State Budgetary Educational Institution of Higher Professional Education
« NORTH OSSETIAN STATE MEDICAL ACADEMY»
Health ministry of Russian Federation

Department of Pathological Anatomy and Forensic Medicine

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METHODICAL RECOMMENDATION

Theme: "DYSTROPHIES. GENERAL CHARACTERISTIC. MORPHOGENESIS.PARENCHYMAL DYSTROPHIES."

Knowledge of the topic is necessary for the assimilation of other topics from the course of pathological anatomy, as well as for clinical and anatomical analysis in the study of clinical disciplines and in the practical work of the doctor.

I. AIMS

It is necessary to know	• The definition of the term Dystrophy • Classification of dystrophies • Mechanisms of dystrophy development • Morphogenesis and morphological manifestations of parenchymal dystrophy
The student must be able to	• interpret morphological changes in cells and determine the main morphological characteristics of protein, fat and carbohydrate parenchymal dystrophy • to predict the outcome of these processes and assess their significance on the basis of the nature, extent, prevalence and localization of parenchymal dystrophy.

II. The required knowledges

1. Histological structure of the tissues

2. Biochemical metabolic processes

from the current lesson:

1. Morphogenetic mechanisms of development of dystrophy

2. Classification of dystrophies

3. Hyaline-droplet dystrophy: development mechanism, macro-and microscopic characteristics, outcome, functional value.

4. Hydropic dystrophy: development mechanism, macro-and microscopic characteristics, outcome, functional value.

5. Keratinization: development mechanism, macro-and microscopic characteristics, outcome, functional value.

6. Parenchymal lipidosis (fat dystrophy) : morphogenesis, microscopic diagnosis, functional value, outcome.

7. Parenchymatous carbohydrate dystrophy: morphology, microscopic diagnosis, the functional significance of the outcome.

III. Object of study :

Microscopic view:

1. Hyaline-droplet dystrophy of renal tubules (hematoxylin and eosin staining)

2. Hydropic degeneration of renal tubules (hematoxylin and eosin staining)

3. Fatty degeneration of the myocardium (stained with Sudan III)

Tables:

1. Hyaline droplet degeneration of the kidney

2. Hydropic degeneration of the kidney

3. Fatty liver dystrophy

IV. Information part

Dystrophy (from Greek. dys- disorder and tropho-feed) are the quantitative and qualitative structural changes in cells and/or intercellular substance of organs and tissues caused by disorder of metabolic processes. When dystrophies as a result of trophic disorders in cells or intercellular substance accumulate various metabolic products (proteins, fats, carbohydrates, minerals, water). The morphological nature of the dystrophies is expressed in:

- increasing or decreasing the amount of any substances contained in the body normally (for example, increasing the amount of fat in the fat depot);
- changes in the quality - the physical and chemical properties of substances inherent in the body normally (for example, changes in the tinctorial properties of collagen fibers with mucoid swelling and fibrinoid changes);
- the appearance of ordinary substances in an unusual place (for example, the accumulation of fat vacuoles in the cytoplasm of parenchymal cells in fatty dystrophy);
- appearance and accumulation of new substances which are not inherent to organ normally (for example, amyloid protein).

Thus, dystrophy is a morphological expression of metabolic disorders of cells and tissues.

Morphogenesis of dystrophies:

There are four mechanisms that can lead to dystrophy: infiltration, decomposition (phanerosis), distorted synthesis and transformation.

Infiltration is excessive penetration of metabolism products from the blood and lymph to cells or extracellular matrix and/or disorder of their inclusion in the metabolism, with further accumulation. For example, protein infiltration of epithelium of proximal tubules of kidney in nephrotic syndrome, lipoprotein infiltration of the intima of the aorta and large arteries in atherosclerosis.

Decomposition (phanerosis) – the distruction of chemical complexes. For example, the distruction of lipoprotein complexes and the accumulation of fat in the cell (fatty degeneration of cardiomyocytes in diphtheria intoxication). Disintegration of polysaccharide-protein complexes is the basis of fibrinoid changes in connective tissue in rheumatic diseases.

Transformation-the transition of one substance to another. For example the transformation of carbohydrates into triglycerides in diabetes, increased polymerization of glucose to glycogen etc.

Distorted synthesis is a synthesis in cells or tissues of substances that do not occur in them normally. This includes: the synthesis of an abnormal protein amyloid in the cell and the formation of abnormal protein-polysaccharide complexes of amyloid in intercellular substance, the synthesis of protein - alcoholic hyaline of hepatocytes, synthesis of glycogen in the epithelium of the thin segment of the nephron in diabetes.

Classification

There are several principles in classification of dystrophy:

I. I. Depending on localization and metabolic disorders
1. 1. parenchymatous;
2. 2. stromal-vascular;
3. 3. mixed.

II. II. Depending on disorder of metabolism type
1. 1. protein;
2. 2. lipid;
3. 3. carbohydrate;
4. 4. mineral.

III. III. Depending on genetic factors effect:
1. 1. acquired ;
2. 2. hereditary.

IV. IV. Depending on dissemination of process:
1. 1. general;
2. 2. local.

PARENCHYMATOUS DYSTROPHY

Parenchymatous dystrophy-a structural change in highly functional specialized cells associated with metabolic disorders.

One of the manifestations of metabolic derangements in cells is the intracellular accumulation of abnormal amounts of various substances. The stockpiled substances such as water, lipids, proteins, and carbohydrates, that accumulates in excess; but it also can be an abnormal substance, either exogenous, such as a mineral or products of infectious agents, or endogenous, such as a product of abnormal synthesis or metabolism. These substances may accumulate either transiently or permanently, and they may be harmless to the cells, but on occasion they are severely toxic. The substance may be located in either the cytoplasm (frequently within phagolysosomes) or the nucleus. In some instances the cell may be producing the abnormal substance, and in others it may be merely storing products of pathologic processes occurring elsewhere in the body.

Protein dystrophy.

Morphologically visible protein accumulation is less common than lipid accumulations; they may occur when excesses are presented to the cells or if the cells synthesize excessive amounts. Most of cytoplasmic proteins connected with lipids, forming lipoprotein complexes.

Changes in physical and chemical properties of substances lead to liquefactive transformation of cells (*from lat.* liquor – liquid), which means the disintegration of polypeptide chains into fragments, that leads to hydration of the cytoplasm. After damage to any etiology in the cell immediately increases the synthesis of proteins of the whole family – this is the so-called protein temperature shock. Among the temperature shock proteins, ubiquitin is most studied, which is supposed to protect other cell proteins from denaturation. Connecting with damaged proteins, it promotes their utilization and reconstruction of structural components of intracellular organelles. Serious damages and excessive accumulation of the complexes of ubiquitin-protein form cytoplasmic inclusions (for example Mallory bodies in hepatocytes – ubiquitin/keratin; Louis bodies in neurons in Parkinsonism – ubiquitin/neurofilament).

HYALINE DROPLETS DYSTROPHY characterized by appearance of large hyaline-like drops in cytoplasm. This drops can grow and coalesce. It leads to destruction of ultrastructural elements of the cell - focal coagulative necrosis. In kidney, for example, trace amounts of albumin filtered through the glomerulus re normally reabsorbed by pinocytosis in the proximal convoluted tubes. However, in disorders with heavy protein leakage across the glomerular filter (e.g. nephrotic syndrome), there is much larger reabsorption of protein, and vesicles containing this protein accumulate, giving the histologic appearance of pink, hyaline cytoplasmic droplets are metabolized and disappear.

In liver it also appear hyaline-like globules, it is so called alcoholic hyaline - irregular aggregates of microfibers and irregular forms of hyaline inclusions (Mallory bodies).

The outcome of this dystrophy is unfavorable: it ends with irreversible process, which leads to total coagulative necrosis and sharp function decrease of organs.

VACUOLAR DEGENERATION, HYDROPIC CHANGES. It is a difficult morphologic change to appreciate with the light microscope; it may be more apparent at the level of the whole organ. When it affects many cells, it causes some pallor, increased turgor, and increase in weight of the organ. On microscopic examination, small clear vacuoles may be seen within the cytoplasm; these represent distended and pinched-off segments of the ER. This injury is nonlethal, but can also lead to liquefactive necrosis. Swelling of cells is reversible. Cells may also show increased eosinophilic staining, which becomes much more pronounced with progression to necrosis.

Mechanism of the development of vacuolar dystrophy is very difficult and depend mainly on water and electrolyte metabolism disorder. An important role plays disorder of membranes permeability and their destruction.

KERATINIZATION

Another type of protein dystrophy is related with excessive keratinization of stratified epithelium (hyperkeratinization, ichthyosis) or formation of keratosis in tissues or substances in which keratosis do not occur normally – pathological keratinization of mucous membranes, (oral

mucosa for example (leukoplakia) etc.). Keratinization can be general or local; acquired or hereditary.

Causes of this types of dystrophy can be different: chronic inflammation, physical and chemical effects, congenital disorders of skin development, etc.

The outcome can be both; favorable – reconstruction of the tissue in case of etiological factor elimination, unfavorable – cell death.

Fatty dystrophy

All major classes of lipids can accumulate in cells: triglycerides, cholesterol/cholesterol esters, and phospholipids. We concentrate on triglyceride and cholesterol accumulations.
The terms steatosis and fatty change describe abnormal accumulations of triglycerides within parenchymal cells. Fatty change is often seen in the liver because it is the major organ involved in fat metabolism, but it also occurs in heart, muscle, and kidney.
The causes of steatosis include toxins, protein malnutrition, diabetes mellitus, obesity, and anoxia. In developed nations the most common causes of significant fatty change in the liver (fatty liver) are alcohol abuse and nonalcoholic fatty liver disease, which is often associated with diabetes and obesity.
Different mechanisms account for triglyceride accumulation in the liver. Free fatty acids from adipose tissue or ingested food are normally transported into hepatocytes. In the liver they are esterified to triglycerides, converted into cholesterol or phospholipids, or oxidized to ketone bodies. Some fatty acids are synthesized from acetate as well. Release of triglycerides from the hepatocytes requires association with apoproteins to form lipoproteins, which may then be transported from the blood into the tissues. Excess accumulation of triglycerides within the liver may result from excessive entry or defective metabolism and export of lipids. Several such defects are induced by alcohol, a hepatotoxin that alters mitochondrial and microsomal functions, leading to increased synthesis and reduced breakdown of lipids.

Morphology. Fatty change is most often seen in the liver and heart. In all organs fatty change appears as clear vacuoles within parenchymal cells. Intracellular accumulations of water or polysaccharides (e.g., glycogen) may also produce clear vacuoles.
Liver. In the liver, mild fatty change may not affect the gross appearance. With progressive accumulation, the organ enlarges and becomes increasingly yellow until, in extreme instances, the liver may weigh two to four times normal and be transformed into a bright yellow, soft, greasy organ.
Fatty change begins with the development of minute, membrane-bound inclusions (liposomes) closely applied to the ER. Accumulation of fat is first seen by light microscopy as small vacuoles in the cytoplasm around the nucleus. As the process progresses the vacuoles coalesce, creating cleared spaces that displace the nucleus to the periphery of the cell. Occasionally contiguous cells rupture and the enclosed fat globules coalesce, producing so-called fatty cysts.
Heart. Lipid is found in cardiac muscle in the form of small droplets, occurring in two patterns. In one, prolonged moderate hypoxia, such as that produced by profound anemia, causes intracellular deposits of fat, which create grossly apparent bands of yellowed myocardium alternating with bands of darker, red-brown, uninvolved myocardium (tigered effect). The other pattern of fatty change is produced by more profound hypoxia or by some forms of myocarditis (e.g., diphtheria infection) and shows more uniformly affected myocytes.

Carbohydrate dystrophy

The cause of carbohydrate dystrophy is disorder of glycogen and glycoprotein metabolism. Glycogen is a readily available energy source stored in the cytoplasm of healthy cells. Excessive intracellular deposits of glycogen are seen in patients with an abnormality in either glucose or glycogen metabolism. Whatever the clinical setting, the glycogen masses appear as clear vacuoles within the cytoplasm. Glycogen dissolves in aqueous fixatives; for its localization, tissues are best fixed in absolute alcohol.

Diabetes mellitus is the prime example of a disorder of glucose metabolism. In this disease glycogen reserve of tissues is poor, because of β cells of pancreas pathology. First of all glycogen synthesis in liver decrease and it leads to fatty accumulation of hepatocyte. Meanwhile in nucleus appear glycogen inclusions. This inclusions become light – so called "empty nucleuses". Glycogen accumulate in epithelial tissue of convoluted tubule of nephron, glomerulus and nephron's capillaries are also damaged.

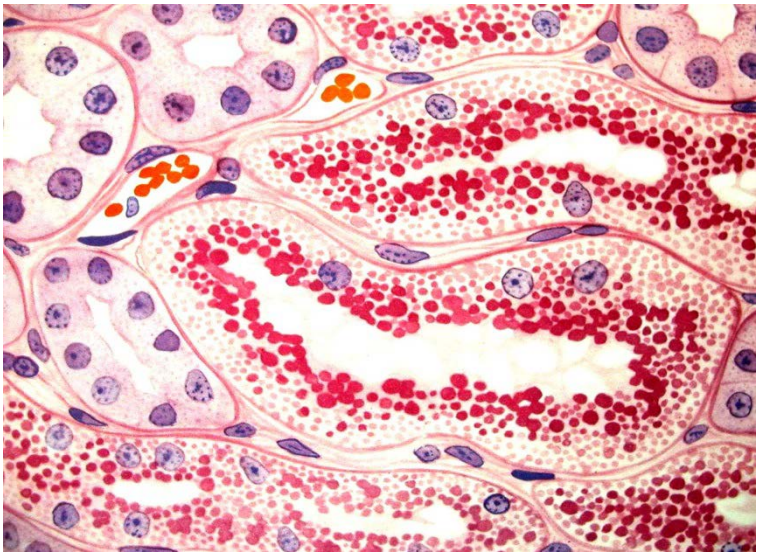
Glycogen accumulates within the cells in a group of related genetic disorders that are collectively referred to as the glycogen storage diseases, or glycogenoses. In these diseases enzymatic defects in the synthesis or breakdown of glycogen result in massive accumulation, causing cell injury and cell death.

There are several types of glycogen genetic disorders: Hepatic type - Gierke disease (type I); Myopathic type - McArdle syndrome (type V); Miscellaneous types Pompe disease (type II); Glycogen storage disease type III – Forbes – Cori disease.

I. Practical part

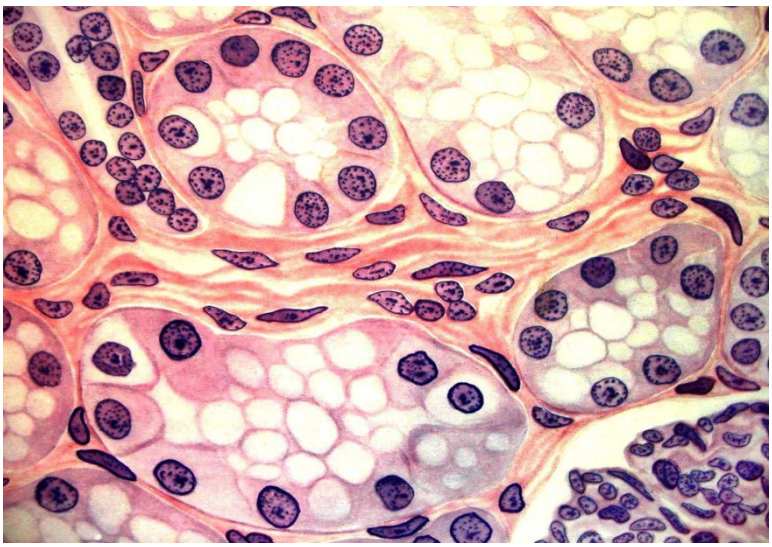
1. Hyaline droplets dystrophy in epithelial tissue of convoluted tubule.

Sketch microscopic view and describe.
Haematoxylin and eosin stain

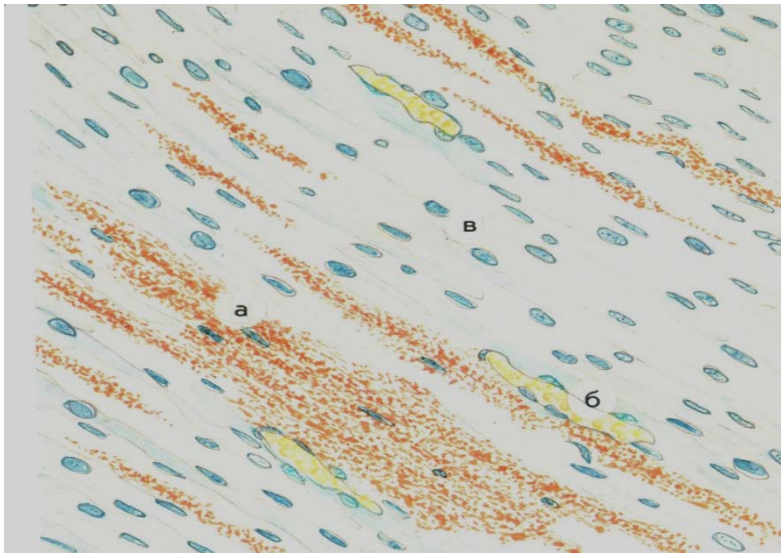


2. Hydropic dystrophy in epithelial tissue of convoluted tubule.

Sketch microscopic view and describe.
Haematoxylin and eosin stain



3. **Fatty dystrophy of cardiac muscle cells.**
   Sketch microscopic view and describe.
   Sudan III stain.



Theme: "STROMAL-VASCULAR DYSTROPHY"

Stromal-vascular protein dystrophy.

There are several types of protein dystrophy:

- Mucoid distrophy
- Fibrinoid distrophy
- Hyalinosis
- Amyloidosis

Mucoid distrophy, fibrinoid dystrophy and hyalinosis are the stages of connective tissue disorganization.

Amyloidosis is the result of infiltration with protein-polysaccharide complexes include abnormal, not found in normal fibrillar protein amyloid that is synthesized by special cells amyloidblast.

Mucoid distrophy is an increase in the number and redistribution of mucopolysaccharides, mainly glycosaminoglycans, in the main substance of the connective tissue. Accumulation of glycosaminoglycans always begins with damage of the microcirculatory vessels, which leads to the development of tissue hypoxia, activation of hyaluronidase and weakening of the connection between glycosaminoglycans and protein.

Glycosaminoglycans have pronounced hydrophilic properties, which against the background of increased vascular tissue permeability leads to hydration (swelling) of the main substance of the connective tissue. At the same time, the concentration of proteoglycans and glycoproteins increases.

Mucoid distrophy develops most often in the walls of arteries, heart valves, endo - and epicardium, in joint capsules.

Etiology:

- Infection
- Allergy
- Connective tissue disease (rheumatism, systemic lupus erythematosus, rheumatoid arthritis etc.)
- Atherosclerosis
- Hypertension
- Hypoxia

Mucoid dystrophy is reversible process. If the pathogenic factor would be removed, a complete restoration of the structure and function is possible, but if the pathogenic effect continues mucoid distrophy may progress in fibrinoid dystrophy. Function of the organ, where mucoid distrophy develops disturbed slightly.

Fibrinoid dystrophy is irreversible disorganization of connective tissue, which is based on the disintegration of the protein (collagen, fibronectin, laminin), which leads to the destruction of its main substance and fibers, accompanied by an increase in vascular permeability and the formation of fibrinoid.

Fibrinoid is a complex substance formed by proteins and polysaccharides, decaying collagen fibers, as well as plasma proteins and nucleoproteins of destroyed connective tissue cells. A mandatory component of fibrinoid is fibrin.

The mechanism of development is infiltration and decomposition.

Macroscopically, the organs and tissues in which fibrinoid distrophy develops are the same as healthy. Microscopically in the area of fibrinoid changes revealed destruction of collagen fibers and fibrins.

Fibrinoid dystrophy can be local and systemic.

Systemic can be seen in:

- infectious diseases (fibrinoid of vessels in tuberculosis);
- allergic and autoimmune diseases (rheumatic diseases, glomerulonephritis);
- in hypertensive disease and arterial hypertension.

Locally fibrinoid is detected in chronic inflammation. For example, in the bottom of chronic gastric ulcer, trophic skin ulcers.

As the outcome of fibrinoid distrophy sometimes develops fibrinoid necrosis, characterized by complete destruction of connective tissue. Around the foci of necrosis is usually expressed reaction of macrophages. In the future, the focus of destruction is replaced by connective tissue (sclerosis) or hyalinosis. Fibrinoid dystrophy leads to function disturbance of function of the organs.

Hyalinosis in the connective tissue formed a homogeneous translucent tight mass (hyaline), resembling hyaline cartilage.

Classification:

- Hyalinosis of vessels
- Hyalinosis of connective tissues

Etiology:

- Hypertension
- disease accompanied by hypertension (kindey diseases, tumors of endocrine and sex glands)
- diabetes
- connective tissue diseases
- atherosclerosis

Mechanisms:

- the destruction of fibrous structure
- increased vascular permeability

Increased vascular permeability leads to impregnation of tissue with plasma proteins and their adsorption on fibrous structures followed by precipitation and the formation of protein – hyaline.

Hyalinosis of small vessels is systemic change, but mostly expressed in brain`s, kindey`s, retina`s, skin`s and pancreas arteries.

Microscopically arteries turned to thick tube with a narrow lumen.

This process irreversible and it leads to atrophy, deformation and total loss of function of the organ. Vessels become fragile and hemorrhages develops in organs.

Systemic hyalinosis of connective tissue and vessels usually develops in the outcome of fibrinoid distrophy, leading to the destruction of collagen and tissue impregnation with plasma proteins and polysaccharides. This mechanism is a part of pathogenesis of immune disorders (rheumatic diseases).

Local hyalinosis develops in scars, in artery wall as an outcome of atherosclerosis, in organization of thrombus, infarction, in ulcer recovering, in stroma of a tumor etc. Local hyalinosis caused by metabolic disorders of connective tissue.

Microscopy. Collagen fibers loose their structure and become monomorphic cartilage-like mass, cellular components compressed.

Macroscopy. Fibrous connective tissue becomes dense, cartilaginous, whitish, translucent.

Outcome. In most cases, unfavorable due to the irreversibility of the process, but the resorption of hyaline masses possible. Thus, hyaline in the scars – the so-called keloids-may be resorpted. Breast hyalinosis can be also reversible in case of glands hyperfunction.

Meaning. Hyalinosis can be a cause of organs or tissue disfunction. Hyalinosis in scars do not cause disfunction.

Amyloidosis is a group of diseases in which abnormal protein, known as amyloid fibrils, builds up in tissue and it caused by hard protein metabolism disorders.

Classification of amyloidosis.

1. Depending on the type of specific amyloid protein: AA-, AL-, ATTR (FAP), ASC (SSA)-amyloidosis;
2. Depending on etiology: primary, secondary, hereditary, senile;
3. Depending on localization: general, local.

Morphogenesis.

- Cellular transformation of mononuclear phagocyte system with appearance of amyloidoblasts, which are able to synthesize amyloid protein;
- Synthesis of main amyloid component by amyloidoblasts
- Aggregation of this protein and formation of the base for amyloid substance
- The connection of aggregated fibers with plasma proteins and glycosaminoglycans
- As the result formation of complex protein – amyloid

Types of amyloid

Types of amyloid	main source	diseases	localization
AL	light chains of immunoglobuline	Primary amyloidosis Multiple myeloma B-cell lymphoma	tongue, heart, gastrointestinal tract, liver, spleen, kidney
AA	A protein (α_1-globuline)	rheumatoid arthritis	tongue, heart, gastrointestinal tract
AA	A protein (α_1-globuline)	Chronic infections (tuberculosis, leprosy, bronchiectasis, chronic osteomyelitis) Hodgkin's lymphoma	liver, spleen, kidney

		urinary bladder infection	
AA	A protein (α_1-globuline)	Familial Mediterranean fever	liver, spleen, kidney
AF	prealbumine	familial amyloidosis	**peripheral nervous system,** kidney
AS	prealbumine	heart amyloidosis senile amyloidosis cerebral amyloid angiopathy	heart heart spleen pancreas brain vessels
AE	predecessor of peptide hormones (ex. Calcitonin)	thyroid cancer adenoma of pancreatic islets	tumor
AD	Неизвестен	Lichenoid amyloidosis	skin (derma)
Альцгеймер	A4 peptide* or protein predecessor of beta amyloid	**Alzheimer's disease** Down syndrome	brain vessels angiopathy

The fragments or actual proteins are at risk of misfolding as they are synthesized, to make a poorly functioning protein. This causes proteolysis, which is the directed breakdown of proteins by cellular enzymes called proteases or by intramolecular digestion; proteases come and digest the misfolded fragments and proteins. The problem occurs when the proteins do not dissolve in proteolysis because the misfolded proteins sometimes become robust enough so that they are not dissolved by normal proteolysis. When the fragments do not dissolve, they get spit out of proteolysis and aggregate to form oligomers. The reason they aggregate is that the parts of the protein that do not dissolve in proteolysis are hydrophobic β-pleated sheets. They are usually sequestered in the middle of the protein, while parts of the protein that are more soluble are found near the outside. When they are exposed to water, these hydrophobic pieces tend to aggregate with other hydrophobic pieces. This ball of fragments gets stabilized by GAGs (glycosaminoglycans) and SAP (serum amyloid P), a component found in amyloid aggregations that is thought to stabilize them and prevent proteolytic cleavage. The stabilized balls of protein fragments are called oligomers. The oligomers can aggregate together and further stabilize to make amyloid fibrils.

