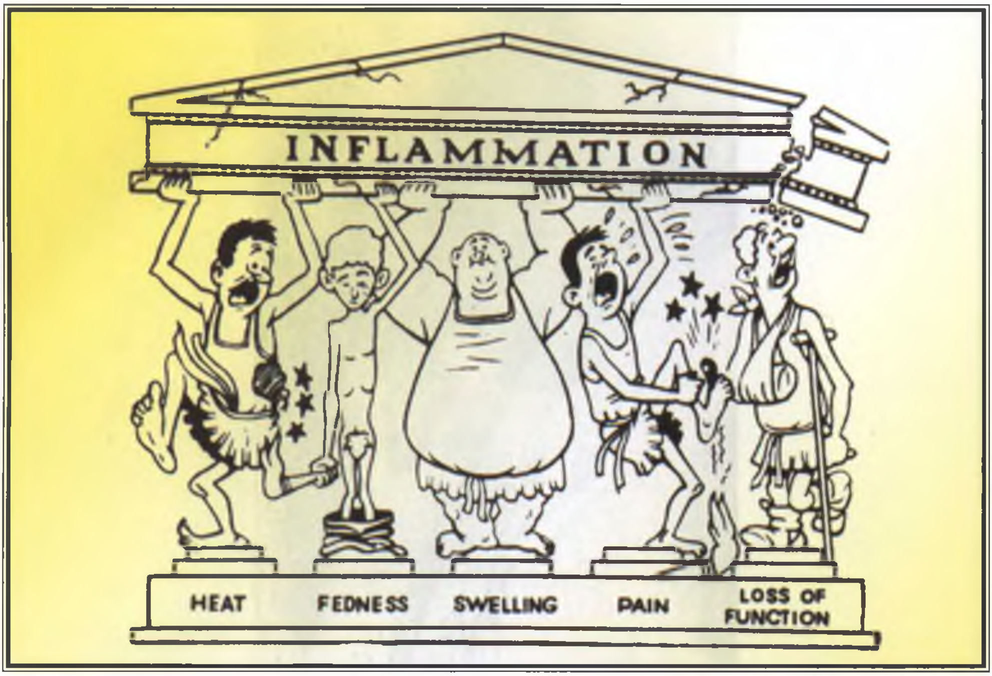


Fig. 111. Clinical signs of inflammation (heat, redness, swelling, pain, loss of function) (after D.A. Willoughby and W.G. Spector, 1968).

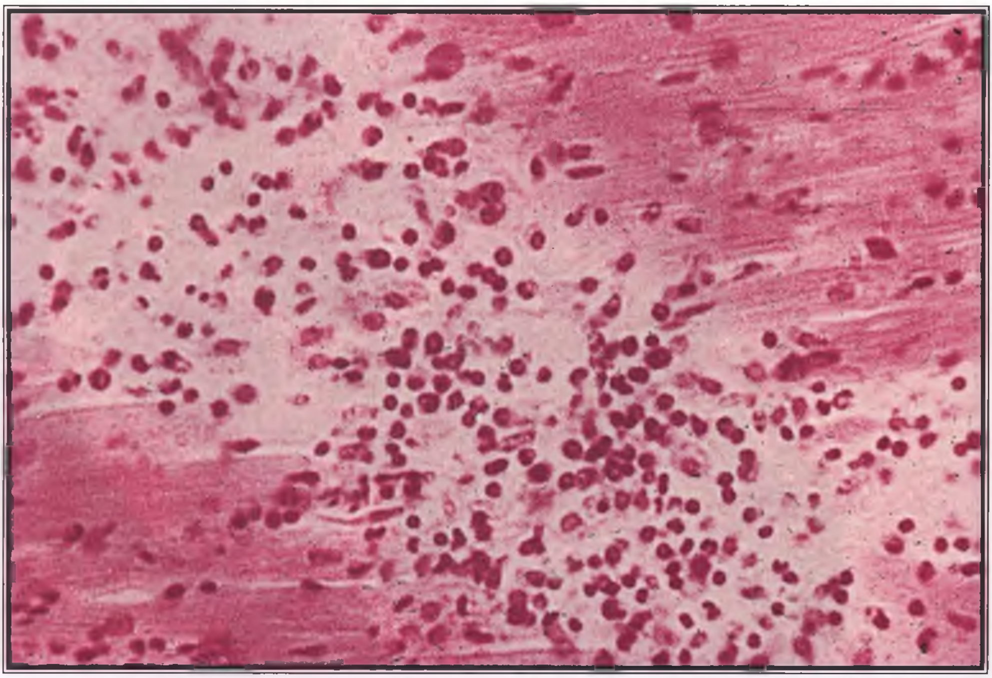


Fig. 112. Cellular infiltrate in the inflammatory site (interstitial productive myocarditis) (H.E. stain, × 70).

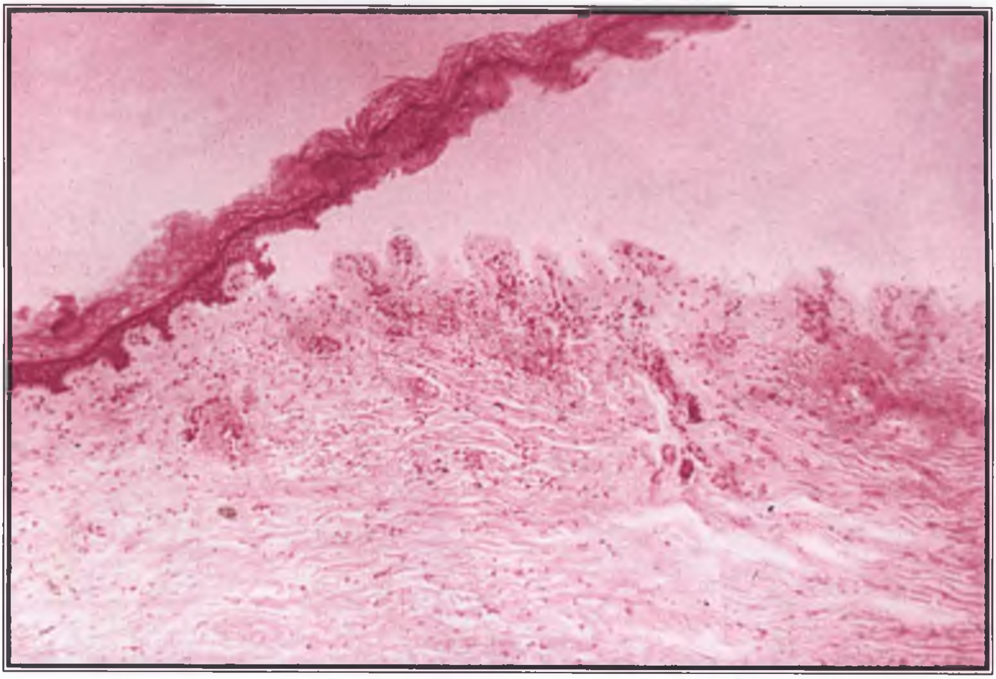


Fig. 113. Epidermal vesicle containing serous exudate (H.E. stain, × 70).

Fig. 114. Bullous dermatitis.

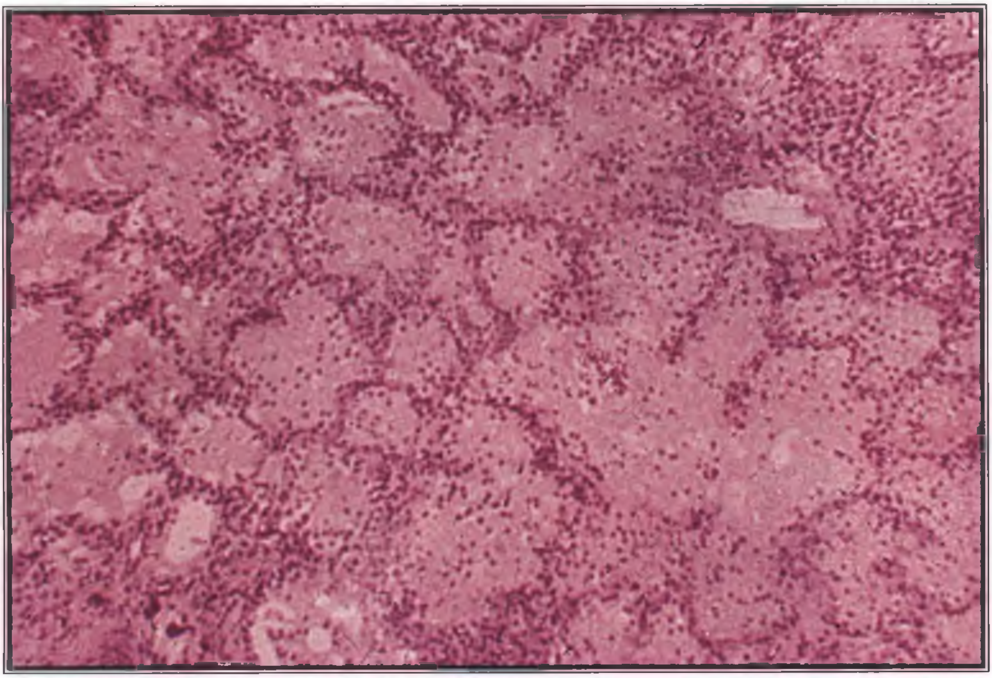


Fig. 115. Serous focal pneumonia (H.E. stain, × 70).

Fig. 116. Croupous tracheitis in diphtheria (diphtheric croup).

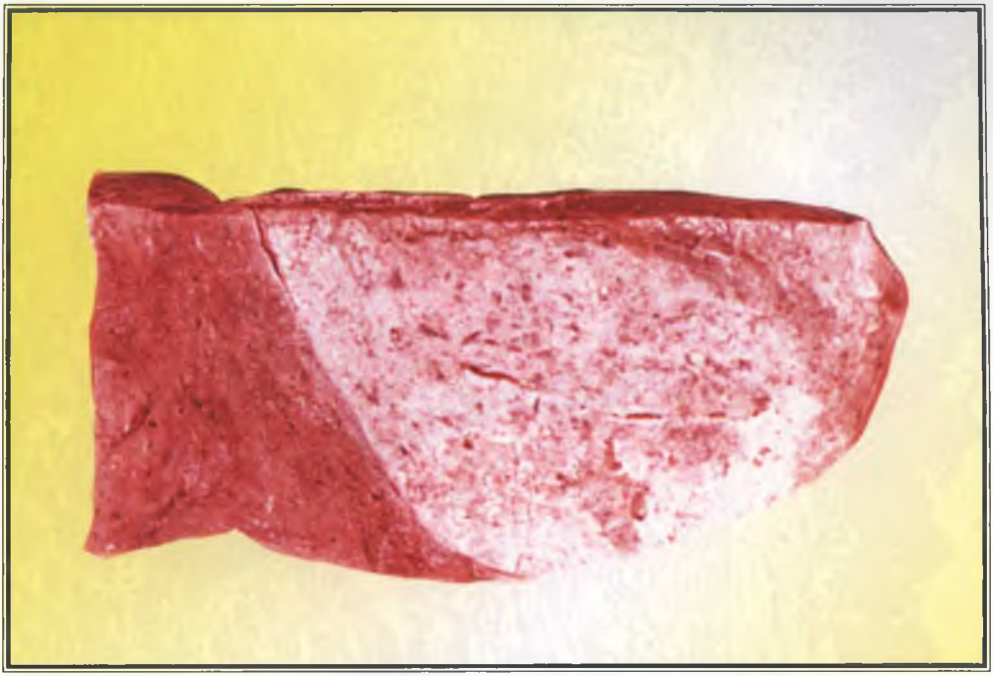


Fig. 117. Pneumococcal lobar pneumonia (stage of gray hepatization).

Fig. 118. Fibrinous pericarditis (villous heart).

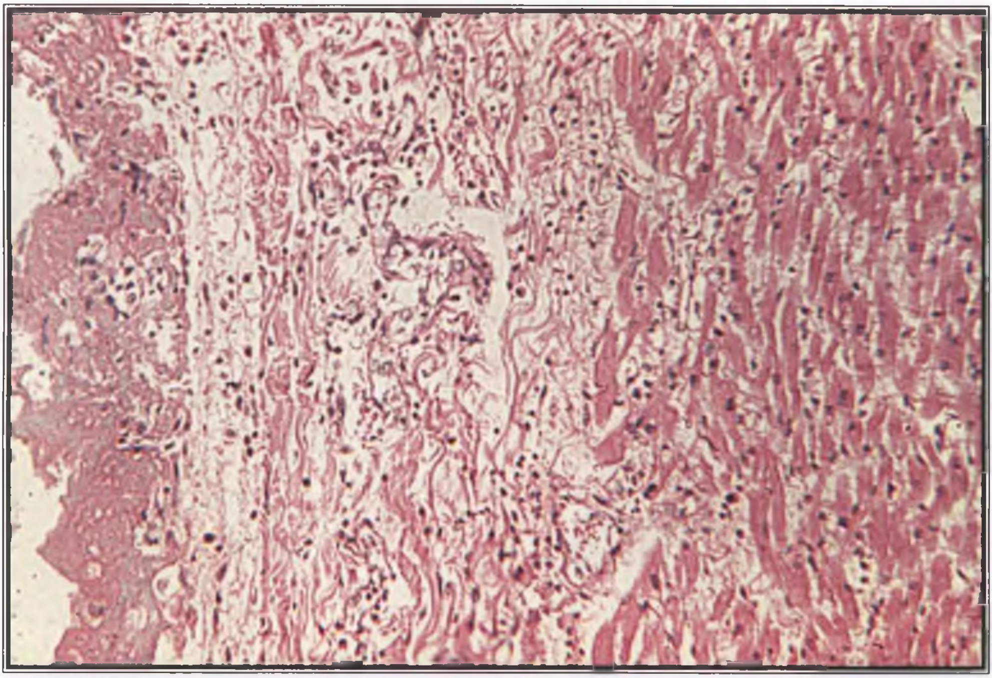


Fig. 119. Fibrinous pericarditis (H.E. stain, × 70).

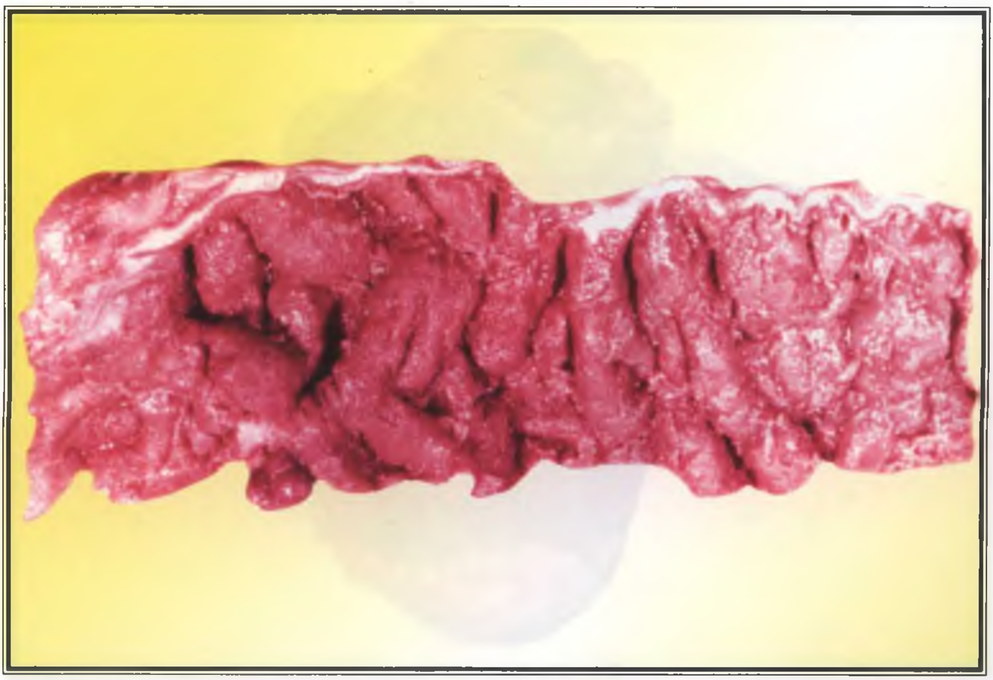


Fig. 120. Diphtheroid fibrinous colitis.

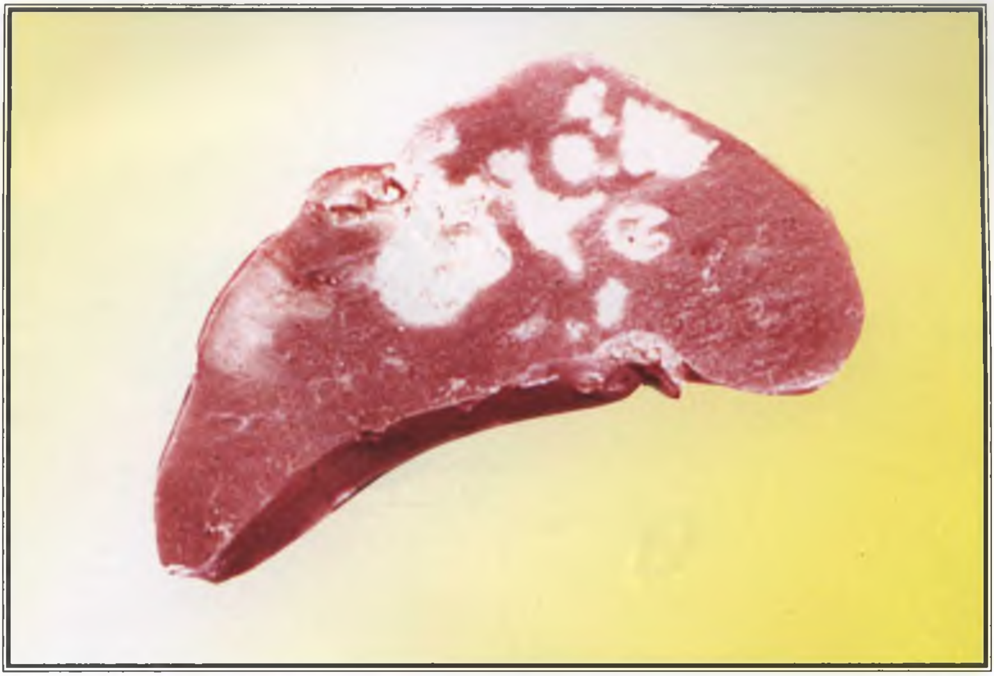


Fig. 121. Hepatic abscesses.

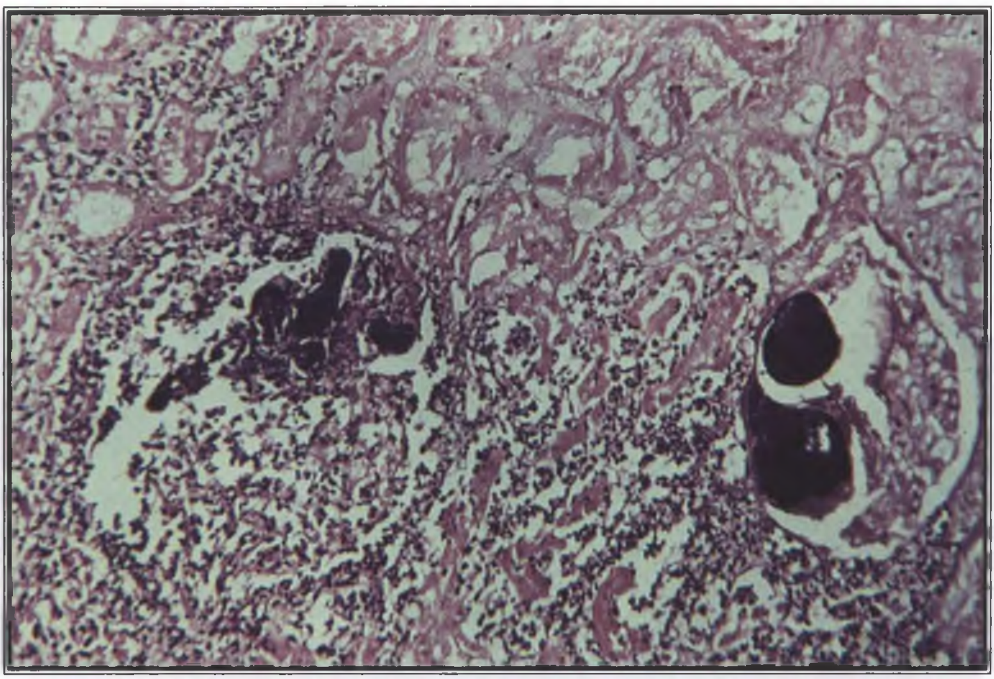


Fig. 122. Metastatic abscesses in kidneys (H.E. stain, × 70).

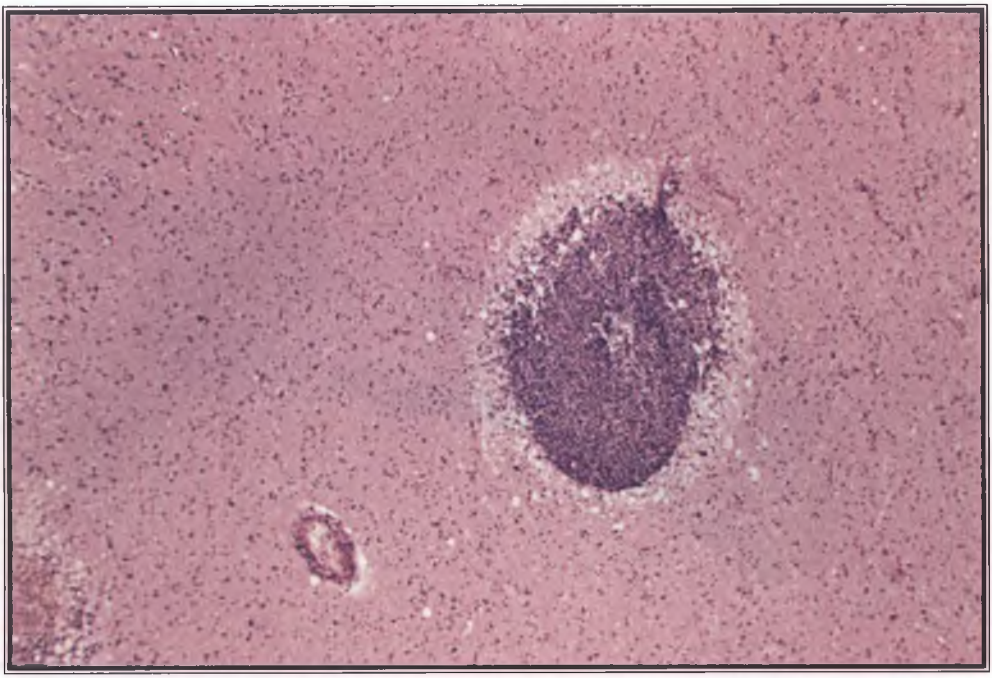


Fig. 123. Acute cerebral abscess (H.E. stain, × 70).

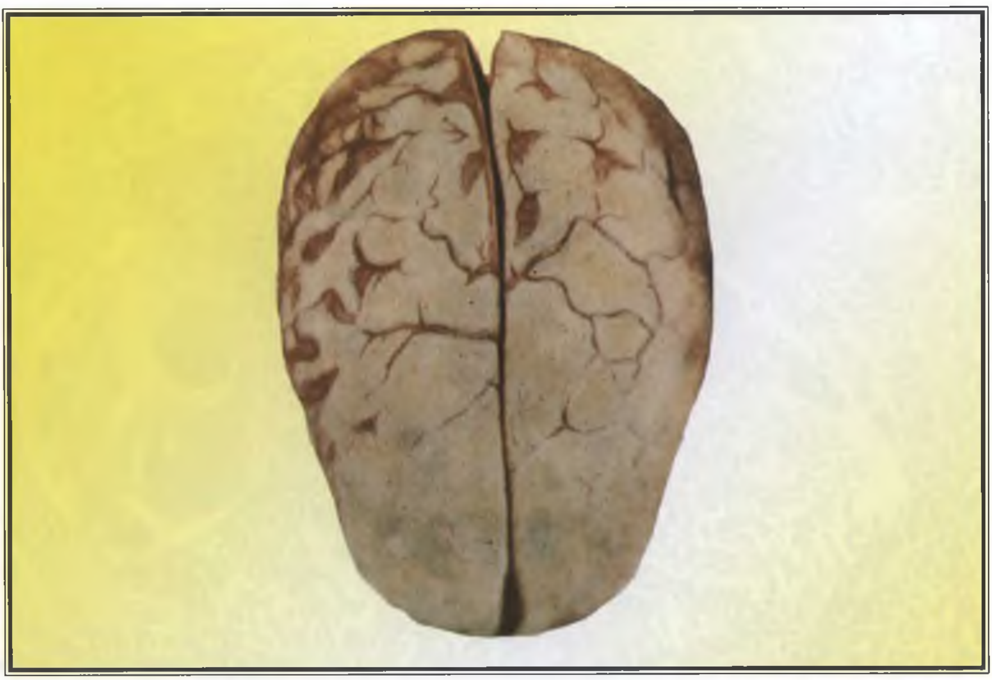


Fig. 124. Purulent leptomeningitis.

Fig. 125. Acute phlegmonous appendicitis.

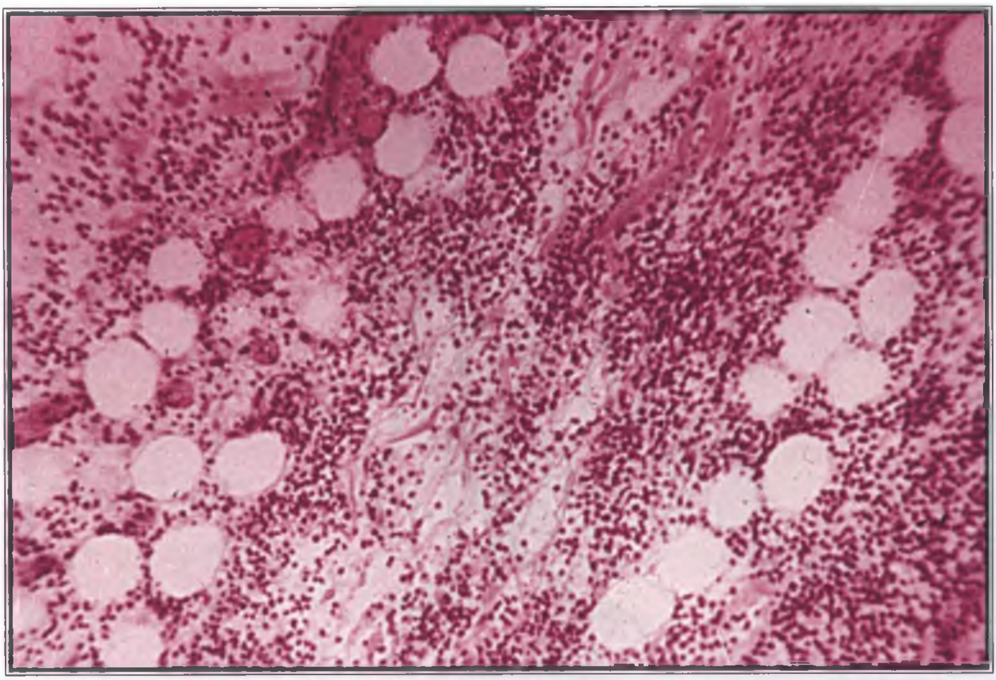


Fig. 126. Phlegmonous inflammation of the cellular adipose tissue (phlegmonous cellulitis) (H.E. stain, × 110).

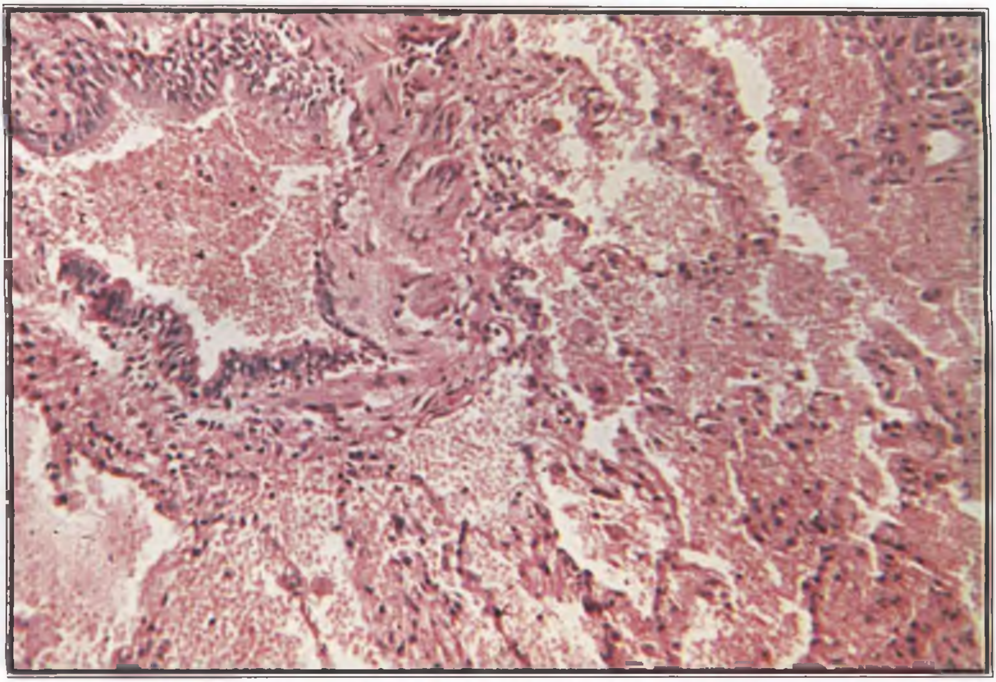


Fig. 127. Influenzal hemorrhagic bronchopneumonia (H.E. stain, × 70).

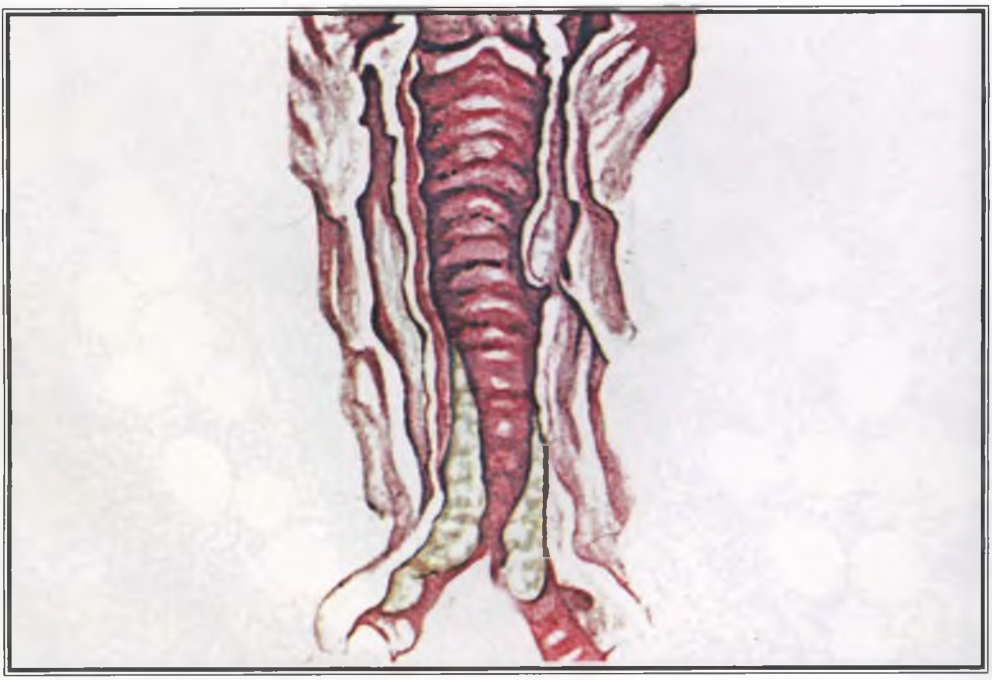


Fig. 128. Catarrhal tracheitis.

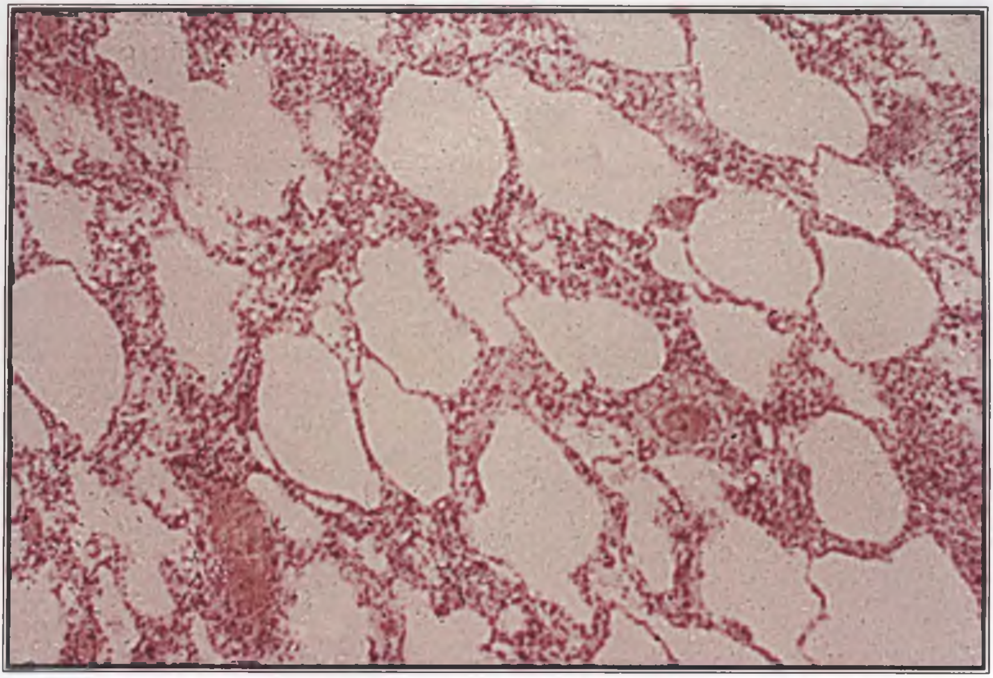


Fig. 129. Interstitial pneumonia (H.E. stain, × 70).

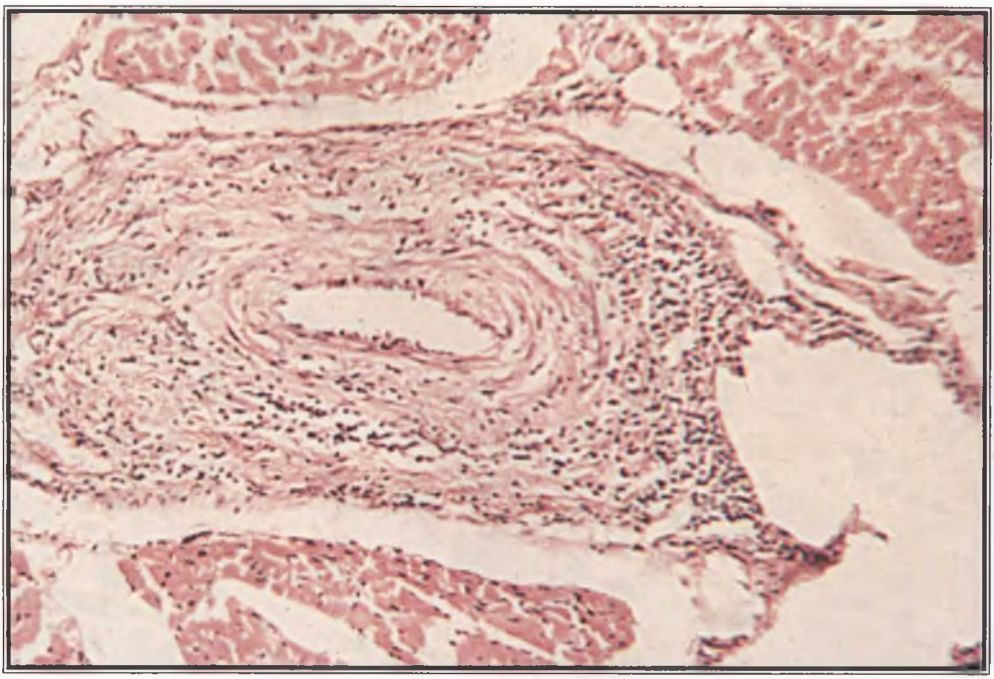


Fig. 130. Productive vasculitis in periarteritis nodosa (H.E. stain, × 70)..

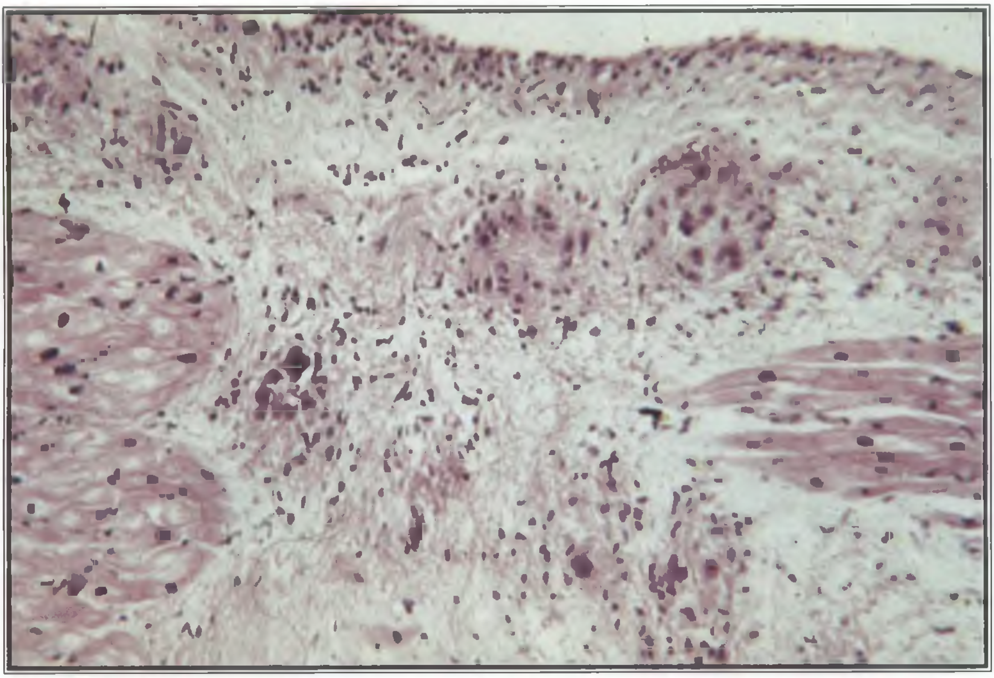


Fig. 131. Granulomatous inflammation of the endo- and myocardium in rheumatism (H.E. stain, × 40).

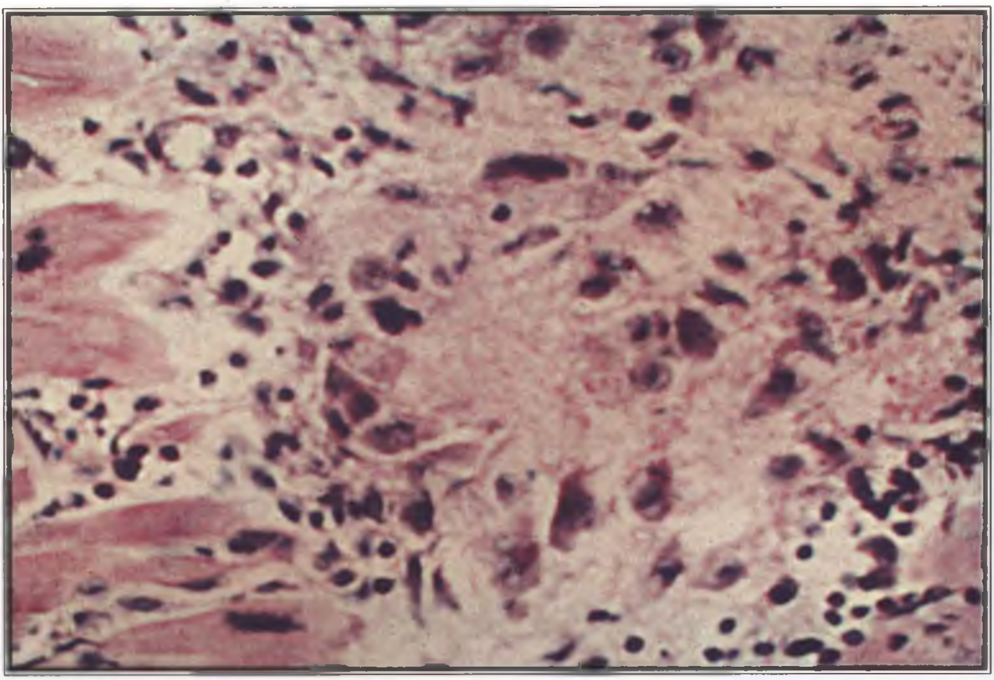


Fig. 132. Rheumatic granuloma (H.E. stain, × 110).

Fig. 133. Granulomatous productive inflammation in hepatic echinococcosis, macroscopic aspect.

Fig. 134. Granulomatous productive inflammation in hepatic echinococcosis, microscopic aspect (H.E. stain, × 70).

