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GOMEL STATE MEDICAL UNIVERSITY

Department of pathologic anatomy
with the course of the forensic medicine

CELL INJURY, ADAPTATION, APOPTOSIS AND NECROSIS

Laboratory manual of 3-ed year's students

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Повреждение клетки, адаптация, апоптоз и некроз: учеб.-метод.
П 42 пособие по патологической анатомии для студентов 3 курса факультета по подготовке специалистов для зарубежных стран = Cell injury, adaptation, apoptosis and necrosis: laboratory manual of 3-ed year's students / С. Н. Нимер [и др.]. — Гомель: учреждение образования «Гомельский государственный медицинский университет», 2008. — 20 с.

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В пособии материал распределен на апоптоз, некроз и компенсаторные и приспособительные реакции, а также патоморфологические фотографии для данного раздела, постановка вопросов соответствует клиническому направлению кафедры.

Утверждено и рекомендовано к изданию Центральным учебным научно-методическим советом учреждения образования «Гомельский государственный медицинский университет» 19 сентября 2008 г., протокол № 9.

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URGENCY OF THE THEME

Apoptoses — genetically programmed death of cells in the living organism. The dominant role of apoptoses — establishment of the homeostatic equilibrium between the processes of proliferation and loss of cells. Differences in apoptoses from the necrosis: 1. Apoptoses grips always only separate cells or their groups. 2. In contrast to the necrosis the destruction of cell is occurred by the not activated hydrolytic enzymes, but with the participation of special calcium — magnesium of the dependent endonucleases, which «will cut» nucleus to many fragments. 3. Resultant fragments of cells (apoptoses bodies) are phagocytized by the adjacent cells — parenchymatous and stromal 4. Apoptoses is not accompanied by the development of inflammatory reaction. Table «comparative characteristic of necrosis and apoptoses of cells».

Necrosis — Necrosis is a form of cell death, common to ischemic injury. Affected cells show nuclear pyknosis, karyolysis, and karyorrhexis. Pyknosis occurs when the nucleus shrinks into a condensed mass and appears as a dark, basophilic blob. Karyolysis is the formation of nuclear «dust» due to fading of basophilia in chromatin. Karyorrhexis is the fragmentation of the nucleus. There are several types of necrosis.

PURPOSE OF OCCUPATIONS

Were studied reasons, morphology and outcomes of different forms of necrosis. Was distinguished the concept of necrosis and necrobiosis.

Emphasized the variety of the etiological factors of necrosis (necroses straight lines — traumatic, toxic and indirect — vascular, allergic and trophoneurotic). Dismantled the clinico- anatomical forms of necrosis — coagulation, kollikvatsionnyy, gangrene — dry, moist and its variety — infarction, sequestration, bedsore. It connected the special features of necrosis with the structure with the special features of the blood supply of the organ, in which it was developed.

Were studied microscopic changes in the cell nucleus (kariopicanoses, karyohexis, karyolysis), the cytoplasm (coagulation, plazmorrhexisis, plasmolysis) and the fibrous structures. Focused attention on thedestructive changes in the necrotized tissues, which arise from of fermentative autolysis and for the ratio of woven detrite to the paintings. It follows it examined the changes, which are developed on the boundary of the necrotized and living tissue and the outcomes of necrosis (organization, petrifaction, the formation of cyst, ossification, aseptic and purulent melting) depending on it saw, the places of formation and state of the reactivity of organism. Was determined the value of necrosis, caused by localization and size of the become numb section. Examined the phenomenon of apoptoses, its value in the vital activity of organism was determined, were studied morphological differences from the necrosis, were named the structural elements, which participate in apoptoses.

TASKS

1. Determination of necrosis, it explained its essence.
2. TO explained the dynamics of necrotic process.
3. The macroscopic, microscopic and ultrastructural signs of necrotic changes.
4. Characteristic of etiological and clinical-morphological forms of necrosis.
5. Outcomes of various forms of necrosis, it estimated their functional value.
6. Determine the concept of apoptoses, the reasons, morphological criteria of difference from the necrosis, mechanisms of development.
7. Determine the value of apoptoses in the vital activity of macroorganism.

ADDITIONAL MATERIALS ON THE THEME

Macro-preparations:

1. Gangrene of foot.
2. Gangrene of gut.
3. Shock kidney.
4. Traumatic kidney.
5. Gangrene of stomach.

Micro-preparations:

1. Necrosis of the epithelium of the convoluted tubules of kidney.
2. Lymph node with tuberculosis.

MATERIALS FOR THE CONTROL AFTER MASTERING OF THE THEME

Terminology

Gangrene (gangraina — fire) — the necrosis of the tissues, which are touched with the environment. The infarction (infarcire — it stuffed) — the necrosis of tissues, which appears with the disturbance of blood circulation. The form of the necrosis, which develops with the sharp disturbance of blood circulation (thrombosis, embolism, prolonged vascular spasm) in the organs with the functional- end vessels.

Maranticheskiy necrosis - bedsores in the exhausted patients, old people, with the phenomena of cachexia and marasmus. Myomalakas (malakas — soft) — the melting of dead tissues. Mummification (mumificatio — drying) — drying, packing of dead cloth. Nome (nome — «water cancer») — the moist gangrene of soft tissues of cheeks in children. Necrosis (necrose — corpse) — deadening, the loss of cells and tissues in the living organism. Necrobiosis (necrose — corpse, basic input-output system — life) — the changes, which precede necrosis, the reversible dystrophic processes. Process of slow extinction.

Sequestration (sequestrum) — the section of dead cloth, which does not undergo autolysis, is not replaced by connective tissue and it is freely located among the living tissue. Elastolis — swelling, disintegration, the melting of elastic fibers.

Practical part

Overview of Cell Injury:

• Cells actively control the composition of their immediate environment and intracellular milieu within a narrow range of physiological parameters («*homeostasis*»);

• Under physiological stresses or pathological stimuli («*injury*»), cells can undergo adaptation to achieve a new steady state that would be compatible with their viability in the new environment;

• If the injury is too severe («*irreversible injury*»), the affected cells die.

Causes of Cell Injury:

• Hypoxia and ischemia -Hypoxia (oxygen deficiency) and ischemia (blood flow deficiency);

• Chemical agents: including drugs and alcohol;

• Physical agents: including trauma and heat;

• Infections;

• Immunological reactions: including anaphylaxis and loss of immune tolerance that results in autoimmune disease;

• Genetic defects;

• Nutritional defects: including vitamin deficiencies, obesity leading to type II DM, fat leading to atherosclerosis;

• Aging: including degeneration as a result of repeated trauma, and intrinsic cellular senescence.

