МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ БЕЛАРУСЬ

УЧРЕЖДЕНИЕ ОБРАЗОВАНИЯ
«ГОМЕЛЬСКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ»

Кафедра патологической физиологии

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ЧАСТНАЯ ПАТОФИЗИОЛОГИЯ

Учебно-методическое пособие для иностранных студентов,
обучающихся на английском языке

В двух частях

Часть 2

SYSTEMIC PATHOLOGICAL PHYSIOLOGY

Teaching workbook for foreign students educated in English

In two parts

Part 2

Гомель
ГомГМУ
2012

УДК 616–092(072)=20
ББК 52.52
Е 72

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Е 72 Частная патофизиология: учеб.-метод. пособие для иностранных студентов, обучающихся на английском языке: в 2 ч. = Systemic pathological physiology: teaching workbook for foreign students educated in English: in two parts / О. А. Ермакова, Т. С. Угольник; пер. на англ. яз. О. А. Ермакова. — Гомель: учреждение образования «Гомельский государственный медицинский университет», 2012. — Ч. 2. — 112 с.
ISBN 978-985-506-380-4

Цель учебно-методического пособия — углубить и закрепить знания студентов при изучении общей патологической физиологии.

Составлено в соответствии с типовой учебной программой по патологической физиологии для студентов медицинских вузов, обучающихся на английском языке, утвержденной Министерством здравоохранения Республики Беларусь 7 июля 2009 г.

Утверждено и рекомендовано к изданию Центральным учебным научно-методическим советом учреждения образования «Гомельский государственный медицинский университет» 27 апреля 2011 г., протокол № 5.

УДК 616–092(072)=20
ББК 52.52

ISBN 978-985-506-380-4 (Ч. 2)
ISBN 978-985-506-371-2

THE LIST OF ABBREVIATION

ACC	— American College of Cardiology
ACh	— acetylcholine
ACTH	— adrenocorticotropic hormone
ADH	— antidiuretic hormone
AHA	— American Heart Association
ALL	— Acute lymphoblastic leucosis
ALT	— Alanine transaminase
AML	— Acute myeloid leucosis
ANA	— antinuclear antibodies
ANS	— autonomic nervous system
anti-TB drugs	— antitubercular drugs
APTT	— activated partial thromboplastin time
ARDS	— adult respiratory distress syndrome
AST	— aspartate transaminase
ATP	— adenosine triphosphate
BAS	— biologically active substances
BMR	— basal metabolic rate
Ca	— calcium
CagA	— cytotoxin association gene A
CCK	— cholecystokinin
CFR	— creatinine filtration rate
CLL	— chronic lymphocytic leucosis
CML	— chronic myeloid leucosis
CNCP	— chronic noncancer pain
CNS	— central nervous system
COX	— cyclooxygenase
CPS	— complex partial seizure
Cu	— cuprum
CVD	— cardiovascular diseases
DIC-syndrome	— disseminated intravascular coagulation syndrome
DNA	— deoxyribonucleic acid
EBV	— Epstein Barr Virus
EEG	— electroencephalogram
e. g.	— from Latin *exampli gratia* meaning «for example»
Er	— erythrocytes
esp.	— especially

FAB-classification — Franch-American-British classification
FC — functional classes
Fe — ferrum
FEV_1 — forced expiratory volume in one second
FSH — follicle-stimulating hormone
G-6-PD — glucose-6-phosphate dehydrogenase
GBM — glomerular basement membranes
GF — glomerular filr
GH — growth hormone
GHS — glutathione
GIP — glucose-dependent insulinotropic polypeptide
GIT — gastrointestinal tract
GLP-1 — glucagon-like peptide-1
GnRH — gonadotropin-releasing hormone
GSSG — glutathione disulfide
GTH — gonadotropic hormone
Hb — hemoglobin
HCl — hydrochloric acid
HDL — high-density lipoprotein
HIV — human immunodeficient virus
IASP — International Association for the Study of Pain
ICP — intracranial pressure
i. e. — from Latin *id est* meaning «that is»
Ig — immunoglobulin
IGF — insulin-like growth factor
IHD — ischemic heart disease
IL-1 — interleukin-1
ISF — intensity of structure functioning
LCAT — lecithin-cholesterol acyltransferase
LDH — lactate dehydrogenaze
LDL — low-density lipoprotein
Le — leucocytes
LGM — lymphogranulomatosis
LH — luteinizing hormone
LKM — liver/kidney microsomes
LT C_4 — leukotriene C_4
MCV — mean cell volume

MDS	— myelodysplastic syndrome
Me	— metal
MI	— myocardial infarction
N	— normal
NADPH	— nicotinamiddinucleatide phosphate
NS	— nervous system
NSAID	— nonsteroidal anti-inflammatory drugs
PA	— pernicious anemia
PAF	— platelet activating factor
PCR	— polymerase chain reaction
PIH	— prolactin-inhibitory hormone
PT	— prothrombin
PTT	— partial thromboplastin time
PYY	— peptide YY
RARS	— refractory anemia with ringed sideroblasts
RBC	— red blood cells
RES	— reticuloendothelium system
SLA	— soluble liver antigen
SLE	— systemic lupus erythematosus
SMA	— smooth muscle antibodies
STH	— somatotropic hormone
TH	— thyroid hormone
Tr	— trombocytes
TRH	— thyroid-releasing hormone
TSH	— thyroid-stimulating hormone
TTH	— thyroitropic hormone
UDP	— glucuronide transferase activity
VacA	— vacuolating cytotoxin gene A
VLDL	— very low dense lipoproteins
VPR	— ventilation-perfusion ratio
vWF	— von Willebrand factor
WHO	— World Healthcare Organization

PATHOLOGICAL PHYSIOLOGY OF THE ERYTHROCYTE SYSTEM

Anemia means deficiency of hemoglobin in the blood, which can be caused by either few RBCs or too little Hb in the cells.

The classitication of anemia is shown in the table 1.

Table 1 — Classification of anemia

According to cause	Primary Secondary
According to the rate of development	Acute Chronic
According to mechanism	Post-hemorrhagic Hemolytic Dyserythropoietic
According to hemopoietic type	Erythroblastic Megaloblastic
According to regeneratoric ability of bone marrow	Regeneratoric — 0,2–1 % of reticulocytes; hyperregeneratoric — more than 1 % of reticulocytes; hyporegeneratoric less than 0,2 % of reticulocytes; aregeneratoric — 0 % of reticulocytes; aplastic — 0 % of reticulocytes
According to color index	normochromic — 0,85–1,05; hyperchromic — more than 1,05; hypochromic — less tha0,85
According to Er size	normocytic — 7,2–8,3 mcm; microcytic — less tha7,2 mcm; macrocytic — more than 8,3–12 mcm; megalocytic — 12–15 mcm
According to severity	mild — Hb > 100g/l; Er >3,0·10^{12} /l; medium — Hb – 100–66g/l; Er – 3,0 – 2,0·10^{12} /l; severe — Hb <66g/l; Er< 2,0·10^{12} /l

Some types of anemia and their physiologic causes are the following:

Iron deficiency anemia

Iron is important for Hb formation and also myoglobin, cytochromes, cytochrome oxidase, peroxidase, catalase. The total quantity of iron in the body averages 4 to 5 g, about 65 percent of which is in the form of Hb. About 4 % in the form of myoglobin, 1 % in various heme compounds, that promote intracellular oxydation, 0,1 % is combined with the proteinin the blood plasma, and 15 to 30 % is stored for later use, mainly in the reticuloendothelial system and liver parenchymal cells in the form of ferritin.

The causes of iron deficiency are shown in the table 2.

Table 2 — Causes of iron deficiency

Reproductive system	Menorrhagia
GI tract	Oesophagits, oesophageal varices, hiatus hernia (ulcerated), peptic ulcer, inflammatory bowel disease, haemorrhoids, carcinoma, stomach, colorectal pathology (rarely angiodysplasia, hereditary haemorrhagic telangiectasia)
Malabsorption	Coeliac disease, atrophic gastritis (note may also result from Fe deficiency), gastroectomy
Physiological	Growth spurts, pregnancy
Dietary	Vegans, elerly
Genitourinary system	Haematuria (uncommon cause)
Others	PNH, e. g. frequent venecection, blood donation
Worldwide	Commonest cause is hookwork infestation
Assesment	
Clinical history	Review potential sources of blood loss, especially GIT loss
Menstrual loss	Quatitation may be difficult, ask about number of tampons used per day, how often these require changing, and duration
Other sources of blood loss	E. g., haematuria and haemoptysis (these are not common causes of iron deficiency). Ask patient if he/she has been a blood donor — regular blood donation over many yearsmay cause chronic iron store depletion
Drug therapy	E. g. NSAIDs and corticosteroids may cause GI irritation and blood loss
Past medical history	E. g. previous gastric surgery (results in malabsorption). Ask about episodes of anemia and treatment with iron

Laboratory tests

— Hb and hematocrit are depressed usually to moderate levels;
— associated with hypochromia, microcytosis and some poikilocytosis;
— the serum iron and serum ferritin are low;
— the transferring concentration is high.

Megaloblastic anemias

The causes of megaloblastic anemias are shown in the table 3.

Table 3 — Causes of megaloblastic anemias

Pernicious anemia	Commonest due to autoimmue gastric atrophy resulting in loss of intrinsic factor production required for absorption of $B_{12.}$ Incidence increases more than 40 years and often associated with other autoimmune problems, e. g. hypothyroidism
Following total gastroectomy	May develop after major partial gastroctomy
Ileal disease	Resection of ileum, Crohn's disease
Blind loop syndromes	E. g. diverticuolae or localized inflammatory bowel changes allowing bacterial over growth which then completes for available B_{12}
Fish tapeworm	Diphylobothrium latum
Malabsorptive disorders	Tropical sprue, celiac disease
Dietary deficiency	E. g. vegans

Other causes of megaloblastic anemias

Megaloblastic anemia not due to actual deficiency of either B_{12} or folate is uncommon, but may occur in the following situations.

Congenital

Transcobalamin II deficiency — absence of the key B_{12} transport protein result in severe megaloblastic anemia (will correct with parenteral B_{12}).

Congenital intrinsic factor deficiency — autosomal recessive, result in failure to produce intrinsic factor. Presents as megaloblastic anemia up to age of 2 years and responds to parenteral B_{12}.

Inborn errors of metabolism — errors in folate pathways, also occurs in orotic aciduria and Lesch-Nychan syndrome.

Megaloblastosis commonly present in the congenital dyserythropoitic anaemias.

Acquired

MDS — often present in sideroblastic anaemia (RARS).

Acute leukemia — megaloblastic-like erythroid dysplasia in AML M6.

Drug induced — secondary to antimetabolic drugs inducing 6-mercaptopurine, cytosine arabinoside, zidovudine and hydroxyurea.

Anaesthetic agents — transient megaloblastic change after nitrous oxide.

Alcohol excess — may result in absence of measurable folate deficiency.

Vitamin C deficiency — occasionally results in megaloblastic change.

- *Vitamin B_{12}* and *folic acid* are essential for the synthesis of DNA, because each in a different way is required for the formation of thymidine triphosphate, one of the essential building blocks of DNA. Therefore, lack of either the *B_{12}* or *folic acid* caused abnormal and diminished DNA and, consequently, failure of nuclear maturation and cell division.
- The erythroblastic cells of the bone marrow produce macrocytes, and the cell itself has a flimsy membrane and is often irregular large, and oval instead of the usual biconcave disc.
- These poorly formed cells, after entering the circulating blood, are capable of carrying oxygen normally, but their fragility causes them to have a short life, one half to one third normal.
- Deficiency of vitamin *B_{12}* or folic acid causes maturation failure in erythropoiesis.
- Vitamin B_{12} and folic acid intrinsic factor from the stomach mucosa, one can readity understand that loss of any one of these can lead to slow reproduction of erythroblasts in bone marrow.
- As a result, RBCs grow too large, with odd shapes and are called megaloblasts.
- Maturation failure caused by poor absorption of vitamin B_{12} from the GIT — *Pernicious anemia.*

Pernicious anemia

• In Pernicious anemia the basic abnormality is an atrophic gastric mucosa that fails to produce normal gastric secretions. The parietal cells of the gastric glands secrete a glycoprotein called intrinsic factor, which combined with the B_{12} in food and makes the B_{12} available for absorption by the gut.

• Intrinsic factor binds tightly with the vitamin B_{12}. In this bound state the B_{12} is protected from digestion by the gastrointestinal secretions.

• Still in the bound state, intrinsic factor binds to specific receptor cites on the brush border membranes of the mucosal cells in the ileum.

• Then the B_{12} is transported into the blood by pinocytosis, carrying intrinsic factor and the vitamin together through the membrane.

• Pernicious anemia is associated with atrophy of stomach mucous membrane.

Presenting heamatological abnormalities

• Macrocytic anemia (MCV usually > 110 fl). In extreme cases RBC anisopoikilocytosis can result in MCV values lying just within normal range.

• RBC changes induce oval macrocytosis, poikilocytosis, basophilic stipping, Howell-Jolly bodies, circulating megaloblasts.

• Hypersegmented neutrophils.

• Leucopenia and thrombocytopenia common.

• Bone marrow shows megaloblastic change: marked erythroid hyperplasia with predominance of early erythroid precusors, open atypical nuclear chromatin patterns, mitotic figures and «giant» metamyelocytes.

• Iron stores usually increases.

• Serum B_{12} decreases.

• Serum/red cell folate usually on the same level or increases.

• LDH levels markedly increases ineffective erythropoiesis.

• Autoantibody screen in pernicious anemia: 80–90 % presents circulating gastric parietal cell antibodies, 55 % have circulating intrinsic factor antibodies. Note: parietal cell antibodies are not diagnostic since found in normals. IFAS is only found in 50% patients with PA but is diagnosed.

Hemolytic anemia

Any situations in which there is a reduction in RBC life-span due to increased RBC destruction. Failure of compensatory marrow response results in anemia. Predominant site of RBC destruction is red pulp of the spleen.

Hereditary cause suggested if history of anemia refractory to treatment in infancy, e. g. other affected members, anemia, gallstones, jaundice, and splenectomy. Aquired hemolytic anemia is suggested by sudden onset of symptoms (signs in adulthood). Intravascular haemolysis — takes place in peripheral circulation. Extravascular haemolysis occurs in RES.

Hemolytic anemia is classified into: hereditary and acquired.

Membranopathias

Hereditary sherocytosis

German therapeutist Minkowski distinguished this disease from the group of hemolytic syndromes in 1990. French therapeutist A. Chauffard noted a decrease in Er resistance and hemolysis activation in hereditary sherocytosis. Autosome-recessive type of transmission.

Pathogenesis

Deficiency of erythrocytic membrane protein (ankyrin, spectrin) or ankyrin function impairment results in hemolysis activation, stimulation of lipid metabolism, loss of superficial substances, change in cell volume and forming of spherocytes.

Laboratory tests

Normochromic anemia, reticulocytosis, sherocytosis

Enzymopathias

(glucose-6-phosphate dehydrogenese)

Firstly, it was described by Carson&co-authors in 1956. X-linked type of transmission.

Pathogenesis

Glucose-6-phosphate dehydrogenese deficiency decreases the defence against oxidant injury. The disposal of H_2O_2, a potential oxidant, is dependent on the adequacy of GHS, which is generated by the action of NADPH. The synthesis of NADPH is dependent on the activity of G-6-PD, GSSG, oxidized glutathione. So, G-6-PD deficiency results in a decrease in NADPH synthesis and the decrease in defence against oxidant action.

Clinical forms of glucose-6-phosphate dehydrogenese deficiency

- Acute intravascular hemolysis.
- Favism.
- Hemolytic newborn disease, not associated with the blood group and resus.
- Hereditary chronic (non-spherocytic) hemolytic anemia.
- Latent form.

Hemoglobinopathias

1. Quantative — abnormality of primary structure (Sickle cell anemia).
2. Qualitative — impairment of synthesis or absence of one of the globin chains in case of intact primary structure (thalassemia).

Sickle cell anemia

Autosome-dominant type of transmission. It results from point mutation: replacement of glutation acid (HbA) by valine (HbS). This replacement results in: an increase in bond between hemoglobin molecules, a decrease in deoxygenated HbS solution, structural instability of HbS.

Factors promoting erythrocyte sickle: a decrease in pH 8,5 to 6,5, an increase in the body temperature up to 37 °C, drugs, a decrease in oxygen partial pressure.

Thalassemia major

Beta-Thalassemia is the most common in Mediterranean countries and parts of Africa and Southeast Asia. In the United States, the incidence is highest in immigrants from these areas. The genotype of affected patients can be β+/β+, β0/β0, or β0/β+. With all these genotypes, the anemia manifests 6 to 9 months after birth, as hemoglobin synthesis switches from HbF to HbA. In untransfused patients, hemoglobin levels range between 3 and 6 gm/dl. The peripheral blood smear shows severe red cell morphologic abnormalities, including marked anisocytosis and poikilocytosis (variation in size and shape, respectively), microcytosis (small size), and hypochromia (poor hemoglobinization). Target cells (so called because hemoglobin collects in the center of the cells), basophilic stippling, and fragmented red cells are also common. Inclusions of aggregated α-chains are efficiently removed by the spleen and not easily found in peripheral blood smears. The reticulocyte count is elevated, but because of ineffective erythropoiesis is lower than expected for the severity of anemia. Variable numbers of poorly hemoglobinized normoblasts are seen in the peripheral blood due to «stress» erythropoiesis and abnormal release of progenitors from sites of extramedullary hematopoiesis. The red cells can completely lack HbA (β0/β0 genotype) or contain small amounts (β+/β+ or β0/β+ genotypes). HbF is markedly increased and indeed constitutes the major red cell hemoglobin. HbA2 levels may be normal, low or high.