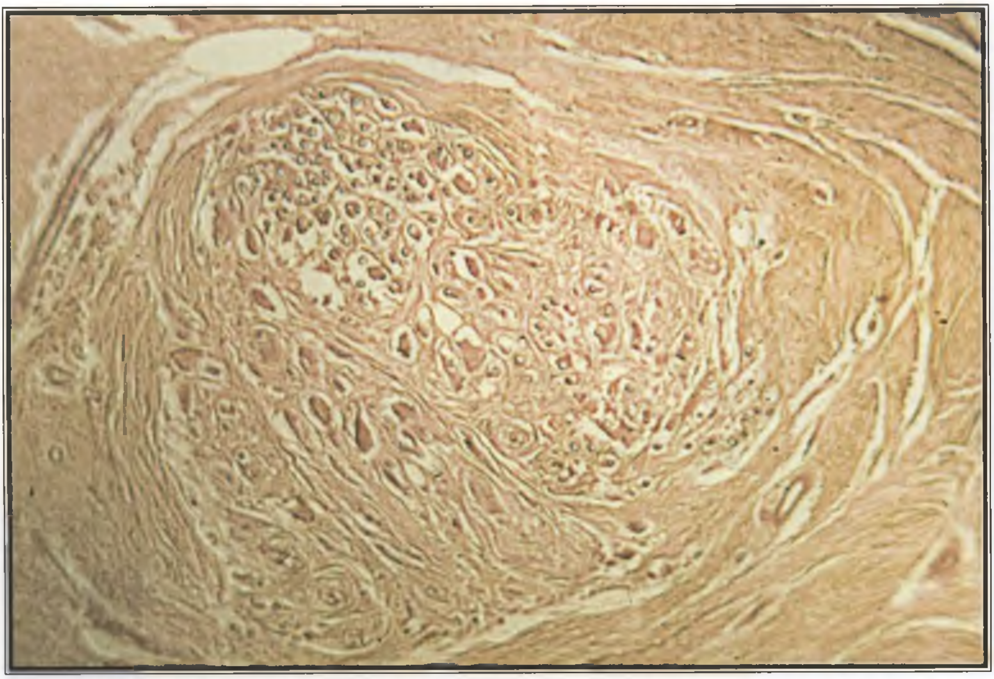


Fig. 135. Foreign body granuloma (suture granuloma) (H.E. stain, × 70).

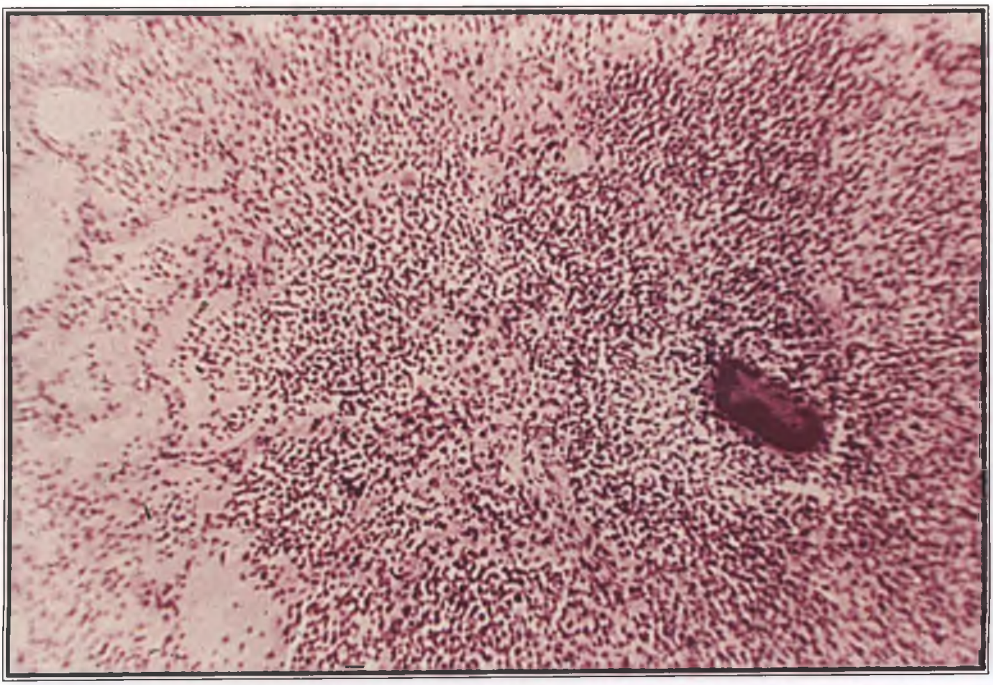


Fig. 136. Actinomycotic granuloma in the lung (H.E. stain, × 70).

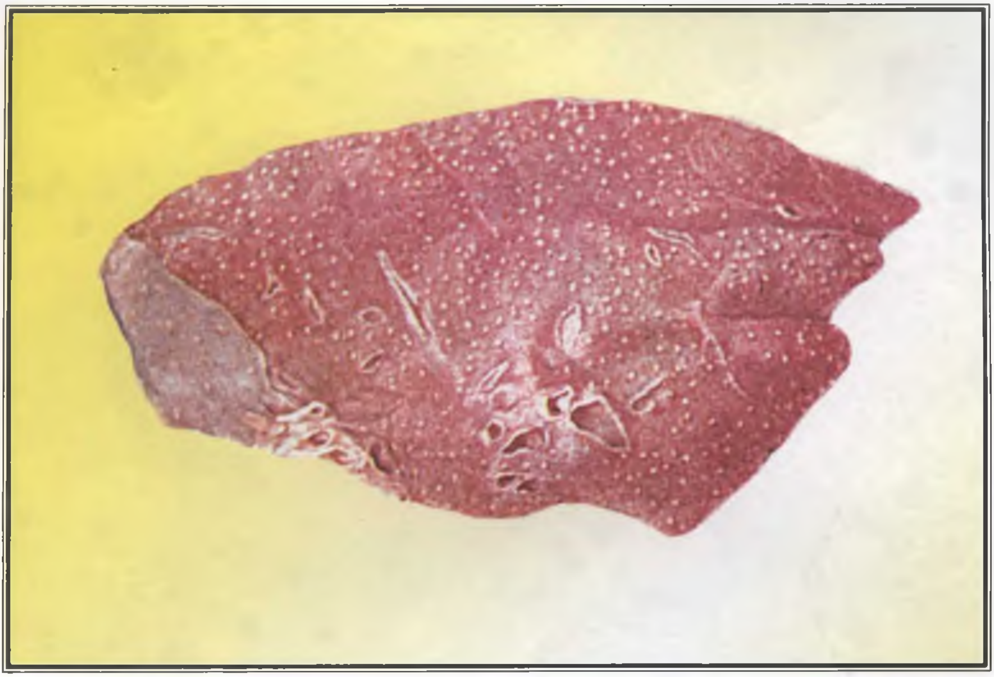


Fig. 137. Miliary pulmonary tuberculosis.

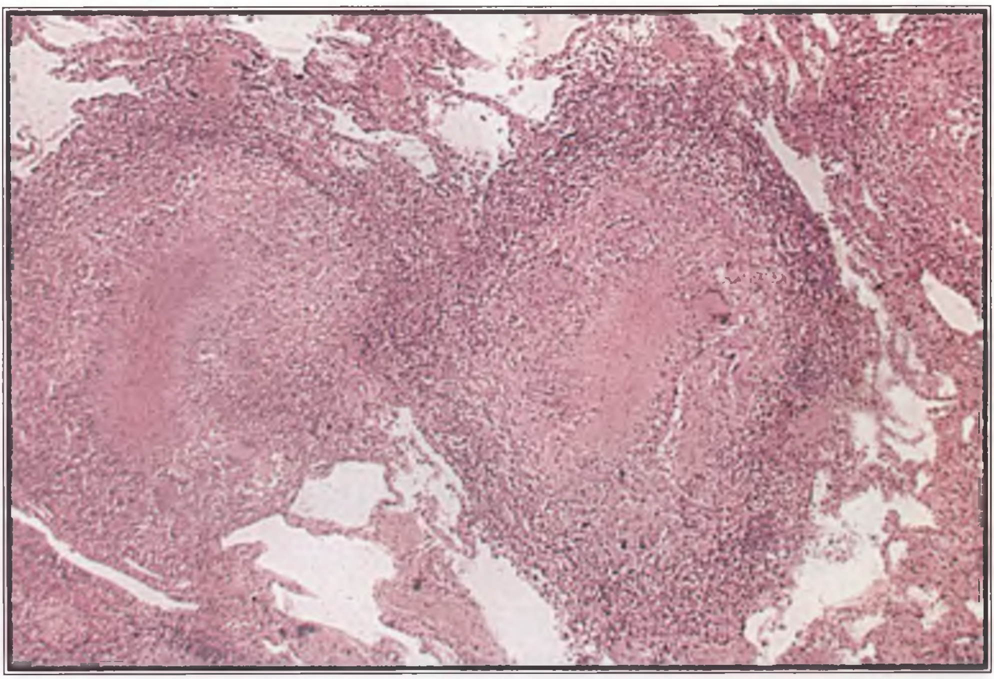


Fig. 138. Tuberculous granuloma in the lung (H.E. stain, × 70)

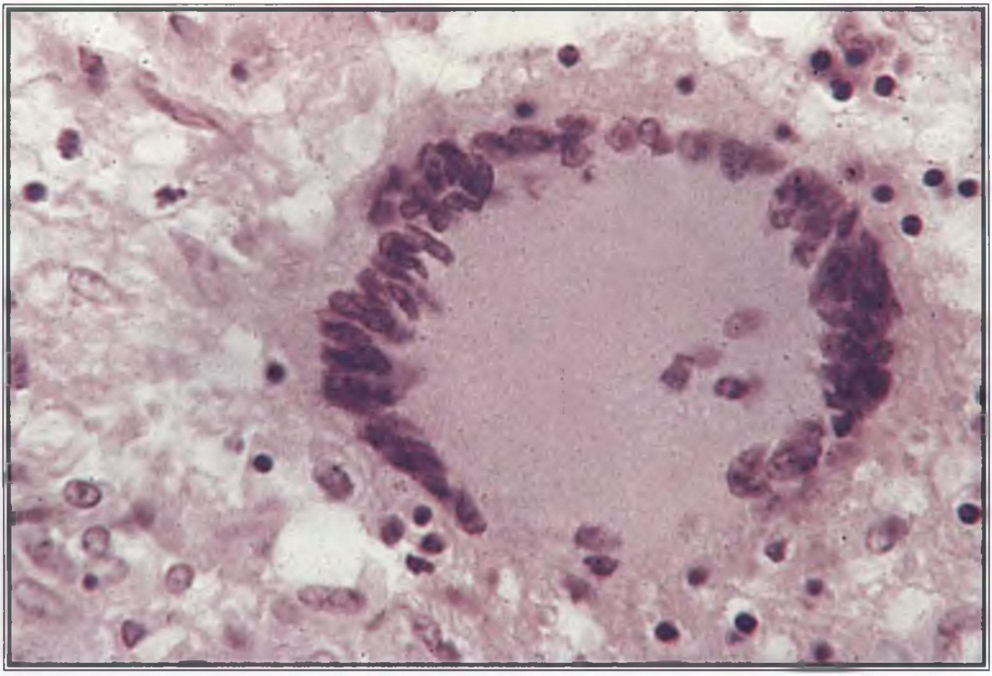


Fig. 139. Langhans giant cell (H.E. stain, × 280).

Fig. 140. Syphilitic gumma in the liver, macroscopic aspect.

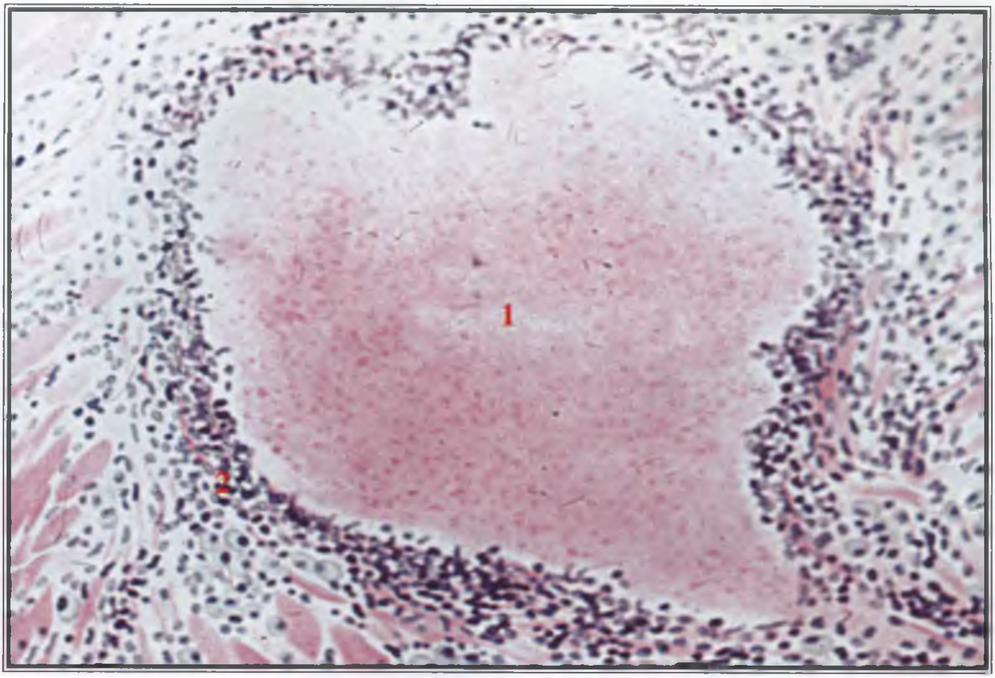


Fig. 141. Syphilitic gumma, microscopic aspect (H.E. stain, × 70): 1- necrotic focus; 2- cellular column.

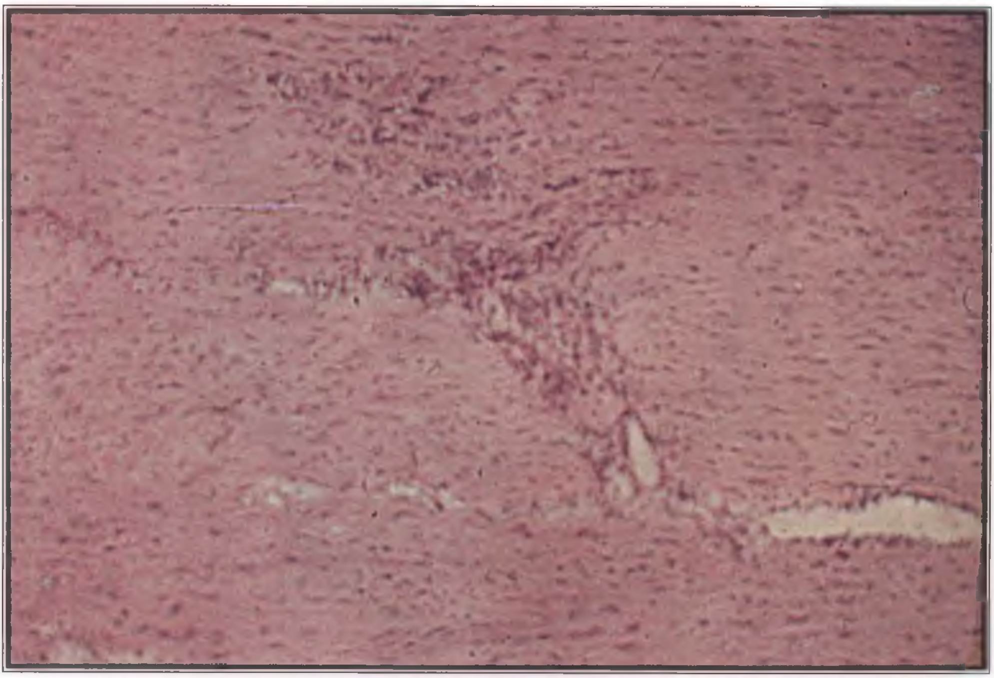


Fig. 142. Syphilitic mesaortitis (H.E. stain, × 70).

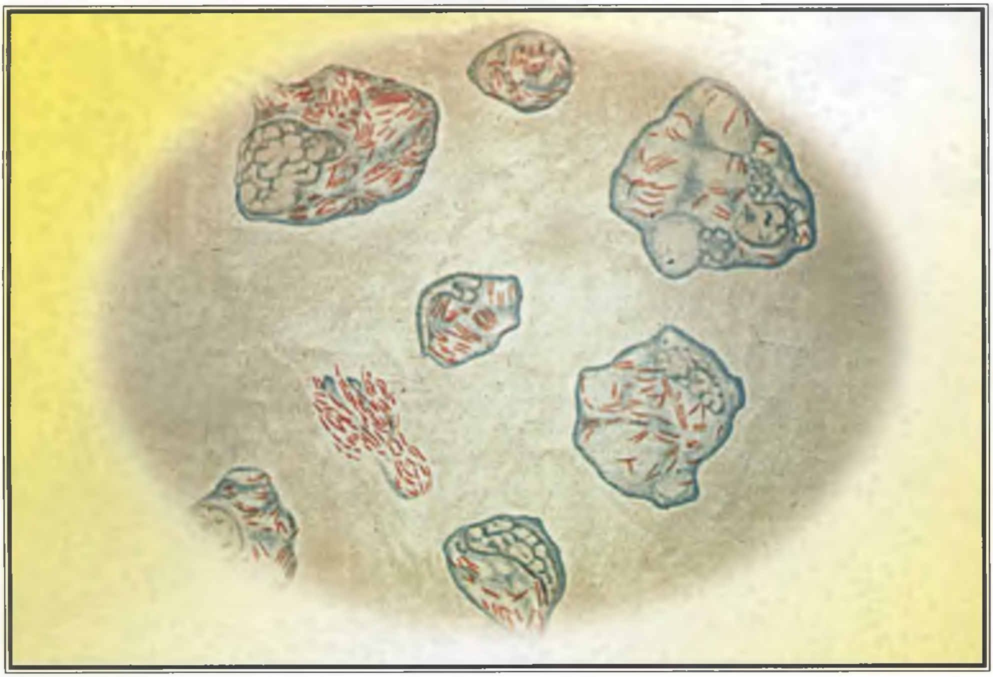


Fig. 143. Lepromatous leprosy, Virchow giant cells in the leproma (Ziehl-Nielsen stain, × 140).

Fig. 144. Lepra, macroscopic aspect of the lepromas.

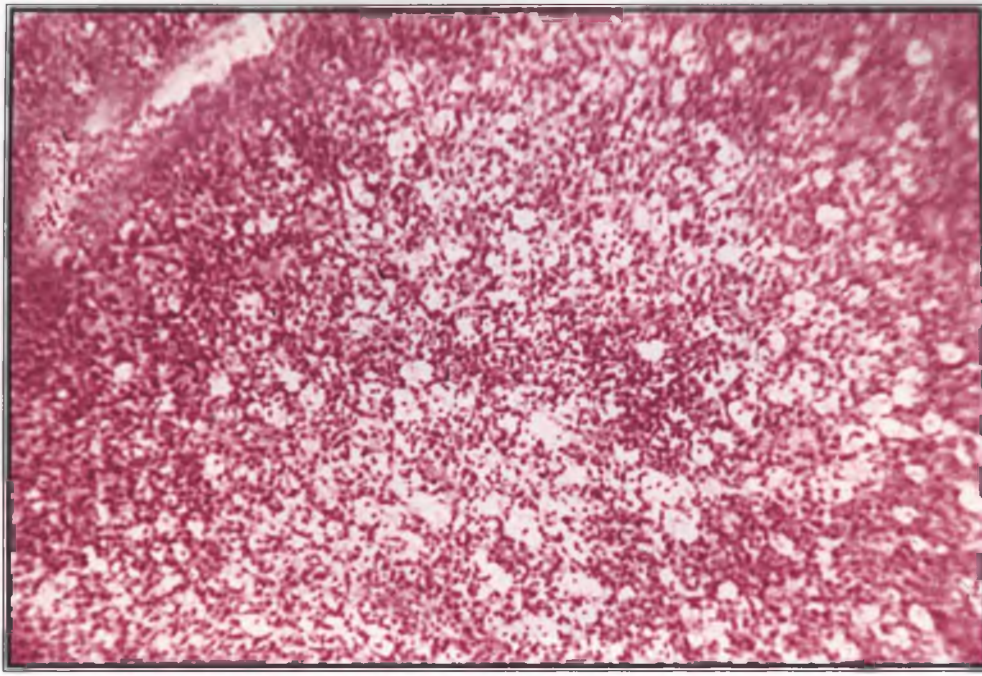


Fig. 145. Rhinoscleromatous granuloma (H.E. stain, × 70)

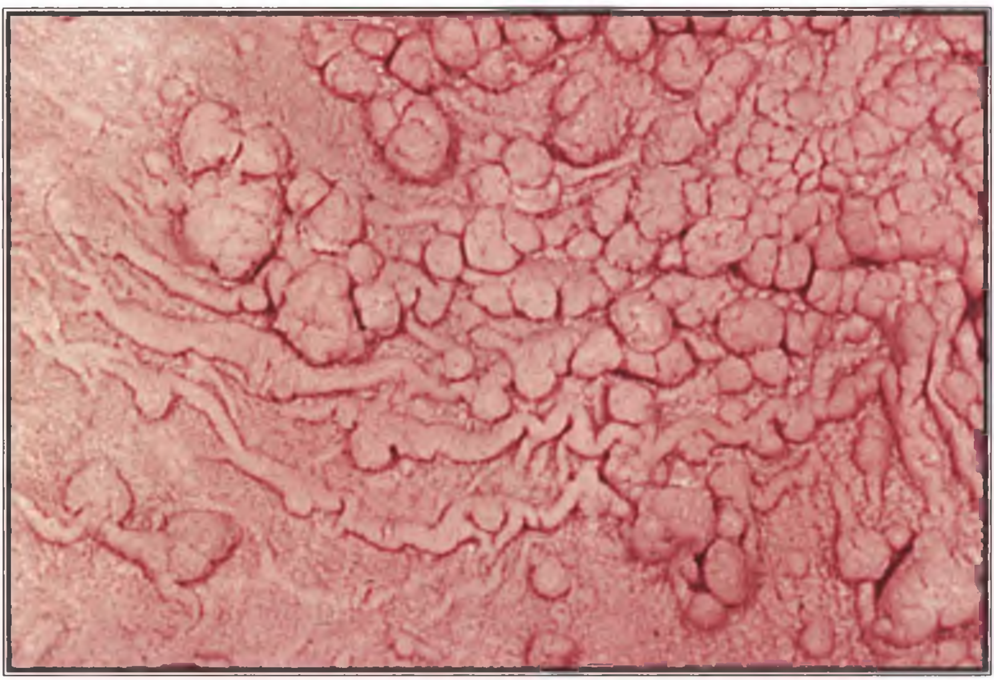


Fig. 146. Gastric polyposis.

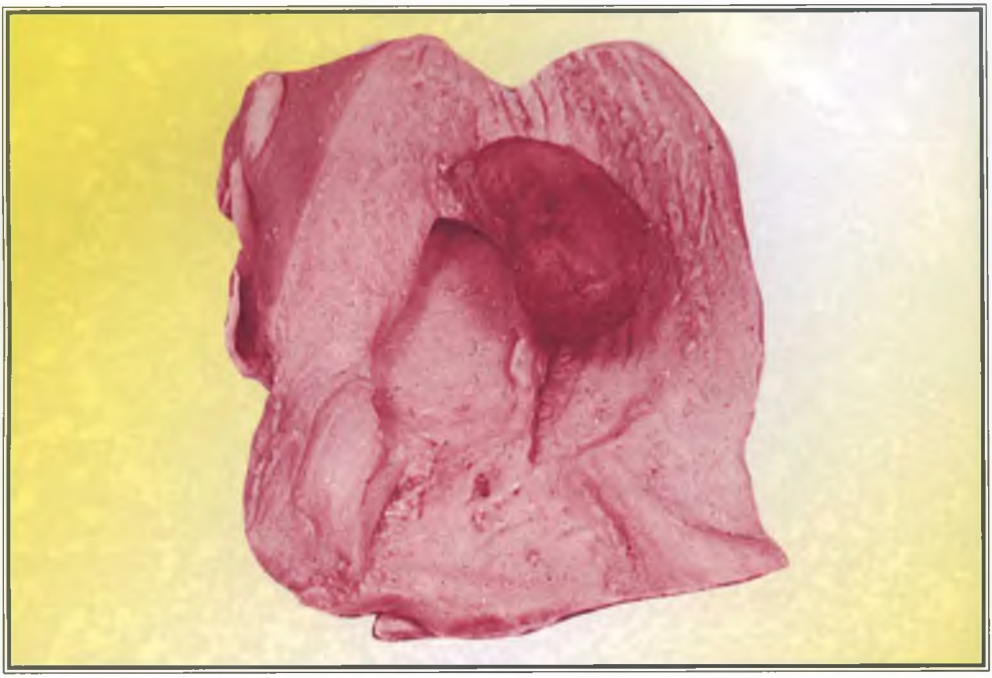


Fig. 147. Endometric polyp, macroscopic aspect.

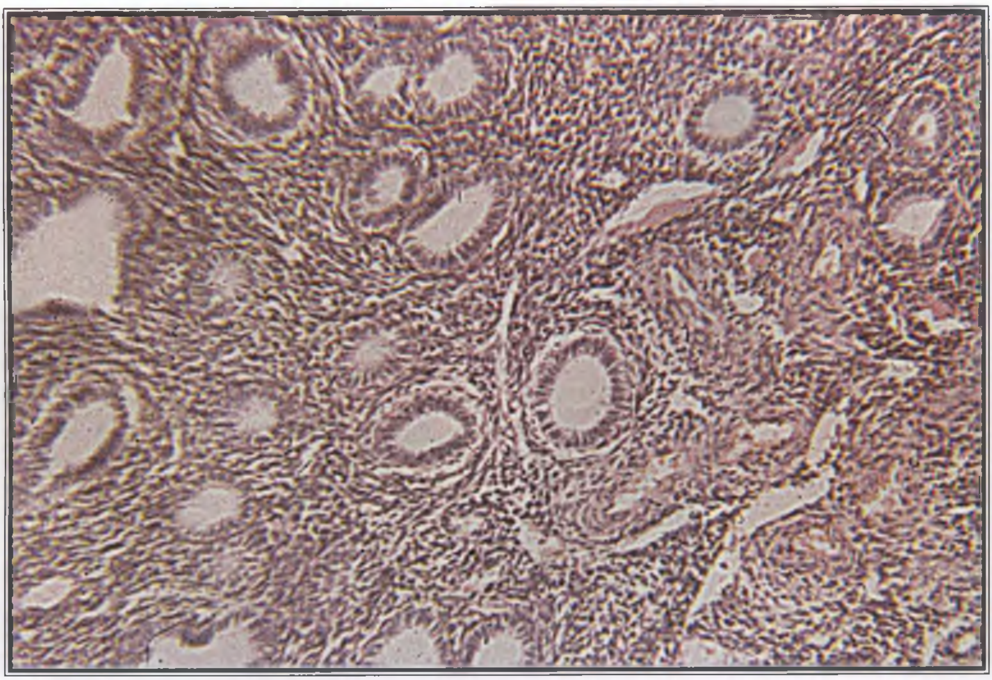


Fig. 148. Endometric polyp, microscopic aspect (H.E. stain, × 70).

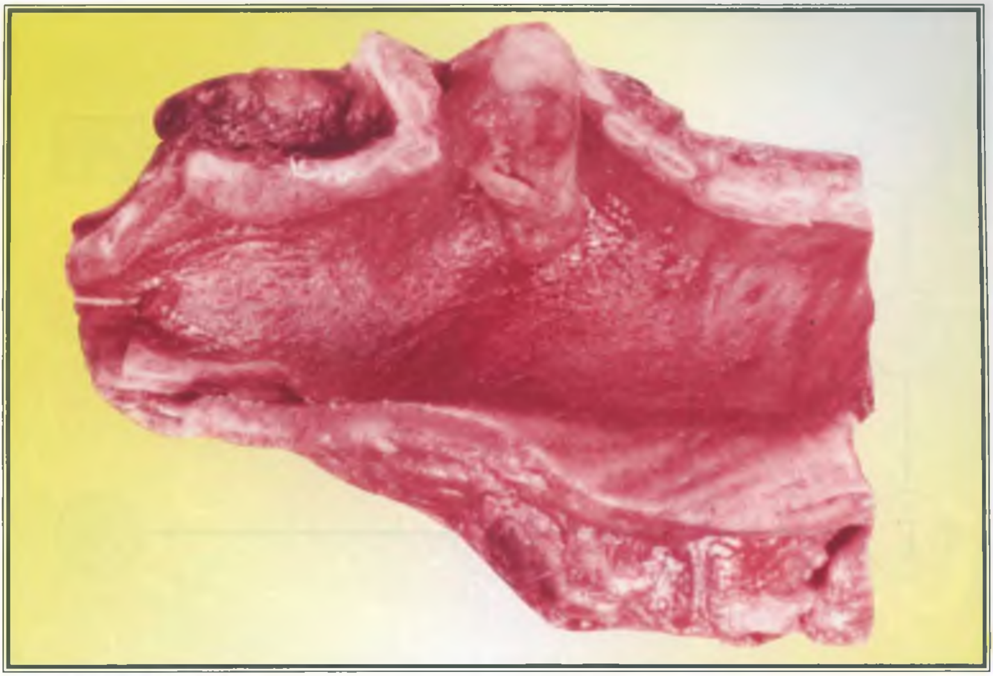


Fig. 149. Tracheal polyp.

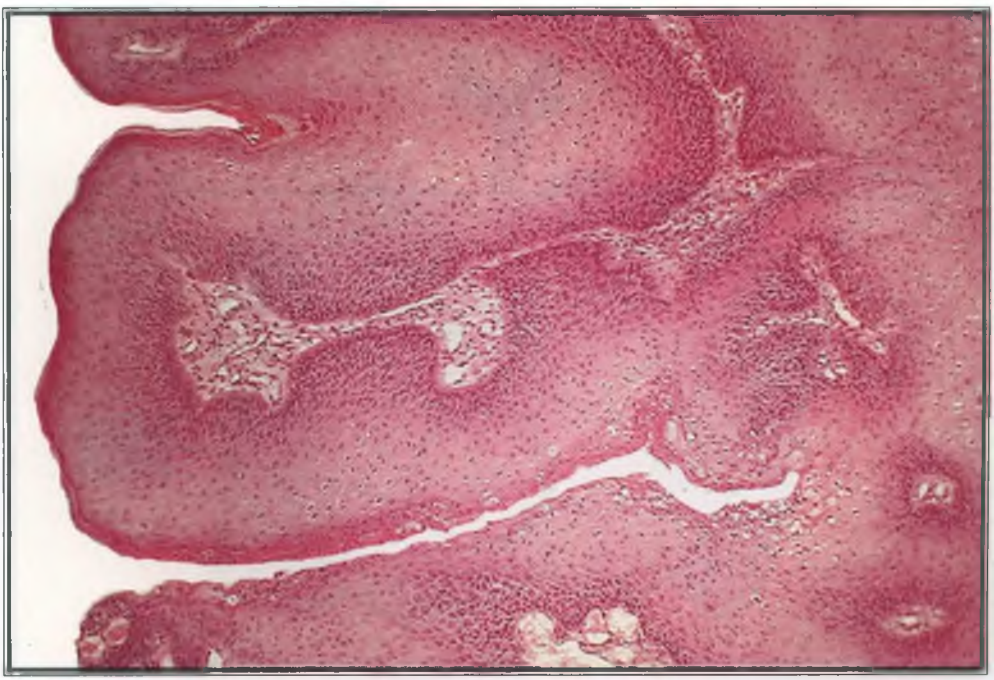


Fig. 150. Condyloma acuminatum (H.E. stain, × 70)..

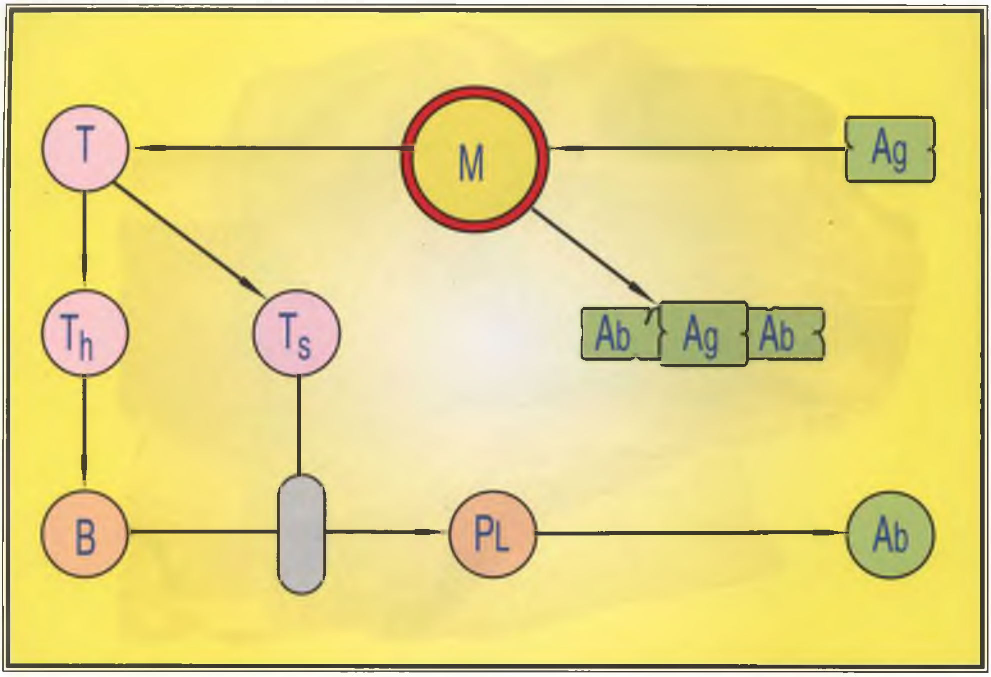


Fig. 151. Schematic diagram of the humoral immune reaction: B – B lymphocyte; T – T lymphocyte; M – macrophage; Ag – antigen; Ab – antibody; T_h – helper T lymphocyte; T_s – supressor T lymphocyte; PL – plasma cell (plasmocyte).

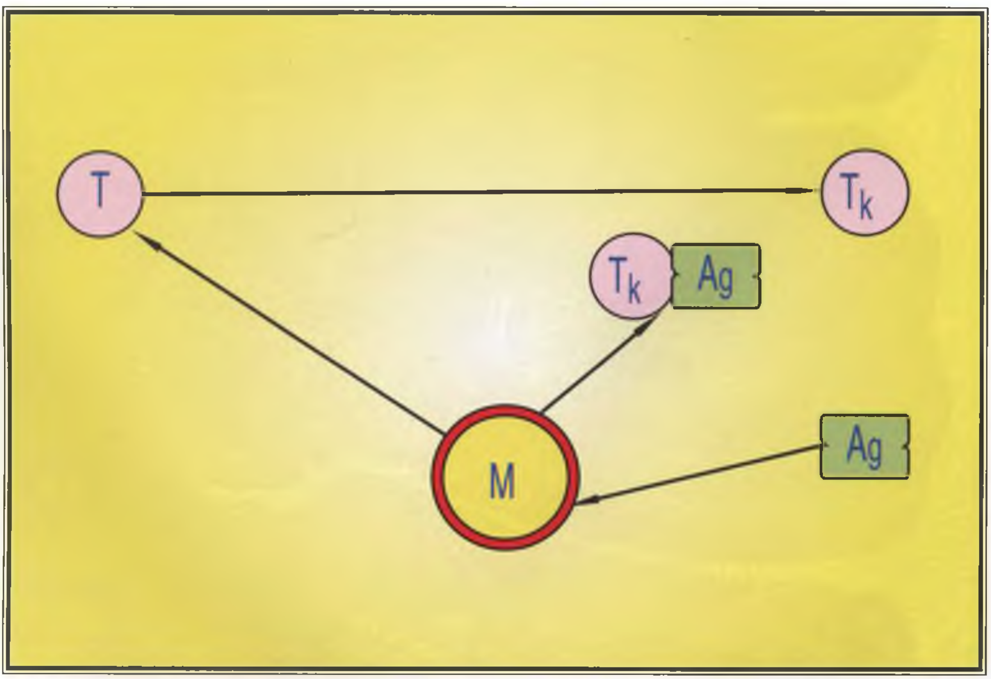


Fig. 152. Schematic diagram of the cellular immune reaction: T – T lymphocyte; T_k – killer (cytotoxic) T lymphocyte; M – macrophage; Ag – antigen.

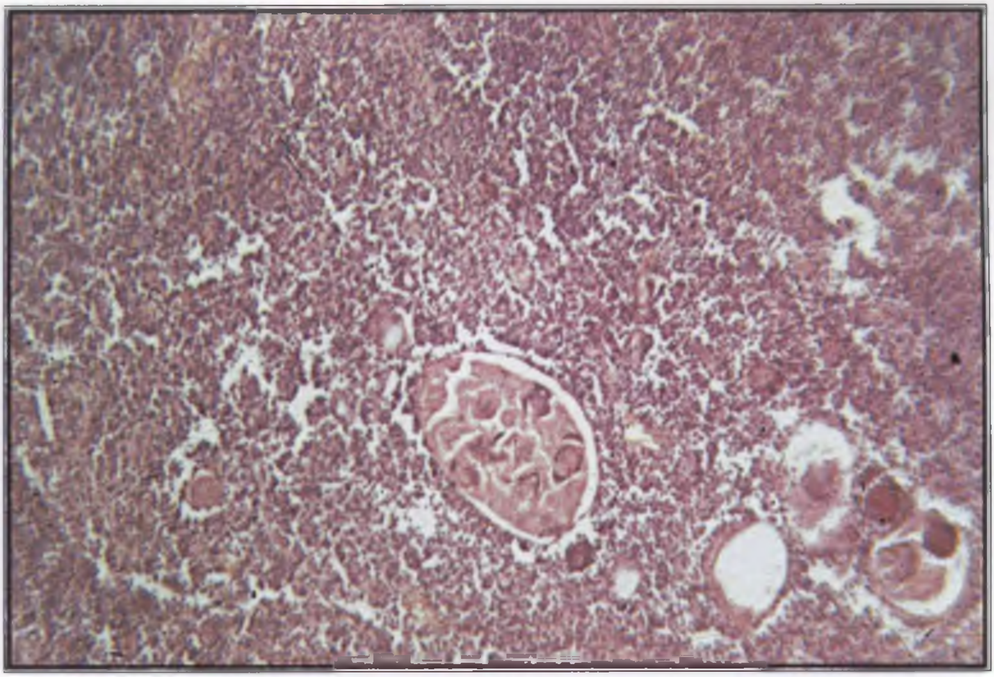


Fig. 153. Accidental involution of the thymus (H.E. stain, × 70).

Fig. 154. Thymomegaly.

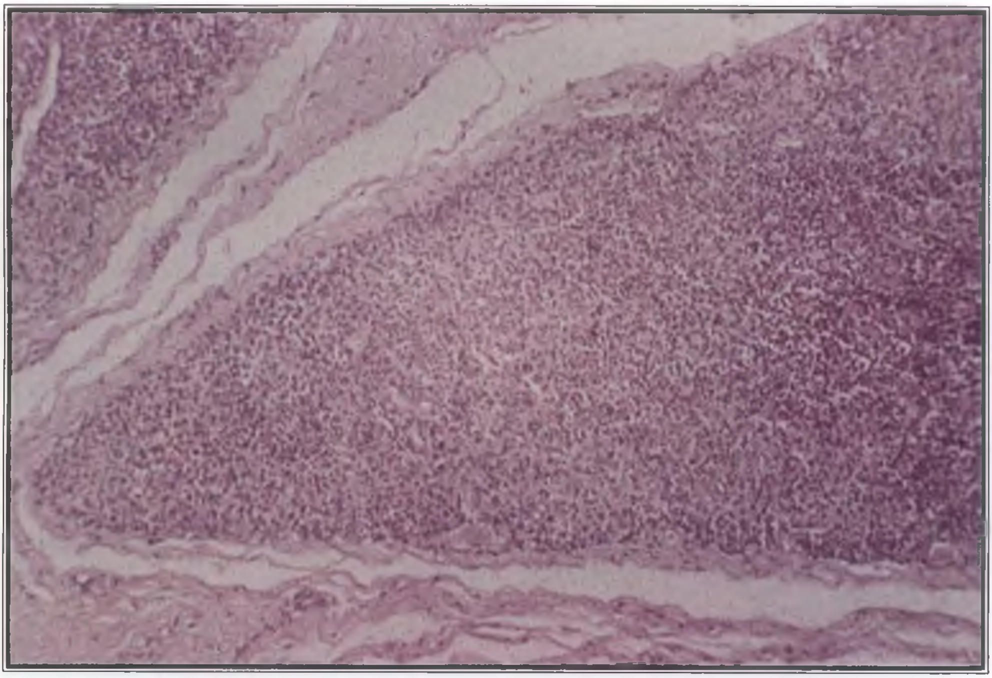


Fig. 155. Thymic hypoplasia in the mixed immunodeficient syndrome (H.E. stain, × 70).

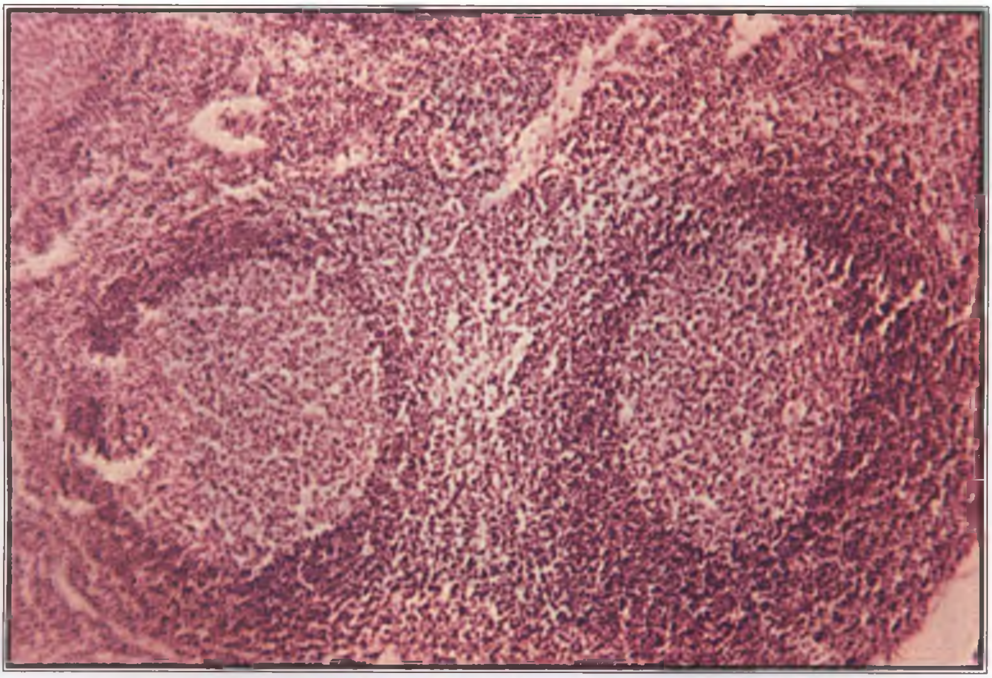


Fig. 156. Hyperplasia of the lymphatic ganglion's follicles in the antigenic stimulation (H.E. stain, × 70).

