Avicenna Tajik State Medical University

Department of pathological anatomy

A.B. Rajabova, Ibodov S.T., Kh. Yu. Sharipov

PATHOLOGICAL ANATOMY

Book I

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Content:

PATHOLOGY

Pathology-is the study *(logos)* of disease *(pathos)*. More specifically, it is devoted to the study of the structural, biochemical, and functional changes in cells, and organs that underlie disease.

Includes:

- Anatomical pathology (pathological anatomy)
- Clinical anatomy

Pathological anatomy is the study about **structural** bases of diseases.

By the use of molecular, microbiologic, immunologic, and morphologic techniques, pathological anatomy attempts to explain the whys and wherefores of the signs and symptoms manifested by patients while providing a rational basis for clinical care and therapy. It thus serves as the bridge between the **basic science**s and **clinical medicine**, and is the scientific foundation for all of medicine.

Pathological anatomy is itself divided in subspecialties:

- ***surgical pathology*** -Surgical pathology involves the gross and microscopic examination of surgical specimens
- ***cytopathology*** -is a sub-discipline of anatomical pathology concerned with the microscopic examination of whole, individual cells obtained from smears or fine needle aspirates.
- ***forensic pathology*** - specialized training in determining the cause of death and other legally relevant information from the bodies of persons who died suddenly with no known medical condition, those who die from non-natural causes, as well as those dying as a result of homicide, or other criminally suspicious deaths.

Traditionally, the study of pathology is divided into:

General pathology is concerned with the reactions of cells and tissues to abnormal stimuli and to inherited defects, which are the main causes of disease. Thus, it discovers all the pathological processes in the organism, such as: inflammation, hemorrhage, stasis, thrombosis etc.

Systemic pathology examines the alterations in specialized organs and tissues that are responsible for disorders that involve these organs. Thus, it discovers specific diseases.

The core of pathology:

- ***Etiology*** *– the cause of disease or any pathological process*
- ***Pathogenesis*** *–the process or steps of its development*
- ***Pathological anatomy (morphology)****- gross and micro examinations*

(molecular and morphologic changes)

- ***Clinical manifestations***
- ***Results***
- ***Complications***

Main examinations in pathological anatomy

Gross examinations (macroscopic) is examination of diseased tissues with the naked eye. This is important especially for large tissue fragments, because the disease can often be visually identified (Fig. 1, 2).

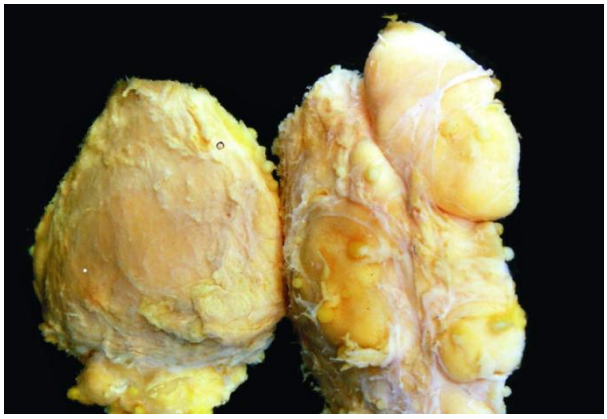


Fig. 1. Lipoma

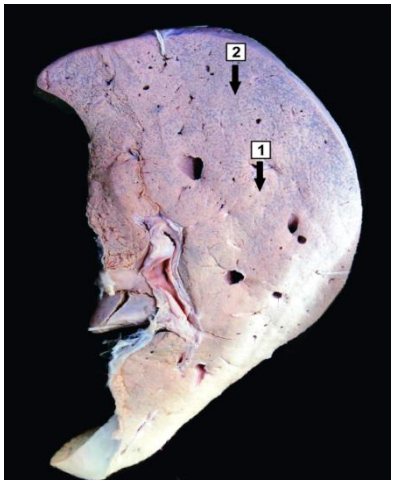


Fig. 2. Nutmeg liver

Microscopic examination - examination of stained tissue sections using histological techniques. The standard stains are haemotoxylin and eosin, but many others exist. The science of staining tissues sections is called **histochemistry** (Fig.3, 4)

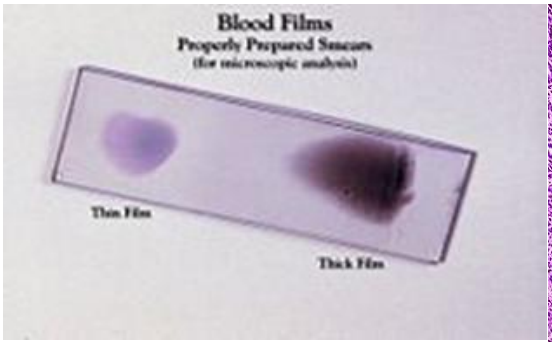


Fig. 3. Blood film.

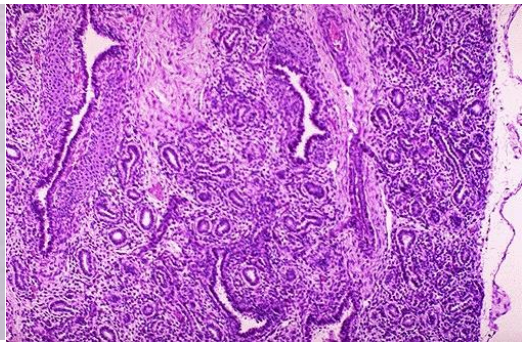


Fig. 4. Microscopic examination of the lung.

Methods

- **Autopsy-** is used to determine the disease factors contributing to a person's death. Autopsies are important in the ongoing medical education of clinicians, and in efforts to improve and verify the quality of medical care. Post mortem diagnostic.
- **Biopsy –** determining the disease factors in alive person.

THANATOLOGY

Is the academic, and often scientific study of death among human beings. It investigates the circumstances surrounding a person's death.

Death is the termination of the biological functions that sustain a living organism

I. **Natural**

II. **Pathological:**

a) **Murder**

b) **Homicide**

c) **Accident**

Signs and symptoms of death

- Cessation of breathing
- Cessation of metabolism
- No pulse
- Pallor mortis - paleness which happens within 15–120 minutes after death

- Livor mortis - settling of the blood in the lower (dependent) portion of the body
- Algor mortis - the reduction in body temperature following death. This is generally a steady decline until matching ambient temperature
- Rigor mortis - the limbs of the corpse become stiff (Latin *rigor*) and difficult to move or manipulate
- Decomposition - the reduction into simpler forms of matter, accompanied by a strong, unpleasant odor.

NECROSIS

Necrosis is an irreversible destruction of cells as a result of severe injury in a setting where they are not able to activate the needed metabolic pathways for survival or orderly degeneration (local or restricted death)

Etiology and pathogenesis

Due to etiology it can be:

- Toxic
- Traumatic
- Allergic
- Trophoneurotic
- Vascular

Etiological agents can act directly or indirectly through the vascular, nervous and immune systems

Direct: traumatic and toxic

Indirect: allergic, trophoneurotic and vascular

Stages of necrosis:

- **Paranecrosis –** like a necrosis but reversible changes
- **Necrobiosis –** irreversible changes
- **Cellular death**
- **Autolysis –** decomposition of the dead substratum under the action of the hydrolytic enzymes

Clinic-morphologic types:

Coagulative - occurs in the tissues that are not rich by and have lack of hydrolytic ferments and liquid

Colliquative - occurs in the tissues that are rich by liquid

Sequester – is the part of dead tissue that is not decayed (decomposed)

Infarct - area of dying or dead tissue whose blood supply has been obstructed *(white, red/hemorrhagic and white with the hemorrhagic halo)* (fig. 6).

Gangrene - localized death of soft tissue, caused by prolonged interruption of the blood supply that may result from injury or infection. *(dry, wet and bedsore)* (fig.5).

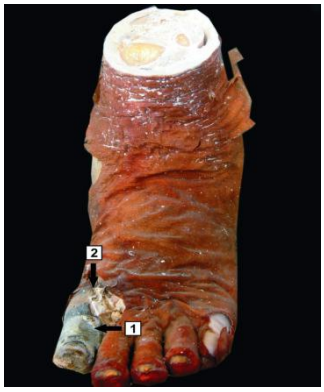


Fig.5 Dry gangrene foot

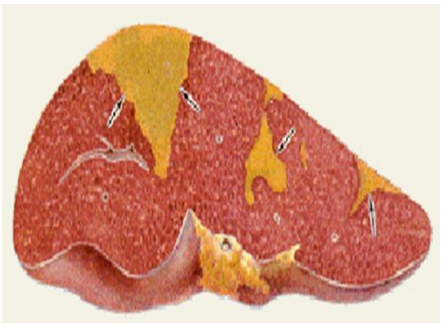


Fig.6. Infarct of the spleen.

Results

Positive:

- Scarring
- Encapsulation
- Ossification

Negative: Purulent decomposition with generalization of the process

APOPTOSIS

Apoptosis- genetically programmed death of cells at specific times during embryogenesis, metamorphosis, and during cell turnover in adults.

The body's normal method of disposing of damaged, unwanted, or unneeded cells.

DYSTROPHY.
PARENCHYMAL DYSTROPHY

Dystrophy (from the Greek. *dys* - the violation and *tropho* - entertain**) - *a quantitative and qualitative structural changes in cells and / or the intercellular substance of organs and tissues caused by the violation of metabolic processes.***

Dystrophy as a result of violations in the trophic processes accumulates various metabolic products (proteins, fats, carbohydrates, minerals, water).

Morphological essence of dystrophy is expressed in:

- increasing or decreasing the amount of any substance contained in the body in the norm (e.g., increased fat in the fat depots)
- appearance and accumulation of new substances that are not inherent to him in the norm (e.g., amyloid protein).

Etiology

I. Toxic substances (including toxins, microorganisms)

II. Physical and chemical agents: high and low temperatures, certain chemicals (acids, alkalis, salts of heavy metals, many organic substances), ionizing radiation

III. Acquired or inherited enzymopathies

IV. Viruses

V. Violations of the functions of energy and transport systems, providing metabolism and structural integrity of tissues (hypoglycemia, hypoxia)

VI. Violations of the endocrine and nervous regulation (diseases of the endocrine organs (hyperthyroidism, diabetes, hyperparathyroidism, etc.); diseases of the central and peripheral nervous systems (innervation, brain tumors).

Pathogenesis

1. **Infiltration -** excessive penetration of metabolic products from the blood and lymph to the cells or intercellular substance. (fig.7)
2. **Decomposition -** decay in the complex chemical substances.
3. **Transformation -** the transition from one substance to another. (fig.8)
4. **Perverted synthesis** - the synthesis of unusual quality, not found in normal substances (amyloid, alcoholic hyaline, Mallory bodies, etc.) (fig. 9)

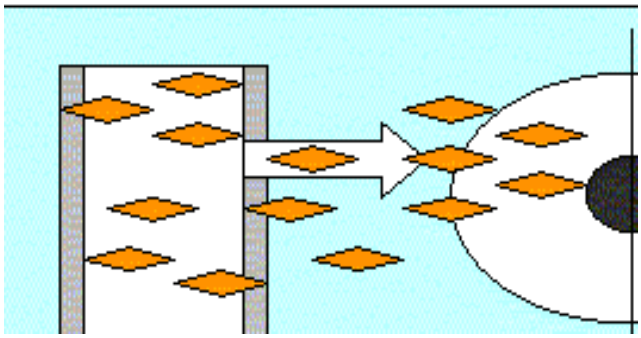


Fig. 7. Infiltration. The number of metabolites is increased and they are actively entering the tissue structures.

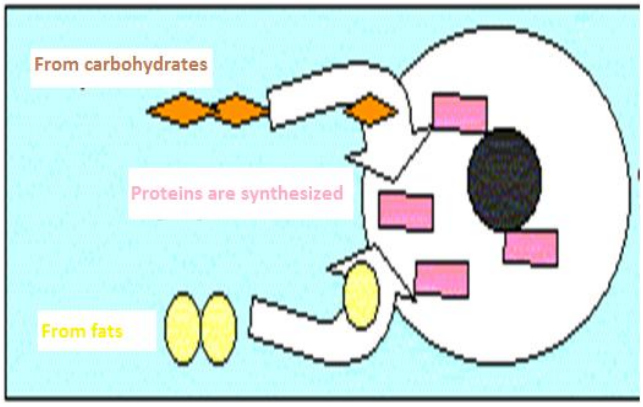


Fig. 8. Transformation.

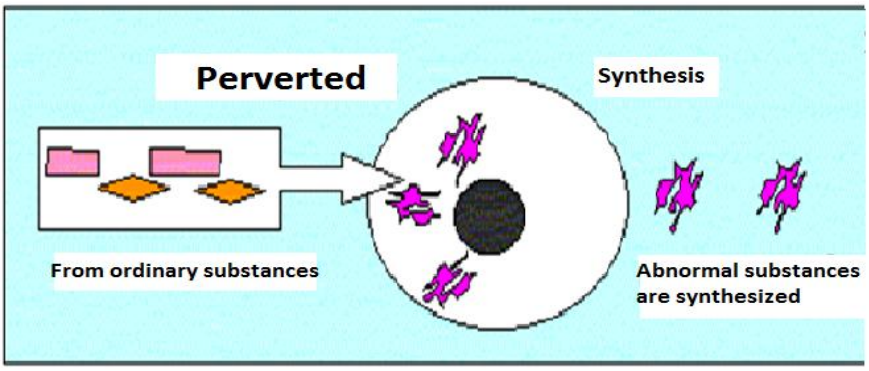


Fig. 9. Perverted synthesis.

Classification

Due to localization:

I. *Parenchymal (intracellular)*

II. *Mesenchymal (extracellular)*

III. *Mixed*

Due to violation of metabolism:

I. *Protein*

II. *Fat*

III. *Mineral*

IV. *Carbohydrate*

Depending on the influence of genetic factors:

a. *Hereditary*
b. *Acquired*

As the prevalence of the process:

a. *General*

b. *Local*

PARENCHYMAL DYSTROPHY

Parenchymal dystrophy is a dystrophy characterized by structural changes in the highly specialized cells that are functionally associated with metabolism.

Protein parenchymal dystrophies:

A. Granular dystrophy

B. Hyaline droplet

C. Hydropic

D. Horns

Granular dystrophy

Granular dystrophy is a process when in the cytoplasm of cells of parenchymatous organs appears pronounced grain, due to the accumulation of grain protein in the cell.

Macroscopic examination: bodies themselves increased in size, became flabby and dull on the cut, as if scalded with boiling water.

Microscopic examination: cells look like muddy, swollen.

This process is reversible.

Hyaline droplet dystrophy

In ***hyaline droplet dystrophy*** in the cytoplasm appear large hyaline-like protein droplets, merging with each other and filling the cell body, thus there is a destruction of ultra-structural elements of cells. This kind of dystrophy is often found in the kidneys, rarely - in the liver and very rarely - in the myocardium.

The appearance of the kidneys at this degeneration does not have any features, it is determined primarily by features of the underlying disease (glomerulonephritis, amyloidosis).

Hyaline droplet degeneration of hepatocytes is often the morphological basis of many disorders of the liver.

Hydropic dystrophy

Hydropic dystrophy is characterized by the appearance in the cell vacuoles filled with cytoplasmic fluid. It occurs more frequently in the epithelium of the skin, renal tubules, in hepatocytes, muscle, and nerve cells, as well as in cells of the adrenal cortex.

Macroscopic examination. The appearance of organs and tissues there is little change in the hydropic dystrophy, it is usually found under the microscope.

Microscopic examination: cells are increased in volume, their cytoplasm filled with vacuoles containing clear liquid. The nucleus is shifted to the periphery, sometimes vacuolised or shrinking (Fig. 10).

The outcome of *hydropic dystrophy*, as a rule, is unfavorable, and it ends in the form of focal or total necrosis of the cells.

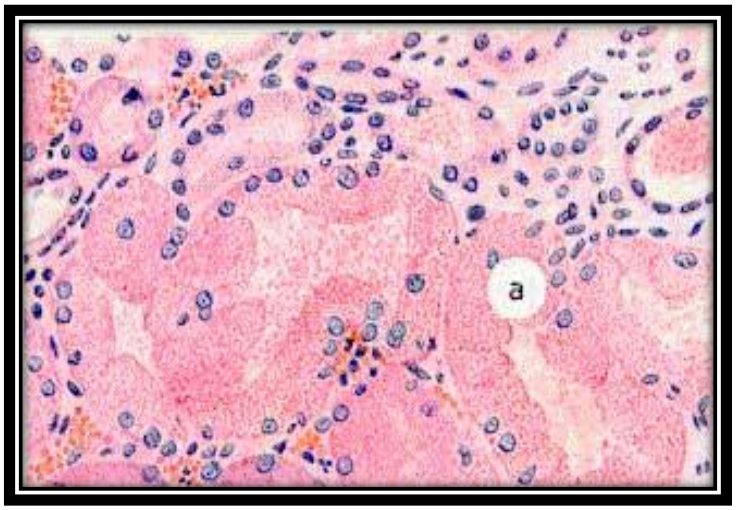


Fig. 10. Hydropic dystrophy

Horns dystrophy

Horns dystrophy, or pathological keratinization, characterized by excessive formation of keratin in the keratinizing epithelium (**hyperkeratosis, ichthyosis**) or the formation of keratin, where normally it does not happen (pathological cornification on the mucous membranes, or **leukoplakia**)

Etiology:

a. Any developmental disorder of the skin

b. Chemical and physical agents

c. Chronic inflammation

d. Viral infections

e. Avitaminosis (Beriberi, etc.)