Morphology

The major morphologic alterations, in addition to those found in all hemolytic anemias, involve the bone marrow and spleen. In the untransfused patient, there is striking expansion of hematopoietically active marrow, particularly in facial bones. This erodes existing cortical bone and induces new bone formation, giving rise to a «crew-cut» appearance on X-rays. Both mononuclear phagocytic cell hyperplasia and extramedullary hematopoiesis contribute to enlargement of the spleen, which can weigh up to 1500 g.

Clinical features

Symptoms of anemia, e. g. breathlessness fatigue. Urinary changes, e. g. red or dark brown of haemoglobinuria. Symptoms of underlying disorder.

Autoimmune hemolytic anemias

Warm antibody immunohemolytic anemia

This is the most common form (48 to 70 %) of immune hemolytic anemia. About 50 % of cases are idiopathic (primary); the remainder arise secondarily in the setting of a predisposing condition or drug exposure. Most causative antibodies are of the Ig G (IgG) class; only sometimes are IgA antibodies culpable. Most red cell destruction in this form of hemolytic disease is extravascular. IgG-coated red cells bind Fc receptors on monocytes and splenic

macrophages, which results in loss of red cell membrane during partial phagocytosis. As in hereditary spherocytosis, the loss of cell membrane converts the red cells to spherocytes, which are sequestered and removed in the spleen, the major site of red cell destruction in this disorder. Thus, moderate splenomegaly is characteristic of this form of anemia. As with other forms of autoimmunity, the cause of autoantibody formation is largely unknown. In many cases, the antibodies are directed against the Rh blood group antigens. The mechanisms of drug-induced hemolysis are better understood.

Hapten model. The drugs — exemplified by penicillin and cephalosporins — act as haptens by binding to the red cell membrane. Antibodies directed against the cell-bound drug result in the destructive sequence cited before. This form of hemolytic anemia is usually caused by large intravenous doses of the antibiotic and occurs 1 to 2 weeks after onset of therapy. Sometimes the antibodies bind only to the offending drug, as in penicillin-induced hemolytic anemia. In other cases, such as quinidine-induced hemolysis, the antibodies recognize a complex of the drug and a membrane protein. In drug-induced hemolytic anemias, the destruction of red cells can occur intravascularly after fixation of complement or extravascularly in the mononuclear phagocyte system.

Autoantibody model. These drugs, of which the antihypertensive agent α-methyldopa is the prototype, in some manner initiate the production of antibodies directed against intrinsic red cell antigens, in particular the Rh blood group antigens. Approximately 10 % of patients taking α-methyldopa develop autoantibodies, as assessed by the direct.

Coombs test. However, only 1 % develops clinically significant hemolysis.

Cold agglutinin immunohemolytic anemia

This form of immunohemolytic anemia is caused by so-called cold agglutinins, IgM antibodies that bind and agglutinate red cells avidly at low temperatures (0 to 4 °C). It is less common than warm antibody immunohemolytic anemia, accounting for 16 to 32 % of cases of immunohemolytic anemia. Such antibodies appear acutely during the recovery phase of certain infectious disorders, such as mycoplasma pneumonia and infectious mononucleosis. In these settings, the disorder is self-limited and rarely induces clinical manifestations of hemolysis. Other infectious agents associated with this form of anemia include cytomegalovirus, influenza virus and HIV. Chronic cold agglutinin immunohemolytic anemias occur in association with certain lymphoid neoplasms or as an idiopathic condition. Clinical symptoms result from binding of IgM to red cells at sites such as exposed fingers, toes, and ears where the temperature is below 30 °C. IgM binding agglutinates red cells and rapidly fixes complement on their surface. As the blood recirculates and warms, IgM is rapidly released, usually before complement-mediated hemolysis can occur. However, the transient interaction with IgM is sufficient to deposit sublytic quantities of C3b, an excellent opsonin, leading to rapid removal of affected red cells by mononuclear

phagocytes in the liver and spleen. The hemolysis is of variable severity. Vascular obstruction caused by red cell agglutinates results in pallor, cyanosis of the body parts exposed to cold temperatures, and *Raynaud phenomenon*.

Cold hemolysin hemolytic anemia

Cold hemolysins are autoantibodies responsible for an unusual entity known as paroxysmal cold hemoglobinuria, characterized by acute intermittent massive intravascular hemolysis, frequently with hemoglobinuria, after exposure to cold temperatures. This is the least common form of immunohemolytic anemia. Lysis is clearly complement dependent. The autoantibodies are IgGs that bind to the blood group antigen on the red cell surface at low temperatures. Complement-mediated intravascular lysis does not occur until the cells recirculate to warm central regions, as the enzymes of the complement cascade function more efficiently at 37 °C. The antibody, also known as the Donath-Landsteiner antibody, was first recognized in association with syphilis. Today, most cases of paroxysmal cold hemoglobinuria follow infections such as mycoplasma pneumonia, measles, mumps, and ill-defined viral and «flu» syndromes. The mechanisms responsible for production of such autoantibodies in these settings are unknown.

PATHOLOGICAL PHYSIOLOGY OF LEUKOCYTE SYSTEM

Typical changes in leukocyte system

— change in the number of Le in a blood volume unit (leukocytosis, leucopenia);

— change in biologic features of Le (biochemical, biophysical, structural-functional changes);

— change in correlation of leukocyte types: cytosis (cytopenia): relative, absolute;

— leukogram shifts: to the left, to the right.

Leukocyte changes

• quantative:

— absolute an increase, a decrease in total amount of Le, single Le forms relative an increase, a decrease (%) in different forms (leukogram);

• qualitative

— maturation impairment;

— production of pathological leukocytes.

Leukocytosis

Leukocytosis is an increase in total amount of Le in a unit of blood (above the upper age norm level $4–9 \times 10^9$/l)

Mechanisms of leukocytosis:

— increase in normal leukopoiesisd;
— redistribution of Le in vessels;
— increased tumor transformed Le formation;
— hemoconcentration.

Types of leukocytosis by biological meaning

1. *Physiologica*l (functional, protective-adaptive) — it has an adaptive character, it is adequate to causing factors, it is accompanied by activation of leukocyte function (phagocytic), it promotes an increase in resistance to infectious and non-infectious pathogenic actions.

2. *Pathological* — it doesn't have an adaptive meaning in leukemia (it develops in an increase in the number of leukocytes because of their tumor origin), in leukemia leukocytes – impairment of functional activity, a decrease in ability to synthesize and release cytokines, a decrease in phagocytic activity.

3. *Functional* — it is caused by certain function accomplishment: in pregnancy, after a prolonged physical exercise, after absorption of digested food in the blood vessels of the intestines.

Protective-adaptive: in inflammation, in cell and tissue injury (in infarction, stroke, tissue trauma), in stress.

Etiology of neutrophilia: acute infectious and other inflammatory reactions (MI, podagra, collagenosis), intoxications (uremia, eclampsy, intoxications), acute post-hemorrhagic anemia, malignant tumors, myeloleukemia, polycytemia, myelofibrosis, hereditary neutrophilia.

Etiology of eosinophilia: parasitic disease, allergic disease, dermatoses, blood diseases, tumors, radiation, hereditary abnormalities, idiopathic eosinophilia, connective tissue diseases, hyper-eosinophilic syndrome, physiological eosinophilia — in prematurely form.

Etiology of basophilia: viral infections, iron deficiency, pregnancy, ovulation, stress, thyroiditis, hyperthyroiditis, introduction of foreign protein, tumors (CML), splenectomy.

Etiology of lymphocytosis: in some acute infections (infectious mononucleosis), in chronic infections (brucellosis, tuberculosis, syphilis), lympholeukosis, hairy cell leucosis, sarcoma.

Etiology of monocytosis:

— disease caused by protozoa, Rickettsia (malaria, typhus);
— malignant tumors (ovarian carcinoma, black cancer);
— systemic vasculitis;
— tetrachloroethane intoxication;
— steroid hormone prolonged intake;
— recovery in case of infectious disease.

Leukopenia

Leukopenia is a decrease in the number of Le in a unite of blood volume less than lower limit of age norm

Classification

— hereditary (primary);

— secondary (aquired).

Etiology of leucopenia: infectious (virus, bacteria, protozoa), generalized infections (miliary tuberculosis, septicemia), chemical and physical agents causing hypo- and aplasia of bone marrow, anemia (pernicious, aplastic), cachexy, anaphylactic shock, family hereditary abnormality.

Mechanisms of leukopenia

— leucopoiesis impairment;

— an increase in loss or destruction of Le;

— redistribution of leukocyte pool;

— hemodelution leukopenia.

Agranulocytosis

It is a clinical hematological syndrome characterized by the absence or excessive decrease in all granulocyte absolute number (neutrophils, eosinophils, basophils). It is associated with leucopenia.

Agranulocytosis is taken for:

— the decrease in the absolute number of granulocytes less than $0{,}75 \times 10^9$/ l;

— the decrease in the total amount of Le less than $1{,}0 \times 10^9$/ l;

(neutropenia – a decrease in the absolute number of neutrophils less than $1{,}5 \times 10^9$/ l).

Classification of agranulocytosis:

— by mechanism: immune, myelotoxic;

— by clinical course: flash-like, acute, subacute, recurrent, cyclic;

— by origin: congenital, aquired.

Myelotoxic agranulocytosis is associated with cytostatic influence the bone marrow (taking arsenic, vincristin, myelosan in big doses)

Immune agranulocytosis develops in case of taking amidopyrine, phenacetin, anti-TB drugs, and anti-epileptic drugs. Target-cells are the cells of neutrophilic line.

Clinical manifestations:

— fever, swollen lymph nodes, hemorrhages, gangrenous ulcers of the oral cavity, joining Gram negative infections may lead to generalization of process;

— leucopenia, decrease in the number of granulocytes (up ton 1–2 %), toxic granulosity of neutrophils, Er and Tr are not changed (or slightly decrease in the number);

— death results from sepsis, pneumonia, hemorrhages, necroses.

Flash-like form: it begins suddenly, high temperature fever, ague, pallor, exhaustion, gangrenous, pitting of gums and tonsils, soft palate and lips, tongue, gullet, in the surrounding tissues — minimal inflammatory reaction.

Panmyelophtisis

It was described by P. Erlich in 1888. It is characterized by anemia, absence of regeneratoric signs, decrease in the number of Le and Tr, inhibition of the bone marrow function.

It is manifested by:

— thrombocytopenia;

— leucopenia;

— anemia.

Leukogram changes in leukocytosis:

— True leukocytosis (regeneratoric, absolute) developing in result of increase in myelocytic cell proliferation and associated with leukogram changes.

— Changes are caused by increase or decrease in the number of immature myelocytic cells and appearance of cell forms, which are absent in norm.

— In such cases we mean change in mature and immature Le ratio — granulocytic nuclear shift to the left or to the right.

The normal leukogram of healthy adult is shown in the table 4.

Table 4 — Normal leukogram of healthy adult (%)

***granulocytes*:**	
— basophils	0–1
— eosinophils	0,5–5
— myelocytes	0
— meta-myelocytes	0–1
— non-segmented neutrophil	1–5
— segmented neutrophil	45–70
***agranulocytes*:**	
— lymphocytes	20–40
— monocytes	2–10

Nuclear shift index (NSI) is showen in the formula 1.

Nuclear shift index (NSI)

$$NSI = \frac{\text{promyelocytes (\%) + myelocytes (\%) + metamyelocytes (\%) + non-segmented (\%)}}{\text{segmented cells (\%)}} \quad (1)$$

NSI in healthy man equals 0,05 up to 0,10.

Increase in index means nuclear shift to the left.

Decrease in index means nuclear shift to the right.

Nuclear shift to the left

Nuclear shifts to the left are determined by immature (young) neutrophil form appearance.

Types of neutrophil nuclear shift to the left

➢ *hyporegeneratoric* (an increase in non-segmented cell number, leukocytosis — 10–11 × 10^9/l);

➢ *regeneratoric* (meta-myelocyte appearance, an increase in non-segmented cell number, leukocytosis — 13–18 × 10^9/l);

➢ *hyperregeneratoric* (myelocyte appearance, an increase in the meta-myelocyte number, an increase in the non-segmented cell number, leukocytosis up to 20–25 × 10^9/l, alsp Le number could be normal, leukopenia could be in case of myeloid line exhaustion);

➢ *regeneratoric-degeneratoric* (an increase in myelocyte number, an increase in meta-myelocyte number, an increase in non-segmented cell number, a decrease in segmented cell number, signs of degenerative changes, leukocytosis);

Nuclear shift to the right: an increase in segmented cell number. It may be associated with the decrease in non-segmented cell number and signs of leukocyte degeneration.

Leukocyte changes:

— anisocytosis, poikilocytosis;

— toxic punctuation;

— cytoplasm vacuolization;

— change in the structure and contour of nucleus;

— Kniazkova-Dele's bodies (round or oval formations in the peripheral parts of cytoplasm, coloring blue, firstly they were described in scarlet fever, they are revealed in severe infections, burns and cytotoxic agent action);

— Botkin-Gumprecht's bodies (CLL);

— change in segment neutrophil quantity: hypersegmentation, hyposegmentation.

Leukemoid reactions

Leukemoid reaction is a reactive state of organism characterized by changes in hemopoietic organs and blood that look like leukemia. But it differs from leukemia by etiology, pathogenesis.

Unlike leukemia, there is no transformation of normal hemopoietic cells into tumor cell in bone marrow, but there is an activation of normal cell proliferation.

In leukemoid reactions stimulation of leukopoietic lines results from:

— an imncrease in the number and activity of leukopoietic stimulators;

— an increase in the level of stimulators of Le differentiation;

— a decrease in inhibiting factors of cell proliferation.

Etiology *of leukemoid reactions*: BAS, viruses, bacteria, helmints

The types of leukemoid reactions and their characteristics are shown in the table 5.

Table 5 — Types of leukemoid reactions and their characteristics

Type of leukemoid reaction	Causes	Peripheral blood smear
1. Myeloid type		
Neutrophilic		
Pseudoblastic	Outcome of immune agranulocytosis	A lot of blast cells
Promyelocytic	Primary tuberculosis. Severe toxic infections (diphteria, tetanus and others). Sepsis	A lot of typical promyelocytes
Like chronic myeloid leukemia	Infections (bacterial, viral, fungous). Inflammation (chronic vasculitis, dermatitis, podagra, myositis and others). Intoxications (endocrine pathologies, metabolism impairments, uremia, intoxications). Malignant neoplasms (breast cancer, neoplasm in kidney, liver, lungs). LGM	Neutrophilia with hyperregeneratoric nuclear shift to the left, normal number of eosinophils, basophils, degenerative changes in neutrophils (toxic granulation, karyopyknosis)
Marked eosinophilia	Parasitosis (filariasis, lambliasis, opisthorchiasis and others) Allergic reactions (bronchial asthma, allergic reactions, drug-induced allergic reaction); collagenosis (rheumatoid arthritis, nodular periartheritis, scleroderma systematica, SLE). Loeffler endocarditis. Immune deficient state (Wiskott-Aldrich syndrome, IgA deficiency) Malignant neoplasms (thyroid gland cancer, stomach cancer, renal cell carcinoma, LGM, Hodgkin's disease, CML). Idiopathic hereditary forms	Increased number of eosinophils (more than 15 %) and changes in cell morphology (nucleus and cytoplasm vacualization)
2. Monocytic-lymphocytic type		
Like acute lymphoblastic leukemia	Infectious mononucleosis	Lymphocyte number — 20×10^9/l and more, increased number of monocytes, «atypical mononuclears» (more than 10 %), neutropenia
Acute infectious lymphocytosis	Enteroviral infection caused by Coxsackie virus. Cat scratch disease. Bacterial infections (whooping-cough, yersiniosis, tuberculosis and others). Protozoal invasion (toxoplasmosis, malaria)	Lymphocyte number — 15–100 $\times$ 10^9/l and more, lymphocytosis (more than 60 %) without changesin cell morphology, monocytosis

The continuation of the table 5

Type of leukemoid reaction	Causes	Peripheral blood smear
Stress-lymphocytosis	Cardiovascular pathology (cardiovascular collapse, acute heart failure, myocardial infarction, septic shock and others). Immediate hypersensitivity reactions. Surgical treatment. Trauma. Epilepsy	Short-lasting leukocytosis up to 5×10^9/l and more
Long-lasting lymphocytosis	Rheumatoid arthritis. Malignant tumors (thymoma). Chronic inflammatory diseases (sarcoidosis, Wegener's granulomatosis). Delayed hypersensitivity reactions. Hyposplenism. Smoking	Long-lasting lymphocytosis $3,8 \times 10^9$/l and over
Reactive monocytosis	Infectious inflammatory disease (tuberculosis, chronic pyelonephritis, sarcoidosis, sprue). Malignant neoplasms (breast cancer and ovarian cancer, LGM, multiple myeloma)	Increased monocyte number (more than $0,8 \times 10^9$/l)

Infectious mononucleosis

It is a leukemoid reaction of lymphocytic type. Children suffer it more often than adults because of peculiarities of the immune system.

— heterogenic positive forms — EBV;

— heterogenic negative forms — cytomegalovirus, herpes virus simplex, rebella virus, hepatitis B, adenoviruses.

Pathogenesis

Epstein Barr Virus enters oropharynx epithelial cells or B-lymphocytes. That results in proliferation and differenciation B-lymphocytes into plasma blasts. At the same time T-lymphocytes are proliferating actively. In case of T-lymphocyte reactions absence (T-lymphocyte reactions are cytotoxic to virus) uncontrolles B-lymphocyte proliferation takes place and B-cellular lymphoma may develop.

Peripheral blood film: leukocytosis, sometimes anemia, absolute lympho- or monocytosis.