Mechanisms of Cell Injury: General Principles:

• Cell response to injury is not an all-or-nothing phenomenon;

• Response to a given stimulus depends on the type, status, and genetic make-up of the injured cell;

• Cells are complex interconnected systems, and single local injuries can result in multiple secondary and tertiary effects;

• Cell function is lost far before biochemical and subsequently morphological manifestations of injury become detectable.

Cell response to injury is not an all-or-nothing phenomenon: The stronger and the longer the stimulus, the larger the damage.

Response to a given stimulus depends on the type, status, and genetic make-up of the injured cell: Contrast ischemia in skeletal muscle (tolerates 2 hours) versus cardiac muscle (tolerate 20 minutes); contrast neurons and glia.

Cells are complex interconnected systems, and single local injuries can result in multiple secondary and tertiary effects: Cyanide indirectly affects osmotic regulation by loss of function of Na/K-ATPase.

Cell function is lost far before biochemical and subsequently morphological manifestations of injury become detectable: This has big implications for the use of pathology as gold standard for evaluation of new technologies that could detect changes before they are morphologically apparent.

General Biochemical Mechanisms

1. Loss of energy (ATP depletion, O2depletion).
2. Mitochondrial damage («permeability transition»).
3. Loss of calcium homeostasis.
4. Defects in plasma membrane permeability.
5. Generation of reactive oxygen species (O2•, H2O2, OH•) and other *free radicals.*

Free Radicals

• Free radicals are chemical species with a single unpaired electron in an outer orbital

• Free radicals are chemically unstable and therefore readily react with other molecules, resulting in chemical damage.

• Free radicals initiate autocatalytic reactions; molecules that react with free radicals are in turn converted to free radicals.

Intracellular Sources of Free Radicals

• Normal redoxreactions generate free radicals.

• Nitric oxide (NO) can act as a free radical.

• Ionizing radiation (UV, X-rays) can hydrolyze water into hydroxyl (OH•) and hydrogen (H•) free radicals.

• Metabolism of exogenous chemicals such as CCl4can generate free radicals.

• Free radical generation is a "physiological" antimicrobial reaction.

Neutralization of Free Radicals

1. Spontaneous decay.
2. Superoxidedismutase(SOD): $2O_2^{\bullet} + 2H \rightarrow O_2 + H_2O_2$.
3. Glutathione (GSH): $2OH^{\bullet} + 2GSH \rightarrow 2H_2O + GSSG$.
4. Catalase: $2H_2O_2 \rightarrow O_2 + H_2O$.
5. Endogenous and exogenous antioxidants (Vitamins E, A, C and β-carotene).

Free Radical-Induced Injury

• If not adequately neutralized, free radicals can damage cells by three basic mechanisms:

1. Lipid peroxidationof membranes: double bonds in polyunsaturated membrane lipids are vulnerable to attack by oxygen free radicals.

2. DNA fragmentation: Free radicals react with thymine in nuclear and mitochondrial DNA to produce single strand breaks.

3. Protein cross-linking: Free radicals promote sulfhydryl-mediated protein cross-linking, resulting in increased degradation or loss of activity.

Reperfusion Damage

• If cells are *reversibly*injured due to ischemia, restoration of blood flow can paradoxically result in accelerated injury.

• Reperfusion damage is a clinically important process that significantly contributes to myocardial and cerebral infarctions.

• Exact mechanisms are unclear, but

– Restoration of flow may expose compromised cells to high concentrations of calcium, and

– Reperfusion can result in increase free radicals production from compromised mitochondria and the circulating inflammatory cells.

Chemical Injury

• Direct damage such as binding of mercuric chloride to sulfhydryl groups of proteins.

• Generation of toxic metabolites such as conversion of CCl4to CCl3•free radicals in the SER of the liver.

***Sub*cellularResponses to Cell Injury**

• Autophagicvacuoles.
• Induction/hypertrophy of RER.
• Abnormal mitochondria.
• Cytoskeletalabnormalities.

Pathologic Calcification

• *Dystrophic calcification*is the abnormal deposition of calcium phosphate in dead or dying tissue.

• Dystrophic calcification is an important component of the pathogenesis of atherosclerotic disease and valvular heart disease.

• *Metastaticcalcification*is calcium deposition in normal tissues as a consequence of hypercalcemia:

– Increased PTH with subsequent bone resorption.
– Bone destruction.
– Vitamin D disorders (intoxication, Sarcoidosis, Williams syndrome).
– Renal failure with 2º↑PTH.

Cell Death

There are two types to the cell death- apoptosis and necrosis (Figure 1).

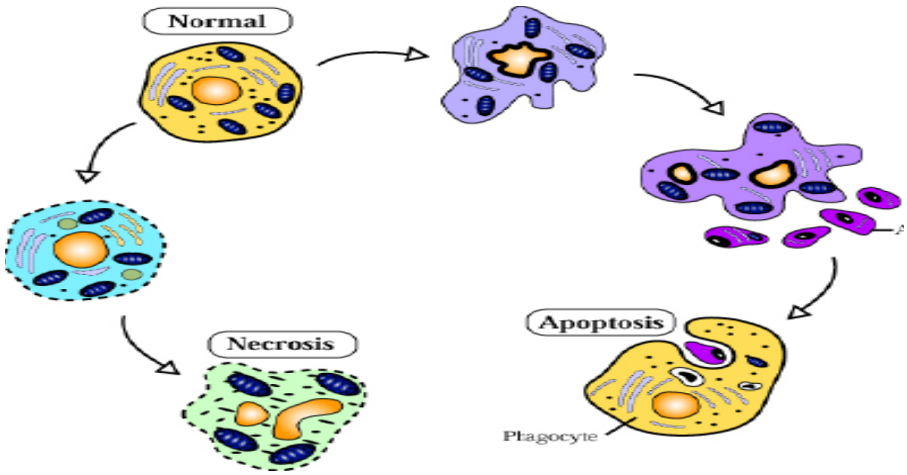

Figure 1 — Mechanisms of the cell death

Table 1 — Coagulative Necrosis vs. Apoptoses

	Apoptoses	Necrosis
Stimuli	Hypoxia, toxin	Physiological and pathological factors
Histological appearance	Cellular swilling, coagulation, necrosis, disruption of organelles	Single cells chromatin condensation, apoptotic bodies
DNA breakdown	Random, diffuse	Internuclosomal
Mechanism	ATP depletion, membrane injury, free radical damage	Gene Activation. End nucleases. Proteases
Tissue reaction	Inflammation	No Inflammation. Phagocytosis of apoptotic bodies

Etiological forms of the necrosis:

1. Traumatic — appears under the effect of physical and chemical factors.
2. Toxic — appears under the effect of toxins of bacterial and other nature.
3. Trophoneurotic — is connected with the damage of microcirculation and innervation of tissues.
4. Allergic — develops with the immunopathologic reactions.
5. Vascular — is connected with the ischemia of organ or tissues.