The outcome can be twofold:

removing the causes of the "caller" at the beginning of the process can lead to the restoration of tissue, but in advanced cases, cell death occurs.

PARENCHYMAL FAT DYSTROPHY

Parenchymal fat dystrophy is based on violation of cytoplasmic lipids' metabolism.

Metabolic cytoplasmic lipids may show an increase in their content in the cells, where they discovered in norm, and the appearance of lipids, where they are not commonly found, and in the formation of unusual chemical composition of fats. Typically, the cells accumulate "neutral fats**".** Parenchymal fat dystrophy occurs most often in the same place as protein parenchymal dystrophy - in the myocardium, liver, kidneys.

Macro- and Micro Examinations

In the myocardium, fat dystrophy characterized by the appearance in the muscular cells the smallest fat droplets *(dust obesity).* From the endocardium visible yellow-white striations, particularly well expressed in the papillary muscles and trabeculae of the heart ventricles ***("tiger heart").***

In the liver, fat dystrophy (obesity) shows a sharp increase in fat content in hepatocytes and changes in their composition. The appearance of the liver rather characteristic: *it is enlarged, flabby, yellow-brown color.* In the section on the knife edge and the cut surface is visible plaque of fat (Fig. 11).

In the kidneys with fat dystrophy fats appear in the epithelium of proximal and distal tubules.

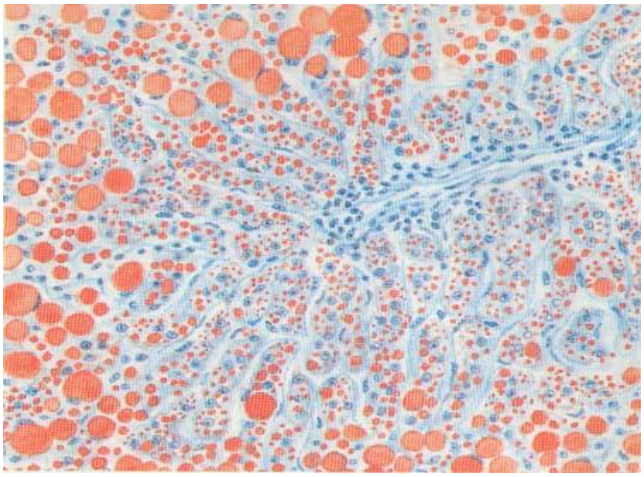


Fig. 11. Fat dystrophy. There are drops of fat in the cytoplasm of hepatocytes

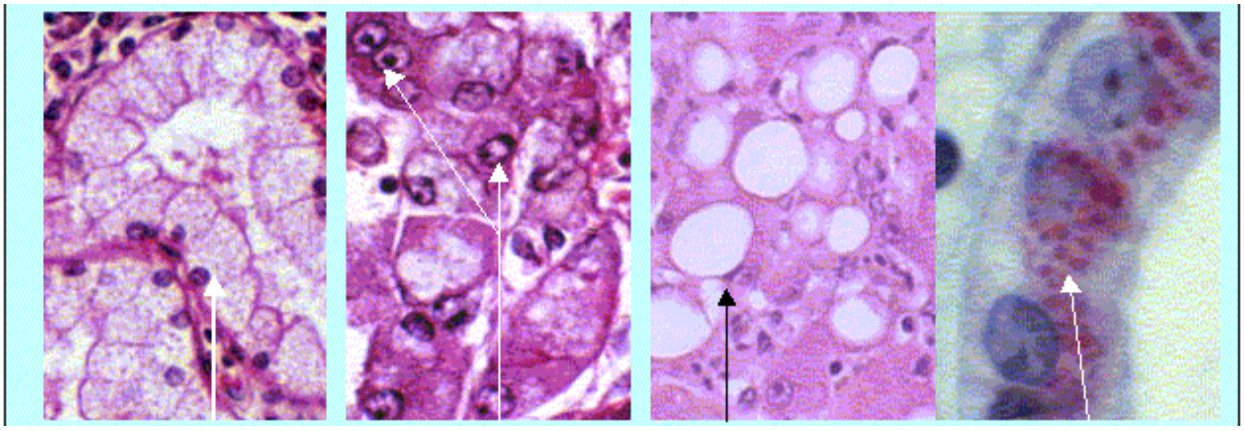
PARENCHYMAL CARBOHYDRATE DYSTROPHY

Carbohydrate parenchymal dystrophy may be associated with impaired glycogen metabolism or glycoproteins, the main reserves of which are localized in liver and skeletal muscles.

Violations of glycogen metabolism appears in reduction or increase in the number of its occurrence in the tissues and where it is not normally detected. These disorders are most pronounced for patients with diabetes and hereditary carbohydrate – glycogen dystrophies .The number of glycogen increases sharply in the epithelium of renal tubules - cells with high foamy cytoplasm. Due to the inclusions of glycogen nuclei of hepatocytes become "hole", "empty" basal membrane of the glomerular capillaries thickens

Comparison of the different types of parenchymal dystrophies.

Fig. 12 Hydropic dys. Carbohydrate dys. Fat dystrophy



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MESENCHYMAL DYSTROPHY

Mesenchymal (stromal-vascular) dystrophy develops as a result of imbalances in the connective tissue and detected in the stroma of organs and vascular walls.

Mesenchymal dystrophy due to metabolic type :

I. protein

II. fat

III. carbohydrate

MESENCHYMAL PROTEIN DYSTROPHY

- mucoid swelling
- fibrinoid swelling;
- hyalinosis

- amyloidosis

Often mucoid swelling, fibrinoid swelling and hyalinosis are stages of disorganization of connective tissue. Amyloidosis is different from these processes so that it builds on the synthesis of abnormal protein-polysaccharide complex.

Mucoid swelling

Mucoid swelling- superficial and reversible disruption of the connective tissue. At the same time in the matrix of connective tissue occurs accumulation and redistribution of glycosaminoglycans. The accumulation of them leads to the appearance of metachromasia – a property to change the color of dye. So when stained with hematoxylin-eosin, the connective tissue is bluish in color, when it should be painted in pink as usual.

Etiology

More often mucoid swelling occurs in the vascular walls, endocardium, heart valves in rheumatic diseases, but may also occur during intoxication, infections, hypoxia, etc.

Macroscopic examination: changes are not obvious

Microscopic examination: collagen fibers are swollen and abnormally stained

Results

- surface disruption of the connective tissue usually ends in:
- restoration of tissue structure
- transition in fibrinoid swelling

Fibrinoid swelling

Fibrinoid swelling it is a deep irreversible disruption of the connective tissue, which can be completed by:

- necrosis
- hyalinosis
- sclerosis

Macroscopic examination: changes are becoming obvious only when the process is turned into necrosis

Microscopic examination: collagen fibers are swollen and lose there bundle structure. Metachromasia with fibrinoid swelling is not expressed or very weakly expressed.

Results

- surface disruption of the connective tissue usually ends in**:**
- necrosis
- transition into hyalinosis

Hyalinosis

Hyalinosis is a type of mesenchymal protein dystrophy. As a result of this degeneration in the tissues and organs appears a homogeneous mass of translucent substance (hyaline), resembling hyaline cartilage. ***Hyaline*** **-** a fibrous protein in combination with plasma proteins, fibrin, immune complexes.

Hyaline masses are highly resistant to acids, alkalis, enzymes.

Etiology

Sometimes it is delayed in physiological conditions - the old men in the vessels of the spleen.

Hyalinosis may develop in the outcome of:

- fibrinoid swelling
- plasmatic impregnation
- chronic inflammation
- sclerosis

Due to hypertonic diseases arteries and arterioles are affected by hyalinosis, thus, these vessels are looking like a " glass tubules", becoming homogenious, thin in their walls (diameter) and become brittle (fragile).

Classification

Local - occurs during fibrinoid swelling and plasmatic impregnation

Systemic - happens during inflammation, sclerosis and necrosis.

Hyalinosis of the vessels is usually systemic in nature, but the most typical damage to the kidneys, brain, retina, pancreas and skin.

Especially characteristic hyalinosis of vessels for essential hypertension, symptomatic hypertension, diabetes and autoimmune diseases.

Hyalinosis usually develops as an outcome of fibrinoid swelling in rheumatic diseases.

There are 3 types of vascular hyaline:

- **simple**
- **lipohyaline**
- **complex hyaline**

Results

In most cases, there is an unfavorable outcome in hyalinosis

Amyloidosis

Amyloidosis- mesenchymal dystrophy, accompanied by the formation of the complex substance – amyloid in the mesenchyme. Amyloid is a protein-polysaccharide complex, consisting of F - component (fibrous protein), P - component (plasma component), T-component (tissue).

Microscopic examination

a) Congo-red

b) Iodine-Grün in gentian violet - painting is based on the metachromasia of amyloid.

Classification by etiology:

- Primary (idiopathic)
- Hereditary (genetic, family)
- Secondary (acquired)
- senile

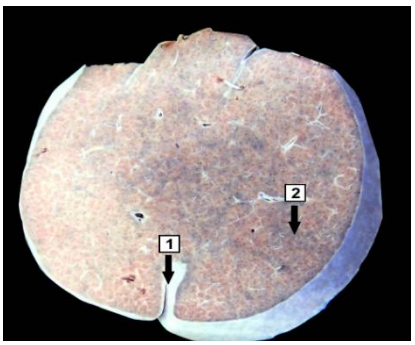


Fig. 13 Amyloidosis spleen—Sago spleen:
The slice of spleen is identified by its dark color and presence of notches (1). The sectioned surface shows presence of pale waxy translucency seen around the gray central arterioles (2) forming nodular pattern (sago spleen)

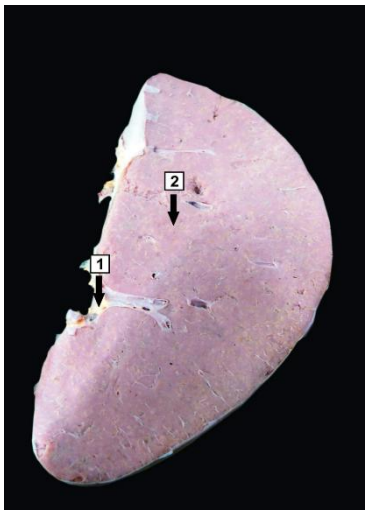


Fig. 14 Amyloidosis spleen—Lardaceous spleen: The slice of spleen is identified by its dark color and presence of notches (1). The sectioned surface shows presence of pale waxy translucency seen as map-like areas corresponding to red pulp (2) forming diffuse pattern (lardaceous spleen).

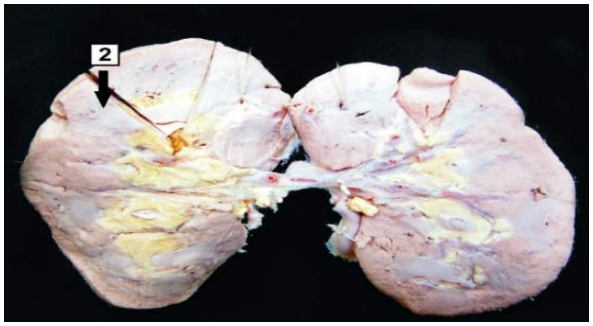


Fig. 15 Amyloidosis of kidney: the kidney is small and pale in color (1). Cut section shows pale waxy loss of cortico-medullary distinction

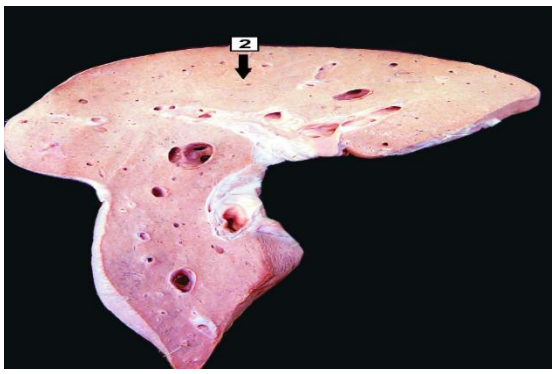


Fig. 16 Amyloidosis of liver:

Classification of the amyloidosis according to prevalence:

- generalized form
- local form

Classification based on the effected organs and systems

- cardiopathic
- nephropathic
- epinephropatic
- neuropathic
- hepatopathic
- mixed

Pathogenesis

Amyloid in the organs is delayed in the course of three structures:

- in the stroma
- in the vessels of various calibres
- under the basal membrane of glands

In the kidney, amyloid deposits in glomeruli, vascular walls, tubular basement membrane, stroma (Fig. 15).

Depending on the course of any delayed amyloid fibers distinguish 2 types of amyloidosis:

- **Perireticular amyloidosis (parenchymal) -** it is formed along the reticular fibers
- **Pericollagenic amyloidosis (mesenchymal) -** it is delayed in the course of collagen fibers.

Primary amyloidosis

is characterized by:

- absence of prior disease;
- predominant injury of mesodermal tissues (CVS, muscles, nerves and skin);
- generalized nature of the lesion;
- volatility of colorful reactions;
- tendency to form nodular deposits of amyloid.

Hereditary amyloidosis

is characterized by a predisposition to amyloidosis of certain ethnic groups (Jews, Arabs, Armenians and others).

Secondary (acquired) amyloidosis

Occurs as a complication of some diseases:

- chronic infections (especially tuberculosis)
- disease with purulent-destructive processes (osteomyelitis, suppuration of wounds)
- cancer
- rheumatic diseases (especially rheumatoid arthritis)

Secondary amyloidosis occurs most frequently in:

- spleen (in the form of sago or tallow spleen)
- kidney
- liver

- adrenals
- intestine

Senile amyloidosis

predominantly affects:

- **heart**
- **brain**
- **pancreas**

This so-called *Schwartzman triad.*

Results

Progressive amyloidosis accompanied by the displacement and replacement of stroma of the organ, which leads to chronic lack of organ functions.

MESENCHYMAL FAT DYSTROPHY

Occur during the exchange of neutral fats, cholesterol and its esters. Metabolic cholesterol appears frequently atherosclerosis, which affects the large arteries. Metabolic neutral fat may occur increasing fat deposits in adipose depots. This may be general and local. The total increase of neutral fat is called ***obesity.***

When there is local increase in **quantity** of fat say about ***lipomatosis***. Among them are of greatest interest: **disease of Dercum** (polyglandular endocrinopathy - knotted painful deposits of fat in the subcutaneous tissue of limbs and trunk).

Classification of the obesity connected by:

- etiology
- external manifestations (types of obesity),
- morphological changes in adipose tissue (variants of obesity).

Classification of obesity

Due to etiology:

- **Primary**
- **Secondary :**

a) *alimentary* (unbalanced diet, physical inactivity),

b) *cerebral* (developed with brain injury, brain tumors, neuroinfections)

c) *endocrine* (Itsenko-Cushing's, etc.)

d) *hereditary*

Classification of obesity due external manifestations (types of obesity)

I. *Symmetrical (universal) obesity*

II. *Upper type*

III. *Average type*

IV. *Lower type*

Morphology

The morphological changes in adipose tissue differentiate between 2 options of obesity:

- ***hypertrophic*** **variant** (fat cells increased in volume, the disease is malignant)
- ***hyperplastic*** **variant** (increased number of fat cells, the disease is benign).

The importance of obesity:

Obesity is particularly dangerous for heart, when fat is delayed under the epicardium and between the muscle fibers, causing them to atrophy. Patients die from a heart attack, heart failure.

It can also be:

- **General**
- **Local**

General form. The overall decline in amount of fat called depletion or *cachexia*

Cachexia is due to:

- nutritional (fasting)
- cancer

- pituitary
- cerebral
- with other diseases, such as Mts infections (tuberculosis).

MESENCHYMAL CARBOHYDRATE DYSTROPHY.

Mesenchymal carbohydrate dystrophy associated with metabolic disturbances glycoproteins and GAGs (glycosaminglycans). Mesenchymal dystrophy, metabolic disturbances associated with glycoproteins, called ***mucilaginized*** tissues.

Reasons of mucilaginized: dysfunction of the endocrine glands (myxedema); cachexia different genesis. In contrast to the mucoid swelling in this case is replaced collagen fibers mucoid mass.

MIXED DYSTROPHY.

All quantitative and qualitative structural changes, which are due to metabolic abnormalities detected simultaneously in the parenchyma, stroma and vascular walls of organs and tissues are called *mixed dystrophy*. The cells and the intercellular substances accumulate various metabolic products of **complex proteins.**

Complex proteins

Complex proteins- proteins, which consist of protein and non-protein parts

Complex proteins are :

- chromoproteins
- nucleoproteins
- lipoproteins

Chromoproteins - stained proteins (endogenous pigments) - play an important role in the life of the organism

Their function:

- respiration (hemoglobin, cytochromes);
- production secrets (bile) and the hormone (serotonin);

- protecting the organism from the effects of radiation energy (melanin);
- replenishment of iron (ferritin);
- balance of vitamins (lipochromes), etc.