A peculiar type of lymphocyte appearance «atypical mononuclear» is observed. Nucleus looks like the monocytic nucleus, sometimes placed in periphery; it may contain 1-2 nuclei, having a bean-shaped, oval nucleoli and indistinct contour. Cytoplasm plasmatization is possible. It resembles plasma cell cytoplasm.

Diagnostics:

— Paul-Bunnel's reaction (it is non-specific for EBV);

— finding out the virus-capside antigene;

— finding out the antibody to the early antigen;

— finding out the antibody to the nuclear antigen.

HEMOBLASTOSIS. LEUKEMIA

Leukemia is a cancer of stem cells with the primary injury of bone marrow.

Theories of leukemia occurrence

— Theory of chemical leukogenesis.
— Radiation theory.
— Viral theory.
— Genetic theory.

Leukemia is described as an acute or chronic depending on the suddenness of appearance and how well differentiated the cancerous cells are.

Acute leukemia is characterized by the rapid increase of immature blood cells with a complete cessation of differentiation.

Chronic leukemia is characterized by the excessive production of relatively mature, but still abnormal, white blood cells and their accumulation. Cells of chronic leukemia are usually well differentiated, but it is stopped on a determined level.

Pathogenesis

Transformation of normal hemopoietic cell in tumor results from changes in genome.

The main chain of pathogenesis is chromosomal abnormality. Genome instability results in new sub-clone occurrence in the primary tumor clone. New sub-clones are chosen as autonomic during the vital activity and treatment.

Franch-American-British classification

French-American-British (FAB) classification of *acute leukemia* based on the study of microscopic features and cytochemistry of blast cells; it subdivides acute myelogenous leukemia into 8 groups (M_0–M_7) and acute lymphoblastic leukemia into 3 groups (L_1–L_3).

The revised FAB classification of acute leukemia is shown in the table 6.

Table 6 — Revised French-American-British classification of acute leukemia

Class	
M_0	Minimary differentiate AML
M_1	AML without differentiation
M_2	AML with maturation
M_3	Acute promyelocytic leukemia
M_4	Myelomonocytic leukemia
M_5	Acute monocytic leukemia
M_6	Acute erythroleukemia
M_7	Acute megalocaryocytic leukemia
L_1	Acute lymphoblastic leukemia
L_2	Acute lymphoblastic leukemia
L_3	Acute lymphoblastic leukemia

The CD-markers in leukemia differentiated diagnostics are shown in the table 7.

Table 7 — CD-markers in leukemia differentiated diagnostics

CD	Redistribution	Leukemia
HLA-DR	Early myelomonocytic and B-cells	OLL, OML, CLL, hairy leukemia
CD1	Early T	T-OLL
CD2	T-cell	T-OLL
CD3	Maturet-cell	T-CLL, retrovirus T-lymphleuemia of adults
CD5	T	T-oll, b-cll
CD7	T	T-oll, 20 % oml
CD19	Pre–B, early T	OLL L_1, L_2
CD13	Myelomonocytic	Oml (all groups)
CD14	Myelomonocytic	Oml (m_4, m_5)
CD15	Myelomonocytic	Oml (more differentiated groups)
CD16	NK and granulocytes	Lymphoid leukemia and lymphoma from NK-cells and T-lymphocytes
CD19	B	B–oll, b–cll and haiy cell leukemia
CD20	B	B–oll, b–cll and haiy cell leukemia
CD21	B cells on the intermediate stage of differentiation	CLL
CD25	Active T- and B-lymphocytes	Hairy cell leukemia, retrovirus T-cell leukemia of adults
CD33	Early myelomonocytic	Oml (all groups)
CD34	Hemopoietic stem cells	Oll and oml (m_0–m_2)

Clinical manifestations

Acute leukemia has marked clinical manifestations. Chronic leukemia progresses slowly and may have few symptoms until advanced.

— *Hyperplastic syndrome*. An increase in cell proliferation: an increase in lymph node sizes, hepatomegaly, splenomegaly, tonsil hyperplasia, gum hyperplasia, skin infiltrates. Leukemic infiltration may occure in skin, CNS, mammary glands and ovaries.

— *Anemia* results from leukemic hyperplasia and bone marrow infiltration (hemopoiesis inhibition). Pallor and fatigue results from anemia.

— *Bleeding and bruising* results from the thrombocytopenia and coagulation disorders.

— *Intoxication* — fever, loss of weight, fatigue

— *Infectious syndrome*

— *Osteoarthritic syndrome* is caused by accumulation of cancer cells in the bone marrow, which leads to increased pressure and cell death.

Multiple myeloma

Multiple myeloma is a clonal disorder characterized by proliferation of one type of B– lymphocyte, and plasma cells derived from that lymphocyte. These

cells disperse throughout the circulation and deposit primarily in the bone, causing bone breakdown, inflammation, and pain. Antibodies produced by the plasma cells are usually clonal IgG or IgA. Monoclonal fragments of these antibodies may be found in the urine of patients with the disease. These fragments are called Bence-Jones proteins. The cause of multiple myeloma is unknown, but risk factors are believed to include occupational exposures to certain materials and gases, ionizing radiation, and possibly multiple drug allergies. Survival rate is generally low, although some patients may live a long time with this disease.

Clinical manifestations

— Bone pain and fracture may occur.

— Weight loss and fatigue may occur.

— Neurologic dysfunction resulting from high blood calcium levels is seen with bone breakdown.

— Recurrent infections from reduced B-cell function are common.

— Diagnostic Tools.

— Bone biopsy and blood analysis confirm the disease. Urine may also be diagnostic with the presence of Bence Jones proteins.

— Hypercalcemia may be present when bones are involved.

— Complications.

— Renal failure may develop as a result of Bence–Jones proteins depositing in the renal tubules.

— Patients may become severely anemic.

Hodgkin lymphoma (Hodgkin's Disease)

Hodgkin lymphoma, formerly called Hodgkin's disease, is a cancer of the lymphoid tissue, usually the lymph nodes and spleen. It is one of the most common cancers in young adults, especially young males. There is a 2nd peak in incidence in the 6th decade of life.

Hodgkin lymphoma is a clonal disorder, arising from one abnormal cell. The abnormal cell population appears to be derived from a B-cell or, less frequently, a T-cell or monocyte. Neoplastic cells of Hodgkin lymphoma are called Reed-Sternberg cells. These cells intersperse among normal lymph tissue present in the lymph organs. Because of its B-cell and clonal nature, in 2005, Hodgkin's disease was reclassified by the WHO as a lymphoma and renamed Hodgkin lymphoma.

There are 4 major classifications of Hodgkin lymphoma, based on the cells involved and whether the neoplasms are nodular in form. Staging of Hodgkin lymphoma is important because it guides treatment and strongly influences outcome. The early stages of the disease, stages I and II, are usually curable. Cure rates for stages III and IV are approximately 75 and 60 %, respectively.

The cause of Hodgkin lymphoma is unknown. However, individuals with the disease and in remission from it demonstrate reduced T-cell mediated

immunity. In addition, sporadic case clusters suggest that a virus, perhaps one of the herpes strains, especially the Epstein-Barr virus, may be involved. There is likely a genetic tendency to develop the disease.

Clinical manifestations

— Painless enlargement of lymph nodes, especially in the neck and under the arms.

— Evening fevers and night sweats may occur.

— Weight loss accompanies advanced stages of the disease treatment.

— Chemotherapy may prolong life. One type of chemotherapy involves the use of an old drug, thalidomide, which is an immunomodulator as well as an inhibitor of blood vessel development. Other drug therapies include proteasome inhibitors (bortezomib) and alkylating agents.

— Radiation therapy is used to reduce the size of bone lesions and relieve pain.

— Bone marrow transplant may be successful in some patients.

Diagnostic Tools

Lymph node biopsy can diagnose Hodgkin lymphoma.

Complications

Secondary malignancies and cardiotoxicity may develop after aggressive treatment. Because of these and other treatment complications, Hodgkin lymphoma patients have a higher chance of dying from acute and late treatment toxicities than from the disease itself.

Non-Hodgkin lymphoma

Non-Hodgkin lymphomas are cancers of the lymph tissue that are not Hodgkin lymphoma. Non-Hodgkin lymphoma usually occurs in older adults and is typically discovered at a more advanced stage than Hodgkin lymphoma. Non-Hodgkin lymphoma is not confined to a single group of lymph nodes as in Hodgkin lymphoma, but rather is diffusely spread throughout the lymphoid organs, including the lymph nodes, liver, spleen, and occasionally the bone marrow. Disease may also be found in the sinuses. Like Hodgkin lymphoma, non-Hodgkin disease is classified under several divisions, primarily related to whether the neoplastic tissue is nodular or diffuse.

Non-Hodgkin disease appears to develop primarily from a malignancy of the B-cells, but T-cells and macrophages may also be the original site of the cancer. Causes of non-Hodgkin lymphoma are unclear, but viral infection, including HIV infection, appears to be responsible for at least some cases. Overall, non-Hodgkin lymphoma has a poorer prognosis than Hodgkin lymphoma, but there are multiple types of this disease, with some aggressive and others less so; therefore, prognosis varies greatly.

Clinical manifestations:

— Painless enlargement of lymph nodes.

— Splenomegaly.
— Gastrointestinal complications may occur.
— Fever, fatigue.
— Weight loss.
— Back and neck pain with hyper-reflexia.

Diagnostic Tools. Lymph node biopsy can diagnose non-Hodgkin lymphoma.

PATHOLOGICAL PHYSIOLOGY OF HEMOSTASIS

Normal hemostasis is attained by cooperation and interaction of primary (vascular platelet) and secondary (coagulation) mechanisms of hemostasis impairments. Causes of hemostasis impairments are presented by various factors of hereditary and acquired origin. Hemastasis impairments are presented by bleeding (hemorrhage syndrome), thrombosis, DIC-syndrome.

Typical forms of hemostasis impairments:

1) by pathogenesis:

— vasopathia;
— change in quantity and properties of thrombocytes;
— coagulopathias.

2) by the character of impairments:

— hypocoagulative — hemorrhage conditions;
— hypercoagulative — hemorrhage conditions;
— complex impairments (thrombotic-hemorrhage conditions).

TYPES OF BLEEDING

Capillary or microcirculatoric (pethechial bruise) type of hemorrhage. It is characterized by the appearance of small painless pointed or spotted hemorrhagies on the skin. Hemorrhages are often associated with menorrhagias, gum bleeding, rarely with the retina hemorrhage and gastric bleedings. Hemorrhages are easily provoked by mechanical traumas of microvessels. This hemorrhage type is characteristic of thrombocytopenia and thrombocytopathia, von Willebrand disease, prothrombin complex factor insufficiency (VII, X, V, II), some hypo- and disfibrinogenemias, moderate overdosage of anticoagulants. The bruise type of hemorrhage is often admitted in hereditary thrombocytopathias; the pethechial type of hemorrhage is not characteristic.

Hematoma. It is characterized by painful strained hemorrhages in subcutaneous cellular tissue, muscles, large joints, in peritoneum and retroperitoneal space. It may lead to nerve compression, joint destruction, bone tissue destruction, locomotor apparatus impairments. Renal and gastrointestinal bleedings may develop.

Prolonged bleedings in knife cut wound, wounds, tooth extractions, surgical operations may develop. It is observed in hereditary blood coagulation impairments (hemophilia A, B, excess insufficiency of factor VII), in hereditary thrombocytopathia with thrombocytic factor 3 absence, acquired coagulopathias associated with appearance of factors VIII, IX, VIII + V inhibitors in blood, in overdosage of anticoagulants.

Complex capillary-hematoma type of bleeding. It is characterized by pethechial-bruise hemorrhages associated with numerous dense hemorrhages and hematomas. In the absence of joint and bone injury (unlike hematoma), bruises may be large and painful. This type of hemorrhage is observed in hereditary (excess insufficiency of VII and VIII factors, severe form of von Willebrand disease) and acquired impairments (acute, subacute DIC-syndrome, overdosage of direct and non-direct anticoagulants).

Vasculitis purple type of hemorrhage. It is characterized by the appearance of monomorphis papulous-hemorrhage on palpation. The eruption elements do not disappear on touch. Nephritis development and intestinal bleedings are possible. This type of hemorrhage is observed in infectious and immune vasculites.

Angiomatous hemorrhage. It is characterized by recurring local bleedings. It is observed in angiomas, arterial venular anastamoses, teleangioectasias (Rendu-Osler disease). Bleeding is associated with slight injury of vascular wall in angioectasia loci and decreased stimulation of adhesion and aggregation of thrombocytes in this area. There are 3 types of teleangioectasias: early — small irregular form spots; intermedial — vascular spiders; late (nodular) — bright red nodes 5–7 mm.

MICROCIRCULATORY HEMOSTASIS IMPAIRMENTS

Thrombocytopenia

Thrombocytopenia is a decrease in the number of Tr below 150,000/mm^3 Hemorrhagic syndrome depends on degree of Tr number decrease. Clinical signs of thrombocytopenia are manifested in the decrease in the number of thrombocytes below 50,000/mm^3 and include: gum bleeding, menorrhagias, the increased ability of incutaneous bleedings, the appearance of pethechias of different localization. There are gastric and nasal bleedings in severe cases.

Pathogenic classification of thrombocytopenia

*Decreased production of platelets***.** It is caused by the impairment of Tr formation. In patients with vitamin B_{12} or folic acid deficiency, there is accelerated destruction of megakaryocytes, in the bone marrow (ineffective megakaryopoiesis) because DNA synthesis is impaired. It is observed in case of bone marrow inhibition by cytotoxic drugs, radiation, thiazides, estrogenes, alchohol, in bone marrow infiltration in leukemia, disseminated cancer.

Dilutional. It develops in massive transfusions after severe blood loss.

Distributional. It is observed in patients who have a marked splenomegaly and an increase in platelet pool of spleen.

Consumption. It develops in case of the increased platelet utilization above the bone marrow compensatory possibilitiy. This is a cause of thrombocytopenia developing by immunologic and non-immunologic mechanisms. Immunologic destruction: thrombocytopenic purpura in children and adults, neonatal alloimmune purpura. Non-immunologic destructioh: DIC, sepsis, endothelial injury by viruses.

THROMBOCYTOPATHIA

Thrombocytopathia is a defective platelet function state. Unlike thrombocytopenia, thrombocytopathia is characterized by stable functional, biochemical and morphologic changes in platelets and normal platelet count. Severe hemorrhagic diathesis is not characteristic of thrombocytopathia.

Classification of thrombocytopathia

1. Congenital disorders:

1) Deficiency / insufficiency of membrane glycoproteins:

— Glanzmann's thrombasthenia;

— Bernard-Soulier syndrome.

2) Congenital abnormality of plasma proteins:

— von Willebrand disease.

3) Insufficiency of granules:

— dense body deficiency;

— alpha granule deficiency;

— primary defect of granule release.

2. Acquired disorders:

1) *Secondary defects of granule release:*

— taking aspirin and other non-steroid anti-inflammatory drugs;

— uremia;

— congenital heart defect with cyanosis.

2) *Granule insufficiency***:**

— stem cell disfunction (myeloproliferative disorders, acute leukemia);

— as a result of partial activation (DIC, severe diseases of heart valves).

3*) Impairment of interaction between thrombocyte membrane and extracellular matrix proteins:*

— paraproteinemia;

— DIC;

— immune thromcytopenic purpura.

Glanzmann's thombasthenia

It is a hereditary disorder transmitted as an autosomal recessive trait. It develops owing to the deficiency of glycoprotein IIb-IIIa, the fibrinogen receptor. Clinically it is manifested by incutaneous bleedings, gum bleedings, nasal bleedings.

Von willebrand disease

In the 30s of the XX century professor E. A. von Willebrand (Helsinki) described hemorrhagic diathesis in a boy and some members of his family. This hemorrhagic diathesis looks like thrombovasopathy (prolonged time of bleeding) and hemophilia (it differs from hemophilia only in transmission trait and some clinical manifestations). The author called this disease «hereditary pseudo hemophilia» (von Willebrand disease).

Von Willebrand disease is the most common inherited disorder of bleeding (autosome-dominant type of inheritance). It is caused by qualitative and quantitative defects involving factor VIII – vWF complex. This disease is revealed in both sexes. The most important function of vWF is to facilitate the adhesion of platelets to sub-endothelial collagen (in case of injury). vWF is bound with factor VIII and also stabilizes this factor.

Clinically it is manifested by bleedings into the skin and mucose membranes: nasal bleedings, ecchymoses, menorrhagies, hematuria, severe bleedings from a slight traumas or surgical wounds (in tonsillectomy, tooth extraction). The above listed helps to take von Willebrand disease from slight form of hemophilia A (these symptoms are absent in a slight form of hemophilia A).

Patients with von Willebrand disease have prolonged bleeding time with normal platelet count and also prolonged PTT.

Coagulation hemostasis impairments

Hemophilia A is a congenital bleeding disorder caused by the defective production of factor VIII (70 % of cases). Inhibition forms of hemophilia A are caused by antibody production to factor VIII. It is caused by X-linked recessive inheritance. Severity of disease depends on the coagulation factor activity.

Clinical presentations are characterized by hematomas in newborns, and the 1st years of life in children with easy bruising and bleeding out of proportion to injury. Hemoarthrosis; spontaneous bleeding into joints associated with contractures.

Bleeds into muscles, muscles contractures, subperiosteous bleeds, gastrointestinal and renal bleeds are observed.

Hemophilia B is a congenital disorder caused by defective production of factor IX, X-linked recessive inheritance. Factor IX is activated by the TF/factor VIIa complex. It appears because of deletion in gene FIX.

Unlike hemophilia A bleeds in hemophilia B are seldom.

Hemophilia C is a congenital factor XI deficiency, autosome-recessive inheritance. It is observed in both sexes (0,3–5 % of cases).