Depending on the mechanism etiological factor they release:

1. Direct necrosis (under the direct effect on the tissues of traumatic or toxic agent).
2. Indirect (defined by example action through the vascular, nervous and immune system). **In the development of necrosis stages release:**

1. Paranecrosis — reversible changes.
2. Necrobiosis — irreversible dystrophic changes.
3. Death of cell.
4. Autolysis — decomposition of dead substratum under the action of hydrolytic enzymes, that separate from the damaged cell.

Microscopic signs concern both the nucleus and cytoplasm of cells, and also extracellular matrix.

1. Change in the nucleus: a) of kariopikinoses -wrinkling of nuclei in connection with the condensation of chromatin; b) karyohexis — nuclear decomposition to the small lumps;

c) Karyolitic — dissolution of nucleus in connection with hydrolase activation.

2. Change in the cytoplasm: a) plasma coagulation — denaturing and the coagulation of protein with the manifestation in the cytoplasm of vivid- pink small lumps; b) of plazmorrhexix — disintegration of cytoplasm to the small lumps;

c) of plasmolyses — hydrolytic melting of cytoplasm.

3. Changes in the extracellular matrix are manifested in splitting of reticular, collagenic and elastic fibers under the action of proteases, lipases:

The clinical-morphological forms of necrosis are the coagulation, kollikvatsionnym necrosis and gangrene. Release also the varieties of necrosis in the form infarction, sequestration and bedsores.

Coagulation (dry necrosis is characterized by predominance in the dead cloths of the processes of coagulation, dehydration, packing. By the forms of coagulation necrosis can it served coagulated, fibrinoid and waxlike necrosis. Macro-preparation «shock kidney». Kidney is increased in the sizes, that swelled, edematic. Fibrous capsule is stressed, easily removed. Wide pale gray cortical layer is sharply delimited from the dark red pyramids. In the intermedial'noy zone of kidney and the wash-tub are noted the hemorrhages.

Micro-preparation the «necrosis of the epithelium of the convoluted tubules of kidney» (stain H&E). Together with the painted balls and the epithelium of the straight ducts, in cells of which it is contained nucleus, the epithelium of the ducts of the proximal and distal divisions of nephron is not contained nuclei (karyolysis), cytoplasm of some cells is homogeneous, is eosinophilic (in the state of coagulation), in other cells the cytoplasm takes the form of small lumps (plasmoreksis). The nonuniformity of hyperemia of different structures of the kidney focuses attention: the anemia of the capillaries of balls and the plethora of the vessels of medullary layer. Slide «necrotic nephrosis».

Micro-preparation «lymph node with Tuberculosis» (stain H&E). In the tissue of lymph node the centers of caseous necrosis, which are surrounded by granulomatous growths with the presence in them of epithelioid, lymphoid cells and giant cells of Pirogov, are visible. The kollikvatsionnyy (moist) necrosis is characterized by the melting of the necrotized tissue, by its hydration. It encounters in the tissues with the high liquid-water content. Softening (ischemic infarction) brain is an example. Gangrene - necrosis of cloths touching with the environment and having black painting as a result of the formation of sulfurous iron. Two morphological varieties of gangrene are distinguished dry and moist. 1. Dry gangrene is accompanied by the mummification, well expressed by the zone of demarcation inflammation. Frequently it appears in the lower extremities. Macro-preparation «gangrene of foot». In the preparation are visible the cloths of foot, reduced in the volume, dry, black colors. This is dry gangrene. Black color to the necrotized tissues imparts sulfurous iron, which was formed from the pigments of the blood under the action of air.

The sections of dry gangrene can be torn away (mutilyatsiya). 2. Moist gangrene develops in the cloths with the connection of putrefactive flora. It encounters in the bowels, the lungs. Slide «gangrene of lung».

Infarction — necrosis of tissues, which appears with the disturbance of blood circulation (vascular, ischemic necrosis). It develops as a result of the thrombosis, the embolism, the prolonged spasm of arteries or functional overvoltage of organ under the conditions of insufficient blood supply. Sequestration — section of dead cloth, which does not undergo autolysis, is not

replaced by connective tissue and it is freely located among the living tissues. As a rule, it is accompanied by the development of purulent inflammation with the formation of the fistula motions, through which the fragments of sequestration can leave outside. It appears predominantly in the bones, is borne coagulation nature. Bedsore — variety of necrosis, which appears as a result of the trophoneurotic disturbances the weakened, recumbent patients have in the sections of body, which are undergone the greatest pressure.

The outcomes of necrosis are favorable: a) organization — substitution of necrotic masses by connective tissue; b) encapsulation — delimitation of the section of necrosis by connecting capsule. c) Petrifaction — impregnation of the section of necrosis by salts of calcium (dystrophic calcification); d) ossification — appearance in the section of the necrosis of bone tissue; e) the formation of cyst; f) Aseptic melting (autolysis). Unfavorable outcome — the purulent melting of necrotic masses in this case is possible the generalization of process with the development of sepsis.

COMPENSOTORY-ADAPTIVE REACTION

MATERIALS ON THE THEME

MACROPREPARATIONS:
1. Myocardial hypertrophy.
2. Hydronephrosis.
3. Polypus's of stomach.
4. Large-focal post infarction sclerosis (after myocardial infarction).

MICROPREPARATIONS:
1. Hyperplasia of adrenal glands.
2. A brown atrophy of liver.
3. Atrophy of kidney because of overpressure (compression) — hydronephrosis.
4. Myocardial hypertrophy.
5. Glandular hyperplasia of endometrial.
6. Granulation tissue.
7. Adenomatous stomach polyp.

MATERIALS FOR STUDY

Terminology

Cellular Adaptation to Injury

• Cellular adaptations can be induced and/or regulated at any of a number of regulatory steps including receptor binding, signal transduction, gene transcription or protein synthesis.