Both the oligomers and amyloid fibrils are toxic to cells and can interfere with proper organ function.

The appearance of organs in amyloidosis depends on the degree of development of the process. If the amyloid deposits are small, the appearance of the organ changes little and amyloidosis is diagnosed only with microscopic examination. With pronounced amyloidosis, the organs increase in volume, pale, with a greasy luster (hepatosplenomegaly, cardiomegaly, thickening of the peripheral nerves, macroglossia). Damaged tissues have a denser consistency and reduced elasticity compared to normal tissues. Therefore, blood vessels affected by amyloidosis may not contract sufficiently and tend to bleed if damaged; therefore, a diagnostic biopsy may be accompanied by bleeding.

In *spleen* amyloidosis usually infiltrates lymph nodes and as well all over the pulp. In the first case, the amyloid modified follicles of the enlarged and dense spleen on the section have the form of translucent grains (sago spleen). In the second case, the spleen is enlarged, dense, brown-red, smooth, has a greasy luster on the cut (sebaceous spleen). The sago and sebaceous spleen represent stages of the process.

Kidney amyloid is infiltrates the walls of the afferent and efferent arterioles, capillary loops and in the basal membranes of the tubules and the stroma. Kidneys become dense, large and "greasy." As the process increases, the glomeruli are completely replaced by amyloid, connective tissue grows and amyloid renal scarring develops.

In *liver* deposition of amyloid is observed in the walls of blood vessels, ducts and in the connective tissue of the portal tracts, in the reticular stroma of the lobules. As the accumulation of amyloid liver cells atrophy and die. In this case, the liver is enlarged, dense, looks "greasy".

In *bowel*, amyloid infiltrates the stroma of the villi of the mucous membrane, as well as in the walls of the vessels of both the mucous membrane and the submucosal layer. With pronounced amyloidosis, the glandular apparatus of the intestine atrophies.

Amyloidosis of the *adrenal glands*, usually bilateral, deposition of amyloid appears in the cortical substance in the course of the blood vessels and capillaries.

In *heart muscle*, amyloid is found under the endocardium, in the fibers and vessels of the stroma, as well as in the epicardium along the veins. The deposition of amyloid in the heart leads to amyloid cardiomegaly. It becomes very dense, the myocardium becomes greasy.

In *skeletal muscles*, as in the myocardium, amyloid falls in the course of intermuscular connective tissue, in the walls of blood vessels and nerves (perivascular and perineural). Muscles become dense, translucent.

The outcome of amyloidosis is anfavourable. This process is irreversible and pronounced amyloidosis leads to dystrophy and atrophy of the parenchyma and sclerosis of the stroma of the organs, to their functional failure. In severe amyloidosis is most frequently observed chronic renal, rarely – liver, heart, lung, adrenal, intestine (malabsorption syndrome) failure.

STROMAL-VASCULAR FAT DISTROPHHY

Stromal-vascular fat dystrophy occur in violation of the exchange of fat (neutral fats) or cholesterol and its esters.

Disorder of neutral fat exchange

Neutral fats are labile fats that provide energy reserves of the body. In the free state, they are localized in the fat cells of the fat depot: subcutaneous, retroperitoneal and mediastinal tissue, mesentery, omentum, epicardium, bone marrow. Adipose tissue performs not only metabolic, but also supporting, mechanical function, so it is able to replace atrophied tissue. Reserves of adipose tissue increases because of neutral fat exchange disorders.

Obesity is an increase in the amount of neutral fats in fat depots. Mostly it is expressed in excess fat in the subcutaneous tissue, omentum, mesentery, mediastinum, epicardium.

There are several types of obesity:

- Primary
- Secondary :
    - Alimentary (nutritional) obesity
    - Cerebral (tumor, especially hypothalamus
    - Endocrine (Cushing`s disease, hypothyroidism, hypogonadism)
    - Genetic (Glycogen storage disease type I)

There are four stages of obesity:

- I stage – excess body weight up to 30%;
- II stage – excess body weight up to 50%;
- III stage – excess body weight up to 99%;
- IV stage – excess body weight from 100% and more.

The number and size of adipositіes there are two option:

- hypertrophic;
- hyperplastic.

In hypertrophic number of adipocyte stays the same, but size of the cells increase as they contain a lot of triglycerides. In hyperplastic type number of cells increase, but metabolis disorders in them are not found.

Obesity of the heart has a great clinical meaning. Adipose tissue grows under the epicardium and between the muscle bundles, squeezing them and covering. This leads to atrophy of the muscle fibers. Usually obesity is pronounced in the right half of the heart, which leads to the replacement of the myocardium with adipose tissue. It is possible that heart rupture can occur.

The outcome of General obesity is rarely favorable.

Metabolic cholesterol and its esters disorder

Metabolic disorders of cholesterol and its esters are the basis of widespread worldwide disease – atherosclerosis. With hypercholesterolemia, it penetrates from the blood into the intima of the vessels. Cholesterol in microscopic examination in polarized light gives a characteristic picture: its crystals have a positive double refraction. β-low-density lipoproteins and the proteins of blood plasma also accumulate in vessels intima. The accumulated substances further disintegrate, acting toxically, they lead to necrosis of intima. In the intima is formed fat-protein detritus (athere is pasty mass), and then grows connective tissue (sclerosis) and formed plaque.

STROMAL VASCULAR CARBOHYDRATE DISTROPHIES

Stromal-vascular carbohydrate dystrophy may be associated with of glycoproteins and glycosaminoglycans metabolism disorder. Stromal-vascular carbohydrate dystrophy associated with the accumulation of glycoproteins. In contrast to the mucoid distrophy, this process is the replacement of collagen fibers in mucoid mass. Fibrous connective tissue, stroma organs, adipose tissue, cartilage become swollen, translucent, mucosa-like, and their cells have a stellate appearance.

Etiology:

- dysfunction of the endocrine glands (myxedema in case of thyroid gland failure)
- cachexia of any genesis.

Outcome. The process can be reversible. Its progression leads to the liquefactive necrosis of tissue with the formation of cavities filled with mucus.

The value is determined by the severity of the process, its duration and the nature of the tissue.

Mixed distrophies

Mixed distrophy called such distrophies, in which metabolic disorders are observed both in the parenchyma of organs and stroma. They occur in violation of the exchange of complex proteins-chromoproteins. Mixed distrophies also includes metabolic disorders of minerals.

All organs and tissues of the animal and plant world have a particular color, which is due to the presence of substances of a certain color in them. Some of these substances can be dissolved in tissues and are not available for morphological determination, others have the form of grains, crystals, drops, which are able to histochemical determination. And in fact, in both cases, we are talking about pigmentation. But not every tissue`s color or changes are due to the ratio of the pigment or the disappearance of it. Shades of color of muscles, liver, kidneys, lungs, etc. are primarily related to blood circulation or with structural changes, with different contents of water, fat, glycogen, etc. These changes in shades of color irrelevant to the question of the pigmentations are not.

Endogenous pigments are divided into three groups:

1. Hemoglobin and its derivatives;

2. Proteinogenic or tyrosine - associated with the exchange

tyrosine and tryptophan;

3. Formed in connection with the exchange of fat.

Hemoglobin - is the iron-containing oxygen-transport metalloprotein in the red blood cells. The rupturing of red-blood cells is called *hemolysis.* Hemolysis essentially a physiological phenomenon associated with aging of erythrocytes and their continuous destruction under the influence of physiological hemolysin, especially in conditions of slow flow or stop it in the sinuses of the spleen, liver, and bone marrow.

Free hemoglobin doesn`t make any toxic effect on tissues. But in the transition to methemoglobin under the influence of some hemolytic factors (arsin, potassium chlorat, anaerobic infection, long-term crush syndrome, etc.) manifestation of methemoglobinemia and methemoglobinuria are fatal. Methemoglobin leads to severe disruption of tissue respiration due to the difficulty of oxygen dissociation. And the resulting kidney damage (hemoglobinuric nephrosis) ends with acute renal failure (anuria and uremia).

The outcome of physiological lysis of red blood cells is formation of pigments – ferritin, hemosiderin, bilirubin.

In pathological conditions some new pigments may occur such as hematoidin, hematin, porphyrin.

An increase in the total amount of iron in the body is observed in hemosiderosis and hemochromatosis. Excess iron accumulates in macrophages and parenchymal cells in the form of ferritin and hemosiderin and can cause damage to parenchymal cells.

Ferritin-ferroproteide (conjugated protein) containing up to 23% iron. Ferritin iron is associated with a protein called apoferritin.

There is an inactive (oxidized) form of ferritin – SS-ferritin.

With a lack of oxygen, the recovery of ferritin in active form – N-ferritin, which has vasopressive and hypotensive properties.

Depending on the origin there are two types of ferritin: anabolic and catabolic. Anabolic ferritin is formed from iron, absorbed in the intestine. Catabolic – iron grossly hemolysis of erythrocytes.

Ferritin has antigenic characteristics. A large amount of ferritin is found in the liver (ferritin depot), spleen, bone marrow and lymph nodes, where its exchange is associated with the synthesis of hemosiderin, hemoglobin and cytochromes. In pathological conditions amount of ferritin may increase both in circulating blood and in tissues. Ferritinemia explain the irreversibility of shock, accompanied by vascular collapse, as SH-ferritin acts as an antagonist of adrenaline.

DISORDER OF HEMOSIDERIN METABOLISM.

Hemosiderin or haemosiderin is an iron-storage complex. It is only found within cells (as opposed to circulating in blood) and appears to be a complex of ferritin, denatured ferritin and other material. The iron within deposits of hemosiderin is very poorly available to supply iron when needed. Hemosiderin can be identified histologically with "Perls' Prussian-blue" stain. In normal animals, hemosiderin deposits are small and commonly inapparent without special stains. Excessive accumulation of hemosiderin is usually detected within cells of the mononuclear phagocyte system (MPS) or occasionally within epithelial cells of liver and kidney.

Several disease processes result in deposition of larger amounts of hemosiderin in tissues; although these deposits often cause no symptoms, they can lead to organ damage.

Hemosiderin is most commonly found in macrophages and is especially abundant in situations following hemorrhage, suggesting that its formation may be related to phagocytosis of red blood cells and hemoglobin. Hemosiderin can accumulate in different organs in various diseases.

Haemosiderin often forms after bleeding (haemorrhage). When blood leaves a ruptured blood vessel, the red blood cell dies, and the haemoglobin of the cell is released into the extracellular space. Phagocytic cells (of the mononuclear phagocyte system) called macrophages engulf (phagocytose) the haemoglobin to degrade it, producing haemosiderin and biliverdin. Excessive systemic accumulations of haemosiderin may occur in macrophages in the liver, lungs, spleen, kidneys, lymph nodes, and bone marrow. These accumulations may be caused by excessive red blood cell destruction (haemolysis), excessive iron uptake/hyperferraemia, or decreased iron utilization (e.g. anaemia of copper toxicity) /uptake hypoferraemia (which often leads to iron deficiency anaemia).

This process can be local – erythrocyte distruction ocurrs out of the vessels (hematoma). Local hemosiderosis can occur within not only the area of tissue (hematoma), but also the whole organ. This is a hemosiderosis of the lungs, occurs when the mitral heart defect.

General hemosiderosis is observed in intravascular destruction of red blood cells (intravascular hemolysis).

Causes of common hemosiderosis:

- diseases of the organs of hematopoiesis (anemia, hematological malignancies);
- intoxication caused by hemolytic poisons (saponins, snake venom, acetic acid, potassium chlorate salt, arsenical hydrogen, some types of mushrooms) and salts of heavy metals (Pb);
- some infectious diseases (sepsis, malaria, brucellosis, anaerobic infections, some spirochaetes, e.g. relapsing fever , syphilis, etc.));
- ABO-incompatible blood transfusion and bacterial contaminated blood

Iron overload (hemochromatosis)

Hemochromatosis is close to the general hemosiderosis, a disease, the main difference between which is the degree of iron overload and the presence of damage to parenchymal cells.

Hemochromatosis can be *primary* and *secondary.*Primary hemochromatosis - disease of accumulation. It is transmitted by autosomal dominant and is associated with a hereditary defect of intestine enzymes, which leads to increased absorption iron from food, which in the form of hemosiderin is deposited in large amount in the organs.

The main symptoms of the disease are:

- bronze color of the skin;
- diabetes mellitus (bronze diabetes);
- pigmentary cirrhosis of the liver, leading to liver failure;
- pigmented cardiomyopathy, which can cause death.

Secondary hemochromatosis – occurs in case of acquired enzymes failure, which provide the exchange of iron and leads to general hemosiderosis. Cause of this process may be excessive consumption of iron from food (iron-containing drugs), gastric resection, chronic alcoholism, repeated blood transfusions, etc.

Clinical manifestation are almost the same as in primary hemochromatosis

- diabetes mellitus (bronze diabetes);
- pigmentary cirrhosis of the liver, leading to liver failure;
- pigmented cardiomyopathy, which can cause death.

DISORDER OF BILIRUBIN METABOLISM.

Bilirubin is a yellow compound that occurs in the normal catabolic pathway that breaks down heme in vertebrates. This catabolism is a necessary process in the body's clearance of waste products that arise from the destruction of aged red blood cells. First the hemoglobin gets stripped of the heme molecule which thereafter passes through various processes of porphyrin catabolism, depending on the part of the body in which the breakdown occurs. For example, the molecules excreted in the urine differ from those in the feces. The production

of biliverdin from heme is the first major step in the catabolic pathway, after which the enzyme biliverdin reductase performs the second step, producing bilirubin from biliverdin.

Bilirubin is excreted in bile and urine, and elevated levels may indicate certain diseases. It is responsible for the yellow color of bruises and the yellow discoloration in jaundice. Its subsequent breakdown products, such asstercobilin, cause the brown color of faeces. A different breakdown product, urobilin, is the main component of the straw-yellow color in urine.

BilIrubin is transported by blood to the liver in

- unbound form (indirect or unbound bilirubin, unconjugated))
- in combination with albumin (direct or associated bilirubin, conjugated).

Indirect (unbound) bilirubin is soluble in lipids. In the liver, bilirubin enzymatically binds to glucuronic acid, forming a water-soluble direct (bound) bilirubin, which is excreted by the liver cells into the bile, and then enters the intestine (cholebilirubin). In the intestine, due to bacterial activity, it is converted into urobilinogen, which is then excreted in one of three ways.

Ways of excretion of urobilinogen:

1. Directly excreted in the feces (as stercobilin);

2. When absorbed from the intestine into the bloodstream, enters the liver and is re-excreted in the bile (enterohepatic circulation);

3. Normal in small amounts excreted in the urine as urobilin.

The symptom complex, characterized by an increase in the amount of bilirubin in the blood with its accumulation in the tissues and jaundice staining of the skin, sclera, mucous membranes, serous membranes and internal organs is called jaundice, also known as icterus.

Mechanism	Definition
pre-hepatic	the pathology is occurring prior to the liver due to either: a. intrinsic defects in red blood cells b. extrinics causes external to red blood cells
hepatic/hepatocellular	parenchymal cells diseases of liver
post-hepatic	pathology located after the conjugation of bilirubin in the liver due to obstruction

Pre-hepatic . Pre-hepaticular jaundice is caused by anything that causes an increased rate of hemolysis (breakdown of red blood cells). Unconjugated bilirubin comes from the breakdown of the heme pigment found in red blood cells' hemoglobin. The increased breakdown of red blood cells leads to an increase in the amount of unconjugated bilirubin present in the blood and deposition of this unconjugated bilirubin into various tissues can lead to a jaundiced appearance. In tropical countries, severe malaria can cause jaundice in this manner. Certain genetic diseases,

such as sickle cell anemia, spherocytosis, thalassemia,pyruvate kinase deficiency, and glucose 6-phosphate dehydrogenase deficiency can lead to increased red cell lysis and therefore hemolytic jaundice. Commonly, diseases of the kidney, such as hemolytic uremic syndrome, can also lead to coloration.

In jaundice secondary to hemolysis, the increased production of bilirubin leads to the increased production of urine-urobilinogen. Bilirubin is not usually found in the urine because unconjugated bilirubin is not water-soluble, so, the combination of increased urine-urobilinogen with no bilirubin (since, unconjugated) in urine is suggestive of hemolytic jaundice.

Laboratory findings include:

- Urine: no bilirubin present, urobilinogen > 2 units (i.e., hemolytic anemia causes increased heme metabolism; exception: infants where gut flora has not developed).
- Serum: increased unconjugated bilirubin.
- Kernicterus is associated with increased unconjugated bilirubin not carried by albumin. Newborns are especially vulnerable to this due to increased permeability of the blood brain barrier.

Hepatocellular (hepatic) jaundice can be caused by acute or chronic hepatitis, hepatotoxicity, cirrhosis, drug-induced hepatitis and alcoholic liver disease. Cell necrosis reduces the liver's ability to metabolize and excrete bilirubin leading to a buildup of unconjugated bilirubin in the blood. Other causes include primary biliary cirrhosis leading to an increase in plasma conjugated bilirubin because there is impairment of excretion of conjugated bilirubin into the bile. The blood contains an abnormally raised amount of conjugated bilirubin and bile salts, which are excreted in the urine. Jaundice seen in the newborn, known as neonatal jaundice, is common in newborns as hepatic machinery for the conjugation and excretion of bilirubin does not fully mature until approximately two weeks of age. Rat fever (leptospirosis) can also cause hepatic jaundice. In hepatic jaundice, there is invariably cholestasis. Defects in bilirubin metabolism also leads to jaundice, as in Gilbert's syndrome (a genetic disorder of bilirubin metabolism that can result in mild jaundice, which is found in about 5% of the population) andCrigler-Najjar syndrome, Type I and II.

Laboratory findings depend on the cause of jaundice.

- Urine: Conjugated bilirubin present, urobilinogen > 2 units but variable (except in children). Kernicterus is a condition not associated with increased conjugated bilirubin.
- Plasma protein show characteristic changes.
- Plasma albumin level is low but plasma globulins are raised due to an increased formation of antibodies.

Bilirubin transport across the hepatocyte may be impaired at any point between the uptake of unconjugated bilirubin into the cell and transport of conjugated bilirubin into biliary canaliculi. In addition, swelling of cells andoedema due to inflammation cause mechanical obstruction of intrahepatic biliary tree. Hence in hepatocellular jaundice, concentration of both unconjugated and conjugated bilirubin rises in the blood. In hepatocellular disease, there is usually interference in all major steps of bilirubin metabolism—uptake, conjugation and excretion. Excretion is the rate-limiting step, however, and usually impaired to the greatest extent. As a result, conjugated hyperbilirubinaemia predominates.

The unconjugated bilirubin still enters the liver cells and becomes conjugated in the usual way. This conjugated bilirubin is then returned to the blood, probably by rupture of the congested bile canaliculi and direct emptying of the bile into the lymph leaving the liver. Thus, most of the bilirubin in the plasma becomes the conjugated type rather than the unconjugated type, and this

conjugated bilirubin, which did not go to intestine to become urobilinogen, gives the urine the dark color.

Post-hepatic jaundice, also called obstructive jaundice, is caused by an interruption to the drainage of bile containing conjugated bilirubin in the biliary system. The most common causes are gallstones in the common bile duct, and pancreatic cancer in the head of the pancreas. Also, a group of parasites known as "liver flukes" can live in the common bile duct, causing obstructive jaundice. Other causes include strictures of the common bile duct, biliary atresia, cholangiocarcinoma, pancreatitis, cholestasis of pregnancy, andpancreatic pseudocysts. A rare cause of obstructive jaundice is Mirizzi's syndrome (gallstone impaction in the cystic duct or gallbladder neck, with the enlarged gallbladder squeezing on the common hepatic duct).

In complete obstruction of the bile duct, no urobilinogen is found in the urine, since bilirubin has no access to the intestine and it is in the intestine that bilirubin gets converted to urobilinogen by microorganisms, with the urobilinogen later being partially reabsorbed from the intestine into the general circulation, and then excreted into the urine. In this case, presence of bilirubin (conjugated) in the urine without urine-urobilinogen suggests obstructive jaundice, either intra-hepatic or post-hepatic.

The presence of pale stools and dark urine suggests an obstructive or post-hepatic cause as normal feces get their color from bile pigments. They can, however, occur in many intra-hepatic illnesses and are therefore not a reliable clinical feature to distinguish obstruction from hepatic causes of jaundice.

Patients also can present with elevated serum cholesterol, and often complain of severe itching or "pruritus" because of the direct and indirect effects of pruritogens in bile such as bile salts.

No single test can differentiate between various classifications of jaundice. A combination of liver function tests is essential to arrive at a diagnosis.

DISORDER OF HEMATOIDIN, HEMATIN, HEMATOPORFIRINE METABOLISM.

Hematoidin- is iron-free pigment crystals which have the form of bright orange rhombic plates or needles, rarely – grains. It occurs with the breakdown of red blood cells and intracellular destruction of hemoglobin, 5-10 days after hemosiderin, but unlike hemosiderin does not remain in the cells and after their death is free lying among the necrotic masses. Chemically, it is identical to bilirubin. Hematoidin has no special clinical significance

Hematins are an oxidized form of heme and are formed by hydrolysis of oxyhemoglobin. They have the form of dark brown or black diamond-shaped crystals or grains, give double refraction in polarized light (anisotropic), contain iron in a bound state.

Hematoporphyrin -fluorescent pigment, similar in structure to bilirubin, contains iron, however, is not determined by conventional histochemical methods. Normally, a small amount is contained in the blood and urine, plays the role of an antagonist of melanin and increases the sensitivity of the skin to light. Metabolic disorders of porphyrin lead to growth of its content in the blood (porphyrinuria) and in urine (porphyrinuria). Urine, that contains large amounts of porphyrin becomes red. The pigment is also found in the feces. This condition is called porphyria.

Causes of porphyria:

- intoxication (Pb, sulfonal, barbiturates intoxication);

- deficiency of PP vitamin (pellagra);
- congenital defects of metabolic disorders - porphyria congenita.

Melanin - is a broad term for a group of natural pigments found in most organisms. Melanin is produced by the oxidation of the amino acid tyrosine, followed by polymerization. The melanin pigments are produced in a specialized group of cells known as melanocytes. Melanocytes and melanophages contained in epidermis, dermis, iris and retina of the eye, in pia mater. Amout of melanin in tissues depends on the individual and racial characteristics. Regulation of melanogenesis is carried out by the nervous and endocrine systems. Its formation is stimulated by ultraviolet rays. The appearance of a tan is a protective adaptive biological response. Melanin is excreted by the kidneys and intestines.

Metabolic disorders of melanin are expressed in its enhanced formation or its disappearance. There are acquired and congenital melanosis. It can be local and general.

General acquired hypermelanosis in the clinic is manifested in the form of skin hyperpigmentation.

Causes of common acquired hypermelanosis:

- tuberculosis or tumor of adrenal gland (f.e. Addison's disease), amyloidosis;
- endocrine disorders (hypogonadism, hypopituitarism);
- deficiency of vitamin (pellagra, scurvy);
- hydrocarbon intoxication.

Common congenital hypermelanosis (pigment xeroderma) is characterized by increased sensitivity of the skin to ultraviolet rays and is expressed in spotty pigmentation of the skin with hyperkeratosis and edema.