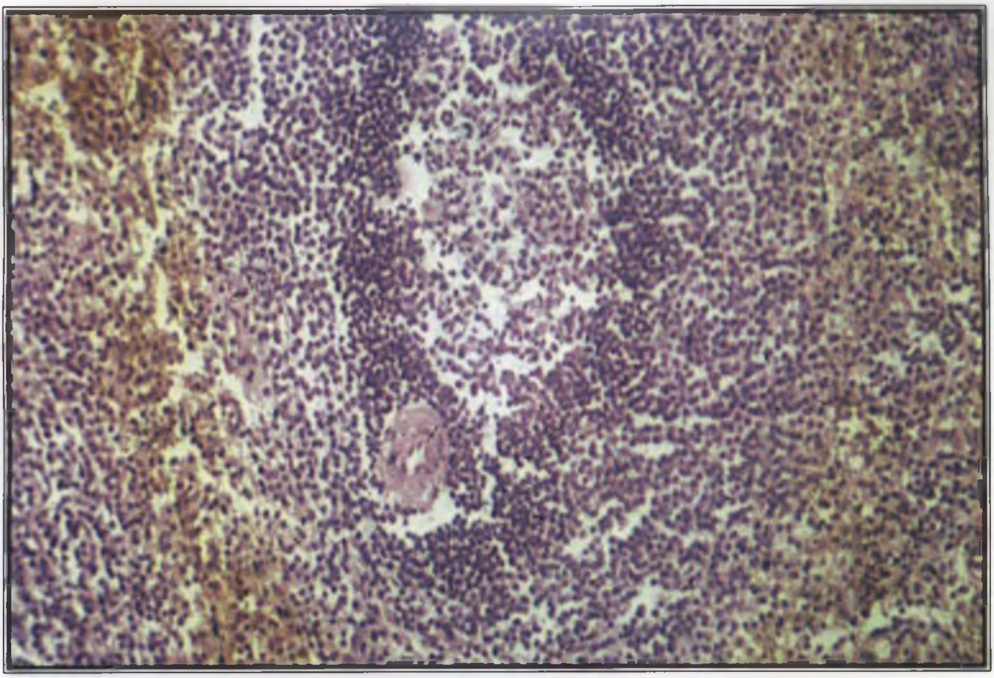


Fig. 157. Hyperplasia and the plasmatisation of the lienal follicles in antigenic stimulation (H.E. stain, × 70).

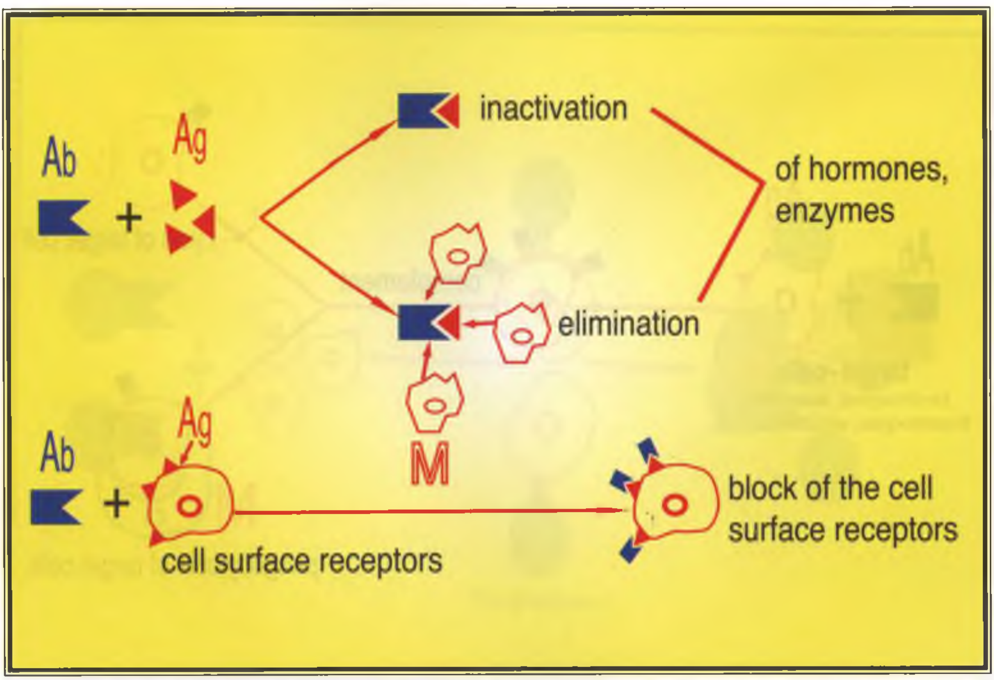


Fig. 158. Schematic representation of the neutralization and inactivation reaction: Ab – antibody, Ag – antigen, M – macrophage.

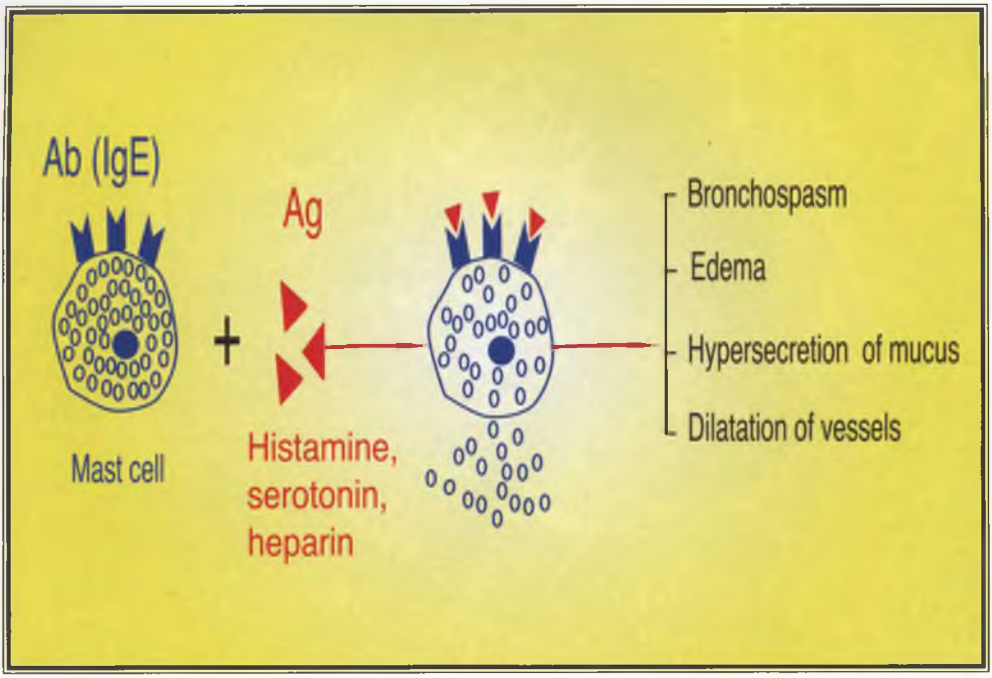


Fig. 159. Schematic representation of the immediate anaphylactic reaction: Ab – antibody, IgE immunoglobulin E, Ag – antigen.

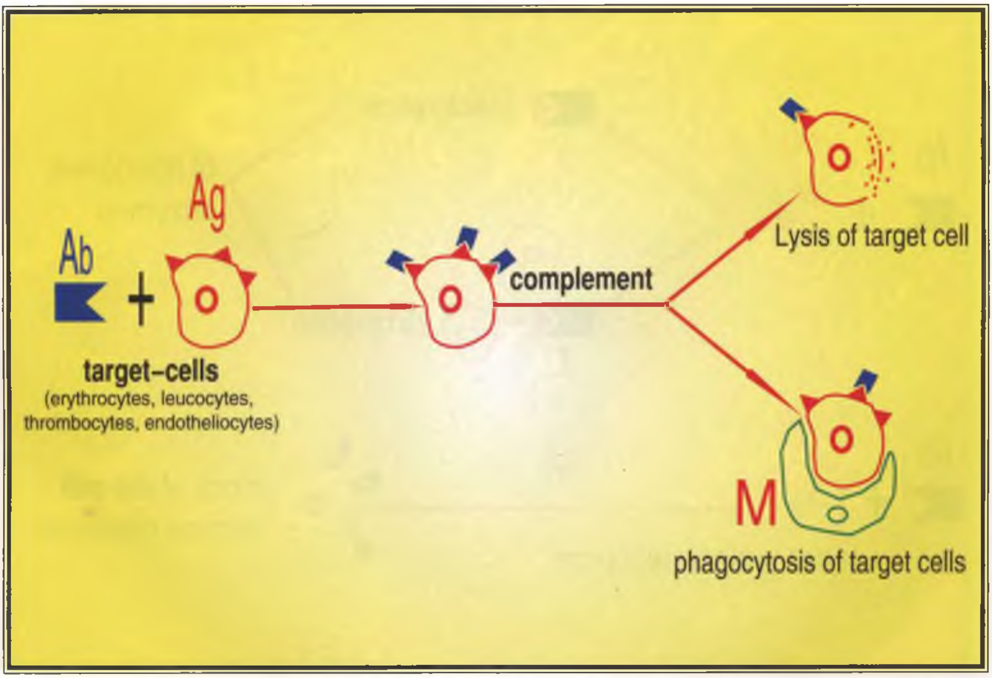


Fig. 160. Schematic representation of the cytolytic and cytotoxic reactions: Ab – antibody, Ag – antigen, M – macrophage.

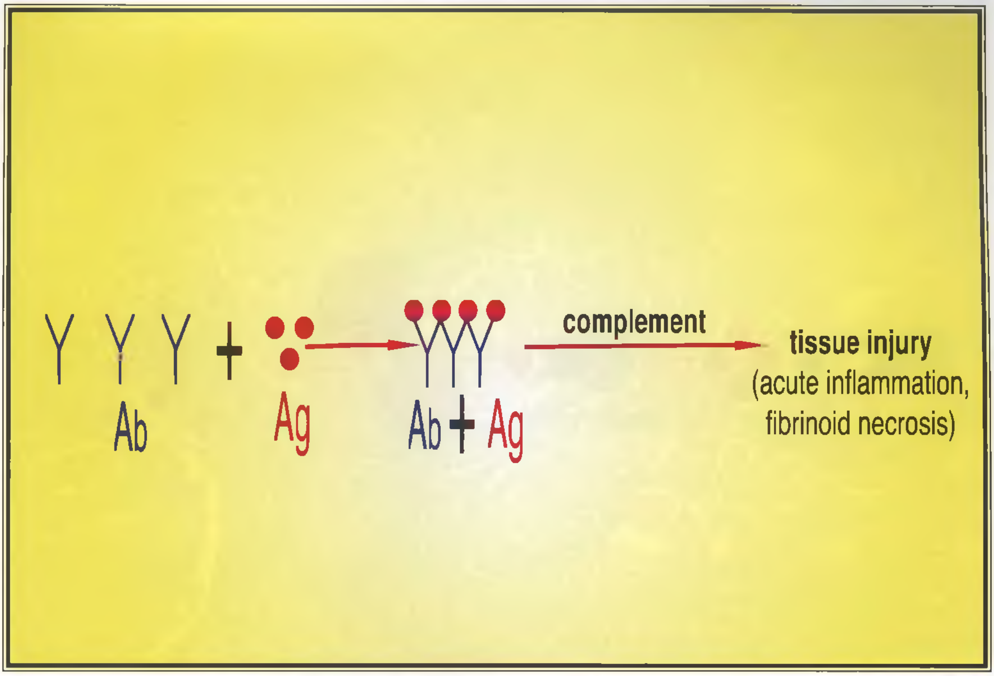


Fig. 161. Schematic representation of the reaction of toxic immune complexes: Ab – anti body, Ag – antigen.

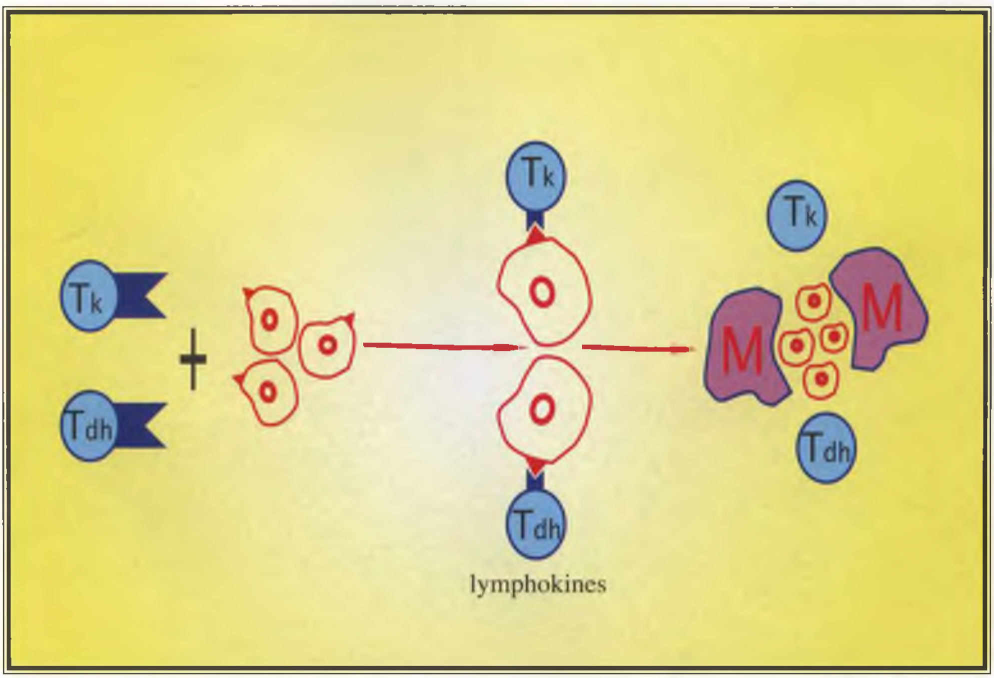


Fig. 162. Schematic representation of the delayed hypersensitivity reaction (cellular type): Tk - killer (cytotoxic) T lymphocyte, Tdh - delayed hypersensitivity T lymphocyte, M - macrophage.

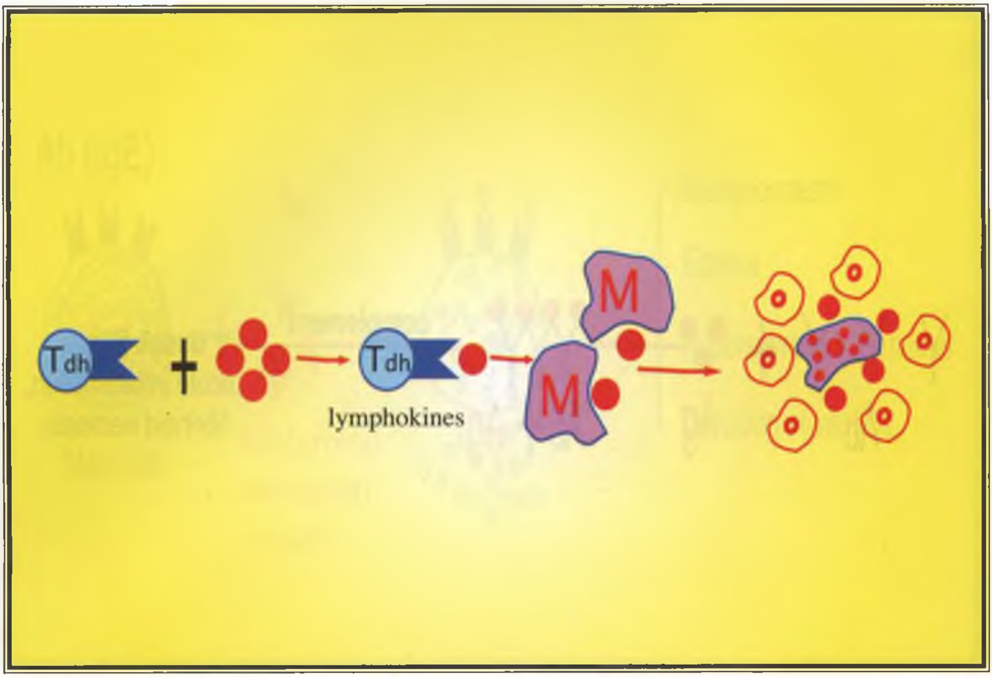


Fig. 163. Schematic representation of the granulomatous reaction: Tdh – delayed hypersen sitivity T lymphocyte, M - macrophage

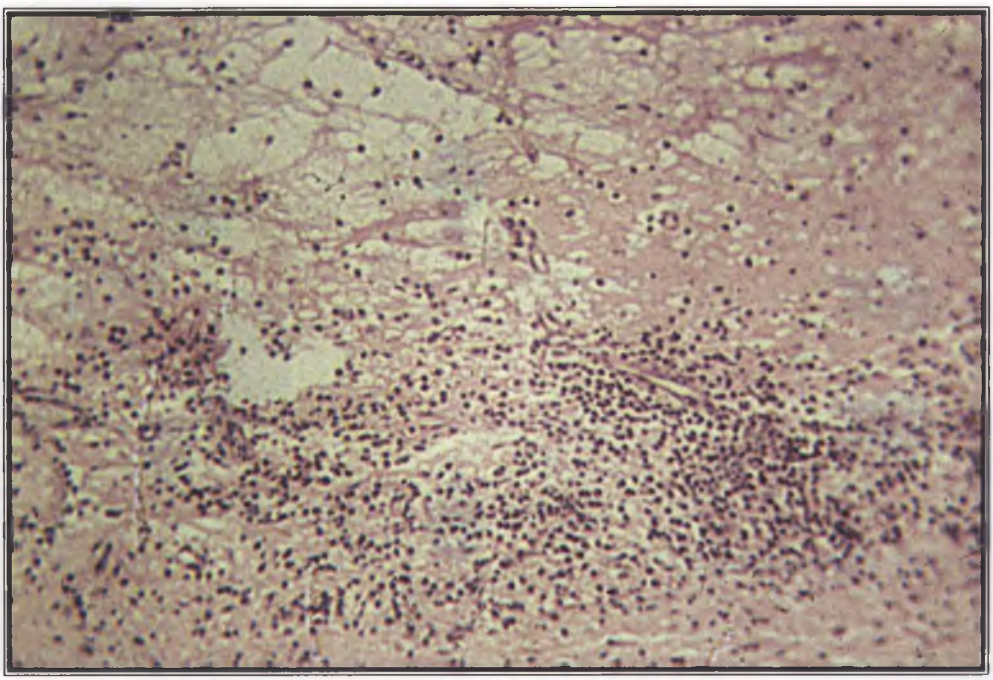


Fig. 164. Allergic rhinitis (H.E. stain, × 70).

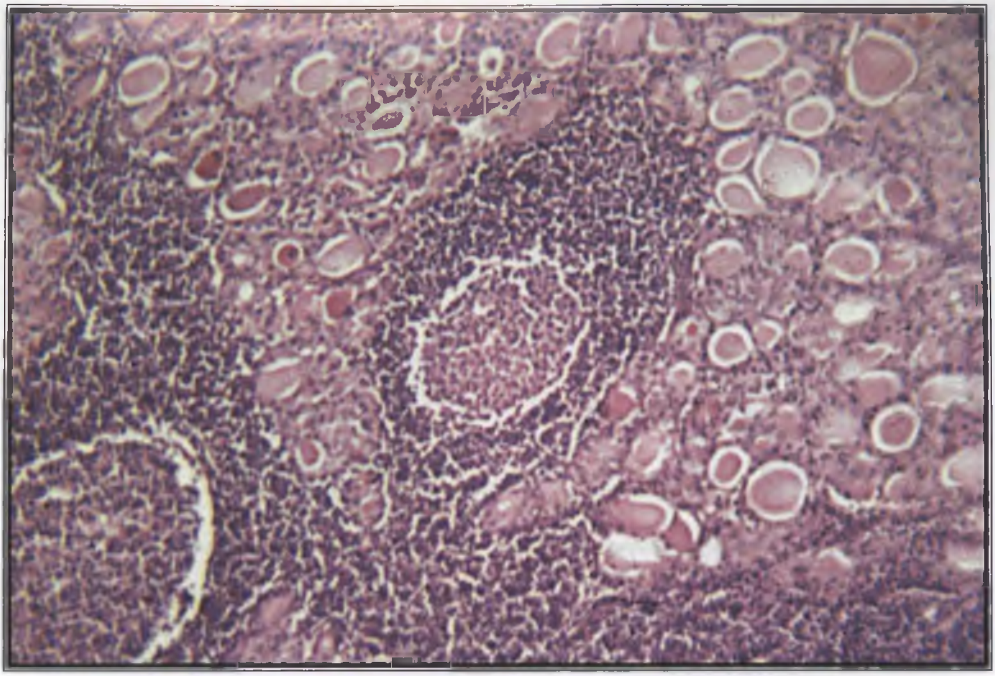


Fig. 165. Autoimmune thyroiditis, lymphoid follicles between the atrophic thyroid follicles (H.E. stain, × 70).

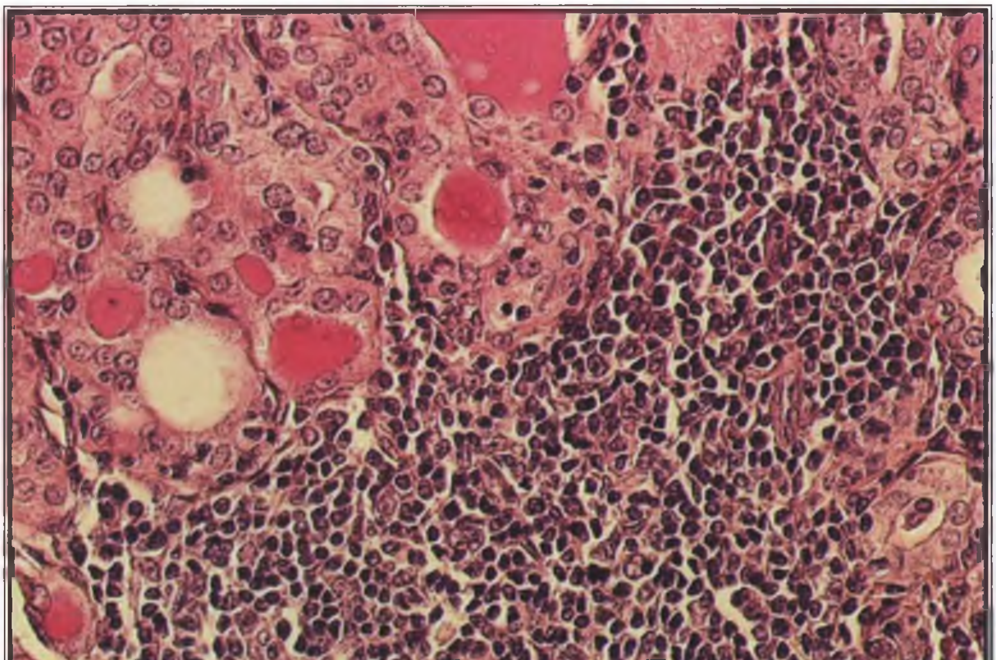


Fig. 166. Autoimmune (Hashimoto's) thyroiditis: diffuse lymphocytic infiltration and replacement of thyroid parenchyma (H.E. stain, × 112).

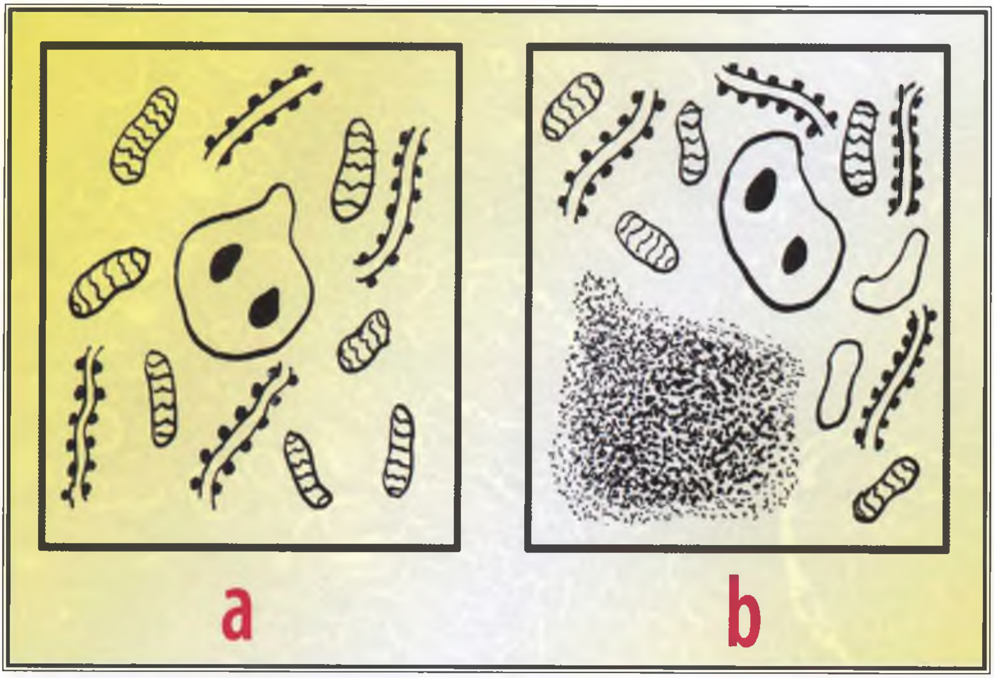


Fig. 167. Schematic representation of the intracellular regeneration: a - normal cell; b - partial necrosis of the cell and hyperplasia of the remaining cytoplasmic organelles with the reestablishment of their number.

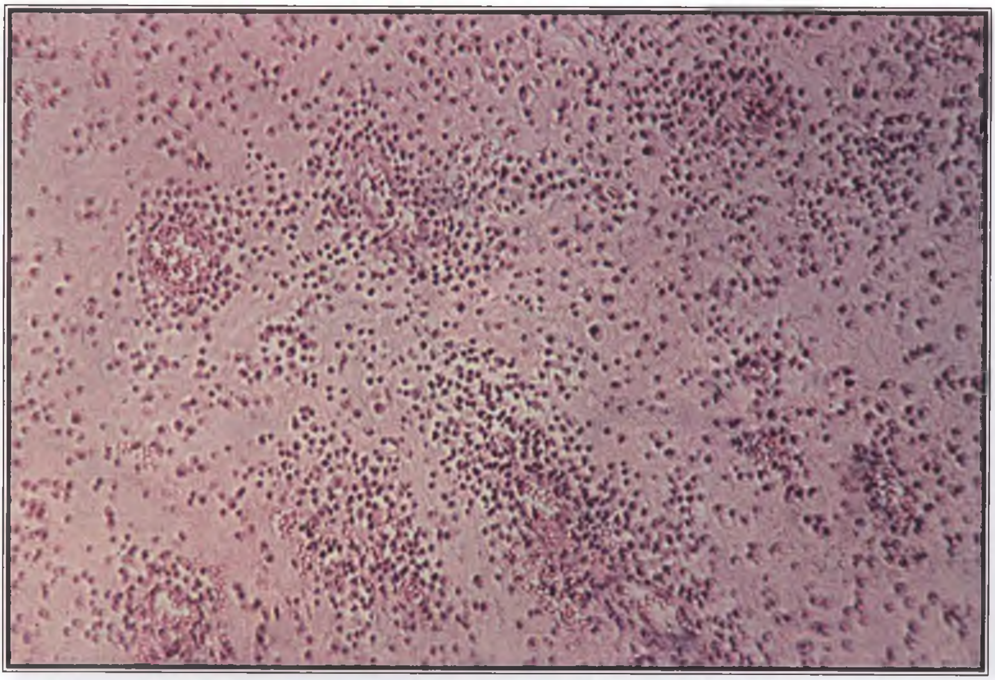


Fig. 168. Granulation tissue (H.E. stain, × 70).

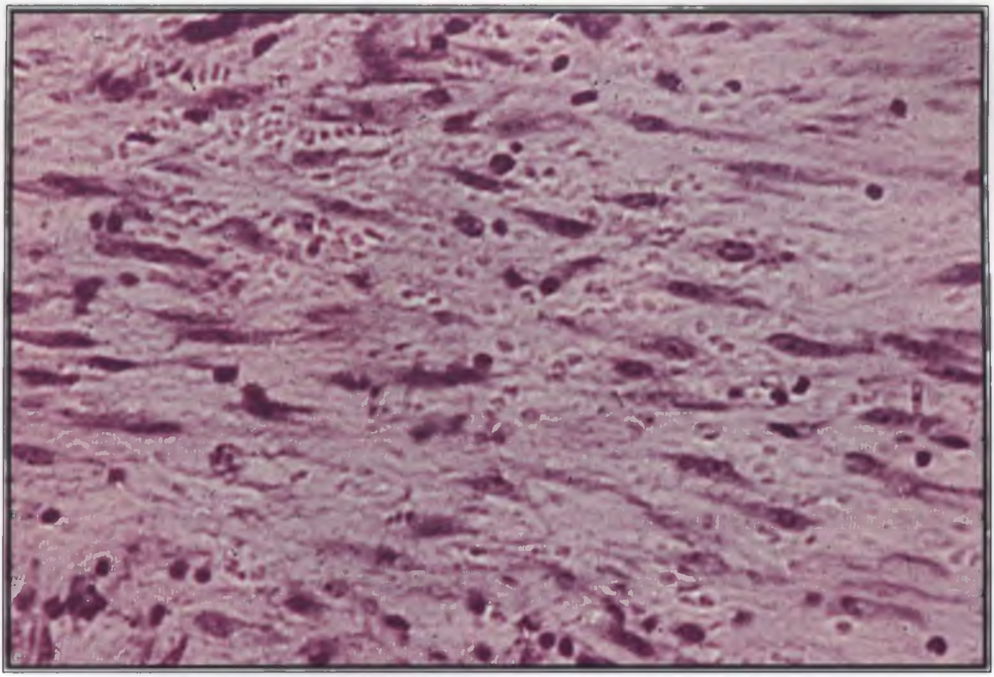


Fig. 169. Granulation tissue during maturation (H.E. stain, × 70).

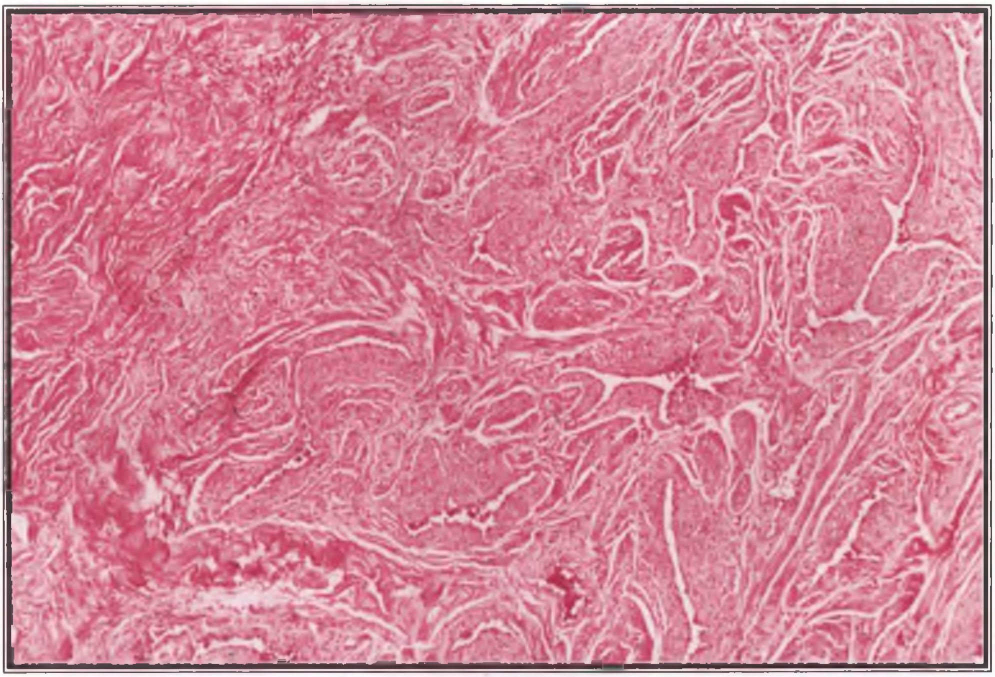


Fig. 170. Fibrous connective tissue (cicatriceal) (H.E. stain, × 70).

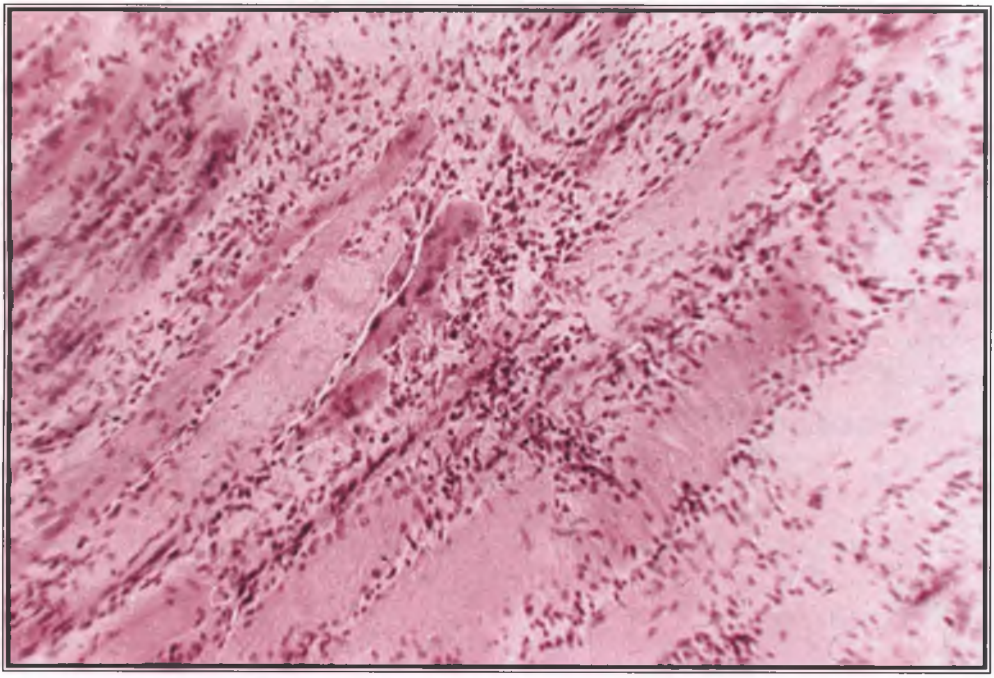


Fig. 171. Regeneration of striated skeletal muscle (H.E. stain, × 70).

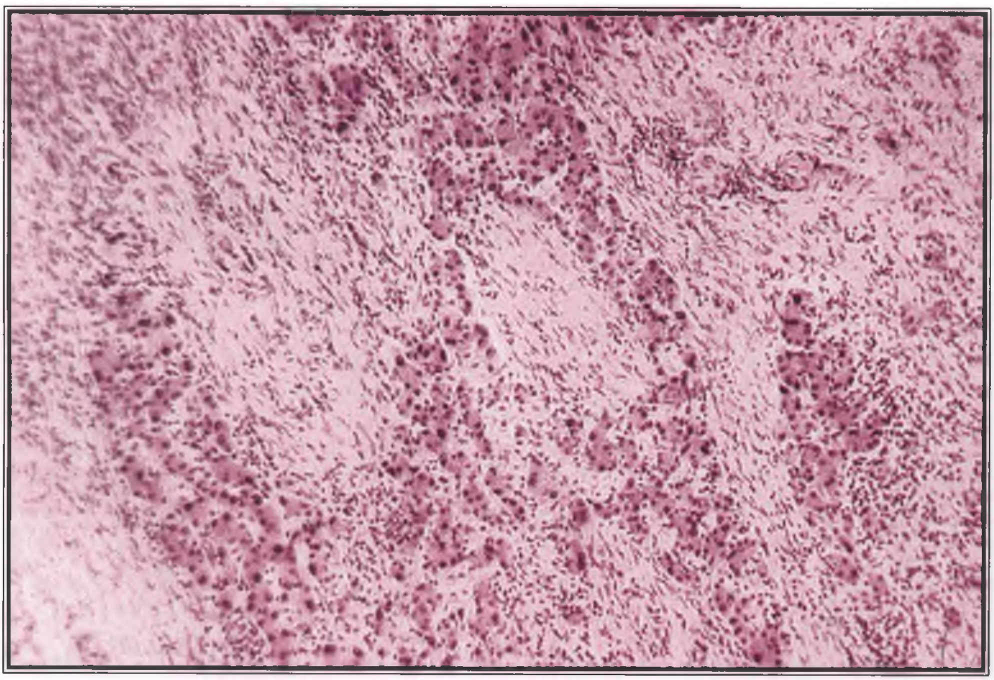


Fig. 172. Regeneration of liver in cirrhosis (H.E. stain, × 70).


Fig. 173. Macrofocal postinfarction cardiosclerosis, macroscopic aspect.

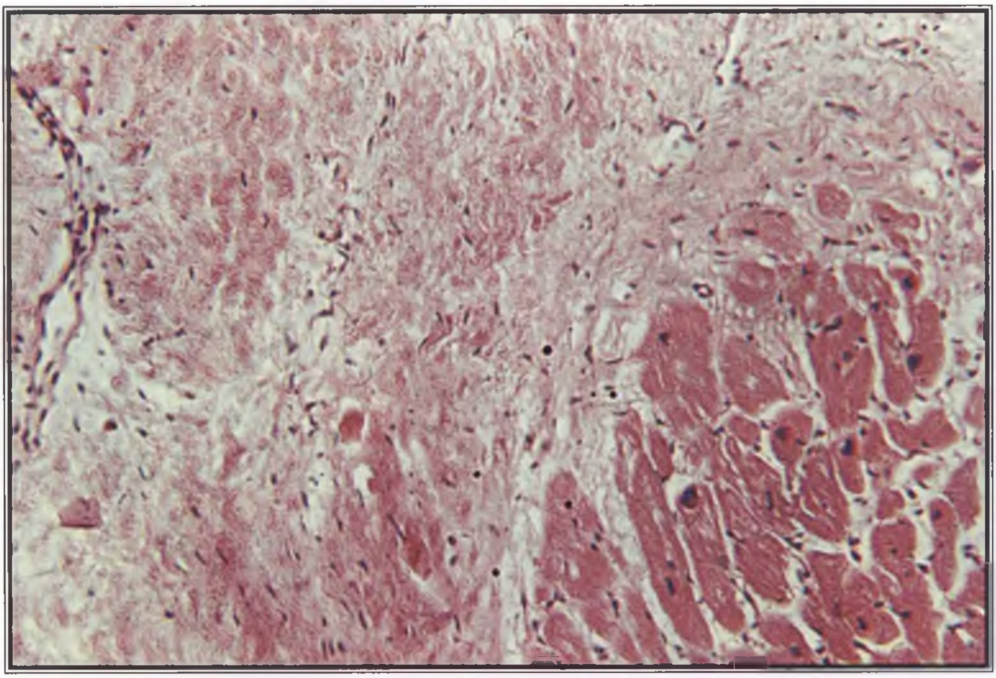


Fig. 174. Macrofocal postinfarction cardiosclerosis, microscopic aspect (H.E. stain, × 70).

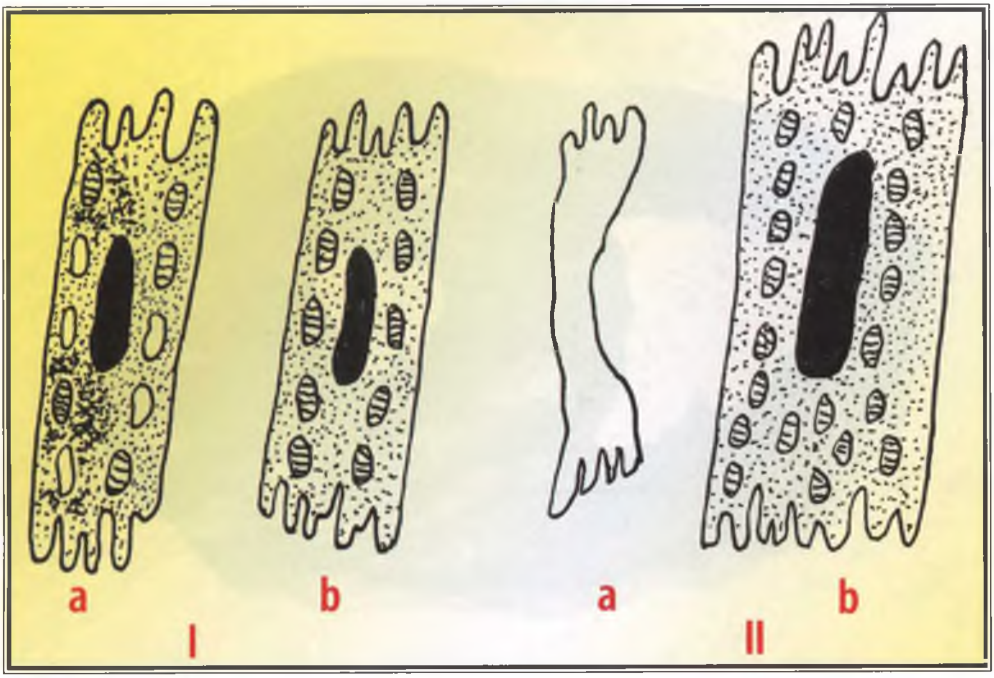


Fig. 175. Schematic representation of the intracellular regeneration of the myocardium: I (a, b) - intracellular reparative regeneration; II (a, b) - intracellular regeneration with regenerative hypertrophy of the remaining cardiomyocytes (after D.S. Sarkisov, 1970).