• The most common morphologically apparent adaptive changes are

❖ **Atrophy** (decrease in cell size).

❖ **Hypertrophy** (increase in cell size).
❖ **Hyperplasia** (increase in cell number).
❖ **Metaplasia** (change in cell type).

Atrophy

• Atrophy is the shrinkage in cell size by *loss of cellular substance.*
• With the involvement of a sufficient number of cells, an entire organ can become *atrophic.*
• Causes of atrophy include decreased workload, pressure, diminished blood supply or nutrition, loss of endocrine stimulation, and aging.
• Mechanisms of atrophy are not specific, but atrophic cells usually contain increased *autophagicvacuoles* with persistent residual bodies such as *lipofuscin.*

Hypertrophy

• Hypertrophy is an increase in cell size by *gain of cellular substance.*
• With the involvement of a sufficient number of cells, an entire organ can become *hypertrophic.*
• Hypertrophy is caused either by increased functional demand or by specific endocrine stimulations.
• Not only the size, but also the phenotype of individual cells can be altered in hypertrophy.
• With increasing demand, hypertrophy can reach a limit beyond which.

Hyperplasia

• Hyperplasia constitutes an increase in the number of indigenous cells in an organ or tissue.
• Pathological hyperplasia if typically the result of excessive endocrine stimulation.
• Hyperplasia is often a predisposing condition to neoplasia.

Metaplasia

• Metaplasia is a «reversible» change in which one adult cell type is replaced by another adult cell type.
• Metaplasia is a cellular adaptation in which indigenous cells are replaced by cells that are better suited to tolerate a specific abnormal environment.
• Because of metaplasia, normal protective mechanisms may be lost.
• Persistence of signals that result in metaplasia often lead to neoplasia.

EXAMPLES:

1. Squamous metaplasia (epidermal).
2. Metaplasia of squamous epithelium (prosoplasia, cytomorphosis).
3. Intestinal metaplasia of the gastric epithelium.
4. Gastric metaplasia of intestinal epithelium.
5. In the territory of connective tissue we can see metaplasia of cartilage or soft tissues into the osseous tissue and vice versa.

Dysplasia — is the pathological process described by proliferation and cells' differentiation infringement (first of all in epithelial tissues) with subsequent cellular atypical development together with broken histoarchitectonics. Allocate three degrees of dysplasia: 1st — mild, 2nd — moderate and 3rd — heavy (severe). Heavy dysplasia (3rd degree) is considered as the precancerous process.

Acromegaly — is enlarging of some organs or their parts (nose, hand).

Hydrocephaly — is liquid accumulation in the cerebral ventricles.

The organization — is replacement of the damaged (injured) tissue by connective tissue and its derivatives. Superfluous growth of the mature dense connective tissue refers to as a **sclerosis.**

Classification of sclerosis taking the etiology and pathogenesis into account:

1. Sclerosis as an outcome of a chronic productive inflammation.
2. Sclerosis as an outcome of system or local disorganization of connective tissue.
3. Replaceable — is an outcome of necrosis and atrophies of tissues.
4. Scar formation as a result of wounds healing.
5. The organization of blood clots, hematomas.

Depending on morphogenesis features we allocate the following mechanisms of sclerosis development:

1. The new growth of a young connective tissue.
2. Amplified synthesis of collagen by fibroblasts.
3. Sclerosis at the stroma collapse in result of necrosis or atrophy in parenchyma of internal organs.

From the point of view of convertibility we divide the scleroses processes on:

1. Labile (convertible).
2. Stable (partially convertible).
3. Irreversible (progressing).

Compensation — is the complex reaction arising in reply to damaging (injuring) action of many environmental factors. It is directed on compensation of organs or tissues defects (or on homeostasis keeping).

Adaptation — is the biological concept which unites all processes of ability to live, bases on underlying interactions between organism and environment and directed on biological species keeping (so it's discussed in conception of species evolution).

Compensatory-adaptive reactions can be of the following types:

1. Regeneration.
2. Hypertrophy.
3. Hyperplasia.
4. Atrophy.
5. Metaplasia.
6. Organization.

Regeneration — is the defection's compensation or structural elements restoration instead of injured? It can be carried out on molecular, sub cellular, cellular, tissue and organ levels.

Regulation of regenerative process can be carried out with the help of humoral, immune, nervous and functional mechanisms.

Phases of regenerative process:

1. Cells proliferation.
2. Cells differentiation.
3. Tissue differentiation.

Types of regeneration:

1) Physiological;
2) Reparative regeneration:
   а) Complete (restitution);
   б) Incomplete (substitution).
3) Pathological regeneration.

Wound healing — is the possible tissue reparation after injure. Allocate the following kinds of wounds healing:

1. Direct closing of epithelial defect.
2. Healing under the scab.
3. Healing a wound by the first tension.
4. Healing a wound by the second tension (through suppuration).

At wounds healing by the first and especially by the second tension granulation tissue is formed. Granulation tissue consists of layers passing each other:

1. Superficial leukocytic-and-necrotic layer.
2. Superficial layer of vascular loops.
3. A layer of vertical vessels.
4. A maturing layer.
5. A layer of horizontally located fibroblasts.
6. A fibrous layer.

MACROPREPARATION «Polypus's of stomach». Mucous membrane of pyloric part of stomach there are plural formations on the stem towering above the surface.

MACROPREPARATION «Myocardial hypertrophy». The mass and size of heart are increased. Left ventricle wall is considerably thickened. Cavities of heart are narrowed (concentric hypertrophy).

MICROPREPARATION «Myocardial hypertrophy». Muscular cells are sharply thickened; nuclei are round and enlarged. The stroma amount is increased.

MICROPREPARATION «Glandular hyperplasia of endometrial». Thickened functional layer of endometrium with a big number of glands is present in micro specimen. Simple atypical hyperplasia, glands are cystically dilated, with occasional outpunching surrounded by abundant cellular stroma. Sometimes glands are only minimally dilated but focally crowded. Rounded nuclei with chromatin irregularities, nucleoli, and loss of polarity.

Complex atypical hyperplasia, almost invariably demonstrates marked architectural complexity with irregular outlines and back-to-back crowding. Cytological atypia is present, manifested as rounded nuclei with chromatin irregularities, evident nucleoli and loss of polarity.