Local acquired hypermelanosis. Examples:

- melanosis of the colon (in people with chronic constipation);
- pigmented skin spots (freckles, lentigo);
- focal hyperpigmentation in pituitary gland adenomas, hyperthyroidism, diabetes mellitus,
- pigment nevus, melanomas.

General hypomelanosis or *albinism* (from lat. albus – white), is associated with hereditary deficiency of tyrosinase. Albinism is manifested by the absence of melanin in the hair follicles, epidermis and dermis, in the retina and iris.

Local acquired hypomelanosis (vitiligo). Reasons:

- leprosy;
- syphilis;
- diabetes;
- hyperparathyroidism.

Theme: "CELL INJURY AND APOPTOSIS"

Knowledge of the topic is necessary for the assimilation of other topics from the course of pathological anatomy, as well as for clinical and anatomical analysis in the study of clinical disciplines and in the practical work of the doctor.

III. AIMS

It is necessary to know	• Causes and mechanisms of development of different types of necrosis, their functional significance • Morphological differences of necrosis from other pathological processes
The student must be able to	• See the difference between necrosis and other pathological processes
The student must possess	Knowledge of anatomical pathology to understand morphogenesis and to be able to diagnose necrosis

IV. The required knowledges

1. Histological structure of the tissues

2. Biochemical metabolic processes

3. The definition of dystrophy.

4. Morphogenetic mechanisms of development of dystrophy

from the current lesson:

1. The definition of necrosis.

2. Sages of necrotic process.

3. Ethiological and pathogenetical types of necrosis, mechanisms of their development.

4. Morphological forms of necrosis and their macroscopic and microscopic diagnostics.

5. Functional meaning and possible outcomes of necrosis.

6. Apoptosis.

7. The difference of necrosis and apoptosis.

8. Death. Symptoms of death.

III. Object of study :

Microscopic view:

1. Necrosis in heart muscle

2.Necrosis in epithelial tissue of convoluted tubule

Tables:

1. Caseous necrosis

2. Gangrene of the foot

IV. Information part

NECROSIS - is a form of cell injury which results in the premature death of cells in living tissue by autolysis. Quite often necrosis appear as outcome of cell dystrophy, but usually it is the outcome of acute circulatory system disorder (acute ischemia) or injury of cells by strong toxins. External factors may involve mechanical trauma (physical damage to the body which causes cellular breakdown), damage to blood vessels (which may disrupt blood supply to associated tissue). Thermal effects (extremely high or low temperature) can result in necrosis due to the disruption of cells.

Macroscopy. Common characteristics of necrosis are changes in consistency, color and, possibly, a certain smell of necrotic masses. Often necrotic area white or yellow color. Cellular death due to necrosis does not follow the apoptotic signal transduction pathway, but rather various receptors are activated, and result in the loss of cell membrane integrity and an uncontrolled release of products of cell death into the extracellular space. This initiates in the surrounding tissue an inflammatory response which attracts leukocytes and nearby phagocytes which eliminate the dead cells by phagocytosis, which delimit necrotic area - inflammatory infiltrate (torus demarcationis). Imbibition of necrotic area with different hemoglobin pigments or bile pigments will lead to color transformation – red, brown, green etc.

*Morphology***.** Necrotic cells show increased eosinophilia in hematoxylin and eosin (H & E) stains, attributable in part to the loss of cytoplasmic RNA (which binds the blue dye, hematoxylin) and in part to denatured cytoplasmic proteins (which bind the red dye, eosin). The necrotic cell may have a more glassy homogeneous appearance than do normal cells, mainly as a result of the loss of glycogen particles. When enzymes have digested the cytoplasmic organelles, the cytoplasm becomes vacuolated and appears motheaten. Dead cells may be replaced by large, whorled phospholipid masses called myelin figures that are derived from damaged cell membranes. These phospholipid precipitates are then either phagocytosed by other cells or further degraded into fatty acids; calcification of such fatty acid residues results in the generation of calcium soaps. Thus, the dead cells may ultimately become calcified. By electron microscopy, necrotic cells are characterized by discontinuities in plasma and organelle membranes, marked dilation of mitochondria with the

appearance of large amorphous densities, intracytoplasmic myelin figures, amorphous debris, and aggregates of fluffy material probably representing denatured protein.

Nuclear changes appear in one of three patterns, all due to nonspecific breakdown of DNA. The basophilia of the chromatin may fade **(karyolysis)**, a change that presumably reflects loss of DNA because of enzymatic degradation by endonucleases. A second pattern (which is also seen in apoptotic cell death) is **pyknosis**, characterized by nuclear shrinkage and increased basophilia. Here the chromatin condenses into a solid, shrunken basophilic mass. In the third pattern, known as **karyorrhexis**, the pyknotic nucleus undergoes fragmentation. With the passage of time (a day or two), the nucleus in the necrotic cell totally disappears.

Ethiological classification of necrosis

Coagulative necrosis is a form of necrosis in which the architecture of dead tissues is preserved for a span of at least some days. The affected tissues exhibit a firm texture. Presumably, the injury denatures not only structural proteins but also enzymes and so blocks the proteolysis of the dead cells; as a result, eosinophilic, anucleate cells may persist for days or weeks. Ultimately the necrotic cells are removed by phagocytosis of the cellular debris by infiltrating leukocytes and by digestion of the dead cells by the action of lysosomal enzymes of the leukocytes. Ischemia caused by obstruction in a vessel may lead to coagulative necrosis of the supplied tissue in all organs except the brain. A localized area of coagulative necrosis is called an infarct.

Liquefactive necrosis, in contrast to coagulative necrosis, is characterized by digestion of the dead cells, resulting in transformation of the tissue into a liquid viscous mass. It is seen in focal bacterial or, occasionally, fungal infections, because microbes stimulate the accumulation of leukocytes and the liberation of enzymes from these cells. The necrotic material is frequently creamy yellow because of the presence of dead leukocytes and is called pus. For unknown reasons, hypoxic death of cells within the central nervous system often manifests as liquefactive necrosis.

Gangrenous necrosis is not a specific pattern of cell death, but the term is commonly used in clinical practice. It is usually applied to a limb, generally the lower leg, that has lost its blood supply and has undergone necrosis (typically coagulative necrosis) involving multiple tissue planes. When bacterial infection is superimposed there is more liquefactive necrosis because of the actions of degradative enzymes in the bacteria and the attracted leukocytes (giving rise to so-called wet gangrene).

Caseous necrosis is encountered most often in foci of tuberculous infection. The term “caseous” (cheeselike) is derived from the friable white appearance of the area of necrosis. On microscopic examination, the necrotic area appears as a collection of fragmented or lysed cells and amorphous granular debris enclosed within a distinctive inflammatory border; this appearance is characteristic of a focus of inflammation known as a granuloma.

Fat necrosis is a term that is well fixed in medical parlance but does not in reality denote a specific pattern of necrosis. Rather, it refers to focal areas of fat destruction, typically resulting from release of activated pancreatic lipases into the substance of the pancreas and the peritoneal cavity. This occurs in the calamitous abdominal emergency known as acute pancreatitis. In this disorder pancreatic enzymes leak out of acinar cells and

liquefy the membranes of fat cells in the peritoneum. The released lipases split the triglyceride esters contained within fat cells. The fatty acids, so derived, combine with calcium to produce grossly visible chalky-white areas (fat saponification), which enable the surgeon and the pathologist to identify the lesions. On histologic examination the necrosis takes the form of foci of shadowy outlines of necrotic fat cells, with basophilic calcium deposits, surrounded by an inflammatory reaction.

Fibrinoid necrosis is a special form of necrosis usually seen in immune reactions involving blood vessels. This pattern of necrosis typically occurs when complexes of antigens and antibodies are deposited in the walls of arteries. Deposits of these "immune complexes," together with fibrin that has leaked out of vessels, result in a bright pink and amorphous appearance in H&E stains, called "fibrinoid" (fibrin-like) by pathologists.

Infarct. An infarct is an area of ischemic necrosis caused by occlusion of either the arterial supply or the venous drainage. Tissue infarction is a common and extremely important cause of clinical illness.

Nearly all infarcts result from thrombotic or embolic arterial occlusions. Occasionally infarctions are caused by other mechanisms, including local vasospasm, hemorrhage into an atheromatous plaque, or extrinsic vessel compression (e.g., by tumor). Rarer causes include torsion of a vessel (e.g., in testicular torsion or bowel volvulus), traumatic rupture, or vascular compromise by edema (e.g., anterior compartment syndrome) or by entrapment in a hernia sac. Although venous thrombosis can cause infarction, the more common outcome is just congestion; in this setting, bypass channels rapidly open and permit vascular outflow, which then improves arterial inflow. Infarcts caused by venous thrombosis are thus more likely in organs with a single efferent vein (e.g., testis and ovary).

Morphology. Infarcts are classified according to color and the presence or absence of infection; they are either red (hemorrhagic) or white (anemic) and may be septic or bland.

• Red infarcts occur with venous occlusions (e.g., ovary), in loose tissues (e.g., lung) where blood can collect in the infarcted zone, in tissues with dual circulations (e.g., lung and small intestine) that allow blood flow from an unobstructed parallel supply into a necrotic zone, in tissues previously congested by sluggish venous outflow, and when flow is re-established to a site of previous arterial occlusion and necrosis (e.g., following angioplasty of an arterial obstruction).

• White infarcts occur with arterial occlusions in solid organs with endarterial circulation (e.g., heart, spleen, and kidney), and where tissue density limits the seepage of blood from adjoining capillary beds into the necrotic area.

Infarcts tend to be wedge-shaped, with the occluded vessel at the apex and the periphery of the organ forming the base; when the base is a serosal surface there can be an overlying fibrinous exudate. Acute infarcts are poorly defined and slightly hemorrhagic. With time the margins tend to become better defined by a narrow rim of congestion attributable to inflammation.

Infarcts resulting from arterial occlusions in organs without a dual blood supply typically become progressively paler and more sharply defined with time. By comparison, in the lung hemorrhagic infarcts are the rule. Extravasated red cells in hemorrhagic infarcts are phagocytosed by macrophages, which convert heme iron into hemosiderin; small amounts do not grossly impart any appreciable color to the tissue, but extensive hemorrhage can leave a firm, brown residuum.

The dominant histologic characteristic of infarction is ischemic coagulative necrosis. It is important to recall that if the vascular occlusion has occurred shortly (minutes to hours) before the death of the person, no demonstrable histologic changes may be evident; it takes 4 to 12 hours for the tissue to show frank necrosis. Acute inflammation is present along the margins of infarcts within a few hours and is usually well defined within 1 to 2 days. Eventually the inflammatory response is followed by a reparative response beginning in the preserved margins. In stable or labile tissues, parenchymal regeneration can occur at the periphery where underlying stromal architecture is preserved. However, most infarcts are ultimately replaced by scar. The brain is an exception to these generalizations, as central nervous system infarction results in liquefactive necrosis.

Septic infarctions occur when infected cardiac valve vegetations embolize or when microbes seed necrotic tissue. In these cases the infarct is converted into an abscess, with a correspondingly greater inflammatory response. The eventual sequence of organization, however, follows the pattern already described.

Possible outcomes of necrosis:

1. Forming of scar (fibrous tissue)
2. Encapsulation
3. Calcinosis
4. Ossification
5. Aseptic autolysis
6. Outcome in cyst
7. Rejection of necrotic tissue
8. Sequestration of necrotic tissue
9. Septic autolysis with embolism complication

Apoptosis is a pathway of cell death that is induced by a tightly regulated suicide program in which cells destined to die activate enzymes that degrade the cells' own nuclear DNA and nuclear and cytoplasmic proteins.

Death by apoptosis is a normal phenomenon that serves to eliminate cells that are no longer needed, and to maintain a steady number of various cell populations in tissues. It is important in the following physiologic situations:

- The programmed destruction of cells during embryogenesis
- Involution of hormone-dependent tissues upon hormone withdrawal
- Cell loss in proliferating cell populations
- Elimination of potentially harmful self-reactive lymphocytes
- Death of host cells that have served their useful purpose, such as neutrophils in an acute inflammatory response

Morphology. The following morphologic features, some best seen with the electron microscope, characterize cells undergoing apoptosis.

Cell shrinkage. The cell is smaller in size; the cytoplasm is dense; and the organelles, though relatively normal, are more tightly packed. (Recall that in other forms of cell injury, an early feature is cell swelling, not shrinkage.)

Chromatin condensation. This is the most characteristic feature of apoptosis. The chromatin aggregates peripherally, under the nuclear membrane, into dense masses of various shapes and sizes. The nucleus itself may break up, producing two or more fragments.

Formation of cytoplasmic blebs and apoptotic bodies. The apoptotic cell first shows extensive surface blebbing, then undergoes fragmentation into membrane-bound apoptotic bodies composed of cytoplasm and tightly packed organelles, with or without nuclear fragments.

Phagocytosis of apoptotic cells or cell bodies, usually by macrophages. The apoptotic bodies are rapidly ingested by phagocytes and degraded by the phagocyte's lysosomal enzymes.

Plasma membranes are thought to remain intact during apoptosis, until the last stages, when they become permeable to normally retained solutes. This classical description is accurate with respect to apoptosis during physiologic conditions such as embryogenesis and deletion of immune cells. However, forms of cell death with features of necrosis as well as of apoptosis are not uncommon after many injurious stimuli. Under such conditions the severity rather than the nature of the stimulus determines the pathway of cell death, necrosis being the major pathway when there is advanced ATP depletion and membrane damage.

Death.

Death is the irreversible cessation any vital activity that sustain a living organism, the unavoidable natural end of the existence of any living being. Thanatology is the scientific study of death. It investigates the mechanisms of death, such as bodily changes that accompany death and the post-mortem period, as well as wider psychological and social aspects related to death. A continuing goal of thanatology include the creation and improvement of scientific classification of causes and circumstances of death , the development of theoretical and methodological foundations of the doctrine death, improvement of methodological techniques for determining the stage of the onset of the terminal period and the time of clinical and biological death.

Depending on the cause leading to the onset of death, there are natural (physiological), violent and death from diseases. Depending on the development of reversible or irreversible changes in body man classify death on clinical and biological.

Clinical death is the medical term for cessation of blood circulation and breathing, the two necessary criteria to sustain human and many other organisms' lives. It occurs when the heart stops beating, a condition called cardiac arrest. The term is also sometimes used in resuscitation research. Clinical death is reversible process which depends on brain hypoxia duration.

Biological death is an irreversible cessation of physiological processes in cells and tissues, in which resuscitation activities are unsuccessful. Reliable signs of death (biological) are postmortem changes.

Postmortem changes occur in different periods, so they are divided into early and late. These include:

- Pallor mortis, paleness which happens in the 15–120 minutes after death
- Livor mortis, a 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

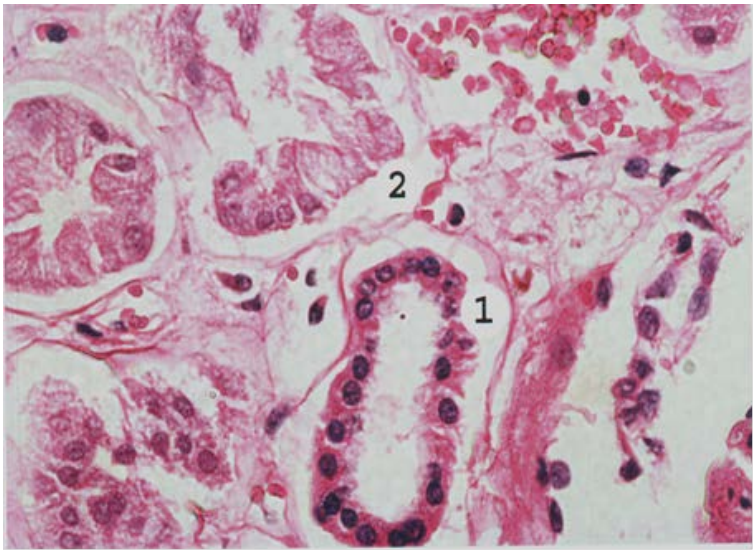
- Decomposition, the reduction into simpler forms of matter, accompanied by a strong, unpleasant odor.

Late postmortem changes are those changes, which lead to corpse dissolution and destruction (autolysis, putrefaction), or natural preservation (mummification, saponification, peat tanning, freezing).

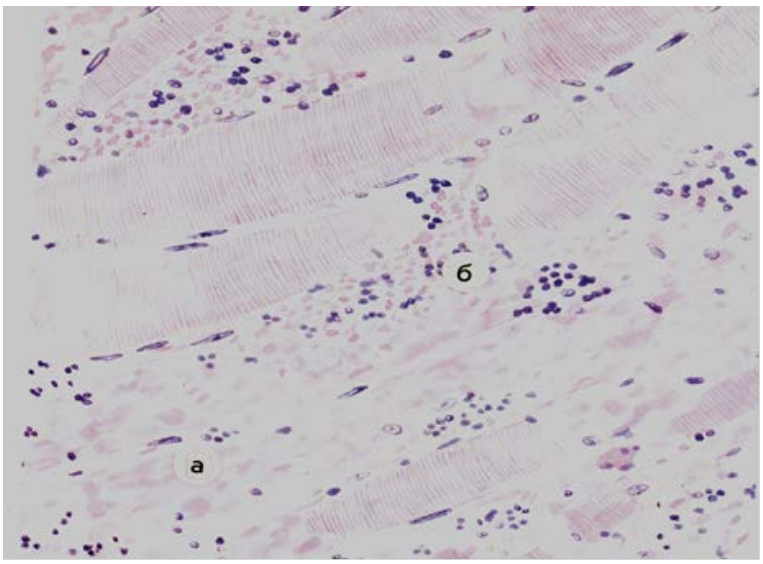
Practical part

Sketch microscopic view and describe.

Pic 1. Necrosis of in epithelial tissue of convoluted tubule.



Pic 2. Necrosis of skeletal muscle.



Haematoxylin and eosin stain

Theme: "GENERAL HEMODYNAMIC DISORDERS"

Knowledge of the topic is necessary for the assimilation of other topics from the course of pathological anatomy, as well as for clinical and anatomical analysis in the study of clinical disciplines and in the practical work of the doctor.

v. AIMS

It is necessary to know	• The definition of venous hyperemia, reasons and mechanisms of its occur • The definition of shock, classification • The definition of disseminated intravascular coagulation (DIC) • Types of edema
The student must be able to	• Give morphological characterization of organs in shock • Differ shock from thrombosis • To evaluate the meaning of venous hyperemia for organism
The student must possess	Knowledge of anatomical pathology to understand morphogenesis and to be able to diagnose hemodynamic disorders

vi. The required knowledge

1. Histological structure of the tissues

2. Biochemical metabolic processes

3. The definition of dystrophy.

4. Morphogenetic mechanisms of dystrophy development.

from the current lesson:

1. General hemodynamic disorders.

2. General arterial hyperemia.

3. General venous hyperemia.

4. Anemia.

5. Acute anemia.

6. Chronic anemia.

7. Lymphatic drainage disorder.

8. Disseminated intravascular coagulation (DIC).

9. Shock.

III. Object of study :

Microscopic view:

1. Chronic venous hyperemia - “nutmeg liver”

2. Brown lung induration

Tables:

1. Chronic venous hyperemia - “nutmeg liver”

2. Brown lung induration

IV. Information part

The circulatory system coordinates and links together functionally different organs and systems in the interests of life support of the body as a whole thing. Lymphatic system plays an important role as a part of vascular system. Cardiovascular system permits blood to circulate and transport nutrients (such as amino acids and electrolytes), oxygen, carbon dioxide, hormones, and blood cells to and from the cells in the body to provide nourishment and help in fighting diseases, stabilize temperature and pH, and maintain homeostasis. All nutritious substances carried away by veins and lymphatic vessels.

General hemodynamic disorders

- General arterial hyperemia
- General venous hyperemia
- Anemia – acute and chronic
- Lymphatic drainage disorder
- Disseminated intravascular coagulation (DIC)
- Shock

General arterial hyperemia (hyperemia universalis arteriosa) increase in the number of blood cells (erythrocytes), sometimes combined with an increase of circulating blood volume. The process occur relatively rare when man climbing to a height (climbers), residents of mountain areas, in persons with lung disease as a compensatory-adaptive reaction, as well as in newborns after umbilical cord ligation. Clinically observed redness of the skin and mucous membranes, increased blood pressure. In practice, the most important thing is the General arterial hyperemia in the disease of Vaquez (true polycythemia) — a disease in which there is a true hyperproduction of red blood cells.

General venous hyperemia is one of the most common hemodynamic disorders. General venous hyperemia is clinical symptom of heart failure and lung-heart failure. It is the transient increase in organ blood flow that occurs following a brief period of ischaemia. Following ischaemia there will be a shortage of oxygen and a build-up of metabolic waste.

Mechanism of development:

1. Heart disorders, called heart failure

- Congenital and acquired heart defect;

- Inflammatory heart diseases-pericarditis, myocarditis, endocarditis;

- Cardiosclerosis of different etiology (atherosclerotic, postinfarct and etc.);

-Infarct of heart muscle.

2. Lung disorders, with decreased blood volume in pulmonary circulation

- Lung emphysema;

-Chronic non-specific pneumonia;

-Pneumosclerosis;

- Pneumoconiosis .

3. **Chest trauma**

- Pleurisy;

- Pneumothorax;

-Deformity of the chest.

General venous hyperemia begins from stasis in vena cava inferior and portal vein. It explains why liver suffer first of all organs. Central areas are red and slightly depressed compared with the surrounding tan viable parenchyma, forming a “nutmeg liver” pattern (so-called because it resembles the cut surface of a nutmeg. Centrilobular necrosis can be seen with degenerating hepatocytes and hemorrhage. Other hepatocytes become hypertrophic and in case of progression of oxygen starving, liver tissue can be replaced by connective tissue. The outcome of this process is cirrhosis – nutmeg cirrhosis. Similae process take a place in heart muscle.

It is necessary to mark, that after a long time oxygen starving collagen fibrils become more tight in all organ’s stroma – **cyanotic induration** (spleen, kidneys etc.)

In long-standing cases of pulmonary venous heperemy, such as those seen in mitral stenosis, hemosiderin-laden macrophages are abundant, and fibrosis and thickening of the alveolar walls cause the soggy lungs to become firm and brown - **brown induration**. These changes not only impair normal respiratory function but also predispose to infection.

Outcome. General venous hyperemia is reversible process if the reason, that caused hyperemia will be eliminate in time. The long term state of tissue hypoxia leads to irreversible changes in tissues and organs. Such as atrophy and sclerosis.

Anemia.

Anemia is defined as a reduction of the total circulating red cell mass below normal limits. Anemia reduces the oxygen-carrying capacity of the blood, leading to tissue hypoxia. In practice, the measurement of red cell mass is not easy, and anemia is usually diagnosed based on a reduction in the hematocrit (the ratio of packed red cells to total blood volume) and the hemoglobin concentration of the blood to levels that are below the normal range. These values correlate with the red cell mass except when there are changes in plasma volume caused by fluid retention or dehydration.

Possible causes:

- Acute blood loss;

-Common chronic blood loss;

- Increased red cell destruction (hemolysis);

- Decreased red cell production;

-Chronic infection disease (tuberculosis, syphilis);

-Chronic parasitic disease (helminthiasis);

- Starving, vitamin deficiency.

Pathological manifestation

Paleness skin, mucous membranes, internal organs. Dystrophic changes in parenchymal organs (especially often-fatty degeneration). With increased hemolysis of red blood cells may be a common hemosiderosis. As a result of hypoxia hemorrhages can occur.

Outcome

The process is reversible, but also can lead to death in case of progression. Death occurs due to irreversible metabolic disorders associated with oxygen starvation.

Shock.

Shock is the final common pathway for several potentially lethal clinical events, including severe hemorrhage, extensive trauma or burns, large myocardial infarction, massive pulmonary embolism, and microbial sepsis. Shock is characterized by systemic hypotension due either to reduced cardiac output or to reduced effective circulating blood volume. The consequences are impaired tissue perfusion and cellular hypoxia . At the outset the cellular injury is reversible; however, prolonged shock eventually leads to irreversible tissue injury that often proves fatal.

The causes of shock fall into three general categories:

• *Cardiogenic shock* results from low cardiac output due to myocardial pump failure. This can be due to intrinsic myocardial damage (infarction), ventricular arrhythmias, extrinsic compression (cardiac tamponade; Chapter 12), or outflow obstruction (e.g., pulmonary embolism).