Endogenous pigments

Represented by three groups:

- **Hemoglobinogenic** (derivatives of hemoglobin).
- **Proteinogenic** or tyrosine-tryptophan number associated with the exchange of tyrosine and tryptophan.
- **Lipidogenic** (lipopigments) or formed during the exchange of fat.

Metabolic chromoproteins disturbance

Metabolic Hemoglobinogenic Pigments

- **Hemoglobin** (high chromoproteid) - iron-containing respiratory pigment, forming the basis of red blood cells and acting as a carrier of oxygen.

Hemolysis

Essentially a physiological phenomenon associated with the aging of red blood cells and their continuous destruction under the influence of physiological hemolysins, especially in a slow flow or stop it, which takes place in the sinuses of the spleen, liver and bone marrow with the removal of **hemoglobin (Hb).**

As a result of **physiological decay** of red blood cells and hemoglobin pigments formed:

- Ferritin
- Hemosiderin
- Bilirubin

In pathological conditions, in addition to the resulting increase in the rate of hemoglobinogenic pigments, may appear a number of **new pigments** :

- Hematoidin
- Hematin

- Porphyrin

Ferritin *ironproteid* containing up to 23% iron. Iron of ferritin is associated with the protein, which is called apoferritin. There is inactive (oxidized) form of ferritin- SS-ferritin. With the shortage of oxygen is restored to the active form of ferritin - SH-ferritin, which has vasoparalytic and hypotensive properties.

Classification of ferritin

Due to the origin allocated:

- Anabolic- is composed of iron absorbed from the intestine.
- Catabolic- iron from hemolysed erythrocytes.
- Ferritin and apoferritin have antigenic properties

A large number of ferritin found in the liver (depot ferritin), spleen, bone marrow and lymph nodes, where the exchange it is connected with the synthesis of hemosiderin, hemoglobin and cytochromes. In the pathology of ferritin may increase both in blood and in tissues. Ferritinemia explains the irreversibility of the shock, accompanied by cardiovascular collapse, as the SH-ferritin acts as an antagonist of adrenaline.

Metabolic hemosiderin

Hemosiderin - golden-yellow, usually amorphous pigment, which is formed during the decomposition of heme and is a polymer of ferritin**.**

Hemosiderin is a product of the intracellular hemolysis. Hemosiderin occurs after 24 hours from the time of hemorrhage. Cells in which hemosiderin is formed, called sideroblasts. Hemosiderin is constantly found in the reticular and endothelial tissue of the spleen, liver, bone marrow and lymphatic nodes. Hemosiderin may be tested by the several specific reactions as: Berlin azure (Perl's reaction), turn into bluish blue.

Hemosiderosis is an overproduction of hemosiderin**.**

Local –takes part due to extravascular hemolysis in the areas with hemorrhage (hematoma, Mitral heart defect, cardiosclerosis, cardiostenosis etc.)

General – due to intravascular hemolysis (intoxications by hemolytic poisons, malaria, sepsis, typhoid recurrent, undulant fever, syphilis, overcoming of iron into the organism due to multiple blood transfusion etc.)

Morphology

Macroscopical examination: spleen, bone marrow and lymphatic nods are grayish-brown

Intracellular Iron DEPO is decreased → free Iron is accumulated in the tissues and restored → free radicals with an active oxygen.

Hemochromatosis

Is a close to the general hemosiderosis disorder that is differentiated by the level of Iron overloading and appearing of the parenchymal cells' injury

- **Primary (hereditary)**
- **Secondary**

Primary (hereditary) is an independent disorder, passed through autosomal-dominant way and connected with a hereditary fermentative defect of small intestine. Which leads to the increase of the alimentary iron absorption in the form of hemosiderin that laid down in the organs and tissues. Iron metabolism in the erythrocytes is not changed. Amount of the iron in the organism is increased and is about 50-60 gr. Leads to: hemosiderosis of liver, pancreas, intestinal mucous membranes, retina of the eye and synovial membranes in the same time in the tissues amount of ferritin increased.

Clinics

Main sign of the disorder is – bronze color of the skin as in:

- **Diabetes (bronze diabetes)**
- **Pigmentary cirrhosis that leads to the hepatic failure**

Pigmentary cardiomyopathy → death.

Secondary is a disorder that occurs due to acquired failure of the fermentative systems, applying the alimentary iron metabolism which accompanied by the generalized hemosiderosis.

Etiology

Alimentary iron's entrance into the organism, resection of the stomach, chronic alcoholism, secondary blood transfusion, etc.

Clinic of the secondary hemochromatosis is the same with primary one.

Bilirubin

Hemoglobin →Hem →Biliverdin (a green pigment present in the bile, formed from bilirubin by oxidation) **– Indirect Bilirubin** + **albumin →Direct Bilirubin**

JAUNDICE

Characterized by the increase of bilirubin in the blood with its accumulation in tissues and coloring yellow the skin, sclera, mucosa and internal organs.

Etiology

a. Increase of the bilirubin metabolism
b. decrease of the excretion
c. obstruction of the bile duct

Classification of jaundice

Due to mechanism :

- *Suprahepatic (hemolytic)*
- *Hepatic (parenchymal)*
- *Subhepatic (mechanical)*

Hemolytic jaundice

Increase of the bilirubin metabolism due to hemolysis
increase of the indirect bilirubin in blood

Etiology

Intoxications by hemolytic poisons, malaria, sepsis, typhoid recurrent, undulant fever, syphilis, overcoming of bilirubin into the blood due to multiple blood transfusion, massive blood hemorrhages etc.

Clinics

Spleen and liver enlarged, indirect bilirubin increased in blood.

Hepatic jaundice

Hepatic jaundice -occurs due to the hepatocytes' damage and results fastening of the bilirubin and its excretion, which leads to its maintenance in the blood

Etiology

Infections (chronic and acute viral hepatitis), intoxications, autoinfection. Direct and indirect bilirubin is increased in the blood, indirect bilirubin is increased in the urine that causes its different, dark color.

Subhepatic jaundice

Subhepatic jaundice -occurs due to obstruction of the biliary ducts

Etiology

Stones of the biliary tract, cancer of the biliary ducts, compression by the head of the pancreas, parasitic diseases.

Pigments that appear due to hemolysis in pathology

- **Hematin-** black colored pigment, which accumulates during malaria and is called "**pigment of malaria".**
- **Porphyrin –** antagonist of melanin, that increases sensitivity of skin to UV rays**.** An increase of porphyrin is called Porphyria and characterized by appearing of erythemas, turning into ulcers and appearing of porphyrin in blood and urine.
- **Hematoidin** – non-containing iron pigment, which crystals are bright – orange in color. It's accumulated due to intravascular hemolysis after hemosiderin in 5-10 days. And after the cells death it lays among the necrotic masses.

Proteinogenic pigments.	**Lipidogenic pigments**
Melanin	Lipofuscin
Adrenochrome	Ceroid
	Lipochrome

Nucleoproteins

Nucleoproteins are formed from proteins and nucleic acids (DNA and RNA). Final products of nucleoproteins metabolism are the uric acid and its salts, that are excreted by the kidneys. Metabolic disturbances of the nucleoproteins are represented by the over formation of uric acid.

HEMODYNAMIC DISORDERS. HYPEREMIA. CONGESTION. ISCHEMIA. STASIS. HEMORRHAGE.

Normal functioning of the organism is difficult to imagine without the organs of blood circulation and lymph circulation, which are closely structurally-functional unity.

The term "microcirculation" refers to a number of processes, especially such as:

- patterns of blood circulation and lymph flow in micro vessels,
- the behavior of blood cells (strain, aggregation, adhesion),
- the mechanisms of blood clotting and,
- most important mechanisms of transcapillary exchange.

Through microcirculation provided tissue homeostasis

Circulatory disorders can be divided into 3 groups:

I. Disorders of blood supply, provided congestion (arterial and venous);

II. Violation of the permeability of vascular walls, which include bleeding (hemorrhage) and plazmorrhagia

III. Violations of the flow (i.e., rheology) and the state of blood in the form of stasis, sludge-phenomenon, thrombosis, embolism.

Circulatory disorders:

1) arterial and venous hyperemia;

2) ischemia;

3) stasis;

4) thrombosis;

5) embolism;

6) bleeding and hemorrhage.

Arterial Hyperemia

Increased blood circulation due to increased inflow of arterial blood (Fig. 17).

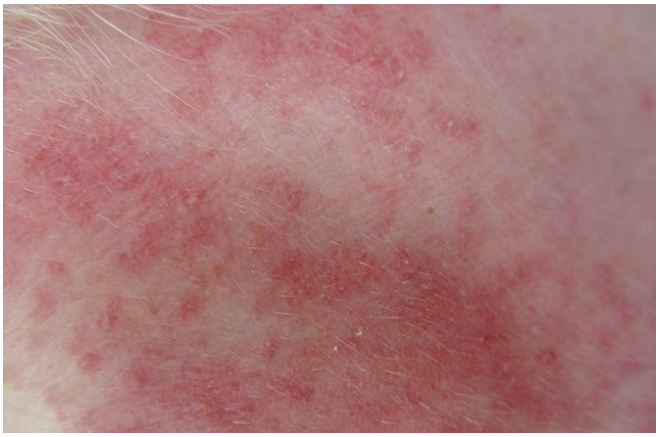


Fig. 17. Arterial hyperemia

- It can be **general**, which is observed with an increase in blood volume or the number of red blood cells. In such cases, marked with a red coloration of the skin and mucous membranes and high blood pressure.
- Mostly arterial congestion is **local** in nature and arises from various causes.

Classification

- There are **physiologic arterial hyperemia** occurring under the action of adequate doses of physical and chemical factors, with a sense of shame and anger (flushed), with enhanced functions of the organs (the working hyperemia), and **pathological arterial hyperemia**.

Types of pathological arterial hyperemia

I. ***angio-neurotic (neuroparalytic)***

II. ***collateral***

III. ***hyperemia after anemia (postanemic)***

IV. ***vacate***

V. ***congestion on the basis of arteriovenous fistula***

VI. ***inflammatory***

As the prevalence of disorders of blood flow may be:

1) diffuse

2) generalized

3) local

Angio-neurotic (Angioedema congestion)

Is observed as a consequence of stimulation of vasodilator nerves or paralysis of the vasoconstrictor nerves. The skin, mucous membranes are red, slightly swollen, warm to the touch, or hot.

This type of hyperemia may occur in certain parts of the body in violation of innervations, the skin and mucous membranes of the person with some infections that accompany lesion sites of sympathetic nervous system. Typically, the congestion passes quickly and leaves no traces.

Collateral hyperemia

Arises in connection with obstruction of blood flow on the main (major) arterial trunk, closed by thrombus or embolism. In these cases, the blood rushes from collateral vessels. Educate them reflexively increasing, the arterial blood flow increases and the tissue gets a larger amount of blood.

Hyperemia after anemia (**postanemic**)

Develops in cases where a factor leading to compression of the artery (swelling, fluid accumulation in the cavity, ligation, etc.) and anemia of tissue, rapidly eliminated. In these cases, the vessels previously bloodless tissue rapidly expand and fill with blood, which can lead not only to their rupture and hemorrhage, and anemia to other organs such as brain, due to a sharp redistribution of blood. Therefore, such manipulations as extraction of fluids from body cavities, removal of large tumors, removal of the elastic rope, produce slowly.

Vacate hyperemia

Vacate hyperemia (from Lat. ***Vacuus*** - empty) develops due to a decrease in barometric pressure. It may be **general**, for example in divers and caisson workers with the rapid rise to the high pressure region. The resulting of congestion combined with gas embolism, thrombosis and hemorrhage.

Local vacate hyperemia is also distinguished which appears on the skin under the influence, for example, medical cans, creating over a certain section of its vacuum.

Inflammatory hyperemia

This type of hyperemia appears due to inflammatory processes of different origins

Hyperemia due to arteriovenous fistula

Arises in cases where, for example, gunshot wounds or other trauma is formed anastomosis between the artery and vein and arterial blood rushes into a vein.

Venous congestion

Increased blood filling of an organ or tissue due to a decrease (difficulty) of the outflow of blood. The blood flow in this case is not changed or reduced.

The stagnation of venous blood (congestive hyperemia) leads to the expansion of veins and capillaries, slowing blood flow in them, what has caused the development of hypoxia, increased permeability of basal membranes of capillaries.

Classification

Venous congestion may be

I. **General**

II. **Local**.

General (Total) venous congestion develops in the pathology of the heart, leading to acute or chronic heart (cardiovascular) failure.

I. **Acute**

II. **Chronic**

Chronic general venous congestion

Develops due to the syndrome of chronic heart (cardio vascular) disease, complicates many chronic heart disease (defects, coronary heart disease, chronic myocarditis, cardiomyopathy, endocardial fibroelastosis, etc .

It leads to severe, often irreversible, changes in organs and tissues long maintaining the state of tissue **hypoxia**, it determines the development of not only plazmorrhagia, edema, stasis and hemorrhage, degeneration and necrosis, atrophic and sclerotic changes

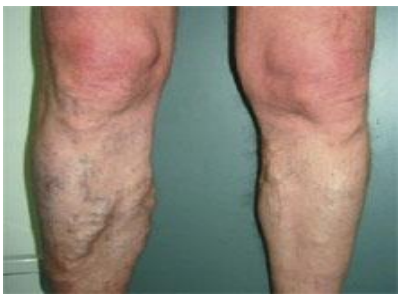


Fig. 18 Chronic venous congestion

Changes in organs

Changes in organs with chronic venous congestion, despite the number of common features (congestive indurations), have a number of features. **The skin,** especially the lower extremities becomes cold and acquires a bluish color (cyanosis)

The liver in chronic venous congestion increased, dense, its edges are rounded, the surface of the cut mottled, grayish-yellow with dark red color and speckled like nutmeg, so this is called **nutmeg liver**.

The lungs in chronic venous congestion developed two types of changes - multiple heamorrhages, causing **pulmonary hemosiderosis,** and proliferation of connective tissue, i.e. **sclerosis**.

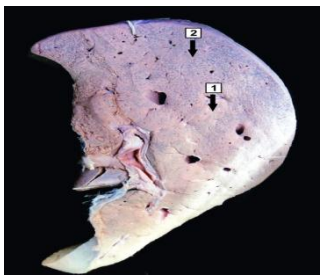


Fig.19 Nutmeg liver. The liver is enlarged, dense and has tense capsule (normal weight M 1400-1600 gm, F 1200-1400 gm). Cut surface shows characteristic nutmeg appearance i.e. alternate tan and yellow color corresponding to centrilobular haemorrhage **(1)** and peripheral fatty change **(2)** respectively.

Ischemia

Local anemia in a given body part mostly resulting from vasoconstriction, thrombosis or embolism

Stasis

Stasis - termination (stop) of the blood flow or the lymph flow in a container (e.g., blood or lymph in the case of obstruction of the vessel on which they occur, or intestinal contents in violation of his advance (peristalsis).

Etiology of stasis

- Physical factors (high and low temperature)
- Chemical (toxins) factors
- Infectious
- Infectious -allergic
- Autoimmune diseases
- Diseases of the heart and blood vessels,

Pathogenesis

- Changes in the blood rheology
- Changes in the innervation
- Changes in the amount of proteins
- Increase of the vascular permeability
- Changes in the structure of erythrocyte

The mechanism of development

Of great importance are **changes in blood rheology** caused by the development of sludge-phenomenon (born sludge - sludge), which is characterized by sticking together of red blood cells, white cells, platelets and the increase in plasma viscosity, which leads to difficulty perfusion of blood through the vessels of microcirculation.

Classification

depending on the causes of stasis are distinguished:

I. Ischemic

II. Stagnant

III. The true capillary stasis

- **In ischemic stasis** in microvessels pressure gradient is reduced due to a significant decrease in arterial pressure in their departments, which may be associated with the cessation of blood flow in larger arteries, such as due to thrombosis, embolism, spasm.

- **Stagnant** stasis occurs with a decrease in pressure gradient for microvessels due to a sharp increase in pressure in the vein of their departments in stagnation of blood due to venous congestion, thrombosis of larger veins, compression of the tumor, etc.

- **The true capillary** stasis is associated with a significant increase in primary resistance to blood flow in the corresponding microvessels. Capillaries in histological preparations appear enlarged and filled with homogeneous contents, in which the boundaries of red blood cells are indistinguishable, and therefore it has the form of a homogeneous hyaline –like mass. **However**, electron microscopic shows precise contours of red blood cells, firmly attached one to another.

- **Stasis - a reversible phenomenon.** Prolonged stasis leads to irreversible hypoxic changes - necrobiosis and necrosis.

Bleeding (Hemorrhage)

Bleeding – Loss blood from the circulatory system. Blood may run out of blood vessels inside the body or outside, or from natural openings, such as mouth, nose, anus, or through damage to the skin etc. Normally, healthy people can survive without medical complications, loss of 10-15% of blood volume. Donors pass 8-10% of blood volume.

Depending on vessel type, bleeding can be:

- Capillary
- Arterial
- Venous
- Parenchymatous

Capillary bleeding

Bleeding surface, the color of blood is close to the arterial, looks like a deep red liquid. Blood flows in a small amount slowly. Tight bandaging carries out stopping the bleeding. With adequate clotting ability of blood the bleeding may stop without any medical assistance.