MICROPREPARATION «Brown atrophy of liver» (stain H&E). Hepatic cells and their nuclei are reduced in sizes. Many fine granules of a brown pigment — lipofuscin — can be found in the cytoplasm of hepatocytes, especially in the centers of lobules.

Distinguish the following types of a local atrophy:

1. Dysfunctional (from inactivity).
2. From blood supply insufficiency.
3. From overpressure (atrophy of kidney at difficulty of urine outflow (hydronephrosis); atrophy of brain tissue at difficulty of liquor outflow with the following hydrocephaly).

MACROPREPARATION «hydronephrosis». Kidney is sharply increased in sizes, cortical and medullar layers are thinned. In pelvis of the kidney cavity several stones are visible.

MICROPREPARATION «Atrophy of kidney because of overpressure (compression) — hydronephrosis». Cortical and medullar layers are sharply thinned. The majority of glomeruli is atrophic and replaced with connective tissue. Renal convoluted tubules are atrophic, only in the some of them lumen is sharply expanded and filled with hyaline-like cylinders. In the stroma of organ the overgrowth of a loss connective tissue. Small vessels are sclerosed.

4. Neurotic. It is caused by infringement of organs communication with the nervous system because of destruction of nervous conductors (nerves).
5. From physical and chemical factors influence (for example at influence of radioactive radiation).

MACROPREPARATION «large-focal post infarction cardio sclerosis». Whitish scar is seen in the wall of heart.

MICROPREPARATION «Granulation tissue» In a preparation between numerous neogenic vessels the young cells of connective tissue are visible — leukocytes, lymphocytes, plasmatic cells, fibroblasts. Fibers of collagen are located between the cells.

Inspection questions

NECROSIS

1. Necrosis, definition, the stage of necrotic process.
2. Microscopic signs of necrosis.
3. Classification of necrosis.
4. Clinical-morphological forms of necrosis.
5. Coagulation and kollikvatsionnyy necrosis, the mechanisms of development, morphological special features.
6. Gangrene. Forms of gangrenes. Special features of development.
7. Outcomes of necrosis. Functional value.
8. Posthumous changes.
9. Apoptoses. Determination. Morphogenesis of apoptoses. Differences in apoptoses from the necrosis. Value of apoptoses in the vital activity of macroorganism.

Compensation and adaptation

1. Compensation and adaptation. Definition of terms.
2. Phases of compensatory-adaptive reactions.
3. Types of compensatory-adaptive reactions.
4. Regeneration. Definition, kinds of regeneration. Phases of regenerative process.
5. Structural levels of regeneration, regulation of regeneration. Conditions of regenerative process formation.
6. Metaplasia, definition. Types of epithelial and connective tissue metaplasia. Value for an organism.
7. Atrophy, definition, type, morphological features. Value for an organism.
8. Healing of wounds. Types of healing. Morphological features.
9. Granulation tissue. Its structure, functional value.
10. Sclerosis. Definition. Classification. Path morphology.
11. Value of compensatory-adaptive reactions for an organism.

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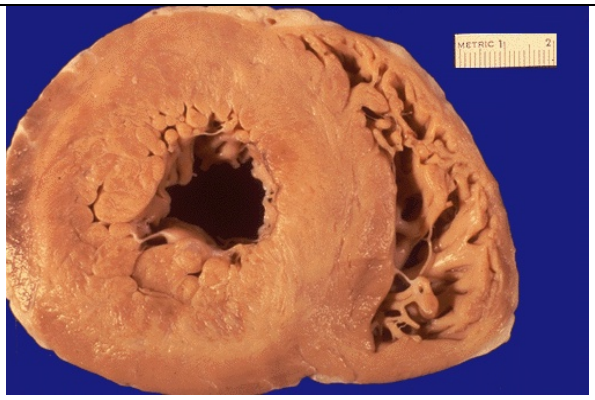
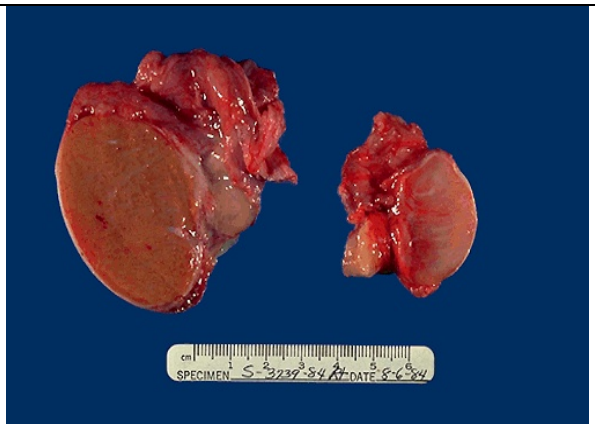
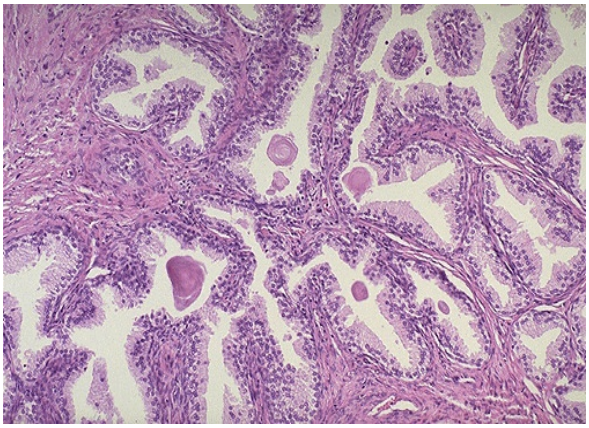
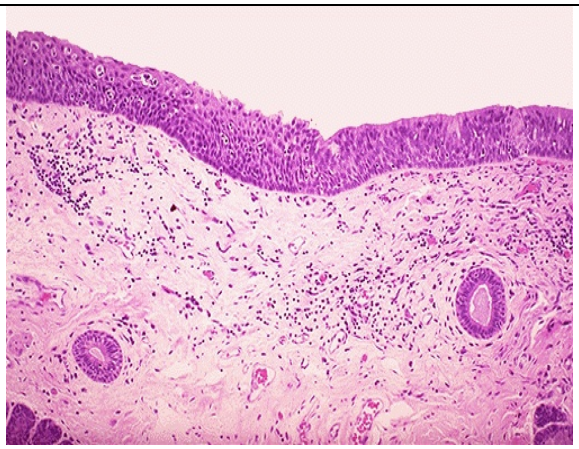
APPENDIX

	**Figure 1** — This is cardiac hypertrophy involving the left ventricle. The number of myocardial fibers does not increase, but their size can increase in response to an increased workload, leading to the marked thickening of the left ventricle in this patient with systemic hypertension.
	**Figure 2** — The testis at the right has undergone atrophy and is much smaller than the normal testis at the left.
	**Figure 3** — Here is one of the nodules of hyperplastic prostate. The cells making up the glands are normal in appearance, there are just too many of them.
	**Figure 4** — Metaplasia of laryngeal respiratory epithelium has occurred here in a smoker. The chronic irritation has led to an exchanging of one type of epithelium (the normal respiratory epithelium at the right) for another (the more resilient squamous epithelium at the left). Metaplasia is not a normal physiologic process and may be the first step toward neoplasia.