• *Hypovolemic shock* results from low cardiac output due to the loss of blood or plasma volume, such as can occur with massive hemorrhage or fluid loss from severe burns.

• *Septic shock* results from vasodilation and peripheral pooling of blood as part of a systemic immune reaction to bacterial or fungal infection. Its complex pathogenesis is discussed in further detail below.

Three general phases:

• *An initial nonprogressive* phase during which reflex compensatory mechanisms are activated and perfusion of vital organs is maintained

• *A progressive stage* characterized by tissue hypoperfusion and onset of worsening circulatory and metabolic imbalances, including acidosis

• *An irreversible stage* that sets in after the body has incurred cellular and tissue injury so severe that even if the hemodynamic defects are corrected, survival is not possible

Morphology.

The cellular and tissue changes induced by cardiogenic or hypovolemic shock are essentially those of hypoxic injury; changes can manifest in any tissue although they are particularly evident in brain, heart, lungs, kidneys, adrenals, and gastrointestinal tract. The **adrenal** changes in shock are those seen in all forms of stress; essentially there is cortical cell lipid depletion. This does not reflect adrenal exhaustion but rather conversion of the relatively inactive vacuolated cells to metabolically active cells that utilize stored lipids for the synthesis of steroids. The **kidneys** typically exhibit acute tubular necrosis. The **lungs** are seldom affected in pure hypovolemic shock, because they are somewhat resistant to hypoxic injury. However, when shock is caused by bacterial sepsis or trauma, changes of **diffuse alveolar damage** may develop, the so-called shock lung. In septic shock, the development of DIC leads to widespread deposition of fibrin-rich microthrombi, particularly in the brain, heart, lungs, kidney, adrenal glands, and gastrointestinal tract. The consumption of platelets andcoagulation factors also often leads to the appearance of petechial hemorrhages on serosalsurface and the skin.

With the exception of neuronal and myocyte ischemic loss, virtually all of these tissues may revert to normal if the individual survives. Unfortunately, most patients with irreversible changes due to severe shock die before the tissues can recover.

Disseminated intravascular coagulation (DIC)

Disorders ranging from obstetric complications to advanced malignancy can be complicated by DIC, the sudden or insidious onset of widespread fibrin thrombi in the microcirculation. Although these thrombi are not grossly visible, they are readily apparent microscopically and can cause diffuse circulatory insufficiency, particularly in the brain, lungs, heart, and kidneys. To complicate matters, the widespread microvascular thrombosis results in platelet and coagulation protein consumption (hence the synonym consumption coagulopathy), and at the same time, fibrinolytic mechanisms are activated. Thus, an initially thrombotic disorder can evolve into a bleeding catastrophe. It should be emphasized that DIC is not a primary disease but rather a potential complication of any condition associated with widespread activation of thrombin.

Edema.

Approximately 60% of lean body weight is water. Two thirds of the body's water is intracellular, and the remainder is in extracellular compartments, mostly the interstitium (or third space) that lies between cells; only about 5% of total body water is in blood plasma. The movement of water and low molecular weight solutes such as salts between the intravascular and interstitial spaces is controlled primarily by the opposing effect of vascular hydrostatic pressure and plasma colloid osmotic pressure. Normally the outflow of fluid from the arteriolar end of the microcirculation into the interstitium is nearly balanced by inflow at the venular end; a small residual amount of fluid may be left in the interstitium and is drained by the lymphatic vessels, ultimately returning to the bloodstream via the thoracic duct. Either increased capillary pressure or diminished colloid osmotic pressure can result in increased interstitial fluid. If the movement of water into tissues (or body cavities) exceeds lymphatic drainage, fluid accumulates. An abnormal increase in interstitial fluid within tissues is called edema, while fluid collections in the different body cavities are variously designated hydrothorax, hydropericardium, and hydroperitoneum (the last is more commonly called ascites). Anasarca is a severe and generalized edema with widespread subcutaneous tissue swelling.

The four main **mechanisms of edema** genesis are:

- Increased hydrostatic pressure;

- Reduced plasma osmotic pressure;

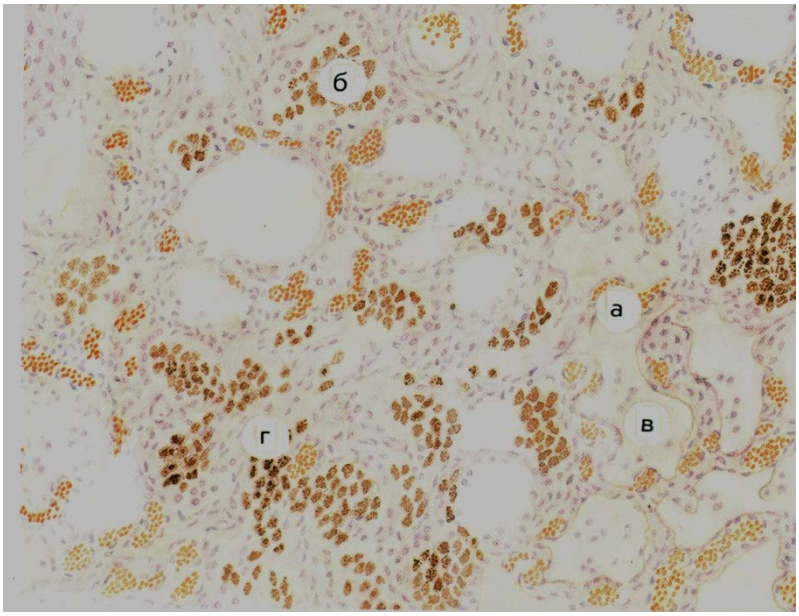
- Sodium and water retention;

- Lymphatic obstruction.

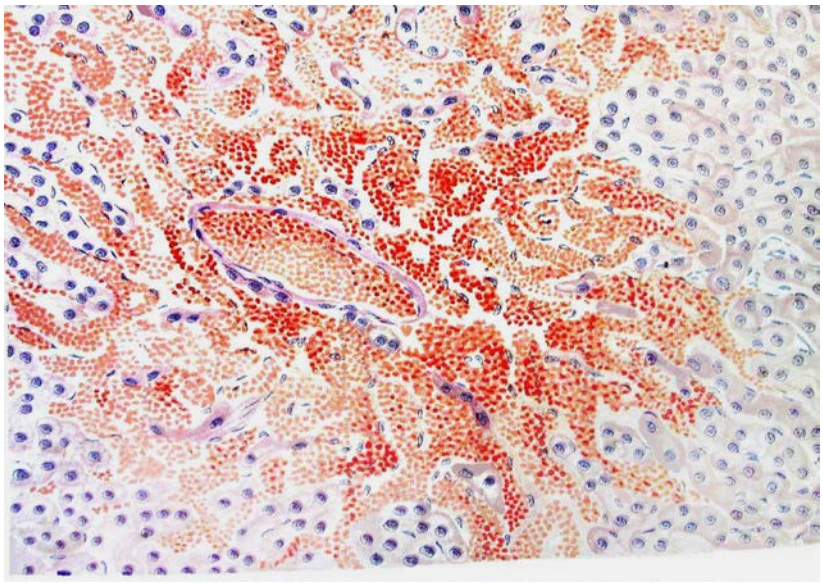
Morphology. Edema is easily recognized grossly; microscopically, it is appreciated as clearing and separation of the extracellular matrix and subtle cell swelling. Any organ or tissue can be involved, but edema is most commonly seen in subcutaneous tissues, the lungs, and the brain. Subcutaneous edema can be diffuse or more conspicuous in regions with high hydrostatic pressures. In most cases the distribution is influenced by gravity and is termed dependent edema (e.g., the legs when standing, the sacrum when recumbent). Finger pressure over substantially edematous subcutaneous tissue displaces the interstitial fluid and leaves a depression, a sign called pitting edema.

Edema as a result of renal dysfunction can affect all parts of the body. It often initially manifests in tissues with loose connective tissue matrix, such as the eyelids; periorbital edema is thus a characteristic finding in severe renal disease. With pulmonary edema, the lungs are often two to three times their normal weight, and sectioning yields frothy, bloodtinged fluid—a mixture of air, edema, and extravasated red cells. Brain edema can be localized or generalized depending on the nature and extent of the pathologic process or injury. With generalized edema the brain is grossly swollen with narrowed sulci.

Practical part
Sketch microscopic view and describe.



Pic. 1 Chronic brown lung induration



Pic 2. Chronic venous hyperemia (nutmeg liver)

Theme: "LOCAL HEMODYNAMIC DISORDERS"

Knowledge of the topic is necessary for the assimilation of other topics from the course of pathological anatomy, as well as for clinical and anatomical analysis in the study of clinical disciplines and in the practical work of the doctor.

VII. AIMS

It is necessary to know	• The definition of thrombosis, reasons and mechanisms of its occur • The definition of embolism, classification • The definition of infarct causes and stages
The student must be able to	• Give morphological characterization of thrombosis • Differ thrombosis from blood clot • To evaluate the meaning of embolism for organism
The student must possess	Knowledge of anatomical pathology to understand morphogenesis and to be able to diagnose hemodynamic disorders

VIII. The required knowledge

1. Histological structure of the tissues

2. Biochemical metabolic processes

3. The definition of dystrophy.

4. Morphogenetic mechanisms of dystrophy development.

from the current lesson:

1. Local hemodynamic disorders.

2. Local venous hyperemia.

3. Bleeding and hemorrhage.

4. Thrombosis.

5. Embolism.

6. Ischemia.

7. Infarct.

III. Object of study :

Microscopic view:

1. Organization and recanalization of thrombus

2. Adipose Embolism

3. Cerebral hemorrhage

Tables:

1. Kidney rupture

2. Adipose Embolism

IV. Information part

Local hemodynamic disorders

- Local arterial hyperemia;
- Local venous hyperemia;
- Stasis;
- Thrombosis;
- Embolism;
- Ischemia;
- Infarct .

LOCAL ARTERIAL HYPEREMIA

There are physiological and pathological hyperemia.

An example of physiological arterial hyperemia can be shame paint on the face, pink-red areas of the skin at the site of its thermal or mechanical effect.

Man distinguish the following types of pathological arterial hyperemia:

Angioneurotic hyperemia – occur in case of irritation of vasoconstrictor nerves or sympathetic ganglions. For example systemic lupus erythematosus, On patients face can be pink-red areas seen or redness on patient's face in infection process. Angioneurotic hyperemia characterized by acceleration of blood circulation. Skin and mucous membranes become red, slightly swollen and warm.

Collateralization.

In medicine, collateralization, also vessel collateralization and blood vessel collateralization, is the growth of a blood vessel or several blood vessels that serve the same end organ or vascular bed as another blood vessel that cannot adequately supply that end organ or vascular bed sufficiently.

Coronary collateralization is considered a normal response to hypoxia and may be induced, under some circumstances, by exercise. It is considered to be protective.

Collateral or anastomotic blood vessels also exist even when blood supply is adequate to an area, and these blood vessels are often taken advantage of in surgery. Some notable areas where this occurs include the abdomen, rectum, knee, shoulder, and head.

Hyperemia after ischemia (hyperemia after anemia)

This type of hyperemia develops in cases where a factor (eg tumor), causing local anemia (ischemia), quickly removed. The blood vessels of the previously bloodless tissue become sharply dilate and overflow with blood. The danger of such arterial hyperemia is that the overflowing vessels, especially in the elderly people, can break and lead to bleeding and hemorrhage. Besides, there may be anemia of other organs, such as the brain, which cn lead to development of syncope.

Inflammatory hyperemia is one of the most important symptoms of inflammation.

Hyperemia for the reason of arteriovenous shunt. The development of shunt between arteria and vein, after trauma for example, and arterial blood goes in vein. There is a huge risk of shunt rupture and as outcome bleeding.

LOCAL VENOUS HYPEREMIA

Local venous hyperemia occurs in case of disorder of *blood outflow* (e.g. occlusion of vessel with thrombus, thrombophlebitis of portal vein).

Compression of vein by edema, tumor, growing connective tissue.

Collateral venous hyperemia occurs after occlusion of big vein (portal, vena cava inferior etc.)

STASIS

The loss of fluid and increased vessel diameter lead to slower blood flow, concentration of red cells in small vessels, and increased viscosity of the blood. These changes result in dilation of small vessels that are packed with slowly moving red cells, a condition termed stasis, which is been as vascular congestion (producing localized redness) upon examination of the involved tissue.

The most common reason is inflammation and autoimmune disease.

Stasis is a reversible process, that cause organs and tissue dystrophy. A long term stasis causes necrosis.

BLEEDING

Bleeding, also known as hemorrhaging or haemorrhaging, is blood escaping from the circulatory system. The effects of acute blood loss are mainly due to the loss of intravascular volume, which

if massive can lead to cardiovascular collapse, shock, and death. The clinical features depend on the rate of hemorrhage and whether the bleeding is external or internal. If the patient survives, the blood volume is rapidly restored by the intravascular shift of water from the interstitial fluid compartment. This fluid shift results in hemodilution and a lowering of the hematocrit. The reduction in oxygenation triggers increased secretion of erythropoietin from the kidney, which stimulates the proliferation of committed erythroid progenitors (CFU-E) in the marrow. It takes about 5 days for the progeny of these CFU-Es to mature and appear as newly released red cells (reticulocytes) in the peripheral blood.

Bleeding due to rupture of the vessel wall or heart, (*haemorrhagia per rhexin*) – the rupture can be caused in case of blood vessel's or heart wall sclerosis, necrosis of heart wall (myocardial infarction), necrosis of aorta's wall, inflammation of aorta (e.g. specific infections—syphilis), rupture of aortic aneurysm etc.

Bleeding due to vessel's wall erosion, *(haemorrhagia per diabrosin)*- vessel erosion in ulcer disease, caseous necrosis in tuberculosis, in cancer, abscess, phlegmon. Vessel erosion also occurs in ectopic pregnancy (chorion villi grow into fallopian tube).

Bleeding due to vessel's permeability *(haemorrhagia per diapedesin)* without visible vessel rupture. Occur in system vasculitis, inflammatory and allergy processes, anemia, tumors of the hematopoietic and lymphoid tissues, coagulopathy, vitamin deficiency etc.

Tissue hemorrhage can occur in distinct patterns, each with its own clinical implications:

• Hemorrhage may be external or contained within a tissue; any accumulation is called a *hematoma*. Hematomas may be relatively insignificant or so massive that death ensues.

• Minute 1- to 2-mm hemorrhages into skin, mucous membranes, or serosal surfaces are called *petechiae*. These are most commonly associated with locally increased intravascular pressure, low platelet counts (thrombocytopenia), or defective platelet function (as in uremia).

• Slightly larger (≥3 mm) hemorrhages are called *purpura*. These may be associated with many of the same disorders that cause petechiae or can be secondary to trauma, vascular inflammation (vasculitis), or increased vascular fragility (e.g., in amyloidosis).

• Larger (>1 to 2 cm) subcutaneous hematomas (i.e., bruises) are called *ecchymoses.* The red cells in these lesions are degraded and phagocytized by macrophages; the hemoglobin (red-blue color) is then enzymatically converted into bilirubin (blue-green color) and eventually into hemosiderin (gold-brown color), accounting for the characteristic color changes in a bruise.

• Depending on the location, a large accumulation of blood in a body cavity is denoted as a *hemothorax, hemopericardium, hemoperitoneum*, or *hemarthrosis* (in joints). Patients with extensive bleeding can develop jaundice from the massive breakdown of red cells and hemoglobin.

The outcome: Full blood resorption – the best outcome; organization - the ingrowth of connective tissue, encapsulation – the pathologic area limited with casual, calcification (petrification) – deposition of calcium.

THROMBOSIS

Thrombosis is the formation of a blood clot in a blood vessel, obstructing the flow of blood through the circulatory system. If a blood vessel is injured, human body uses thrombocytes and fibrin to form a blood clot to stop blood loss.

The blood clots may also form in the body under certain conditions.

The three primary abnormalities that lead to thrombus formation (called Virchow's triad) :

- *endothelial injury* -dysfunctional endothelial cells can produce more procoagulant factors (e.g., platelet adhesion molecules, tissue factor, PAIs) or may synthesize less anticoagulant effectors (e.g., thrombomodulin, PGI2, t-PA). Endothelial dysfunction can be induced by a wide variety of insults, including hypertension, turbulent blood flow, bacterial endotoxins, radiation injury, metabolic abnormalities such as homocystinemia or hypercholesterolemia, and toxins absorbedfrom cigarette smoke.

- *stasis or turbulent blood flow* - turbulence contributes to arterial and cardiac thrombosis by causing endothelial injury or dysfunction, as well as by forming countercurrents and local pockets of stasis; stasis is a major contributor in the development of venous thrombi. Normal blood flow is laminar such that the platelets (and other blood cellular elements) flow centrally in the vessel lumen, separated from endothelium by a slower moving layer of plasma. Stasis and turbulence therefore:

    - Promote endothelial activation, enhancing procoagulant activity, leukocyte adhesion, etc., in part through flow-induced changes in endothelial cell gene expression.
    - Disrupt laminar flow and bring platelets into contact with the endothelium
    - Prevent washout and dilution of activated clotting factors by fresh flowing blood and the inflow of clotting factor inhibitors

- *hypercoagulability of the blood* - (also called thrombophilia) is a less frequent contributor to thrombotic states but is nevertheless an important component in the equation, and in some situations can predominate. It is loosely defined as any alteration of the coagulation pathways that predisposes to thrombosis; it can be divided into primary (genetic) and secondary (acquired) disorders. Of the inherited causes of hypercoagulability, point mutations in the factor V gene and prothrombin gene are the most common.

Morphology. Thrombi can develop anywhere in the cardiovascular system (e.g., in cardiac chambers, on valves, or in arteries, veins, or capillaries). The size and shape of thrombi depend on the site of origin and the cause. Arterial or cardiac thrombi usually begin at sites of turbulence or endothelial injury; venous thrombi characteristically occur at sites of stasis. Thrombi are focally attached to the underlying vascular surface; arterial thrombi tend to grow retrograde from the point of attachment, while venous thrombi extend in the direction of blood flow (thus both propagate toward the heart). The propagating portion of a thrombus is often poorly attached and therefore prone to fragmentation and embolization.

Thrombi often have grossly and microscopically apparent laminations called lines of Zahn; these represent pale platelet and fibrin deposits alternating with darker red cell–rich layers. Such laminations signify that a thrombus has formed in flowing blood; their presence can therefore distinguish antemortem thrombosis from the bland nonlaminated clots that occur postmortem (see below).

Thrombi occurring in heart chambers or in the aortic lumen are designated mural thrombi. Abnormal myocardial contraction (arrhythmias, dilated cardiomyopathy, or myocardial infarction) or endomyocardial injury (myocarditis or catheter trauma) promotes cardiac mural thrombi, while ulcerated atherosclerotic plaque and aneurysmal dilation are the precursors of aortic thrombus.

Arterial thrombi are frequently occlusive; the most common sites in decreasing order of frequency are the coronary, cerebral, and femoral arteries. They typically cosist of a friable meshwork of platelets, fibrin, red cells, and degenerating leukocytes. Although these are usually superimposed on a ruptured atherosclerotic plaque, other vascular injuries (vasculitis, trauma) may be the underlying cause.

Venous thrombosis (phlebothrombosis) is almost invariably occlusive, with the thrombus forming a long cast of the lumen. Because these thrombi form in the sluggish venous circulation, they tend to contain more enmeshed red cells (and relatively few platelets) and are therefore known as red, or stasis, thrombi. The veins of the lower extremities are most commonly involved (90% of cases); however, upper extremities, periprostatic plexus, or the ovarian and periuterine veins can also develop venous thrombi. Under special circumstances, they can also occur in the dural sinuses, portal vein, or hepatic vein.

Postmortem clots can sometimes be mistaken for antemortem venous thrombi. However, postmortem clots are gelatinous with a dark red dependent portion where red cells have settled by gravity and a yellow “chicken fat” upper portion; they are usually not attached to the underlying wall. In comparison, red thrombi are firmer and are focally attached, and sectioning typically reveals gross and/or microscopic lines of Zahn.

Thrombi on heart valves are called vegetations. Blood-borne bacteria or fungi can adhere to previously damaged valves (e.g., due to rheumatic heart disease) or can directly cause valve damage; in both cases, endothelial injury and disturbed blood flow can induce the formation of large thrombotic masses (infective endocarditis). Sterile vegetations can also develop on noninfected valves in persons with hypercoagulable states, so-called nonbacterial thrombotic endocarditis. Less commonly, sterile, verrucous endocarditis can occur in the setting of systemic lupus erythematosus.

The outcome of the Thrombus:

If a patient survives the initial thrombosis, in the ensuing days to weeks thrombi undergo some combination of the following four events:

• Propagation. Thrombi accumulate additional platelets and fibrin.

• Embolization. Thrombi dislodge and travel to other sites in the vasculature. This process is described below.

• Dissolution. Dissolution is the result of fibrinolysis, which can lead to the rapid shrinkage and total disappearance of recent thrombi. In contrast, the extensive fibrin deposition and crosslinking in older thrombi renders them more resistant to lysis. This distinction explains why therapeutic administration of fibrinolytic agents such as t-PA (e.g., in the setting of acute coronary thrombosis) is generally effective only when given in the first few hours of a thrombotic episode.

• Organization and recanalization. Older thrombi become organized by the ingrowth of endothelial cells, smooth muscle cells, and fibroblasts. Capillary channels eventually form that re-establish the continuity of the original lumen, albeit to a variable degree.

EMBOLISM

An embolus is a detached intravascular solid, liquid, or gaseous mass that is carried by the blood to a site distant from its point of origin. Almost all emboli represent some part of a dislodged thrombus, hence the term thromboembolism. Rare forms of emboli include fat droplets, nitrogen bubbles, atherosclerotic debris (cholesterol emboli), tumor fragments, bone marrow, or even foreign bodies. Emboli lodge in vessels too small to permit further passage, causing partial or complete vascular occlusion; a major consequence is ischemic necrosis (infarction) of the downstream tissue. Depending on where they originate, emboli can lodge anywhere in the vascular tree; the clinical outcomes are best understood based on whether emboli lodge in the pulmonary or systemic circulations.

There are two types of embolism, due to its motion:

-*retrograde*- motion of emboli against blood flow

-*paradoxical* (PE) - in the presence of defects in the atrial or interventricular septum, embol from the veins of a large circle, bypassing the lungs, enters the arteries.

Fragmented thrombi from DVTs (deep vein thrombosis) are carried through progressively larger channels and the right side of the heart before slamming into the pulmonary arterial vasculature. Depending on the size of the embolus, it can occlude the main pulmonary artery, straddle the pulmonary artery bifurcation (saddle embolus), or pass out into the smaller, branching arteries.

• Most pulmonary emboli (60% to 80%) are clinically silent because they are small. With time they become organized and are incorporated into the vascular wall; in some cases organization of the thromboembolus leaves behind a delicate, bridging fibrous web.

• Sudden death, right heart failure (cor pulmonale), or cardiovascular collapse occurs when emboli obstruct 60% or more of the pulmonary circulation.

• Embolic obstruction of medium-sized arteries with subsequent vascular rupture can result in pulmonary hemorrhage but usually does not cause pulmonary infarction. This is because the lung has a dual blood supply, and the intact bronchial circulation continues to perfuse the affected area. However, a similar embolus in the setting of left-sided cardiac failure (and compromised bronchial artery flow) can result in infarction.

• Embolic obstruction of small end-arteriolar pulmonary branches usually does result in hemorrhage or infarction.

• Multiple emboli over time may cause pulmonary hypertension and right ventricular failure.

Systemic thromboembolism

Systemic thromboembolism refers to emboli in the arterial circulation. Most (80%) arise from intracardiac mural thrombi, two thirds of which are associated with left ventricular wall infarcts and another quarter with left atrial dilation and fibrillation. The remainder originate from aortic aneurysms, thrombi on ulcerated atherosclerotic plaques, or fragmentation of a valvular vegetation, with a small fraction due to paradoxical emboli ; 10% to 15% of systemic emboli are of unknown origin. In contrast to venous emboli, which tend to lodge primarily in one vascular bed (the lung), arterial emboli can travel to a wide variety of sites; the point of arrest depends on the source and the relative amount of blood flow that downstream tissues receive. Major sites for arteriolar embolization are the lower extremities (75%) and the brain (10%), with the intestines, kidneys, spleen, and upper extremities involved to a lesser extent. The consequences of embolization in a tissue depend on its vulnerability to ischemia, the caliber of the occluded vessel, and whether there is a collateral blood supply; in general, arterial emboli cause infarction of the affected tissues.