Fig. 176. Regenerative hypertrophy of the myocardium (electronomicrography, × 16000): hyperplasia of mitochondria and of myofibrills.

Fig. 177. Regenerative hypertrophy of the myocardium (electronomicrography, × 16000): mitochondrial hypertrophy (gigantic mitochondria).

Fig. 178. Atonic (trophic) ulceration of the skin in the varicose dilatation of the lower extremity veins.

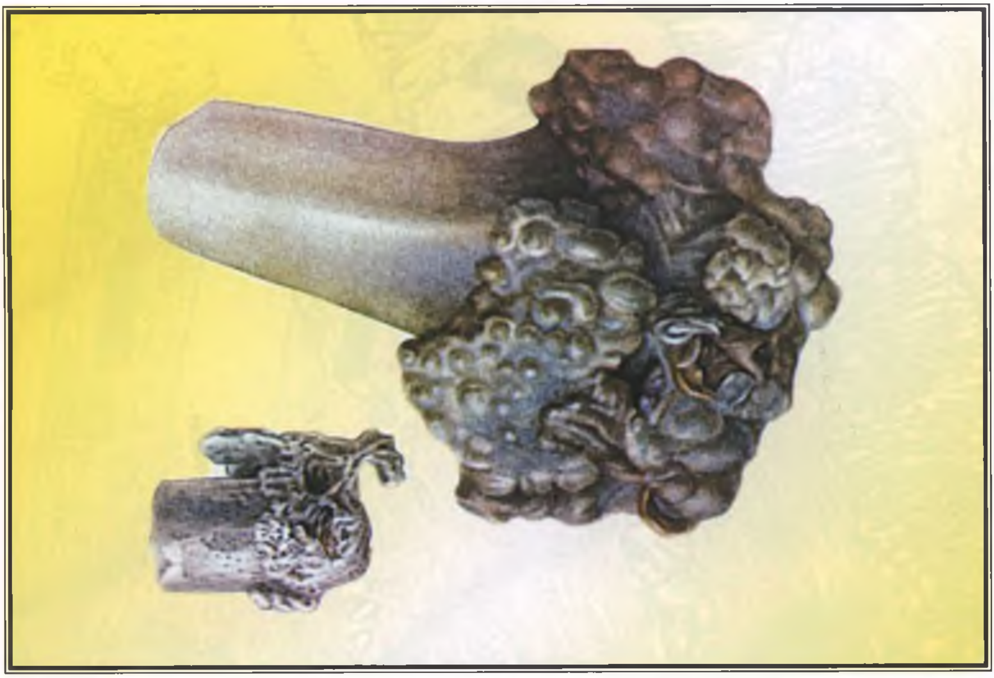


Fig. 179. Exostosis in the region of the femoral head and of the amputational bont of the femoral bone.

Fig. 180. Vicious callus in femoral fracture.

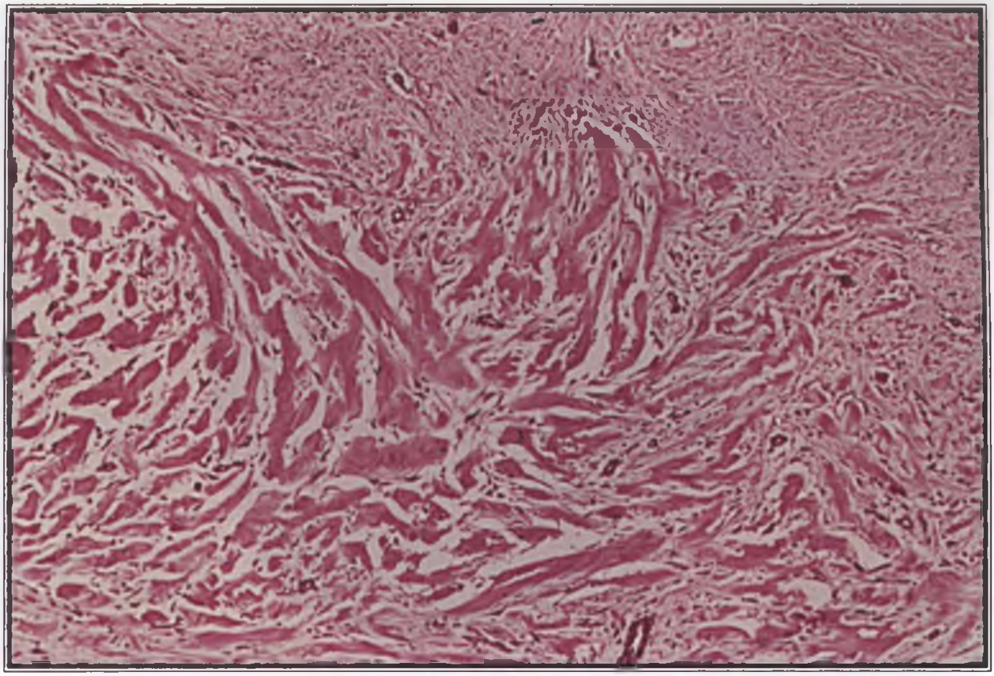


Fig. 181. Keloid cicatrix (H.E. stain, × 70).

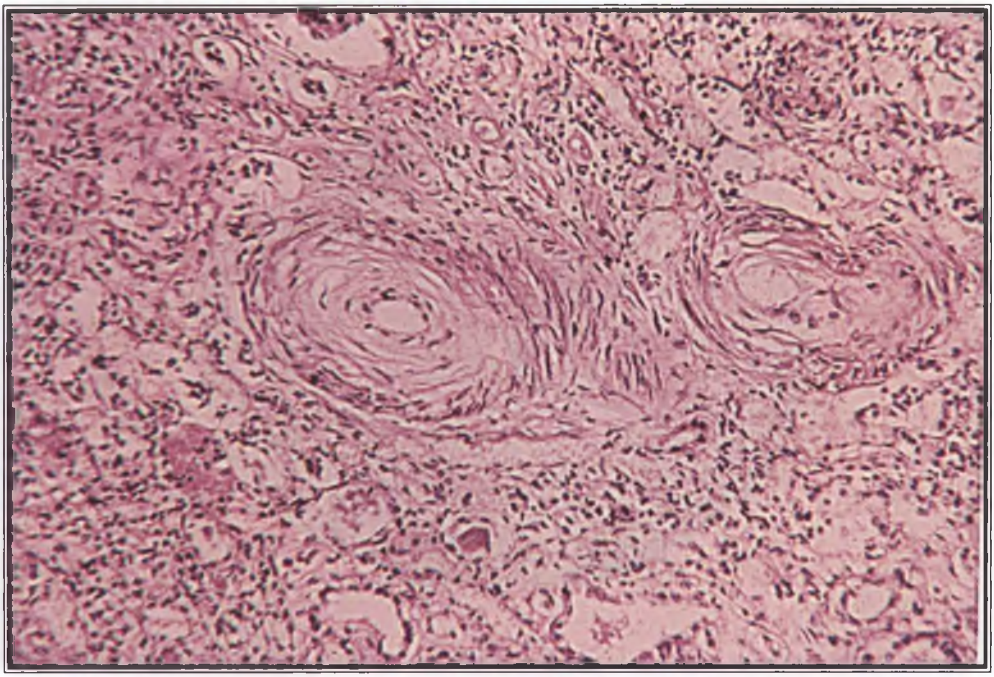


Fig. 182. Hyperplasia of the arterial elastic membrane in arterial hypertension (H.E. stain, × 70).

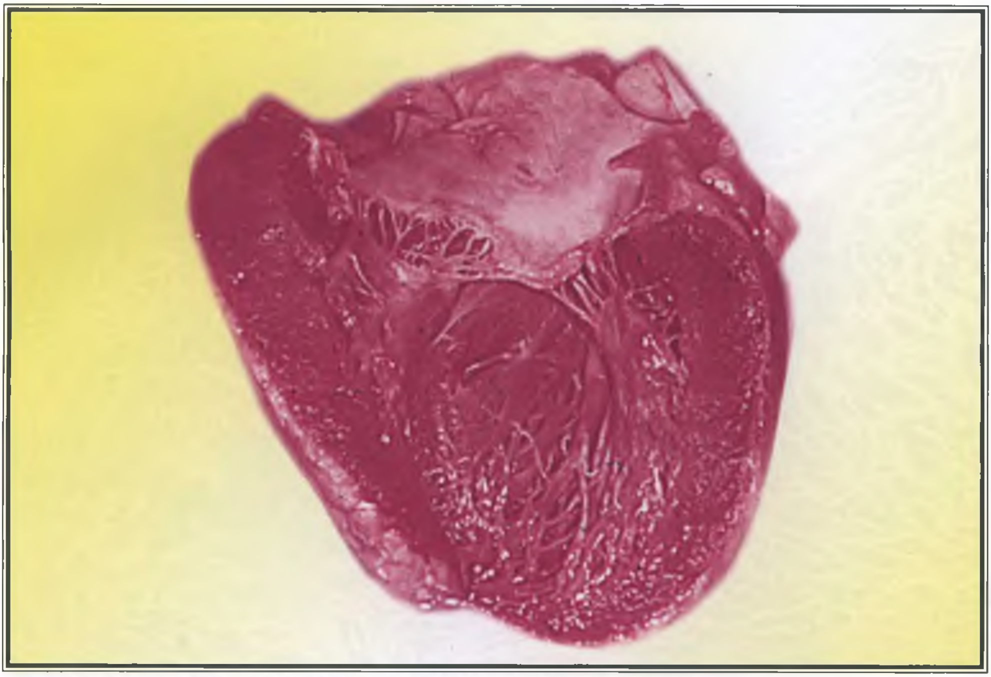


Fig. 183. Hypertrophy of the left ventricle, longitudinal section.

Fig. 184. Hypertrophy of the left ventricle, transverse section.

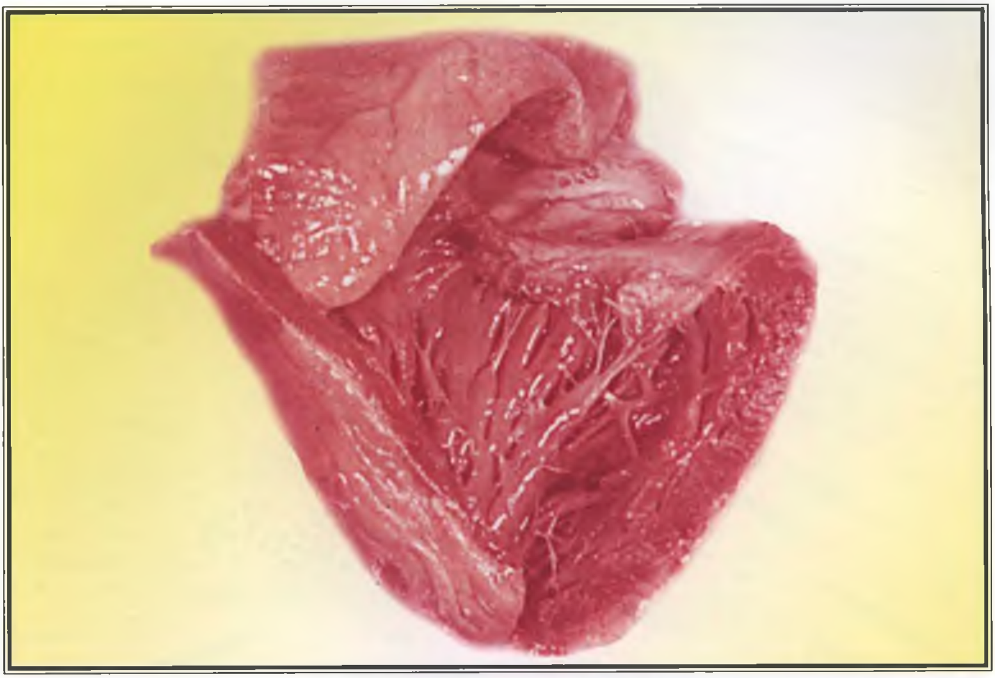


Fig. 185. Hypertrophy of the right ventricle.

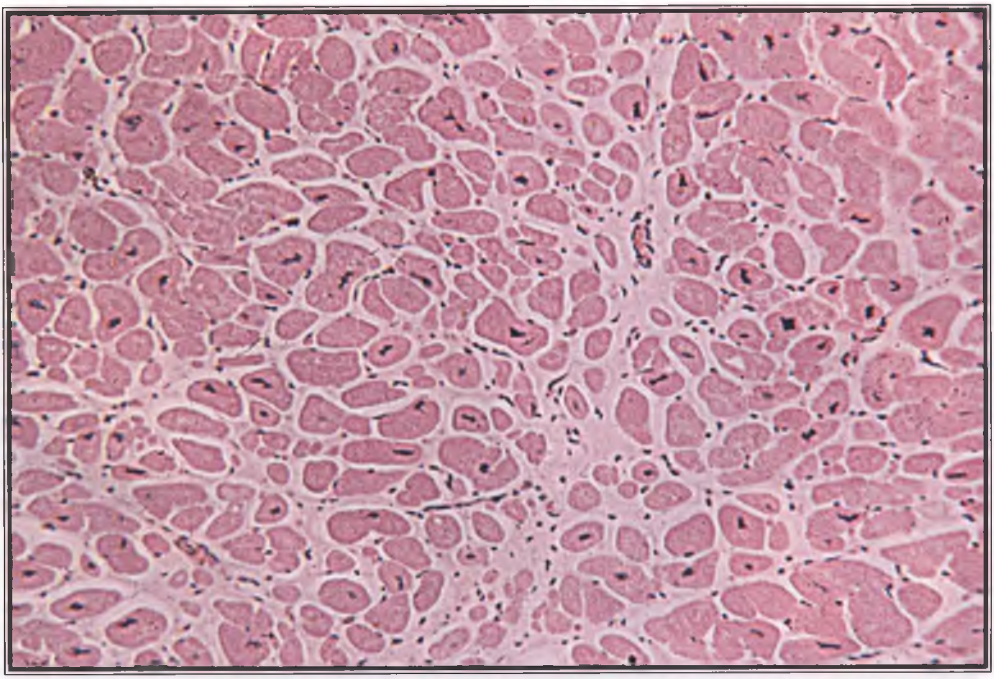


Fig. 186. Hypertrophy of the myocardium (H.E. stain, × 70).

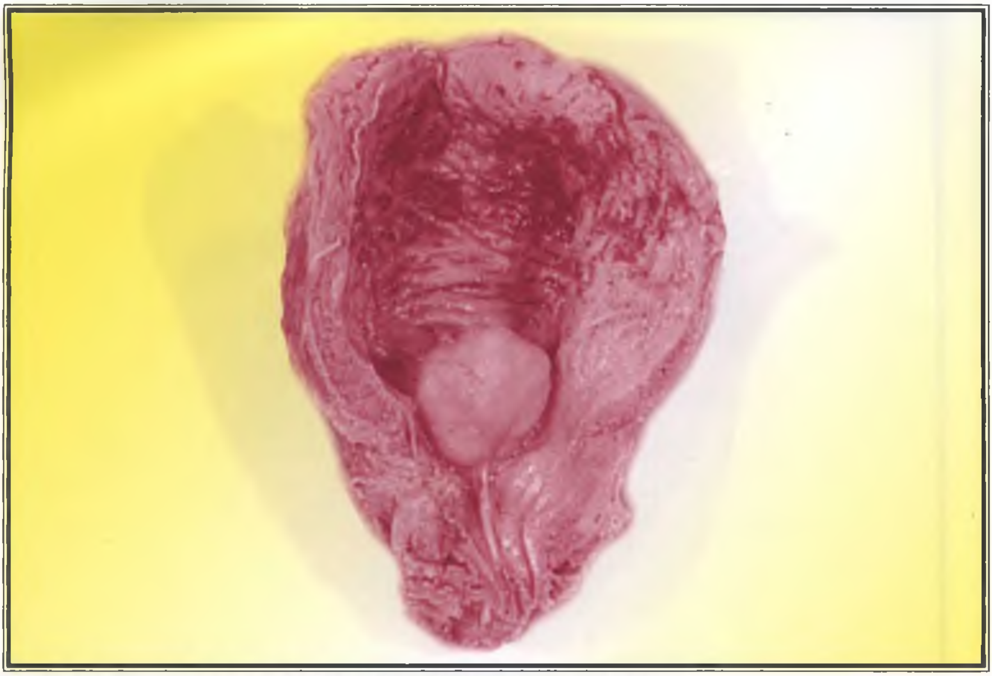


Fig. 187. Hypertrophy of the bladder wall (in prostate adenoma).

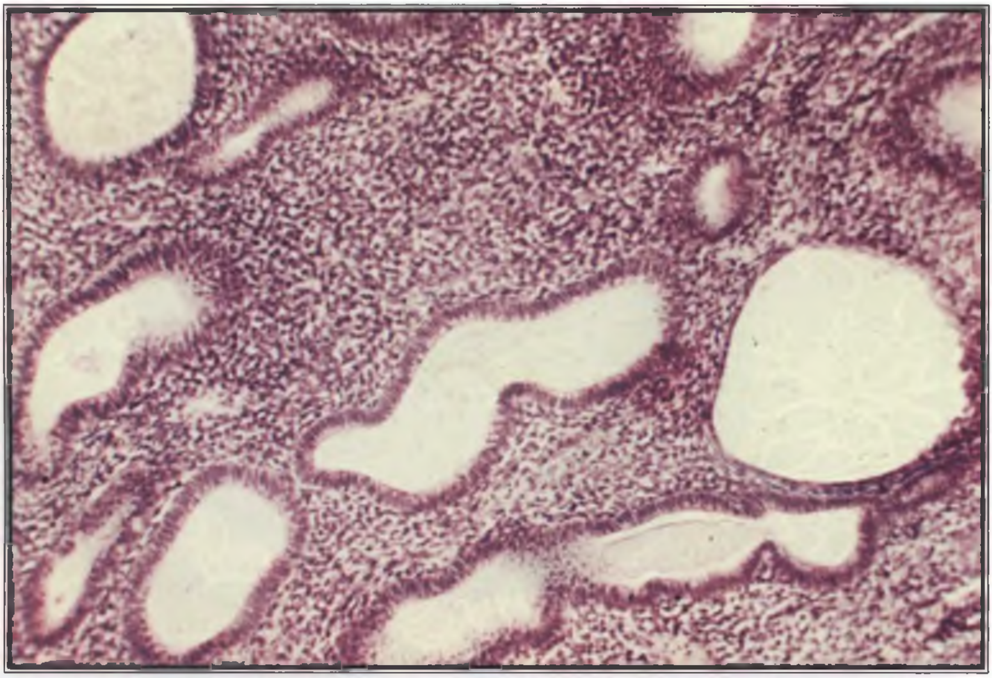


Fig. 188. Glandular (glandulocystic) hyperplasia of the endometrium (H.E. stain, × 70).

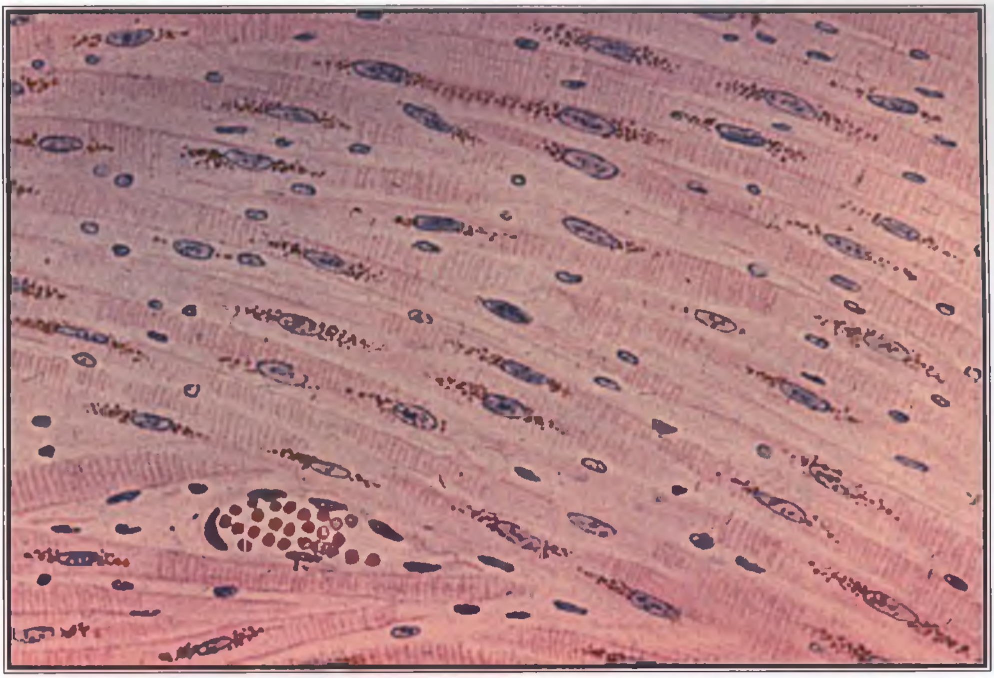


Fig. 189. Brown atrophy of the heart (lipofuscinosis of the myocardium) (H.E. stain, × 70).

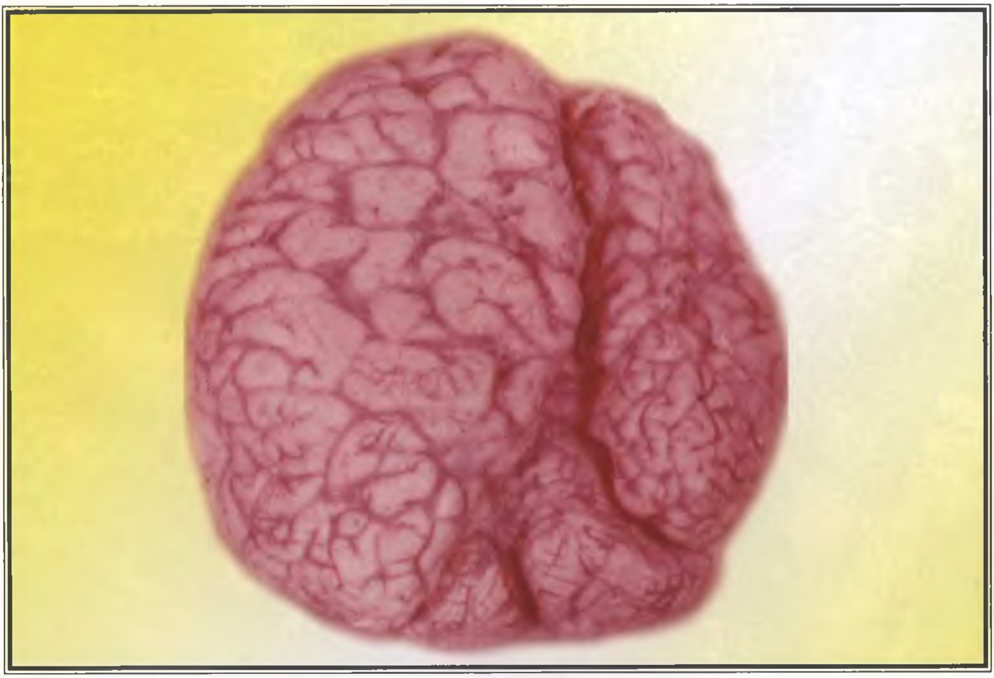


Fig. 190. Ischemic atrophy of the brain hemisphere.

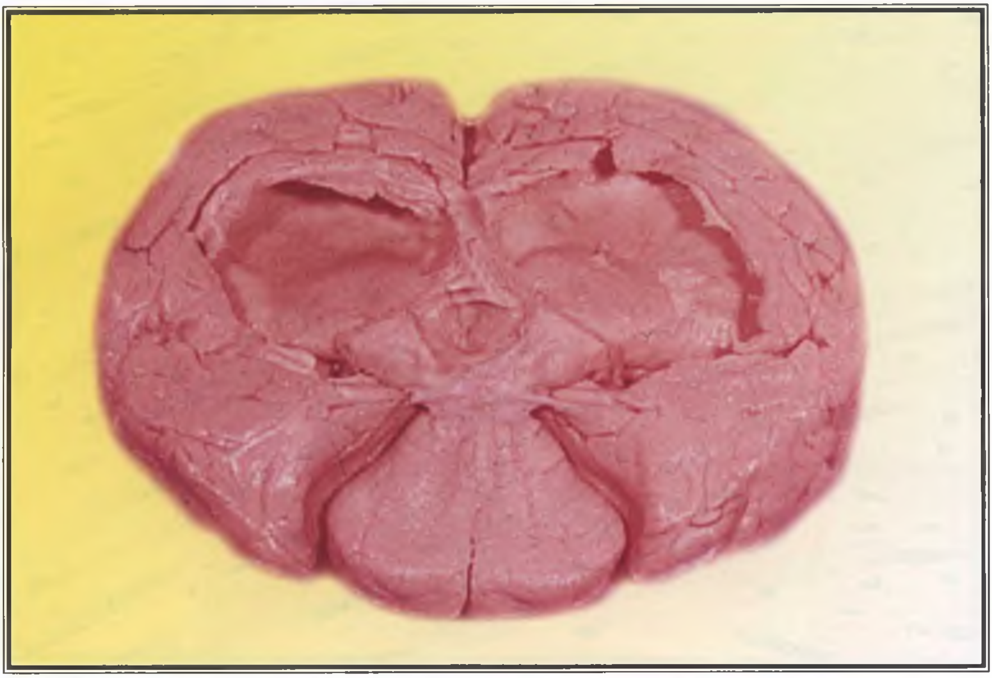


Fig. 191. Internal hydrocephaly with atrophy by compression of the cerebral tissue.

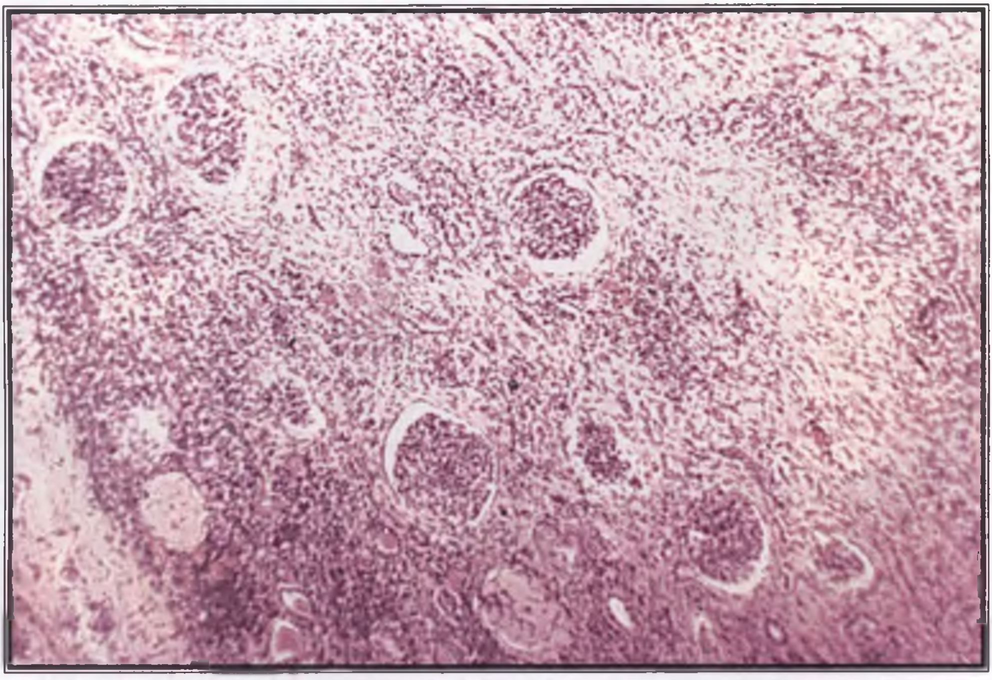


Fig. 192. Atrophy of renal parenchyma by compression in hydronephrosis (H.E. stain, × 70).

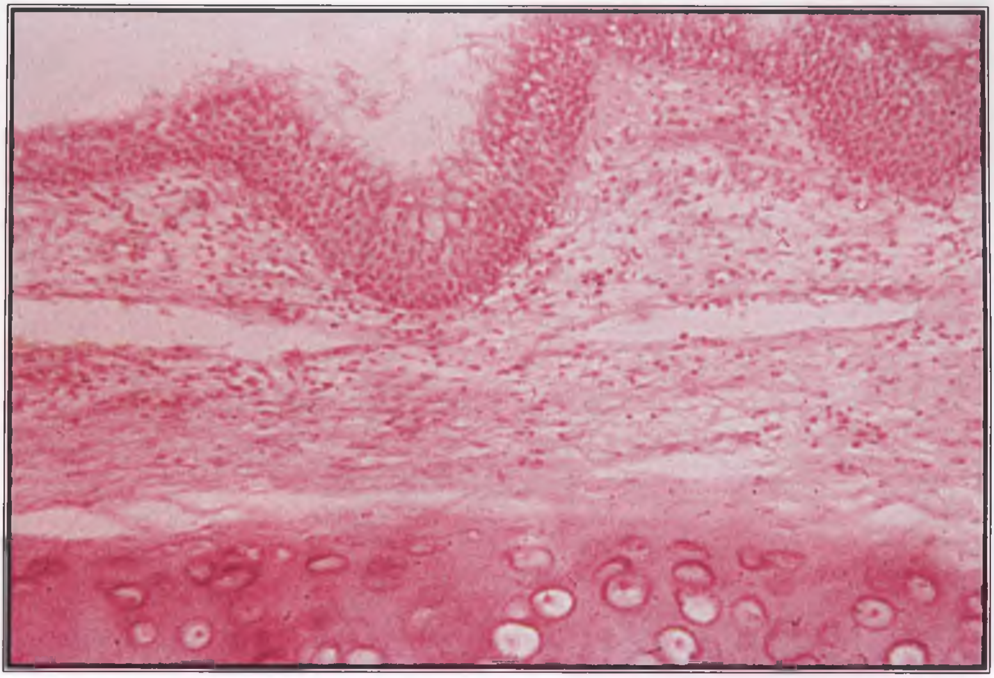


Fig. 193. Squamous metaplasia of the bronchial mucous membrane epithelium (H.E. stain, × 70).

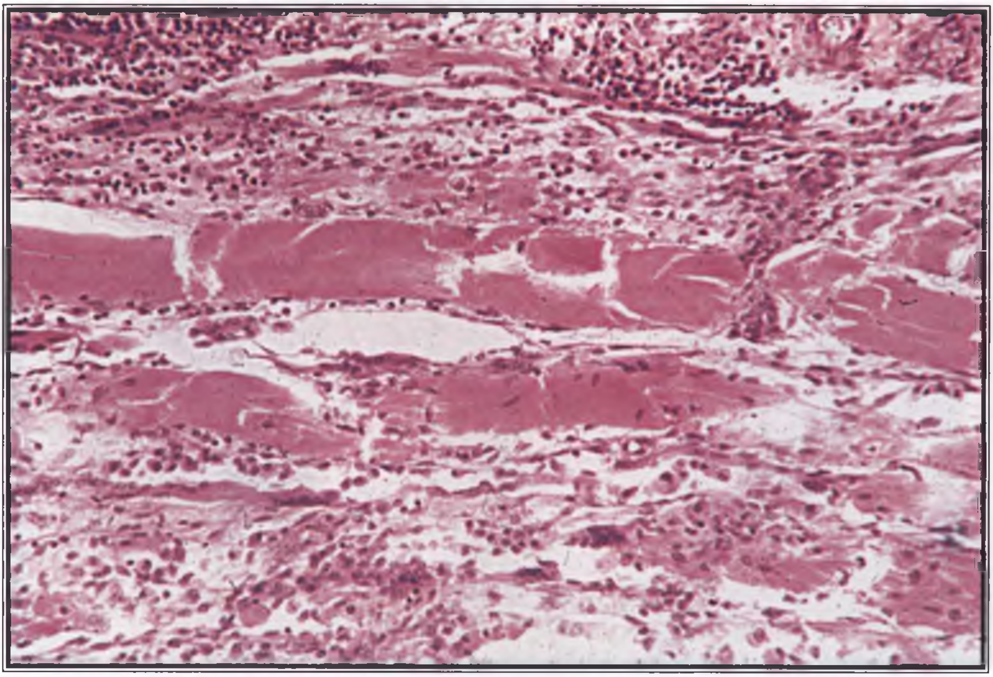


Fig. 194. Organization of a necrotic zone in the striated muscle (H.E. stain, × 70).

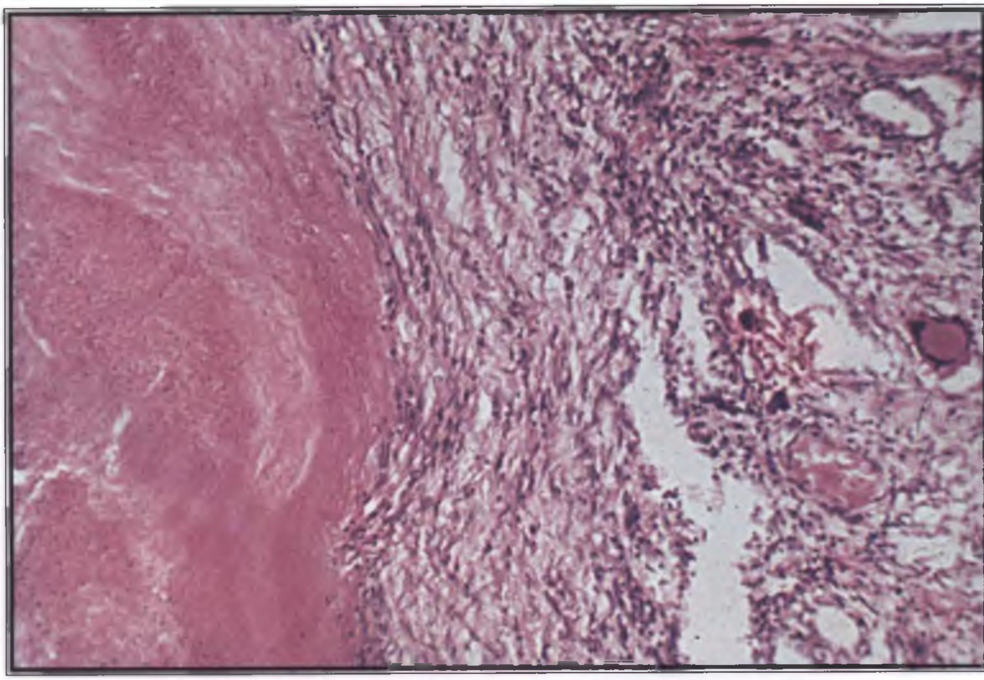


Fig. 195. Encapsulation of a caseous necrotic focus in tuberculosis (H.E. coloring, × 70).

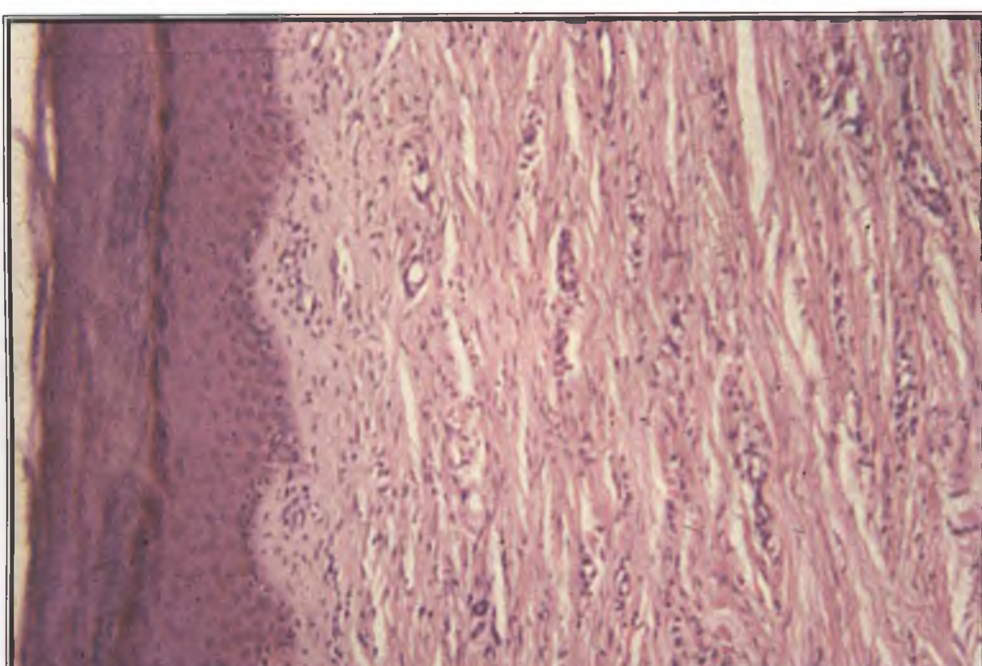


Fig. 196. Healing of a cutaneous wound (H.E. stain, × 70).

Fig. 197. Pulmonary chondroma.

Fig. 198. Neurofibromatosis of skin.

Fig. 199. Myxoma of the heart.

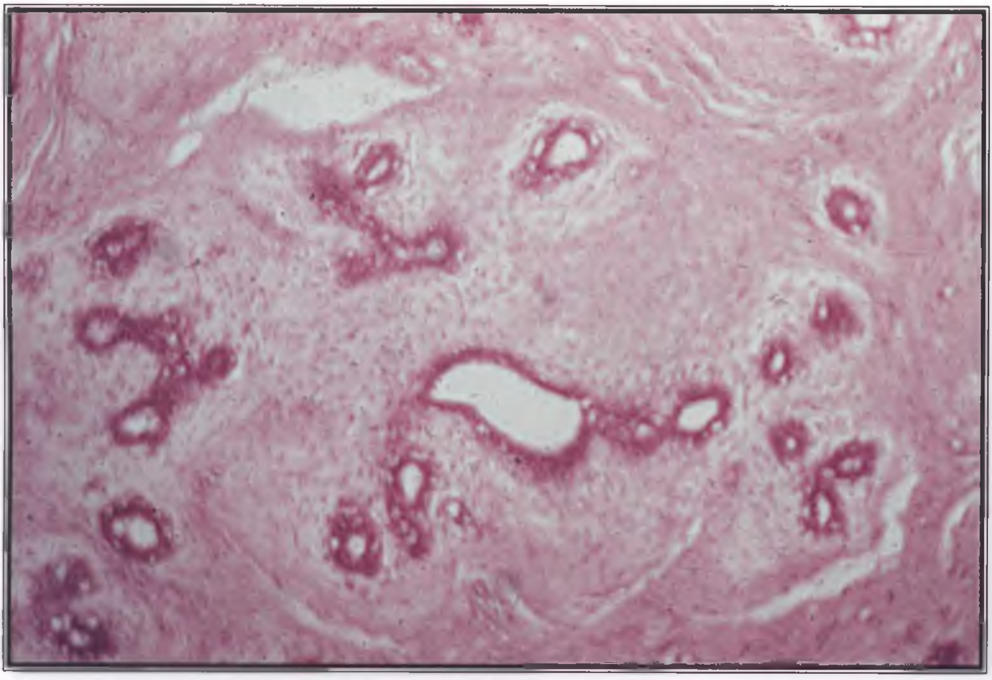


Fig. 200. Tissular atypism in fibroadenoma of the breast (H.E. stain, × 70).

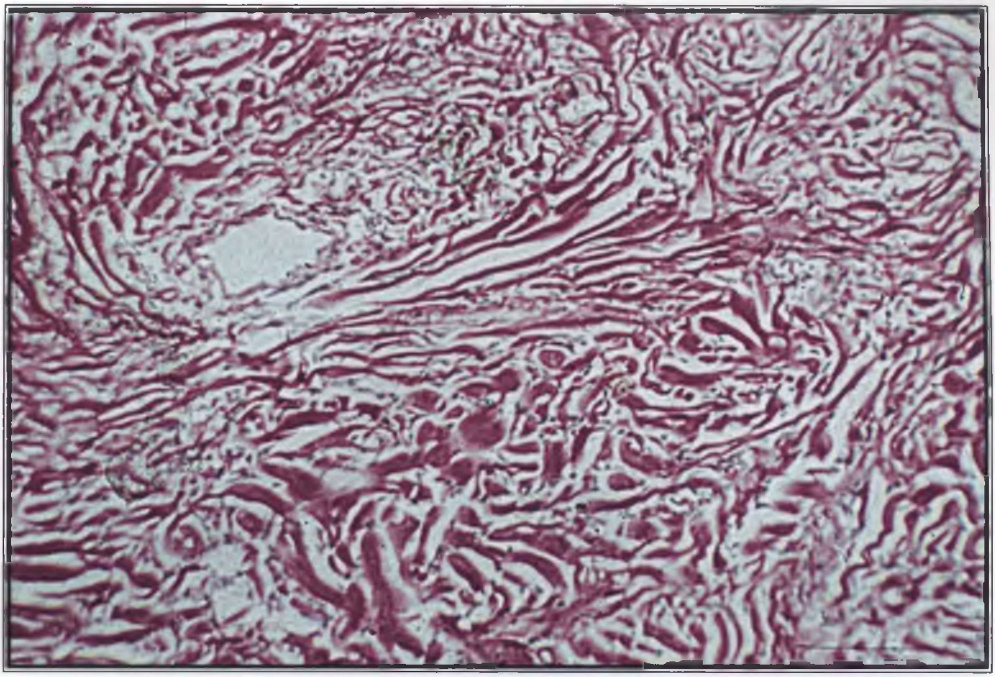


Fig. 201. Tissular atypism in leiomyoma (Van Gieson stain, × 70).