Hemophilias are characterized by isolated intrinsic mechanism of blood coagulation impairment presented by prolonged APTT (it is also in hemophilia C) in normal PT and TT parameters, bleeds time (AV) and all types of platelet aggregation.

Parahemophilia (Ourens disease) is a deficiency of factor V. Autosome-dominant and autosome-recessive transmission trait. Pethechial bruise type of hemorrhage. Bleeds in muscles and subcutaneous hematomas, joints and internal organs bleeds are not characteristic.

Female hemophilia meets very seldom (only 50 cases). It is a genetically heterogenous disease. The main variants of female hemophilia:

1. Diseased with normal chromosome package (XX) and double inheritance of true hemophilia — appears in girls whose fathers have hemophilia and mothers are conductors of disease (incest).
2. Diseased with normal chromosome package (XX) and one sided hemophilia inheritance
3. Patients with incomplete chromosome package and one X-chromosome (XO). These diseased may have severe hemophilia form, as men from this family.
4. Hemophilia in women with testicular feminization (XY).
5. Autosome-dominant forms of factor VIII deficiency (except von Willebrand disease).

Other blood coagulation factors deficiency

Abnormalities of fibrinogen are autosome-dominant type of inheritance. Hypofibrinigenemias are asymptomatic as a rule. Afibrinogenemias are associated with bleedings. Disfibrinogenemias are presented by bleedings and thromboses depending on the clinical form.

Factor XII deficiency (*Hageman's factor*), it is described in 100 diseased. It has autosome-recessive transmission trait. Signs of bleedings are not marked.

Factor XIII (fibrin stabilizing factor) deficiency. It may be congenital or acquired.

By ISTH, 1999 there are 3 forms of factor XIII deficiency: subunit A deficiency, subunit B deficiency, A and B complex deficiency.

Most often factor XIII deficiency is observed in men. Clinical presentations: complex (microcirculatory-hematoma) hemorrhages. It is manifested by prolonged bleeds in knife cut wounds, poor wound and fracture healing (neonatal umbilical stump bleeding). High risk of cerebral hemorrhage in 12–72 hours after trauma or surgical operations is noted.

Thombophilia is an inherited or acquired disorders of hemostasis mechanism predisposing to thrombosis and blood vessel obliteration, ischemia and infarction.

Classification of hematogenous thrombophilia principal types

Group I. *Hemoreologic forms*. It takes place in myeloproliferative diseases, polyglogulias, erythrocyte size and shape abnormalities associated with plasma hyperviscosity.

Group II. *Forms caused by angiothrombotic hemostasis*. Hyperthrombocytoses, forms with the increased spontaneous and stimulating by agonists of thrombocytes aggregation, forms associated with the increased production and polymerity of vWF, non-differentiated forms.

Group III. Forms caused by deficiency or abnormalities of physiologic anti-coagulants. Deficiency or abnormality of antithrombin III, protein C and S, heparin cofactor II deficiency, hyperproduction of rich histidine glycoproteid, complex forms.

Group IV. Forms associated with deficiency or hyperproduction or abnormality of plasma coagulation factors. Thrombogenic fibrinogenemias, symptomatic hyperfibrinogenemias, the increase in activity of factor VII, VIII, in resistency of factor Va to activated protein C, abnormality of factor II, hereditary deficiency of factor XII.

Group V. Forms associated with fibrinolysis impairment. These forms associated with factor XII deficiency, deficiency of kallekrein-kinin system and protein C and S, deficiency and defect in tissue plasminogen, activated release from endothelium, increase in concentration of tissue plasminogen activator inhibitors, exhaustion of fibrinolysis in DIC-syndrome, drug oppression of fibrinolysis.

Group VI. **Metabolic forms** in hyperlipidemia, atherosclerosis, diabetes, diabetic angiopathia, hyperhomocysteinemia (uria).

Group VII. **Autoimmune or infectious-immune forms** in antiphospholipid syndrome, allergoses, immune or viral thrombovasculitic fevers, bacterial endocarditis and other variants of chronic sepsis.

Group VIII. **Paraneoplastic thromboembolic syndromes.** Thrombotic complications in all cancer types (visceral forms) in surgical operations and chemiotherapy.

***Group IX. I*atrogenic (medical) forms**. In catheterization and surgical operations of heart and vessels, vessel and valve replacement, in bone marrow stem cell transplantation, drug-induced forms.

Group X. Complex forms of thrombophilia. These groups are presented by 2 or more impairments.

The most known forms of thrombophilia are hypermonocysteinemia and antiphospholipid syndrome.

Hyperhomocysteinemia refers to a group of rare metabolic disorders. It is a disorder of methionine metabolism. It is manifested by high levels of circulating homocysteine.

Blood serum level of homocysteine depends on various factors: sex, enthnicity, ingestion. It increases during the life time (puberthy, vertility), after menopause sex distinguishes are decreased. Children of both sexes have the decreased levels of homocysteine about 6 micromole/l. During the life time concentration of homocysteine increases by 3–5 mmole/l, in age of 40–42 it is in male — 11 mmole/l, in female — 9 mmole/l.

Hyperhomocysteinemia classification

Moderate — from 11,1 to 15,0 mmole/l.
Medium — from 15,1 to 20,0 mmole/l.
High — more than 20,1 mmole/l.

Hyperhomocysteinemia occurs in case of point mutations responsible for enzyme synthesis: cystathion-beta-synthetase, methylene-tetrahydrofolate-reductase, beta-inhomocysteine-methyl-transferase or vitamin B_6, B_{12} and folate deficiency.

There are 2 pathways of homocysteine metabolism: in remethylation we observe run of methionine in folic acid, methylene-tetrahydrofolate-reductase, and B_{12}-dependent methyltransferase (alternative pathway is realized with the help of B_{12}-independent beta-inhomocysteinmethyltransferase); in trans – sulphuration homocysteine joins to serine in B_6-cystathion-beta-synthetase participation, due to it we observe cystation formation.

Block of endothelial NO-synthatase, decrease in NO production, impairment of S-nitrozo-homocystein production possessing the ability of vasodilatator and antithrombocytic agent. Homocysteine also induce 3-hydroxy-3-methylglutaryl-cofactor A-reductase leading to the increased synthesis of cholesterol in cells and cholesterol deposition loci of endothelium impairment.

Homocysteine inhibit COX activity. Due to it there is a decrease in prostacyclin production and an increase in thromboxane A_2, an increase in aggregation activity of Tr. Hyperhomocysteinemia accompanied by the increased production of tissue factor, the decreased production activity of natural anticoagulants and tissue activator of plasminogen.

For the hidden forms of hypercysteinemia revealing we use methionine load test.

Disseminated intravascular coagulation syndrome

Disseminated intravascular coagulation syndrome is a nonspecific polyetiologic pathological process caused by disseminated activation of coagulative, than fibrinolytic parts of hemocoagulation, impairment of the microcirculation system by thrombotic process and development of thrombohemorrhage disfunction of many organs and tissues.

Disseminated intravascular coagulation syndrome is an acquired coagulopathy caused by clotting factor consumption, fibrinolysis activation, microthrombus formation and hemorrhage occurrence simultaneously or subsequently.

Classification

1) By clinical course:

— Acute.
— Subacute.
— Chronic.
— Recurrent.
— Latent.

2) By process localization:

— Disseminated intravascular clotting (the organism level).
— Localized intravascular clotting (in organ or part of organ limits).

3) By process severity:

— Compensated.
— Subcompensated.
— Decompensated.

Etiology of acute and sub-acute forms of disseminated intravascular coagulation syndrome

Infection-septic: bacterial, viral, toxic-shock causes.

Massive tissue injury: burns, traumatic, intravascular hemolysis, extensive surgery, hemoblastoses, necrosis of tissue and organs, acute radiation sickness.

Obstetric complications: abruptio placentae, amniotic fluid embolism, retained dead fetus, septic abortion, toxemia.

Shock (in terminal conditions), in the process of intensive chemiotherapy, organ transplantation.

The peculiar group of acute DIC-syndrome includes: malignant newborn purpura, symmetric peripheral gangrene.

Causes of chronic disseminated intravascular coagulation syndrome

Chroniosepsis, including chronic sepsic endocarditis, chronic immune and immune-complex diseases, chronic viral diseases (hepatitis), HIV, tumors (cancer, lymphoma, leukemia).

Chronic DIC-syndrome, such as may occur in patient with cancer, tends to present initially with thrombotic complications.

Stages of disseminated intravascular coagulation syndrome:

I stage: hypercoagulation.

II stage: coagulopathia of consumption.

III stage: afibrinogenemia with pathologic fibrinolysis.

IV stage: restorative.

The main parts of disseminated intravascular coagulation syndrome pathogenesis

Initial activation of hemocoagulation cascade and Tr by endogenous factors: tissue thromboplastin, leukocytic proteases, products of tissue destruction, tumoral procoagulants.

Long-lasting thrombinemia with the increased level of its markers in blood.

Exhaustion of the natural anticoagulant system with the decrease in the level of antithrombin III, protein C, plasminogen and the increased level of thrombomodulin.

Systemic endothelial injury and the decrease in its antithrombotic potential

Micro blood clot formation and block of microcirculation in target-organs (a brain, adrenal glands, a liver, kidneys, an intestine, a stomach). These organs dystrophy and destruction development.

Fibrinolysis activation in a zone of microcirculation block and its release exhaustion in blood circulation.

Consumption of clotting factors and platelets (thrombocytopathia and thrombocytoipenia). Consumption leading to systemic hemorrhage and terminal hypocoagulation up to complete in-coagulation of blood (hemorhagic phase of the syndrome).

The impairment of the barrier function of gastric and intestinal mucose membrane with transformation of aseptic DIC-syndrome into septic.

Secondary severe endogenous intoxication.

There are three major mechanisms of DIC syndrome trigger: primary micro-circulatory, secondary macro-circulatory and primary and secondary simultaneously.

The main sub-syndromes observed in disseminated intravascular coagulation syndrome

Transformation of aseptic DIC-syndrome into septic. It is mostly associated with infection of the tissue damaged loci or barrier function impairment of intestinal mucose membrane with the subsequent massive entrance of bacterial population in blood. It is presented by fever, leukocytosis with nuclear shift to the left, the increased ESR, the inceased level of acute phase proteins (C reactive protein), interleukins, participate in the development of terminal hemorrhagic syndrome.

Sub-syndrome of respiratory failure. Respiratory symptoms such as dyspnea, cyanosis and respiratory difficulty may dominate in the bleeding of DIC. Sub-syndrome of respiratory failure needs in controlled ventilation.

Sub-syndrome of acute renal and hepatorenel insufficiency. It is often needs in hemodialysis and plasmapheresis.

Sub-syndrome of the other organs impairment and injury (adrenal glands, a brain, a heart) forms the poly-organic insufficiency syndrome.

Sub-syndrome of the stomach and intestine injury has three clinical manifestations: bleeding erosion and ulcer formation (shock or hypoxic ulcers), diffuse bleedings of mucosal membrane barrier function impairment with transformation of aseptic DIC into septic.

The listed above impairments result in organism intoxication by products of tissue destruction, secondary bacteremia, severe thrombo-hemorrhagic syndrome development.

The subacute DIC-syndrome characterized by bleeding diathesis, whereas chronic DIC tends to present initially with thrombotic complications. Latent DIC-syndrome characterized by indefinite clinical challenge.

Accurate clinical observation and laboratory studies are necessary for the diagnosis. It is usually necessary to monitor fibrinogen, platelets, PT, PTT, fibrin degradation products.

Each patient must be treated individually, and depending on the clinical picture, potent anticoagulants such as heparin or coagulants in the form of fresh–frozen plasma may be administered. Platelet transfusions may sometimes be necessary.

Principals of therapy

— Etiotropic therapy.
— Pathogenic therapy.
— Symptomatic therapy.
— Prevention.

PATHOLOGICAL PHYSIOLOGY OF CARDIOVASCULAR SYSTEM. IMPAIRMENT OF HEART FUNCTION

According to WHO, CVD have the 1st rank among the causes of disability and death of working-age population in the developed countries. Death from CVD is 45–52 % of overall mortality. Causes of the increased mortality from CVD are: the disappearance of serious infectious diseases (plague, smallpox), the increased life expectancy, the high pace of life, urbanization, rejuvenation of pathology (an increase in incidence of CVD in young people up to 35 years).

Heart failure

The definition of the ACC / AHA 2001: *heart failure* — is a complex syndrome that can be caused by any structural or functional heart disease, which impair ventricular blood fill or banish it.

The main causes of heart failure

Direct damaging effect on the myocardium:

— *Physical factors*: compression of the heart (exudate, blood, emphysematous lungs, a tumor); effects of electric current (electric shock, cardiac defibrillation); mechanical injury of the heart.

— *Chemical factors*: chemical compounds (uncouplers OX-F salt Ca, lipid hydroperoxides), drugs in inadequate doses (antagonists of Ca^{2+}, glycosides, blockers), lack of oxigen and the compounds needed for metabolism (salt of Me).

— *Biological factors*: high levels or lack of BAS, long-term ischemia or infarction, cardiomyopathy, myocarditis, myocardiodystrophy.

Cause of heart failure can be functional overload of the heart:

• *Diastolic blood flowing volume overload* (an increase in pre-load): with hypervolemia, polycythemia, valve insufficiency, open Botallos duct.

• *Systolic pressure overload* with a high resistance to ejection (an increase in post-load): in hypertension, valve stenosis, narrowing of major arterial trunks.

***Classification of heart failure*:**

1. According to origin: *myocardial, overload, mixed.*

2. According to the rate of development: acute (minutes up to hours) — in acute MI, acute cardiac tamponade, infectious diseases, pulmonary embolism, *chronic* (weeks, months up to years) — in hypertension, chronic anemia, heart pathologies, progressive atherosclerosis.

3. According to the primary mechanism of development: *primary* (cardiogenic) — mainly a decrease in contractility of the heart at close to normal value of venous blood flow; *secondary* (non-cardiogenic) — mainly a decrease in venous flow to the heart at close to normal value of myocardial contractile function.

4. According to the primary lesion of the heart:

— *left ventricular*.

Cause: over left ventricle — in aortic stenosis, hypertension; a decrease in contractive function, papillary muscle isolation.

It results in: a decrease in ejection of blood in the systemic blood circle, overdistension of left atrium, and standstill in the pulmonary blood circle.

Clinically: cardiac asthma and pulmonary edema.

— *right ventricular.*

Cause: right ventricular overload — when the pulmonary artery valve is reduced in size, it results in high pressure into the pulmonary artery.

It results in: a decrease in ejection of blood in the pulmonary circle, overdistension of right atrium and standstill in systemic circle.

— *total.*

5. According to the predominant lack of cardiac cycle phases.

— ***Diastolic*** (a decrease in ventricular filling).

Cause: hypertrophic cardiomyopathy, isolated mitral stenosis, and constrictive pericardial effusion, cardiosclerosis, amyloidosis, sarcoidosis, etc.

It results in: an increase in the final diastolic pressure and the occurence of heart failure.

Systolic (chronic) — associated with a number of diseases.

It results in: violation of the pumping heart function, a decrease in cardiac output.

There are changes in intracardiac hemodynamics in patients with heart failure. Heart failure is accompanied by characteristic changes in intracardiac hemodynamics:

- an increase in final systolic volume as a result of incomplete systole due to myocardial damage, an increase in resistance in the aorta, excessive blood flow due to valvular insufficiency;
- an increase in final diastolic pressure as a result of myocardial sub-contracture associated with an excess of calcium in the cytosol and myofibrils of cardiomyocytes;
- an increase in arterio-venous oxygen ratio;
- dilatation of the heart;
- an increase in pressure in the heart cavities results in supply of blood to the primarily affected part of the heart;
- a decrease in systolic contractions and diastolic relaxation as a result of decreased energy supply, damage of myofibrile membrane, sarcoplasmic network and sarcoplasm, a decrease in activity of calcium-dependent ATP-ases.

Basic cellular and molecular mechanisms of pathogenesis of heart failure: lack of energy in cardiomyocytes, damage of membranes and enzymes in cardiomyocytes, imbalance of ions and fluid in cardiomyocytes, violation of the genetic program of cardiomyocyte, the disorders of neurohumoral regulation of heart activity.

Insufficiency of energy supply results from damage of energy production, transport and disposal. Higher fatty acids (65–70 %), glucose (15–20 %), lactic acid (10–15 %) and oxidation of a molecule of palmitic acid are the main substrates for ATP synthesis in aerobic conditions.

Coronary insufficiency

Coronary insufficiency is a typical form of heart disease, which is characterized by the excess of myocardial oxygen demands and metabolic substrates over their influx by the coronary arteries, as well as a violation of the outflow from the myocardium of exchange products, active substances, ions and other agents.

The leading pathogenic factor — myocardial ischemia (a mismatch between the needs of oxygen and the level of cardiomyocyte oxygenation). Clinical manifestations – IHD. The term «coronary heart disease» was proposed by WHO in 1962.

Pain syndrome in ischemic heart disease — *angina*. Angina pectoris (in Latin ango — «squeeze», *angina pectoris* — «chest compression»). Clinical classification of HID according to Medical Disease Classification 10, column I 20-2:

1. Sudden coronary death (primary cardiac arrest).
2. Angina:
2.1. Angina:
2.1.1. For the first time emerged (de novo).
2.1.2. Stable, indicating FC (from I to IV).
2.1.3 Progressing.
2.2. Spontaneous (vasospastic) angina.
3. Myocardial infarction:
3.1. Q wave MI (macrofocal, transmural).
3.2. MI without Q wave (small focal, intramural, subendocardial).
4. Myocardial infarction (MI).
5. Cardiac arrhythmias.
6. Circulatory failure (ischemic cardiomyopathy).
7. Painless (silent) ischemia.
8. Microvascular (distal), coronary artery disease — small vessel disease.
9. New ischemic syndromes («hibernate», «stating», «intermittent ischaemia»).