Fat and marrow embolism

Microscopic fat globules—with or without associated hematopoietic marrow elements—can be found in the circulation and impacted in the pulmonary vasculature after fractures of long bones (which have fatty marrow) or, rarely, in the setting of soft tissue trauma and burns. Fat and associated cells released by marrow or adipose tissue injury may enter the circulation after the rupture of the marrow vascular sinusoids or venules. Fat and marrow PEs are very common incidental findings after cardiopulmonary resuscitation and are probably of no clinical consequence. Indeed, fat embolism occurs in some 90% of individuals with severe skeletal injuries, but less than 10% of such patients have any clinical findings.

Air embolism

Gas bubbles within the circulation can coalesce to form frothy masses that obstruct vascular flow (and cause distal ischemic injury). For example, a very small volume of air trapped in a coronary artery during bypass surgery can occlude flow with dire consequences. Generally, more than 100 clinical cases of air embolismare required to have a clinical effect in the pulmonary circulation; however, this volume of air can be inadvertently introduced during obstetric or laparoscopic procedures, or as a consequence of chest wall injury.

Tumor embolism

Cancer cells can get into system bloodstream by destroying blood vessel’s walls. This process is basis for metastasis. It can be a separate cells or small group of cells which may not disorder blood stream, but can form new focuses of tumor.

LOCAL ANEMIA - ISCHEMIA

Ischemia - is a restriction in blood supply to tissues, causing a shortage of oxygen. It comprises not only insufficiency of oxygen, but also reduced availability of nutrients and inadequate removal of metabolic wastes.

There are four types of local anemia, depending on reasons:

-*angiospasmic* it occurs due to spasm of the arteries due to the action of various irritations. Angiospasm appears in various injuries, especially which are accompanied by pain and fear.

-*obstructive ischemia* - it occurs as a result of blockage of the arterial vessel and is most often associated with either thrombosis or embolism of the arteries, as well as with the growth of connective tissue in the artery in inflammation of its wall (obliterating endarteritis) or narrowing of the arteriy with an atherosclerotic plaque.

-*ischemia due to compression* – occurs as a result of vessels compression with surgical suture, after applying tourniquet, tumor compression, edema compression etc.

-*ischemia due to redistribution of blood* – (e.g. brain ischemia after quick removal of ascitic fluid from abdominal cavity.

INFARCTION

An infarct is an area of ischemic necrosis caused by occlusion of either the arterial supply or the venous drainage. Tissue infarction is a common and extremely important cause of clinical illness. Roughly 40% of all deaths in the United States are caused by cardiovascular disease, and most of these are attributable to myocardial or cerebral infarction. Pulmonary infarction is also a common complication in many clinical settings, bowel infarction is frequently fatal, and ischemic necrosis of the extremities (gangrene) is a serious problem in the diabetic population.

Nearly all infarcts result from thrombotic or embolic arterial occlusions. Occasionally infarctions are caused by other mechanisms, including local vasospasm, hemorrhage into an atheromatous plaque, or extrinsic vessel compression (e.g., by tumor). Rarer causes include torsion of a vessel (e.g., in testicular torsion or bowel volvulus), traumatic rupture, or vascular compromise by edema (e.g., anterior compartment syndrome) or by entrapment in a hernia sac. Although venous thrombosis can cause infarction, the more common outcome is just congestion; in this setting, bypass channels rapidly open and permit vascular outflow, which then improves arterial inflow. Infarcts caused by venous thrombosis are thus more likely in organs with a single efferent vein (e.g., testis and ovary).

Morphology.

Infarcts are classified according to color and the presence or absence of infection; they are either red (hemorrhagic) or white (anemic) and may be septic or bland.

• Red infarcts occur with venous occlusions (e.g., ovary), in loose tissues (e.g., lung) where blood can collect in the infarcted zone, in tissues with dual circulations (e.g., lung and small intestine) that allow blood flow from an unobstructed parallel supply into a necrotic zone, in tissues previously congested by sluggish venous outflow, and when flow is re-established to a site of previous arterial occlusion and necrosis (e.g., following angioplasty of an arterial obstruction).

• White infarcts occur with arterial occlusions in solid organs with endarterial circulation (e.g., heart, spleen, and kidney), and where tissue density limits the seepage of blood from adjoining capillary beds into the necrotic area.

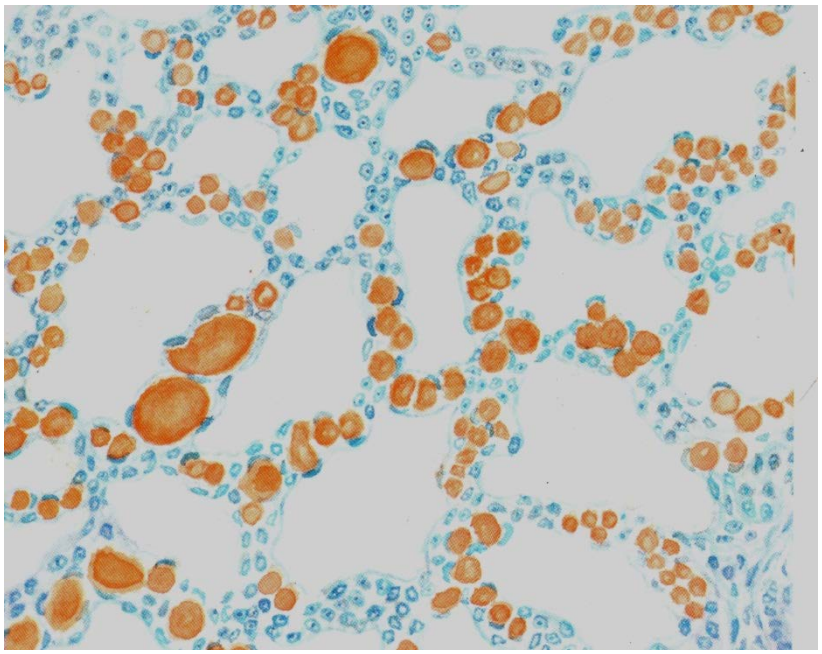
Infarcts tend to be wedge-shaped, with the occluded vessel at the apex and the periphery of the organ forming the base; when the base is a serosal surface there can be an overlying fibrinous exudate. Acute infarcts are poorly defined and slightly hemorrhagic. With time the margins tend to become better defined by a narrow rim of congestion attributable to inflammation.

Infarcts resulting from arterial occlusions in organs without a dual blood supply typically become progressively paler and more sharply defined with time. By comparison, in the lung hemorrhagic infarcts are the rule. Extravasated red cells in hemorrhagic infarcts are phagocytosed by macrophages, which convert heme iron into hemosiderin; small amounts do not grossly impart any appreciable color to the tissue, but extensive hemorrhage can leave a firm, brown residuum.

The dominant histologic characteristic of infarction is ischemic coagulative necrosis. It is important to recall that if the vascular occlusion has occurred shortly (minutes to hours) before the death of the person, no demonstrable histologic changes may be evident; it takes 4 to 12 hours for the tissue to show frank necrosis. Acute inflammation is present along the margins of infarcts within a few hours and is usually well defined within 1 to 2 days. Eventually the inflammatory response is followed by a reparative response beginning in the preserved. In stable or labile tissues, parenchymal regeneration can occur at the periphery where underlying stromal architecture is preserved. However, most infarcts are ultimately replaced by scar. The brain is an exception to these generalizations, as central nervous system infarction results in liquefactive necrosis. Septic infarctions occur when infected cardiac valve vegetations embolize or when microbes seed necrotic tissue. In these cases the infarct is converted into an abscess, with a correspondingly greater inflammatory response. The eventual sequence of organization, however, follows the pattern already described.

Practical part

Sketch microscopic view and describe.



Pic.1.Fat embolism of pulmonary arteries.
Sudan III staining.

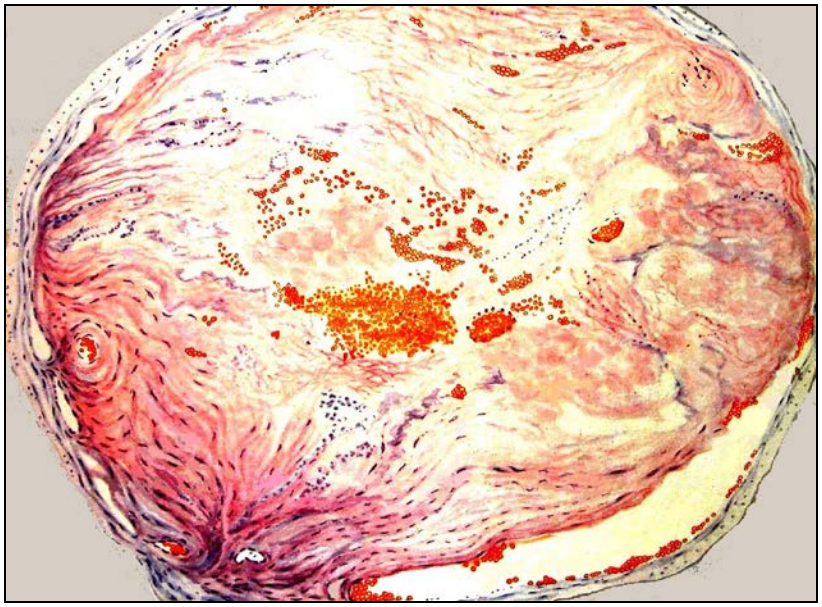


Рис 2. Thrombi obturates the vessel.
H&E staining

Theme: "INFLAMMATION"

Knowledge of the topic is necessary for the assimilation of other topics from the course of pathological anatomy, as well as for clinical and anatomical analysis in the study of clinical disciplines and in the practical work of the doctor.

IX. AIMS

It is necessary to know	• The definition inflammation • Etiology of inflammation • Morphology of inflammation • Classification
The student must be able to	• Give morphological characterization of inflammation • To prognose the outcome of forming inflammation
The student must possess	Knowledge of anatomical pathology to understand morphogenesis and to be able to diagnose inflammation disorders

X. The required knowledge

1. Histological structure of the tissues

2. Biochemical metabolic processes and pathological mechanisms of inflammation's process.

from the current lesson:

1. Morphogenetic mechanisms of inflammation development.

2. Classification of inflammation

III. Object of study :

Microscopic view:

1. Fibrinous pericarditis by rheumatism (H&E)

2. Serous dermatitis by eczema (H&E)

Tables:

1. Fibrinous inflammation

2. Exudative inflammation

IV. Information part

Inflammation 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).

Inflammation is a complex reaction in tissues that consists mainly of responses of blood vessels and leukocytes. The body's principal defenders against foreign invaders are plasma proteins and circulating leukocytes (white blood cells), as well as tissue phagocytes that are derived from circulating cells. The presence of proteins and leukocytes in the blood gives them the ability to home to any site where they may be needed. Because invaders such as microbes and necrotic cells are typically present in tissues, outside the circulation, it follows that the circulating cells and proteins have to be rapidly recruited to these extravascular sites. The inflammatory response coordinates the reactions of vessels, leukocytes, and plasma proteins to achieve this goal.

The vascular and cellular reactions of inflammation are triggered by soluble factors that are produced by various cells or derived from plasma proteins and are generated or activated in response to the inflammatory stimulus. Microbes, necrotic cells (whatever the cause of cell death) and even hypoxia can trigger the elaboration of inflammatory mediators, and thus elicit inflammation. Such mediators initiate and amplify the inflammatory response and determine its pattern, severity, and clinical and pathologic manifestations.

Etiology

Inflammatory reactions may be triggered by a variety of stimuli:

• Infections (bacterial, viral, fungal, parasitic) and microbial toxins are among the most common and medically important causes of inflammation.

• Tissue necrosis from any cause, including ischemia (as in a myocardial infarct), trauma, and physical and chemical injury (e.g., thermal injury, as in burns or frostbite; irradiation; exposure to some environmental chemicals).

• Foreign bodies (splinters, dirt, sutures) typically elicit inflammation because they cause traumatic tissue injury or carry microbes.

• Immune reactions (also called hypersensitivity reactions) are reactions in which the normally protective immune system damages the individual's own tissues. The injurious immune responses may be directed against self antigens, causing autoimmune diseases, or may be excessive reactions against environmental substances or microbes..

All inflammatory reactions share the same basic features, although different stimuli may induce reactions with some distinctive characteristics.

Morphology of inflammation.

Inflammation has three major components: alteration, exudation, proliferation.

Alteration is tissue damage that morphologically manifests itself by various types of dystrophy and necrosis. Damage can develop by the influence of a disease-causing factor, or indirectly – by neurohumoral system. In this phase of inflammation is the release of biologically active substances - mediators of inflammation. It's a trigger for inflammation.

Exudation is a complex process of formation of inflammatory effusion, the sources of which can be blood, lymph and local tissue cells, in which the inflammatory process develops. The formation of inflammatory effusion, which is called exudate, occurs as a result of microcirculatory and cellular reactions.

Exudate necessarily consists of two parts:

- liquid part, which includes water, plasma proteins-albumins, globulins, fibrinogen, mineral salts,
- the cell part, which includes both cells of hematogenous origin-neutrophils, lymphocytes, monocytes, histiocytes, erythrocytes, and local tissue cells – macrophages, epithelial, mesothelial cells.

The ratio of the liquid and the cell part, as well as the predominance of certain cellular forms in various forms of inflammation will be different.

Proliferation of cells is the final phase of inflammation. In the focus of inflammation there is a proliferation of cambial cells of connective tissue, B-and T-lymphocytes, monocytes, as well as local tissue cells, in which the inflammation occurs – mesothelial, epithelial cells. There is also cellular differentiation and transformation. B-lymphocytes give rise to the formation of plasma cells, monocytes-histiocytes and macrophages. Macrophages can be a source of epithelioid and giant cells (foreign body cells and cells such as Pirogov-Langhans).

Classification of inflammation.

Depending on predominance of inflammation components:

- exudative inflammation
- productive inflammation

Depending on the term of process:

- acute (up to 20 minutes)
- subacute (up to 6 month)
- chronic (that occurs for years)

Depending on localization:

- parenchymatous
- interstitial
- mixed

Depending on tissue reaction:

- specific
- non-specific

Exudative inflammation is characterized by the predominance of the response of microcirculatory vessels with the formation of exudate, while the alterative and proliferative components are less expressed.

Depending on the exudate characteristics, the following types of exudative inflammation are distinguished:

- serous
- hemorrhagic
- fibrinous
- purulent
- mixed

Serous inflammation is marked by the outpouring of a thin non-viscous serous fluid that may be derived from the plasma or from the secretions of mesothelial cells lining the peritoneal, pleural, and pericardial cavities. Accumulation of fluid in these cavities is called an effusion. The skin blister resulting from a burn or viral infection represents a large accumulation of serous fluid, either within or immediately beneath the epidermis of the skin.

The outcome of serous inflammation is usually favorable. Even a significant amount of exudate can dissolve. In the internal organs in the outcome of serous inflammation in its chronic course sometimes develops sclerosis.

Hemorrhagic inflammation is marked by forming effusion, which consist first of all red blood cells. It occurs because of acute increase in microvascular permeability. Sometimes the percentage of red cells is so high, that exudate reminds bleeding.

Causes of occurrence may be – the flu (influenza), plague, anthrax, deficiency of C vitamin etc.

The outcome of hemorrhagic inflammation depends on cause of its occurrence.

Fibrinous inflammation

With greater increase in vascular permeability, large molecules such as fibrinogen pass the vascular barrier, and fibrin is formed and deposited in the extracellular space. A fibrinous exudate develops when the vascular leaks are large or there is a local procoagulant stimulus (e.g., cancer cells). A fibrinous exudate is characteristic of inflammation in the lining of body cavities, such as the meninges, pericardium and pleura. Histologically, fibrin appears as an eosinophilic meshwork of threads or sometimes as an amorphous coagulum. Fibrinous exudates may be removed by fibrinolysis and clearing of other debris by macrophages. If the fibrin is not removed, over time it may stimulate the ingrowth of fibroblasts and blood vessels and thus lead to scarring. Conversion of the fibrinous exudate to scar tissue (organization) within the pericardial sac leads to opaque fibrous thickening of the pericardium and epicardium in the area of exudation and, if the fibrosis is extensive, obliteration of the pericardial space.

Purulent inflammation; abscess

This type of inflammation is characterized by the production of large amounts of pus or purulent exudate consisting of neutrophils, liquefactive necrosis, and edema fluid. Certain bacteria (e.g., staphylococci) produce this localized suppuration and are therefore referred to as pyogenic (pus-producing) bacteria. A common example of an acute suppurative inflammation is acute appendicitis. Abscesses are localized collections of purulent inflammatory tissue caused by suppuration buried in a tissue, an organ, or a confined space. They are produced by deep seeding of pyogenic bacteria into a tissue. Abscesses have a central region that appears as a mass of necrotic leukocytes and tissue cells. There is usually a zone of preserved neutrophils around this necrotic focus, and outside this region vascular dilation and parenchymal and fibroblastic proliferation occur, indicating chronic inflammation and repair. In time the abscess may become walled off and ultimately replaced by connective tissue.

PROLIFERATION (division) of cells is a finale phase of inflammation. In inflammation area can be seen the proliferation of connective tissue cells, large amount of T- and B- lymphocytes, monocytes. B- lymphocytes transform in plasmocytes, monocytes into macrophages. Macrophages can be source of Langhans-type giant cells (with many nuclei arranged in a horseshoe-like pattern at the edge of the cell).

PRODUCTIVE INFLAMATION

The reason of productive inflammation are

- biological factors (viruses, rickettsias, bacteria, fungi, parasites)
- physical and chemical factors (more often there is a prolonged exposure to non-damaging but potentially toxic substances such as asbestos, silicon oxide (IV), etc.; foreign bodies, etc)
- immune reactions, in particular those that occur, for example, against their own tissues in autoimmune diseases

There are several types of productive inflammation:

- stromal (intermedial) inflammation
- granulomatous inflammation
- inflammation with formation of polyps and candyloma (wart)

Stromal (intermedial) inflammation is characterized by formation of local or general inflammatory infiltration in stroma of organs such as f.ex. myocardium, liver, kidneys, lungs etc. The infiltration is formed by lymphocytes, macrophages, plasmocytes, singular neutrophils, eosinophils, mast cells. Parenchymatous cells and tissues are usually suffered by distrophic and necrotic processes.

The *outcome* of chronic stromal (intermedial) inflammation leads to connective tissue proliferation. In some diseases in liver chronic stromal (intermedial) inflammation leads to cirrhosis.

Granulomatous inflammation

The most active cells in this type of inflammation are macrophages. Morphological substratum is ***granuloma.***

Grauloma is a local accumulation of monocytes-macrophages cells, that are able to phagocytosis.

Morphogenesis of granuloma: 1. Accumulation of young monocytes that are able to phagocytosis 2. Maturation in macrophages 3. Maturation and transformation in epitheliod cells

4. transformation of epitheliod cells into giant Langhans cells.

There are two types of granulomatous inflammation:

- *infectious* (specific) include granulomas with typhoid and abdominal typhoid, rabies, viral encephalitis, actinomycosis, schistosomiasis, tuberculosis, leprosy, syphilis, etc

- *Non-infectious* (non-specific) granulomas develop when ingested organic and inorganic dust: wool, flour, silica, asbestos, etc., foreign bodies, drug effects (granulomatous hepatitis

The *granulomas of tuberculosis* tend to contain necrosis ("caseating tubercules"), but non-necrotizing granulomas may also be present. Multinucleated giant cells with nuclei arranged like a horseshoe (Langhans giant cell) and foreign body giant cells are often present, but are not specific for tuberculosis. A definitive diagnosis of tuberculosis requires identification of the causative organism by microbiologic cultures.

In leprosy, granulomas are found in the skin and tend to involve nerves. The appearance of the granulomas differs according to the precise type of leprosy.

Sarcoidosis is a disease of unknown cause characterized by non-necrotizing ("non-caseating") granulomas in multiple organs and body sites, most commonly the lungs and lymph nodes within the chest cavity. Other common sites of involvement include the liver, spleen, skin and eyes. The granulomas of sarcoidosis are similar to the granulomas of tuberculosis and other infectious granulomatous diseases. However, in most cases of sarcoidosis, the granulomas do not contain necrosis and are surrounded by concentric scar tissue (fibrosis). Sarcoid granulomas often contain star-shaped structures termed asteroid bodies or lamellar structures termed Schaumann bodies. However, these structures are not specific for sarcoidosis. Sarcoid granulomas can resolve spontaneously without complications or heal with residual scarring. In the lungs, this scarring can cause a condition known as pulmonary fibrosis that impairs breathing. In the heart, it can lead to rhythm disturbances, heart failure, and even death.

Crohn's disease is an inflammatory condition of uncertain cause characterized by severe inflammation in the wall of the intestines and other parts of the abdomen. Within the inflammation in the gut wall, granulomas are often found and are a clue to the diagnosis.

IMMUNE SYSTEM PATHOLOGY

Immunity is the way of protection from living bodies and substances, that have signs of foreign antigenic information. An antigen is a molecule capable of inducing an immune response.

The immune system consists of central and peripheral organs of immunogenesis. **The central** include the thymus gland, bone marrow and tonsils,

the peripheral - lymph nodes, spleen, blood and reticulo-endothelial system. Schematically distinguish two levels of immunity - humoral and cell-meditated immunity.

Humoral immunity involves substances found in the humors, or body fluids. It contrasts with cell-mediated immunity. Its aspects involving antibodies are often called antibody-mediated immunity. Humoral immunity is provided by B lymphocytes (immunoglobulin classes A, M, G, E, D), as well as the ability of body fluids to kill the pathogen. So, blood, saliva, lacrimal fluid, the secret of the bowel – rich in lisozyme, interferon, anti-bacterial substrates.

Cell-mediated immunity is an immune response that does not involve antibodies, but rather involves the activation of phagocytes, antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen. CD4 cells or helper T cells provide protection against different pathogens. Naive T cells, mature T cells that have yet to encounter an antigen, are converted into activated effector T cells after encountering antigen-presenting cells (APCs). These APCs, such as macrophages, dendritic cells, and B cells in some circumstances, load antigenic peptides onto the major histocompatibility complex (MHC) of the cell, in turn presenting the peptide to receptors on T cells. The most important of these APCs are highly specialized dendritic cells; conceivably operating solely to ingest and present antigens.

Immunopathology studies the processes and diseases a resulting of the immune conflict, and the violation of immunological homeostasis. The immune response can be specific and non-specific.

The non-specific immune response consists of mechanical protection, humoral and cellular mechanisms.

Mechanical protection is the first barrier to pathogenesis and is carried out by the epithelial cover due to the movement of cilia (cough, vomiting, sneezing, peristalsis, lacrimal fluid, etc.).

The specific immune response - protection against a specific causative agent (antigen).

Usually immune reactions doesn`t have any clinical manifestation, while they lead either to the complete destruction of the antigenic aggressor, or to a partial suppression of its pathogenic action, providing the body with a state of immunity. However, under some circumstances, these reactions may develop unusually.

Injurious immune reactions are grouped under hypersensitivity, and the resulting diseases are called hypersensitivity diseases. This term is originated from the idea that persons who mount immune responses against the antigen are sensitized to the antigen, so pathologic or excessive reactions represent manifestations of a hypersensitive state.

Type I Hypersensitivity.

Fast response which occurs in minutes, rather than multiple hours or days. Free antigens cross link the IgE on mast cells and basophils which causes a release of vasoactive biomolecules.

In type 1 hypersensitivity, B-cells are stimulated (by CD4+TH2 cells) to produce IgE antibodies specific to an antigen. The difference between a normal infectious immune response and a type 1 hypersensitivity response is that in type 1 hypersensitivity, the antibody is IgE instead of IgA, IgG, or IgM. During sensitization, the IgE antibodies bind to FcεRI receptors on the surface of tissue mast cells and blood basophils. Mast cells and basophils coated by IgE antibodies are "sensitized". Later exposure to the same allergen cross-links the bound IgE on sensitized cells, resulting in anaphylactic degranulation, which is the immediate and explosive release of pharmacologically active pre-formed mediators from storage granules and concurrent synthesis of inflammatory lipid mediators from

arachidonic acid; some of these mediators include histamine, leukotriene (LTC4 and LTD4 and LTB4), and prostaglandin, which act on proteins (e.g., G-protein coupled receptors) located on surrounding tissues. The principal effects of these products are vasodilation and smooth-muscle contraction.