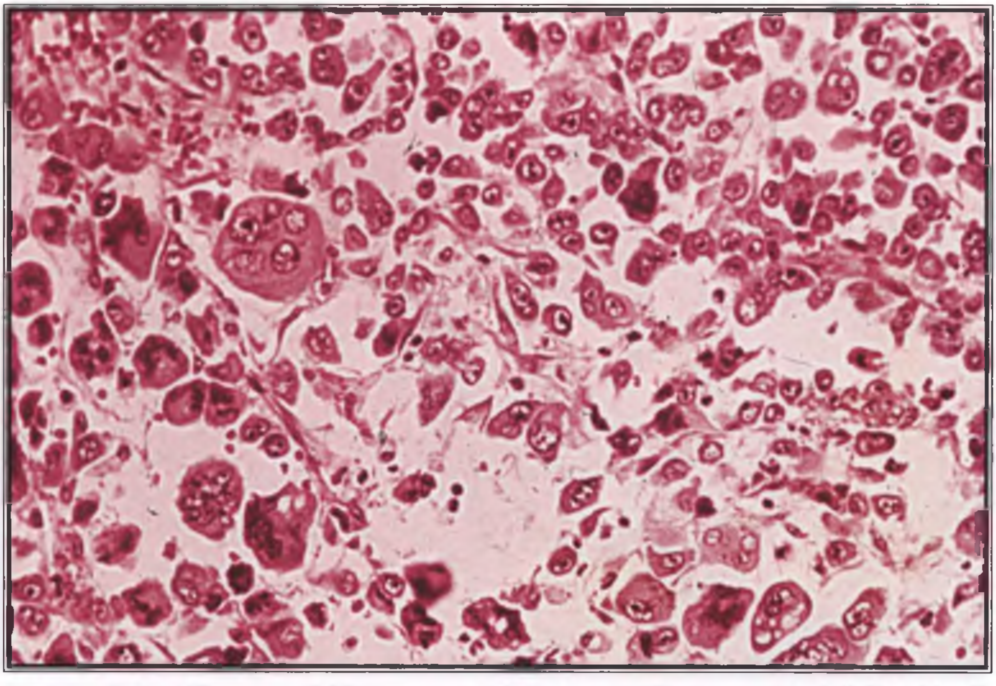


Fig. 202. Cellular atypism in undifferenciated carcinoma (H.E. stain, × 70).

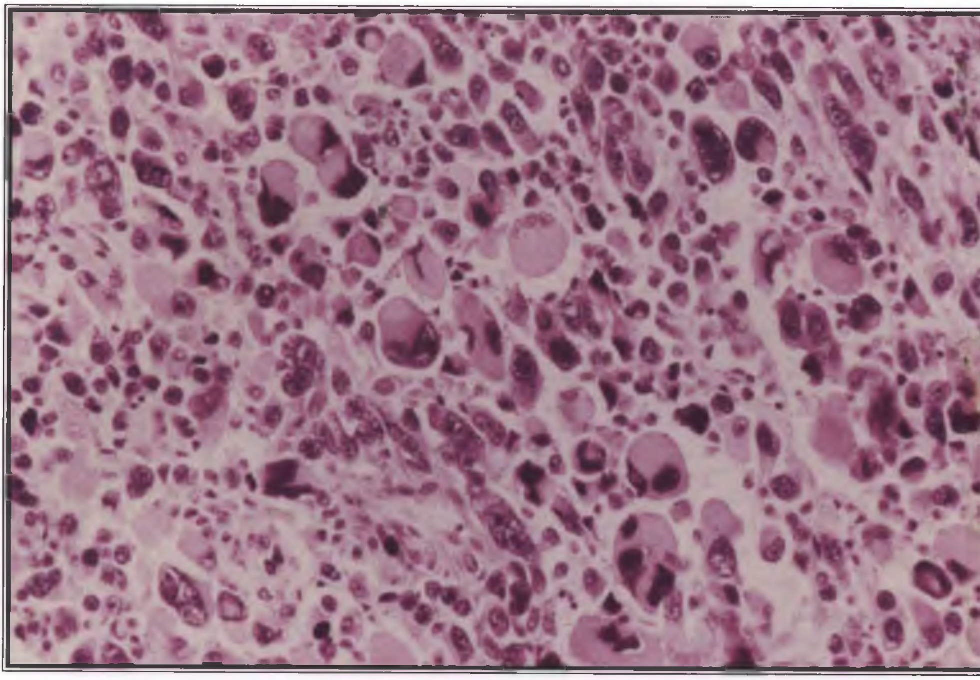


Fig. 203. Cellular atypism in rhabdomyosarcoma (H.E. stain, × 70)..

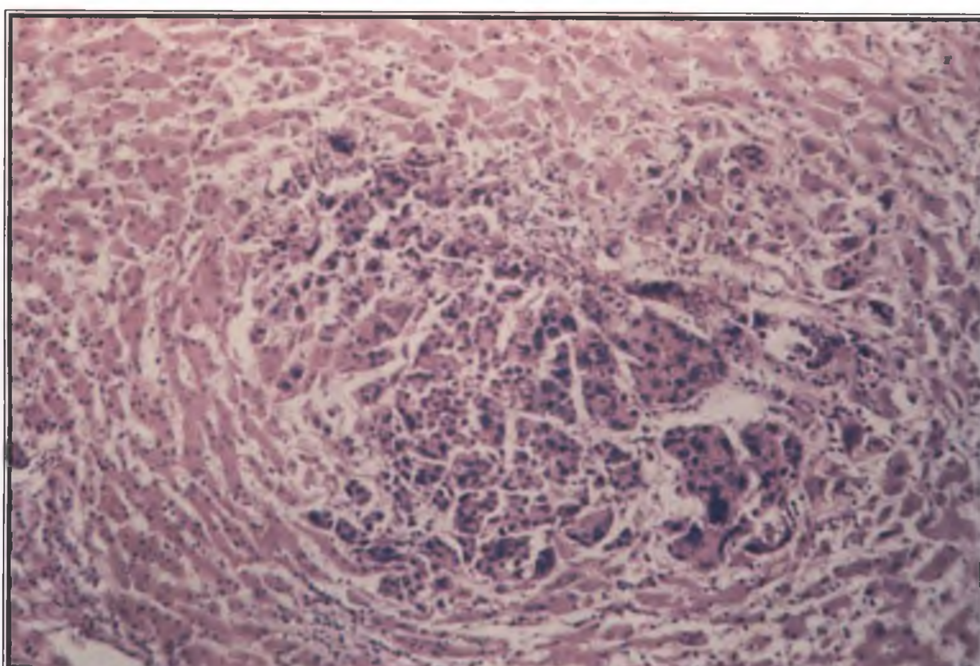


Fig. 204. Cellular atypism in the hepatocellular carcinoma (H.E. stain, × 70).

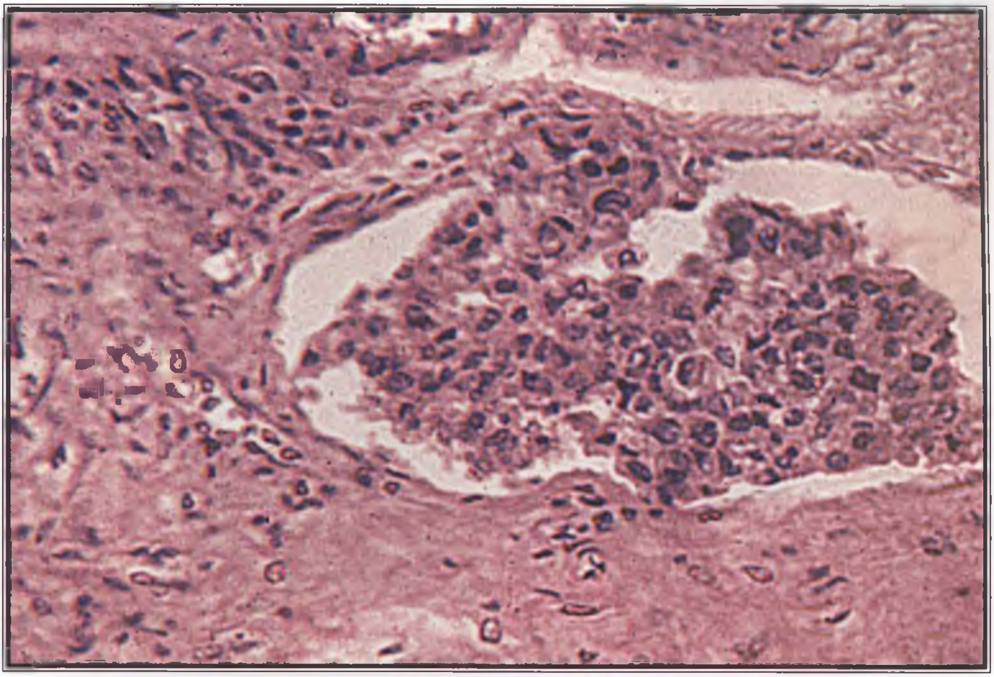


Fig. 205. Tumor embolus in a blood vessel (H.E. stain, × 70).

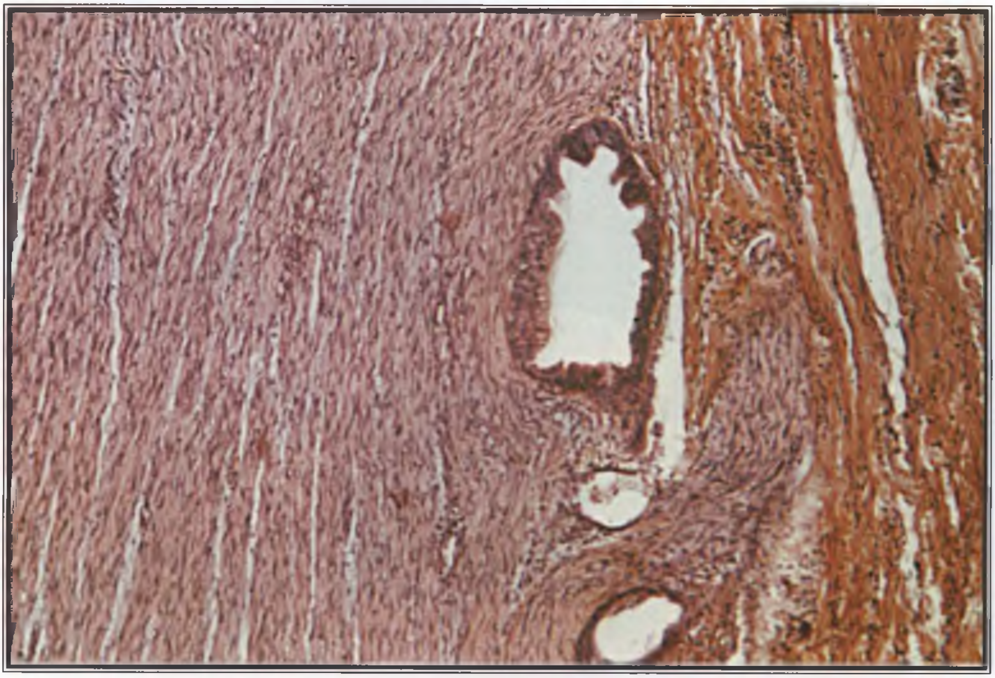


Fig. 206. Perineural spreading of the glandular carcinoma (H.E. stain, × 70).

Fig. 207. Carcinoma metastasis in liver.

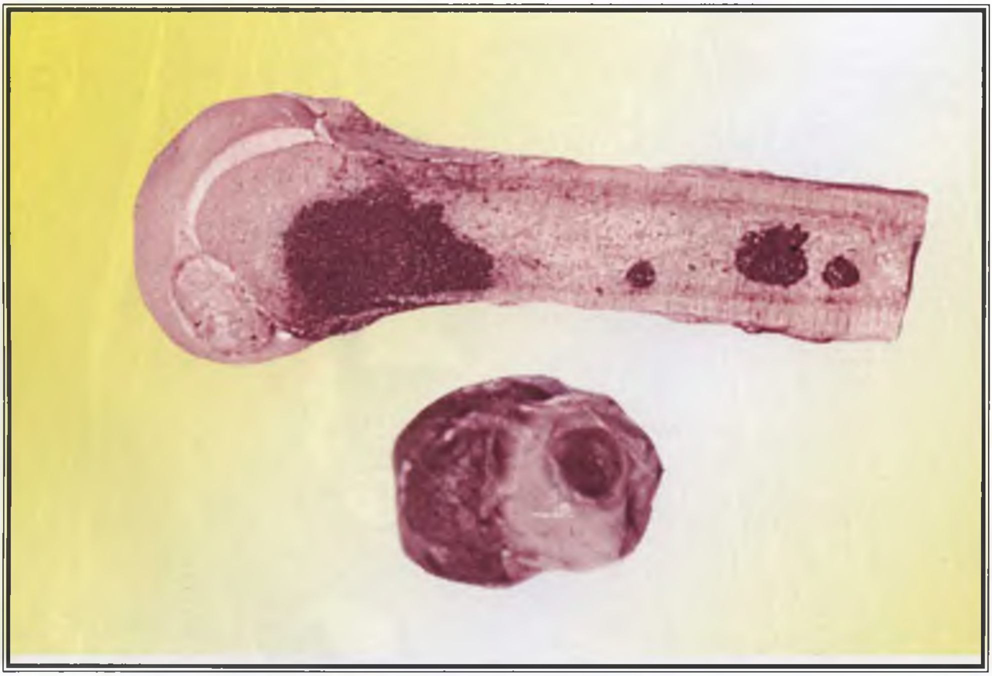


Fig. 208. Ocular melanoma metastasis in bones.

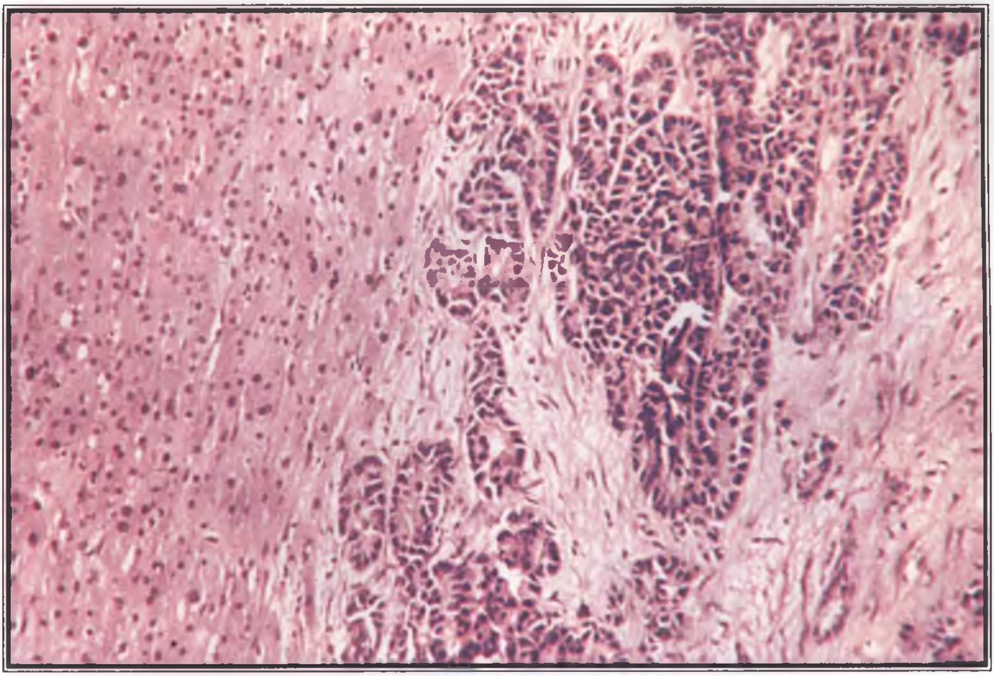


Fig. 209. Gastric adenocarcinoma metastases in the liver (H.E. stain, × 70).

Fig. 210. Papilloma of the skin, macroscopic aspect.

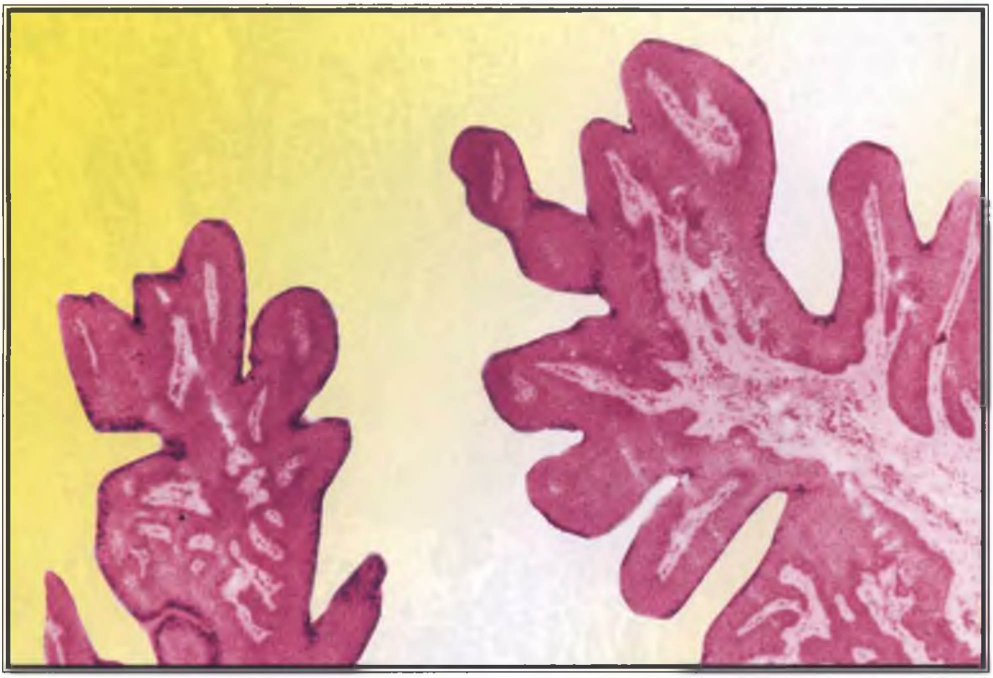


Fig. 211. Papilloma, microscopic aspect (H.E. stain, × 70).

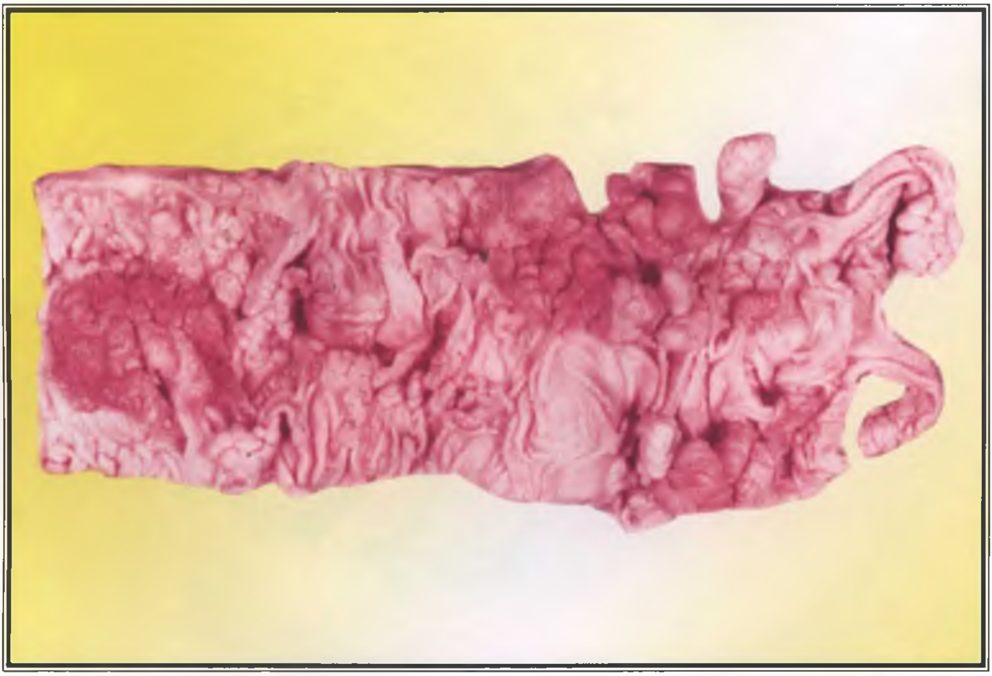


Fig. 212. Adenomatous polyps of the colon.

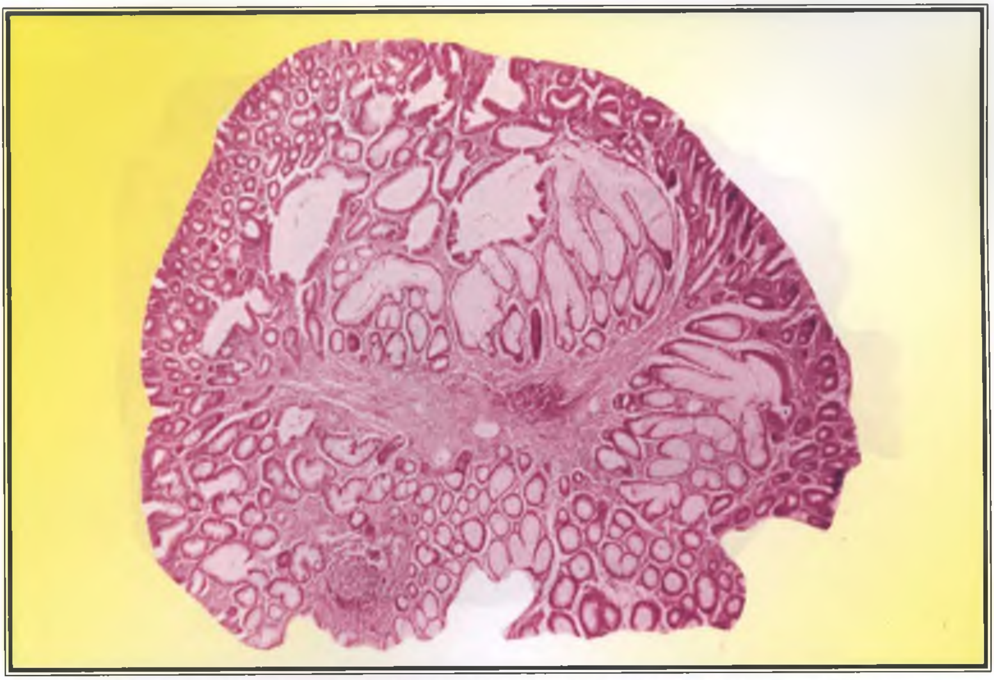


Fig. 213. Adenoma (adenomatous polyp) of the large intestine (H.E. stain, × 70).

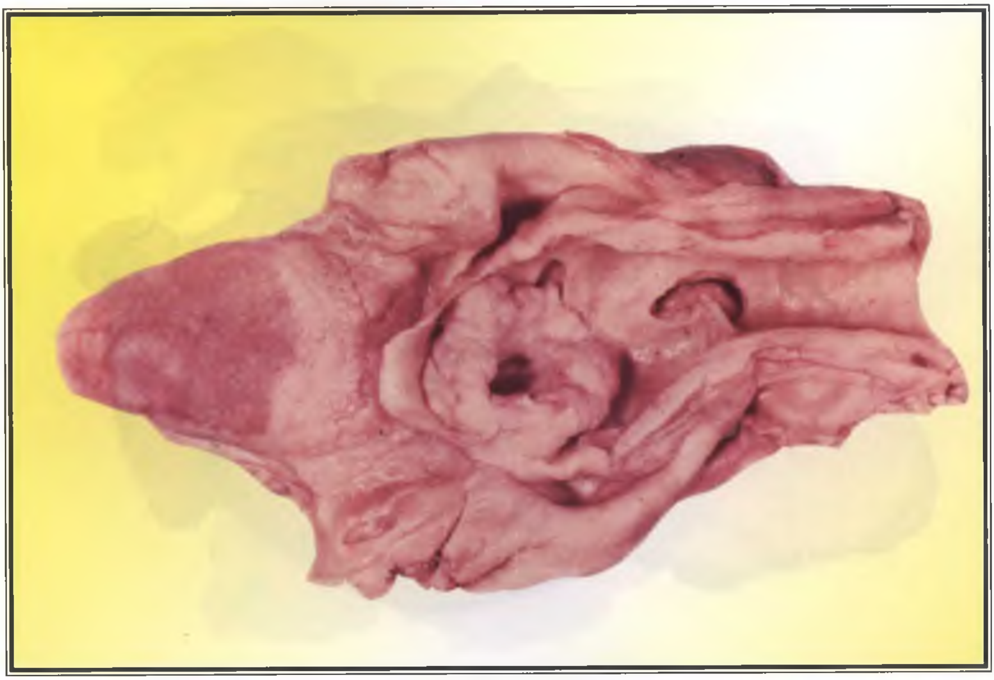


Fig. 214. Laryngeal carcinoma.

Fig. 215. Fungiform gastric carcinoma.

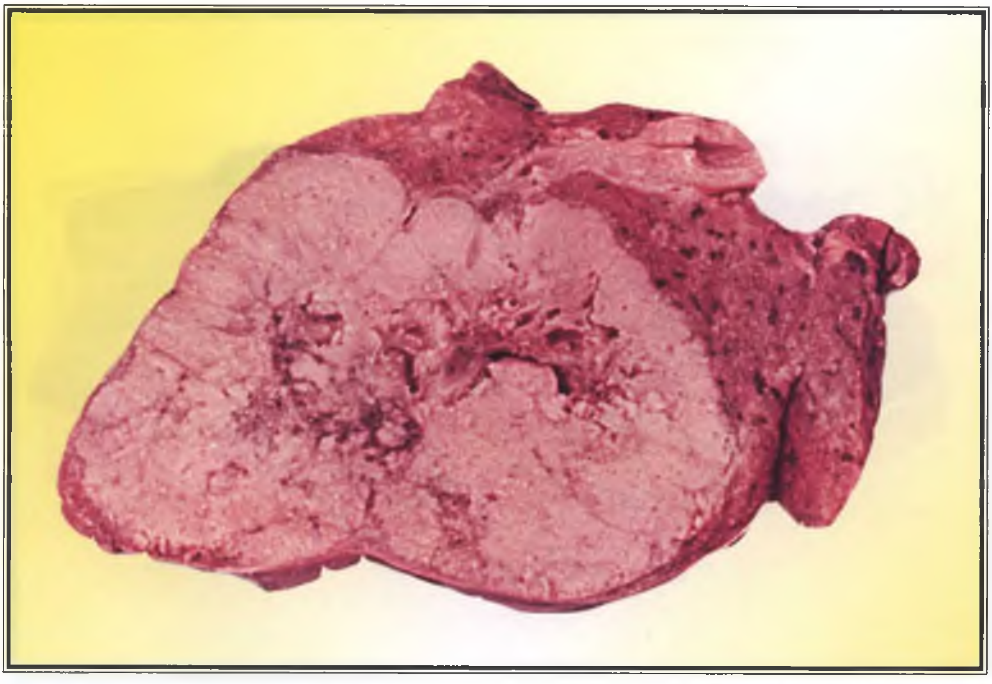


Fig. 216. Peripheral pulmonary carcinoma.

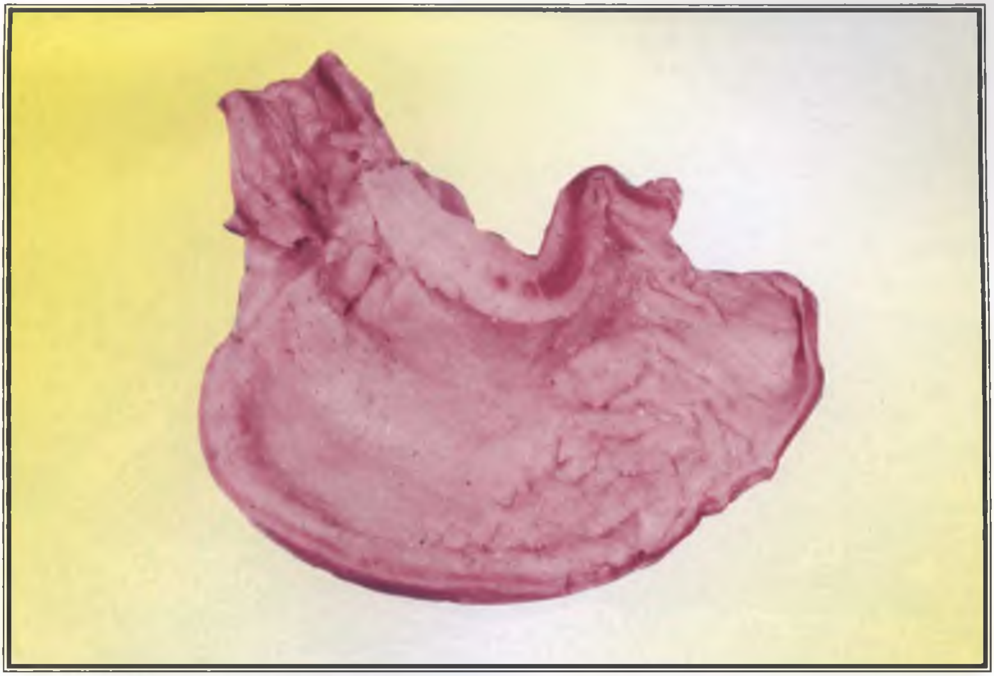


Fig. 217. Diffuse gastric carcinoma.

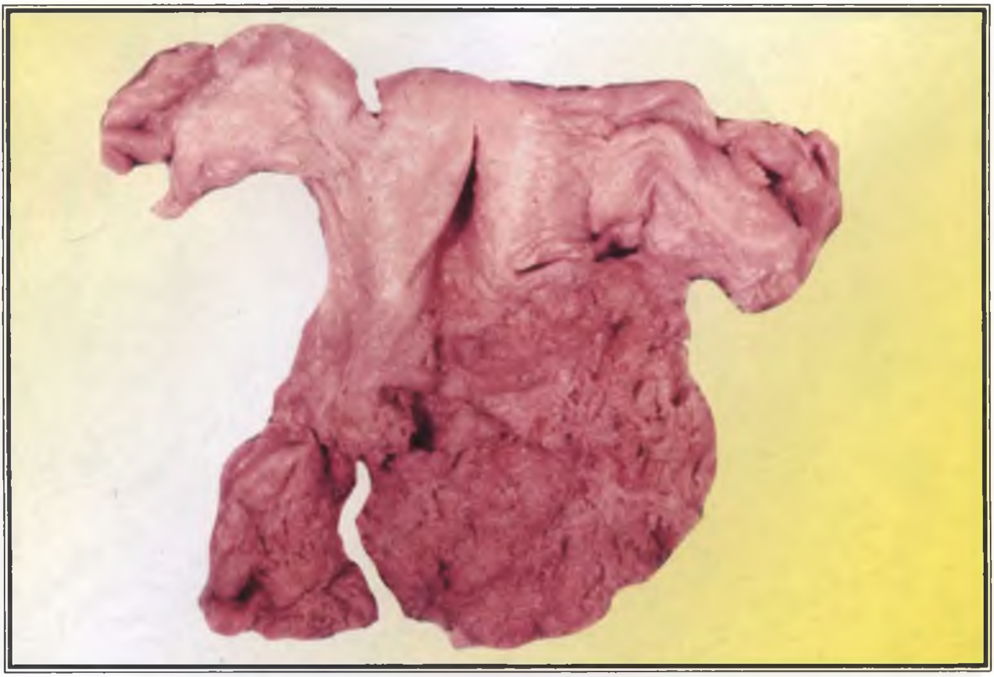


Fig. 218. Carcinoma of the cervix.

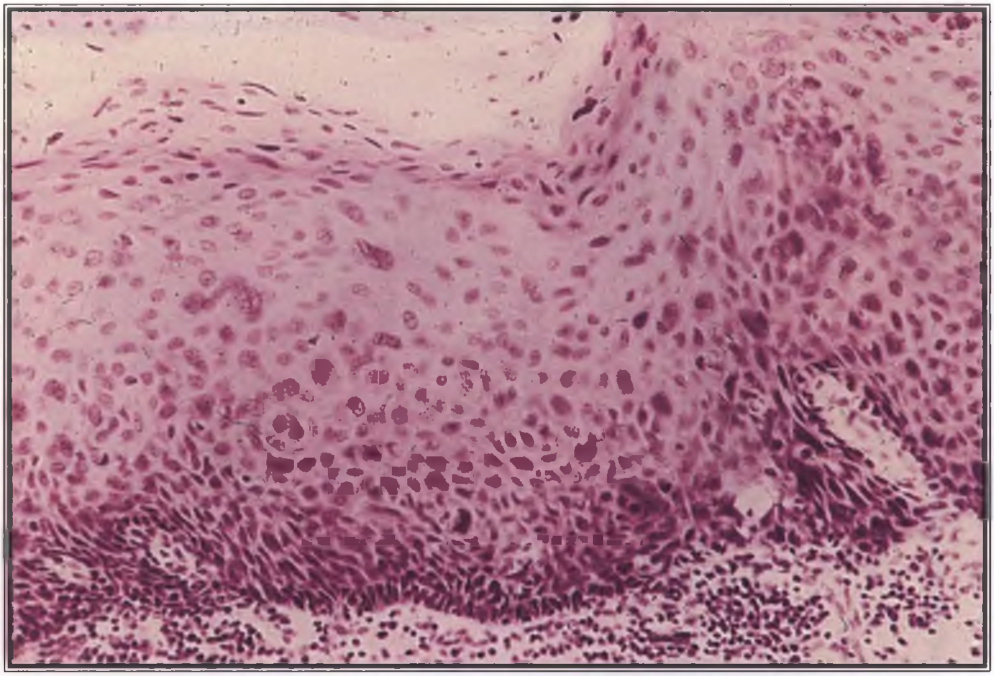


Fig. 219. Carcinoma in situ (H.E. stain, × 70).

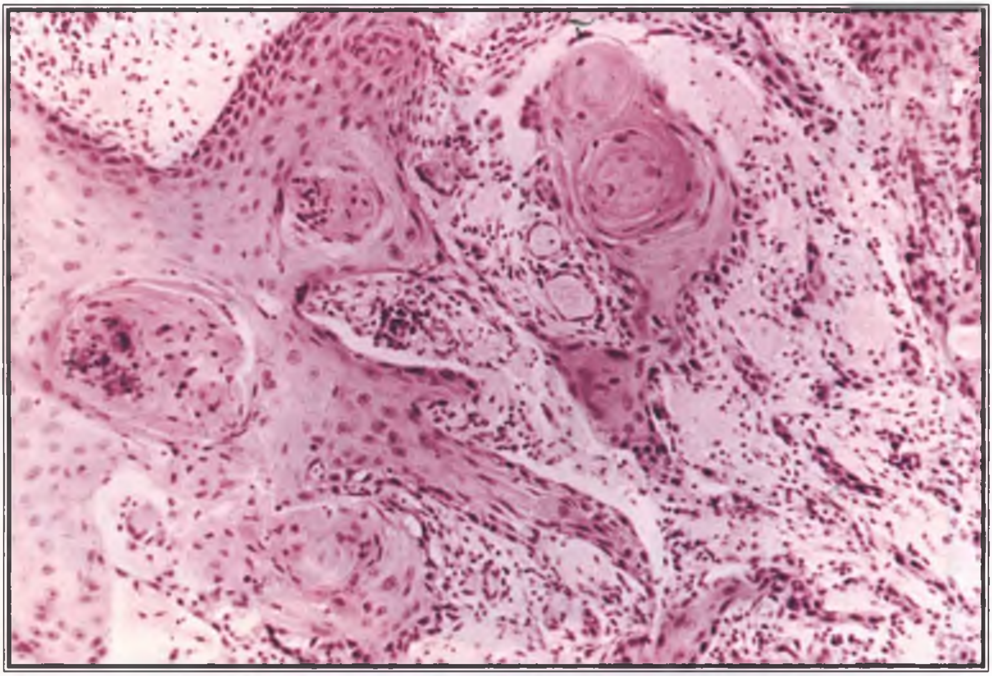


Fig. 220. Epidermoid (squamous) keratinizing carcinoma (H.E. stain, × 70).

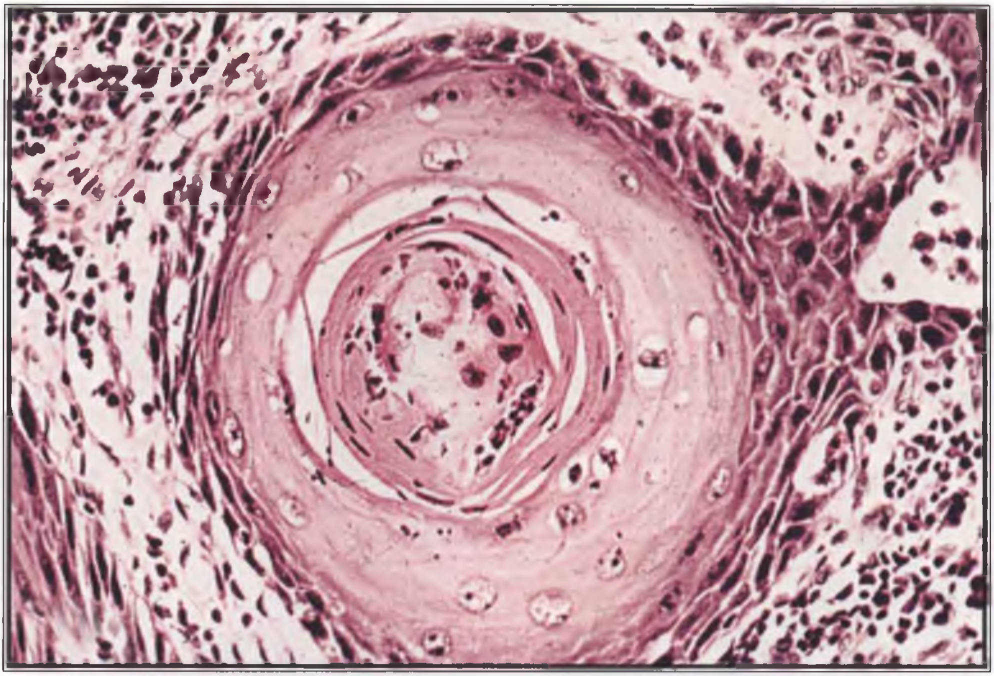


Fig. 221. Keratin pearl (H.E. stain, × 70).

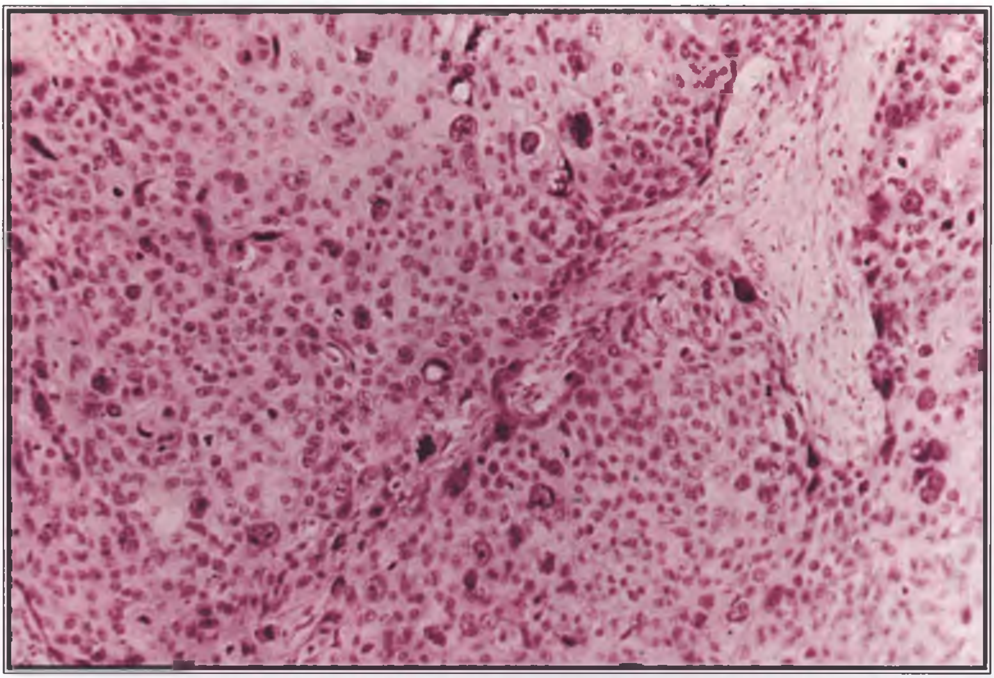


Fig. 222. Epidermoid (squamous) non-keratinizing carcinoma (H.E. stain, × 70).

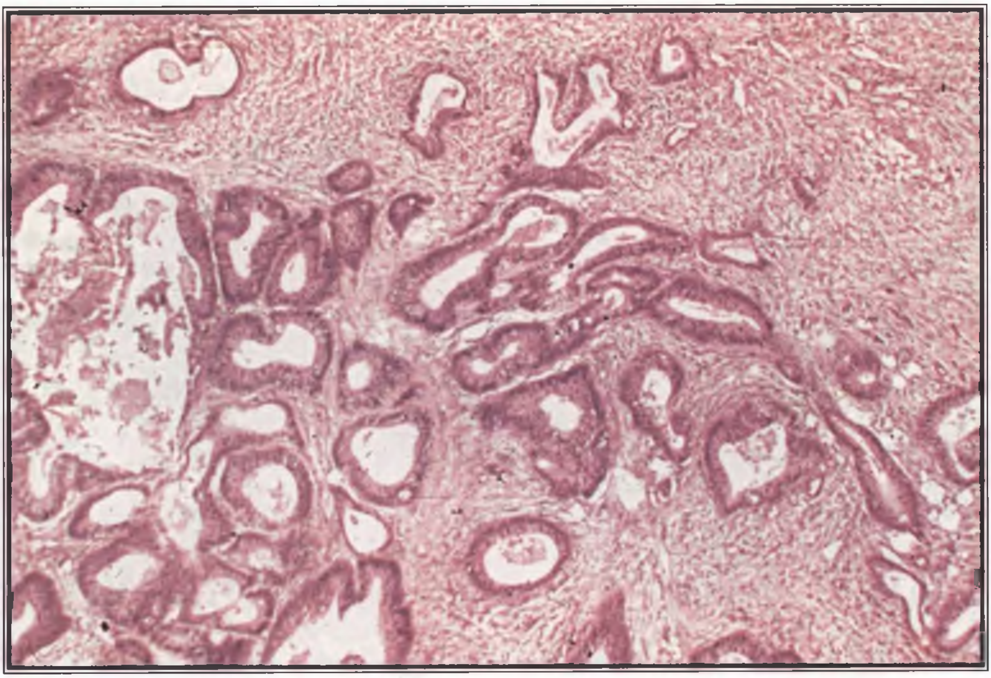


Fig. 223. Tubular adenocarcinoma (H.E. stain, × 70).