Coronary insufficiency according to the mechanism of occurrence is classified into:

1) absolute — the basis for the limitation of blood flow in aa. coronaris;

2) relative — increase in oxygen supply in absence of coronary blood flow limitation.

Differences between reversible and irreversible coronary insufficiency.

Reversible is manifested by the following clinical forms: stable and unstable angina, variable, the state after myocardial revascularization. Irreversible infarction is manifested by MI.

All possible causes of coronary insufficiency are classified into: coronarogenic and non-coronarogenic.

Coronarogenic factor causing the absolute decrease in coronary blood flow: atherosclerosis of aa. coronaris, blood particle conglamerates and blood clots in aa. coronaris, spasm of a. coronaris, a decrease in blood flow to the heart and perfusion pressure in aa. coronaris. The concept of dynamic stenosis of aa.coronaris is based on the mechanism of the complex interaction of the triad of factors: contraction of smooth muscles, a decrease in diameter of aa.coronaris, obstruction of the blood vessel lumen by blood particles.

Noncoronarogenic factors: a significant increase in level of catecholamines in the heart, a prolonged hypertrophy the heart, resulting from:

— excessive physical exertion;
— acute hypertension;
— marked haemoconcentration;
— prolonged tachycardia;
— activation of sympathetic nervous system;
— hypervolemia.

The phenomenon of hormone neuromediator dissociation of catecholamines occurs in coronary insufficiency. It is characterized by a significant increase in adrenaline (and at the same moment a decrease in noradrenaline) in ischemic myocardium. In this state myocardium injury results from:

— a decrease in utilization of oxygen and substrate exchange by chronotropic (positive) and inotropic effects;
— a decrease in effectiveness of the mechanisms of ATP resynthesis;
— a decrease in of coronary blood flow;
— an excess of reactive oxygen and lipid peroxides.

There are experimental models of noncoronary lesions of *cor*, which is certain extent and reflect the situation observed *in vivo.*

Syndrome of hibernating myocardium. It is a violation of local contractility and function of the left ventricle due to a lengthy and pronounced decrease in coronary blood flow, which is partially or completely disappeared after the restoration of coronary blood flow, or a decrease in myocardial oxygen demand. It is a pometabolic state of myocardium for energy conservation (Hochachka, 1986).

«Stunned» myocardium. It is a state of local post-ischemic myocardial dysfunction that persists for several hours or days, following the onset of reperfusion, despite the absence of irreversible changes in the myocardium and restoration of the coronary blood flow. Unlike hibernation, sustainable the inhibition of differentiated cell functions of the heart, in spite of effective revascularization. Unlike myocardial infarction, there are no irreversible changes in the myocardium.

Reperfusion injury is characterized by the phenomenon of «NO reflow» (renewed blood flow). It means maintenance of blood supply deficiency after the resumption of coronary perfusion, feeding the ischemic myocardial areas.

Factors affecting the coronary RED microcirculation after reperfusion:

— swelling of endothelial cells;

— aggregation of the blood particles and increased blood viscosity;

— the formation of blood clots;

— margination of leukocytes

There are two modern hypotheses of reperfusion mechanisms:

1. «Calcium» hypothesis — an overload of cardiomyocytes with calcium ions results in reperfusion contracture, a decrease in diastolic volume and cardiac output.

2. «Free radical» hypothesis — the toxic effect of oxygen on the myocardium in reoxygenation after ischemia.

Ischemic syndromes also include:

— Ischemic preconditioning «intermittent ischemia», phenomeon of metabolic adaptation that occurs after one or several short intermediate 5 minute ischemia reperfusion and to increase the stability of myocardium to the damaging effect of a long period of ischemia and reperfusion.

— The mechanism of the phenomenon is associated with activation of ATP-dependent potassium channel => formed a tendency to normalization of intra– and extracellular ion balance.

Mechanisms for emergency hemodynamic compensation in heart failure

Intracardial hemodynamic compensation mechanisms:

1. *Heterometric mechanism*, Frank-Starling (volume overload) — the linear relationship between the degree of stretching the muscle fiber and forced contractions, which provides an increase in myocardial tension => increase *in vivo*.

2. *Homeometric mechanism* (pressure overload) – an acute increase in tension of muscle fibers in their length = it strengthens each subsequent contraction of the previous one.

***Extracardiac unloading reflexes*:**

1. *Bainbridge reflex* — an increase in heart rate in response to an increase in circulating blood volume during the stimulation of mechanoreceptors in *vv. cavae* and pulmonary veins => an increase in minute cardiac volume.

2. *Bezold–Jarisch reflex* — increased dilation of systemic circle arteries in response to stimulation of mechano– and chemoreceptors of ventricles and atria => a decrease in blood pressure and cardiac rate => unloading of left ventricle.

3. *Increased activity of sympathetic nervous system* => beta-adrenergic stimulation of myocardium (increase in arterial blood pressure) and cells of juxtaglomerular apparatus (an increase renin secretion) => an increase in cardiac output and minute cardiac volume

4. *Parin's reflex* (overload of right ventricle resulting in pulmonary embolism) — strengthening tonic effect on n. Vagus => a decrease in arterial blood pressure, minute cardiac volume, and circulating blood volume.

Mechanisms of long-term compensation of cardiac function

— Compensatory hyperfunction of the heart.

— Compensatory hypertrophy of the myocardium.

Stages of compensatory hypertrophy of the heart:

1. *Emergency* — an increase in intensity of functioning of myocardial structures => normal.

Activation energy production, protein synthesis, and nucleic acid => an increase in mitochondrion number and the number of the myocardial functioning structures => normal ISF.

2. *Final hypertrophy* — normal ISF of myocardium, the prevalence of compensatory reactions.

The level of ATP and glycogen in the cardiomyocytes are normal.

The significant increase in lactate level. Moderate cardiosclerosis.

3. *Progressive cardiosclerosis and decompensation* - depletion of the genetic apparatus of cardiomyocytes => a relative decrease in number of myofibril and mitochondria => Increased ATP synthesis => a decrease in cardiac pump function => cronic heart failure progression, dystrophic and sclerotic processes.

Main elements of the mechanism of decompensation of hypertrophic myocardium:

— delayed growth of capillaries and nerve fibers of muscles;

— cell volume increases more than the specific surface area => worsen conditions for the transport of metabolic products;

— a decrease in plastic cell supply;

— change in incell structure ratio;

— activation of cardiomyocyte apoptosis => cardiosclerosis.

It results in myogenic dilation of the heart: a decrease in heart contractions.

PATHOLOGICAL PHYSIOLOGY OF CARDIOVASCULAR SYSTEM. IMPAIRMENT OF BLOOD VESSEL FUNCTION

Arterial hypertension

It is a sustained elevated systolic pressure above 140 mm Hg or sustained diastolic blood pressure above 90 mm Hg is considered as hypertension.

Etiology and classification

Essential hypertension (unknown cause or familial).

Secondary hypertension:

Renal: acute glomerulonephritis, chronic renal disease, polycystic kidney disease, renal vasculitis, rennin prosducing tumors.

Endocrine: adrenocortical hyperfunction (Cushing's syndrome, primary aldosterobnism, congenital adrenal hyperplasia); Exogenous hormones (glucocorticoids, estrogene including oral contraceptives, sympathomimetics. Tyramine-containing foods, monoamine oxidase inhibitiors). Acromegaly. Hyperthyroidism. Pregnancy-induced.

Cardiovascular: caorctation of aorta (upper extremity), polyarteritis nodosa, increased intravascular volume, increased cardiac output, rigidy of the aorta.

Neurologic: psycogenic, increased intracranial pressure, spleen apnea, acute stress, including surgery.

Pathogenesis

Sympthomatic is secondary to disease in some other organ and mainly due to increased peripheral resistance.

Primary/essential hypertension: environmental risk and genetic are involved. Genetic risk factors: mutation in enzymes involved in aldosterone metabolism leading to increased levels of aldosterone and mutation in protein specific for sodium reabsorption causing increased sodium retention. Environmental risk factors: stress, obesity, smoking, physical inactivity and increased intake of salt.

Morphology: 2 morphologic patterns are seen:

— *Hyaline arteriosclerosis*: homogenous pink, hyalinic thickening of walls of arterioles with narrowing of the lumen → ischemia of organ; Hyaline arteriosclerosis of kidney and benign nephrosclerosis. This pattern is commonly seen in chronic hypertension and diabetes.

— *Hyperplastic arteriosclerosis*:

— Concentric, laminated thickening of the arterioles with progressive narrowing of lumen (onion skin appearance).

— Smooth muscle proliferation and thickened reduplication besement membrane.

— Deposits of fibriniod necrosis (necrotizing arteriosclerosis).

— Example: malignant hypertension.

Malignant hypertension

Malignant hypertension: rapidly rising blood pressure, which if untreated leads to death within 1 year.

The syndrome involves:

— Diastolic blood pressure → 120 mm Hg.

— Renal failure.

— Retinal hemorrhages.

— Papillaedema.

Atherosclerosis

It is defined as a chronic focal inflammation of the arterial wall characterized by the formation of cholesterol-rich fibrofatty plaques in the intima, intimal thickening and smooth muscle proliferation leading eventually to ischemia of an organ due to blockage of the arterial lumen.

Risk factors of atherosclerosis

Major:

— *Nonmodifiable*: increasing age, male gender, family history, genetic abnormalities.

— *Potentially modifiable*: dyslipidemia, high LDL cholesterol, low HDL cholesterol, high cholesterol, hypertension, cigarette smoking, diabetes.

Non-quantitated: obesity, physical inactivity, stress, homocysteine, postmenopausal estrogendeficiency, high carbohydrate intake, alcohol, lipoprotein, hardened unsaturated fat intake, Chlamydia pneumonia infection.

Order concepts:

Insudation hypothsis: held that infiltration of the intima with lipid and protein is the primary atherogenic event (accelerated by hypercholesterolesterolemia).

Encrustation or thrombogenic hypothesis: proposed that organization of repeated mural thrombi on the intimal surface leads to buildup of plaques filled with lipids from the breakdown of platelets and leukocytes.

Monoclonal hypothesis: suggested that monoclonal sooth muscle migration and proliferation is analogous to tumor growth and is a primary rather than a secondary event. Hyperlipidemia may incite the proliferation.

Current concept: it views the primary event as injury to (or dysfunction of) arterial endothelium, which may be produced by hypercholesterolemia, mechanical injury, hypertension, immune mechanisms, toxins, or viruses or their infectious agents. Hyperlipidemia may initiate endothelial injury, promote foam cell formation, act as a chemotactic factor for monocytes, inhibit macrophages motility, or injure smooth muscle cells.

Development of atheromatous plaque: a) monocytes and lipids enter into subendothelium, sometimes with platelet adhesion and aggregation at the injury site; b) platelets (and perhaps also monocytes) release mitogenic (i. e. mitosis or growth including) factors (e. g., platelet-derived growth factor and possibly fibroblast growth factor-a); c) these growth factor cause migration and proliferation of smooth muscle cells into intima, with the production of connective tissue matrix proteins (collagen, elastin, glycosaminoglycans, and proteoglycans); d) monocytes and smooth muscle cells engulf lipids and transform into lipid-laden cells, this process is mediated by the beta-VLDL receptors, and the scavenger receptors, which recognize modified LDL-cholesterol; e) the aggregation of foam cells covered by fibrous cap is the atheromatous plaque.

Vessels involved:

— lower abdominal aorta;
— coronary arteries;
— popliteal arteries;
— descending thoracic aorta;
— internal carotic aorta;
— circle of Willis.

Complications of atherosclerosis

- rupture, ulceration, hemorrhage, superimposed formation (with total or partial occlusion of the arteries cutting off the blood supply and resulting in infarction, e. g., acute MI);
- thromboembolism;
- aneurismal dilation (due to arterial wall weaking).

PATHOLOGICAL PHYSIOLOGY OF RESPIRATORY SYSTEM

The respiratory system has a vital charge: to provide for the exchange of oxygen and carbon dioxide between the air and the blood. Oxygen is required by all cells so that the life-sustaining energy source, ATP can be produced. Carbon dioxide is produced by metabolically active cells and forms an acid that must be removed from the body. For gas exchange to be performed, the cardiovascular and respiratory systems must work together. The cardiovascular system is responsible for perfusion of blood through the lungs. The respiratory system performs 2 separate functions: ventilation and respiration.

Physiologic concepts

Alveolus

The functional unit of the lungs is the alveolus (plural, alveoli). There are more than a million alveoli in each lung. Alveoli are small, air-filled sacs across which oxygen and carbon dioxide and other gases diffuse. The large number of small alveoli ensures that the total area available for the diffusion of gas in each lung is enormous. If the airflow into an alveolus is blocked, it collapses and is unavailable for gas exchange. If airflow into several alveoli is blocked, exchange of gases may be impaired to the extent that the person becomes hypoxic or unconscious or dies.

Ventilation

The movement of air from the atmosphere into and out of the lungs is called ventilation. Ventilation occurs by bulk flow. Bulk flow is the movement of a gas or a fluid from high to low pressure.

Impairments of alveolar ventilation, alveolar hyper- and hypoventilation

Ventilation — the movement of air from the atmosphere into and out of the lungs is called ventilation. Ventilation occurs by bulk flow. Bulk flow is the movement of a gus or fluid from high to low pressure.

Ventilation is determined by the formula 2:

$$F = P / R,$$

where F — the bulk flow air;

P — the difference in pressure between the atmosphere and alveoli;

R — the resistance offered by the conducting airways.

Alveolar hyperventilation exists when P_aCO_2 is below 37 mm Hg. Hypoxemia controls ventilation by stimulating the peripheral chemoreceptors. In pulmonary disorders and congestive heart failure, hyperventilation results from stimulation of afferent vagal receptors in the lungs and airways. Low cardiac output and hypotension stimulate the peripheral chemoreceptors and inhibit the baroreceptors, both of which increase ventilation. Metabolic acidosis that occurs in many conditions activates both the peripheral and central chemoreceptors. Psychogenic states and severe cerebrovascular insufficiency may interfere with the inhibitory influence normally exerted by cortical structures of the brainstem respiratory neurons. Fever and sepsis also cause hyperventilation through the effects on midbrain and hypothalamus.

The alkalemia associated with hypocapnia may produce dizziness, visual impairment, syncope and seizure which are secondary to cerebral vasoconstriction. Tetany is secondary to decreased free serum calcium and muscle weakness is secondary to hypophosphatemia. Patients with a primary respiratory alkalosis are also prone to periodic breathing and central sleep apnea.

Alveolar hypoventilation is clinically important when $PaCO_2$ is generally in the range of 50 to 80 mm Hg.

Mechanisms of alveolar hypoventilation:

I. Disturbances of respiratory mechanics:

a) obstructive disorders;

b) restrictive disorders (parenchymal and extraparenchymal).

II. Dysfunction of respiratory control:

a) abnormalities in peripheral and central chemoreceptors;

b) impaired function of brainstem respiratory neurons.

Obstructive hypoventilation is characterized by an increase in resistance to airflow owing to partial or complete obstruction at any level, from trachea to respiratory bronchioles. The major obstructive disorders are emphysema, chronic bronchitis, bronchiectasis and asthma as well as a compression or obturation of airways. Any process that narrows the airway lumen leads to early airway closure. Patients must increase their resistance work in order to overcome increased airways resistance forces. In this condition, the interpleural pressure may become positive leading to airway compression and further increasing airway resistance. Excess mucus production and contraction of bronchial smooth muscle, as occurs in asthma and chronic bronchitis, or loss of radial traction on the airways due to destruction of alveolar septa, as occurs in emphysema, are most common causes of early airway closure.

In obstructive diseases, the total lung capacity is normal or increased. The hallmark of an obstructive disorder is a decrease in the forced expiratory volume in one second (FEV_1) and a reduction of the ratio of FEV_1 to forced vital capacity.

Restrictive hypoventilation is characterized by reduced expansion of lung parenchyma with decreased total lung capacity. Most common parenchymal restrictive

disorders are sarcoidosis, idiopathic pulmonary fibrosis, pneumoconiosis and drug- or radiation-induced interstitial lung diseases. Adult respiratory distress syndrome illustrates an example of acute restrictive disease. Extraparenchymal restrictive disorders include neuromuscular disorders and chest wall disorders. Most common neuromuscular disorders are poliomyelitis, peripheral neuropathy, myasthenia gravis, muscular dystrophies and high cervical trauma whereas chest wall disorders include obesity, pleural diseases, kyphoscoliosis and ankylosing spondylitis.

The hallmark of a restrictive pattern, found in either parenchymal and extraparenchymal restrictive disorders, is a decrease in lung volumes, primary total lung capacity and vital capacity.

Dysfunction of respiratory control may result from abnormalities in peripheral and central chemoreceptors as well as brainstem respiratory neurons. Defect of peripheral and central chemoreceptors may be observed in carotid body dysfunction, prolonged hypoxia and metabolic acidosis. Impaired function of brainstem respiratory neurons occurs in bulbar poliomyelitis, encephalitis, brainstem infarction and primary alveolar hypoventilation syndrome.

Pressure

Alveolar pressure varies with each inspiration and drives the flow of air. With the onset of inspiration, the thoracic cavity expands. As the thoracic cavity expands, the lungs also expand. According to Boyle's law, if the volume of an air-filled chamber increases, the pressure of the air in the chamber decreases. Therefore, as the lungs expand, pressure in the alveoli decreases to below atmospheric pressure, and air rushes into the lungs from the atmosphere (from high pressure to low pressure). At the end of inspiration, the thoracic cavity relaxes, causing pressures in the alveoli, which are filled with the air of inspiration, to be higher than in the atmosphere. Air then flows out of the lungs and down the pressure gradient.