Type 1 hypersensitivity can be further classified into immediate and late-phase reactions. The immediate hypersensitivity reaction occurs minutes after exposure and includes release of vasoactive amines and lipid mediators, whereas the late-phase reaction occurs 2–4 hours after exposure and includes the release of cytokines.

Common antigens which cause Type I Hypersensitivity reaction

Pollen

– Birch tree, Rag weed, Oil seed rape.

Food

– Eggs, Nuts, Sea food.

Drugs

– Pencillin, Salicylates.

Insect Products

– Bee venom, House dust mite.

Animal Hair

– Cat hair, Dander.

The immediate or rapid or initial response characterized by

- Vasodilatation
- Vascular leakage
- Smooth muscle spasm
- Glandular secretion

Type II hypersensitivity reactions: Antibody-mediated cytotoxicity

Type II hypersensitive reactions involve antibody-mediated destruction of cells. This type of reaction is best seen by blood-transfusion reactions, in which host antibodies react with foreign antigens on the incompatible transfused blood cells and mediate destruction of these cells. Antibody can mediate cell destruction by activating the complement system to create pores in the membrane of the foreign cell. Antibody can also mediate cell destruction by antibody-dependent cell-mediated cytotoxicity (ADCC). In this process, cytotoxic cells with Fc-receptors bind to the Fc-region of antibodies on target cells and promote killing of the cells.

ABO incompatibility

If a blood group A individual is accidentally transfused with blood from a blood group A donor, the anti-B isohaemagglutinins bind to the B blood cells and mediate complement-mediated lysis a massive intravascular of the transfused red blood cells follows. Typical symptoms of a transfusion reaction include fever, chills, nausea, and pain in the lower back. Within hours, free haemoglobin can be detected in the plasma; it is filtered through the kidneys, re¬sulting in haemoglobinuria. Some of the haemoglobin converts to bilirubin, which at high levels is toxic to brain. There is a clotting within blood vessels, too. A treatment involves prompt termination of the transfusion and maintenance of urine flow with a diuretic because the accumulation of haemoglobin in the kidney can cause acute tubular necrosis. Transfusion reactions can be prevented by a proper cross¬-matching between the donor's and the recipient's blood. The cross-matching can reveal the presence of the antibodies in donor or recipient sera that can cause these reactions.

Haemolytic disease of the newborn

Haemolytic disease of the newborn develops when maternal IgG antibodies specific for foetal blood-group antigens cross the pla¬centa and destroy foetal red blood cells. It most commonly develops in the Rh-negative mother bearing her Rh-positive foetus (i.e. the Rh(D) anti¬gens are expressed on its red blood cells). During her first pregnancy the Rh-negative woman is usually not exposed to sufficient quantity of foetal red blood cells (RBC) to activate her Rh(D)-specific B cells. At the time of delivery, however, separation of the placenta from the uterine

wall allows larger amounts of foetal umbilical-cord blood to enter the mother's circulation. These foetal red blood cells activate the Rh(D)-specific B cells, resulting in production of the Rh(D)-specific antibodies and appearance of memory B cells in the mother. The secreted IgM antibody clears the Rh(D)+ foetal red blood cells from the mother's circulation and disappear in the time course; however, the memory B cells remain. When the woman is pregnant the second time, the Rh(D)-positive erythrocytes of the foetus cross the placenta and activate the memory B cells what results in production of antibodies. However, this time, they are of the IgG class (the secondary immune response. The IgG anti-Rh(D) antibodies cross the placenta and bind to the Rh(D) antigens; the complement system activation follows resulting in destruction of foetal red blood cells. Depending on the extent of RBC lysis, less severe haemolytic anaemia or more severe, sometimes also fatal, erythroblastosis foetalis, develops.

The development of haemolytic disease of the newborn by Rh(D) incompatibility can be detected by testing materna1 serum at intervals during pregnancy for antibodies to Rh(D) antigen. A rise in the titer of these antibodies as pregnancy progresses indicates that the mother has been exposed to Rh(D) antigens and is producing increasing amounts of antibodies. The presence of maternal IgG on the surface of foetal erythrocytes can be detected by a Coombs test.

The treatment haemolytic disease caused by the Rh(D) incompatibility is based on an exchange transfusion, primary to remove bilirubin; the infant is also exposed to low levels of UV light to break down the bilirubin and prevent any cerebral damage.

To prevent the Rh-isoimmunisations, all Rh-negative women are given anti-Rhesus antibodies 72 h after delivery at the latest. The antibodies originate from immunisation of men by the Rhesus-positive erythrocytes. The antibodies destroy foetus RBC and so prevent of the immunisation of the Rh-negative women.

Drug-induced haemolytic anaemia

Some drugs (e.g. penicillins, cephalosporins, etc.) can adsorb non-specifically to proteins on RBC membranes, forming a complex similar to a hapten-carrier complex. In some patients, such drug-protein complexes induce formation of antibodies, which then bind to the adsorbed drug on red blood cells, inducing complement-mediated lysis and thus progressive anaemia. When the drug is withdrawn, the haemolytic anaemia disappears.

Type III hypersensitivity reactions: Immune complexes induced inflammation

Complexes between antigens and antibodies, so called immune complexes, are formed whenever an antigen binds to its specific antibody; mononuclear phagocytes engulf and degrade them immediately. However, in dependence from relative concentration ratios of antigens and antibodies, respectively, immune complexes can sometimes induce immunopathological reactions. Large immune complexes are insoluble and are rapidly cleared by mononuclear phagocytes; also small complexes fail cause any damage, as they do not activate the complement system. However, when intermediate size immune complexes are formed, they tend to be deposited into tissues and organs where they induce inflammation and their damage.

The extent of immune complex deposition depends from a general capacity of the organism to degrade them, esp. from a physiological status of the monunuclear-phagocytic system and the complement system. Phagocytosis disorders are connected with persistence of immune complexes and their deposition to the tissues. Similarly, the deficiencies of C2 and C2 components of the complement system are associated with immune complex diseases, e.g. with SLE.

When immune complexes are deposited in tissues, they induce an inflammatory process. They activate the complement system what results in formation of C3a and C5a anaphylatoxins. These molecules activate mast cells to release permeability factors permitting localisation of immune complexes along the endothelial cell basement membranes. Neutrophils, macrophages, lymphocytes and other cells with membrane Fc-receptors are activated. The activated neutrophils are especially important. They release proteolytic enzymes and produce reactive oxygen intermediate products (ROI) that cause a damage of the tissue. Platelets can be subsequently activated resulting in blood clotting and microtrombi formation; local ischemy and tissue necrosis follows. As it contains fibrin, the term fibrinoid necrosis was coined.

Historically, generalized type III reactions were often observed at the administration of antitoxins containing foreign proteins, such as horse anti-tetanus or anti-diphtheria serum; the condition is known as serum sickness. The clinical symptoms include fever, weakness, generalised vasculitis (rash) with oedema and erythema, lymphadenopathy, arthritis, and sometimes glomerulonephritis. As immune complexes are continuously degraded, the clinical manifestations spontaneously vanish.

Formation of circulating immune complexes contributes to the pathogenesis of a number of conditions other than serum sickness. These include SLE (systemic lupus erythematosus), rheumatoid arthritis, Goodpasture's syndrome, poststreptococcal glomerulonephritis and others.

Except of generalised type III hypersensitivity reaction, there is also a localised type. It was Nicholas Maurice Arthus who first described it in 1903. Arthus showed that injection of an antigen intradermally or subcutaneously into an animal that had had high levels of circulating antibody spe¬cific for the antigen produced local inflammation that progressed to a haemorrhagic necrotic ulcerating skin lesion.

Arthus reactions are rare in humans. After an insect bite, a sensitive individual may have a rapid, localized type I reaction at the site. Often, some 48 hrs later, a typical Arthus reaction also develops at the site, pronounced by erythema and oedema.

Type IV hypersensitive reactions: Delayed type of hypersensitivity

Type IV hypersensitive reactions (delayed type of hypersensitivity - DTH) develop when antigen activates sensitised TDTH cells; these cells belong to TH1 subset, although sometimes cytotoxic T cells (CTLs) are involved. Activation of T cells by antigen on appropriate antigen-presenting cells results in the secretion of various cytokines, including IL-2, IFN-gama, MIF (macrophage migration inhibitory factor, and TNF (tumour necrosis factor). The overall effect of these cytokines is to draw macrophages into the area and activate them, promoting increased phagocytic activity and increased concentrations of lytic enzymes for more effective killing. As lytic enzymes leak out of the activated macrophages into the surrounding tissue, localised tissue destruction can ensue. These reactions typically take 48 to 72 h to develop, the time required for initial T cell activation and cytokine secretion to mediate accumulation of macrophages and the subsequent release of their lytic enzymes. The hallmarks of a type IV reaction are the delay in time required for the reaction to develop and the recruitment of macrophages as opposed to neutrophils, as found in a type III reaction. Macrophages are the major component of the infiltrate that surrounds the site of inflammation.

The type IV reaction is important in host defence against parasites and bacteria that can live within cells, such as Mycobacterium tuberculosis, Mycobacterium leprae, Brucela species and others. Once these organisms are inside the host's cells,

circulating antibodies cannot reach them. However, the heightened phagocytic activity and the build up of lytic enzymes from macrophages in the area of infection lead to non-specific destruction of cells, and thus of the intracellular pathogen. When this defence process is not entirely effective, the continued presence of the pathogen's antigens can provoke a chronic DTH reaction, which is characterised by excessive numbers of macrophages, continual release of lytic enzymes, granuloma formation and consequent tissue destruction.

T cells mediate many contact dermatitis reactions, including the responses to formaldehyde, trinitrophenol, nickel, various cosmetics and hair dyes, poison oak, poison ivy, and others. Most of these substances are small molecules that can complex with skin proteins. This complex is internalised by antigen-presenting cells in the skin (i.e. Langerhans cells), processed and presented together with class II MHC molecules, causing activation of sensitised T cells. In the reaction to poison oak, for example, a pentadecacatechol compound from leafs of the plant complexes with skin proteins. When TH cells react with this compound appropriately displayed by local antigen presenting cells, they differentiate into sensitised T cells; a subsequent exposure to pentadecacatechol will elicit activation of T cells and induce cytokine production. Approximately 48-72 h after this secondary exposure, the secreted cytokines cause macrophages to accumulate at the site. Activation of these macrophages and release of their lytic enzymes results in the redness and pustules that characterise a reaction to poison oak.

Type V hypersensitivity reactions

Type V hypersensitivity reactions were additionally added to the scheme originally described by Coombs and Gell. Contrary to type IV and in agreement with types I, II, and III, respectively, they are mediated by antibodies too. The type V reactions are sometimes considered as a subtype of the type II hypersensitivity. As its mechanisms do not destroy target cells, they are responsible for induction of organ/tissue dysfunctions only most of authors prefer it to be and independent, the 5th type of hypersensitivity reactions.

Cells receive information from their microenvironment in which they live; they sense signals that process and transduce into the cell nucleus by means of second signals. The specificity of binding between the signal and its receptor is mediated by complementarities of structures. For instance, thyroid-stimulating hormone (TSH) released from the adenohypophysis, by binding to its receptors in

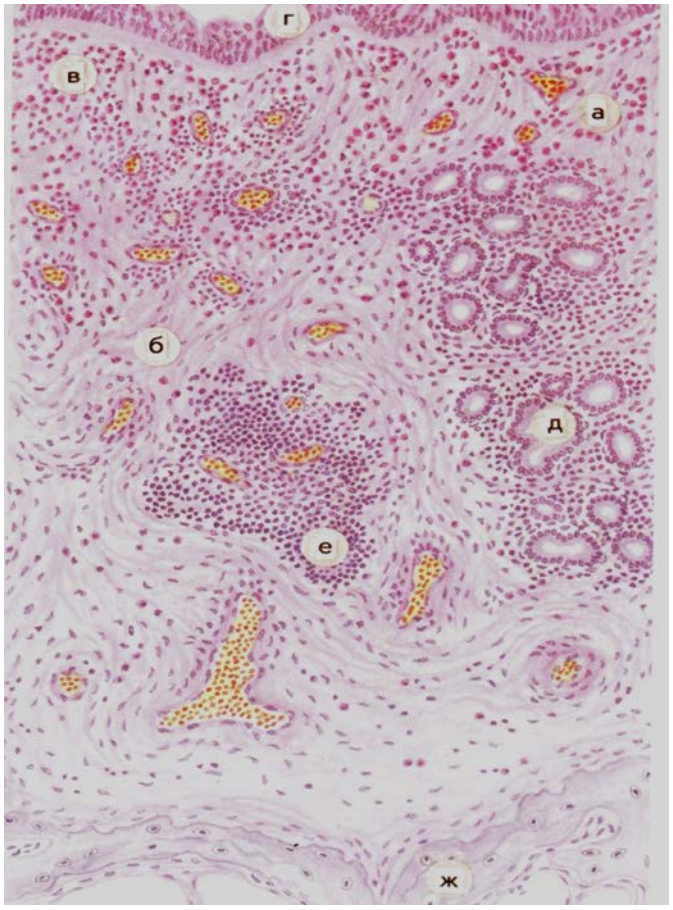
membranes of the thyroid gland stimulates adenylate-cyclase system what results in production of hormones.

Morbus Graves is characterised by production of antibodies directed against the TSH binding receptor that subsequently stimulate the thyroid gland, resulting in production of hormones (thyroxine and triiodothyronine). Contrary to physiological situation, there is no feedback mechanism – the increased levels of the thyroid gland hormones do not stop its hormones production as at the physiological condition when elevated amounts of thyroxines switch off the production of TSH and subsequent synthesis of hormones. The result is the hormone overproduction and appearance of clinical symptoms of hyperthyroidism. As antibodies increase the function of a target organ, this type of hypersensitivity is called stimulatory.

Autoantibodies cannot only stimulate cells of a target organ/tissue, however, on the contrary, also to inhibit it (hence the designation - inhibitory hypersensitivity reactions). A prototype of such a situation is myastenia gravis. It is an autoimmune disease characterised by production of autoantibodies directed against the acetylcholine receptors (AchR) present in neuro-muscular plates. By occupying the receptors, they inhibit a physiological binding of acetylcholine to, resulting in precluding signal transmission and muscle activation. The result of the events is a paralysis of striated muscles. In some cases the anti-acetylcholine receptors antibodies activate the complement system; a destruction of cell present in neuro-muscular plates follows; the condition is more severe than in the previous situation and is incurable.

Pernicious anemia (PA) is a disease is characterised by vitamin B12 deficiency caused by the absence of intrinsic factor. Vitamin B12 cannot be produced by the human body and must be obtained from the diet. When foods containing B12 are eaten, the vitamin is usually bound to protein and is released by stomach acid. Following its release, most B12 is absorbed by the body in the ileum after binding to a protein known as intrinsic factor. It is produced by parietal cells of the gastric mucosa and the intrinsic factor-B12 complex is absorbed by receptors on the ileum epithelial cells. In patients suffering from PA, antibodies to parietal cells cause the destruction of the gastric mucosa, in which the parietal cells are located, leading to the subsequent loss of intrinsic factor synthesis. In other subgroup of PA patients, antibodies to intrinsic factor are directly induced. Without intrinsic factor, the ileum can no longer absorb the B12 and the disease develops.

Practical part.



Allergic rhinitis.

А -mucosal vessels dilated, full-blooded,

б-connective tissue is swollen,

в-inflammatory infiltrate is dominated by eosinophilic leukocytes

г – epithelium

д - glands

е - lymphoid follicle.

ж -bone beams

Stained with hematoxilin and eosin.

Adaptation - a broad biological concept that combines all the processes of life, that ensure relationship between human body and environment. This definition covers both health and disease. *Compensation* - a particular manifestation of the adaptation for the correction of functional disorders in the disease, to" save yourself " in a critical situation.

Adaptation in pathology may reflect different functional condition: functional voltage, reduction or perversion of the function of the organ or tissue. In this regard, it can be manifested by various pathological processes: atrophy, hypertrophy, hyperplasia, organization, tissue restructuring, metaplasia, dysplasia.

Hypertrophy is the increase in the volume of an organ or tissue due to the enlargement of its component cells.

Pathogenesis of hypertrophy can be different. Depending on pathogenesis hypertrophy can be:

- Working hypertrophy
- Substitutive hypertrophy
- Humoral or neurohumoral

The most common type of hypertrophy is working hypertrophy. That can occur both in physiological conditions and pathological conditions. Etiology or working hypertrophy is increased workingload of organ or tissue. Example – hypertrophy of skeletal muscle and myocardium in athletes.

In abnormal conditions hypertrophy occurs as the result of pathological process that stimulates increase of organ`s function. So that means that working hypertrophy is hypertrophy of heavily functioning organ (tissue).

Working hypertrophy is observed in tissues consisting of stable, indivisible cells, in which adaptation to increased load can not be realized by increasing the number of cells. This type of hypertrophy is often found in hollow organs that have a wall of smooth muscles: the wall of the stomach, intestines, bladder. It is a morphological expression of chronic obstruction. The causes of this obstruction are various, for example, cicatricial stenosis of the pylorus result in the healing of ulcers of the stomach or of the bulb 12 duodenal ulcer, exophytic growing (i.e. growing in the lumen) intestinal tumors, adenomatous prostatic hyperplasia, which, squeezing the urethra, prevents the excretion of urine from the bladder. Compensation for the function of these organs is due to an increase in the smooth muscle of the wall above the obstacle. In clinical practice, the most important is the working hypertrophy of the heart.

Causes of heart hypertrophy can be:

- Intracardiac
- Extracardiac

Intracardiac means that a patient has a heart disease ex. Heart defects (both congenital and acquired).

Congenital heart defects are structural changes associated with distortion of the stages of intrauterine morphogenesis of the heart (atrial or ventricular septal defect, complete absence of

interventricular or atrial septum – three-chamber heart) or the final formation of the cardiovascular system after birth.

Acquired heart defects are characterized by lesion of the valvular apparatus of the heart, aorta, and occur as a result of heart disease after birth. The most common cause of these defects is rheumatism, at least – bacterial endocarditis, atherosclerosis, syphilis.

Intracardial causes of left ventricular hypertrophy:

- aortic stenosis;
- aortic valve insufficiency;
- mitral (bicuspid) valve insufficiency.

All extracardial causes, both in the small and in the large circle of blood circulation are united by one clinical symptom-hypertension, that is, an increase in intravascular pressure, in which the heart is forced to work hard.

Both of these mechanisms are accompanied by a reflex increase of the heart rate. To hard-working organ the flow of arterial blood increases, which leads to an increase in the level of metabolic processes. And if these factors act for a long time, working heart hypertrophy develops.

Intracardial causes of left ventricular hypertrophy:

- aortic stenosis;
- aortic valve insufficiency;
- mitral (bicuspid) valve insufficiency.

Non cardiac causes of hypertrophy of the left ventricle:

These are diseases that are accompanied by an increase in blood pressure in the large circle of blood circulation:

- hypertension;
- symptomatic hypertension (in diseases of the kidneys, endocrine glands-thyrotoxicosis, adrenal tumors, pituitary gland, etc.));
- General obesity (due to the increase in the volume of the microcirculatory bed).

Intracardiac causes hypertrophy of the right ventricle:

- stenosis of the mouth of the pulmonary artery;
- pulmonary valve insufficiency;
- insufficiency of the tricuspid valve;
- stenosis of the left atrioventricular orifice (mitral);
- mitral valve insufficiency (in the stage of left ventricular decompensation).

Extracardial causes of hypertrophy of the right ventricle of the heart can be lung diseases, accompanied by a decrease in the volume of the small circle of blood circulation and an increase in blood pressure in the pulmonary artery system:

- chronic diffuse emphysema of the lungs;
- pneumosclerosis of various etiologies: chronic nonspecific pneumonia, fibrosing alveolitis, chronic forms of pulmonary tuberculosis, pneumoconiosis (dust lung disease);
- chronic obstructive bronchitis;
- primary pulmonary hypertension.

Macroscopic view of hypertrophy of the heart: the heart is increased in volume, its mass increases. If the normal weight of the heart is on average 250.0-280.0 grams, in conditions of pathology it can reach one kilogram, and in rare cases more. The muscular wall of the hypertrophied heart is sharply thickened. Normal thickness of the left ventricular wall of 0.8-1.0 cm, in hypertrophy, up to 2-3 cm Normal thickness of right ventricle 0,2-0,4 cm, in hypertrophy thickened to 1.0-1.5 cm. Thickened interventricular septum, the papillary and trabecular muscles. The heart cavities are usually dilated, that is, hypertrophy develops according to the type of eccentric.

Microscopically, cardiomyocytes increase in volume, thicken, their nuclei become large, hyperchromic. At the same time in the stroma there is an increase in the number of capillaries and argyrophil fibers. Ultrastructural increase in the volume and number of cytoplasmic organelles in cells (mitochondria, myofibrils), synthetic apparatus (which includes endoplasmic reticulum, ribosomes and Golgi apparatus).

The outcome of the working hypertrophy. In principle, the working hypertrophy is reversible process provided that the cause is eliminated in time. For example, if the patient is timely made reconstructive surgery for congenital or acquired heart disease, the changes in the heart can have a reverse development and there is a return to normal.

As the weight of the organ increases, there is a relative lack of blood supply, that is, there is chronic ischemia. Metabolic processes in the hypertrophied heart are disturbed, dystrophic changes occur, and then irreversible changes - the death of cells with the growth of connective tissue in their place, that is, decompensation develops.

Vicar hypertrophy develops in paired organs (kidneys) or when removing part of the body, for example, in the liver, in the lungs.

Hormonal or correlative hypertrophy. An example of physiological hormonal hypertrophy is hypertrophy of the uterus during pregnancy. In conditions of pathology hormonal hypertrophy occurs as a result of disorders of the endocrine glands. An example of such hypertrophy can be acromegaly, due to hyperfunction of the anterior pituitary gland with excessive production of somatotropic hormone, which usually occurs on the basis of eosinophilic adenoma. In acromegaly increase size of organs and protruding parts of the skeleton. When the tumor is removed, the process is reversible.

There are also pathological hypertrophy. Pathological hypertrophy occurs in the absence of an appropriate stimulus – an increased functional need. Myocardial hypertrophy, occurring for

no apparent reason (in the absence of hypertension, valvular defects and congenital heart disease), is considered as an example of pathological hypertrophy and is called hypertrophic cardiomyopathy.

HYPERPLASIA

Hyperplasia or hypergenesis, is an increase in the amount of organic tissue that results from cell proliferation. It may lead to the gross enlargement of an organ, and the term is sometimes confused with benign neoplasia or benign tumor.

Hyperplasia is a common preneoplastic response to stimulus. Microscopically, cells resemble normal cells but are increased in numbers. Sometimes cells may also be increased in size (hypertrophy). Hyperplasia is different from hypertrophy in that the adaptive cell change in hypertrophy is an increase in the size of cells, whereas hyperplasia involves an increase in the number of cells.

Hyperplasia may be due to any number of causes, including proliferation of basal layer of epidermis to compensate skin loss, chronic inflammatory response, hormonal dysfunctions, or compensation for damage or disease elsewhere. Hyperplasia may be harmless and occur on a particular tissue. An example of a normal hyperplastic response would be the growth and multiplication of milk-secreting glandular cells in the breast as a response to pregnancy, thus preparing for future breast feeding.

Perhaps the most interesting and potent effect IGF has on the human body is its ability to cause hyperplasia, which is an actual splitting of cells. By contrast, hypertrophy is what occurs, for example, to skeletal muscle cells during weight training and steroid use and is simply an increase in the size of the cells. With IGF use, one is able to cause hyperplasia which actually increases the number of muscle cells present in the tissue. Weight training with or without anabolic steroid use enables these new cells to mature in size and strength. It is theorized that hyperplasia may also be induced through specific power output training for athletic performance, thus increasing the number of muscle fibers instead of increasing the size of a single fiber.