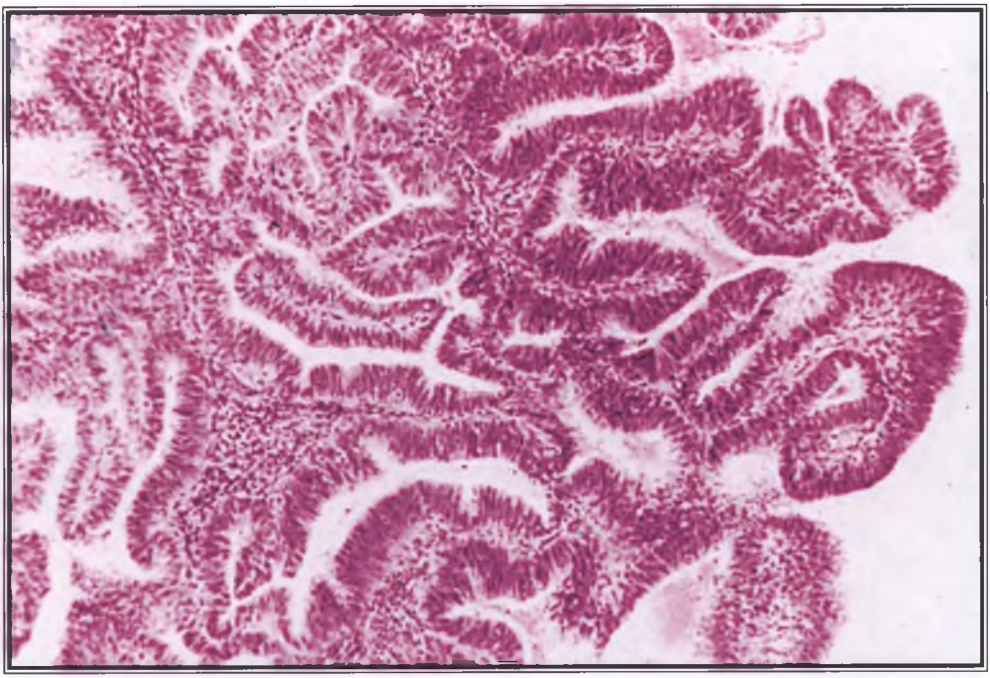


Fig. 224. Papillary adenocarcinoma (H.E. stain, × 70).

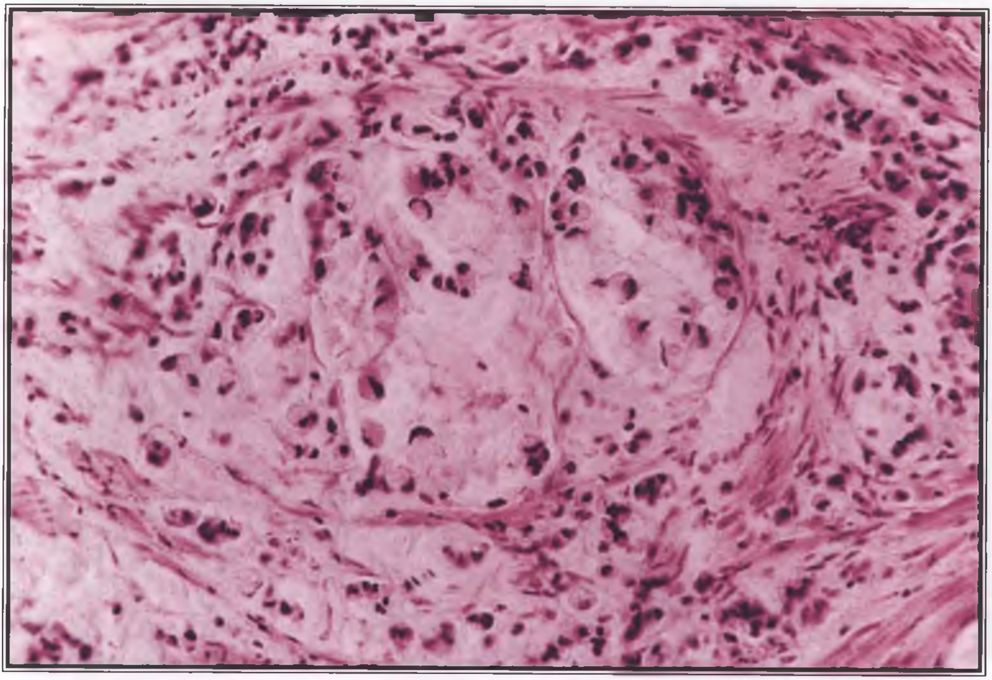


Fig. 225. Muciparous carcinoma (H.E. stain, × 70).

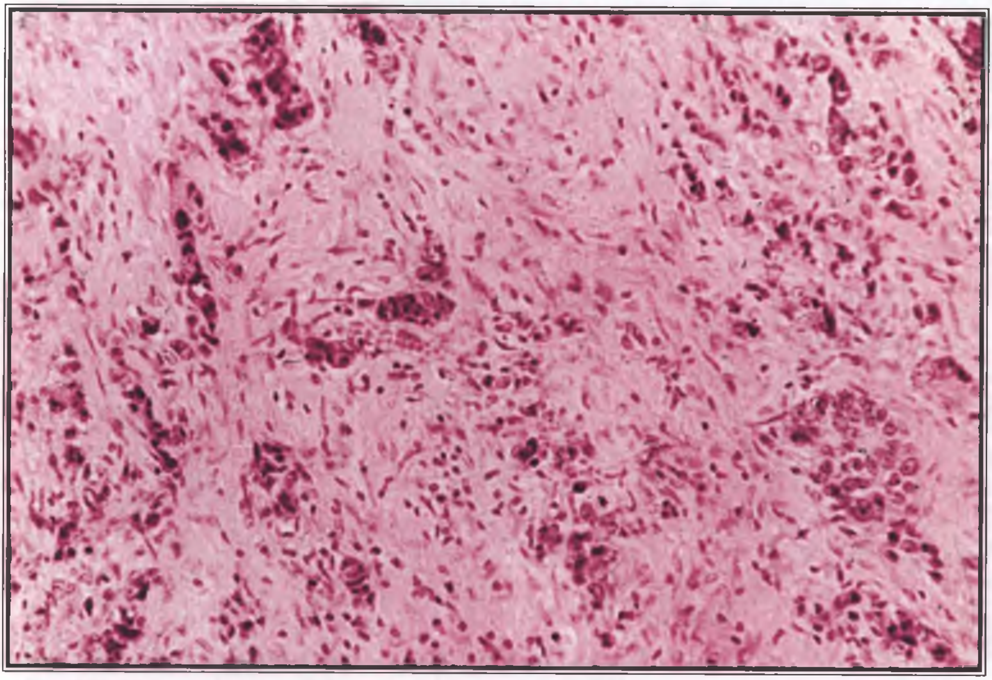


Fig. 226. Scirrhous carcinoma (H.E. stain, × 70).

Fig. 227. Carcinoma with small cells (H.E. stain, × 70).

Fig. 228. Fibroma, macroscopic aspect.

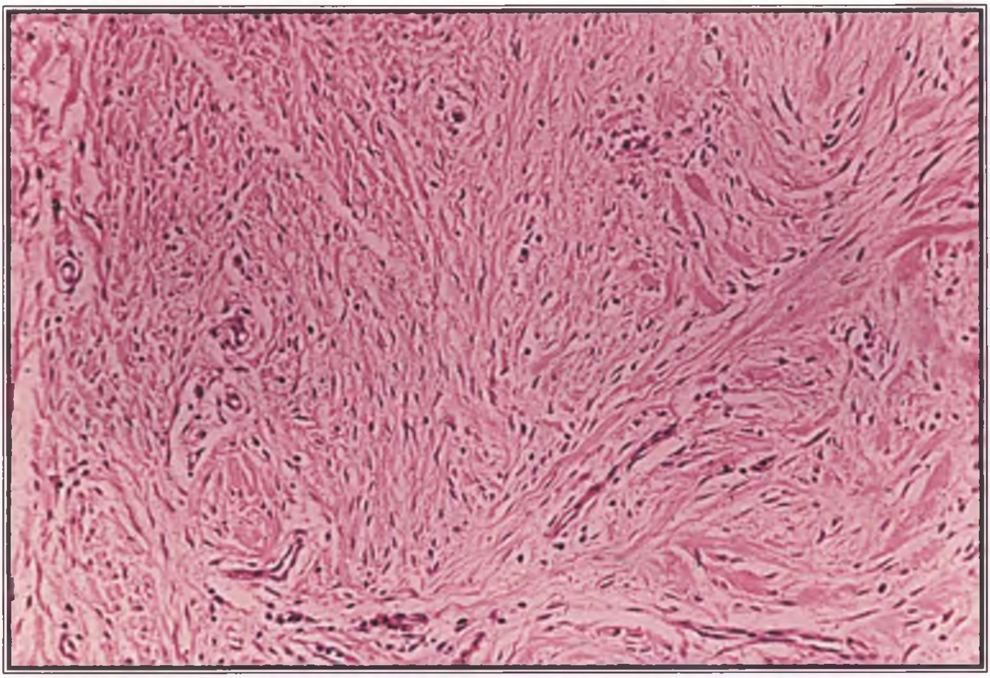


Fig. 229. Fibroma, microscopic aspect (H.E. stain, × 70).

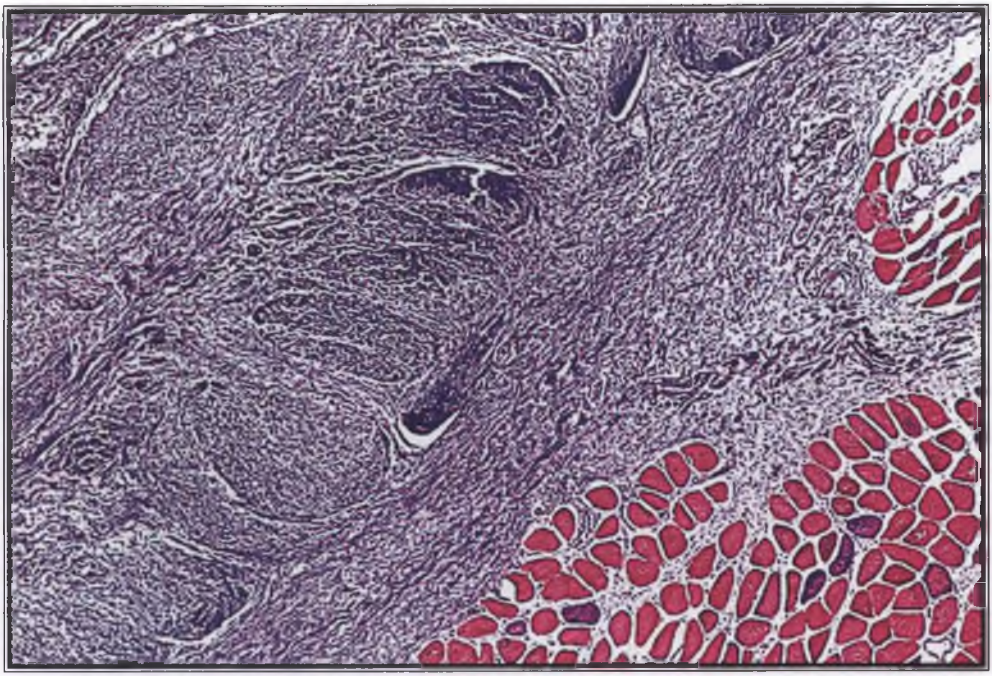


Fig. 230. Desmoid tumor (Masson trichrome stain, × 70).

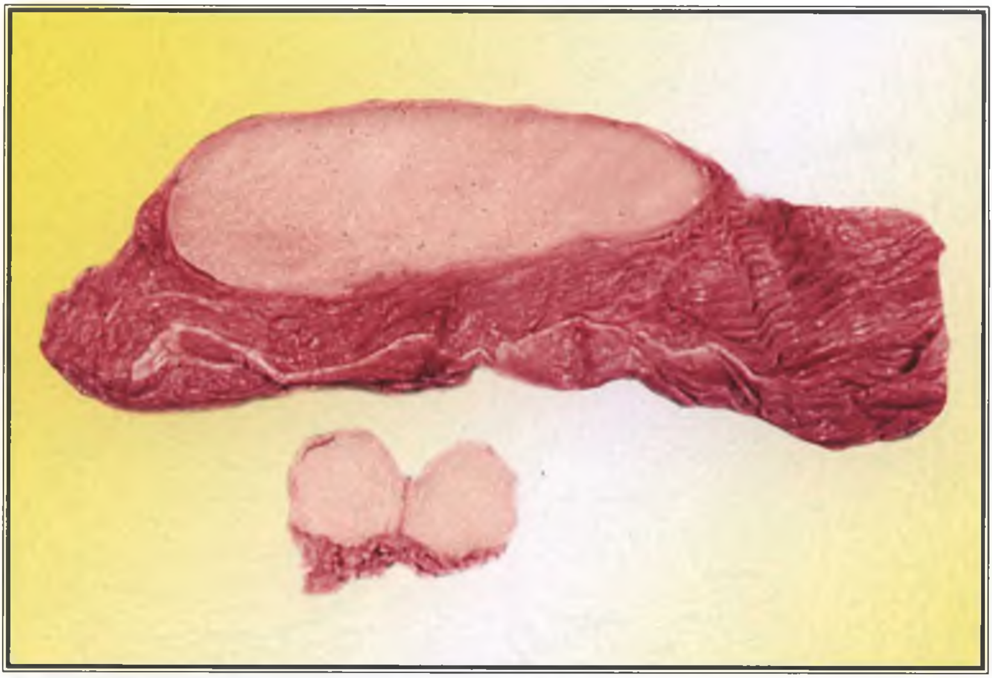


Fig. 231. Lipoma, macroscopic aspect.

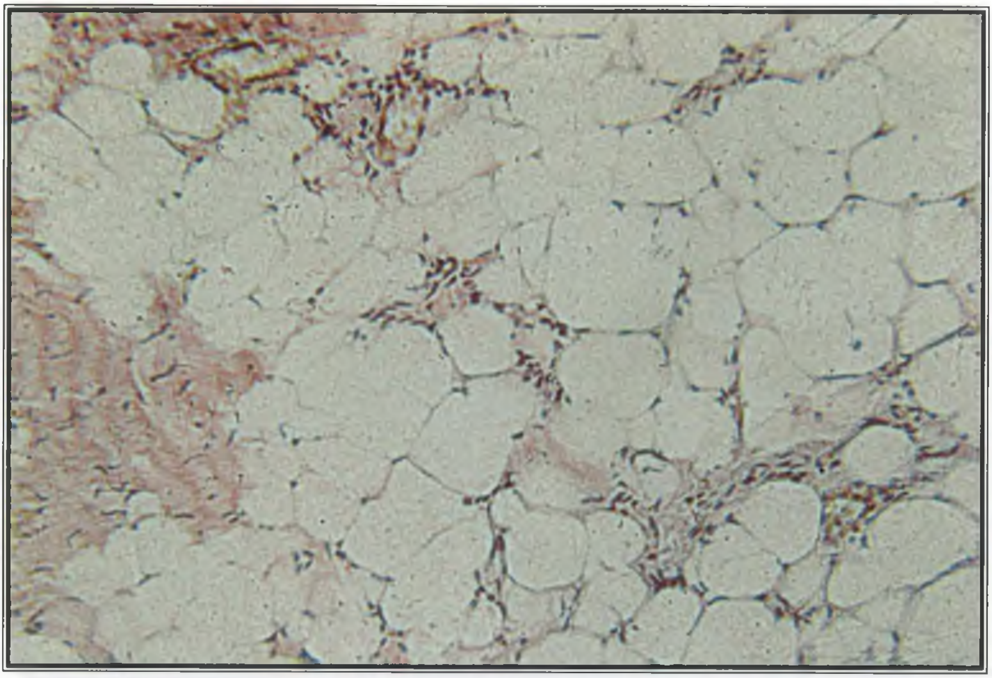


Fig. 232. Lipoma, microscopic aspect (H.E. stain, × 70).

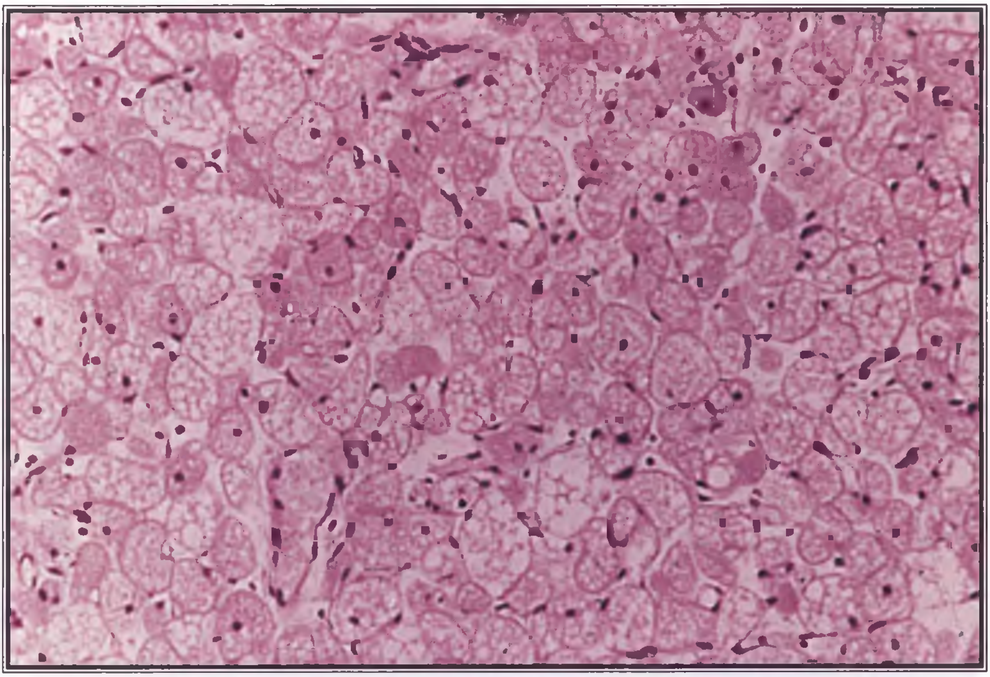


Fig. 233. Hibernoma (H.E. stain, × 70).

Fig. 234. Uterine fibroleiomyoma.

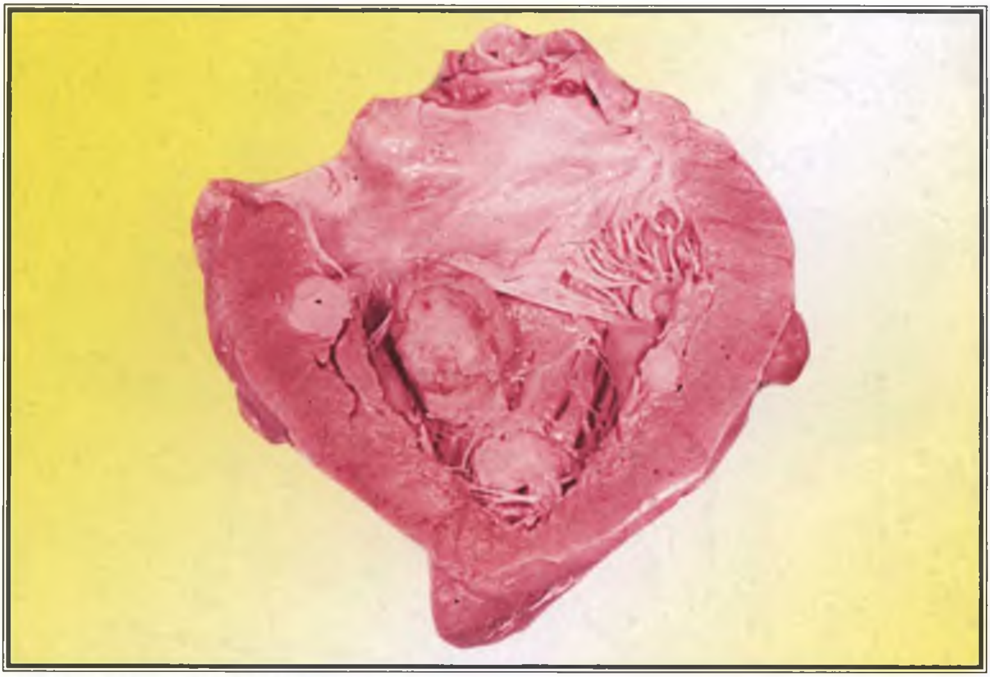


Fig. 235. Myocardial rhabdomyoma.

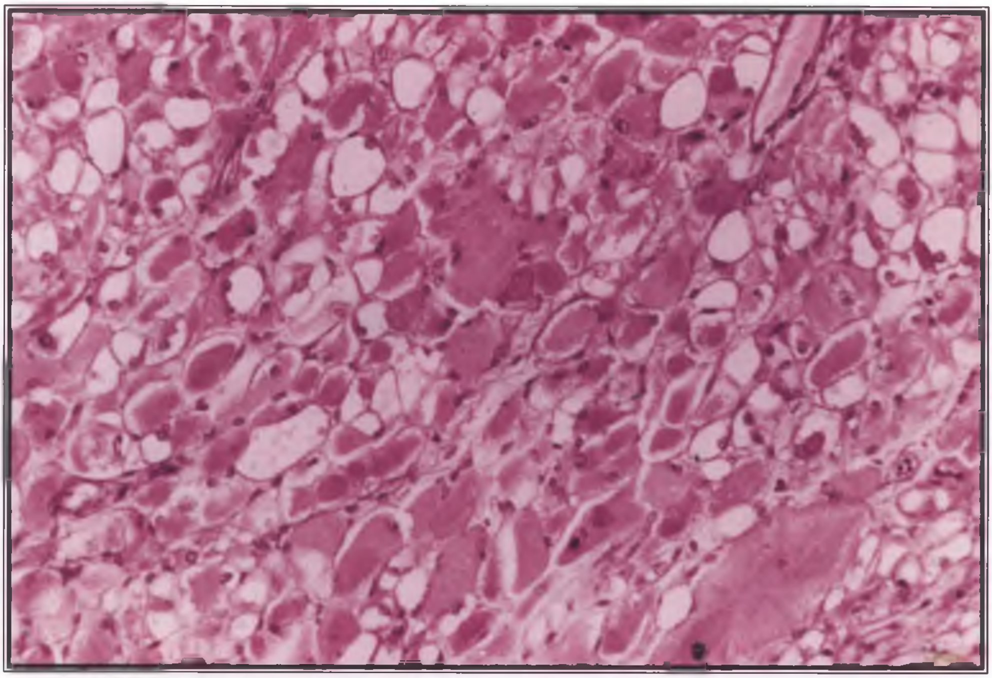


Fig. 236. Rhabdomyoma (H.E. stain, × 70).

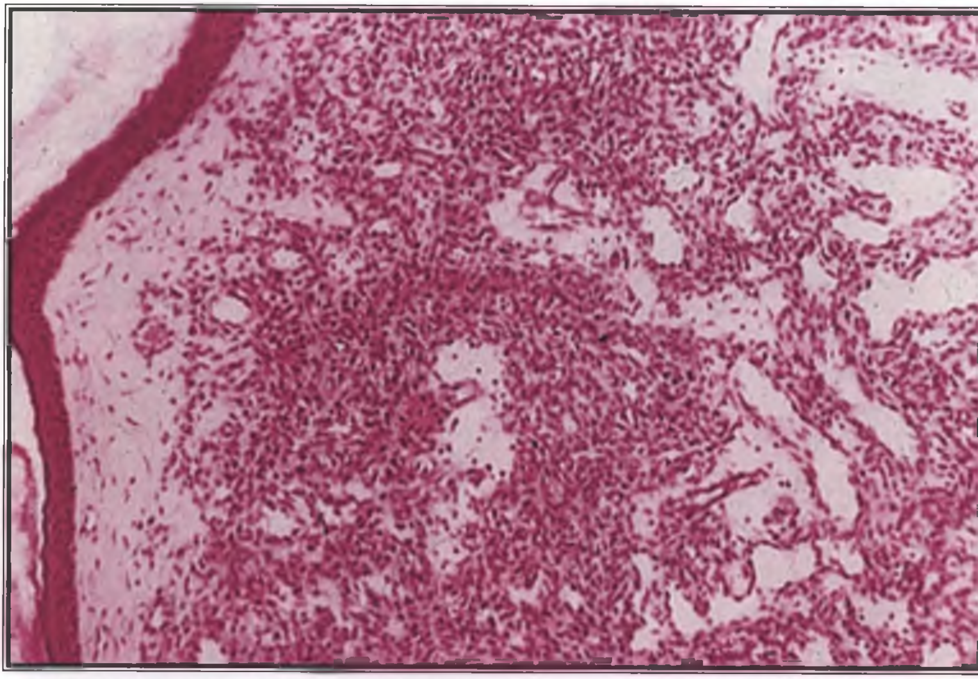


Fig. 237. Capillary hemangioma (H.E. stain, × 70).

Fig. 238. Cavernous hemangioma of the liver, macroscopic aspect.

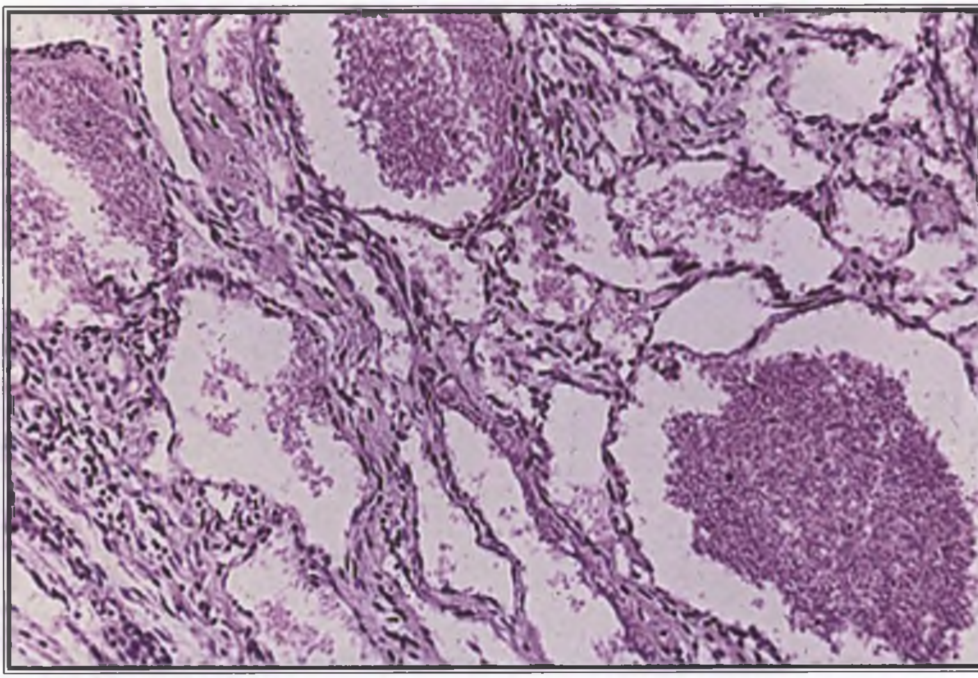


Fig. 239. Cavernous hemangioma, microscopic aspect (H.E. stain, × 70).

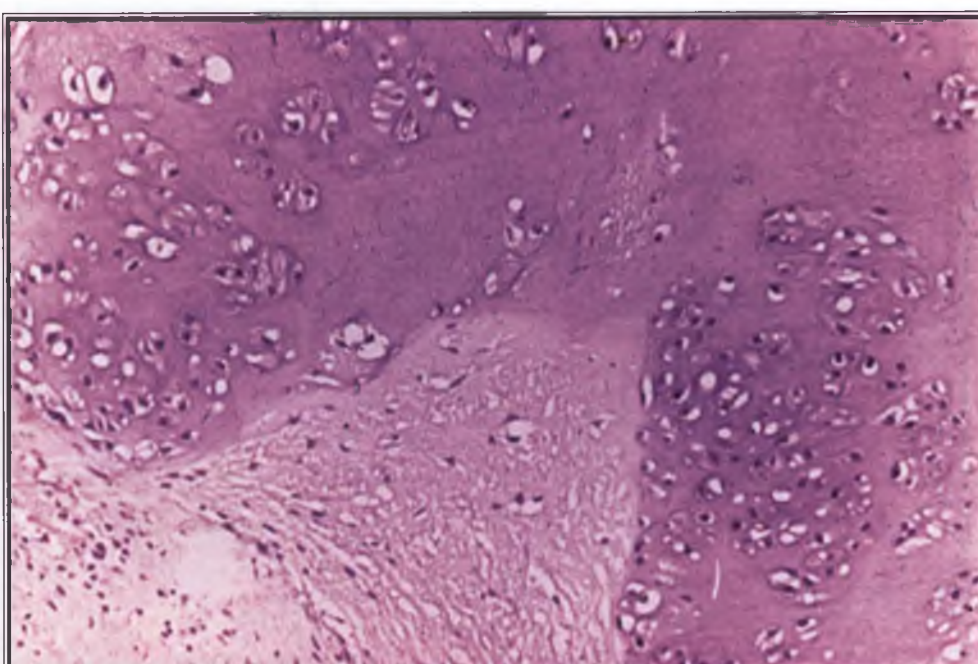


Fig. 240. Chondroma (H.E. stain, × 70).

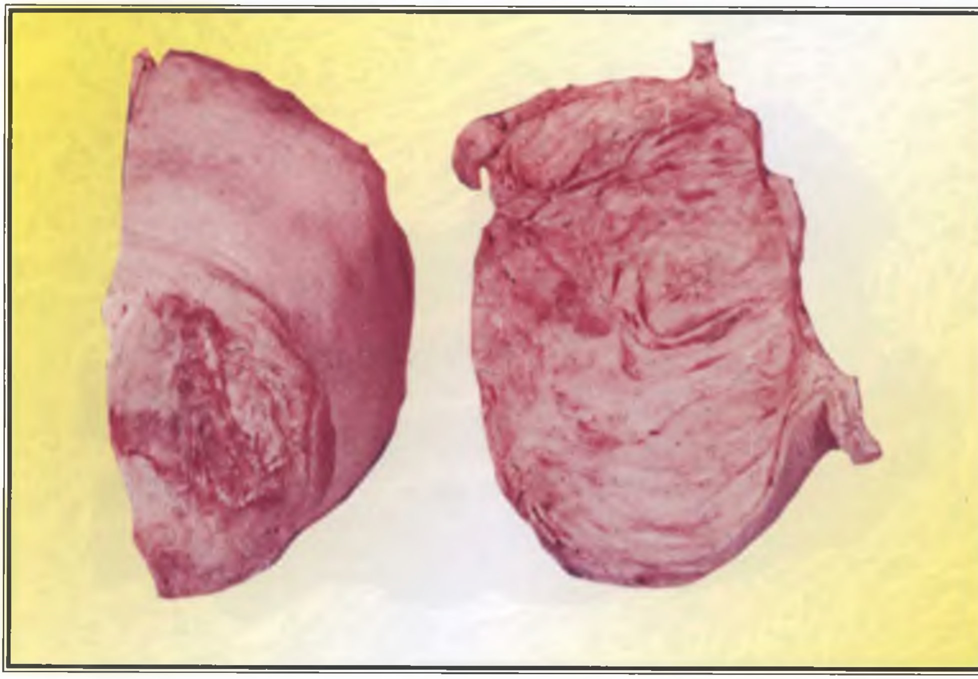


Fig. 241. Fibrosarcoma.

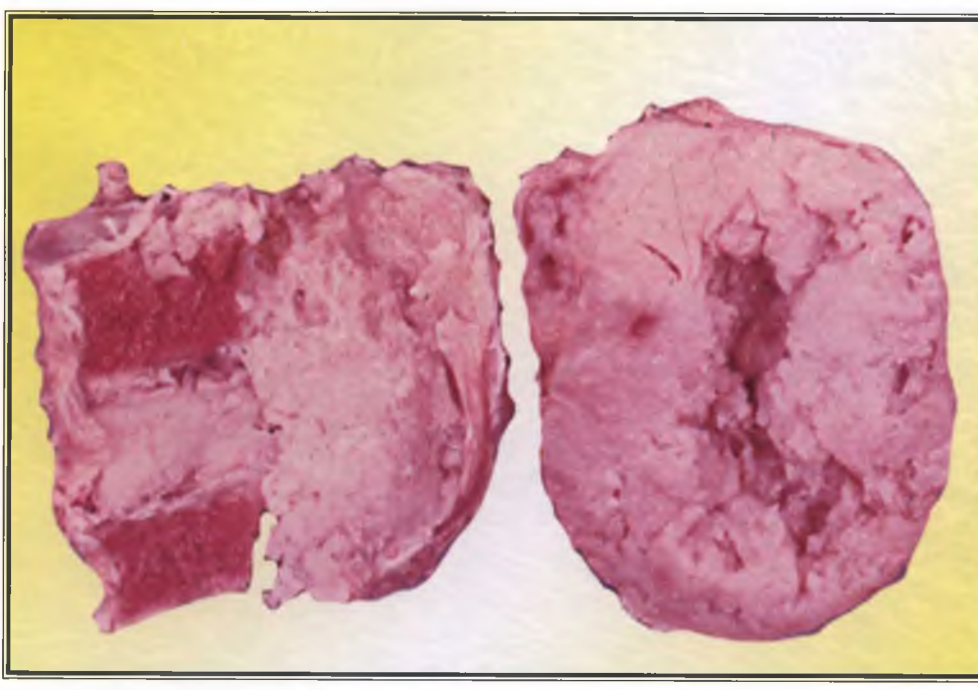


Fig. 242. Chondrosarcoma.

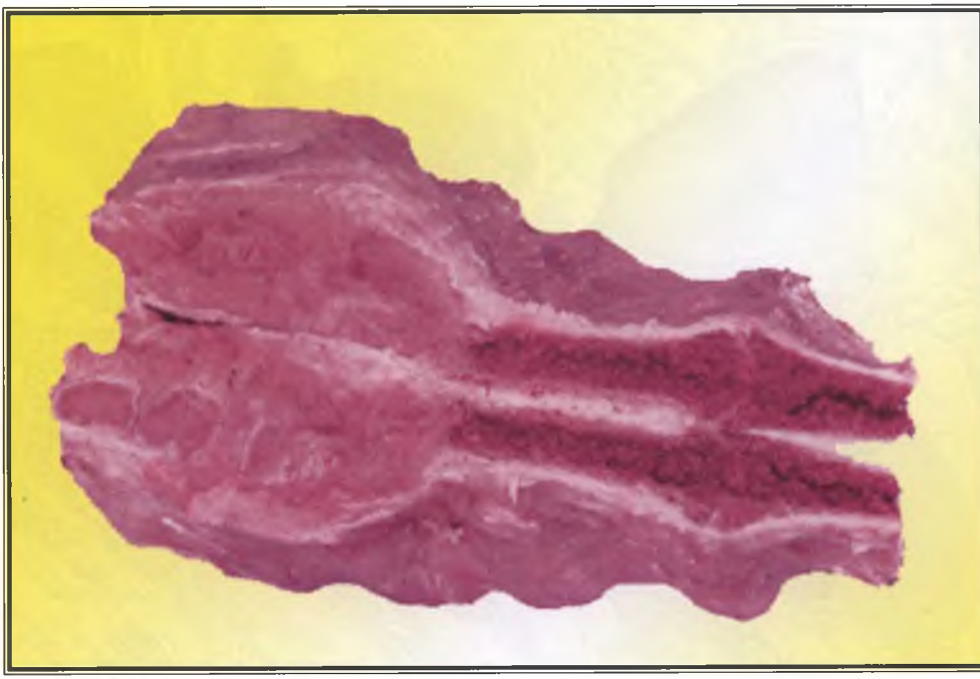


Fig. 243. Osteosarcoma.

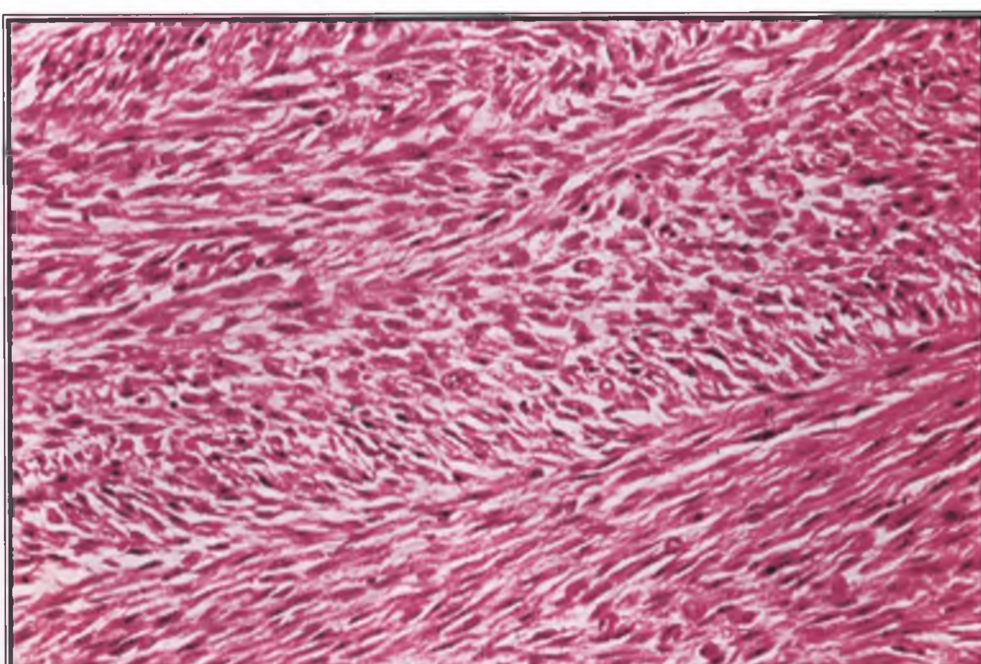


Fig. 244. Fibrosarcoma (H.E. stain, × 70).

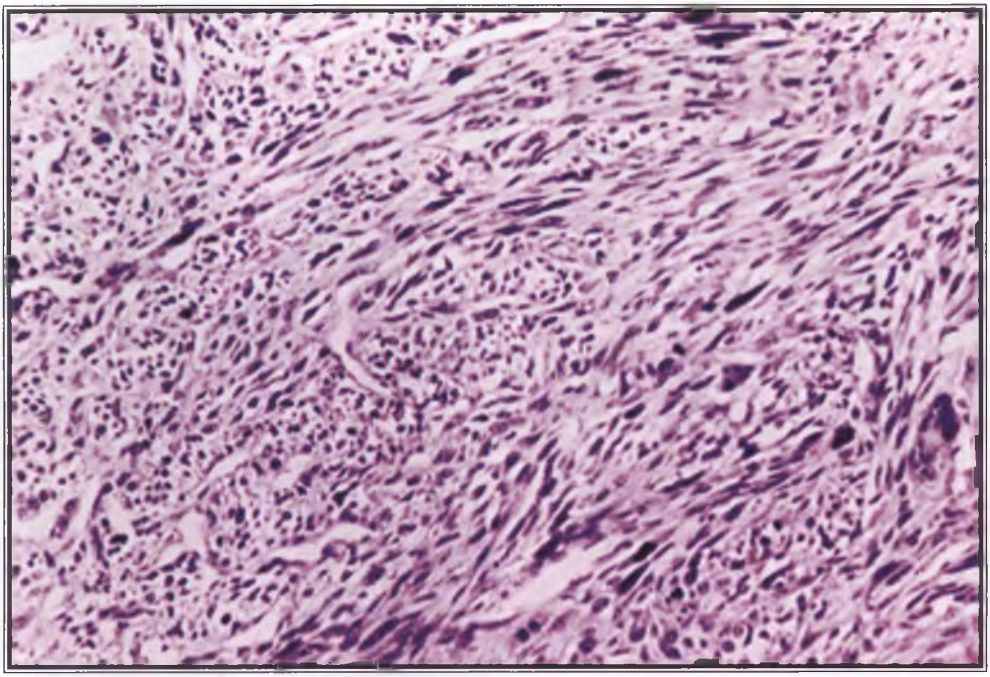


Fig. 245. Leiomyosarcoma (H.E. stain, × 70).

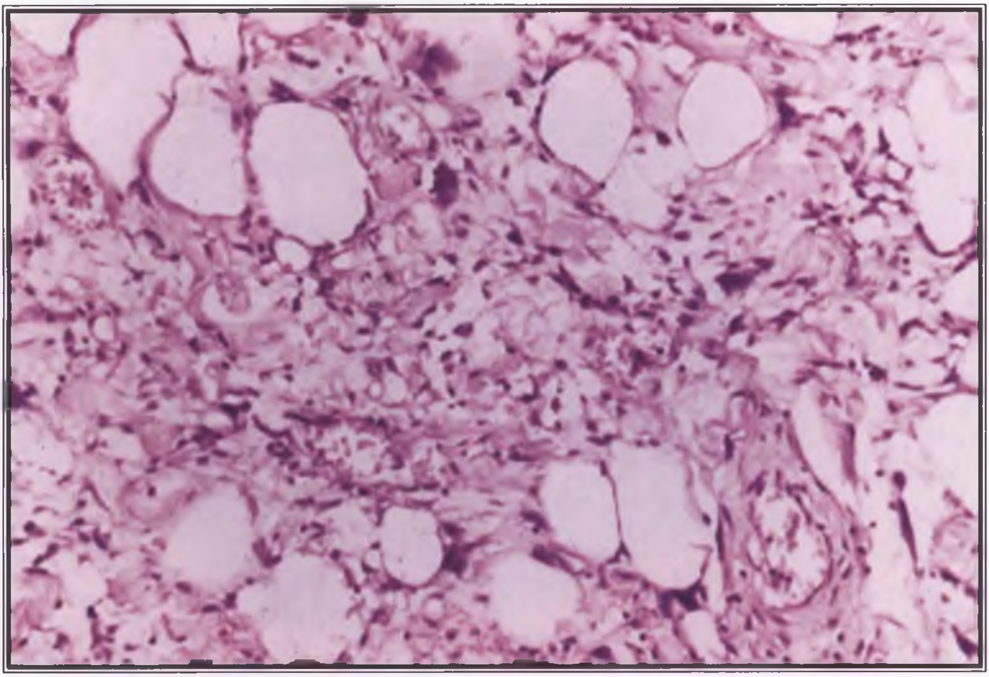


Fig. 246. Liposarcoma (H.E. stain, × 70).