Venous bleeding

Venous bleeding is characterized by the fact that flowed from the wound by the color of dark venous blood (a dark cherry color). Blood clots that arise when damaged, can come off the blood stream, so you may experience loss of blood. In assisting in the wound is necessary to impose a gauze bandage or a tourniquet (need to put a soft liner to avoid damage to the skin). In case of damage to a major vein there may be a jet of blood pulsing in the rhythm of breath

Arterial bleeding

Arterial bleeding is easily identified by a pulsating jet of bright red blood, which flows very quickly. When arterial blood is pouring the bright red, it beats strong intermittent stream (fountain), emissions of blood consistent with the rhythm of cardiac contractions. First aid should start by clamping the vessel above the injury site. Then impose a tourniquet, which leaves on a limb to a maximum of 1 hour (in winter - 30 minutes) in adults and in 20-40 minutes - in children. If kept longer, tissue necrosis can occur.

Parenchymatous bleeding

Observed in wounds of parenchymatous organs: Liver, Kidney, Pancreas, Lungs, Cancellous bone and the cavernous tissue

Clinics of the parenchymal bleeding

- It bleeds all wound surface.
- Bleeding can be very abundant (profuse) and often life-threatening.
- The so-called symptom of "bloody dew", the blood appears on the surface area covered slowly in the form of small, slowly growing drops, resembling drops of dew or condensation(as the sponge) .

Classification of Bleeding

- Physiological
- Pathological

Due to localization

- External
- Internal

Due to origin:

- Traumatic- caused by damage to blood vessels
- Non-traumatic- associated with their destruction by a pathologic process or to increased permeability of the vascular wall.

Pathological bleeding

Pathological bleeding is a consequence of pathophysiological processes occurring in the patient. The reason it may be a violation of any of the components of cardiovascular and blood coagulation. This type of bleeding is developed with minimal impact provocative or do without.

Classification

Due to severity

- Easy - 10-15% of circulating blood volume (CBV), up to 500 ml, hematocrit 30%
- Average - 16-20% of CBV, from 500 to 1000 ml, hematocrit 25%
- Heavy - 21-30% CBV, from 1000 to 1500 ml, hematocrit less than 25%
- Massive - > 31% of CBV, more than 1500 ml

Due to time

- Primary-bleeding can occur immediately after injury
- Recycled (secondary)earlier - there shortly after the final stop bleeding, often as a result of the lack of monitoring hemostasis during surgery.
- Recycled (secondary)later - is the result of destruction of blood vessel walls. Bleeding is not easily stop.

From a macroscopic pattern distinguish:

- hemorrhagic infiltration - permeation blood tissue without disturbing its integrity.
- hematoma - blood pools in the tissue with a violation of her integrity and the formation of the cavity;
- Spot - petechial and ecchymosis;
    - Bruise - planar hemorrhage in the skin and mucous membranes;

Results

- Complete resorption of blood - the most favorable outcome of bleeding and hemorrhage.
- Organization – is the replacement of the lost (came out) blood by connective tissue.
- Encapsulation - sprawl around lost (came out) blood connective tissue with the formation of the capsule.
- Petrification - outfall of Ca^{2+} in the blood

Plasmorhhage

Plasmorhhage - the output of the plasma from the bloodstream. It is a manifestation of impaired vascular permeability, providing a normal transcapillary exchange. Microscopic examination of the plasma vessel wall permeation makes it thick, homogeneous.

Etiology

Plasmorhhage occurs most frequently with:

- Hypertension
- Atherosclerosis
- Decompensated heart diseases
- Infectious
- Infectious -allergic
- Autoimmune diseases.

Pathogenesis

Is determined by two basic conditions:

- microvascular damage
- changes in blood constants that contribute to increased vascular permeability
- Damage to the microvascular division is associated most often with the neuro-vascular disorders (spasm), tissue hypoxia, immuno-pathological reactions.
- Changes in the blood that contribute to plazmorrhagia be reduced to an increase in plasma vasoactive substances (histamine, serotonin), natural anticoagulants (heparin, fibrinolysin), coarse protein, lipoprotein, the appearance of immune complexes, disruption of rheological properties.

Results

At the end of plasmatic imbibition develop

- Fibrinoid necrosis
- Vascular hyalinosis

INFARCTION. THROMBOSIS. EMBOLISM. THROMBOEMBOLIC SYNDROME.

Infarction

- Infarction (from lat. *Infarcire- to begin, to pack*) area of dead tissue (localized necrosis), resulting from obstruction of the blood supply.
- Forms of infarction. Usually infarct has a sphenoid shape, due to which its peaked part is inverted to the gates of organ, and its wide part is coming over the periphery of the organ (e.g. under the capsule of the organ, under the pleura, under the peritoneum etc.)
- The magnitude of infarction. Infarct may cover most or the entire organ (subtotal or total infarction) or detectable only under a microscope (micro infarct).

Classification of infarction

Depending of type of mechanism and appearance are distinguished:

- White (ischemic) infarction (resulting in complete cessation of arterial blood flow to organs);
- Red (hemorrhagic) infarction (due out in a zone of necrotic myocardial blood vessels of the microvasculature);
- White infarct with hemorrhagic rim

Distinguish

- **Aseptic infarctions**
- **Septic infarctions**.

Most heart attacks internal organs, not in contact with the external environment, are aseptic.

Septic infarcts occur in contact with secondary bacterial infection in the necrotic tissue.
Microscopically, the dead area is different loss structure, contours of cells and disappearance of nuclei.

The greatest clinical significance are heart attack (infarction), brain, colon, lung, kidney, spleen

At the heart of infarction is usually **white with a hemorrhagic halo** has an irregular shape, more common in the left ventricle and interventricular septum is extremely rare - in the right ventricle and atria. Necrosis can be localized under the endocardium, epicardium, in the thickness of the myocardium or cover the entire thickness of the myocardium. In the area of infarction in thrombotic endocardium often formed, and the pericardium - fibrinous overlay, which is associated with the development of reactive inflammation around areas of necrosis

Results

Its purulent meltdown in the heart - and myomalation true with the development of cardiac rupture hematoma-like pericardial cavity.

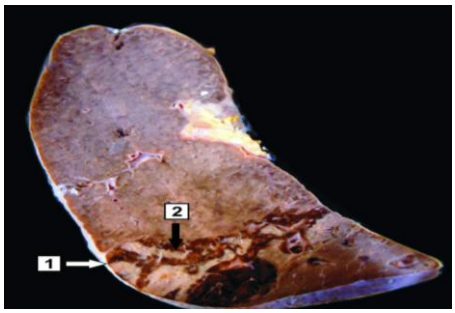


Fig.20 Pale infarct spleen: On the capsular surface, a small gray white depressed area is seen **(1)**. On cut section, the corresponding area shows a wedge-shaped pale area with base resting under the capsule while the margin of infarct is congested **(2)**.

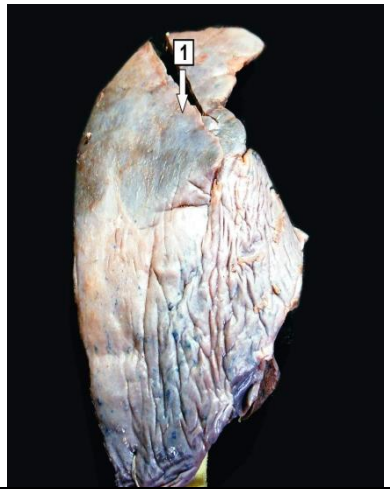


Fig. 21. Hemorrhagic infarct lung. The pleural surface shows a dark tan area in the apex of the lung (1). Cut section of the corresponding area shows a wedge-shaped firm and dark tan area with base on the pleura.

Thrombosis

Thrombosis (thrombo - clot) - lifetime clots of blood in the lumen of blood vessel or the heart cavities.

Etiology

- Clot is formed by the interaction of coagulation factors (protein molecules that are normally found in the blood) and platelets (blood cells).
- Defeat of the vascular wall (atherosclerotic, inflammatory and other origin)
- Slowing blood flow
- Increased coagulability and viscosity of blood

Virchow's triad

- Stasis of blood
- Systemic or local hypercoagulation
- Endothelial dysfunction

Types of Thrombosis

A. **White thrombus** consists of platelets, fibrin and leukocytes, is formed slowly in the fast stream of blood (***usually in the arteries).***

B. **Red thrombus**, in addition to platelets, leukocytes and fibrin, contains a large number of red blood cells, is formed rapidly in a slow stream of blood (***usually in the veins***).

C. **Mixed thrombus**, which has a layered structure (layered thrombus) and mottled appearance, contain elements of both white and red thrombus (***the most frequently encountered***).

D. **Hyaline thrombus** - a special type of blood clots, that rarely contains fibrin, consists of the destroyed red blood cells, platelets and precipitating plasma proteins, with thrombotic masses resemble hyaline. These blood clots occur in the ***microvascular system***.

Mixed thrombi

- In the mixed thrombus distinguished **head** (has the structure of white thrombus), the **body** (actually mixed thrombus) and **tail** (has the structure of a red thrombus) (Fig. 22).

- The head is attached to the endothelial lining of the vessel, which features thrombus from the post-mortem clot. Laminated thrombi formed more often in the veins, in the cavity of the aneurysm of the aorta and heart.

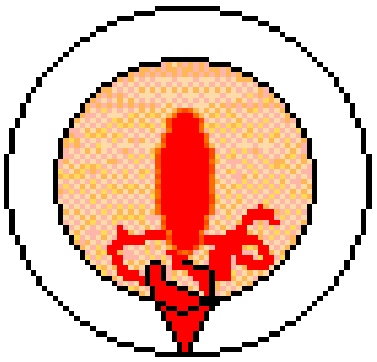


Fig. 22. Mixed thrombus. *Vascular injury leads to the turbulence and twist of the blood flow that catches platelets into the damaged area.*

Classification

Due to lumen of the vessel

- Parietal , whereas most of the lumen is free. Parietal thrombus is often found in the valve of the heart or the parietal endocardium with its inflammation (tromboendocarditis) in eyelets and between trabeculas with chronic heart failure (heart disease, chronic ischemic heart disease), in the large arteries in atherosclerosis, the inflammation of the veins in them, in aneurysms of the heart and blood vessels.
- Occluding, occlusive lumen (occlusive thrombus). Occluding thrombus is formed more often in the veins and small arteries with an increase in parietal thrombus, rarely - in the large arteries and aorta.

Results

The favorable outcomes include:

A. **Aseptic autolysis** thrombus arising under the influence of proteolytic enzymes of leukocytes. Small blood clots can be fully aseptically **autolyzed**.

B. **Organization.** Most thrombi, especially large ones, are replaced by connective tissue, i.e. organized.

C. **Canalization**. The growing of the connective tissue in the clot begins in the head of the intimae of the vessel, then the whole mass of blood clot is replaced by connective tissue in which there are gaps or **channels** lined with

endothelium, is the so-called **sewage thrombus**. Later, lined with endothelial channels are transformed into vessels containing blood, in such cases say **vascularization thrombus.**

D. **Calcification** of a blood clot, his petrification in the veins there are sometimes stones - flebolytias.

Negative outcomes of thrombosis include :

A. **separation of a blood clot** or part of it and becoming a **thromboembolism**

B. **septic thrombus melting**, which occurs by ingestion of thrombotic masses of pyogenic bacteria, which leads to **trombobacterial embolism** of vessels of various organs and tissues (sepsis).

Clinical Value

- The value of thrombosis is defined speed of its development, localization and spread, as well as outcome. In some cases we can speak of a favorable value of thrombosis, such as thrombosis of the aneurysm, when the thrombus "reinforces" its wall. In most cases thrombosis - a dangerous phenomenon, because occlusive thrombi in the arteries can cause a heart attack or gangrene.
- At the same time, parietal, slowly forming blood clots, even in the large arterial trunks can not lead to serious consequences, since in such cases, the time to develop collateral circulation.
- Most dangerous is the progressive thrombosis and septic thrombosis. Occlusive thrombi in large veins produce different manifestations, depending on their localization.

Embolism

Embolism (Greek ἐμβολή - invasion) typical pathological process caused by the presence and circulation in the blood or lymph particles that are not found there in normal conditions, often causing the occlusion of the vessel with subsequent disturbance of local blood supply.

Types of Embolism

Due to structure

- Tissue embolism (tumor, valve other tissues etc.)
- Gas embolism (due to barometric pressure changes)

- Air embolism (when air through the damaged with fluids or injuries vessel (usually in the upper half of the body) can be sucked into the venous blood system through the negative pressure in the chest cavity)
- Fat embolism (fractures of the long tubular bones)
- Thromboembolism
- Foreign bodies' embolism
- Microbes' embolism

Due to flow (orientation):

- Orthograde
- Retrograde
- Paradoxical

Thrombus-embolic syndrome

About thrombus-embolic syndrome, say, in cases where the clot or part of it breaks off, turns into a thromboembolism, circulates in the blood over a large range of circulatory and obstructing lumen of the arteries, causes the development of multiple infarctions. The source of thromboembolism more often thrombi in mitral or aortic valves, intratrabecular thrombi of the left ventricle and left atrial appendage, thrombi of the aneurysm of the heart (coronary artery disease, heart defects), the aorta and major arteries (atherosclerosis).

Thromboembolic syndrome often occurs in cardiovascular, oncology, infectious (sepsis) diseases in the postoperative period, with various surgical interventions. A variant of thromboembolic syndrome can be considered and pulmonary embolism with the development of pulmonary infarction

SHOCK. DIC-SYNDROME. DISTURBANCES OF LYMPH SUPPLY.

Shock

Shock – is an acutely developing pathological process, conditioned by the influence of strong irritants and characterized by disorder of CNS, metabolism, and principally autoregulation of microcirculation, that lead to destructive changes in organs and tissues

Following types of shock are distinguished:

1. Hypovolemic, in the basis of which lies acute decrease in circulatory blood volume.
2. Traumatic, occurs due to excessive afferent (mostly pain) impulses.
3. Cardiogenic, occurring as a result of rapid decrease in contractility of myocardium and increase in afferent (mostly hypoxic) flow of impulses.
4. Septic, caused by endotoxins of pathogenic microflora

Morphology

Characteristic features of shock include changes in hemocoagulation in the form DIC-syndrome, hemorrhagic diatheses, and liquid cadaveric blood, which may be the basis for diagnosis of shock in autopsy. Microscopic changes in hemodynamics and rheological properties of blood are represented by distributed spasm of vessels, microthrombs in the system of microcirculation, signs of increased permeability of capillaries, hemorrhages. In viscera develop many general changes in the form dystrophy and necrosis, conditioned by hemodynamics disorders, hypoxia, destructive influence of biogenic amines.

In shock kidneys, the proximal canals of nephrons undergo dystrophic and necrotic changes; necrotic nephrosis develops, that conditions development of acute renal failure.

Shock lung is characterized by focuses of atelectasis, serous-hemorrhagic edema with accumulation of fibrin in alveoli cavity

Structural changes of myocardium in shock are represented by dystrophic and necrobiotic changes of cardiomyocytes.

DIC-syndrome

Syndrome of disseminated intravascular coagulation (DIC-syndrome, thrombohemorrhagic syndrome, consumption coagulopathy) is characterized by the formation of disseminated-governmental thrombus (fibrin and red cells, hyaline) in the microcirculatory bed in combination with incoagulability of blood, leading to multiple massive hemorrhage.

Etiology

It is based on the discoordination functions of coagulation and anticoagulation systems of blood responsible for hemostasis. Therefore, DIS-syndrome often occurs as a complication of pregnancy and childbirth, with irresistible uterine bleeding, major trauma, with anemia, hemoblastoses, infection (especially sepsis), and intoxication, autoimmune diseases and shock.

Pathogenesis

Due to the massive flow of blood in the tissue thromboplastin activates blood coagulation and platelet hemostasis, leading to multiple thrombosis (**hypercoagulation phase** syndrome, DIC), and then - to the depletion of clotting factors (**hypocoagulation phase** syndrome, DIC).

Classification

I. **Acute course.** Generalized hemorrhagic syndrome resulting from acute thrombocytopenia and depletion of plasma coagulation factors.

II. **Subacute DIC** - more typical of thromboembolic syndrome, bleeding is less common.

III. **Chronic** with relapses and without them.

Clinics

The clinical picture consists of the main symptoms of pathology and syndrome of DIC. In acute during the first phase of hypercoagulation occurs rapidly and can be replaced in minutes hypocoagulation. Thrombi, especially common in lung microvessels, kidneys, liver, adrenal, pituitary, brain, gastrointestinal tract, skin, combined with multiple hemorrhages, dystrophy and necrosis of organs and tissues (cortical necrosis, renal necrosis and hemorrhage in the lungs, brain, adrenal, pituitary, etc.). Many organs are "shocked“, develops an acute mono- or multiple organ failure.

On the first stage of the disease can be assumed if the background of the underlying disease (pathological processes listed above), there are signs of multiple organ failure due to thrombosis, are not typical for background pathology, such as cyanosis, dyspnea, cough, congestion wheezing, oliguria, anuria, jaundice, congestion, confusion.