- Benign prostatic hyperplasia, also known as prostate enlargement.
- Cushing's disease – Physiopathology of hyperplasia of adrenal cortex due to increased circulating level of ACTH (adrenocorticotropic hormone).
- Congenital adrenal hyperplasia – Inherited disorder of gland (adrenal).
- Endometrial hyperplasia – Hyperproliferation of the endometrium, usually in response to unopposed estrogen stimulation in the setting of polycystic ovary syndrome or exogenous administration of hormones. Atypical endometrial hyperplasia may represent an early neoplastic process which can lead to endometrial adenocarcinoma. The development of endometrial adenocarcinoma from endometrial hyperplasia is a typical example of how the effects of pathologic hyperplasia can lead to neoplasia, and females who exhibit hyperplasia of the endometrium are indeed more likely to develop cancer of these cells.

- Hemihyperplasia when only half (or one side) of the body is affected, sometimes generating limbs of different lengths.

- Hyperplasia of the breast – "Hyperplastic" lesions of the breast include usual ductal hyperplasia, a focal expansion of the number of cells in a terminal breast duct, and atypical ductal hyperplasia, in which a more abnormal pattern of growth is seen, and which is associated with an increased risk of developing breast cancer.

ATROPHY is the partial or complete wasting away of a part of the body. Causes of atrophy include mutations (which can destroy the gene to build up the organ), poor nourishment, poor circulation, loss of hormonal support, loss of nerve supply to the target organ, excessive amount of apoptosis of cells, and disuse or lack of exercise or disease intrinsic to the tissue itself. In medical practice, hormonal and nerve inputs that maintain an organ or body part are said to have trophic effects. A diminished muscular trophic condition is designated as atrophy. Atrophy is reduction in size of cell, organ or tissue, after attaining its normal mature growth. In contrast, hypoplasia is the reduction in size of a cell, organ, or tissue that has not attained normal maturity.

Agenesis refers to the failure of an organ to develop during embryonic growth and development due to the absence of primordial tissue.

Aplasia is defined in general as "defective development or congenital absence of an organ or tissue.

Hypoplasia is underdevelopment or incomplete development of a tissue or organ.

Atrophy is the general physiological process of reabsorption and breakdown of tissues, involving apoptosis. When it occurs as a result of disease or loss of trophic support due to other diseases, it is termed pathological atrophy, although it can be a part of normal body development and homeostasis as well.

Muscle atrophies

Disuse atrophy of muscles and bones, with loss of mass and strength, can occur after prolonged immobility, such as extended bedrest, or having a body part in a cast (living in darkness for the eye, bedridden for the legs etc.). This type of atrophy can usually be reversed with exercise unless severe. Astronauts in microgravity must exercise regularly to minimize atrophy of their limb muscles.

There are many diseases and conditions which cause atrophy of muscle mass. For example, diseases such as cancer and AIDS induce a body wasting syndrome called cachexia, which is notable for the severe muscle atrophy seen. Other syndromes or conditions which can induce skeletal muscle atrophy are congestive heart failure and liver disease.

During aging, there is a gradual decrease in the ability to maintain skeletal muscle function and mass. This condition is called sarcopenia, and may be distinct from atrophy in its pathophysiology. While the exact cause of sarcopenia is unknown, it may be induced by a combination of a gradual failure in the satellite cells which help to regenerate skeletal muscle

fibers, and a decrease in sensitivity to or the availability of critical secreted growth factors which are necessary to maintain muscle mass and satellite cell survival.[2]

Dystrophies, myositis, and motor neuron conditions

Pathologic atrophy of muscles can occur with diseases of the motor nerves or diseases of the muscle tissue itself. Examples of atrophying nerve diseases include Charcot-Marie-Tooth disease, poliomyelitis, amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), and Guillain–Barré syndrome. Examples of atrophying muscle diseases include muscular dystrophy, myotonia congenita, and myotonic dystrophy.

Changes in Na+ channel isoform expression and spontaneous activity in muscle called fibrillation can also result in muscle atrophy.

Gland atrophy

The adrenal glands atrophy during prolonged use of exogenous glucocorticoids like prednisone. Atrophy of the breasts can occur with prolonged estrogen reduction, as with anorexia nervosa or menopause. Testicular atrophy can occur with prolonged use of enough exogenous sex steroids (either androgen or estrogen) to reduce gonadotropinsecretion.

Cachexia, or wasting syndrome, is loss of weight, muscle atrophy, fatigue, weakness and significant loss of appetite in someone who is not actively trying to lose weight.

Cachexia is seen in people with cancer, AIDS, coeliac disease, chronic obstructive pulmonary disease, multiple sclerosis, rheumatoid arthritis, congestive heart failure, tuberculosis, familial amyloid polyneuropathy, mercury poisoning (acrodynia), Crohn's disease, untreated/severe type 1 diabetes mellitus, anorexia nervosa and hormonal deficiency.

It is a positive risk factor for death, meaning if the person has cachexia, the chance of death from the underlying condition is increased dramatically. It can be a sign of various underlying disorders; when a patient presents with cachexia, a doctor will generally consider the possibility of adverse drug reactions, cancer, metabolic acidosis, certain infectious diseases (e.g., tuberculosis, AIDS), chronic pancreatitis and some autoimmune disorders. Cachexia physically weakens patients to a state of immobility stemming from loss of appetite, asthenia and anemia, and response to standard treatment is usually poor.

METAPLASIA - is the reversible transformation of one differentiated cell type to another differentiated cell type. The change from one type of cell to another may be part of a normal process, or caused by some sort of abnormal stimulus. In simplistic terms, it is as if the original cells are not robust enough to withstand their environment, so they transform into another cell type better suited to their environment. If the stimulus causing metaplasia is removed or ceases, tissues return to their normal pattern of differentiation. Metaplasia is not synonymous with dysplasia, and is not considered to be an actual cancer. It is also contrasted with heteroplasia, which is the spontaneous abnormal growth of cytologic and histologic elements. Today, metaplastic changes are usually considered to be an early phase of carcinogenesis, specifically for those with a history of cancers or who are known to be susceptible to carcinogenic changes.

Metaplastic change is often viewed as a premalignant condition that requires immediate intervention, either surgical or medical, because metaplasia is associated with cancer.

When cells are faced with physiological or pathological stresses, they respond by adapting in any of several ways, one of which is metaplasia. It is a benign (i.e. non-cancerous) change that occurs as a response to change of milieu (physiological metaplasia) or chronic physical or chemical irritation (pathological metaplasia). One example of pathological irritation is cigarette smoke that causes the mucus-secreting ciliated pseudostratified columnar respiratory epithelial cells that line the airways to be replaced by stratified squamous epithelium, or a stone in the bile duct that causes the replacement of the secretory columnar epithelium with stratified squamous epithelium (Squamous metaplasia). Metaplasia is an adaptation that replaces one type of epithelium with another that is more likely to be able to withstand the stresses it is faced with. It is also accompanied by a loss of endothelial function, and in some instances considered undesirable; this undesirability is underscored by the propensity for metaplastic regions to eventually turn cancerous if the irritant is not eliminated.

The cell of origin for many types of metaplasias are controversial or unknown. For example, there is evidence supporting several different hypotheses of origin in Barrett's esophagus. They include direct transdifferentiation of squamous cells to columnar cells, the stem cell changing from esophageal type to intestinal type, migration of gastric cardiac cells, and a population of resident embryonic cells which are present through adulthood.

TUMORS

Etiology of tumors

Agents that cause the formation of tumors are called oncogenic factors, those agents that cause cancer are called cancerogenic factors.

Nowadays there are four groups of reasons in oncogenesis: chemical, physical, viral and genetic factors.

According to the theory of *monoclonal origin*, the initial cancerogenic agent (the factor causing the tumor) causes mutations of a single cell, the division of which then occurs an amount of tumor cells.

Theory of *"tumoral area"* - cancerogenic agent effect on large amount of cells and it can cause a formation of neoplastic cells. The tumor can then develop as a result of the division of one or more cells within this field.

Theory of *genetic mutation.* Disorders in the genome due to heredity, spontaneous mutations or external agents can cause neoplasia if the growth-regulating genes are damaged. Tumor transformation occurs as a result of the activation (or derepression) of specific DNA sequences known as growth-regulating genes, or proto-oncogenes. These genes encode a number of growth factors and receptors for growth factors.

Theory of *viral oncogenes*.

Some RNA viruses contain nucleic acid sequences that are complementary to proto-oncogenes and can (under reverse transcriptase action) synthesize a viral DNA sequence that is essentially identical. These sequences are called viral oncogenes.

Theory of immune response disorder. According to this theory, neoplastic changes often occur in the cells of the body. As a result of DNA damage, neoplastic cells synthesize new molecules (neoantigens, tumor antigens). The body's immune system recognizes these neoantigens as “foreign”, which leads to the activation of a cytotoxic immune response that destroys neoplastic cells. Clinically detectable tumors occur only if they are not recognized and destroyed by the immune system.

Atypia is a pathologic term for a structural abnormality in a cell, i.e. it is used to describe atypical cells.

It may or may not be a precancerous indication associated with later malignancy, but the level of appropriate concern is highly dependent on the context with which it is diagnosed.

Atypia can be caused by an infection or irritation if diagnosed in a Pap smear, for example. In the uterus it is more likely to be precancerous. For example, already differentiated, specialised cells such as epithelia displaying "cellular atypia" are far less likely to become problematic (cancerous/ malignant) than are myeloid progenitor cells of the immune system. The 'further back' in an already specialised, differentiated cell's lineage, the more problematic cellular atypia is likely to be. This is due to the conferring of such atypia to progeny-cells further down the lineage of that cell type.

In current practice, microscopic analysis of haematoxylin and eosin stained section is the backbone in the diagnosis of breast cancer and other types of cancers. Traditionally, pathologists examine histological slides under a microscope, and make diagnostic decisions. This practice produces results which are subjective. Currently, efforts are being made to develop technology and systems which allow for the use of automated image analysis and machine learning techniques in grading cells which display atypia.

Types of atypia:

- Cell atypia
- Tissue atypia
- Functional atypia
- Antigenic atypia

Metastasis is a pathogenic agent's spread from an initial or primary site to a different or secondary site within the host's body; it is typically spoken of as such spread by a cancerous tumor. The newly pathological sites, then, are metastases (mets). It is generally distinguished from cancer invasion, which is the direct extension and penetration by cancer cells into neighboring tissues.

Cancer occurs after cells are genetically altered to proliferate rapidly and indefinitely. This uncontrolled proliferation by mitosis produces a primary heterogeneic tumour. The cells which constitute the tumor eventually undergo metaplasia, followed by dysplasia then anaplasia, resulting in a malignant phenotype. This malignancy allows for invasion into the circulation, followed by invasion to a second site for tumorigenesis.

Some cancer cells known as circulating tumor cells acquire the ability to penetrate the walls of lymphatic or blood vessels, after which they are able to circulate through the bloodstream to other sites and tissues in the body. This process is known (respectively) as lymphatic or hematogenous spread. After the tumor cells come to rest at another site, they re-penetrate the vessel or walls and continue to multiply, eventually forming another clinically detectable tumor.[citation needed] This new tumor is known as a metastatic (or secondary) tumor. Metastasis is one of the hallmarks of cancer, distinguishing it from

benign tumors. Most cancers can metastasize, although in varying degrees. Basal cell carcinoma for example rarely metastasizes.

When tumor cells metastasize, the new tumor is called a secondary or metastatic tumor, and its cells are similar to those in the original or primary tumor. This means that if breast cancer metastasizes to the lungs, the secondary tumor is made up of abnormal breast cells, not of abnormal lung cells. The tumor in the lung is then called metastatic breast cancer, not lung cancer. Metastasis is a key element in cancer staging systems such as the TNM staging system, where it represents the "M". In overall stage grouping, metastasis places a cancer in Stage IV. The possibilities of curative treatment are greatly reduced, or often entirely removed, when a cancer has metastasized.

Types of tumor growth:

- expansive;
- infiltrative;
- opposition

With the *expansive growth* tumor pushing the surrounding tissue. The tissues surrounding the tumor are atrophied, replaced by connective tissue and the tumor is surrounded by a capsule (pseudocapsule). Expansive tumor growth is usually slow, characteristic of Mature benign tumors. However, some cancers, such as fibrosarcoma, kidney cancer, can grow expansively.

With the *infiltrative growth* the boundaries of the tumor with infiltrative growth are not clearly defined. Infiltrative tumor growth is usually rapid and characteristic of immature, malignant tumors. Malignant neoplasms penetrate into normal tissue and form outgrowths of neoplastic cells, extending in all directions. Malignant neoplasms usually do not form capsules. Cancers and sarcomas have a similar nature of invasion, despite differences in their histogenesis. The germination of the basal membrane distinguishes invasive cancer from intraepithelial (or in situ) cancer.

Appositional tumor growth occurs due to neoplastic transformation of normal cells into tumor cells, which is observed in the tumor field. An example of such growth can serve as the anterior abdominal wall desmoids.

In relation to the lumen of the hollow organ distinguish *endophytic* and *exophytic* tumor growth. Endophytic growth is the infiltrative growth of the tumor deep into the organ wall. Exophytic growth is the expansive growth of a tumor into an organ cavity.

Appearance of the tumor. There are four main types of tumors on the macroscopic picture:

- node;
- infiltration;
- ulcer;
- cyst.

The *node* is a compact tumor with clear boundaries. A node can be in the form of pileus broad stalk of the polyp. Its surface can be smooth, bumpy or papillary and resemble cauliflower.

Infiltrate is a compact tumor without clear boundaries.

Ulcer – macroscopic appearance of the tumor in the tissue defect with near arched edges, bumpy bottom and infiltrative growth.

A cyst is a tumor with clear boundaries that have a cavity.

Blood supply of tumor. Circulation in tumor tissues is carried out from the bloodstream of the body through the vessels that exist in the surrounding tissue. Angiogenin-stimulates neoplasm of the capillary network of the tumor stroma. The tumor vessels are also atypical. Most often they are represented by vessels of sinusoid type with thin walls and a wide lumen. T he wall of the tumor vessels is often represented by a single layer of endothelial cells, located directly on the tumor tissue, or tumor cells itself (unclosed blood circulation system in the tumor).

Such features can lead to secondary changes in the form of hemorrhages, venous stasis, edema, thrombosis, necrosis, various types of dystrophy, inflammation.

NOMENCLATURE

1. According to the clinical course, all tumors are divided into benign and malignant.

A benign tumor is a mass of cells that lacks the ability to invade neighboring tissue or metastasize. These do not spread into, or invade, nearby tissues; however, they can sometimes be quite large. Malignant tumor has irregular shape, cells multiply rapidly, tumor grows by invading and destroying surrounding tissue.

2. Histogenetic-based on the determination of the tumor belonging to a specific tissue source of development. In accordance with this principle distinguish tumors:
    - epithelial tissue;
    - connective tissue;
    - muscle tissue;
    - vessels;
    - melaminovaya fabric;
    - nervous system and brain membranes;
    - blood systems;
    - teratoms.
    -

Epithelial tumors can develop from the epithelial and glandular epithelium.

A Mature benign tumor from the epithelium is called papilloma. A Mature benign tumor from the glandular epithelium is called adenoma.

Papilloma is a benign epithelial tumor growing exophytically (outwardly projecting) in nipple-like and often finger-like fronds. In this context papilla refers to the projection created by the tumor, not a tumor on an already existing papilla (such as the nipple).

When used without context, it frequently refers to infections (squamous cell papilloma) caused by human papillomavirus (HPV), such as warts. Human papillomavirus infection is a major cause of cervical cancer, although most HPV infections do not cause cancer.[citation needed] There are, however, a number of other conditions that cause papilloma, as well as many cases in which there is no known cause.

Adenoma is a benign tumor of epithelial tissue with glandular origin, glandular characteristics, or both. Adenomas can grow from many glandular organs, including the adrenal glands, pituitary gland, thyroid,

prostate, and others. Some adenomas grow from epithelial tissue in nonglandular areas but express glandular tissue structure (as can happen in familial polyposis coli). Although adenomas are benign, over time they may transform to become malignant, at which point they are called adenocarcinomas. Most adenomas do not transform. But even while benign, they have the potential to cause serious health complications by compressing other structures (mass effect) and by producing large amounts of hormones in an unregulated, non-feedback-dependent manner (causing paraneoplastic syndromes). Some adenomas are too small to be seen macroscopically but can still cause clinical symptoms.

Carcinoma is a category of types of cancer that develop from epithelial cells. Specifically, a carcinoma is a cancer that begins in a tissue that lines the inner or outer surfaces of the body, and that arises from cells originating in the endodermal, mesodermal or ectodermal germ layer during embryogenesis.

Carcinomas occur when the DNA of a cell is damaged or altered and the cell begins to grow uncontrollably and become malignant.

Adenocarcinoma

(adeno = gland) Refers to a carcinoma featuring microscopic glandular-related tissue cytology, tissue architecture, and/or gland-related molecular products, e.g., mucin.

Squamous cell carcinoma

Refers to a carcinoma with observable features and characteristics indicative of squamous differentiation (intercellular bridges, keratinization, squamous pearls).

Adenosquamous carcinoma

Refers to a mixed tumor containing both adenocarcinoma and squamous cell carcinoma, wherein each of these cell types comprise at least 10% of the tumor volume.

Anaplastic carcinoma

Refers to a heterogeneous group of high-grade carcinomas that feature cells lacking distinct histological or cytological evidence of any of the more specifically differentiated neoplasms. These tumors are referred to as anaplastic or undifferentiated carcinomas.

Large cell carcinoma

Composed of large, monotonous rounded or overtly polygonal-shaped cells with abundant cytoplasm.

Small cell carcinoma

Cells are usually round and are less than approximately 3 times the diameter of a resting lymphocyte and with little evident cytoplasm. Occasionally, small cell malignancies may themselves have significant components of slightly polygonal and/or spindle-shaped cells.

There are a large number of rare subtypes of anaplastic, undifferentiated carcinoma. Some of the more well known include the lesions containing pseudo-sarcomatous components: spindle cell carcinoma (containing elongated cells resembling connective tissue cancers), giant cell carcinoma (containing huge, bizarre, multinucleated cells), and sarcomatoid carcinoma (mixtures of spindle and giant cell carcinoma). Pleomorphic carcinoma contains spindle cell and/or giant cell components, plus at least a 10% component of cells characteristic of more highly differentiated types (i.e. adenocarcinoma and/or squamous cell carcinoma). Very rarely, tumors may contain individuals components resembling both carcinoma and true

sarcoma, including carcinosarcoma and pulmonary blastoma. A history of cigarette smoking is the most common cause of large cell carcinoma.

Carcinoma of unknown primary

The term carcinoma has also come to encompass malignant tumors composed of transformed cells whose origin or developmental lineage is unknown (see cancer of unknown primary origin; CUP), but that possess certain specific molecular, cellular, and histological characteristics typical of epithelial cells. This may include the production of one or more forms of cytokeratin or other intermediate filaments, intercellular bridge structures, keratin pearls, and/or tissue architectural motifs such as stratification or pseudo-stratification.

Lung diseases

Respiratory system diseases:

1. Bronchitis.
2. Pneumonias
3. Destructive lung diseases:
    a) abscess
    b) gangrene.
4. Chronic non-specific lung diseases.
5. Another lung diseases:
    a) tumors;
    b) malformation.

Bronchitis

1. Acute
2. Chronic

Acute bronchitis can be a separate disease or can be manifestation of other diseases such as pneumonia, chronic decompensated glomerulonephritis (acute uremic bronchitis).

About *chronic bronchitis* we are talking when clinical manifestation (in particular cough and sputum discharge) of disease observed for at least 3 months for at least two years.

Etiology and pathogenesis.

The most common reason of bronchitis:

1. Viral infection, especially respiratory syncytial virus - the so-called RS-virus.
2. Bacterial infection, among which the most common strains:
   a) Haemophilus influenzae;
   б) Streptococcus pneumoniae.
3. Chemical agents:
   a) cigarette smoke;
   b) nitrogen oxides;
   c) chlorine vapours;
   d) sulfur dioxide.
4. Exposure to physical agents:
   a) excessively dry or cold air;
   b) high humidity;
   c) radiation.
5. The impact of dust in high concentration:
   a) household;
   b) industrial.

Pathological anatomy and pathogenesis.

The pathogenic effect of these factors is facilitated by hereditary failure of protective barriers of the respiratory system, primarily mucocellular transport and humoral factors of local protection, and damage to mucocellular transport with the development of acute bronchitis is aggravated.

- Hyperemia desquamation, edema of mucous membranes
- Production of sticky or mucopurulent exudate
- The protective functions of bronchial cilia, phagocytes and lymphatic are disturbed.
- Bacteria may invade the bronchi
- Accumulation of cellular debris and mucopurulent exudate
- Cough, through distressing, is essential to eliminate bronchial secretions

- Airway obstruction :
    - Edema of the bronchial walls
    - Retained secretions
    - In some cases – spasm of bronchial muscules.

Complications of acute bronchitis are often associated with a violation of the drainage function of the bronchi, which contributes to the aspiration of infected mucus in the distal bronchial tree and the development of:

1. Lung tissue inflammation
2. Panbronchitis - inflammation of all layers of bronchial wall.

During prolonged influence of pathogenic factors of acute bronchitis may acquire a chronic form.

Pneumonia

The importance of immune defenses in preventing pul-monary infections is emphasized by patients with inherited or acquired defects in innate immunity (including neutrophil and complement defects) or adaptive immunity (e.g., humoral immunodeiciency), all of which lead to an cellincreased incidence of infections with pyogenic bacteria. For example, patients with mutations in MYD88, an adaptor protein required for signaling by Toll-like recep-tors, are extremely susceptible to severe necrotizing pneu-mococcal infections, while patients with congenital defects in IgA production (the major immunoglobulin in airways secretions) are at increased risk for pneumonias caused by encapsulated organisms such as pneumococcus and H. inluenzae. On the other hand, defects in TH1 cell–mediated immunity lead mainly to increased infections with intracellular microbes such as atypical mycobacteria. Much more commonly, lifestyle choices interfere with host immune defense mechanisms and facilitate infections. For example, cigarette smoke compromises mucociliary clearance and pulmonary macrophage activity, and alcohol impairs neu-trophile function as well as cough and epiglottic relexes (thereby increasing the risk for aspiration).Bacterial pneumonias are classiied according to the speciic etiologic agent or, if no pathogen can be isolated, by the clinical setting in which the infection occurs. Altogether, seven distinct clinical settings are recognized, each associated with a fairly distinct group of pathogens. Thus, consideration of the clinical setting can be a helpful guide when anti-microbial therapy has to be given empirically.

Etiological classification of pneumonia:

Community –Acquired Bacterial Pneumonia

- Streptococcus pneumonia
- Haemophilus influenza
- Moraxella catarrhalis
- Staphylococcus aureus
- Legionella pneumophila
- Enterobacteriaceae (Klebsiella pneumonia) and Pseudomonas spp.
- Mycoplasma pneumonia
- Chlamydia pneumonia

- Coxiella burnetii (Q fever)

Community –Acquired Viral Pneumonia

- Respiratory syncytial virus, human metapneumovirus, parainfluenza virus (children); influenza A and B (adults); adenovirus (military recruits)

Nosocomial

- Gram-negative rods belonging to Enterobacteriaceae (Klebsiella spp ., Serratia marcescens, Escherichia coli) and Pseudomonas spp .
- S. aureus (usuall y methicillin-resistant)

Aspiration Pneumonia

- Anaerobic oral flora (Bacteroides, Prevotella, Fusobacterium, Peptostreptococcus), admix ed with aerobic bacteria (S. pneumoniae, S. aureus, H. influenzae, and Pseudomonas aeruginosa)

Chronic Pneumonia

- Nocardia
- Actinomyces
- Granulomatous: Mycobacterium tuberculosis and atypical mycobacteria, Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis

Necrotizing Pneumonia and Lung Abscess

- Anaerobic bacteria (extremely common), with or without mixed aerobic inf ection
- S. aureus, K. pneumoniae, Streptococcus pyogenes, and type 3 pneumococcus (uncommon)

Pneumonia in the Immunocompromised Host

- Cytomegalovirus
- Pneumocystis jiroveci
- Mycobacterium avium complex (MAC)
- Invasive aspergillosis
- Invasive candidiasis
- “Usual” bacterial, viral, and fungal organisms (listed above)

Morphology.