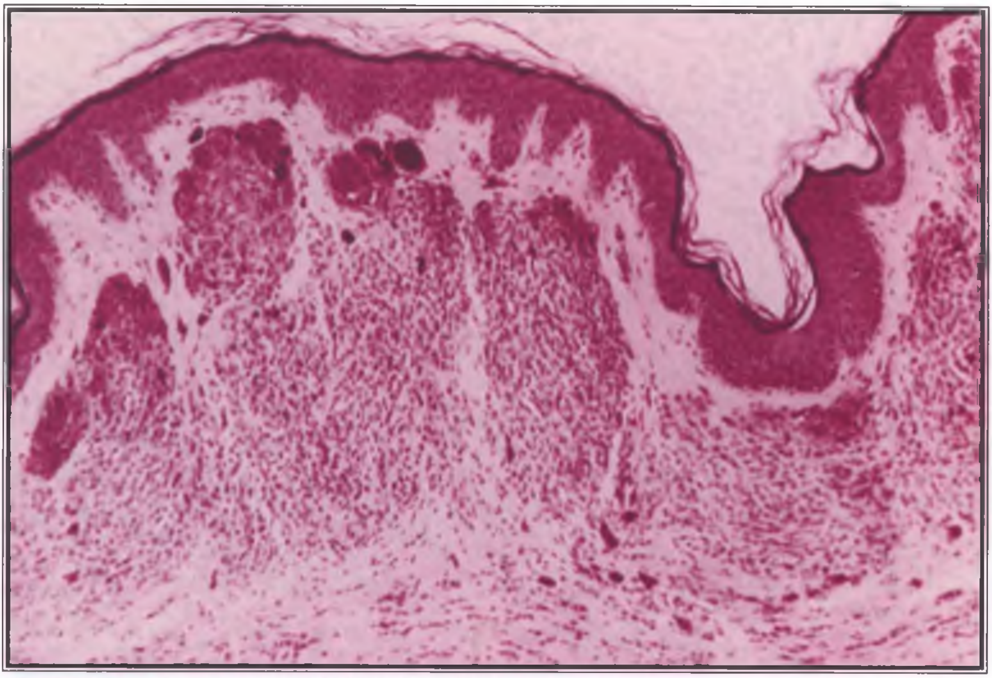


Fig. 247. Intradermal nevus (H.E. stain, × 70).

Fig. 248. Malignant melanoma of the skin.

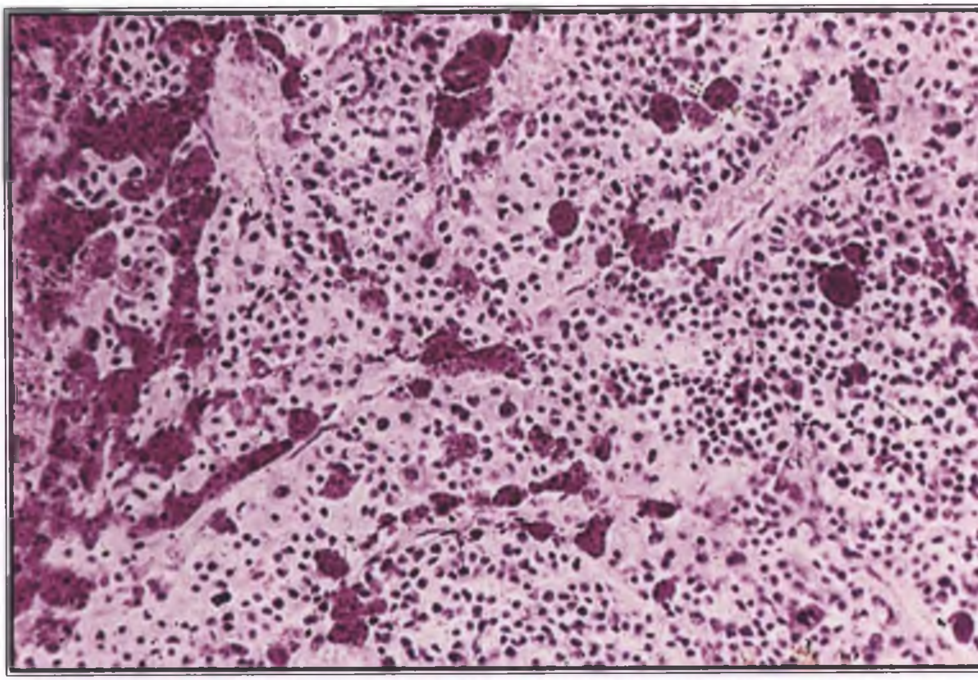


Fig. 249. Malignant melanoma (H.E. stain, × 70).

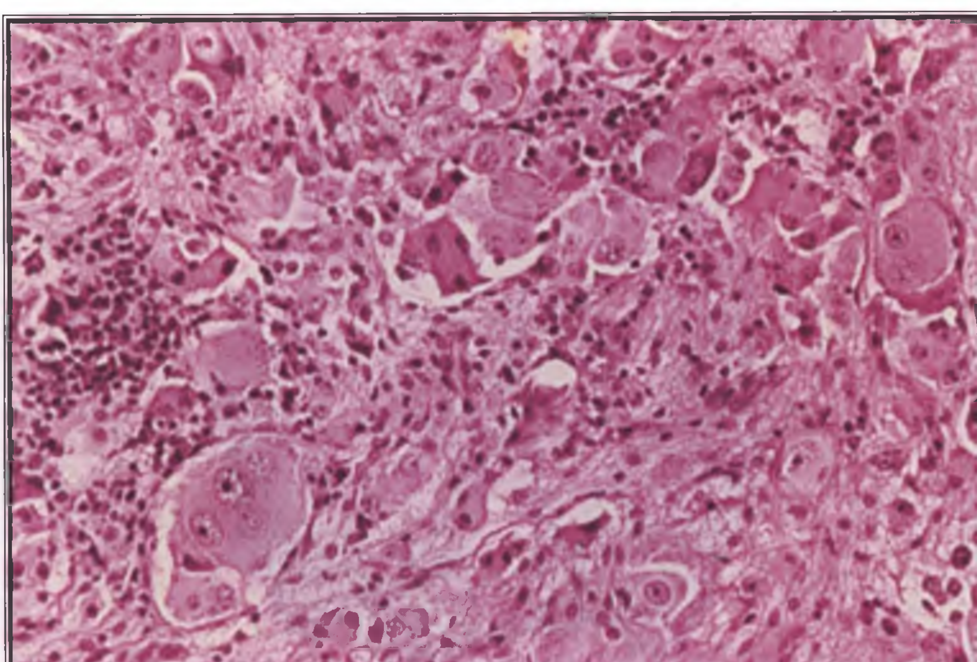


Fig. 250. Ganglioneuroma (H.E. stain, × 70).

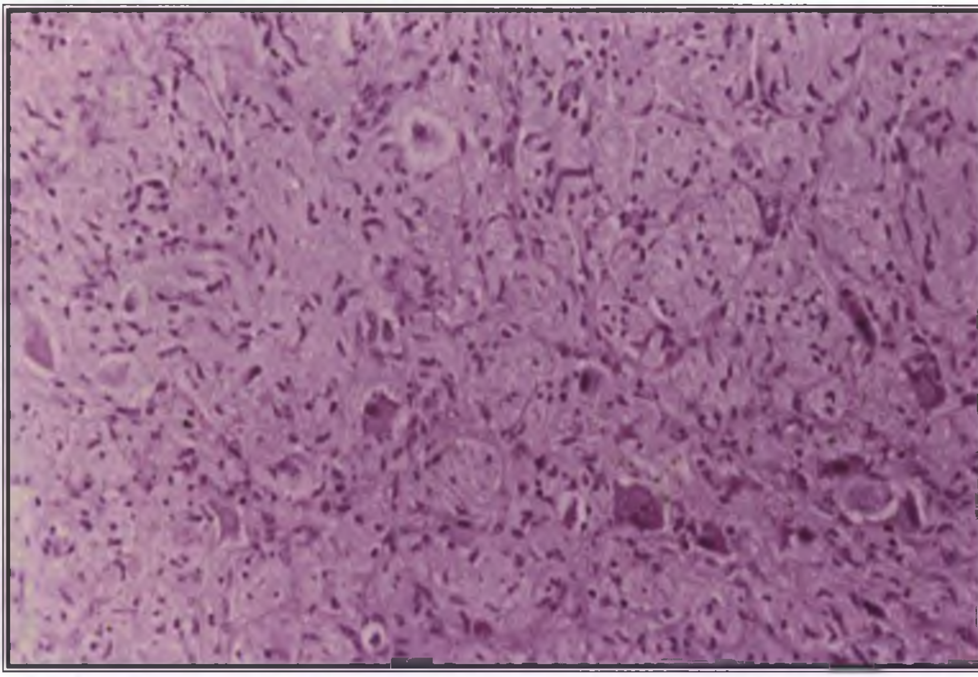


Fig. 251. Ganglioneuroma (H.E. stain, × 70).

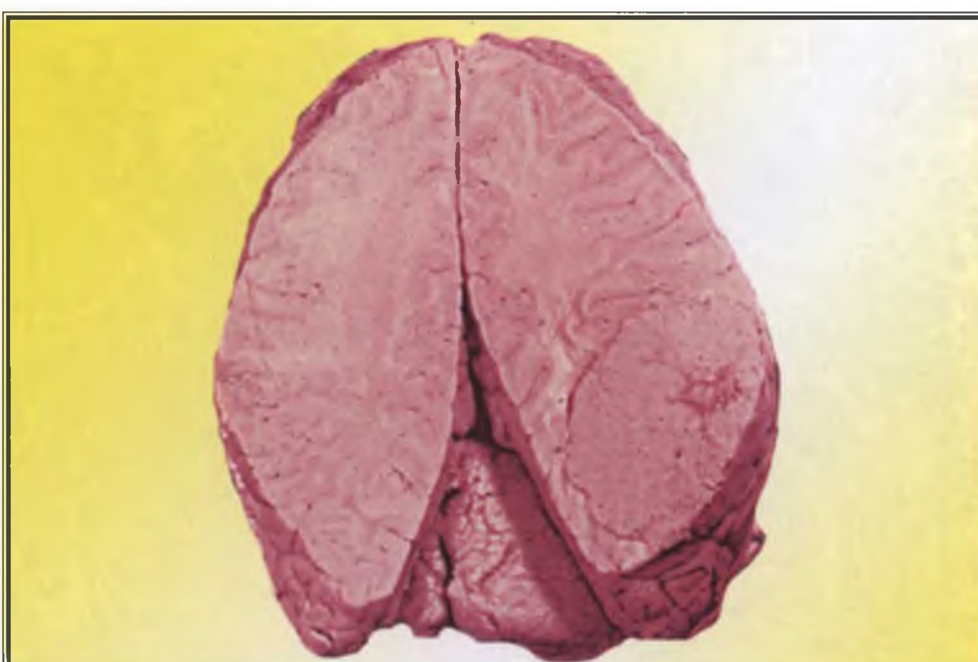


Fig. 252. Astrocytoma, macroscopic aspect.

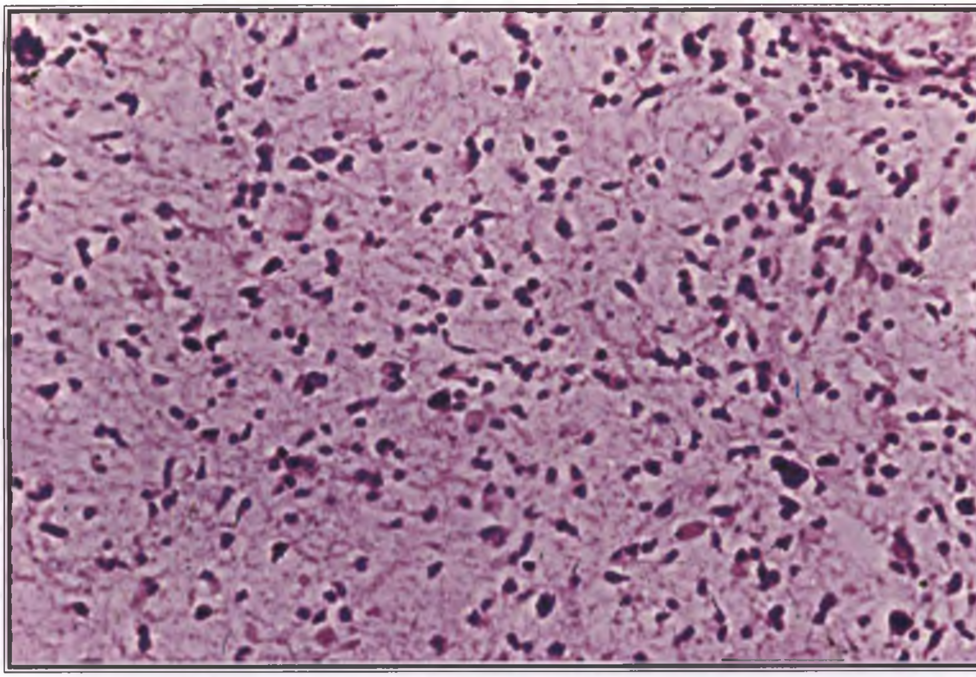


Fig. 253. Astrocytoma, microscopic aspect (H.E. stain, × 70).

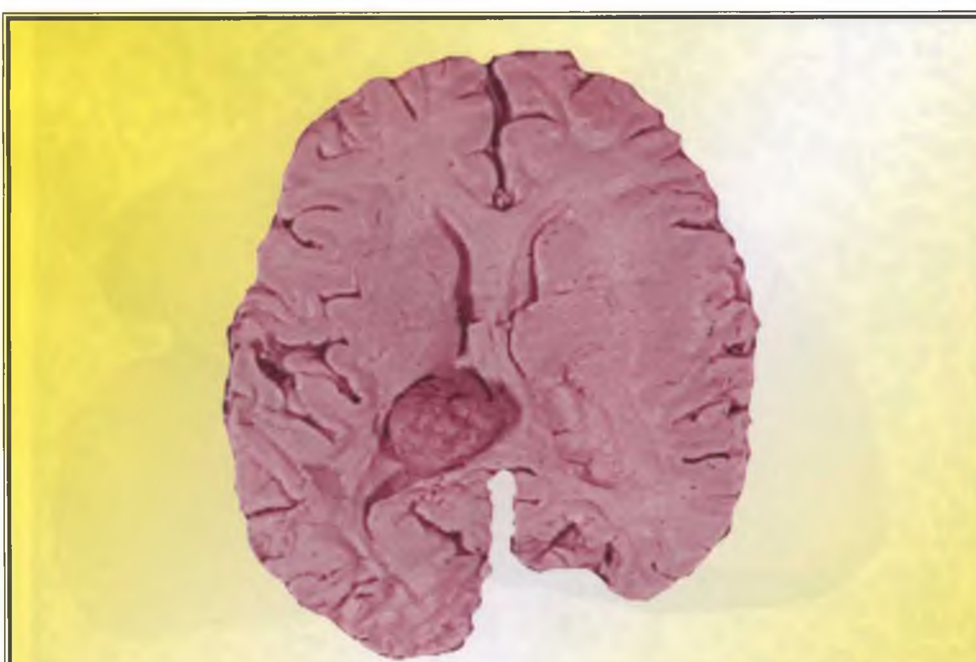


Fig. 254. Ependymoma.

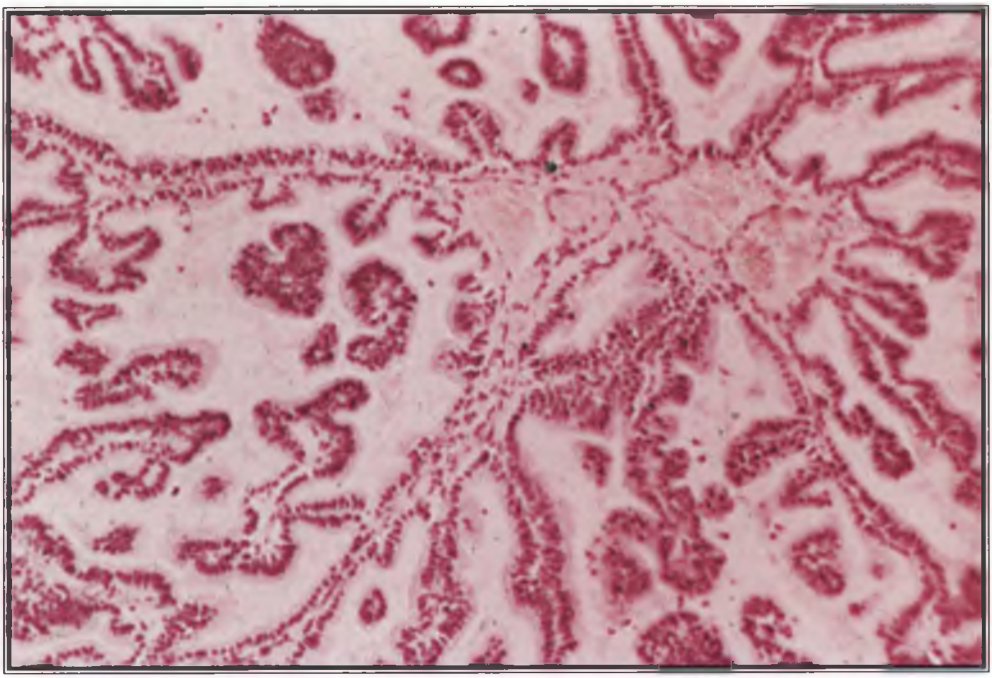


Fig. 255. Choroid plexus papilloma (H.E. stain, × 70).

Fig. 256. Glioblastoma, macroscopic aspect.

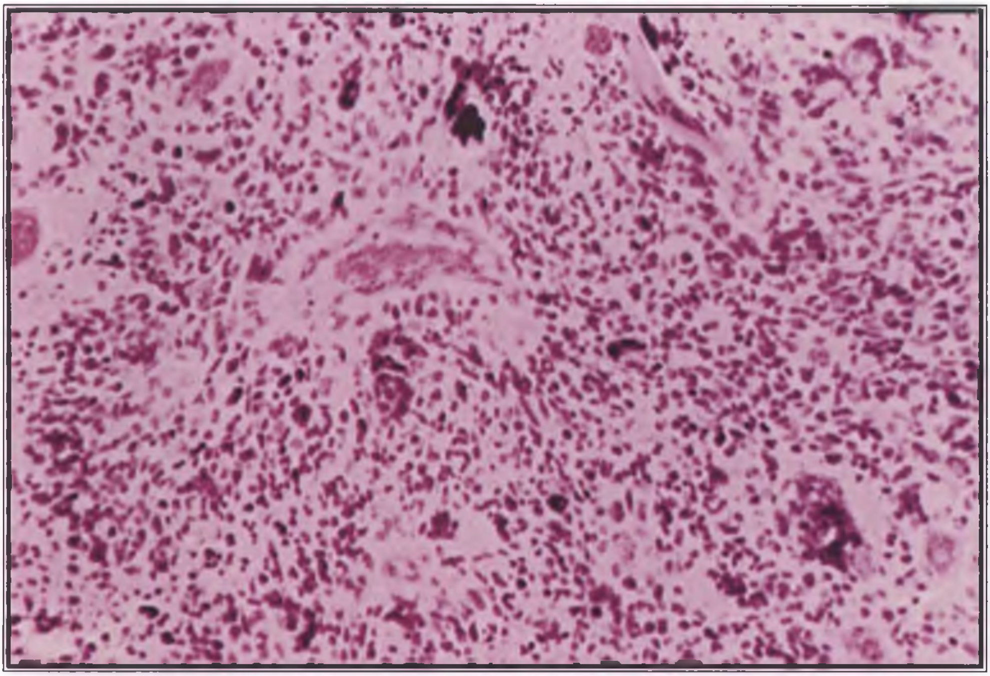


Fig. 257. Glioblastoma, microscopic aspect (H.E. stain, × 70).

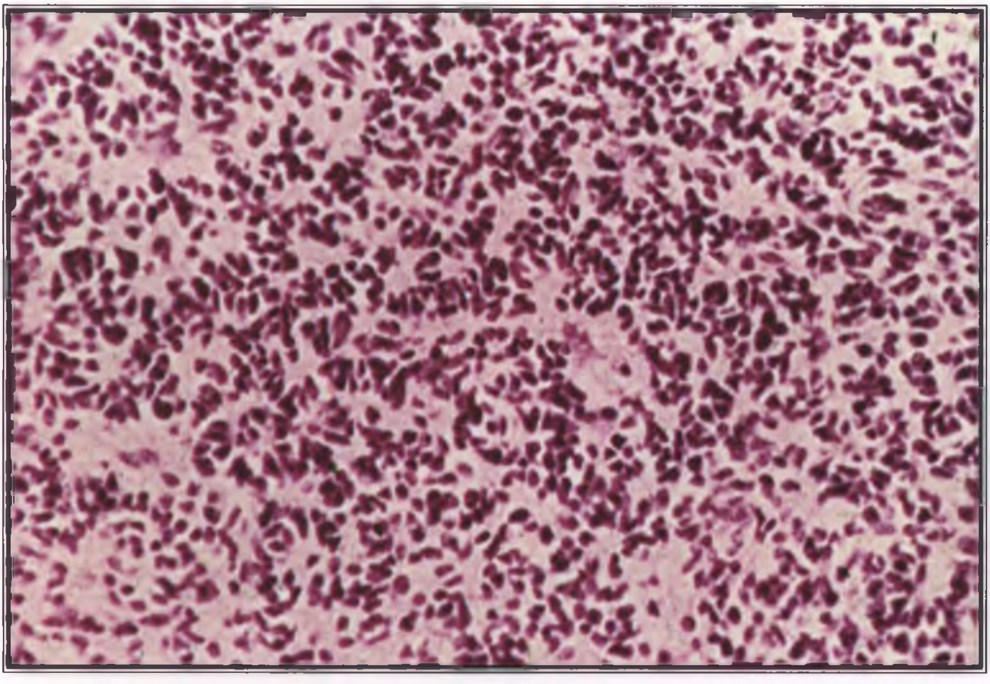


Fig. 258. Medulloblastoma (H.E. stain, × 70).

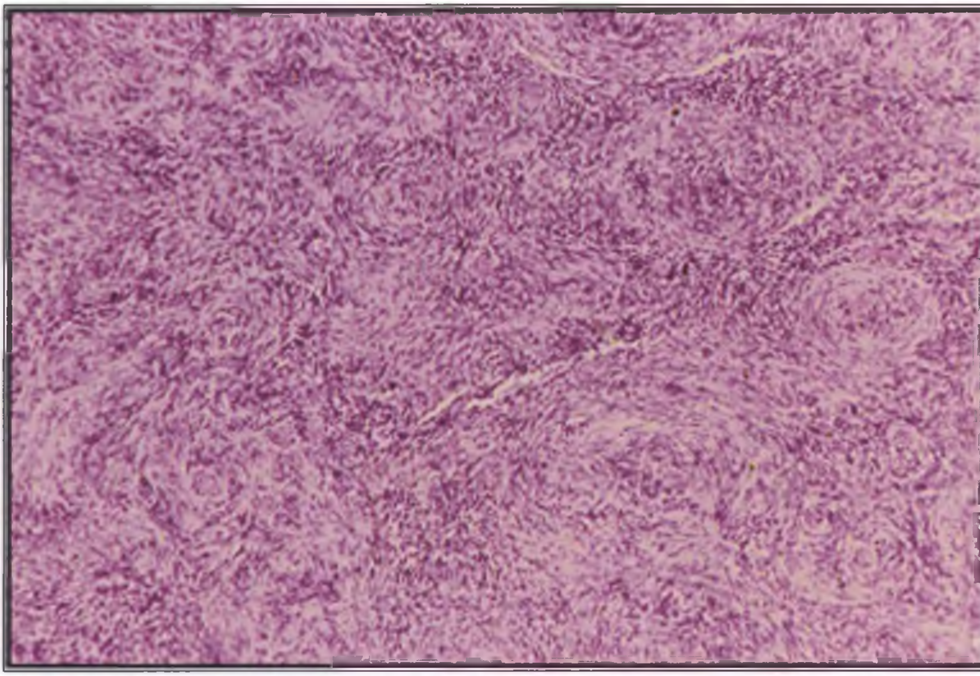


Fig. 259. Fibromatous meningioma (H.E. stain, × 70).

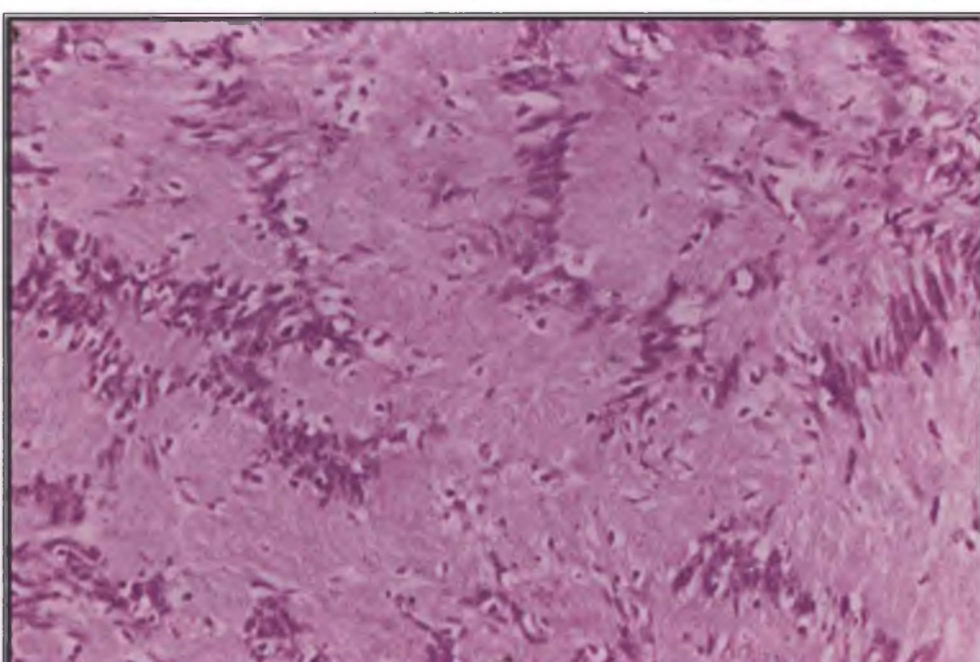


Fig. 260. Neurinoma (H.E. stain, × 70).

Fig. 261. Malignant neurinoma (H.E. stain, × 70).

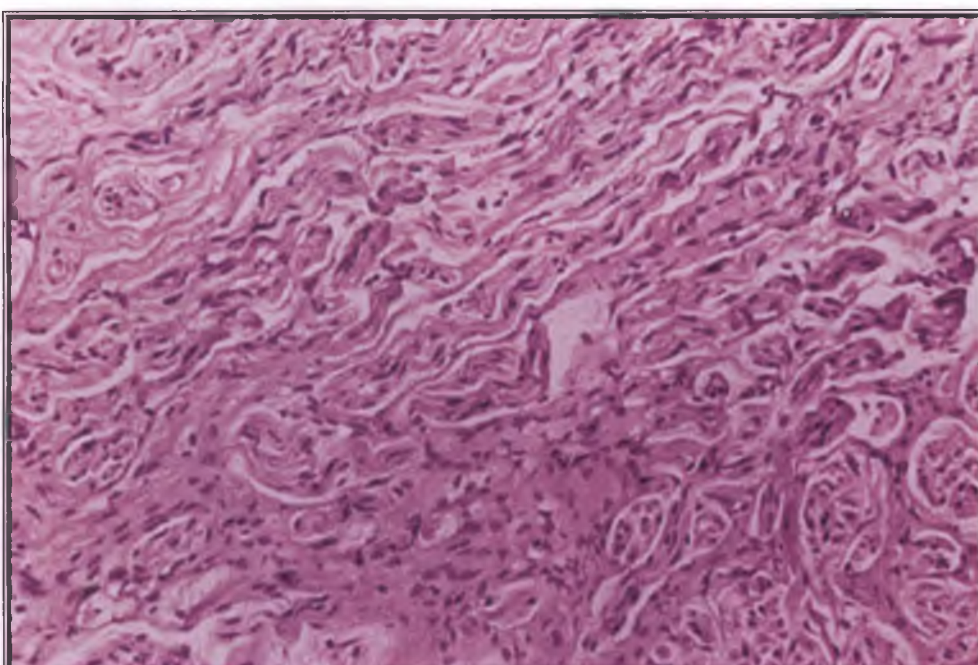


Fig. 262. Neurofibroma (H.E. stain, × 70).

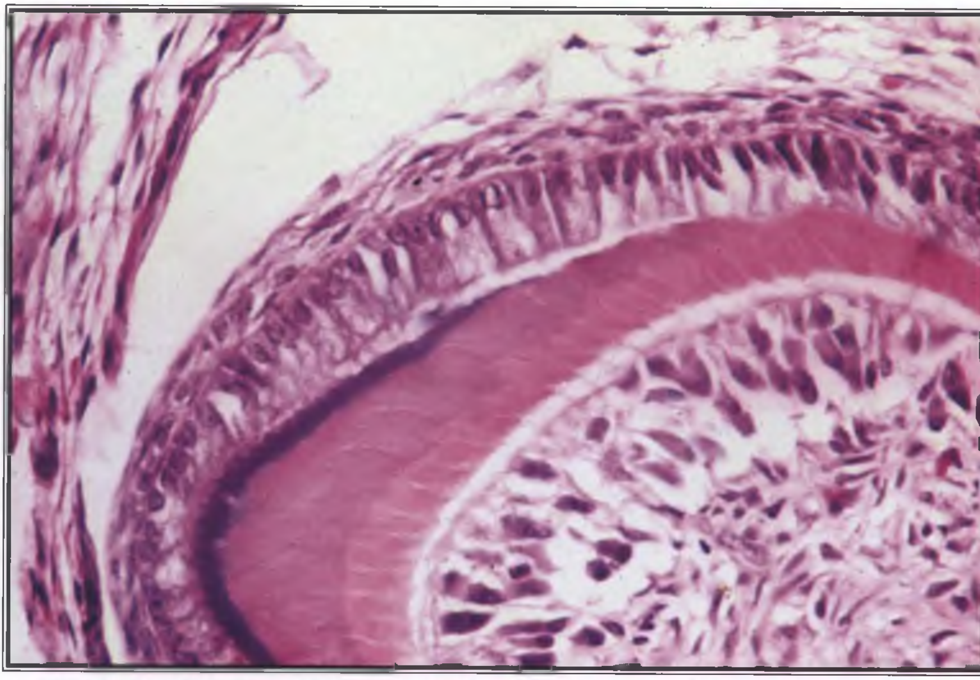


Fig. 263. Normal histology of tooth bud with earliest enamel and dentin formation.

Fig. 264. Oligodontia and microdontia in ectoderm dysplasia.

Fig. 265. Geographic tongue.

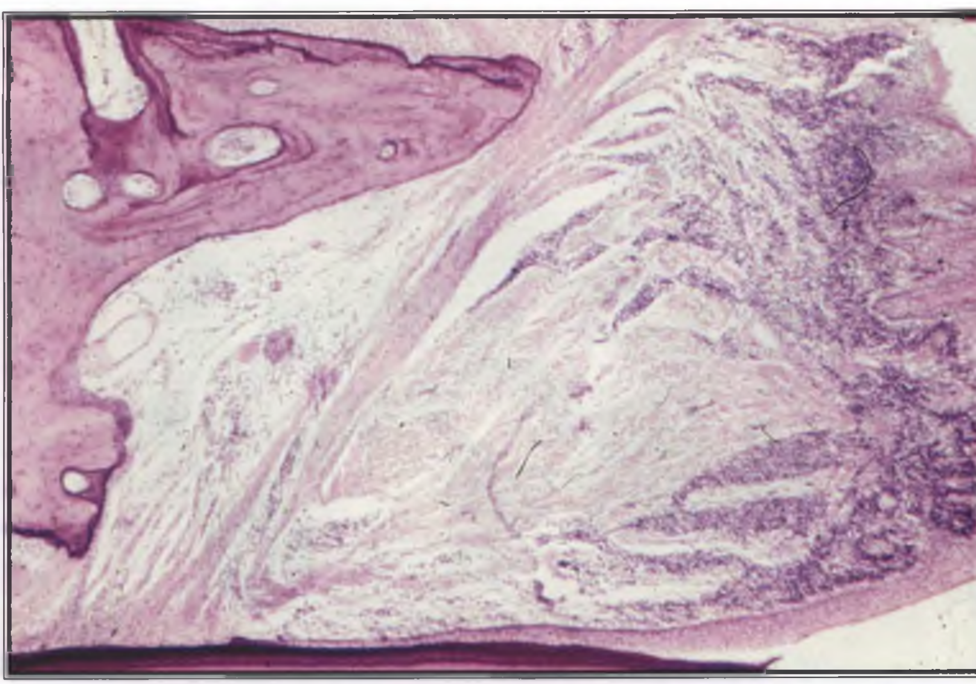


Fig. 266. Periodontitis histology showing low epithelial attachement on cementum and bone resorption.

Fig. 267. Acute necrotizing ulcerative gingivitis (ANUG) with blunt interdental papillae.

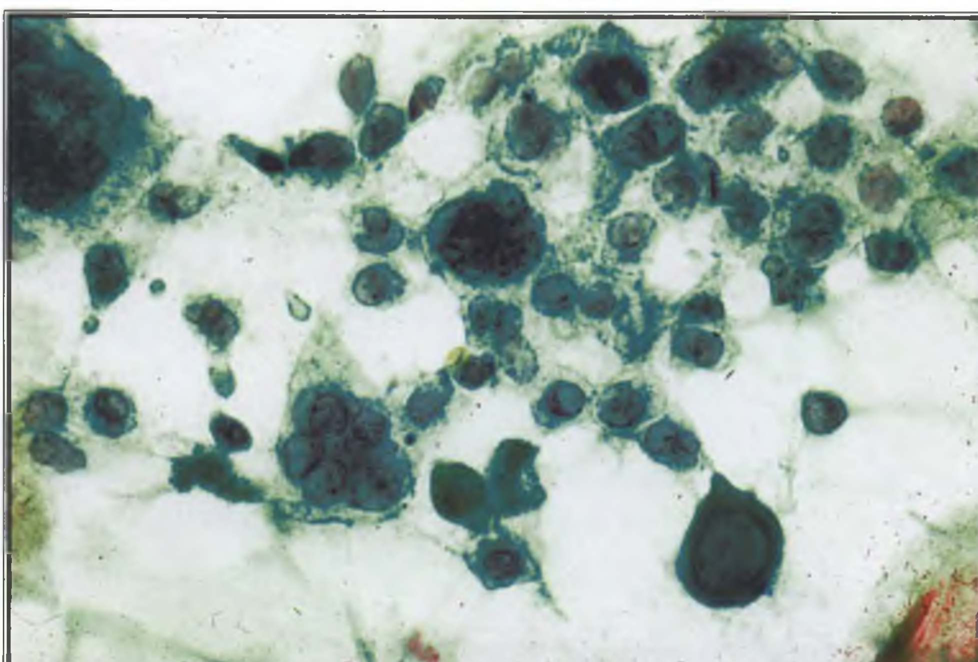


Fig. 268. Cytology of herpes with ballooning degeneration.

Fig. 269. Herpes simplex in the palate.

Fig. 270. Chronic Candida albicans infection.

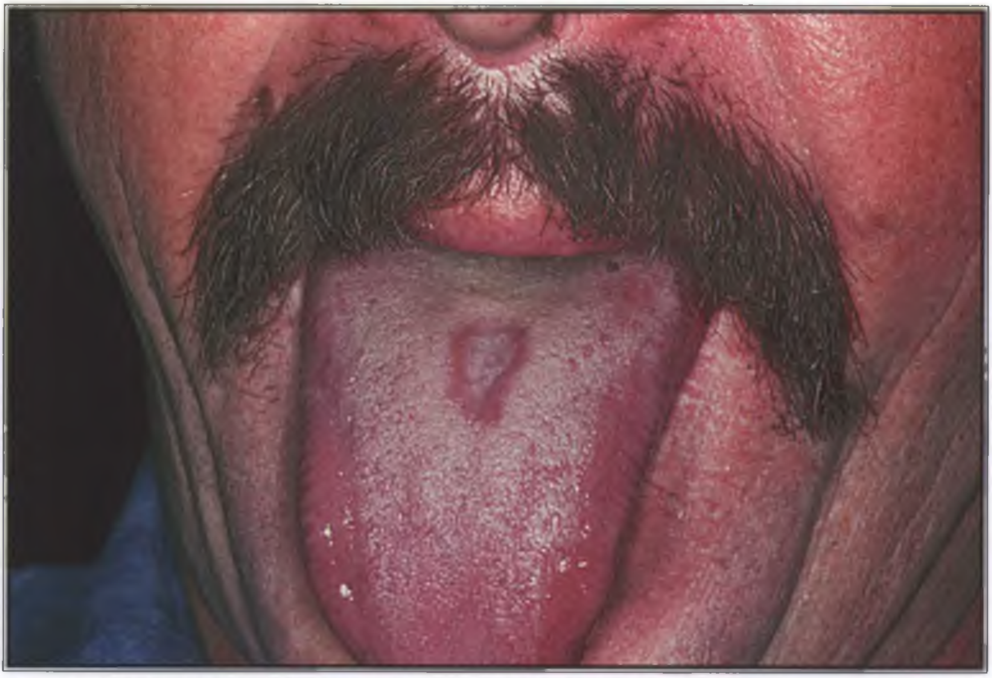


Fig. 271. Median rhomboid glossitis.

Fig. 272. Hairy leucoplakia in AIDS patient.

Fig. 273. Aphthous ulcer.

Fig. 274. Lichen planus with hyperpigmentation, white lines and ulcertaion at the posterior.

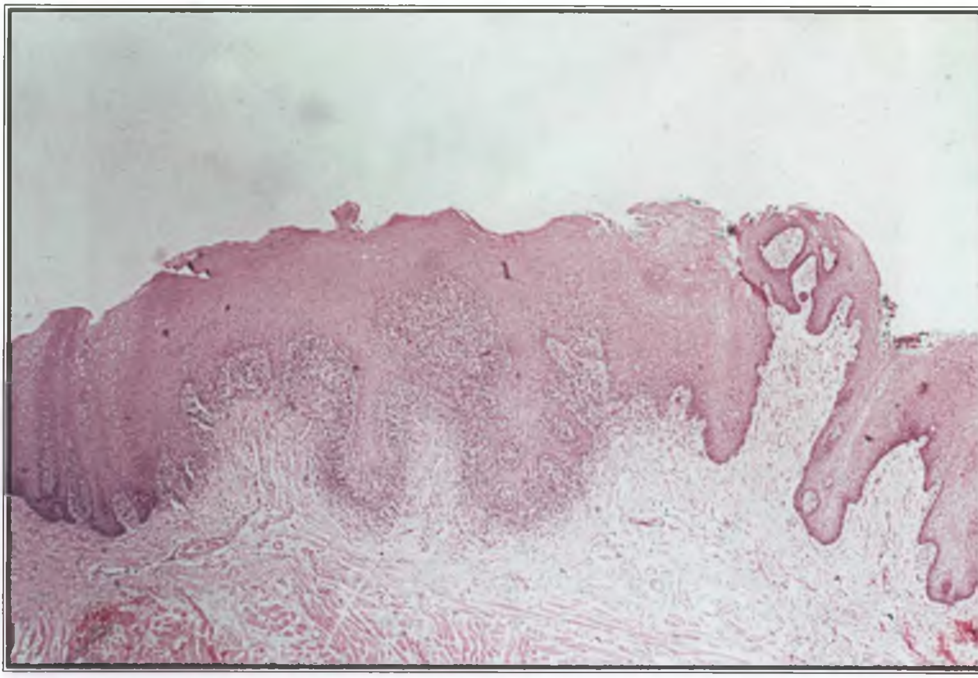


Fig. 275. Histology of lichen planus with long rete ridges and heavy lymphocitic infiltrate in the lamina propria.