When hypocoagulation stage engines appear petechiae and ecchymosis at the injection site overlay cuff tonometer in the field of mechanical friction, bleeding from surgical wounds, metrorrhagia, nasal and gastrointestinal bleeding, bleeding in the skin, mucous membranes, parenchymal organs.

When expressed hemorrhage develops hypovolemic shock, worsening tissue hypoxia and acidosis.

Disturbances of lymph supply

Disturbances of lymph supply are represented by its failure, which might have different forms. Distinguish mechanical, dynamic, and resorptive failures of lymphatic system.

Mechanical failure occurs in connection with influence of factors, which impede the lymph flow and lead to its congestion. Those factors include compression or obstruction of vessels, blockade of lymphatic vessels, with cancer cell for instance and etc.

Dynamic failure appears as a result of intensive filtration in capillaries. In this case lymphatic vessels are not capable of removal of edematous fluid from interstitium.

Resorptive failure of lymphatic system develop as a result of changes in biochemical and disperse properties of tissue proteins or decrease in permeability of lymphatic vessels. Mostly encounter combined forms of lymphatic failure

Morphology

Lymph congestion and widening of lymphatic vessels; development of collateral lymph circulation; formation lymphangioectasy; lymph stasis and formation of coagulant proteins; lymphorrhea and, etc.

Consequences and importance are defined by changes in tissue metabolism, which occur not only as a result of failure of lymphatic system but also venous system. As a consequence of these disorders occur tissue hypoxia, with which predominantly associated dystrophic and necrbiotic changes in acute lymphedema.

Results

In most cases outcomes are favorable – edematous fluid is reabsorbed. But in long-time edemas in tissues hypoxia develops, leading to dystrophy and atrophy of parenchymatous cells and development of sclerosis.

INFLAMMATION. GENERAL STUDY. ACUTE INFLAMMATION.

Inflammation is a complicated vascular -mesenchymal reaction of tissues to injury. *This is fundamentally a protective response*, designed to rid the organism of

both the initial cause of cell injury (e.g., microbes, toxins) and the consequences of such injury (e.g., necrotic cells and tissues).

Etiology

Factors:

- **Physical**
- **Chemical**
- **Biological**

Pathogenesis

I. Alteration - is an injury of cells and tissues that appears in a form of dystrophy and necrosis. There is an ejection of the mediators in the end of alteration.

II. Exudation – complicated process, that consists of several subprocesses such as:

- 1.Starts with blood rheology changes
- 2.Increase of the vascular permeability
- 3.Emigration of the liquid parts of plasma
- 4.Phagocytosis
- 5.Pinocytosis
- 6.Formation of the exudate and infiltrate

III. Proliferation – multiplying of the tissue elements in the inflammatory focus

Inflammation may be:

- *Acute inflammation* is rapid in onset (typically minutes) and is of short duration, lasting for hours or a few days; its main characteristics are the exudation of fluid and plasma proteins (edema) and the emigration of leukocytes, predominantly neutrophils (also called polymorphonuclear leukocytes). When acute inflammation is successful in eliminating the offenders the reaction subsides, but if the response fails to clear the invaders it can progress to a chronic phase.
- *Chronic inflammation* may follow acute inflammation or be insidious in onset. It is of longer duration and is associated with the presence of lymphocytes and macrophages, the proliferation of blood vessels, fibrosis, and tissue destruction.

Acute inflammation

Acute inflammation is a rapid host response that serves to deliver leukocytes and plasma proteins, such as antibodies, to sites of infection or tissue injury (Fig. 23, 24).

Acute inflammation has three major components:

A. **Increased blood flow** due to dilation of blood vessels (arterioles) supplying the region

B. **Increased permeability** of the capillaries, allowing fluid and blood proteins to move into the interstitial spaces

C. **Migration of neutrophils** (and perhaps a few macrophages) out of the capillaries and venules and into interstitial spaces

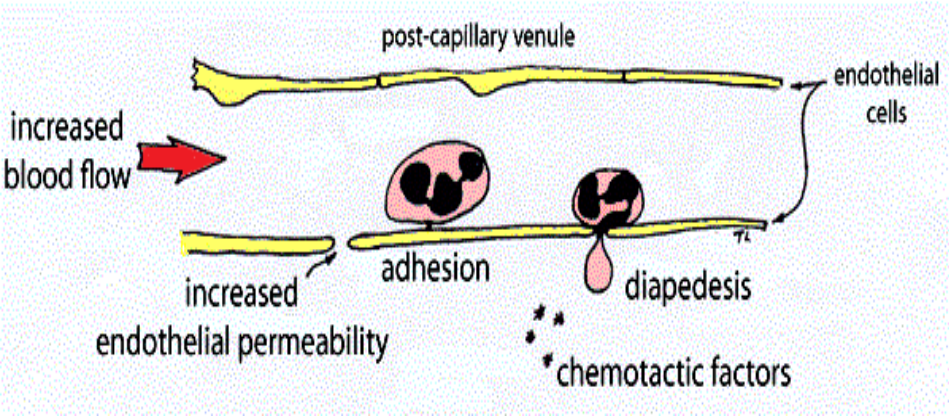


Fig. 23. Major components of acute inflammation.

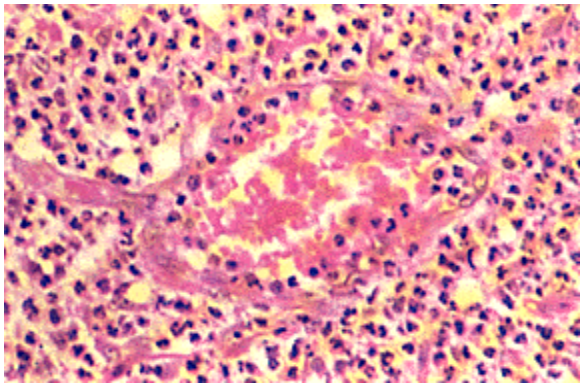


Fig. 24. In this light micrograph of a blood vessel in the lungs you can see a layer of neutrophils adhering to the inner surface of the blood vessel.

Although **clinical features of inflammation** were described in an Egyptian papyrus dated around 3000 bc, Celsus, a Roman writer of the first century ad, first listed the four cardinal signs of inflammation**:**

I. ***rubor* (redness),**

II. ***tumor* (swelling),**

III. ***calor* (heat)**, and

IV. ***dolor* (pain).**

These signs are typically more prominent in acute inflammation than in chronic inflammation. A fifth clinical sign,

V. **loss of function *(functio laesa)***, was added by Rudolf Virchow in the 19th century. In 1793 the Scottish surgeon John Hunter noted what is now considered an obvious fact: that inflammation is not a disease but a nonspecific response that has a *salutary* effect on its host.

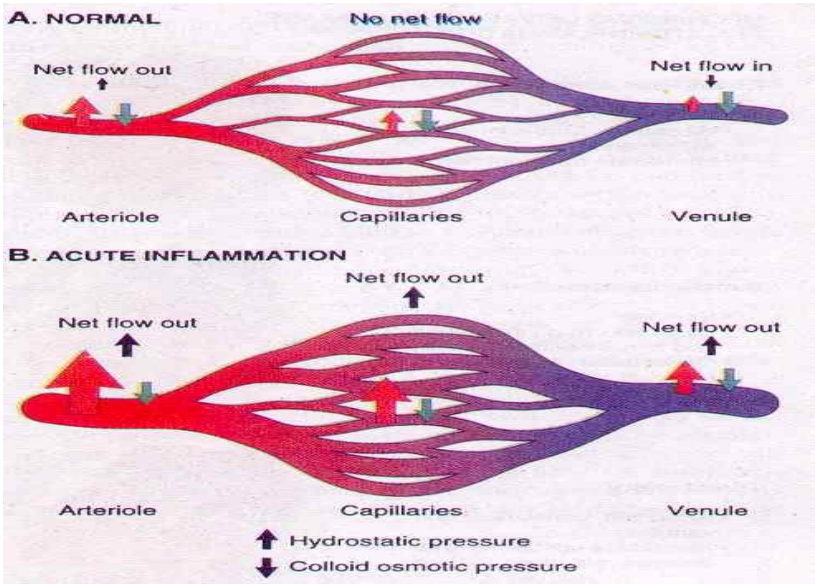


Fig. 25. Change in vessel diameter and permeability due to inflammation

Classification

Due to predomination of the reaction inflammation can be:

I. Alterative

II. Exudative

III. Proliferation

Due to progression:

- Acute
- Subacute
- Chronic
- Remission

Alterative

Passes with predominance of alteration.

Localization :parenchymal organs

Gross examination: organs are increased in their sizes.

Level

- Soft
- Medium
- Hard

Exudative inflammation

Characterized by the exudation

- Catarrh (katarrheo – to drip)
- Serous
- Fibrinous
- Purulent
- Hemorrhagic
- Saprogenic
- Mixed

Outcomes of inflammation

Resolution

The complete restoration of the inflamed tissue back to a normal status. Inflammatory measures such as vasodilation, chemical production, and leukocyte infiltration cease, and damaged parenchymal cells regenerate. In situations where limited or short lived inflammation has occurred this is usually the outcome.

Fibrosis

Large amounts of tissue destruction, or damage in tissues unable to regenerate, can not be regenerated completely by the body. Fibrous scarring occurs in these areas

of damage, forming a scar composed primarily of collagen. The scar will not contain any specialized structures, such as parenchymal cells, hence functional impairment may occur.

Abscess Formation

A cavity is formed containing pus, an opaque liquid containing dead white blood cells and bacteria with general debris from destroyed cells.

Chronic inflammation

In acute inflammation, if the injurious agent persists then chronic inflammation will ensue. This process, marked by inflammation lasting many days, months or even years, may lead to the formation of a chronic wound . Chronic inflammation is characterized by the dominating presence of macrophages in the injured tissue. These cells are powerful defensive agents of the body, but the toxins they release (including reactive oxygen spices) are injurious to the organism's own tissues as well as invading agents. Consequently, chronic inflammation is almost always accompanied by tissue destruction.

PRODUCTIVE INFLAMMATION. CHRONIC INFLAMMATION. GRANULOMATOUS DISEASES.

Proliferative (productive) inflammation is characterized by the dominance of the cellular elements' proliferation over alternation and exudation with occurring of limited cellular infiltrates, looking like nodules or papulae. This nodules are vary in their sizes, from small almost invisible to bigger ones, which are built from the small elements confusion.

Etiology & Pathogenesis

The reasons of the productive inflammation are different:

- biological factors (bacteria, animal parasites, viruses, fungi)
- physical and chemical factors (toxic substances such as asbestos, silica, etc., foreign bodies, etc.
- immune responses, in particular, such that arise, for example, against its own tissues in autoimmune diseases.

Productive inflammation is characterized

- by cell proliferation

- hematogenous
- histiogenous origin,
- differentiation and cellular transformation.

In areas of productive inflammation observed marked proliferation of monocytes. Monocytes emigrate start relatively early, and within 48 hours of becoming dominant. When they reach the extravascular tissues, monocytes undergo transformation into macrophages.

The basis of the appearance of macrophages on the following mechanisms. First, from the circulating blood. This is the most important source. The impetus for the emergence of monocytes are fibrinogen, peptides, some growth factors, as well as fragments of disintegrating collagen and fibronectin.

Phagocytosis - a characteristic feature of productive inflammation, but it is not always complete the full digesting of foreign agent. In many cases, live agents, possessing protective mechanisms to survive within macrophages the process becomes chronic.

Classification

I. Interstitious

II. Granulomatous

III. Papilomas and sharp-tipped condylomas

Cellular elements that reproduce in the focus productive inflammation, may have histiogenic and hematogenic origin. Among **histiogenic** elements predominate histiocytes, fibroblasts, endothelial and adventitial cells of **hematogenic** - lymphocytes, monocytes and macrophages. Possible transformation of macrophages into epithelioid cells, and the last - in the giant cells (foreign body or Pirogov-Langerhans), characterized by increased activity of fibroblasts, culminating in the formation in main tissue.

Intermediate (interstitial) inflammation

An intermediate (interstitial) inflammation characterized by the formation of lesions or diffuse inflammatory cell infiltrate in the stroma of the parenchymal organs - the myocardium, liver, kidneys and lungs. Infiltrate represented by lymphocytes, histiocytes, plasma cells, isolated neutrophils, eosinophils and mast cells.

Parenchymal elements with severe degenerative and sometimes necrobiotic changes. Similar changes were observed in cardiomyocytes, such as myocarditis Abramov-Fiedler, in hepatocytes in viral hepatitis.
At the end of chronic interstitial inflammation of the connective tissue grows. At the heart of developing diffuse small focuses in the myocardium. In the liver, this inflammation occurs much more aggressive, and in the final formed cirrhosis.

Granulomatous inflammation

Granulomatous inflammation is a distinctive pattern of chronic inflammation that is encountered in a limited number of infectious and some noninfectious conditions. Immune reactions are usually involved in the development of granulomas.

Granuloma is a cellular attempt to contain an offending agent that is difficult to eradicate. In this attempt there is often strong activation of T lymphocytes leading to macrophage activation, which can cause injury to normal tissues.

Granuloma is a focus of chronic inflammation consisting of a microscopic aggregation of macrophages that are transformed into epithelium-like cells, surrounded by a collar of mononuclear leukocytes, principally lymphocytes and occasionally plasma cells.

In the usual hematoxylin and eosin–stained tissue sections, the epithelioid cells have a pale pink granular cytoplasm with indistinct cell boundaries, often appearing to merge into one another. The nucleus is less dense than that of a lymphocyte, is oval or elongate, and may show folding of the nuclear membrane. Older granulomas develop an enclosing rim of fibroblasts and connective tissue. Frequently, epithelioid cells fuse to form giant cells in the periphery or sometimes in the center of granulomas. These giant cells may attain diameters of 40 to 50 μm. They have a large mass of cytoplasm containing 20 or more small nuclei arranged either peripherally (Langerhans-type giant cell) or haphazardly (foreign body–type giant cell)

There are two types of granulomas, which differ in their pathogenesis.

Foreign body granulomas are incited by relatively inert foreign bodies. Typically, foreign body granulomas form around material such as talc (associated with intravenous drug abuse) sutures, or other fibers that are large enough to preclude phagocytosis by a single macrophage and do not incite any specific inflammatory or immune response. Epithelioid cells and giant cells are apposed to the surface of the foreign body. The foreign material can usually be identified in the center of the

granuloma, particularly if viewed with polarized light, in which it appears refractile.

Immune granulomas, which are caused by a variety of agents that are capable of inducing a cell-mediated immune response. This type of immune response produces granulomas usually when the inciting agent is poorly degradable or particulate. In such responses macrophages engulf foreign protein antigen, process it, and present peptides to antigen-specific T lymphocytes, causing their activation. The responding T cells produce cytokines, such as IL-2, which activates other T cells, perpetuating the response, and IFN-γ, which is important in activating macrophages and transforming them into epithelioid cells and multinucleate giant cells.

The prototype of the immune granuloma is that caused by infection with Mycobacterium tuberculosis. In this disease the granuloma is referred to as a tubercle. It is often characterized by the presence of central caseous necrosis. In contrast, caseous necrosis is rare in other granulomatous diseases. The morphologic patterns in the various granulomatous diseases may be sufficiently different to allow reasonably accurate diagnosis by an experienced pathologist, however, there are so many atypical presentations that it is always necessary to identify the specific etiologic agent by special stains for organisms (e.g., acid-fast stains for tubercle bacilli), by culture methods (e.g., in tuberculosis and fungal diseases), by molecular techniques (e.g., the polymerase chain reaction in tuberculosis), and by serologic studies (e.g., in syphilis).In proliferation there may be found diffuse (granulomas) that are due to the cells' type divided on:

- Polymorphocellular
- Roundcellular
- Epithelioidcellular
- Eosinophilliccellular
- Plazmacellular infiltrates

Results

- Resolution
- Fibrosis, scarring
- Necrosis

IMMUNOPATHOLOGICAL PROCESSES.

Immunopathological processes are those pathological processes, development of which is connected with immune reactions.

Immunopathology is a study of processes and diseases that are caused by immunological conflict and immunological homeostasis. Includes:

I. Hypersensitivity

II. Immunodeficiency syndrome

III. Autoimmune diseases

IV. Rejection of tissue transplants

V. Autoallergy- (Autoaggression) characterized by appearing of autoantigens and autoantibodies, that lead to the injury of cells and tissues.

Lymphoid Organs divided into generative and peripheral

Generative Lymphoid Organs

The principal generative lymphoid organs are the thymus, where T cells develop, and the bone marrow, the site of production of all blood cells and where B lymphocytes mature.

Peripheral Lymphoid Organs

The peripheral lymphoid organs consist of the lymph nodes, spleen, and the mucosal and cutaneous lymphoid tissues. Pharyngeal tonsils and Peyer's patches of the intestine are two anatomically defined mucosal lymphoid tissues.

There are two types of adaptive immunity:

I. Humoral immunity, which protects against extracellular microbes and their toxins

II. Cell -mediated (or cellular) immunity, *which is responsible for defense against intracellular microbes*

Humoral immunity is mediated by B (bone marrow–derived) lymphocytes and their secreted products, antibodies (also called immunoglobulins, Ig)

Cellular immunity is mediated by T (thymus-derived) lymphocytes. Both classes of lymphocytes express highly specific receptors for a wide variety of substances, called *antigens*.