Bronchial resistance

Resistance of the airways is usually low. Resistance is increased when the smooth muscle of the bronchiolar tubes constricts. Constriction of the bronchi results in a decrease in airflow into the lungs. Resistance is inversely proportional to the radius of a vessel to the fourth power. This means that if the radius of a bronchiolar tube decreases by one-half, the resistance to airflow in that tube increases by 16 (i. e., 2^4). Therefore, when the air passages constrict even slightly, resistance to airflow goes up significantly.

Bronchiolar resistance is determined by parasympathetic and sympathetic nervous system innervation of the smooth muscle of the bronchi and local chemical mediators.

Parasympathetic nerves are carried to the bronchial smooth muscle by way of the vagus nerve and cause contraction or narrowing of the airways, increasing resistance and reducing airflow. Parasympathetic nerves release the

neurotransmitter ACh. ACh acts by binding to cholinergic receptors on the smooth muscle of the bronchi.

Sympathetic innervation of the bronchial smooth muscle occurs by way of nerve fibers from the upper thoracic and cervical ganglia and causes relaxation of the bronchi.

This reduces and increases airflow. Sympathetic nerves release the neurotransmitter norepinephrine. Norepinephrine acts by binding to OI_2 adrenergic receptors on the smooth muscle of the bronchi.

Nervous control of respiration

Ventilation is controlled by the respiratory center in the lower brainstem areas of the medulla and pons. In the medulla, there are inspiratory and expiratory neurons that fire at opposite times in a preset pattern of rate and rhythm. Respiratory neurons drive ventilation by exciting motor neurons that innervate the main muscle of inspiration (the diaphragm) and the accessory muscles (the intercostal muscles).

Central chemoreceptors

Central chemoreceptors in the brain respond to changes in the hydrogen ion concentration of the cerebral spinal fluid. Increased hydrogen ion concentration increases the firing rate of the chemoreceptors, while decreased hydrogen ion concentration decreases the firing rate of the chemoreceptors. Information from the central chemoreceptors is delivered to the respiratory center in the brain, which in response increases or decreases the breathing pattern. Hydrogen ion concentration usually reflects carbon dioxide concentration. Therefore, when carbon dioxide levels rise, hydrogen ion levels rise, and the firing rate of inspiratory neurons is increased, causing an increase in respiratory rate. This is an example of negative feedback, because with an increase in the rate of breathing, the excess carbon dioxide and hydrogen ion will be blown off. With low carbon dioxide and low hydrogen ion levels, the firing rate of the inspiratory neurons returns toward baseline, and respiration slows.

Peripheral chemoreceptors

Peripheral chemoreceptors exist in the carotid and the aortic arteries, and monitor oxygen concentration in arterial blood. These receptors, called the carotid and the aortic bodies, send their impulses to the respiratory center of the medulla and pons primarily to increase the rate of ventilation when oxygen is low. They are less sensitive than the central chemoreceptors. The peripheral chemoreceptors also respond with an increase in firing rate to increased hydrogen ion dissolved in the blood. This is important because under certain circumstances free hydrogen ion increases without causing a change in carbon dioxide concentration (e. g., during conditions of metabolic acidosis caused by prolonged diarrhea or diabetes mellitus). Free hydrogen ion is relatively impermeable across the blood-brain barrier, so it is unable to activate the central chemoreceptors directly.

Motor neurons driving respiration

The major motor neuron controlling respiration is the phrenic nerve. When activated by the central inspiratory neurons, the phrenic nerve causes the diaphragm muscle to contract and the chest to expand. As the chest expands, air begins to flow from the atmosphere into the lungs. Airflow into the lungs is called inspiration. As inspiration continues, firing of the central inspiratory neurons slows and firing of the expiratory neurons increases, causing cessation of motor neuron activity and relaxation of the diaphragm. Chest expansion reverses and air flows out of the lungs. Airflow out of the lungs is called expiration.

Respiration

Respiration refers to the diffusion of gases between an alveolus and the capillary that perfuses it. Respiration occurs by diffusion, which involves the movement of a gas down its concentration gradient.

The rate of defusion of a gas (e.g. oxygen and carbon dioxide) is determined by (formula 3):

$$D = \frac{[(Xa - Xc)] \times SA \times T}{d \times k} \quad (3)$$

where D (with dot above) — is the rate of diffusion;

X_a — is the concentration of gas in the alveolus;

X_c — is the concentration of gas in the capillary;

SA — is the surface area available for diffusion;

T — is the temperature of the solution;

d — is the distance across which diffusion must occur;

k — is a physical constant that takes into account non-variable characteristics of the gas such as its molecular weight and its specific solubility coefficient.

Causes of diffusion impairments: thickening of alveolus wall, thickening of capillary wall, in-alveolar edema, interstitial edema, dilation of capillaries.

Pulmonary circulation

The pulmonary circulation consists of deoxygenated blood traveling in the pulmonary artery from the right side of the heart. This blood perfuses the respiratory portions of the lungs and participates in the exchange of oxygen and carbon dioxide across the capillaries and alveoli. After picking up oxygen and releasing carbon dioxide, the blood returns to the heart by way of the pulmonary vein. Pressure and resistance to flow in the pulmonary circulation are usually low, with a mean pulmonary pressure of approximately 12 mmHg compared with a mean systemic pressure of approximately 90 mmHg. The pulmonary circulation is compliant and can accommodate large variations in blood volume. Therefore, the pulmonary circulation can act as a reservoir for blood that can be called upon in times of decreased systemic blood volume or pressure.

Disorders of pulmonary circulation

All diseases of the respiratory system causing hypoxemia are potentially capable of increasing pulmonary vascular resistance, since alveolar hypoxia is a very potent stimulus for pulmonary vasoconstriction. Pulmonary vascular resistance increases if intraluminal thrombi or proliferation of smooth muscle in vessel walls diminishes the luminal cross-sectional area. Disturbances in the pulmonary vasculature may result from primary cardiac disease or conditions that elevate left atrial pressure, such as mitral stenosis.

Ventilation: perfusion ratio

Ventilation refers to air moving into and out of the lungs. Perfusion is the blood passing through the pulmonary circulation to be oxygenated. The ventilation: perfusion ratio, V/Q, is the ratio of airflow into the lungs divided by the pulmonary blood flow. In this expression, V is the volume of air moved with each breath, expressed as milliliters per minute (ml/min), and Q is the rate of blood flow in the pulmonary circulation, also expressed as mL/min. Normally, perfusion is slightly greater than ventilation and the V/Q ratio is approximately 0,8. Therefore, the alveoli receiving oxygen are well perfused by blood, allowing optimal conditions for gas exchange.

Impairments of ventilation perfusion ratio

Gas exchange depends critically on the proper matching of ventilation and perfusion at the acinar level. Increased ventilation raises the arterial blood oxygen tension toward the inspired oxygen pressure whereas increased blood flow causes the arterial oxygen tension to decline toward the mixed venous oxygen tension. The most efficient gas exchange occurs when VPR is approximately equal to 1. In the presence of pulmonary disease, the VPR can vary from 0 to infinity.

A low VPR occurs in physiologic and anatomic shunts, when blood from areas with low ventilated mixes with blood from well-ventilated areas, the resultant mixture has an oxygen content dependent on the oxygen tension in the two areas as well as the relative amounts of blood flow from each. An anatomic shunt may be intra- or extrapulmonary. Extrapulmonary anatomic shunts may result from congenital cardiac malformation. Shunting of blood through the pulmonary parenchyma occurs if the alveoli are atelectatic or if they are filled with fluid.

A high VPR is caused either by excessive ventilation or inadequate blood flow to an area of the lung. A high VPR does not cause arterial hypoxia per se. However, if the overall ventilation is normal, excessive ventilation in one section of the lung means there is inadequate ventilation in others. In areas of the lung where the VPR exceeds 1, the alveolar and capillary oxygen tensions are high but the oxygen uptake is poor. Because of the plateau of the oxygen-Hb dissociation curve, oxygen exchange is inefficient because very little extra oxygen is added to the blood by excess ventilation.

Elasticity

Elasticity of the respiratory system refers to the degree to which the lungs resist inflation or stretching. The alveoli and other lung tissue normally resist stretching and recoil after the force causing the stretch or expansion is removed. This situation is partially caused by the surface tension of each alveolus and partially by the presence of elastic fibers throughout the lungs, which tend to recoil after stretch. Conditions such as emphysema reduce the elastic recoil of the lungs, resulting in chronic overinflation.

The reciprocal of elasticity of the lungs is termed lung compliance. Compliance refers to the ease of inflation or stretching of the lungs. Lung compliance is reduced by fibrosis, infection, or ARDS.

Pleural pressure

The lungs are surrounded by a thin membrane called the pleura. The outer layer of the pleural membrane is attached to the wall of the thoracic cavity. The inner layer of the pleura is attached to the lungs. With expansion of the thoracic cavity during inspiration, the outer layer is pulled out; this force is transmitted to the inner layer, which expands the lungs. In between the inner and outer layers of the pleura is the pleural space. This space is filled with a few milliliters of fluid that surround and lubricate the lungs. The pleural fluid is at negative pressure and opposes the elastic recoil (collapse) of the lungs. This helps keep the lungs expanded.

Surface tension

Surface tension refers to the tendency of water molecules to pull toward each other and to collapse a sphere. Because each alveolus is lined with a thin water layer, the surface tension within each alveolus could be high, making it extremely difficult to expand an alveolus. With each breath, a certain pressure must be exerted to overcome the surface tension of the water layer. The amount of pressure needed to expand the alveolus is described by Laplace's law.

Surfactant

Certain cells inside the alveolus, called type II alveolar cells, produce an important substance called surfactant that helps reduce the surface tension of the alveolus, making it easier to inflate. Surfactant is a phospholipid that acts like a detergent to intersperse between water molecules in the alveolus, thereby weakening the bonds between them. This reduces surface tension and the tendency of the sphere to collapse.

When surfactant is present, a small alveolus actually requires less pressure to inflate than a large one because the surfactant is packed tightly together, greatly reducing the surface tension of the alveolus. This serves to compensate for the effect of small radius in Laplace's law.

Tests of pulmonary function:lung volumes

Spirometry is the measurement of the volume of air moving into and out of the lungs and is measured as an individual inhales and exhales into a closed chamber. It

is used to determine lung volumes, including tidal, inspiratory reserve, expiratory reserve, and residual volumes, and, calculated from these, vital capacity. The average values presented in the figure for each of these volumes are for an adult male. Values for adult females are approximately 20 to 25 % less.

Tidal volume

The amount of air entering or leaving the lungs during a single breath is the tidal volume. The amount of air inspired at rest (inspiratory volume) usually equals the amount expired (expiratory volume). Tidal volume averages approximately 500 ml at rest.

Inspiratory reserve volume

The amount of air above the normal inspiration that can be maximally inspired with each breath is the inspiratory reserve volume. It averages approximately 3,000 ml.

Expiratory reserve volume

The maximum amount of air that can be exhaled beyond normal exhalation is the expiratory reserve volume. This value averages approximately 1,000 ml.

Residual volume

The air remaining in the lungs after maximum exhalation is the residual volume. The normal value is approximately 1,000 ml.

Vital capacity

The maximum amount of air that an individual can inspire and expire during a single breath is the vital capacity. It is the sum of the normal tidal volume and the inspiratory reserve volume and the expiratory reserve volume. It is measured by having an individual take a maximum breath and then exhale as much as possible into the measurement chamber. In restrictive pulmonary disorders (e. g., resulting from neuromuscular disease, fibrosis, or loss of surfactant-producing cells), vital capacity is reduced.

A common test of pulmonary function is to plot the volume of air an individual can expire in the first second of expiration, called the forced expiratory volume in one second (FEV_1). A healthy individual can expire approximately 80 % of vital capacity as fast as possible in the first second (FEV_1/vital capacity). In obstructive pulmonary diseases such as asthma and emphysema, expiration is particularly affected, and the amount of air an individual can forcefully expire in the first second is reduced. In patients who have restrictive airway disease, expiration is usually normal. Therefore, whereas overall vital capacity is reduced in those who have restrictive airway disease, FEV_1 is normal.

Anatomic dead space

The amount of air in each breath that is measured as part of the tidal volume but that does not actually participate in gas exchange is the anatomic dead space. This air fills the conducting passages of the nose, mouth, pharynx, larynx,

trachea, bronchi, and the bronchioles. With rapid, shallow respirations, a greater percentage of each breath is wasted simply moving air in and out of the anatomic dead space compared with that seen with slow, deeper breathing.

Adult respiratory distress syndrome

Adult respiratory distress syndrome is a disease characterized by widespread breakdown of the alveolar and/or pulmonary capillary membranes. ARDS occurs after a major pulmonary, cardiovascular, or system-wide insult.

Causes of adult respiratory distress syndrome

Adult respiratory distress syndrome can occur as a result of direct injury to the capillaries of the lungs or to the alveoli. However, because the capillary and the alveolus are so intimately connected, extensive destruction of one typically leads to destruction of the other. This destruction occurs because of the release of lytic enzymes when cells die; it also occurs with activation of the inflammatory reaction subsequent to cell injury and death. Examples of conditions that affect the capillaries and/or the alveoli and can lead to ARDS are presented in the following sections.

Capillary Destruction. If breakdown is initially of the capillary membrane, movement of plasma and red blood cells into the interstitial space occurs. This increases the distance across which oxygen and carbon dioxide must diffuse, decreasing the rate of gas exchange. Fluid accumulating in the interstitial space moves into the alveoli, diluting surfactant and increasing surface tension. The exertion of pressure needed to inflate the alveoli is vastly increased. Increased surface tension coupled with edema and swelling of the interstitial space leads to widespread compression atelectasis, resulting in a loss of lung compliance, significantly decreased ventilation, and hypoxia. Causes of pulmonary capillary breakdown include septicemia, pancreatitis, venoms, and uremia. Pneumonia, smoke inhalation, trauma, and near drowning can also destroy the capillary membrane and initiate ARDS.

Alveolar Destruction. When the alveoli are the initial damage site, the surface area available for gas exchange is reduced, and, again, the rate of gas exchange is decreased. Causes of alveolar damage include pneumonia, aspiration, and smoke inhalation. Oxygen toxicity, which occurs after 24 to 36 hours of high-oxygen treatment, can also be a cause of alveolar membrane damage through the production of oxygen free radicals and by damaging the surfactant-producing cells.

Without oxygen, vascular and pulmonary tissues become hypoxic, leading to further cell injury and death. Once the alveoli and capillaries are damaged, inflammatory reactions, including macrophage and neutrophil infiltration and the release of various cytokines, are initiated that lead to swelling and edema of the interstitial space and damage to the neighboring capillaries and alveoli. Within 24 hours of ARDS onset, hyaline membranes form within the alveoli.

These are white fibrin deposits that progressively accumulate and further decrease gas exchange. Eventually, fibrosis obliterates the alveoli. Ventilation, respiration, and perfusion are all compromised. Mortality associated with ARDS is approximately 50 %.

Clinical Manifestations:

— Significant dyspnea.

— Decreased lung compliance.

— Rapid shallow breathing initially, resulting in respiratory alkalosis as carbon dioxide is blown off. Later, as the person fatigues, breathing may become slow and infrequent.

Diagnostic Tools. Arterial blood-gas analysis demonstrates reduced arterial oxygen concentration despite oxygen therapy. Oxygen therapy is ineffective in ARDS, regardless of the amount of oxygen supplied, because diffusion of the gas is limited owing to fibrin accumulation, edema, and capillary and alveolar breakdown.

Complications. Respiratory failure may develop as the disease progresses and the individual has to work harder to overcome decreased compliance of the lungs. Eventually, exhaustion sets in and ventilation slows. This results in respiratory acidosis as carbon dioxide accumulates in the blood. Respiratory slowing and a fall in arterial pH are indications of impending respiratory failure and possible death.

Pneumonia may develop after ARDS because of fluid accumulation in the lungs and poor lung expansion.

Renal failure and gastrointestinal stress ulcer can occur as a result of hypoxia.

Disseminated intravascular coagulation may develop because of the large amount of tissue that can be destroyed during ARDS.

PATHOLOGICAL PHYSIOLOGY OF DIGESTIVE SYSTEM

The alimentary tract provides the body with a continual supply of water, electrolytes and nutritients:

1) movement of food through the alimentary tract;

2) secretion of digestive juices and digestion of the food;

3) absorption of water, various electrolytes and digestive products;

4) circulation of blood through the gastrointestinal organs to carry away the absorbed substances;

5) control of these functions by local nervous and hormonal system.

Typical forms of gastrointestinal system pathology

Impairment of taste appetite, oral cavity digestion, swallowing and esophagus digestion in stomach, digestion in intestines

Taste impairments
(hypogeusia, hypergeusia, parageusia, dysgeusia, ageusia)

The main causes are CNS impairments.

Hypogeusia is taste analizator impairment (receptor, nerve trunks, neurons).
Hypergeusia is cortex neuron impairments, receptor hypersensitization

Impairment of taste adequacy to real irritant: parageusia, dysgeusia.

Parageusia is a false taste.
Dysgeusia is a perversion of taste (use of out-of-date or toxic products).

Appetite impairments
(hyperrexia, hyporexia, pararexia, anorexia)

Hyperrexia is a pathologic increase in appetite. It is associated with polyphagia and acoria.

Hyporexia is a high decrease in appetite. It is presented in severe diseases, oncologic diseases, neuron- and psychogenic impairments.

Pararexia is a pathologic change in appetite (use of inedible products).

The main cause: impairment of central control (trauma, tumor, psychogenic disease).

Impairment of salivation

Hyposalivation (inflammation, neuron-humoral control impairments).

Hypersalivation (intoxication, acute gingivitis, acute stomatitis, helmints, oral cavity infections, activation of parasympathetic system).