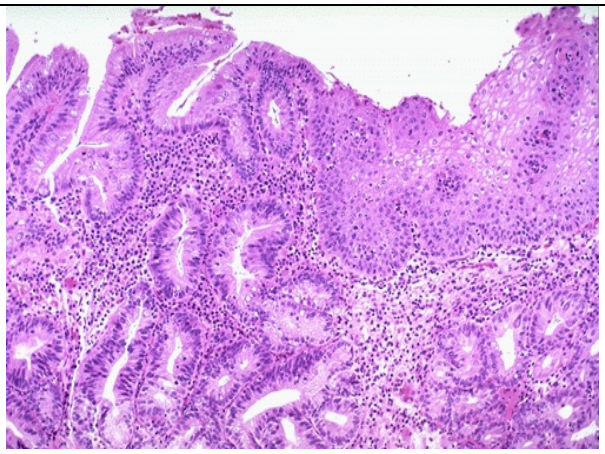


Figure 5 — Metaplasia of esophageal squamous mucosa has occurred here, with gastric type columnar mucosa at the left.

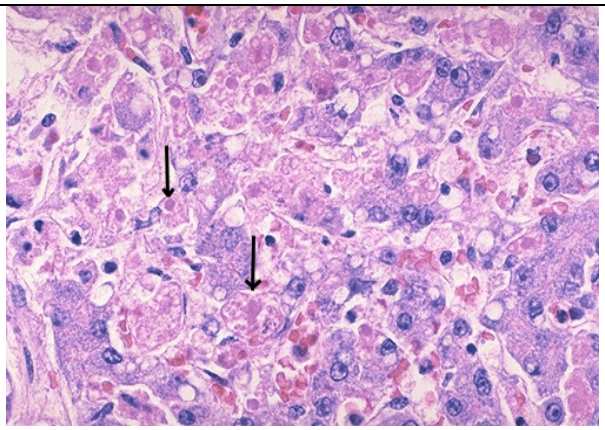


Figure 6 — Apoptosis is a more orderly process of cell death in which there is individual cell necrosis, not necrosis of large numbers of cells. In this example, liver cells are dying individually (arrows) from injury by viral hepatitis. The cells are pink and without nuclei.

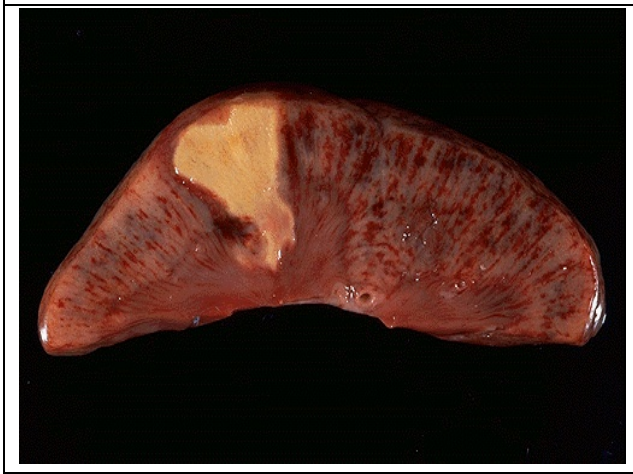


Figure 7 — When many cells undergo necrosis at once, then definable patterns of necrosis are produced, depending upon the nature of the injury, the type of tissue, and the length of time. This is an example of coagulative necrosis. This is the typical pattern with ischemia and infarction (loss of blood supply and resultant tissue anoxia). Here, there is a wedge-shaped pale area of coagulative necrosis (infarction) in the renal cortex of the kidney.