Pathogenesis

All adaptive immune responses develop in steps, consisting of:

I. antigen recognition

II. activation of specific lymphocytes to proliferate and differentiate into effector and memory cells,

III. elimination of the antigen, decline of the response, with memory cells being the long-lived survivors

Mechanisms of hypersensitivity reactions

Individuals who have been previously exposed to an antigen are said to be sensitized. Sometimes, repeat exposures to the same antigen trigger a pathologic reaction; such reactions are described as *hypersensitivity*, implying an excessive response to antigen. There are several important general features of hypersensitivity disorders:

A. Both exogenous and endogenous antigens may elicit hypersensitivity reactions.

B. The development of hypersensitivity diseases (both allergic and autoimmune disorders) is often associated with the inheritance of particular susceptibility genes.

C. A general principle that has emerged is that hypersensitivity reflects an imbalance between the effector mechanisms of immune responses and the control mechanisms that serve to normally limit such responses.

Immediate (Type I) Hypersensitivity

Is a rapid immunologic reaction occurring within minutes after the combination of an antigen with antibody bound to mast cells in individuals previously sensitized to the antigen. These reactions are often called ***allergy***, and the antigens that elicit them are allergens. Immediate hypersensitivity may occur as a **systemic disorder** or as a **local reaction**.

A. **The systemic reaction** usually follows injection of an antigen into a sensitized individual. Sometimes, within minutes the patient goes into a state of shock, which may be fatal.

B. **Local reactions** are diverse and vary depending on the portal of entry of the allergen. They may take the form of localized cutaneous swellings (skin allergy, hives), nasal and conjunctival discharge (allergic rhinitis and conjunctivitis), hay fever, bronchial asthma, or allergic gastroenteritis (food allergy).

Many local type I hypersensitivity reactions have two well-defined phases:

- **1**. **The *immediate* or *initial reaction*** is characterized by vasodilation, vascular leakage, and depending on the location, smooth muscle spasm or glandular secretions. These changes usually become evident within 5 to 30 minutes after exposure to an allergen and tend to subside in 60 minutes. In many instances (e.g., allergic rhinitis and bronchial asthma),
- **2. *Late-phase reaction*** sets in 2 to 24 hours later without additional exposure to antigen and may last for several days. This late-phase reaction is characterized by infiltration of tissues with eosinophils, neutrophils, basophils, monocytes, and CD4+ T cells as well as tissue destruction, typically in the form of mucosal epithelial cell damage.

Morphology

The principal morphologic manifestation of immune complex injury is acute necrotizing vasculitis, with necrosis of the vessel wall and intense neutrophilic infiltration. The necrotic tissue and deposits of immune complexes, complement, and plasma protein produce a smudgy eosinophilic deposit that obscures the underlying cellular detail, an appearance termed fibrinoid necrosis. When deposited in the kidney, the complexes can be seen on immunofluorescence microscopy as granular lumpy deposits of immunoglobulin and complement and on electron microscopy as electron-dense deposits along the glomerular basement membrane.

Antibody-Mediated (Type II) Hypersensitivity

Antibodies that react with antigens present on cell surfaces or in the extracellular matrix cause disease by destroying these cells, triggering inflammation, or interfering with normal functions. The antibodies may be specific for normal cell or tissue antigens (autoantibodies) or for exogenous antigens, such as chemical

or microbial proteins, that bind to a cell surface or tissue matrix. These reactions are the cause of several important diseases.

Immune Complex–Mediated (Type III) Hypersensitivity

Antigen-antibody complexes produce tissue damage mainly by eliciting inflammation at the sites of deposition. The pathologic reaction is usually initiated when antigen combines with antibody in the circulation, creating immune complexes that typically deposit in vessel walls. Less frequently, the complexes may be formed at sites where antigen has been "planted" previously (called in situ immune complexes). The antigens that form immune complexes may be exogenous, such as a foreign protein that is injected or produced by an infectious microbe, or endogenous, if the individual produces antibody against self antigens (autoimmunity). Immune complex–mediated diseases tend be systemic, but often preferentially involve the kidney (glomerulonephritis), joints (arthritis), and small blood vessels (vasculitis), all of which are common sites of immune complex deposition.

T Cell–Mediated (Type IV) Hypersensitivity

The cell-mediated type of hypersensitivity is caused by inflammation resulting from cytokines produced by CD4+T cells and cell killing by CD8+T cells (Fig. 6-18). CD4+ T cell–mediated hypersensitivity induced by environmental and self antigens is the cause of many chronic inflammatory diseases, including autoimmune diseases. CD8+ cells may also be involved in some of these autoimmune diseases and may be the dominant effector cells in certain reactions, especially those that follow viral infections.

Autoimmune Diseases

Immune reactions against self-antigens—*autoimmunity.*

A growing number of diseases have been attributed to autoimmunity. Autoantibodies can be found in the serum of apparently normal individuals, particularly in older age groups. Furthermore, innocuous autoantibodies are also formed after damage to tissue and may serve a physiologic role in the removal of tissue breakdown products.

Classification

I. Immune-Mediated Inflammatory Diseases

A. Diseases mediated by antibodies and immune complexes

1. Organ-specific autoimmune diseases

- Autoimmune hemolytic anemia; Autoimmune thrombocytopenia; Myasthenia gravis; Graves disease; Goodpasture syndrome

2. Systemic autoimmune diseases

- Systemic lupus erythematosus (SLE)

3. Diseases caused by autoimmunity or by reactions to microbial antigens

- Polyarteritis nodosa

B. Diseases mediated by T cells

1. Organ-specific autoimmune diseases

- Type 1 diabetes mellitus; Multiple sclerosis; Systemic autoimmune diseases Rheumatoid arthritis; Systemic sclerosis; Sjogren syndrome

2. Diseases caused by autoimmunity or by reactions to microbial antigens

a) Inflammatory bowel disease (Crohn disease, ulcerative colitis)

b) Inflammatory myopathies

Pathogenesis

Autoimmunity arises from a combination of the inheritance of susceptibility genes, which may contribute to the breakdown of self-tolerance, and environmental triggers, such as infections and tissue damage, which promote the activation of self-reactive lymphocytes . In general, these genetic and environmental influences conspire to create an imbalance between control mechanisms that normally function to prevent self-reactivity and pathways that lead to the generation and activation of pathogenic effector lymphocytes. In the following section we discuss how genetic and other factors contribute to the development of autoimmunity.

Immunodeficiency Syndromes

Immunodeficiencies can be divided into

I. primary immunodeficiency disorders, which are almost always genetically determined, and

II. secondary immunodeficiency states, which may arise as complications of cancers, infections, malnutrition, or side effects of immunosuppression, irradiation, or chemotherapy for cancer and other diseases.

The primary immunodeficiency syndromes are accidents of nature that provide valuable insights into some of the critical molecules of the human immune system.

Primary immunodeficiency

Most primary immunodeficiency diseases are genetically determined and affect the humoral and/or cellular arms of adaptive immunity (mediated by B and T lymphocytes, respectively) or the defense mechanisms of innate immunity (phagocytes, or complement).

Defects in adaptive immunity are often subclassified on the basis of the primary component involved (i.e., B cells or T cells or both). However, these distinctions are not clear-cut; for instance, T-cell defects almost always lead to impaired antibody synthesis, and hence isolated deficiencies of T cells are often indistinguishable clinically from combined deficiencies of T and B cells.

Secondary immunodeficiency

Secondary immune deficiencies may be encountered in individuals with cancer, diabetes and other metabolic diseases, malnutrition, chronic infection, and renal disease. They also occur in persons receiving chemotherapy or radiation therapy for cancer, or immunosuppressive drugs to prevent graft rejection or to treat autoimmune diseases. Some of these secondary immunodeficiency states can be caused by defective lymphocyte maturation (when the bone marrow is damaged by radiation or chemotherapy or involved by tumors, such as leukemias and metastatic cancers), loss of immunoglobulins (as in proteinuric renal diseases), inadequate Ig synthesis (as in malnutrition), or lymphocyte depletion (from drugs or severe infections).

As a group, the secondary immune deficiencies are more common than the disorders of primary genetic origin. The most common secondary immunodeficiency is AIDS.

Rejection of Tissue Transplants

Transplant rejection involves several of the immunological reactions that underlie immune-mediated inflammatory diseases. A major barrier to transplantation is the process of *rejection*, in which the recipient's immune system recognizes the graft as being foreign and attacks it.

Mechanisms of Recognition and Rejection of Allografts

Rejection is a complex process in which both cell-mediated immunity and circulating antibodies play a role; moreover, the contributions of these two mechanisms are often reflected in the histologic features of the rejected organs.

Morphology

On the basis of the morphology and the underlying mechanism, rejection reactions are classified as hyperacute, acute, and chronic.

ADAPTATION AND COMPENSATION

According to numerous receptory apparatus and reflectory function of the nervous system our organism is adapting in different situations. Thus, if there becomes any problem about our adaptation or compensation system the disease starts.

Compensation consists of:

- **Regeneration**
- **Hypertrophy**
- **Hyperplasia**

Adaptation consists of :

- **Atrophy**
- **Metaplasia**
- **Organization**
- **Tissue reconstruction**

Etiology

- **Exogenic**: physical, chemical, biological factors.
- **Endogenic**: insufficiency or lack of enzymes, hormones etc.

Regeneration

Restoration of the tissue elements instead of dead ones.

Regeneration is possible on different levels: molecular, ultrasonic, cellular and tissue, organic is done by the cellular and intracellular hyperplastic processes.

Distinguished:

- Cellular form, characterized by mitotic and amitotic type of multiplying

- Intracellular form, characterized by the increase of ultrastructural size and their number

Types of regeneration:

- **Physiological**
- **Reparative**
- **Pathological**

Physiological– is a long-life physiological process, characterized by continues reparation of the structures, cells and tissues.

Reparative –takes part in pathology and different types of injury of cells and tissues. Distinguished:

- **Complete (restitution)-** restoration of damaged cells and tissues by the same tissue.
- **Incomplete (substitution) –** restoration of damaged cells by the connective tissue

Pathological - due to any pathological process when regeneration is wrong in a form of overproducing or decrease of producing of the tissue (hyper-hyporegeneration) or the conversion of one type of living cell or group of cells into another (metaplasia)

Hypertrophy

Increase of organs, tissues, cells in their size (volume); qualitative changes (Fig. 26.).

- Working
- Neurohumoral
- Hypertrophic
- Vicar

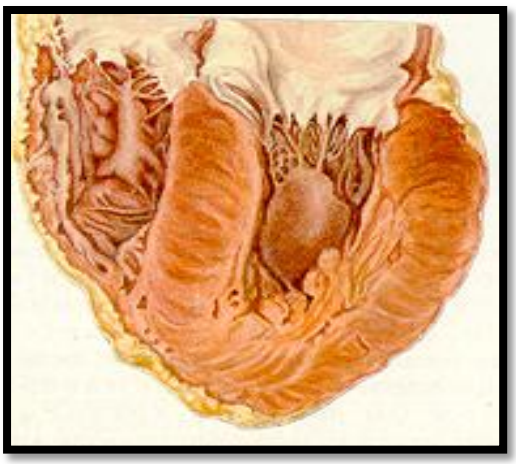


Fig. 26. Left ventricular hypertrophy

Hyperplasia

Increase of the organ or tissue by the cells' multiplying, increase in cells' number; quantitative changes.

Atrophy

Decrease in size of a body part, cells, organ, or tissue.

- In atrophy of an organ or body part, there may be a reduction in the number or in the size of the component cells, or in both.
- Physiological
- Pathological

Pathological atrophy

Can be seen in any age due to different reasons of genesis.

Types due to etiology:

- Endocrine (hormonal)
- Alimentary (cachectical)
- Central (neurogenic)
- Peripheral (neurogenic)

Classification

Local:

- Dysfunctional
- Because of pressure
- Because of hemodynamic' insufficiency
- Neurotic
- Because of chemical and physical factors

General

Morphology

Microscopically observed decrease of cell protoplasm and nucleuses.

GENERAL STUDY OF TUMORS. ETIOLOGY. EPIDEMIOLOGY. EPITHELIAL TUMORS.

Tumor (Neoplasia) means "new growth" presented newly formed tissue, which changes the genetic apparatus of cells is likely to disrupt the regulation of growth and differentations.

Oncology (Greek *oncos* = tumor) is the study of tumors or neoplasms.

Distinguished:

I. Benign tumors

II. Malignant tumors

Benign tumors

A tumor is said to be *benign* when :

1) its microscopic and gross characteristics are considered relatively innocent, implying that it will remain localized, it cannot spread to other sites. (capsula)
2) Benign (mature homologous) tumors composed of cells differentiated to such an extent that it is possible to determine from what tissue they grow.
3) For these tumors are characterized by slow expansive growth,
4) The absence of metastasizes,
5) No overall effect on the body.
6) Benign tumors can be malignant (cancerous turn).
7) In general, benign tumors are designated by attaching the suffix *-oma* to the cell of origin. Tumors of mesenchymal cells generally follow this rule.

Malignant tumors

1) **Malignant tumors** are collectively referred to as ***cancers***, derived from the Latin word ***crab***, because they adhere to any part that they seize on in an obstinate manner, similar to a crab.
2) They may lose their resemblance to the tissue from which they originate.
3) For malignant tumors characterized by rapid, often infiltrative growth

4) Metastasis

5) Cell and tissue irregularities and recurrence

6) General effect on the body.

Comparisons between Benign and Malignant Tumors

Characteristics	Benign	Malignant
Differentiation/ anaplasia	Well differentiated; structure sometimes typical of tissue of origin	Some lack of differentiation with anaplasia; structure often atypical
Rate of growth	Usually progressive and slow; may come to a standstill or regress; mitotic figures rare and normal	Erratic and may be slow to rapid; mitotic figures may be numerous and abnormal
Local invasion	Usually cohesive expansile well-demarcated masses that do not invade or infiltrate surrounding normal tissues	Locally invasive, infiltrating surrounding tissue; sometimes may be seemingly cohesive and expansive
Metastasis	Absent	Frequently present; the larger and more undifferentiated the primary, the more likely are metastases

Etiology

I. Viral genetic theory a crucial role in the development of tumors removes oncogenic viruses, which include: Epstein-Barr virus (Burkitt lymphoma), herpes simplex virus (Hodgkin's disease, Kaposi's sarcoma, brain tumors), retrovirus (chronic lymphocytic leukemia), hepatitis B and C (liver cancer). According to the viral genetic theory of integration of the virus genome with the genetic apparatus of cells can lead to malignant transformation of cells. With further growth and multiplication of cancer cells the virus is no longer play a significant role.

II. Physico-chemical theory of the main cause of tumor development considers the impact of various physical and chemical factors on the cells, carcinogenic substances), which causes them to oncotransformation. In addition to exogenous chemical carcinogens is considered a role in causing cancer of endogenous carcinogens (such as metabolites of tryptophan and tyrosine) through the activation of proto-oncogenes in these substances, which, through the synthesis of oncoproteins will transform the cell into a tumor.

III. The theory of dishormonal carcinogenesis sees as the causes of various disorders of tumors of hormonal balance in the body.

IV. Disontogenetic theory considers violations of embryonic tissues, which is under the influence of precipitating factors can lead to oncotransformation of the tissue cells.

V. Polyetiological theory

Types of tumor growth

I. Depending on the nature of the interaction of a growing tumor with elements of the surrounding tissue:

- expansive growth - tumors grow "out of itself", pushing the surrounding tissue, tissue with a tumor on the border of atrophy, a collapse of the stroma - is formed pseudocapsula;
- infiltrative (invasive, destructive) growth - tumor cells grow into the surrounding tissues, destroying them;
- apposition of the tumor growth is due to the neoplastic transformation of cells in the tumor surrounding tissue.

II. Depending on the ratio of lumen of the hollow body:

- exophytic growth - the expansive growth of the tumor into the lumen of the hollow body, swelling of the closing of the lumen of the body, connecting with his foot wall;
- endophytic growth - infiltrative tumor growth into the interior wall of the body.

III. Depending on the number of focuses of the tumor:

- Unicentric growth - tumors grow from a single focus;
- Multicentric growth - the growth of tumors from two or more lesions.

Metastasis

Metastasis - the spread of cancer cells from primary tumor to other organs to form secondary (daughter) of tumor lesions . Ways of metastasis:

1. hematogenous - the path of metastasis of tumor emboli by propagating through the bloodstream;

2 .lymphogenous - the path of metastasis of tumor emboli by spreading through the lymph vessels;

3. implantation (contact) - the path of metastasis of tumor cells to serosa adjacent to tumor hearth.

4. intracanalicular - the path of metastasis in the natural physiological spaces (synovial sheath, etc.)

5. perineural (a special case intracanalicular metastasis) - in the course of the nerve bundle.

Influence of tumor on the body

I. **Local influence** is compression or fracture (depending on the type tumor) surrounding tissue and organs. Specific manifestations of local action depends on the location of the tumor.

II. **General effect** on the body is characteristic of malignant tumors, manifested by various metabolic disorders, until the development of cachexia.