Impairments of chewing

Impairments of chewing (stomatitis, gingivitis), impairment of muscular joint apparatus of lower jaw, absent of teeth and others.

Dysphagy

Stages of swallowing: 1) oral (voluntary); 2) pharyngeal (quick voluntary); 3) esophageal (slow voluntary).

Damage of the 5, 9 and 10 cerebral nerve can cause paralysis of swallowing mechanism. Such diseases as poliomyelitis or encephalitis can impair normal swallowing by damaging the swallowing center. Paralysis of the swallowing muscles occurs in muscle dystrophy and failure of neuromuscular transmission in myasthenia gravis or botulism.

The abnormalities that occur include: 1) complete arrest of the swallowing act; 2) failure of the glottis close (so that food passes into the lungs instead of the esophagus); 3) failure of the soft palate and uluva to close the posterior nares so that food refluxes into the nose during swallowing.

Impairments of food passage through the esophagus

Achalasia is a condition in which the lower esophageal sphincter fails to relax during the swallowing. So food swallowed into the esophagus fails to pass from the esophagus into stomach.

Causes: damage in the neural network of the myenteric plexus in the lower 2/3 of the esophagus. So the myenteric plexus has lost its ability to transmit a signal to cause «receptive relaxation» of the gastroesophageal sphincter as food approaches this sphincter during the swallowing.

Treatment: stretching the lower end of the esophagus by means of the balloon inflated on the end of a swallowed esophageal tube, use of antispasmotic drugs. Also impairments of food passage through esophagus is presented in diffuse esophageal spasm, systemic sclerodermia.

Impairment of the stomach

Impairment of the stomach motor function: hyper tone — increase in muscular tone, hypo tone — high decrease in muscular tone, atony — absence of muscular tone

Duodenogastric reflux disease. The condition of duodenogastric relux disease is caused by the reflux of duodenum contents into the stomach. It results from the decrease in HCl and gastrin secretion, the increase in cholecystokinin level. The increase in alkaline contents causes the impairment of mucous barrier, microcirculation impairments, dystrophy and necrosis of epithelium.

Impairments of peristalsis

Hyperkinesis is an increase in peristalsis and gastric tone. It occurs in acute pain, hearburn, sometimes in case of vomiting. It is stimulated by histamine, serotonin, substance P.

Hypokinesis is a decrease in peristalsis and gastric tone. It occurs in myocardial infarction, infectious diseases. Stomach motor function is inhibited by somatostatin, secretin, neuropeptide Y, peptide YY.

Motor function impairments

Pyrosis is a technical term for what is popularly called heartburn, a burning sensation in the upper abdomen.

Belching is a normal process to relieve distention from the air that accumulates in the stomach. The upper abdominal discomfort associated with excessive swallowed air may extend into the lower chest, producing symptoms suggesting heart or lung disease.

Hiccough is an extraordinary type of breathing movement involving a sudden intake of air (inspiration) due to an involuntary contraction of the diaphragm accompanied by closure of the vocal apparatus (glottis) of the larynx.

Nausea. Nausea is a subjective, unpleasant sensation that often precedes vomiting. Nausea is caused by distention or irritation anywhere in the GI tract, but it can also be stimulated by higher brain centers. Interpretation of nausea occurs in the medulla, which is either adjacent to or part of the vomiting center.

Vomiting

Vomiting is a complex reflex mediated through the vomiting center in the medulla oblongata of the brain. Afferent impulses travel to the vomiting center as both vagal and sympathetic afferents. Afferent impulses originate in the stomach or duodenum in response to excessive distention or irritation, or sometimes they originate in response to chemical stimulation by emetics (agents that cause vomiting), such as syrup of ipecac. Hypoxia and pain can also stimulate vomiting by means of activation of the vomiting center. Vomiting can also occur through direct stimulation of an area of the brain adjacent to the vomiting center in the brain. Certain drugs initiate vomiting by activating this center, called the chemoreceptor trigger zone, which lies in the floor of the 4th ventricle. Vomiting as a result of rapid motion change is believed to work through stimulation of this trigger zone. Activation of the chemoreceptor trigger zone can cause vomiting either directly or indirectly by its subsequent activation of the vomiting center. Input from higher brain centers in the cortex and increased ICP can also stimulate vomiting, probably by directly stimulating the vomiting center. Projectile vomiting occurs when the vomiting center is directly stimulated, frequently by increased ICP.

When the vomiting reflex is initiated in the vomiting center, it is carried out by activation of several cranial nerves to the face and throat, and spinal motor neurons to the diaphragm and abdominal muscles. Excitation of these pathways results in the coordinated response of vomiting. Certain symptoms generally precede vomiting, including nausea, tachycardia, and sweating.

Dumping syndrome

Dumping syndrome is a pathologic condition results from quick evacuation of gastric contents into duodenum. It develops after the stomach resection.

Pathogenesis: 1) hyperosmolarity of duodenum contents results from concentrated food hitting from the stomach; 2) intensive transport of fluids from the vessels into the intestines according to osmotic pressure gradient; 3) hypovolemia; 4) intensive absorption of glucose → hyperglycemia; 5) stimulation of insulin secretion; 6) hyperglycemia, ionic imbalance, acidosis.

Clinical manifestations: wasting after the food intake, tachycardia, arrhythmia, acute arterial hypotension, drowse, wasting, sweating, dizziness, nausea, muscular tremor, loss of consciousness.

Impairment of secretion

Typical impairments of stomach secretion:

— change in gastric juice volume: increase, decrease, absence;

— impairment of mucosa secretion: increase, decrease, absence;

— impairment of HCl secretion and change in gastric juice acidity: hyperchlohydria, hypochlorhydria, achlorhydria;

— impairment of pepsin secretion: increase, decrease, absence.

Gastrointestinal peptides

Many GI hormones, including gastrin, secretin, CCK, GLP-1, and GIP, play important roles in the digestive function of the GI tract. Other hormones released from the stomach or intestine, including ghrelin and PYY, are involved in controlling appetite. These hormones and their roles are discussed in the text that follows.

Gastrin is secreted from the stomach antrum in response to distention of the stomach after a meal and the presence of protein in the food. In addition, gastrin secretion is stimulated by the release of gastrin-releasing peptide from the nerves of the submucosal plexus as a result of parasympathetic stimulation. Gastrin acts to stimulate the secretion of histamine and gastric juices from the gut lining and HCl from the parietal cells of the stomach. Histamine also stimulates HCl secretion. HCl in turn activates pepsin, the most important digestive enzyme in the stomach. Pepsin and the gastric juices begin the digestion of protein in the stomach, removing the stimulation for further gastrin secretion. Thus, gastrin release is inhibited by excess acid, which is an excellent example of negative feedback. Gastrin also stimulates intestinal motility.

Secretin is secreted from the small intestine primarily in response to HCl present in the chyme entering the small intestine from the stomach. Secretin stimulates intestinal secretions of base as well as the pancreatic release of bicarbonate to neutralize the acid. Neutralization of acid is essential because the enzymes required for digestion in the small intestine cannot work in an acidic environment. Secretin also slows the further passage of food from the stomach into the small intestine, allowing adequate time for digestion of food already in the small intestine.

Cholecystokinin is secreted from the small intestine primarily in response to fat and other food particles entering the intestine in the chyme. CCK causes gallbladder contraction; it also causes the release of pancreatic and intestinal digestive enzymes and of bile. The digestive enzymes and bile serve to promote the digestion and absorption of the food particles.

Glicogon-libe peptid-1 and glucose-dependent insulinotropic poliptide is secreted from the upper small intestine in response to fatty acids, amino acids, and glucose in the chyme. These hormones function to slow further stomach emptying, thereby allowing the effective digestion of the food already present in the small intestine. They also increase the release of insulin from the pancreas; GLP-1 and GIP account for approximately 50 to 60 % of the insulin released during a meal. Evidence suggests that a deficiency in GLP-1 and/or GIP may contribute to glucose intolerance and reduced insulin secretion characteristic of type II diabetes mellitus.

Ghrelin and peptide YY are both appetite-modulating hormones. First identified in 1999, ghrelin is secreted from the stomach and functions to regulate energy balance by stimulating food intake and decreasing fat metabolism. It appears to act with other signals to inform the CNS regarding food intake and body fat mass. Ghrelin also stimulates growth releasing hormone from the hypothalamus. It also appears to affect the hypothalamic-pituitary-gonadal axis.

Peptide YY is co-secreted with GLP-1 from the small intestine in response to food entering from the stomach. PYY levels are proportional to meal energy content, and plasma levels peak postprandially after 1 hour. PYY acts as a satiety hormone in that it inhibits further food intake. It appears to function at the level of the CNS.

Non-peptic ulceration

in stress: impairment of microcirculation → spasm of arterioles of stomach muscular layer → stasis → stasis → bleedings.

— burns (Curling's ulcer);
— cerebral trauma, myocardial infarction, sepsis;
— hemorrhages;
— neurological surgery (Cushing's ulcer).

Drugs: a decrease in mucosa production — aspirin, indometacin, glucocorticoids and prednisolone.

In endocrine pathology: Zollinger-Ellison's syndrome — A-cell-insulinoma, hyperacidosis, ulceration of stomach and duodenum.

Others: chronic adrenal failure, arterial hypertension, atherosclerosis.

Parasympathetic innervations stimulate the production of HCl, proteolytic enzymes and mucosa, gastrin. Also it increases sensitivity of secretion cells to gastrin and histamine. It activates gastric blood circulation, and decreases concentration of somatostatin. Somatostatin inhibits gastrin secretion.

Sympathetic innervations stimulate alpha and beta-adrenoreceptors → decrease in HCl and pepsinogen secretion, decrease in stomach blood circulation.

Peptic ulceration

Cause: imbalance between the rate of secretion:

1) the gastroduodenal mucosal barrier;
2) the neutralization of the gastric acid by duodenal juices.

Pathogenesis of peptic ulceration

Factors of aggression:

1) Endogenous:

— acid-peptic (HCl and pepsin);
— bile acids and lysolecithin, pancreatic enzymes (in duodenogastric reflux)
— ischemia (caused by PAF-factor of thrombocyte activation, LTC_4 – leukotriene C_4);
— motor function impairment.

2) Exogenous:

— helicobacter pylori;
— alcohol;
— NSAID.

H. pylori is a nonsporing curvilinear gram-negative rod measuring approximately 3,5–5,0 μm. H.pylori is a part of genus of bacteria that have adapted to ecologic niche provided by gastric mucosa, which is lethal to most bacteria. The specialized traits that allow it to flourish include:

— Motility (via flagella), allowing it to swim through viscous mucus.

— Elaboration of a *urease,* which produces ammonia and carbon dioxide from endogenous urea, thereby buffering gastric acid in the immediate vicinity of the organism.

— Expression of *bacterial adhesins*, such as BabA, which binds to the fucosylated Lewis B blood-group antigens, enhances binding to blood group O antigen bearing cells.

— Expression of bacterial toxins, such as cytotoxin association gene A *(CagA)* and vacuolating cytotoxin gene A *(VacA)*.

The *H. pylori* genome is 1,65 million base pairs and encodes approximately 1500 proteins. Extensive molecular studies suggest that the bacteria cause gastritis by stimulating production of pro-inflammatory cytokines and by directly injuring epithelial cells (discussed later).

After initial exposure to *H. pylori,* gastritis occurs in two patterns: a predominantly antral-type gastritis with high acid production and elevated risk for duodenal ulcer, and a pangastritis that is followed by multifocal atrophy (multifocal atrophic gastritis) with lower gastric acid secretion and higher risk for adenocarcinoma. The underlying mechanisms contributing to this difference are not completely clear, but host-microorganism interplay appears to be critical. IL-1β^2 is a potent pro-inflammatory cytokine and a powerful gastric acid inhibitor. Patients who have higher IL-1β^2 production in response to *H. pylori* infection tend to develop pangastritis, while patients who have lower IL-1β^2 production exhibit antral-type gastritis.

A number of diagnostic tests have been developed for the detection of *H. pylori*. Noninvasive tests include a serologic test for antibodies, fecal bacterial detection, and a urea breath test.

The breath test is based on the generation of ammonia by bacterial urease. Invasive tests are based on the identification of *H. pylori* in gastric biopsy tissue. Detection methods in gastric tissue include visualization of the bacteria in histologic sections, bacterial culture, a rapid urease test, and bacterial DNA detection by the polymerase chain reaction.

Patients with chronic gastritis and *H. pylori* usually improve when treated with antibiotics. Relapses are associated with reappearance of the organism. The current treatment regimens include antibiotics and hydrogen pump inhibitors. Prophylactic and therapeutic vaccine development is still in the early research stage, but it holds the promise to eradicate or at least greatly reduce the worldwide prevalence of *H. pylori* infection.

Pathogenesis of H. pylori infection: 1) colonization of gastric mucosa (it is possible because of motility, adhesion, urease, resistance to acids); 2) persistence (it

is possible because of the metabolic products, enzymes and meal-binding proteins); 3) injury (it is possible because of pro-inflammatory factors: Cag, neutrophil activating protein, lipopolysaccharide), tissue injury (cytotoxin, ammonium genesis, hyperactivaton of immune system, impairment of HCl synthesis control → ulcer.

Diagnostics of Helicobacter pylori infection

1) bacteriological tests: finding out in imprint smears, culture isolation;

2) serologic tests: Bordet-Gengou test (complement-fixing reaction), red cell-inked-antigen test, immune-enzyme analysis, H. pylori finding out in feces, saliva and oral cavity;

3) morphologic test: cytotoxic — finding out in biopsy material (Romanovsky's stain), histologic;

4) biochemical tests: urease test with biopsy material, urease respiratory test (^{13}C and ^{14}C is found out in expired air after the radiolabeled urea intake);

5) molecular genetic test: PCR.

Pancreatitis

Pancreatic enzymes: amylase, lipase, phospholipase A_2, tripsin, chymotripsin, elastase, carboxypeptidase A and B. All these enzymes are secreted in pancreas in non-active form and activated in duodenum.

Acute pancreatitis

Acute pancreatitis is an inflammation of the pancrease characterized by autodigestion of the pancreas by pancreatic enzymes. Pancreatic cells are injured or killed, leading to areas of cell necrosis and hemorrhage. Stimulation of the immune and inflammatory systems results in the swelling and edema of the organ.

There is an ability to regenerate after the acute pancreatitis as opposed to chronic pancreatitis.

The key chain of pathogenesis is an activation of pancreatic enzymes.

In 80 % of cases acute pancreatitis is caused by a gallstone in the common bile duct. Chronic alcoholism (ethanol action) is associated with pancreatitis because of stimulation of the pancreatic enzyme release.

Tripsin activates pancreatic enzymes: kallikrein, phospholipase A_2, and elastase → autodigestion of pancreas, vasodilation, arterial hypotension, increase in vascular permeability.

Pathogenesis of autodigestion

1) bile and duodenum contents reflux into the pancreatic ducts;

2) tripsinogen transformation in tripsin in pancreatic ducts and gland intersticium, presence of gallstones in bile ducts;

3) activation of zymogens and phospholipase A_2 (destruction of cell membrane);

4) lysolithitin formation (destruction of cell membrane);

5) autolysis;

6) edema and microcirculation impairments.

Impairments of intestinal absorption

*Causes: i*nsufficient digestion, diarrhea, atrophy of intestinal mucous membrane, enteritis, acute intestinal infection, enteroectomy, impairment of intestinal blood and lymph circulation.

Malabsorption

Malabsorption is a failure of the small intestine to absorb certain foodstuffs. There are several types of malabsorption: 1) one type of amino acid, fat, sugar or vitamin; 2) all amino acids, fats, sugars; 3) all fat-soluble vitamins.

Malasorptio is a symptom complex result from the selective or total impairments of digestion (maldigestion) and absorption (malabsorption) in the small intestine.

Types of malabsorption (according to origin)

1) *primary:* genetically determined or congenital enzymopathias in the small intestine, pathology of the absorbing epithelium in the small intestine (non-tropical sprue, tropical sprue);

2) *secondary:* impairments in the single part of the small intestine, or impairments of the whole small intestine as a consequence of other diseases.

Clinical manifestations of malabsorption depend on what is not being absorbed and whether other areas of the bowel can compensate. Specific symptoms are related to the dietary deficiency that occurs. Generalized symptoms usually include those related to the GI tract or to the loss of fat-soluble vitamins:

- Fat malabsorption results in steatorrhea (fat in the stool). Diarrhea, flatulence, bloating, and cramps often occur. Stools are bulky but of light weight, float, and are malodorous.

Bile salt deficiency results in malabsorption of fat-soluble vitamins, causing the following:

— Vitamin A deficiency — night blindness.

— Vitamin D deficiency — bone demineralization and increased risk of fractures.

— Vitamin K deficiency — poor coagulation with prolonged prothrombin time, easy bruising, and petechia (hemorrhagic spots on the skin).

— Vitamin E deficiency — perhaps resulting in poor immune function.

— Lactose malabsorption results in osmotic diarrhea and flatulence (gas).

Diagnostic Tools. The presence of over 7 g of fat per day in the stool of an adult consuming a typical American diet is considered malabsorption. Weight loss or failure to gain weight in infancy or young childhood may indicate malabsorption.

Complications. Failure to thrive may occur in severe cases, leading to malnutrition, infection, and even death.

Nontropical sprue

One type of sprue, called variously *idiopathic sprue*, *celiac disease* (in children), or *gluten enteropathy*, results from the toxic effects of *gluten* present in certain types of grains, especially wheat and rye. Only some people are susceptible to this effect, but in those who are susceptible, gluten has a direct destructive effect on intestinal enterocytes. In milder forms of the disease, only the microvilli of the absorbing enterocytes on the villi are destroyed, thus decreasing the absorptive surface area as much as twofold. In the more severe forms, the villi themselves become blunted or disappear altogether, thus still further reducing the absorptive area of the gut. Removal of wheat and rye flour from the diet frequently results in cure within weeks, especially in children with this disease.