Bacterial pneumonia has two patterns of anatomic distribution: lobular bronchopneumonia and lobar pneumonia. In the context of pneumonias, the term “consolidation,” used frequently, refers to “solidification” of the lung due to replacement of the air by exudate in the alveoli. Patchy consolidation of the lung is the dominant characteristic of **bronchopneumonia**, while consolidation of a large portion of a lobe or of an entire lobe defines **lobar pneumonia**. These anatomic cat-egorizations may be difficult to apply in individual cases because patterns overlap, and patchy involvement may evolve to become confluent over time, producing complete lobar consolidation. Moreover, the same organisms may produce either pattern depending on patient

susceptibility. Most important from the clinical standpoint are identification of the causative agent and determination of the extent of disease.

In **lobar pneumonia**, four stages of the inflammatory response have classically been described. In the first stage of congestion, the lung is heavy, boggy, and red. It is characterized by vascular engorgement, intraalveolar fluid with few neutrophils, and often the presence of numerous bacteria. The stage of **red hepatization** that follows is characterized by massive confluent exudation, as neutrophils, red cells, and fibrin fill the alveolar spaces. On gross examination, the lobe is red, firm, and airless, with a liver-like consistency, hence the term hepatiza-tion. The stage of **gray hepatization** that follows is marked by progressive disintegration of red cells and the persistence of a fibrinosuppurative exudate, resulting in a color change to grayish-brown. In the final stage of **resolution**, the exudate within the alveolar spaces is broken down by enzymatic digestion to produce granular, semifluid debris that is resorbed, ingested by macrophages, expectorated, or organized by fibro-blasts growing into it. Pleural fibrinous reaction to the underlying inflammation is often present in the early stages if the consolidation extends to the surface (**pleuritis**). It may resolve or undergo organization, leaving fibrous thickening or permanent adhesions.

Foci of **bronchopneumonia** are consolidated areas of acute suppurative inflammation. The consolidation may be confined to one lobe but is more often multilobar and frequently bilateral and basal because of the tendency of secretions to gravitate to the lower lobes. Well-developed lesions are slightly elevated, dry, granular, gray-red to yellow, and poorly delimited at their margins. Histologically, a neutrophil-rich exudate fills the bronchi, bronchioles and adjacent alveolar spaces.

Community-Acquired Viral Pneumonias

The most common causes of community-acquired viral pneumonias are inluenza types A and B, the respiratory syncytial viruses, human metapneumovirus, adenovirus, rhinoviruses, rubeola virus, and varicella virus. Nearly all of these agents also cause upper-respiratory tract infections (“common cold”).These pathologic viruses share a propensity to infect and damage resspiratory epithelium, producing an inlam-matory response. When the process extends to alveoli, there is usually interstitial inlammation, but some out-pouring of luid into alveolar spaces may also occur, so that on chest ilms the changes may mimic those of bacterial pneumonia. As a result, it is not possible to distinguish bacterial and viral pneumonia based on radiologic appear-ance alone. Moreover, damage leading to necrosis of the respiratory epithelium inhibits mucociliary clearance and predisposes to secondary bacterial infections. Such serious complications of viral infection are more likely in infants, older adults, malnourished patients, alcoholics, and immunosuppressed individuals.

Hospital-Acquired Pneumonias

Nosocomial, or hospital-acquired, pneumonias are deined as pulmonary infections acquired in the course of a hospital stay. These infections not only have an adverse impact on the clinical course of ill patients, but Infectionsalso add considerably to the burgeoning costs of health care. Nosocomial infections are common in hospitalized individuals with severe underlying disease, those who are immunosuppressed, or those on prolonged antibiotic regimens. Patients on mechanical ventilation are a par-ticularly high-risk group, and infections acquired in this setting

are given the designation ventilator-associated pneumonia. Gram-negative rods (members of Enterobacteriaceae and Pseudomonas spp.) and S. aureus are the most common isolates; unlike community-acquired pneumonias, S. pneu-moniae is not a common pathogen in the hospital setting.

Aspiration Pneumonia

Aspiration pneumonia occurs in debilitated patients or those who aspirate gastric contents while unconscious (e.g., after a stroke) or during repeated vomiting. Those affected have abnormal gag and swallowing relexes that facilitate aspiration. The resultant pneumonia is partly chemical, due to the extremely irritating effects of the gastric acid, and partly bacterial. Typically, more than one organism is recovered on culture, aerobes being more common than anaerobes.

Aspiration pneumonia is often necrotizing, pursues a fulminant clinical course, and is a frequent cause of death in individuals predisposed to aspiration. In those who survive, abscess formation is a common complication. Microaspiration, by contrast, occurs in many individuals, especially those with gastroesophageal relux, and may exacerbate other lung diseases but does not lead to pneumonia.

Lung Abscess

Lung abscess refers to a localized area of suppurative necrosis within the pulmonary parenchyma, resulting in the formation of one or more large cavities. The causative organism may be introduced into the lung by any of the following mechanisms:

- Aspiration of infective material from carious teeth orinfected sinuses or tonsils. This may occur during oralsurgery, anesthesia, coma, or alcoholic intoxication, andin debilitated patients with depressed cough relexes.
- Aspiration of gastric contents, usually accompanied byinfectious organisms originating in the oropharynx.
- As a complication of necrotizing bacterial pneumonias, par-ticularly those caused by S. aureus, Streptococcus pyo-genes, K. pneumoniae, Pseudomonas spp., and, rarely, type3 pneumococci. Mycotic infections and bronchiectasisalso may lead to lung abscesses.
- Bronchial obstruction, particularly with bronchogeniccarcinoma obstructing a bronchus or bronchiole.Impaired drainage, distal atelectasis, and aspiration ofblood and tumor fragments all contribute to the devel-opment of abscesses. An abscess also may form withinan excavated necrotic portion of a tumor
- Septic embolism, from infective endocarditis of the rightside of the heart.
- In addition, lung abscesses may result from hema-togenous spread of bacteria in disseminated pyogenicinfection. This occurs most characteristically in staphy-lococcal bacteremia and often results in multiple lungabscesses.

Anaerobic bacteria are present in almost all lung abscesses, and they are the exclusive isolates in one-third to two-thirds of cases. The most frequently encountered anaer-obes are commensals

normally found in the oral cavity, principally species of Prevotella, Fusobacterium, Bacteroides, Peptostreptococcus, and microaerophilic streptococci.

Morphology

Abscesses range in diameter from a few millimeters to large cavities 5 to 6 cm across. The localization and number of abscesses depend on their mode of development. Pulmonary abscesses resulting from aspiration of infective material **are more common on the right side** (with its more vertical airways) than on the left, and most are single. On the right side, they tend to occur in the posterior segment of the upper lobe and in the apical segments of the lower lobe, because these locations reflect the probable course of aspirated material when the patient is recumbent. Abscesses that develop in the course of pneumonia or bronchiectasis commonly are multiple, basal, and diffusely scattered. Septic emboli and abscesses arising from hematogenous seeding are commonly multiple and may affect any region of the lungs.

As the focus of suppuration enlarges, it almost inevitably ruptures into airways. Thus, the contained exudate may be partially drained, producing an air-fluid level on radiographic examination. Occasionally, abscesses rupture into the pleural cavity and produce bronchopleural fistulas, the consequence of which is **pneumothorax** or **empyema**. Other complications arise from embolization of septic material to the brain, giving rise to meningitis or brain abscess. On histologic examination, as expected with any abscess, the suppurative focus is surrounded by variable amounts of fibrous scarring and mononuclear infiltration (lymphocytes, plasma cells, macrophages), depending on the chronicity of the lesion.

Gangrene of the lung is the most severe type of acute destructive processes of the lungs. It usually complicates pneumonia and lung abscess of any origin when attaching putrefactive microorganisms. The lung tissue is exposed to wet necrosis, becomes gray-dirty, produces a bad smell. Gangrene of the lung usually leading to death.

Inflammatory stomach diseases

Inflammatory processes in stomach, **gastritis** (*gaster* - stomach), like in any other organs can be acute and chronic.

ACUTE GASTRITIS

Acute gastritis most often develops after exposure to various chemicals (such as alcohol, substandard food) or certain drugs (especially non-steroidal anti-inflammatory substances containing aspirin). These substances cause rapid exfoliation of epithelial cells and reduce secretion of mucus, which is accompanied by a decrease in the function of the protective barrier against the action of acid. A huge role in the pathogenesis of this process plays decrease of prostaglandins synthesis . A certain role can be played by the use of spicy, cold or hot food.

Acute neutrophil gastritis (in which the main morphological feature - infiltration of polymorphonuclear leukocytes) is characteristic of the primary response to infection caused by Helicobacter pylori. This condition is temporary, which in most people has no clinical

manifestation and after 3-4 weeks goes into chronic gastritis. Only in a some cases the infection spontaneously disappears and the patients recover. Another infection agents such as Salmonella, Staphylococcus, etc. can lead to development of acute gastritis. It can also develop under the influence of toxic products of endogenous origin, for example, eliminative gastritis in uremia.

Classification due to the area of defeat:

- acute diffuse gastritis;
- acute focal gastritis.

Acute focal gastritis can be mainly localized in fundus, antral, and pylorus, pyloric antrum, pyloroduodenal section of stomach. Depending on the severity of the lesion, changes in the mucosa range from vasodilation and edema of lamina propria to erosion and hemorrhage. Erosion is a portion of the mucous membrane with a partial violation of the epithelium. Erosion in acute gastritis is usually multiple, so bleeding from them can be very dangerous. However, usually there is a rapid (within 24-48 hours) healing by regeneration. With frequent relapses of acute gastritis, chronic gastritis can develop.

CHRONIC GATRITIS

The most common cause of chronic gastritis is infection with the bacillus Helicobacter pylori. Autoimmune gastritis, typically associated with gastric atrophy, represents less than 10% of cases of chronic gastritis but is the most common cause in patients without H. pylori infection.

The signs and symptoms associated with chronic gastritis typically are less severe but more persistent than those of acute gastritis. Nausea and upper-abdominal discomfort may occur, sometimes with vomiting, but hematemesis is uncommon.

Types of chronic gastritis

Etiology	Pathogenesis	Histological changes	Clinical manifestation
Autoimmune	Antibodies to parietal cells and Castle factor`s recetors. Sensitized T-cells.	Atrophy of the glands in the body of the stomach. Intestinal metaplasia.	Pernicious anemia
H. pilori	Cytotoxins. Mucolytic enzymes. Synthesis of ammonium ions by bacterial urease.	Active chronic inflammation. Multifocal atrophy, mainly in a pylorus. Intestinal metaplasia.	Peptic ulcer Gaster cancer

	Tissue damage in the immune response.		
Chemical lesion Nonsteroidal anti-inflammatory drugs Bile reflux Alcohol	Direct damage. Damage to the mucous layer.	Epithelial hyperplasia. Edema. Vasodilation. A small number of cells of inflammation.	Peptic ulcer Gaster cancer

Other forms of gastritis

Separately, there are the following types of chronic gastritis:

- lymphocytic;
- eosinophilic;
- granulomatous.

In **lymphocytic gastritis**, the main histological manifestation is the presence of numerous Mature lymphocytes in the surface layers of the epithelium. This form is sometimes found in patients with specific erosions that go along the enlarged folds of the mucosa. The etiology and relationship with Helicobacter-associated gastritis have not been established.

Eosinophilic gastritis is characterized by mucosal edema and the presence of numerous eosinophils in the inflammatory infiltrate. It is assumed that eosinophilic gastritis is an allergic response to the food antigen to which the patient is sensitized.

Granulomatous gastritis is a rare form of gastritis, in which epithelioid granulomas are formed. These granulomas can be a manifestation of Crohn's disease or sarcoidosis.

PEPTIC ULCER DISEASE OF STOMACH AND DUODENUM

Peptic ulcer disease - is a sore on mucous membrane, accompanied by the disintegration of tissue and the underlying tissues of the digestive tract as a result of damage to their acid and pepsin. Ulcers in the clinical course are divided into acute and chronic.

Acute ulcer:

Causes of acute ulcer may be :

1. Severe acute gastritis. Deep spread of erosions in acute gastritis usually occurs when using non-steroidal anti-inflammatory drugs or alcohol, in the treatment of corticosteroids, which leads to the appearance of deep ulcers.
2. Strong stress. Acute ulcers can occur as a result of various factors that lead to stress, for example, with extensive burns, brain injuries. In this case, ulcers are formed as a result of mucosal ischemia, which leads to a decrease in its resistance to acid.

3. Increase in acidity. Increased acidity, for example, in patients with gastrin-secreting tumors (Zollinger-Ellison syndrome), leads to the formation of multiple ulcers in the antral part of the stomach, 12-duodenum and even jejunum.

Chronic ulcer:

Causes of chronic ulcer may be :

1. *Helicobacter pylori*.
2. Chemical agents, steroid drugs and non-steroidal anti-inflammatory drugs.
3. Chronic distress syndrome.

Chronic peptic ulcers are most often formed in the area of various types of mucous membranes. For example, in the stomach ulcers are observed at the site of the body's transition to the antral part, in the duodenum-in the proximal area on the border with the pylorus, in the esophagus – in the multilayer epithelium before the esophageal – gastric connection, postoperative ulcers are localized in the stoma (in the anastomosis). In other words, ulcers appear in area where acid and pepsin come into contact with the unprotected mucosa.

Pathogenesis. For many years, it was believed that the cause of peptic ulcer is increased acidity. However, in many cases observed patients normal and even reduced acidity of gastric juice. Conversely, patients with high acidity rarely observed the formation of ulcers. In addition, in the treatment of antacids (drugs that reduce acidity), relapses were observed in many cases. This led to the idea that the main importance in the development of ulcers is not acidity, and the ratio of factors of aggression and factors of mucosal protection. I believe that in the Genesis of peptic ulcer of the duodenum plays a major role in the increase of the factors of aggression and the development of gastric ulcer in the first place stands the reduction of the protection factors. While reducing the last possible development of ulcers, even at low pH.

Peptic ulcer disease of stomach. Gastric juice is a highly acidic medium (pH < 2), so the unprotected mucosa is quickly subjected to autologous digestion. Protection of the mucous membrane is carried out by the mucous-bicarbonate barrier and the surface epithelium. The mucous barrier plays a major role in protecting the mucosa. The surface cells of the mucosa secrete viscous neutral glycoproteins, which form a layer of mucus on the surface of the mucosa. Mucus itself has anti-acid properties, however, its protective power is enhanced by the presence of buffer ingredients, mainly bicarbonate ions.

The surface epithelium forms a **second line of protection**; to ensure this function, the correct functioning of both the apical membrane that prevents the transport of ions and the synthetic apparatus that produces bicarbonates is necessary. Both of these functions depend on the blood supply to the mucous membrane

Ulceration occurs as a result of or **violation and destruction of the mucous barrier**, or violation of the integrity of the epithelium. As a result of bile reflux, the mucous barrier is easily destroyed by its components. Acid and bile together destroy the surface epithelium, increasing the permeability and vulnerability of the mucous membrane. This leads to stagnation and swelling in lamina propria, which is observed in reflux gastritis.

The epithelial barrier can also be broken by the use of NSAIDs, because they violate the synthesis of prostaglandins, which normally protect the epithelium. Also in the destruction of the epithelium plays a significant role Helicobacter pylori infection, in which the destructive effect of both cytotoxins and ammonium ions, and inflammatory reaction.

Duodenum ulcer. Increased acidity plays a major role in the development of duodenal ulcers. Half of the patients have hypersecretion of acid, however, even with normal gastric acidity, the daily cycle of secretion may be disrupted: there is no decrease in secretion at night. It is also known that the stimulation of gastrin in patients infected with Helicobacter pylori, acid synthesis 2-6 times higher than that of uninfected.

Factors that damage the anti-acid protection in the stomach usually do not affect the duodenum: Helicobacter pylori does not colonize the mucous membrane of the duodenum, the mucosa is resistant to the action of bile and ions of pancreatic juice, drugs are significantly absorbed before entering the intestine. However, Helicobacter pylori affects ulceration, because the infection promotes gastric hypersecretion, which causes the development of gastric metaplasia in the duodenum, and then the colonization of the metaplastic epithelium Helicobacter pylori, which leads to the development of chronic inflammation, which also provokes ulceration.

Morphological changes. Macroscopically chronic ulcers usually have a rounded or oval shape. Their sizes, as a rule, do not exceed 2 cm in diameter, however cases when ulcers reached 10 cm in diameter and more are described. The depth of the ulcer is different, sometimes it reaches the serous membrane. The edges of the ulcer are clear, dense and rise above the normal surface.

In the period of exacerbation (acute period) microscopically in the bottom of the ulcer is found nekrotized tissue and exudate full of polymorph cells. In the vessels tissues that were replaced by connective tissue, fibrinoid changes and significant narrowing of blood vessels as a result of the proliferation of intima are often observed.

Complications. Healing of ulcers leads to regeneration of the epithelium and fibrosis of the underlying tissues. In this case, as a result of reduction and compaction of scars, **narrowing of the lumen of the organ** can develop: pyloric stenosis or Central narrowing of the stomach (stomach in the form of an hourglass). **Perforation** the wall of the stomach or duodenum is also possible, while the contents of the digestive tract is poured into the abdominal cavity, which leads to the development of peritonitis. When **penetration** occurs, the ulcer perforates into the closer lying organs, for example, the pancreas or liver. Erosion of blood vessels can cause **bleeding**, which can be fatal. At long existence of the stomach ulcer can lead to **malignization**, ulcer 12 duodenal ulcer malignizates very rare.

STOMACH CANCER

Stomach cancer, also known as gastric cancer, is a cancer which develops from the lining of the stomach.

The most common causes are

- infection by the bacterium Helicobacter pylori, which accounts for more than 60% of cases. Certain types of H. pylori have greater risks than others.
- Smoking, dietary factors such as pickled vegetables and obesity are other risk factors.
- About 10% of cases run in families, and between 1% and 3% of cases are due to genetic syndromes inherited from a person's parents such as hereditary diffuse gastric cancer.

Most cases of stomach cancers are gastric carcinomas.This type can be divided into a number of subtypes. Lymphomas and mesenchymal tumors may also develop in the stomach. Most of the time, stomach cancer develops in stages over years.

Globally, stomach cancer is the fifth leading cause of cancer and the third leading cause of death from cancer, making up 7% of cases and 9% of deaths.In 2012, it newly occurred in 950,000 people and caused 723,000 deaths. Before the 1930s, in much of the world, including most Western developed countries, it was the most common cause of death from cancer. Rates of death have been decreasing in many areas of the world since then. This is believed to be due to the eating of less salted and pickled foods as a result of the development of refrigeration as a method of keeping food fresh.[18] Stomach cancer occurs most commonly in East Asia and Eastern Europe. It occurs twice as often in males as in females.

Morphology.

- Gastric adenocarcinoma is a malignant epithelial tumour, originating from glandular epithelium of the gastric mucosa. Stomach cancers are overwhelmingly adenocarcinomas (90%). Histologically, there are two major types of gastric adenocarcinoma (Lauren classification): intestinal type or diffuse type. Adenocarcinomas tend to aggressively invade the gastric wall, infiltrating the muscularis mucosae, the submucosa and then the muscularis propria. Intestinal type adenocarcinoma tumour cells describe irregular tubular structures, harbouring pluristratification, multiple lumens, reduced stroma ("back to back" aspect). Often, it associates intestinal metaplasia in neighbouring mucosa. Depending on glandular architecture, cellular pleomorphism and mucosecretion, adenocarcinoma may present 3 degrees of differentiation: well, moderate and poorly differentiated. Diffuse type adenocarcinoma (mucinous, colloid, linitis plastica or leather-bottle stomach) tumour cells are discohesive and secrete mucus, which is delivered in the interstitium, producing large pools of mucus/colloid (optically "empty" spaces). It is poorly differentiated. If the mucus remains inside the tumour cell, it pushes the nucleus to the periphery: "signet-ring cell".
- Around 5% of gastric malignancies are lymphomas (MALTomas, or MALT lymphoma).
- Carcinoid and stromal tumors may occur.

Complications. Frequent complications of gastric cancer include:

- emaciation (cachexia), which is caused by malnutrition and intoxication;
- chronic anemia associated with fasting (impaired digestion), small frequent blood loss, impaired production of the anti-anemic factor (factor of castle), tumor intoxication metastases, in marrow (violation gemopoaiza);
- General acute anaemia that may occur as a result of large vessel corrosion and cause of death;

- perforation of tumor gastric ulcer and development of peritonitis;
- a phlegmon of stomach as a result of infection;
- the development of gastric and intestinal obstruction, which occurs during germination and compression of the lumen of the pylorus and intestine (more often);
- the development of mechanical jaundice, portal hypertension, ascites as a result of the tumor germination of the head of the pancreas, bile ducts, portal vein or compression of their metastases in the lymph nodes of the liver gate.

APPENDICITIS

Appendicitis is inflammation of the appendix. Acute appendicitis seems to be the end result of a primary obstruction of the appendix. Once this obstruction occurs, the appendix becomes filled with mucus and swells. This continued production of mucus leads to increased pressures within the lumen and the walls of the appendix. The increased pressure results in thrombosis and occlusion of the small vessels, and stasis of lymphatic flow. At this point spontaneous recovery rarely occurs. As the occlusion of blood vessels progresses, the appendix becomes ischemic and then necrotic. As bacteria begin to leak out through the dying walls, pus forms within and around the appendix (suppuration). The end result is appendiceal rupture (a 'burst appendix') causing peritonitis, which may lead to sepsis and eventually death. These events are responsible for the slowly evolving abdominal pain and other commonly associated symptoms.[

The causative agents include bezoars, foreign bodies, trauma, intestinal worms, lymphadenitis and, most commonly, calcified fecal deposits that are known as appendicoliths or fecoliths.[18][19] The occurrence of obstructing fecaliths has attracted attention since their presence in people with appendicitis is higher in developed than in developing countries. In addition an appendiceal fecalith is commonly associated with complicated appendicitis. Fecal stasis and arrest may play a role, as demonstrated by people with acute appendicitis having fewer bowel movements per week compared with healthy controls.

The occurrence of a fecalith in the appendix was thought to be attributed to a right-sided fecal retention reservoir in the colon and a prolonged transit time. However, a prolonged transit time was not observed in subsequent studies. From epidemiological data, it has been stated that diverticular disease and adenomatous polyps were unknown and colon cancer exceedingly rare in communities exempt from appendicitis. And acute appendicitis has been shown to occur antecedent to cancer in the colon and rectum. Several studies offer evidence that a low fiber intake is involved in the pathogenesis of appendicitis. This low intake of dietary fiber is in accordance with the occurrence of a right-sided fecal reservoir and the fact that dietary fiber reduces transit time.

Morphology.

The following morphological forms of appendicitis distinguished:

- simple
- superficial
- destructive:
    - phlegmonous
    - apostematous
    - phlegmonous-ulcerative
    - gangrenous

All these forms are a morphological reflection of the phases of acute inflammation in the Appendix, which, ultimately, ends with necrosis. The duration of this process is 2-4 days.

For **acute simple appendicitis** is characterized by the presence of stasis in the capillaries and venules, edema, hemorrhage, regional standing of leukocytes, leukodepleted most often in the distal Appendix. Externally, the Appendix looks normal, however, the diagnosis is confirmed by histological examination.

Acute superficial appendicitis is characterized by the presence in the distal part of the focus of exudative purulent inflammation in the mucous membrane, referred to as the primary affect.

Changes inherent in simple or superficial appendicitis may be reversible. However, as a rule, they progress and **develop destructive appendicitis**. By the end of the first day leukocyte infiltrate (dominated by neutrophils) extends to the entire thickness of the wall of the process (**phlegmonous appendicitis**). Macroscopically inflamed Appendix looks edematous and red, its surface is often covered with fibrinous purulent exudate. Sometimes on this background revealed multiple small ulcers, in this case this Appendix referred to as aposematism. Acute inflammation of the mucous membrane leads to the formation of ulcers and inflammation of the muscle layer – a **phlegmonous-ulcerative appendicitis**. The purulent-destructive changes are completed by the development of **gangrenous appendicitis**. The process in this form is thickened, the wall of its gray-dirty color, structureless with a fetid smell, pus is released from the lumen. Microscopically, there are extensive foci of necrosis with colonies of microbes, hemorrhages, blood clots in the vessels.

Complications. Local spread of the inflammatory process can lead to the involvement of periappendicular tissues, which is manifested by the development of “appendicular infiltration” or abscess. As a result of perforation, peritonitis may develop. Distant abscesses may also be formed (for example, in the rectal-vesicular and subdiaphragmatic spaces). Very rarely there may be spread of the inflammation in the veins that leads to the development of thrombophlebitis of the portal vein with the formation of multiple pylephlebitis liver abscesses.