Classification by histogenetic principle (proposed by the Committee on Nomenclature of tumors):

I. Epithelial tumors without specific localization (organonspesific);

II. Epithelial tumors of exo-and endocrine glands, and epithelial tumors sheets (organ-specific);

III. Mesenchymal tumors

IV. Melaninproductive tissue tumors

V. Tumors of the nervous system and meninges

VI. Tumors of the blood

VII. Teratomas

TNM classification

This classification uses a numerical designation of different categories to describe the spread of the tumor, as well as the presence or absence of local and distant metastases.

- **T - tumor**
- From the Latin word for tumor - a tumor. Describes and classifies the main focus of the tumor.
- T_{is} $T = _0$ or - the so-called carcinoma «in situ» - that is not germinating the basal layer of epithelium.
- T_{1-4} - varying degrees of focus. For each of the bodies has a separate interpretation of each of the indexes.
- T_x - hardly used. Billed only for the time when detected metastases, but not identified the main focus.

- **N - nodulus**
- From the Latin nodulus - node. Describes and characterizes the presence of regional metastases, that is, in regional lymph nodes.
- N_x - detection of regional metastases has been conducted, their presence is not known.
- N_0 - regional metastases were found in a study for the detection of metastases.
- N_1 - revealed regional metastases.

- **M - metastasis**
- Characteristics of the presence of distant metastases, that is - to distant lymph nodes, other organs and tissues (except for the germination of the tumor).
- M_x - detection of distant metastases has been conducted, their presence is unknown.
- M_0 - Distant metastases were found in a study for the detection of metastases.
- M_1 - identified distant metastases.

- **P, G**
- For some organs or systems are subject to additional parameters (P or G, depending on the organ system), which characterize the degree of differentiation of its cells. G (grade) - characterizes the degree of malignancy. In this case the determining factor is the histological figure - the degree of cell differentiation. Gives only 3 groups of neoplasms.
- P (penetration) - the parameter is introduced only for tumors of hollow organs and shows the degree of germination of their walls.

Nomenclature of Tumors

Tissue of Origin	**Benign**	**Malignant**
COMPOSED OF ONE PARENCHYMAL CELL TYPE		
Tumors of Mesenchymal Origin		
Connective tissue and derivatives	Fibroma	Fibrosarcoma
	Lipoma	Liposarcoma
	Chondroma	Chondrosarcoma
	Osteoma	Osteogenic sarcoma
Endothelial and Related Tissues		
Blood vessels	Hemangioma	Angiosarcoma
Lymph vessels	Lymphangioma	Lymphangiosarcoma
Synovium		Synovial sarcoma
Mesothelium		Mesothelioma
Brain coverings	Meningioma	Invasive meningioma
Blood Cells and Related Cells		
Hematopoietic cells		Leukemias

Lymphoid tissue		Lymphomas
Muscle		
Smooth	Leiomyoma	Leiomyosarcoma
Striated	Rhabdomyoma	Rhabdomyosarcoma

Tumors of Epithelial Origin		
Stratified squamous	Squamous cell papilloma	Squamous cell carcinoma
Basal cells of skin or adnexa		Basal cell carcinoma
Epithelial lining of glands or ducts	Adenoma	Adenocarcinoma
	Papilloma	Papillary carcinomas
	Cystadenoma	Cystadenocarcinoma
Respiratory passages	Bronchial adenoma	Bronchogenic carcinoma
Renal epithelium	Renal tubular adenoma	Renal cell carcinoma
Liver cells	Liver cell adenoma	Hepatocellular carcinoma
Urinary tract epithelium (transitional)	Transitional-cell papilloma	Transitional-cell carcinoma
Placental epithelium	Hydatidiform mole	Choriocarcinoma
Testicular epithelium (germ cells)		Seminoma
		Embryonal carcinoma

Tumors of Melanocytes	Nevus	Malignant melanoma

MORE THAN ONE NEOPLASTIC CELL TYPE—MIXED TUMORS, USUALLY DERIVED FROM ONE GERM CELL LAYER		
Salivary glands	Pleomorphic adenoma (mixed tumor of salivary origin)	Malignant mixed tumor of salivary gland origin
Renal anlage		Wilms tumor
MORE THAN ONE NEOPLASTIC CELL TYPE DERIVED FROM MORE THAN ONE GERM CELL LAYER—TERATOGENOUS		
Totipotential cells in gonads or in embryonic rests	Mature teratoma, dermoid cyst	Immature teratoma, teratocarcinoma

Malignant tumors arising *in mesenchymal tissue are usually called* ***sarcomas*** **(Greek *sar* = fleshy**), because they have little connective tissue stroma and so are fleshy (e.g., fibrosarcoma, chondrosarcoma, leiomyosarcoma, and rhabdomyosarcoma). Malignant neoplasms of epithelial cell origin, derived from any of the three germ layers, are called *carcinomas*. Thus, cancer arising in the epidermis of ectodermal origin is a carcinoma, as is a cancer arising in the mesodermally derived cells of the renal tubules and the endodermally derived cells of the lining of the gastrointestinal tract. Carcinomas may be further qualified.

Epithelial tumors

- **From squamous epithelium**

  Malignant: **carcinoma**
  Benign: **papilloma**

From glandular epithelium

Malignant: **adenocarcinoma**
Benign: **adenoma**

Tumors from the squamous epithelium

Papilloma

Benign tumor of the skin or mucosa with the squamous epithelium, or of the tissues with transitional epithelium (Fig. 27.).

Exophytic or inverted; isolated or multiple

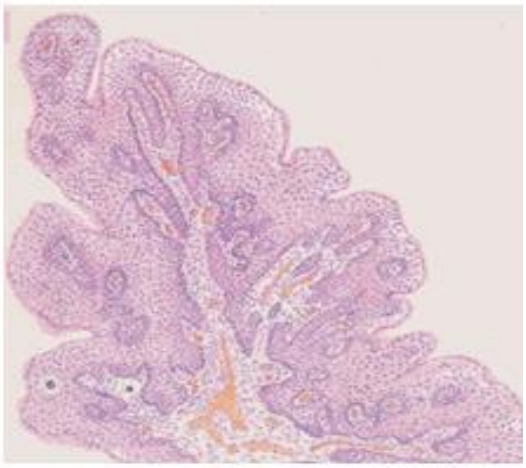


Fig. 27. Squamous cell papilloma of skin

Malignant neoplasms of epithelial cell origin, derived from any of the three germ layers, are called ***carcinomas***.

The word ***carcinoma*** is attached to the type of tissue e.g. malignant epithelial tumor of renal cell is called **renal cell carcinoma**. Carcinomas may be further qualified.

Squamous cell carcinoma would denote a cancer in which the tumor cells resemble stratified squamous epithelium

Adenocarcinoma denotes a lesion in which the neoplastic epithelial cells grow in glandular patterns.

Basal cell carcinoma (Basalioma)

- skin tumor (predominantly on the face) –proliferation of the cells similar to the immature cells of the basal layer of the epidermis
- variable histological features
- grows predominantly endophytic, with the dermis infiltration, and surface exulceration (ulceration)
- without metastasis (semimalignant), locally destructive, with relapses.

Classification of malignant tumors from epithelium

due to structure of neoplasm:

I. **Trabecular** –equal proportion of stroma and parynchyma

II. **Fibrinous** – stromal predominance

III. **Medullary** –parenchymal predominance

Tumors from the glandular epithelium

Classification due to source:

1. –Adenocarcinoma of trabecular glands(liver, hypophysis) are solid with trabecular form
2. –Adenocarcinoma of tubular, acinar and alveolar glands and of cylindric epithelium. Both types resemble original tissue according to the differentation

Classification: according to mucus production

1. –Carcinomas of signet-ringcells–mucus in cytoplasm
2. –Mucinous carcinomas–mucus in stroma

Classification: on the surface of organ with lumen

1. -Exophytic or endophytic
2. -Exophytic can be according to the apperance: papillary, polypus, villous, disciform (central necrosis)

MESENCHYMAL TUMORS. TUMORS OF THE MELANIN PRODUCING TISSUE.

Mesenchymal tissue gives an origin to vessels, muscles, bones, cartilages, serous membranes and blood system. All these tissues are the probable source of tumors whether benign or malignant.

Benign mesenchymal tumors

- **Fibroma -** nonmalignant tumor of connective tissue, built from fibroblasts, fibrocytes and bunches of collagen fibers. Can be:

1. **Soft**- with a predominance of loose connective tissue
2. **Dense-** with a predominance of dense connective tissue

- **Desmoid-** is a special type of the fibroma, characterized by infiltrative growth. And after it's removed it can recur. Mostly seen in females.
- **Dermatofibroma** is built from fibroblasts, histiocytes, macrophages and fibrocytes. This tumor is characterized by appearing of big multinuclear cells inclusive by hemosiderine and lipids (Tuton's cells). Mostly seen on the skin of limbs.
- **Lipoma** is built of lipocytes of the adipose tissue. Can be ***single*** or ***multiple***.
- **Hybernoma** – takes origin from the brown fat's cells. Mostly is single and placed in the intrascapular space.
- **Leiomyoma** - benign tumor of smooth muscle (usually in the uterus or digestive tract) bunches are ramblingly interlaced. Stroma is well developed, that's why this tumor is usually called fibromyoma.
- **Rhabdomyoma**- benign tumor of striated muscle.
- **Granular-cellular tumor** (tumor of Abricosov) - neurogenic origin tumor, developed from the Schwann membranes. Usually placed in the tongue
- **Glomus-angioma**
- **Lymphanioma**
- **Benign synovoima**
- **Hemangioma** - is a complex meaning, that includes:

1. Capillary. 2. Venous. 3. Cavernous. 4. Benign hemangiopericytoma.

Malignant mesenchymal tumors

Malignant tumors arising in mesenchymal tissue are usually called sarcomas (Greek sar = fleshy), Malignant mesenchymal tumors are charecterized by cellular atypism and characterized by hematogenic metastasis.

Distinguished:

- Fibrosarcoma
- Malignant histecytoma
- Liposarcoma
- Malignant hybernoma
- Leiomyosarcoma

- **Rabdomyosarcoma-** malignant tumor of striated (skeletal) muscular tissue.
- **Angiosarcoma -** malignant neoplasm arising from vascular tissue.
- **Malignant synovioma**
- **Osteosarcoma -** also called Osteogenic Sarcoma, the most common malignant tumour of bone. It is found more often in males than in females, occurs mostly under the age of 30, and affects mainly the large long bones
- **Malignant mesotelioma** - a rare form of carcinoma of the mesothelium lining lungs or abdomen or heart; usually associated with exposure to asbestos dust
- **Chondrosarcoma -** malignant tumour of cartilage. Primary chondrosarcoma arises and grows rapidly without a preexisting cartilaginous focus; the secondary type develops slowly from a previously benign tumour of cartilage. Pain is the major symptom. The tumour shows a tendency to recur.

Tumors of the melanin producive tissues

Neavus- benign tumor of the melanin producing tissues

Distinguished:

1. Boundary neavus. 2. Intradermal. 3. Mixed. 4. Epithelioid neavus.

Melanoma- cancer of the cells in the skin that produce melanin. It is a dark-colored tumor most often derived from melanin-pigmented skin cells. Melanomas sometimes are derived from other body tissues but are called melanomas because of their dark color

Tumors of The Central Nervous System and brain coats

GLIOMAS	NEURONAL TUMORS
• Astrocytoma	Ganglioneuroma
• Astroblastoma	Ganglioneuroblastoma
• Oligodendroglioma	Neuroblastoma
• Oligodendroglioblastoma	Meduloblastoma
• Epidermal tumors and of the choroid epithelium	Low differentiated and embryonic tumors
• Ependimoma	
• Ependimoblastoma	

- Choroid papilloma
- Choroid canceroma

Teratomas

Teratoma is found in newborn children, which is made up of a heterigenous mixture of tissues not normally found at that site, as of bone, cartilage and muscle.

Teratoblastoma – malignant tumor that charecterized by cellular atipism and polymorphism, grows very fast and gives metastases.

TUMORS OF THE CIRCULATORY AND LYMPHATIC TISSUE.

BLOOD SYSTEM TUMORS: Leukemia

LYMPHOID SYSTEM TUMORS: Lymphoma

LEUKEMIAS

Leukemias are malignant neoplasms of the hemopoetic stem cells that are characterized by:

- Diffuse replacement of the bone marrow by proliferative leukemic cells.
- In most cases the leukemic cells spillover into the blood where they may be seen in large number.
- Widespread of leukemic infiltrates in the liver, spleen, lymph nodes and other sites through the body.
- Suppression of normal bone marrow by leukemic cells resulting in **anemia, thrombocytopenia,** and loss of normally functioning leukocytes.

CLASSIFICATION

Leukemias are classified on the basis of the following features:

I. Type of cell involvement

II. State of maturity of leukemic cells e.g. *mature or immature*

III. According to the onset and clinical course e.g.

* Acute * Chronic

Etiology – exact cause is unknown

Acute leukemia

Acute leukemia is characterized by sudden onset, replacement of bone marrow with very immature cells (called blast cells) and by rapidly fatal course in untreated patients

Classification

Due to cells' type:

I. Non- differentiated

II. Myeloblastic

III. Lymphoblastic

IV. Erythromyeloblastic

V. Megacaryoblastic

Clinical features

I. Acute onset (mostly within 3 month).

II. Symptoms related to depression of normal marrow function.

- **Fatigue**: due to anemia
- **Fever** : due to infection, resulting from absence of mature leukocytes
- **Bleeding** : secondary to thrombocytopenia

III. Bone pain and tenderness: result from marrow expansion with infiltration of the subperiosteum.

IV. Generalized lymphadenopathy. Generalized

hepatosplenomegaly.

V. CNS manifestations: headache, vomiting and nerve palsies resulting from meningeal spread.

Investigations

1. Complete blood count shows:

- Increase of total WBC count with increased blast cells

- Total WBC count is not increased but blast cells count increased in peripheral blood
- No changes in WBC count- aleukemic leukemia
- Anemia
- Thrombocytopenia

2. Bone marrow examination:

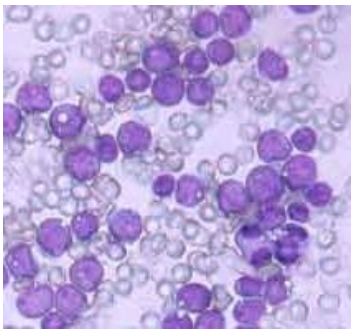
replacement of normal elements by blast cells in th bone marrow.

The presence of Auer rods in cytoplasm of blast cells indicates a myeloblastic type of leukemia

Treatment

1. Radiotherapy 2. Chemotherapy

Fig. 27. Blast cells in the blood with leukemia



Chronic leukemias

Chronic leukemias are characterized by insidious onset and slow clinical course. Proliferating cells are more mature (well differentiated)

Classification of chronic leukemias

Due to cell type:

I. Leukemia of myelocytic origin:
1. **Myeloid leucosis**
2. **Chronic erythromyelosis**
3. **Erythremia**

II. Leukemia of lymphocytic origin :
1. **Chronic lymph leucosis**
2. **Lymphamatosis of skin**
3. **Paraproteinemic leucosis**

III. Leukemia of monocytic origin:
1. **Chronic monocytic leukosis**
2. **Histocytosis**

Characteristics of chronic leukemia

- Longer survival even when untreated (2- 6 years).
- Presence of large number of mature leukocytes in blood.
- Infiltration of organs causing specially splenomegaly, hepatomegaly and lymph node enlargement.

Chronic myelocytic (myeloid) leukemia

The Philadelphia chromosome is present in all these leukemic cells. There's no block of maturation of leukemic cells which is expressed by the large number of mature cell in the peripheral blood.

Clinical features:

- Onset is usually slow and initial symptoms may be non- specific e.g. weight loss, fatigue and weakness
- Massive splenomegaly

Investigations

Blood picture:

- *Marked elevation of WBC count exceeding 100,000 cells per microliter*
- *The circulating cells are mostly: neutrophils and myelocytes but basophils and eosinophils are prominent*
- *Thrombocytosis*

Bone marrow examination:

- *The BM is hypercellular with hypeplasia of granulocytic and megakaryocytic cells*
- *The Philadelphia chromosome is present in all these cells.*

Treatment

1. Radiotherapy

2. Chemotherapy

Lymphomas

The lymphomas are the malignant tumors of lymphoid cells native to lymphoid tissue (i.e. lymphocytes, histocytes, their precursors and derivatives).

Etiology is unknown.

Classification

Due to type:

- Non-Hodgkin's lymphoma
- Hodgkin's disease

Non-Hodgkin's lymphoma (NHL)

These are solid tumors arising in the lymph nodes (65 % cases) and less frequently in nasopharynx, skin and other tissues (35%). This type of lymphoma is characterized by malignant proliferation of lymphoid cells, the majority of cells are B lymphocytes.

Epidemiology

- NHL occur at all ages
- Males are more frequently affected than females

Pathology

NHL originate in T cells or histiocytes but most NHL are of B cell origin. Some B cell lymphomas have nodular appearance due to clustering of neoplastic lymphocytes in lymph nodes and are called nodular or follicular. Other B- cell's tumors spread diffusely in the lymph nodes and are referred to as diffuse lymphomas. Most nodular lymphomas are low- grade tumors and are compatible with long survival without treatment. Diffuse lymphomas are high-grade tumors, very aggressive and rapidly fatal unless treatment.