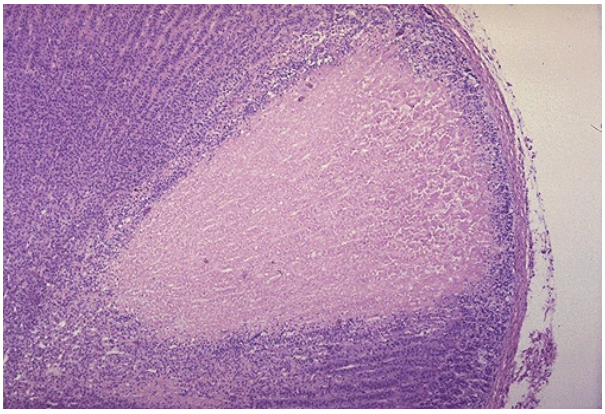
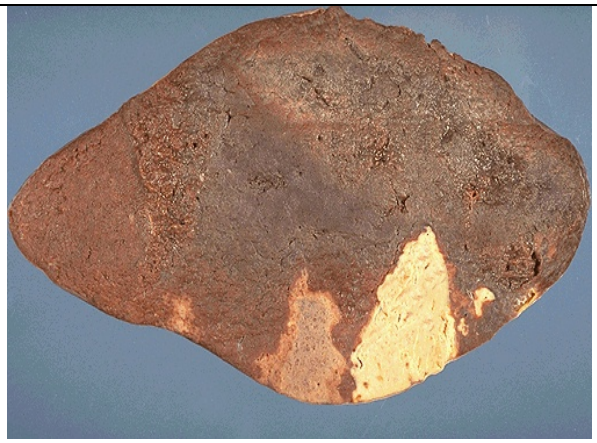
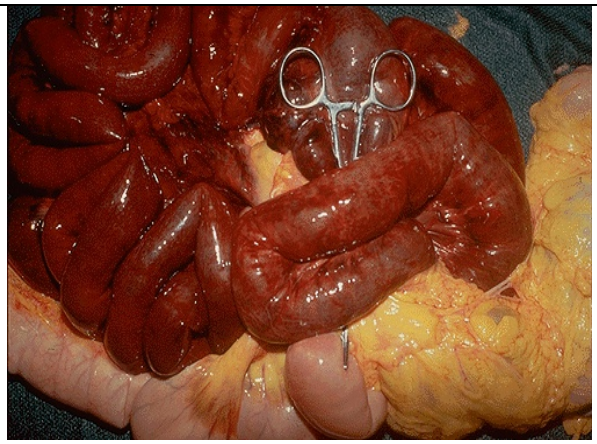
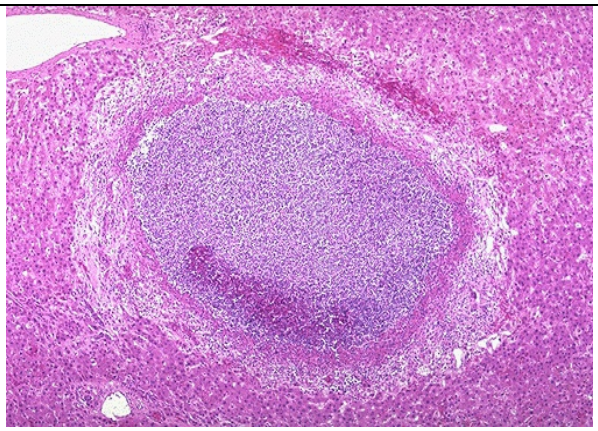
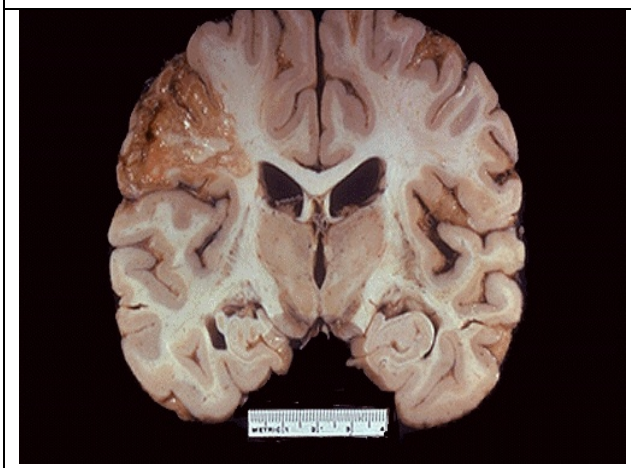
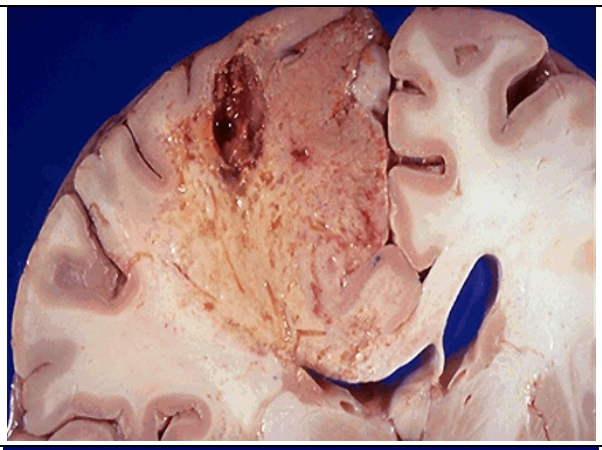
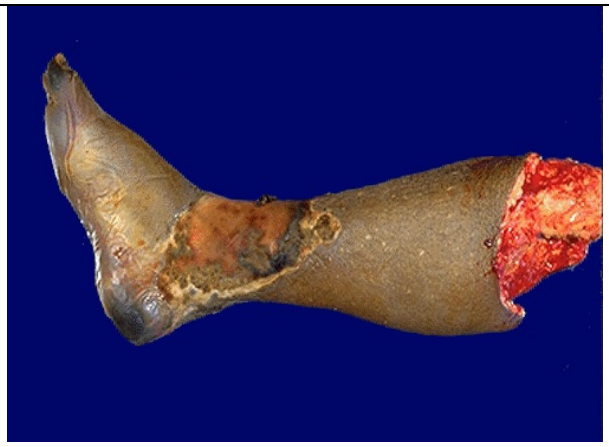
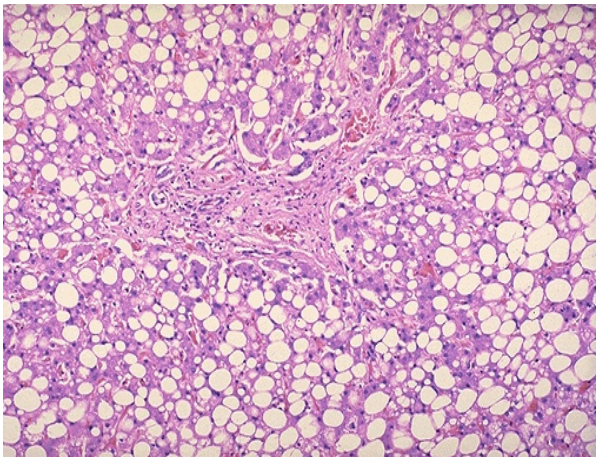
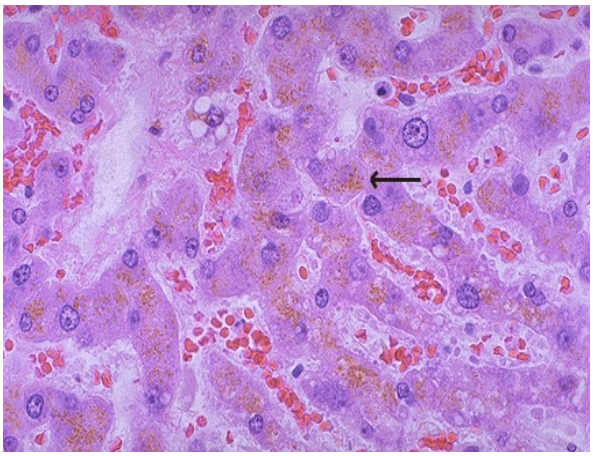
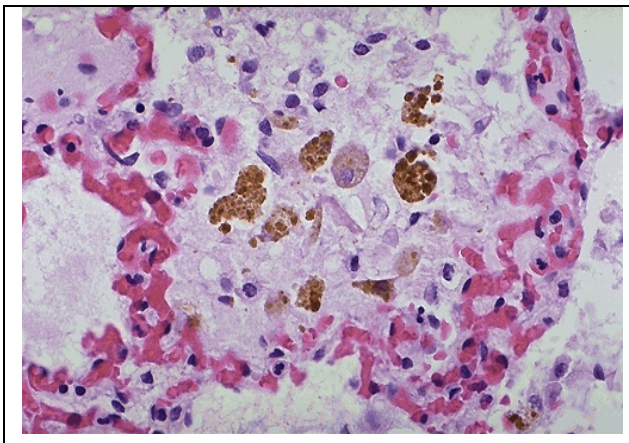
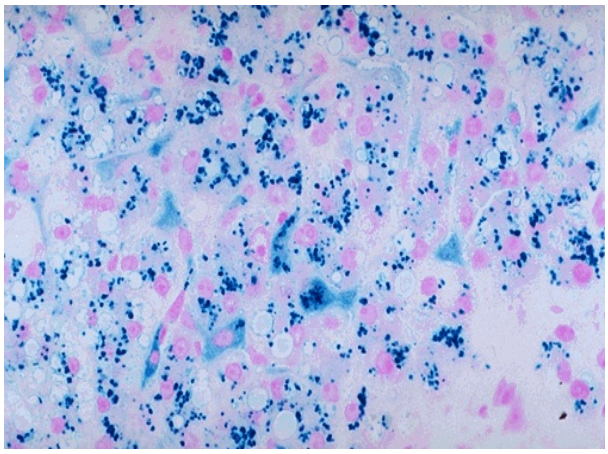
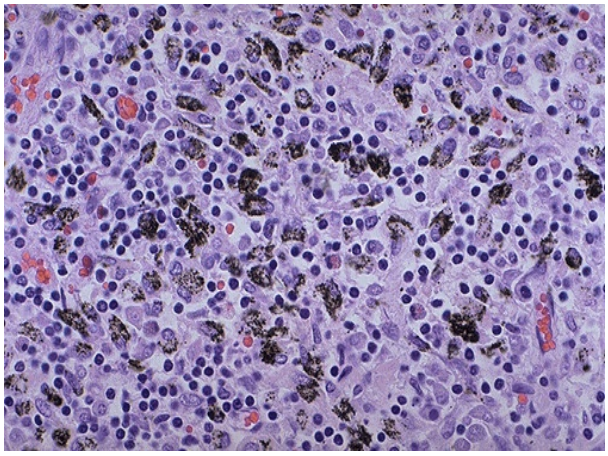
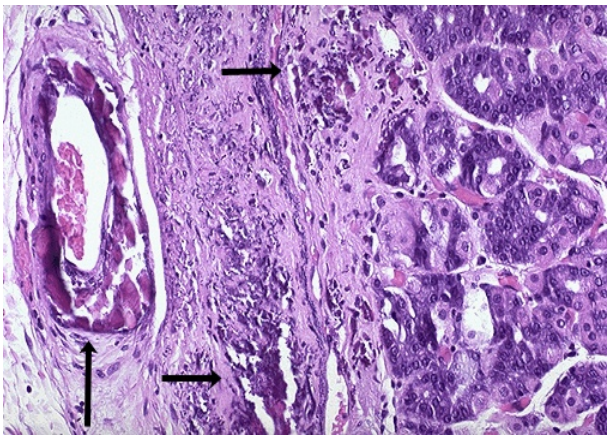