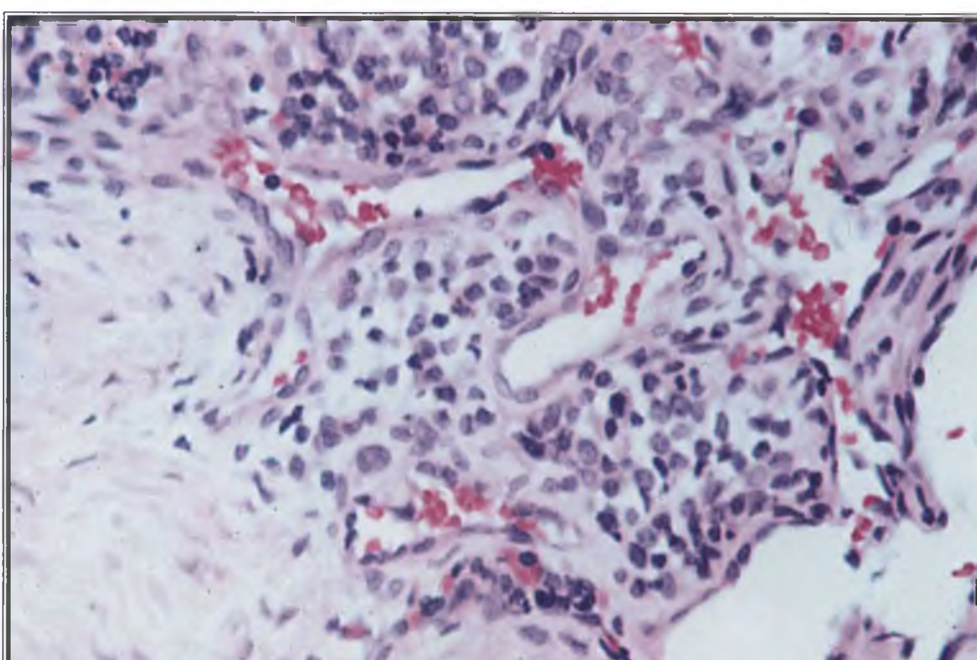


Fig. 276. Histology of pyogenic granuloma with large vessels and inflammatory cells.

Fig. 277. Pyogenic granuloma.

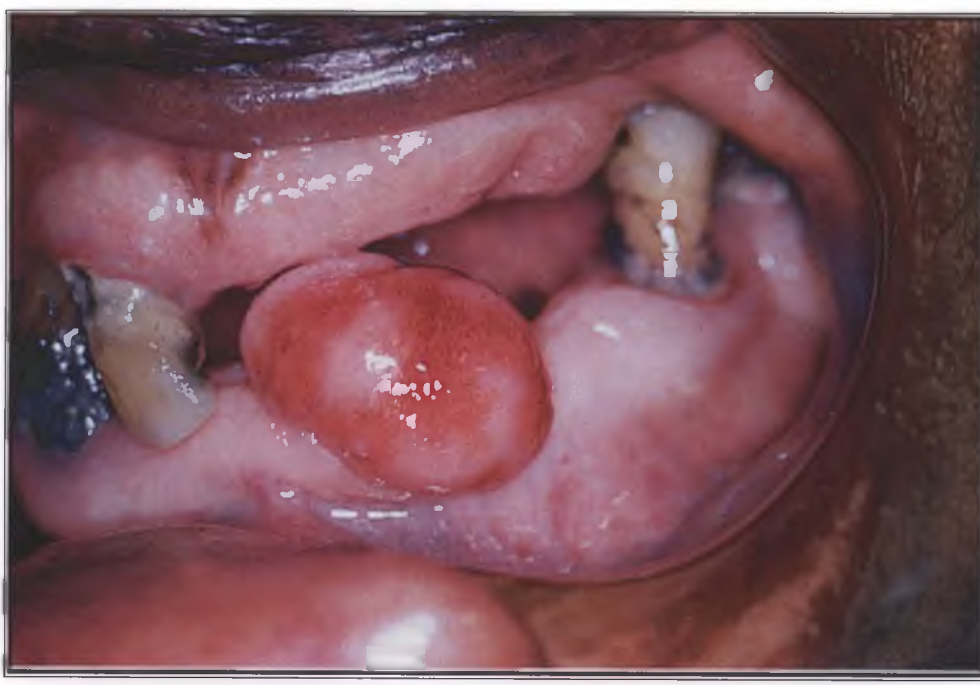


Fig. 278. Giant cell granuloma.

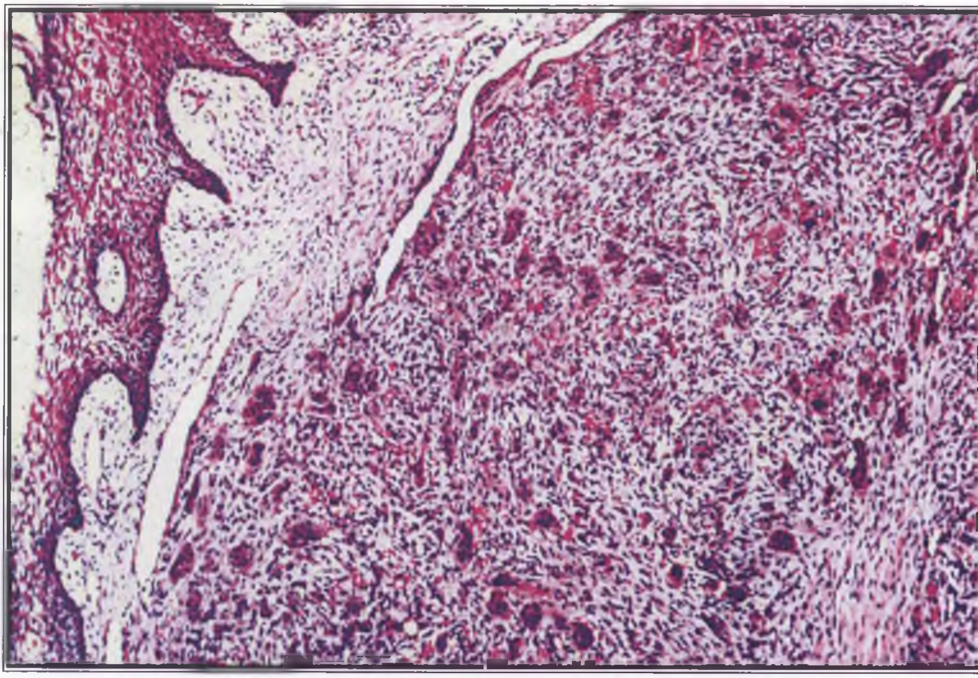


Fig. 279. Histology of giant cell granuloma.

Fig. 280. Papilloma.

Fig. 281. Pleomorphic adenoma.

Fig. 282. Dentigerous cyst with tooth extending below the premolars to the ramus.

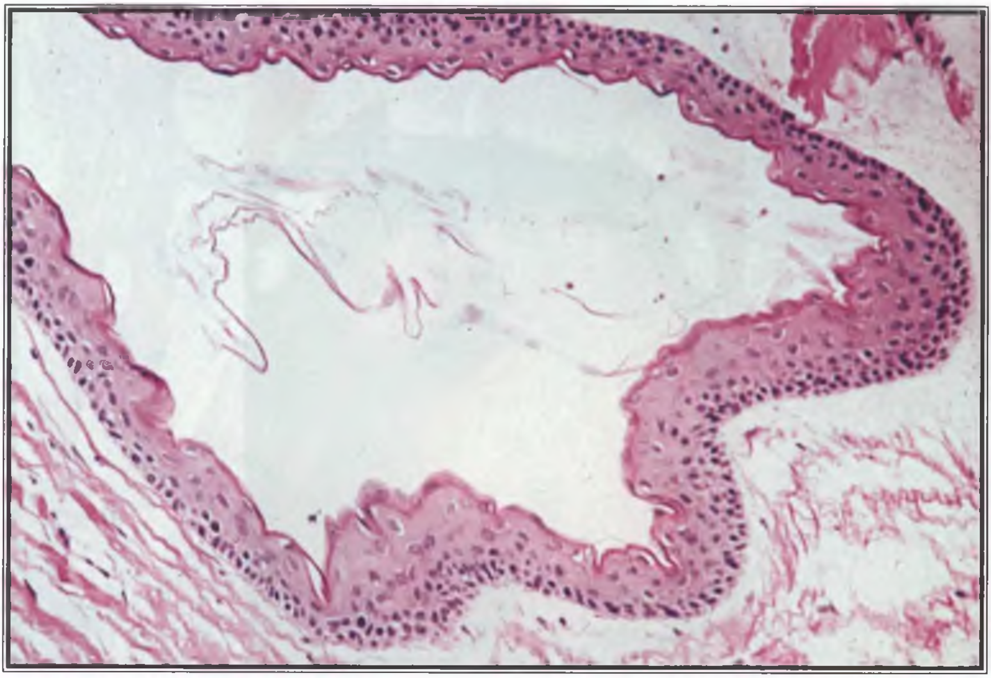


Fig. 283. Histology of odontogenic keratocyst (OKC) with thin epithelial lining and thin corrugated keratin.

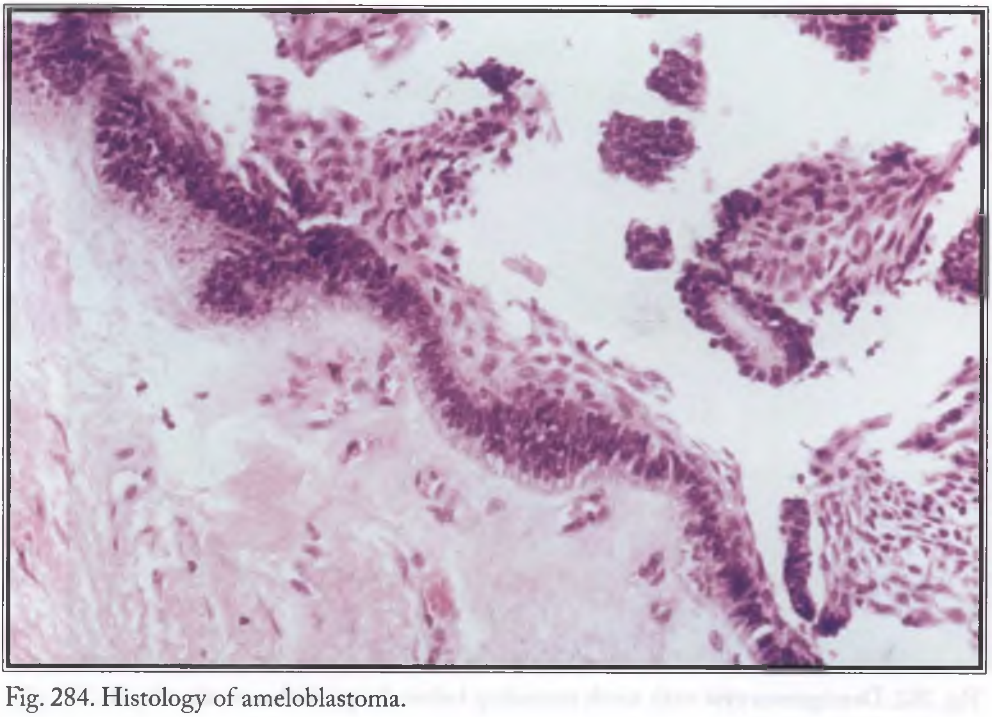


Fig. 284. Histology of ameloblastoma.

Fig. 285. Cementoma on molar roots.

Fig. 286. Basal cell carcinoma with rolled margin and central ulcer.

Fig. 287. Squamous cell carcinoma of the tongue, floor of the mouth and alveolus.

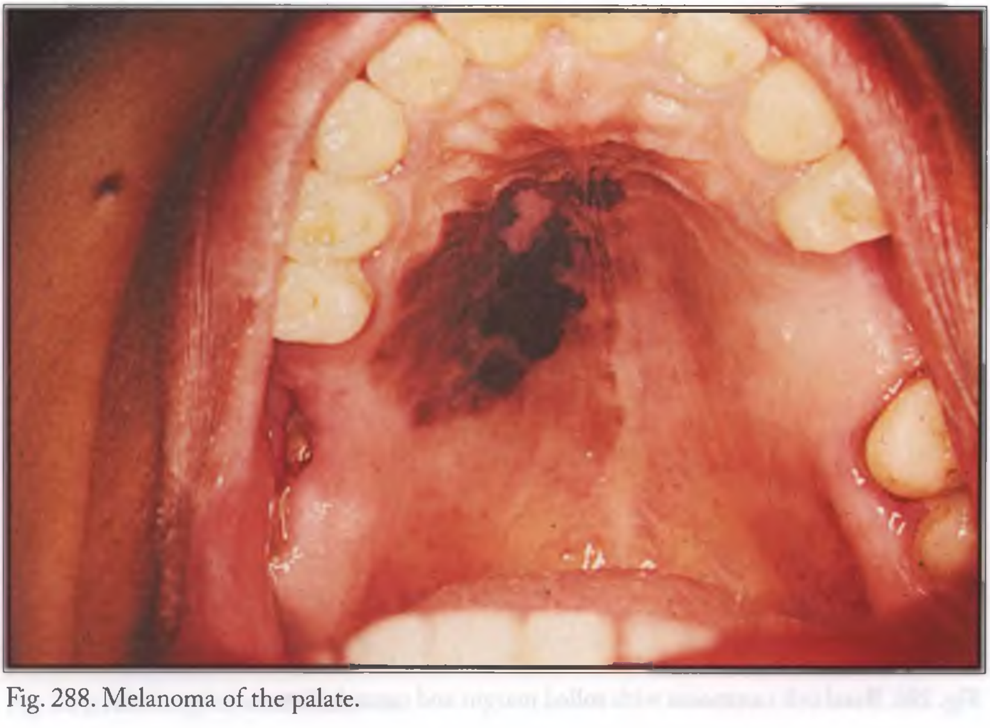


Fig. 288. Melanoma of the palate.

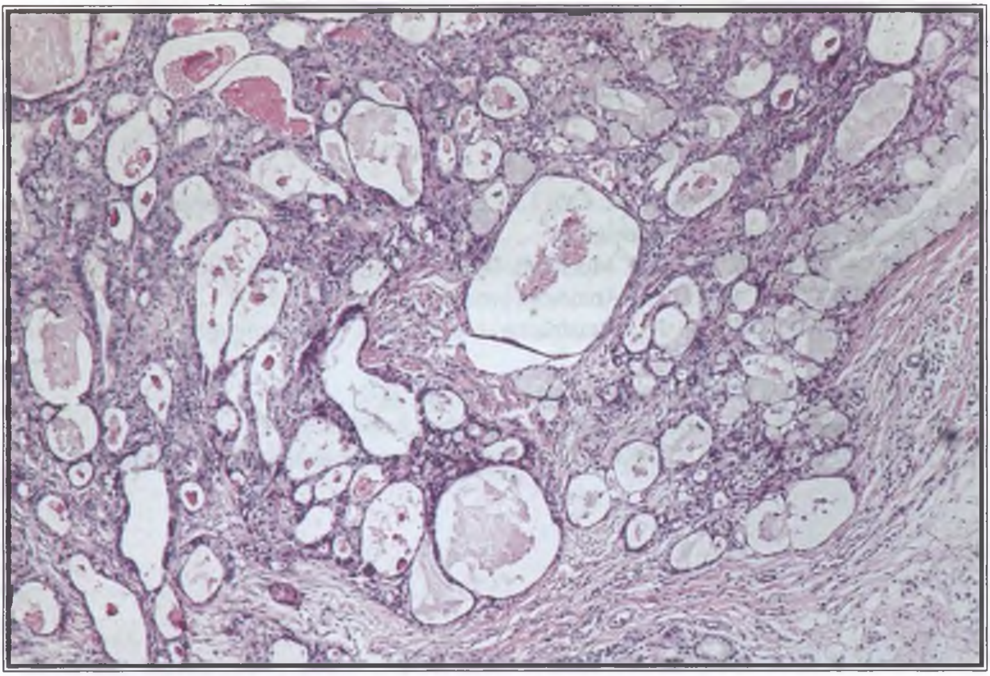


Fig. 289. Histology of muco-epidermoid carcinoma.

Fig. 290. Metastatic thyroid carcinoma.

Chapter 9
STOMATOPATHOLOGY

Diseases in the oral cavity are similar to those seen in other areas of the body with some remarkable additional conditions. These may be classified under developmental disturbances, inflammatory conditions, and neoplasms.

DEVELOPMENTAL DISTURBANCES

CLEFTS AND FISSURAL CYSTS

Fissural cysts are closely related to clefts. In areas where epithelium covered facial processes come together, islands of epithelium may remain and may be stimulated to grow. Enlargement may continue until it is seen clinically in such areas as the mid-line of the palate, between the branchial arches, and along the thyroglossal duct tract.

During the first few weeks of embryonic life there is a great potential for production of defects that will affect the development of the face and oral cavity. During the third to eighth weeks of embryo life, the seven primordia of the face fuse and the mandible and maxilla form. Tooth buds ***(fig. 263)*** and salivary glands originate and processes such as tongue and palate formation are underway. Any small abnormality at these stages may result in extensive effects in the adult. One illustration of that principle is in the condition of cleft lip and cleft palate. These conditions occur when there is improper fusion between the maxillary process and the frontonasal process for cleft lip or between the palatine processes of the maxilla for cleft palate. The cause of the improper fusion is not known, but it may be related to hereditary and environmental factors.

TOOTH ABNORMALITIES

There are numerous hereditary and congenital defects of the teeth. There may be abnormalities in number, size, shape, composition and eruption. In *ectodermal dysplasia* ***(fig. 264)***, there are few or no teeth at all. The opposite condition, when extra teeth appear is called *supernumerary teeth*, and may be associated to syndromes such as cleidocranial dysostosis.

The size of teeth is also a subject to individual variation. In many persons the teeth are too large in relation to the jaw size. This results in crowding and improper occlusion. In other persons the opposite situation occurs – spaces between teeth (diastemas). If two tooth buds lying close together unite, the resulting large tooth is an example of *fusion*. Another method is the division of one tooth bud to produce partially united teeth. This process is called *gemination*.

There are at least two common developmental alterations of normal tooth shape that should be recognized. *Dilaceration* is a condition in which there is a bend in the root of the tooth. *Dens-in-dent* is a fold of enamel and dentin which begins in the lingual pit of maxillary lateral incisor and extends into the pulp, frequently resulting in pulp death.

Diseases of wear and tear are easily confused with developmental abnormalities of tooth shape. Attrition, abrasion and erosion are the common wear-and-tear conditions. *Attrition* is the usual and expected tooth structure loss that occurs with tooth to tooth functional contact. Abrasion occurs when the wear is excessive, such as that caused at the neck of the tooth by improper tooth brushing technique. *Erosion* is the loss of tooth structure by chemical means.

Developmental disturbances also affect the enamel and dentin. *Amelogenesis imperfecta* is a hereditary disturbance of the enamel. In this condition, all the teeth have either soft enamel that readily flakes from the teeth, or pitted enamel. There are two inherited disturbances of dentin. The most common one is *dentinogenesis imperfecta.* In this condition the teeth are brown in color; however, the enamel is not affected. The dentin is laid down in an irregular pattern with large tubules. Significantly, the teeth have very small pulp chambers and show a marked tendency to wear away. *Dentin dysplasia* is the other hereditary condition in which the dentin is abnormal, and root formation is deficient.

Calcification defects are seen in regions where the intake of fluoride is more than 1ppm. These defects also become stained in an irregular, mottled pattern called *fluorosis.* Staining of tooth structure during formation also occurs with intake of tetracycline during tooth development, resulting in brown teeth.

Teeth may not erupt in normal sequence. If a tooth remains in the jaw, it is called impacted and may be associated with cystic enlargement around it or ameloblastoma.

JAW AND MUCOSAL ABNORMALITIES

The most common developmental condition of the jaw bone is an overgrowth of nodules of bone called a *torus.* Tori may be present on the lingual surface of the mandible or at the mid-line of the palate.

One of the most common soft tissue disturbances is *Fordyce's spots.* These are yellowish ovoid collections of sebaceous glands and are most frequently seen in the buccal mucosa of the adults.

The tongue is the site for many soft tissue developmental disturbances. The dorsum may be affected with deep fissures called *fissured or furrowed* tongue. These fissures may entrap food, causing inflammation and infection. The fissured tongue should be brushed and cleansed for preventive measures. *Geographical tongue (fig. 265)* is a wandering rash present on the dorsum of the tongue. Because the border is raised and white and surrounds a slightly depressed, red, atrophic area, it resembles the shoreline on a map and is also known as *migratory glossitis.*

SYNDROMES

One must pay attention to conditions of hereditary or developmental origin in which a number of defects are commonly seen together, producing a syndrome.

For instance, *cleido-cranial dysostosis* is a syndrome in which mid-facial development is deficient, multiple supernumerary teeth are present, and patients have deficient clavicles. By finding one sign or symptom of a syndrome, the other findings may be looked for and therefore better treatment instituted for the patient.

INFLAMMATORY CONDITIONS

DENTAL CARIES

Caries is one of the most prevalent diseases in the world. It is characterized by progressive destruction of the enamel, dentin, and cementum of the tooth which cannot be repaired by the body. It is thought to be caused by a combination of food, susceptible host, and bacteria.

There are a multitude of factors that influence caries activity. The composition of the tooth, its shape and position in the mouth are all important. This is the reason that fluoride and straight teeth are recommended for children. The higher the fluoride content of the surface enamel, the lower the incidence of caries will be. Caries most frequently affects the occlusive surfaces, followed by the mesial, then the distal surfaces of posterior teeth. Saliva is another important factor in caries activity. Its composition, viscosity, and quantity are all related. Saliva contains antibacterial chemicals, enzymes, and buffering agents that are highly influential. Those people who secrete a large volume of saliva have a lower caries rate than those who have a dry mouth. Dietary factors, especially carbohydrates, play a significant role in caries activity. Carbohydrates contain sugar (sucrose), which is easily metabolized by certain bacteria into acids which lead to tooth decalcification. Foods that require more chewing and are not soft and sticky are associated with a lower caries rate.

Types of Caries

Caries is classified into three different types according to location: pit and fissure, smooth surface, and cervical. *Pit and fissure caries* develop on the occlusive surfaces of posterior teeth where food is retained and it is difficult to clean. Teeth are especially susceptible as they erupt if the fluoride content, diet, and cleanliness are not carefully controlled. Microscopically, decay starts in a small enamel defect and widens slightly as it penetrates deeper into the enamel. When it reaches the dentin-enamel junction, it spreads widely and then begins to affect the dentin. The pattern of pit and fissure caries, then, is that of two cones with their broadest bases together at the dentinenamel junction.

Smooth-surface caries begins on smooth enamel surfaces, frequently those mesial and distal on the tooth, where food collects between the teeth. A broad area of decalcification starts, producing a cone of affected enamel with the point toward the dentin-enamel junction. At the junction, the caries spreads widely and then forms a cone with the point extending into the dentin.

Cervical caries are seen in older individuals and involves cementum first, then dentin. Caries spreads laterally in cementum, involving layer after layer until the dentin is reached. The cone with the point into dentin is produced. The microscopic pattern can be easily visualized by viewing the radiographic patterns seen in caries. As caries and decalcification progress, a more radiolucent area is produced on a radiograph. In the mouth, an affected tooth is examined by direct visualization and by feeling with an explorer. Most carious lesions stain light to dark brown. Early lesions may be felt with the explorer by a catch in the decalcified enamel or dentin in pit and fissure and cervical caries, or by surface roughness in smooth surface caries.

Clinical Classification

Caries may also be classified according to the clinical presentation. It may be acute, chronic, or recurrent. Acute caries is usually seen in children and is rapidly progressive. This caries is lightly stained and soft. Acute caries causes severe pain as it gets close to the pulp. Chronic caries is more common in adults. It advances slowly and is dark and leathery in consistency. Pain is usually not a constant feature because the pulp has a chance to build secondary dentin before it is invaded by bacteria. Recurrent caries is the type that forms under restorations. It may be difficult to detect it, because it progresses slowly and is hidden by the restoration.

DISEASES OF THE PULP AND SEQUELAE

Pulpitis

If allowed to progress, the bacteria in carious lesions reach the pulp of the involved tooth. Dentin resists this extension into the pulp by producing reparative dentin and by calcifying the dentinal tubules of the regularly produced dentin. If these mechanisms are not effective, or if the dentist does not operate the tooth, pulpal inflammation follows. Inflammation of the pulp is somewhat different from that seen in other parts of the body because of the thinness of the blood vessel walls and the enclosure of the pulp in hard, non-expanding walls. At first, the inflammed pulp shows an increase in blood supply *(hyperemia)*. This is followed by exudation of edema fluid and then inflammatory cells. Although this may be reversible at an early stage by removing the cause, inflammation commonly continues until an area of necrosis is produced in the pulp. All these stages are types of *pulpitis* and may be quite painful to the patient. After the pulp has been extensively destroyed, the necrotic products spread to and through the apex of the tooth.

Periapical Disease

The most common complications of pulpal disease are abscess and cellulitis, periapical granuloma, and periapical cyst formation. If the pulp is infected by highly pathogenic bacteria, an *abscess* or *cellulitis* may result. An abscess causes pressure and pain as the periapical tissues are involved with a dense infiltration by neutrophils and tissue destruction. The abscess may drain through the tooth if the dentist opens it or out on the gingiva in a lesion called a *parulis*. Cellulitis is a diffuse swelling and infiltration with neutrophils *without* tissue destruction. Of course, if the cellulites occurs near the throat and is extensive, it may restrict breathing and cause death. Abscesses and cellulites are acute manifestations of periapical diseases; granulomas and cysts are chronic manifestations. If the host resistance is high and the ability of the micro-organism to produce disease is low, a granuloma may form at the apex of the tooth. A *granuloma* is a collection of chronic inflammatory cells, blood vessels, fibroblasts, and edema. As this lesion enlarges, it causes bone resorption around the apex of the tooth. This may be seen on a radiograph as a radiolucent area *surrounding* the end of the root. At other times, the inflammation coming from the pulp stimulates growth of small epithelial islands, the *rests o/ Malassez*. As the epithelium grows, the central area degenerates, leaving an epithelium lined space filled with fluid or semi-solid material. These *periapical cysts* may expand so much that a large part of the jawbone may be destroyed.

PERIODONTAL DISEASE

Normal gingiva is pink: and has a slightly rough texture where it is attached to the alveolar bone. There is a sulcus or crevice between the epithelial attachment to the tooth and the free margin of the gingiva. The depth of this crevice is normally 2 to 3 mm. If the gingiva enlarges or the epithelial attachment migrates downward on the root of the tooth, there is an increase in the depth of the crevice. A deepened crevice is referred to as a *periodontal pocket (fig. 266)* and is indicative of periodontal disease. The progression from normal to periodontal disease begins innocently with the collection of plaque on the teeth. The plaque, harboring bacteria and their products, calcifies to form calculus. Calculus may be deposited above the free gingiva (supragingival) or within the gingival crevice (subgingival calculus). The chemicals from the bacteria, plus the mechanical irritants of the rough calcified material cause an inflammatory reaction.

Gingivitis

Inflammation in the gingiva alone is called gingivitis. In simple gingivitis, the tissue between the teeth is swollen and red. Bleeding from the gingiva is common because of ulceration of the crevice epithelium. Gingivitis is seldom painful. In addition to poor oral hygiene, faulty restorations, mouth breathing, allergies, nutrition, drugs, and numerous other factors contribute to the beginning of gingivitis *(fig. 267)*. *Acute necrotizing ulcerative gingivitis* (ANUG) is a specific type of gingivitis that is seen frequently in young people. In these people, gingivitis plus infection with *Borrelia vincentii*, poor nutrition, and stress create ANUG. ANUG, also known as trench mouth, is characterized by painful gums, bad breath, a metallic taste, and excessive salivation. In this condition, the interdental papillae undergo necrosis, leaving blunted, poorly contoured gingival tissues.

Periodontitis

When periodontal ligament fibers have been destroyed by inflammation, interdental bone is resorbed, and the epithelial attachment grows down on the cementum of the tooth. This resorption of bone, destruction of periodontal ligament fibers, and proliferation of epithelial attachment is defined as *periodontitis*. As the severity increases and a significant amount of bone support around the teeth has been lost, the teeth become mobile.

Removal of chemical and mechanical irritants and correction of other modifying factors at this point may reduce the degree of inflammation and significantly slow the progress of the disease. Periodontal disease may be suspected on a radiograph if there is loss of definition of the interdental bone and if the level of the bone is lower than the enamel of the crowns of the teeth. If the periodontal pocket becomes deep enough, there may be such a collection of bacteria, debris, and calculus that an abscess forms. This creates extensive localized bone and tissue destruction. The pus produced may drain out through the periodontal pocket or burrow through the gingiva to produce a parulis. Exaggerated responses in gingival inflammation are seen in several systemic conditions. Two of the most common are pregnancy gingivitis and diabetes.

STOMATITIS

A strict definition of stomatitis includes all the inflammatory conditions of the soft tissues in the mouth. The injury that causes an inflammatory lesion may be mechanical, chemical, thermal, by living microorganism or unknown. Mechanical injuries are common in the mouth, arising from instances such as cheek biting or trauma from hard foods. Depending on the severity of the injury, the mucous membrane may give one of two responses: ulceration or hyperplasia.

Ulceration is the loss of epithelium in an area, exposing connective tissue. Bleeding occurs until the coagulation mechanism clots the blood. A blood clot in the mouth is gray to yellowish in color and consists of fibrin and scattered inflammatory cells. Around the ulcer there is a border of red mucous membrane produced by dilated blood vessels. The membrane or clot over the ulcer base is a good place for microorganisms normally present in the mouth to grow easily. Thus, an ulcer, regardless of the original cause, may become infected. An ulceration heals by forming granulation tissue under the membrane. Epithelium grows over the granulation tissue to reestablish the normal epithelial surface.

If the mechanical injury is constant but not highly traumatic, it may stimulate the epithelium to undergo *hyperplasia* or excess growth. Clinically, this appears as a white patch, much like a callus on the hand. Microscopically, these white lesions have thickened surface layers of keratin and long rete ridges. Chemical and thermal injuries may also cause ulceration and hyperplasia.

Herpetic Ulceration

There are two types of stomatitis caused by living agents that deserve special attention: herpes simplex ulceration and candidosis. Herpes simplex is a virus. When a child is exposed to the virus, he or she first develops primary herpetic gingivostomatitis. This is an acute condition causing fever, malaise, and ulceration throughout the mouth and lips. This condition lasts for approximately two weeks, during which the individual builds antibodies against the virus. The virus may infect a nerve ganglion and lie there for some time without causing any problem. If the individual is subjected to trauma, stress, sun, wind, fever, or other conditions that reduce resistance, the virus may grow, infect the surface epithelial cells, ***(fig. 268)*** and cause painful ulcerative lesions of the lip or attached gingival ***(fig. 269)***.

Candidosis is the name given to an infection with *Candida albicans* ***(fig. 270)***. This fungus is a normal inhabitant of the mouth that usually lives in balance with other mouth organisms. If an antibiotic or a systemic condition upsets the balance, the candida may significantly increase and cause the disease. Median rhomboid glossitis is a candida infection in the mid-dorsum of the tongue ***(fig. 271)***. In many patients, candida causes a small ulceration with a thick yellow membrane on top. At other times the lesions are characterized by thickened layers of keratin on the surface of hyperplastic epithelium. Tongue lesions called hairy leukoplakia ***(fig. 272)*** are seen in many patients with HIV (Human Immunodeficiency Virus) infection of AIDS (Acquired Immunodeficiency Syndrome).

Aphthous Ulceration

The cause of one of the most common types of stomatitis, the aphthous ulcer, is unknown but is likely to be an auto-immune condition. Clinically, aphthous ulcers are usually large, round ulcers that affected individuals have one or two at a time ***(fig. 273)***. The ulcers are found on the unkeratinized lining mucosa. They frequently have a gray membrane covering with a broad, surrounding red band of hyperemia, and are painful. They last for ten to fourteen days and recur periodically.

Skin Diseases

There are large numbers of systemic diseases that affect the skin primarily but that also have oral manifestations. *Lichen planus* and pemphigus are examples of these systemic conditions. Lichen planus is a rather common skin disease that produces a purplish skin rash with a dry, white scale. In the mouth, the lesions are characterized by lacy, white lines or diffuse shallow ulcerations commonly on the buccal mucosa ***(fig. 274, 275)***. *Pemphigus vulgaris* is a potentially fatal disease that may be seen first in the mouth. It is characterized by a peeling off of the upper layers of epithelium and the production of large blisters in the mouth and on the skin. The large blisters are painful and cause such fluid loss and potential for secondary infection that the patient may die unless treated properly.

TUMOR-LIKE PROLIFERATIONS

Inflammation in the mouth may create such rapid, localized hyperplasia that the lesions are often confused with neoplastic lesions. They are different from neoplastic lesions, however, in that the cause, an injury, is known, and they have a limited growth potential. These proliferations are thought to be overzealous attempts by the body to repair injury. The most commonly seen tumor-like proliferations in the mouth are traumatic fibroma, pyogenic granuloma, and denture injury hyperplasia (epulis fissuratum).

Pyogenic granulomas are collections of hyperplastic, newly formed blood vessels and granulation tissues ***(fig. 276)***. They may occur throughout the mouth and on the skin. They are usually soft, red, and bleed easily upon manipulation ***(fig. 277)***. Because they are composed mostly of blood vessels, they are not painful and are easely injured again. Typically, these lesions arise rapidly and stay at their largest size, 1 to 2 cm, until removed. They are commonly seen in pregnant females who already have gingivitis from injury by calculus, debris, and poor oral hygiene. Giant cell granulomas sometimes called epulis are similar clinically but have large numbers of giant cells seen microscopically ***(fig. 278, 279)***. Denture injury hyperplasia may arise after continued trauma from an illfitting denture. This trauma stimulates repair with granulation tissue and fibrous tissue. They are usually firm folds of red to pink connective tissue developed around a denture flange. Because these lesions are much like scar, they may interfere with proper denture function.

ORAL NEOPLASMS

BENIGN EPITHELIAL NEOPLASMS

Because of the great variety of epithelial and connective tissue types in the mouth, the potential for neoplasia is great. In addition, the region contains specialized tissue for salivary gland and tooth production that may also undergo neoplastic changes. The most common benign oral neoplasms are noticed first as localized enlargements that are not painful. Papillomas and salivary gland adenomas are examples of benign epithelial neoplasms.

Fibromas, osteomas, and hemangiomas are examples of benign connective tissue neoplasms. Papillomas in the mouth are commonly found on the soft palate and tongue and are seldom over one centimeter in size ***(fig. 280)***.

Salivary gland tumors are not common tumors, comprising only about one percent of all head and neck tumors. Of the salivary gland tumors, the most common is the benign mixed tumor (*pleomorphic adenoma*). It may arise from either major or minor salivary glands, forming a firm, nodular mass in the gland ***(fig. 281)***. The parotid gland is most commonly affected. Microscopically, the tumor is well named, because the pattern of epithelial and connective tissues is varied. As the epithelial portion of the tumor grows, it condenses the surrounding connective tissue into a thick capsule or covering. This capsule, as well as the tumor itself, must be removed if the tumor is to be cured because growth of the epithelium through the wall frequently occurs.

BENIGN CONNECTIVE TISSUE NEOPLASMS

Benign connective tissue tumors are also common in the mouth. One of the most common is the fibroma. This is a benign tumor of fibrous tissue that usually presents itself as a firm, slow-growing, pink nodule. It may occur on the buccal mucosa, gingiva, and tongue. Because these lesions sometimes interfere with chewing, they may become painful if bitten. These broad-based masses of fibrous tissue are covered by stratified squamous epithelium, which may become ulcerated if traumatized. Fibromas seldom reach a size of more than 1 cm unless allowed to grow for an extended period. Ossifying fibromas and hemangiomas may also be found frequently in oral tissues.

ODONTOGENIC CYSTS AND TUMORS

Dentigerous Cyst

Odontogenic cysts form in the jaws from epithelium associated with tooth formation. If a tooth is formed and the cyst forms around it, it is called a dentigerous cyst ***(fig. 282)***. One odontogenic cyst, the odontogenic keratocyst has an aggressive growth pattern and recurs frequently. The lining is thin and is producing thin laiers of keratin ***(fig. 283)***.

Odontogenic tumors are considered separately, because they make up a group of benign tumors that may have both epithelial and mesenchymal elements, originally intended to form teeth. There are at least three odontogenic tumors - one epithelial, one mesenchymal, and one mixed - that deserve attention.

Ameloblastoma

An *ameloblastoma* is composed of proliferating nests and strands of columnar epithelial cells that resemble the inner enamel epithelium ***(fig. 284)***. These cells may come from the enamel organ, dental lamina, rests of Malassez, or from the lining of dentigerous cysts. A great majority of these tumors is found in the third molar region of the mandible. They are seen most frequently in young adults. Ameloblastomas grow slowly by sending out finger-like projections into the surrounding tissues, so removal presents a significant problem. Radiographically, they present a soap bubble (*multiloculated*) appearance because of this growth pattern. Microscopically, the nests of epithelial cells in an ameloblastoma have a rim of columnar epithelial cells with nuclei placed toward the periphery of the nest. Subclassification of these tumors are made because of growth potential differences which may be predicted by histologic pattern. True ameloblastomas produce no calcified material.

Cementoma

A *cementoma* is a benign, mesenchymal odontogenic tumor that produces no symptoms ***(fig. 285)***. Cementoma are commonly multiple and are discovered upon routine radiographic examination. Most often they are associated with the apex of a lower incisor tooth. These tumors are calcified but have a radiolucent border. Under the microscope, they have a pattern of layered, round calcified bodies. They fuse, forming large radiopaque masses. Females are affected more frequently than males. Because they produce no symptoms and they grow so slowly, removal is not necessary.

Odontoma

Odontomas are benign, mixed odontogenic tumors formed by active ameloblasts and odontoblasts. In *compound* odontomas, the resulting structures bear some resemblance to a tooth; in *complex* odontomas there is a completely irregular arrangement of the resulting enamel, dentin, cementum and pulp. Odontomas of both types are found most commonly in children, keeping permanent teeth from erupting in proper sequence. They produce a variable picture on radiographs because of the degrees of calcification. They are always surrounded by a radiolucent band.

MALIGNANT EPITHELIAL NEOPLASMS

Basal Cell Carcinoma

The skin of the face is the most common place to find basal cell carcinoma because of chronic sun exposure ***(fig. 286)***. The most susceptible patients are those with light pigmentation and those who are more than 50 years of age. These lesions begin as non-healing ulcers on exposed skin surfaces, most commonly on the upper two-thirds of the face and upper lip. They typically have a raised rolled margin, which represents the growth of the neoplasm under the epithelium. Basal cell carcinomas very seldom metastasize but grow slowly and are locally aggressive and destructive. Microscopically, basal cell carcinomas are characterized by nests of epithelial cells resembling cells of the basal layer of epithelium.

Squamous Cell Carcinoma

Squamous cell carcinoma is the most common intraoral and lower lip cancer. It is a surface lesion usually seen in older individuals. On the lower lip, squamous cell carcinoma is also associated with chronic sun exposure. These lesions usually start as small, white scaling patches at the vermillion border. The microscopic pattern is one of nests and individual epithelial cells breaking off of irregular epithelial rete ridges to drop down into the underlying connective tissue. If totally removed, lip cancers have a very good prognosis.

Intraoral squamous cell carcinoma is the most common malignancy found in the mouth. Because of the poor prognosis and the ease of detection, all health-related professionals should be suspicious of any abnormalities in the mouth that could be squamous cell carcinoma. Patient history is extremely important because of the association of tobacco use, alcohol consumption, and chronic irritation with mouth cancer. Males are affected more frequently than females, and most carcinomas occur in individuals more than 50 years of age.

The most common intraoral sites for squamous cell carcinomas are in the floor of the mouth and on the ventral surface of the tongue ***(fig. 287)***. The lesions produced by cancer are frequently rough surfaced and red or ulcerated. Microscopically, these lesions have a poor resemblance to squamous epithelium. The epithelial cells vary in size and nuclear configuration. Cells with an abundance of chromosomal material (*hyperchromatism*) and an increased number and abnormal configuration of mitotic figures are to be expected.

The less the cells look like normal epithelial cells, the poorer the prognosis; the further back in the mouth the lesions are, the poorer the prognosis; the earlier the treatment, the better the prognosis. These cancers grow rapidly and metastasize through the lymphatic system to the lymph nodes in the neck. Any squamous cell carcinoma is hard and may be fixed (attached) to the surrounding tissue. A lymph node with metastatic cancer will be enlarged, hard, fixed, and will not have a well-defined border.

Malignant Melanoma

Malignant melanoma is a pigmented skin and oral mucosa malignant neoplasm demanding early diagnosis. Differentiation from other pigmentations is made easier by remembering A,B,C,D,E. Malignant melanomas are asymmetrical with irregular borders, non-uniform colors, a diameter of 6 mm or greater, and have areas of elevation: A for asymmetry, B for border, C for color, D for diameter, and E for elevation ***(fig. 288)***.

Other epithelial malignancies may occur in salivary glands or in odontogenic tumors. Salivary gland carcinomas are called *adenocarcinomas*. They should be suspected with rapid growth of a nodule in major or minor salivary gland locations. Muco-epidermoid carcinoma ***(fig. 289)*** and adenoid cystic carcinoma are subclassifications of salivary gland adenocarcinoma seen in the oral cavity.

MALIGNANT CONNECTIVE TISSUE NEOPLASMS

As with the benign tumors of the mouth, a malignancy of any of the connective tissues is possible. In contrast to epithelial malignancies, which are surface lesions and occur in older individuals, connective tissue malignancies arise under the surface and occur in younger individuals. Collectively, they are called *sarcomas* because of the fleshy masses of tissue they produce during growth. They metastasize via the blood stream instead of the lymphatic system. Leukemia may be easily confused with inflammatory changes in the gingiva. The redness and swelling of the gingiva seen in types of leukemia look much like inflammation; however, it is progressive and fatal.

Metastatic lesions from other parts of the body may be seen in the oral region. These lesions most frequently appear as radiolucent lesions of the jaw. They commonly come from carcinomas of the breast, prostate, lung, and thyroid ***(fig. 290)***.

BIBLIOGRAPHY

1. COTRAN R.S., KUMAR V., COLLINS T. Pathologic basis of disease, 6th ed., 1999. Saunders Company, Philadelphia.
2. VATAMANU V., ZOTA Ie. Morfopatologie generala. Chisinau-Bucuresti, 1997.
3. STRUKOV A., SEROV V. Anatomia patologica. Chisinau, 1999.
4. CONSTANTINIDES P. Ultrastructural pathology. Amsterdam-New York-Oxford, 1984.
5. HOLLMAN J.H. Pathology. Sprienger-Verlag, 1992.
6. CURRAN R.C. Colour atlas of histopathology. London, 1972.
7. PALITSEV M.A., ANICIKOV N.M. Patologhicescaia anatomia., vol.1 Moscva, 2001.