Clinical features

1. Lymphadenopathy
2. Systemic features (tiredness, weight loss, sweating and fever)
3. Features of extra- lymphatic involvement:
   a. Hepatosplenomegaly
   b. Involvement of GIT causes malabsorbtion, abdominal pain and diarrhea.

Investigations

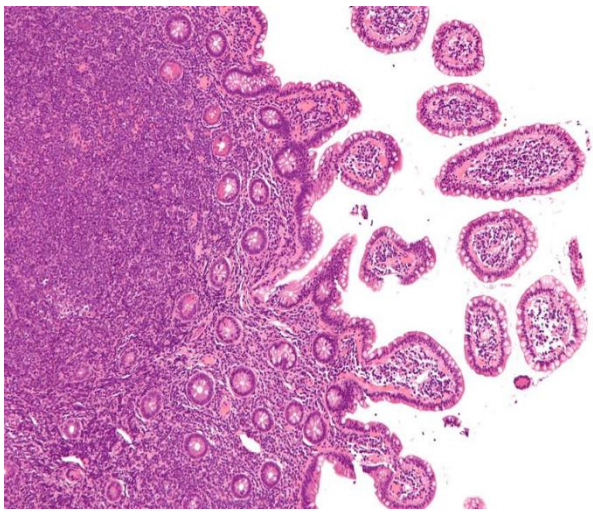
- Lymph node biopsy
- Bone marrow biopsy

- Blood count is usually normal unless bone marrow involvement

Treatment

1. Radiotherapy 2. Chemotherapy

Fig. 28. High grade non hodgkin s lymphoma



Hodgkin's disease

It's a disorder involving primarily the lymphoid tissues in a single node or chain of nodes spreading to the contiguous nodes and pathological hallmark is the presence of Reed- Sternberg cells.

Characteristic features

- Presence of distinctive neoplastic giant cells called **Reed- Stenberg cells.** Admixed inflammatory cells
- Presence of distinctive clinical features including systemic manifestation like fever

Classification

Due to frequency of occurrence:

I. Nodular sclerosis

II. Mixed- cellularity

III. Lymphocytic predominant

IV. Lymphocytic depleted

Pathology

Presence of distinctive neoplastic giant cells called **Reed- Stenberg cells.** The Reed –Sternberg cells are the neoplastic giant cells having two mirror – image nuclei, each nucleolus surrounded by distinctive clear zone, giving an appearance called **owl–eye appearance.**

Clinical features

I. Lymphadenopathy (usually cervical may be mediastinal, axillary rarely abdominal or pelvic)

II. Systemic features (tiredness, weight loss, sweating and fever)

III. Features of extra- lymphatic invovment

Very uncommon

Treatment

1. Radiotherapy 2. Chemotherapy

ANEMIAS

Anemia is a decrease in number of red blood cells (RBCs) or less than the normal quantity of hemoglobin in the blood.

Classification of Anemia According to Underlying Mechanism

Mechanism	Specific Examples
BLOOD LOSS	
Acute blood loss	**Trauma**
Chronic blood loss	**Gastrointestinal tract lesions, gynecologic disturbances**
INCREASED RED CELL DESTRUCTION (HEMOLYSIS)	
Inherited genetic defects	

Red cell membrane disorders	**Hereditary spherocytosis, hereditary elliptocytosis**
Enzyme deficiencies	
Hexose monophosphate shunt enzyme deficiencies	**G6PD deficiency, glutathione synthetase deficiency**
Glycolytic enzyme deficiencies	**Pyruvate kinase deficiency, hexokinase deficiency**

INCREASED RED CELL DESTRUCTION	**(HEMOLYSIS)**
Hemoglobin abnormalities	
Deficient globin synthesis	Thalassemia syndromes
Structurally abnormal globins (hemoglobinopathies)	Sickle cell disease, unstable hemoglobins
Acquired genetic defects	
Deficiency of phosphatidylinositol-linked glycoproteins	Paroxysmal nocturnal hemoglobinuria
Antibody-mediated destruction	Hemolytic disease of the newborn (Rh disease), transfusion reactions, drug-induced, autoimmune disorders
Mechanical trauma	
Microangiopathic hemolytic anemias	Hemolytic uremic syndrome, disseminated intravascular coagulation, thrombotic thrombocytopenia purpura
Cardiac traumatic hemolysis	Defective cardiac valves

Repetitive physical trauma	Bongo drumming, marathon running, karate chopping
Infections of red cells	Malaria, babesiosis
Toxic or chemical injury	Clostridial sepsis, snake venom, lead poisoning
Membrane lipid abnormalities	Abetalipoproteinemia, severe hepatocellular liver disease
Sequestration	Hypersplenism

DECREASED RED CELL PRODUCTION	
Inherited genetic defects	
Defects leading to stem cell depletion	Fanconi anemia, telomerase defects
Defects affecting erythroblast maturation	Thalassemia syndromes
Nutritional deficiencies	
Deficiencies affecting DNA synthesis	B_{12} and folate deficiencies
Deficiencies affecting hemoglobin synthesis	Iron deficiency anemia
Erythropoietin deficiency	Renal failure, anemia of chronic disease
Immune-mediated injury of progenitors	Aplastic anemia, pure red cell aplasia
Inflammation-mediated iron sequestration	Anemia of chronic disease
Primary hematopoietic neoplasms	Acute leukemia, myelodysplasia, myeloproliferative disorders

Space-occupying marrow lesions	Metastatic neoplasms, granulomatous disease
Infections of red cell progenitors	Parvovirus B19 infection
Unknown mechanisms	Endocrine disorders, hepatocellular liver disease

Hemolytic anemias

Hemolytic anemias share the following features:

- Premature destruction of red cells and a shortened red cell life span below the normal 120 days
- Elevated erythropoietin levels and a compensatory increase in erythropoiesis
- Accumulation of hemoglobin degradation products released by red cell breakdown derived from hemoglobin

Morphology

Anemia and lowered tissue oxygen tension trigger the production of erythropoietin, which stimulates erythroid differentiation and leads to the appearance of increased numbers of erythroid precursors (normoblasts) in the marrow.

Compensatory increases in erythropoiesis result in a prominent reticulocytosis in the peripheral blood.

The phagocytosis of red cells leads to hemosiderosis, which is most pronounced in the spleen, liver, and bone marrow. If the anemia is severe, extramedullary hematopoiesis can appear in the liver, spleen, and lymph nodes. With chronic hemolysis, elevated biliary excretion of bilirubin promotes the formation of pigment gallstones (cholelithiasis).

Hereditary Spherocytosis (HS)

This inherited disorder is caused by intrinsic defects in the red cell membrane skeleton that render red cells spheroid, less deformable, and vulnerable to splenic sequestration and destruction

Morphology

The most specific morphologic finding is spherocytosis, apparent on smears as abnormally small, dark-staining (hyperchromic) red cells lacking the central zone of pallor.

Sickle Cell Disease

Sickle cell disease is a common hereditary hemoglobinopathy that occurs primarily in individuals of African descent. Sickle cell disease is caused by a point mutation in the sixth codon of β-globin. The abnormal physiochemical properties of the resulting sickle hemoglobin (HbS) are responsible for the disease.

Morphology

In full-blown sickle cell anemia, the peripheral blood demonstrates variable numbers of irreversibly sickled cells, reticulocytosis, and target cells, which result from red cell dehydration. Howell-Jolly bodies (small nuclear remnants) are also present in some red cells due to the asplenia. The bone marrow is hyperplastic as a result of a compensatory erythroid hyperplasia.

Anemias of Diminished Erythropoiesis

Although the anemias that stem from the inadequate production of red cells are heterogeneous, they can be classified into several major categories based on pathophysiology. The most common and important anemias associated with red cell underproduction are those caused by nutritional deficiencies, followed by those that arise secondary to renal failure and chronic inflammation.

Thalassemia Syndromes

The thalassemia syndromes are a heterogeneous group of disorders caused by inherited mutations that decrease the synthesis of adult hemoglobin, HbA ($\alpha_2\beta_2$). Thalassemia syndromes are endemic in the Mediterranean basin, the Middle East, tropical Africa, the Indian subcontinent, and Asia, and in aggregate are among the most common inherited disorders of humans.

Megaloblastic Anemia

I. Folic acid deficiency/ pernicious anemia

II. Vitamin b_{12} deficiency

Causes of Megaloblastic Anemia

Folic acid deficiency

1. Decreased Intake
2. Inadequate diet, alcoholism, infancy
3. Impaired Absorption
4. Malabsorption states
5. Intrinsic intestinal disease
6. Anticonvulsants, oral contraceptives Increased Loss Hemodialysis
7. Increased Requirement
8. Pregnancy, infancy, disseminated cancer, markedly increased hematopoiesis
9. Impaired Utilization
10. Folic acid antagonists

Vitamin b_{12} deficiency

1. Decreased Intake Inadequate diet, vegetarianism Impaired Absorption
2. Intrinsic factor deficiency
3. Gastrectomy
4. Malabsorption states
5. Diffuse intestinal disease (e.g., lymphoma, systemic sclerosis)
6. Ileal resection, ileitis
7. Competitive parasitic uptake
8. Fish tapeworm infestation
9. Bacterial overgrowth in blind loops and diverticula of bowel

Morphology

The presence of red cells that are macrocytic and oval (macro-ovalocytes) is highly characteristic. Because they are larger than normal and contain ample hemoglobin, most macrocytes lack the central pallor of normal red cells and even appear "hyperchromic". There is marked variation in the size (anisocytosis) and shape (poikilocytosis) of red cells. The reticulocyte count is low.

Iron Deficiency Anemia

Deficiency of iron is the most common nutritional disorder in the world.

Morphology.

The bone marrow reveals a mild to moderate increase in erythroid progenitors. A diagnostically significant finding is the disappearance of stainable iron from macrophages in the bone marrow, which is best assessed by performing Prussian

blue stains on smears of aspirated marrow. In peripheral blood smears, the red cells are small (microcytic) and pale (hypochromic).

Aplastic Anemia

Aplastic anemia refers to a syndrome of chronic primary hematopoietic failure and attendant pancytopenia (anemia, neutropenia, and thrombocytopenia). In the majority of patients autoimmune mechanisms are suspected,but inherited or acquired abnormalities of hematopoietic stem cells also seem to contribute in at least a subset of patients.

Major Causes of Aplastic Anemia

Acquired

- *Idiopathic* (Acquired stem cell defects ; Immune mediated)
- *Chemical Agents (*Dose related; Alkylating agents; Antimetabolites; Benzene; Chloramphenicol ; Inorganic arsenicals)
- *Idiosyncratic* (Chloramphenicol, Phenylbutazone, Organic arsenicals; Methylphenylethylhydantoin, Carbamazapine; Penicillamine, Gold salts)
- *Physical Agents*
- Whole-body irradiation
- *Viral Infections* Hepatitis (unknown virus); Cytomegalovirus infections; Epstein-Barr virus infections; Herpes zoster (Varicella zoster)
- Inherited (Fanconi anemia; Telomerase defects)

Morphology.

The markedly hypocellular bone marrow is largely devoid of hematopoietic cells; often only fat cells, fibrous stroma, and scattered lymphocytes and plasma cells remain. Marrow aspirates often yield little material (a “dry tap”); hence, aplasia is best appreciated in marrow biopsies

ATHEROSCLEROSIS. HYPERTONIC DISEASE.

Atherosclerosis- (*ather*-gruel, porridge, mush and *sclerosis*-hardening or thickening of tissue) is a chronic disease that occurs in the result of disturbances in the protein and lipid metabolism and characterized by affecting the elastic and muscular-elastic type of arteries with the focal form of depositing of lipids and proteins and reactive growth of the connective tissue.

Etiology

- Atherosclerosis is a polyetiological disease, including two groups of factors

I. Exogenic

- Hereditary factors
- Alimentary factors
- Social factors

II. Endogenic

- Metabolic disturbances

Pathogenesis

Generally divided on 4 stages:

1. Initiation

2. Plague progression

3. Plague rupture

4. Atherothrombosis

Theories:

- Theory of "Infiltration"
- Neuro-metabolic
- Immunological
- Infectious
- Theory of "Injury "

Theory of "injury"

Stages:

1. Chronic endothelial injury

2. Endothelial dysfunction

3. Smooth muscle emigration from media to intimae. Macrophage activation

4. Smooth muscle cells and macrophages engulf lipids

5. Smooth muscle proliferation, collagen deposits, extracellular lipids

Morphogenesis

Macroscopically distinguished:

Type I (initial) lesion isolated macrophage foam cells.

Type II (fatty streak) lesion

Mainly intracellular lipid accumulation

Type III (intermediate) lesion

Type II changes + small extracellular lipids

Type IV (atheroma) lesion

Type II changes + core of extracellular lipids

Type V (fibroatheroma) lesion

Lipids core and fibrotic layer, or multiple lipid cores and fibrotic layers, or mainly calcific or mainly fibrotic

Type VI (complicated) lesion

Surface defect, hematoma-hemorrhage, thrombus

Microscopically distinguished stages:

- 1.Before lipidic
- 2.Lipoidosis
- 3.Liposclerosis
- 4.Atheromatosis
- 5.Ulceration
- 6.Atherocalcinosis

Clinic-morphological forms

Due to localization:

- 1.atherosclerosis of aorta
- 2.atherosclerosis of coronary vessels
- 3.atherosclerosis of cerebral arteries (Cerebral form)
- 4. atherosclerosis of renal arteries
- 5. intestinal form
- 6. atherosclerosis of low extremities

Complication

Due to fast progression:	**Due to slow progression**:
• Acute circulatory dysfunction • Necrosis	• Aneurism • Thrombosis

• Infarction	• Embolism

Hypertonic disease

Hypertonic disease (hypertension) is disease that characterized by the increase of blood pressure

Risk factors:

1. Stress
2. Smocking
3. Alcoholism
4. Professional disutility
5. Adynamia

Morphology

I. **Preclinical stage –** characterized by the short spasm of arteries and arterioles with hypertrophy of the heart left ventricle.

II. Morphological changes of vessels with future hyalinosis – obvious hypertension, affection of different vessels as renal, myocardial, brain's vessels etc.

III. Morphological changes in the organs as brain, kidneys, etc.

ISCHEMIC HEART DISEASE. CARDIOMYOPATHIES.

Is a group of diseases that is characterized by the imbalance between myocardial oxygen demand and blood supply.

Includes:

I. **Stable angina**
II. **Unstable angina**
III. **Myocardial infarction**
IV. **Sudden cardiac death**

Etiology

Atherosclerotic narrowing of the coronary arteries, producing ischemia

Risk factors

1. Age
2. Male sex
3. Family history
4. Hyperlipidemia

5. Hypertension
6. Smoking
7. Diabetes mellitus
8. Obesity
9. Lack of exercises
10. Alcoholism, etc.

Pathogenesis

1) Defective oxygen deliver
2) Increased oxygen demand
3) Superimposed lesion, that includes:
    - Acute changes is plaque morphology
    - Local platelet

Morphology

Include fissuring, hemorrhage and rupture of the plaque with embolozation of plaque debris into distal coronary vessels.

Mechanical occlusion of small blood vessels by small platelet aggregates and coronary vasospasm induced by mediators released from the platelet

Cardiomyopathies

Cardiomyopathies are the group of diseases, characterized by primary dystrophic changes in myocardium. This group includes various diseases of non-coronarogenic and non-rheumatogenic origin, different in etiology and pathogenesis, but similar clinically. The main clinical manifestation is – insufficiency of contractility function of myocardium in connection with its dystrophy.

Classification. Cardiomyopathies are divided **primary** and **secondary**.

Primary (idiopathic)

- hypertrophic
- dilatational
- restrictive

Hypertrophic cardiomyopathy has hereditary character. It may be manifested in 2 form: **diffuse** and **local**. In first form occur diffuse thickening of left ventricular myocardium and interventricular septum. In second form the hypertrophy of myocardium embraces mostly upper parts of left ventricle

Dilatational hypertrophy is usually associated with virus myocarditis. For this type of cardiomyopathy is characteristic an abrupt dilation of cardiac cavity. The heart acquires spherical form; its weight is increased.

Restrictive cardiomyopathy occurs diffuse or focal **fibrosis of endocardium.**

Secondary

In the basis of secondary cardiomyopathies, independently on etiological factors, lies dystrophy of cardiomyocytes. Alcoholic cardiomyopathy is most important among secondary cardiomyopathy.

Pathogenesis of alcoholic cardiomyopathy is associated primarily with the biological properties of ethanol - its direct toxic effect on the cardiomyocytes as well as influence of metabolite of ethanol - acetaldehyde. Certainly the value of vascular disorders and related with it hypoxia, damaging effect of catecholamines on the myocardium.

Morphological changes of heart lead to moderate myocardial hypertrophy, the expansion of the heart cavities with parietal thrombi. The myocardium is flabby, clay species, sometimes with small ridges. Coronary arteries are intact, lipid spots and stripes may be present in the intima, expressed atherosclerotic changes are absent.

Microscopic examination reveals the combination of dystrophy (hydropic and fat), atrophy and hypertrophy of cardiomyocytes, focuses of cardiomyocytes lysis and sclerosis usually encounter.

Complications of alcoholic cardiomyopathy include a sudden death (fibrillation of ventricles) or chronic cardiac failure, thromboembolic syndrome.

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