Figure 8 — The contrast between normal adrenal cortex and the small pale infarct is good. The area just under the capsule is spared because of blood supply from capsular arterial branches. This is an odd place for an infarct, but it illustrates the shape and appearance of an ischemic (pale) infarct well.

	**Figure 9 —** Two large infarctions (areas of coagulative necrosis) are seen in this sectioned spleen. Since the etiology of coagulative necrosis is usually vascular with loss of blood supply, the infarct occurs in a vascular distribution. Thus, infarcts are often wedge-shaped with a base on the organ capsule.
	**Figure 10 —** The small intestine is infarcted. The dark red to grey infarcted bowel contrasts with the pale pink normal bowel at the bottom. Some organs such as bowel with anastomosing blood supplies, or liver with a dual blood suppy, are hard to infarct. This bowel was caught in a hernia and the mesenteric blood supply was constricted by the small opening to the hernia sac.
	**Figure 11 —** The liver shows a small abscess here filled with many neutrophils. This abscess is an example of localized liquefactive necrosis.
	**Figure 12 —** Grossly, the cerebral infarction at the upper left here demonstrates liquefactive necrosis. Eventually, the removal of the dead tissue leaves behind a cavity.

	**Figure 13 —** As this infarct in the brain is organizing and being resolved, the liquefactive necrosis leads to resolution with cystic spaces.
	**Figure 14 —** This is gangrene of the lower extremity. In this case the term «wet» gangrene is more applicable because of the liquefactive component from superimposed infection in addition to the coagulative necrosis from loss of blood supply. This patient had diabetes mellitus.
	**Figure 15 —** Intracellular accumulations of a variety of materials can occur in response to cellular injury. Here is fatty metamorphosis (fatty change) of the liver in which deranged lipoprotein transport from injury (most often alcoholism) leads to accumulation of lipid in the cytoplasm of hepatocytes.
	**Figure 16 —** The yellow-brown granular pigment seen in the hepatocytes here is lipochrome (lipofuscin) which accumulates over time in cells (particularly liver and heart) as a result of «wear and tear» with aging. It is of no major consequence, but illustrates the end result of the process of autophagocytosis in which intracellular debris is sequestered and turned into these residual bodies of lipochrome.

	**Figure 17 —** The brown coarsely granular material in macrophages in this alveolus is hemosiderin that has accumulated as a result of the breakdown of RBC's and release of the iron in heme. The macrophages clear up this debris, which is eventually recycled.
	**Figure 18 —** A Prussian blue reaction is seen in this iron stain of the liver to demonstrate large amounts of hemosiderin that are present in hepatocytes and Kupffer cells.
	**Figure 19 —** Here is anthracotic pigment in macrophages in a hilar lymph node. Anthracosis is nothing more than accumulation of carbon pigment from breathing dirty air. Smokers have the most pronounced anthracosis. The anthracotic pigment looks bad, but it causes no major organ dysfunction.

	**Figure 20 —** This is dystrophic calcification in the wall of the stomach. At the far left is an artery with calcification in its wall. There are also irregular bluish-purple deposits of calcium in the submucosa. Calcium is more likely to be deposited in tissues that are damaged.

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