Tropical sprue

A different type of sprue called *tropical sprue* frequently occurs in the tropics and can often be treated with antibacterial agents. Even though no specific bacterium has been implicated as the cause, it is believed that this variety of sprue is usually caused by inflammation of the intestinal mucosa resulting from unidentified infectious agents.

Malabsorption in sprue. In the early stages of sprue, intestinal absorption of fat is more impaired than absorption of other digestive products. The fat that appears in the stools is almost entirely in the form of salts of fatty acids rather than undigested fat, demonstrating that the problem is one of absorption, not of digestion. In fact, the condition is frequently called *steatorrhea*, which means simply excess fats in the stools. In very severe cases of sprue, in addition to malabsorption of fats there is also impaired absorption of proteins, carbohydrates, calcium, vitamin K, folic acid, and vitamin B_{12}. As a result, the person suffers: 1) severe nutritional deficiency, often developing wasting of the body; 2) osteomalacia (demineralization of the bones because of lack of calcium); 3) inadequate blood coagulation caused by lack of vitamin K; and 4) macrocytic anemia of the pernicious anemia type, owing to diminished vitamin B_{12} and folic acid absorption.

The pathological increase in absorption is associated with the increase in intestinal wall permeability in arterial hyperemia, in irritation of the intestinal epithelium, in small children.

Impairments of intestinal motor function. Types: increase in peristalsis, decrease in peristalsis, intestinal obstruction

Diarrhea

Diarrhea is an increase in fluidity and frequency of stools (more than 2–3 times per day). It may be large or small volume and may or not may contain blood. It is associated with the increase in intestinal motor function.

Types and mechanisms of diarrhea

Exudative diarrhea. It results from inflammatory exudates formation because of themucosa becomes extensively irritated. And its rate of secretion becomes greatly enhanced. Motility of the intestinal wall usually increases manifold. As a result, large quantities of fluid are made available for washing the infectious agent toward the anus. At the same time strong propulsive movements propel this fluid forward.

Secretory diarrhea. This type of diarrhea is caused by cholera (and less often by other bacteria such as some pathogenic colon bacilli). Cholera toxin directly stimulates excessive secretion of electrolytes and fluid from the crypts of Lieberkuehn in the distal ileum and colon (up to 10–12 l per day). Although the death can results from loss of fluid and elecrolytes.

Hyperosmotic diarrhea. It results from the increase in intestinal peristalsis and hypersecretion (enterocolitis, syndrome of intestine irritation).

Clinical manifestations and consequences

Hypohydration up to exicosis, hypovolemia, arterial hypotension, electrolyte imbalance and acid-base imbalance.

Obstipation

Obstipation is defined as difficult or infrequent defecation. Because frequency of stool varies among individuals, the 2 half of this definition is subjective and should be interpreted as a relative decrease in the number of stools for that particular individual.

In general, however, bowel movements fewer than once every 3 days are considered to indicate *constipation*.

Types and mechanisms

— **Alimentary** (small volume). It results from the small volume of the intestinal contents. It is observed in chronic malnutrition, small water intake, lack of fruits and vegetables, light food intake. The small volume of intestinal contents and excrements is not sufficient for defecation activation. Defecation is a reflex process.

— **Neurogenic.**

Spastic constipation. It is caused by high increase in n.vagus influences on the intestinal wall. It results in spasm of the intestinal musculature and decrease in feces evacuation.

Atonic constipation. It is caused by decrease in neuroeffector actions on the intestinal musculature. Decrease in neurotonic actions results in intestinal hypotoniaand constipation.

Rectal constipation. It is a consequence of pathologic processes in rectum (rectal fissure, paraproctitis). It is associated with pain. Pain inhibits defecation.

Mechanic constipation. It is a result of mechanical stool retention by scar or tumor.

Intestinal obstruction

Intestinal obstruction is an impairment of intestinal passage results from the mechanic stool retention, or impairment of intestinal function (closed-loop obstruction).

Causes of acute intestinal obstruction: hernia, thrombosis, closed-loop obstruction, invagination, tumor, commissure.

Classification of intestinal obstruction

Congenital intestinal obstruction is associated with maformations

*Acquired intestinal obstruction***:**

Mechanic:

— Obturation type results from the intestine obstruction by tumor or helmints.

— Strangulation type results from the impairment of intestinal passage results from twist of intestinal loop, compression of mesenteric blood vessel by tumor, scar, inflammatory infiltrate.

Dynamic:

— Spastic type results from the impairment of the intestinal peristalsis results from the spasm of the single part of intestine.

— Paralytic type results from the paralysis of the single part of intestine.

PATHOLOGICAL PHYSIOLOGY OF LIVER

Functions of liver

— digestive;
— protein synthesis;
— lipid, mineral and vitamin metabolism, pigment metabolism;
— control of blood coagulation;
— it is a part of immune system;
— barrier;
— blood coagulation;
— hormone metabolism.

Wilson's disease

— Autosome recessive type of inheritance.
— 1:30,000.
— Pathologic gene is localized on chromosome 13.
— Gene codes type P-ase-protein. Type P-ase-protein transfers Cu through the membrane and participate in Cu transferation from hepatocyte lysosomes into the bile. In-cell Cu accumulation results from the lack of type P-ase-protein. High level of in-cell Cu is hepatotoxic.

It is a disease of young and old people. It does not clinically manifested up to 5 years old. It is manifested by 15 years in 50 % of patients. It is rarely diagnosed in 40–50 year-old men. There is a characteristic greenish brown ring in the cornea (the Kayser-Fiescher ring).

The liver is always involved in pathological process — cirrhosis, plus eyes, kidneys, joints are injured. Erythrocyte hemolysis and degeneration of basal ganglions (including lentiform nuclei) are observed.

There is a decrease in caeruloplasmin level in blood serum (caeruloplasmin normally forms a non-toxic complex with copper). Clinical manifestations include: ophthalmologic manifestations, blue demilunes on the nails, neurologic impairments (mental retardation and symptoms resembling parkinsonism, nephrolithiasis, joints pathology, hemolytic anemia).

Experimental modeling of liver pathology

1. Ekk's fistula (1877).

Postcava portal vein anastomosis is in a dog. Portal vein is ligatured above the anastomosis. So, blood from the abdominal cavity flows into the postcava.

— Detoxication.

— Urea formation.

2. Inverse Ekk-Pavlov's fistula (1983).

Postcava portal vein anastomosis. Postcava is ligatured. So, blood from the gastrointestinal tract and back part of the body flows into the liver.

— Functional liver state in different conditions.

3. Angiostomic method of E. S. London (1919).

Metallic cannula is imposed to the wall of portal vein and hepatic vein → their free ends are placed out through the abdominal wall.

— Functional role of the liver in norm and pathology.

— The role of the liver in carbohydrate, protein, lipid, pigment and mineral metabolism).

4. Method of isolated liver perfusion.

Laboratory animals are the donors of the liver (rats, rabbits, cats). The liver of jumbo is also used (dogs, pigs, calve).

— The metabolic role of the liver.

— Transplantation.

5. Extirpation of the liver.

Extirpation of the liver is an experimental model of the hepatic coma. The partial extirpation of the liver does not results in severe metabolic impairments → the intact part of the liver preserve functions and compensation abilities.

6. Administration of infectious and toxic agents.

Parenteral administration (injection) of hepatic toxins.

— CCl_4 → alteration, necrobiosis in the central zone of liver acinus.

— Salt hydrazine → fat hepatitis.

— Alcohol → local dystrophic destructive changes in parenchyma, vascular impairments.

— Chloroform.

— Heliotrope seeds.

For experimental modeling of liver diseases.

Anatomy of the liver

The liver contributes about 2 % of the total body weight or about 1,5 kg in the average adult human. The basic functional unit of the liver is the liver lobule. It has a cylindrical structure (several millimeters in length and 0,8 to 2 mm in diameter). The human liver contains 50,000 to 100,000 lobules.

Kupffer's cells (reticuloendothelial cells), which are resident macrophages that line the sinusoids and are capable of phagocyting bacteria and other foreign matter in the hepatic sinus blood.

Liver acinus is divided into the 3 functional zones.

In the 1st zone hepatocytes are very close to the portal tract, adjoin sinusoids, contain more O_2 . Ischemia results in hepatocyte necrosis in the central zone.

Cells of the 3rd zone are localized around the terminal hepatic vein and contain less O_2, actively participate in drug metabolism. So, hepatic toxin action results in necrosis in the 3rd zone.

Juandice

Juandice is a syndrome, which refers to the yellowing of the body tissues, including a yellowish skin as well as deep tissues. The usual cause of jaundice is large quantities of bilirubin in the extracellular fluids, either non-conjugated bilirubin or conjugated bilirubin.

Bilirubin is easily bound with the elastic tissue. Elastic tissue in large quantity presents in sclera, vascular wall, the skin. An increase in bilirubin level results in sclera, vascular wall and the skin yellowing.

Bilirubin metabolism

80–85 % of bilirubin results from Hb catabolism in old Er (life span 120 days).

15–20 % of bilirubin results from the other sources:

1) ineffective erythropoiesis → an increase in erythrocyte precursors in bone marrow;

2) non-erythrocytic components → cytochromes, myoglobin, heme containing enzymes.

When erythrocytes live out their life span (120 days) and become too fragile to exit in the circulatory system, their cell membranes rupture, and the released Hb is phagocytized by tissue macrophages (also called the reticuloendothelial system) throughout the body.

The hemoglobin is the 1st split into globin and heme, and the heme ring is opened to give free iron, which is transported in the blood by transferring, and a

straight chain of 4 pyrrole nuclei, which are substrate from which bilirubin will eventually be formed. The 1st substance formed is bileverdin, but this is rapidly reduced to free bilirubin, which is gradually released from the macrophages into the plasma. The free bilirubin immediately combines strongly with plasma albumin and is transported in this combination throughout the blood and interstitial fluids. Even when bound with plasma protein, this bilirubin is still called «free bilirubin».

In hours free bilirubin is absorbed through the hepatic cell membrane. In passing to the inside of the liver cells, it is released from the plasma albumin and soon thereafter conjugated about 80 % with glucuronic acid to form bilirubin glucuronide, about 10 % with sulfate to form bilirubin sulfate, and about 10 % with a multitude of other substances. In these forms bilirubin is excreted from the hepatocytes by an active transport processes into the bile canaliculi and then into the intestines.

In the intestine about half of the conjugated bilirubin is covered by bacterial action into the substance urobilinogen, which is highly soluble. Some of the urobilinogen is reabsorbed through the intestinal mucosa back into the blood.

After explosure to air in the urine, the urobilinogen becomes oxidized to urobilin; alternatively, in the feces, it becomes oxidized to stercobilin.

Basic mechanisms of jaundice

— an increase d bilirubin overload on hepatocytes;
— impairment of bilirubin transport into hepatocytes;
— impairment of bilirubin conjugation;
— impairment of bilirubin excretion into bile through canal membrane;
— impairment of bile circulation in bile ducts.

Pathological classification of jaundice

Non-conjugated hyperbilirubinemia:

— an increase in bilirubin production (hemolysis);
— impaired bilirubin capture (drugs, cardiac failure);
— impairment of bilirubin conjugation (Gilbert's syndrome, Cligler-Najar syndrome).

Conjugated hyperbilirubinemia:

— impairment of canal excretion (hepatitis, cirrhosis);
— impairment of intrahepatic bile ducts (cirrhosis, tumor);
— impairment of anhepatic bile ducts (choledocholithiasis, stricture of bile ducts).

Juandice classification

— anhepatic juandice;
— hepatic juandice;
— obstructive or cholestatic juandice.

Hemolytic juandice

Etiology: hemolytic anemia (membranopathy, hemoglobinopathy, autoimmune anemia), intoxications, infections, pulminary apoplexy, large hematoma.

Pathogenesis

In hemolytic juandice, the excretory function of the liver is not impaired, but Er are hemolyzed so rapidly that the hepatic cells simply cannot excrete the bilirubin as quickly as it is formed. Therefore, the plasma concentration of free bilirubin rises to above-normal levels. The rate of urobilinogen formation in the intestine is greatly increased, and much of this is absorbed into the blood and later excreted in the urine.

The characterisitcs of hemolytic juandice are shown in the table 8.

Table 8 — Characterisitcs of hemolytic juandice

Criteria	Hemolytic juandice
Cause	Hereditary (acquired hemolytic anemia)
Color of the skin	A little bit yellowish
Juandice intensity	Insignificant
Color of sclera, mucous membranes	+
Ithes	—
Pain, localization	—
Liver sizes	Normal
Spleen sizes	Increased
Blood analyses	Normal
hyperbilirubinemia	Free bilirubin
Color of urine	Normal or dark
Color of feces	Darker than normal
Laboratory tests	Osmotic fagility; cold and warm antibodies, Coomb's test

Obstructive or cholestatic juandice

Etiology: obstruction of the bile ducts (a gallstone or cancer blocks the common bile ducts), hepatic cell damage (in hepatitis), stricture of the common bile duct, duskinesia of the gall bladder results from the impairment of innervation.

Pathogenesis

In obstructive juandice the rate of bilirubin formation is normal, but the formed bilirubin cannot pass from the blood into the intestines. The free 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 bilirubin in the plasma becomes conjugated type rather than non-conjugated.

Urobilinogen and stercobilinogen are not formed because bile does not get into the intestines.

Acholic syndrome

It is an absence or a high decrease in bile level in intestines. Maldigestion is observed in alcoholic syndrome.

Clinical manifestations: decolorated feces, steatorrhea, dysbacteriosis, meteorism, peristalsis impairments, impairment of protein metabolism, impairment of vitamin metabolism, impairment in procoagulant synthesis → hemorrhagic syndrome.

Cholemia

It is a syndrome characterized by bile component presence in blood (bile acids: glycocholic acid, taurocholic acid, conjugated bilirubin, cholesterol).

Clinical manifestations: yellowish sclera and skin → an increase in conjugated bilirubin, dark color of urine, cholaluria, hyperchlesterinemia (an increase in cholesterol level), xantomas and xanthelasmas → deposits of cholesterol under the epidermis of eyelids, itches results from bile acid action on the nerve endings, a decrease in arterial blood pressure → a decrease in base tone of vascular smooth muscles, bradycardia → the direct inhibiting action of bile acids on sinus node, excitability, irritability, fatigue, sleeplessness.

The characterisitics of cholemia are shown in table 9.

Table 9 — Characterisitics of cholemia

Criteria	Obsstructive or chronic
Cause	Obstruction, compression of the common bile duct
Color of the skin	Greenish grey or brownish grey
Juandice intensity	Very intensive
Color of sclera, mucous membranes	Yellowing is observed
Ithes	Intensive
Pain, localization	Frequent, intensive (gallstone or tumor0
Liver sizes	Increased
Spleen sizes	Normal
Blood analyses	An increase in alkaline phosphotase, ESR, cholesterol level
hyperbilirubinemia	Conjugated bilirubin bilirubin
Color of urine	Very dark due to conjugated bilirubin
Color of feces	Decolorated
Laboratory tests	Echography, X-ray, scanning, computer tomography, biopsy

Hepatic juandice

Etiology: infectous agents (virus, bacterium, plasmodium), non-infectious (hepatotoxic substances and compounds: CCL_4, ethanol, paracetamol), hepatotropic antibodies, CTL, neoplasia.

Pathogenesis

1st stage (preicterus):

— moderate increase in blood bilirubin levels (less than 34 umol/l; icterus is not obvious);

— accumulation of detectable amounts of urobilinogen in the blood and urine;

— increase in serum ALT, AST.

2nd stage (peak of disorder):

— considerable increase in blood bilirubin levels (icterus is obvious) mainly due to the conjugated type;

— significant cholemia;
— high levels of the ALT and AST activity.
3rd stage (final):
— increase in the total blood level of bilirubin more due to the unconjugated type than the conjugated;
— decrease in the blood urobilinogen concentration.

The characterisitics of hepatic juandice are shown in the table 10.

Table 10 — Characterisitics of hepatic juandice

Criteria	Hepatic
Cause	Inflammatory dystrophic changes in liver
Color of the skin	Yellowish
Juandice intensity	Medium
Color of sclera, mucous membranes	Yellowish
Ithes	Medium
Pain, localization	Dull pain in the right subcosta
Liver sizes	A little bit increased
Spleen sizes	Increased
Blood analyses	An increase in AST,ALT
hyperbilirubinemia	An increase conjugated and non-conjugated bilirubin level
Color of urine	Dark due to conjugated bilirubin
Color of feces	Rather pale than normal
Laboratory tests	Echography, biopsy, isotopic liver and spleen examination

The types of primary (hereditary, enzymopathic) jaundice are shown in the table 11.

Table 11 — Types of primary (hereditary, enzymopathic) jaundice

Type of pathology	Manifestations
Gilbert's syndrome	Mild decrease in UDP-glucuronide transferase activity and transport of unconjugated bilirubin into the liver cell; mild asymptomatic increase in the blood level of unconjugated bilirubin
Crigler-Najar syndrome type I	Absence of UDP-glucuronide transferase activity in the liver cells; very high unconjugated bilirubin levels in the serum (340–770 umol/L); no conjugated bilirubin is formed - colorless bile; severe neurologic complications
Crigler-Najar syndrome, type II	Partial deficiency of UDP-glucuronide transferase; high unconjugated bilirubin levels in the serum (103–340 umol/l); neurologic complications are uncommon
Dubin-Johnson syndrome	A defect in biliary excretion of bilirubin, cholephilic dyes, porphyrins; high bilirubin levels in the serum (51–257 umol/l), predominantly of the conjugated type; patients are asymptomatic or have vague constitutional or GI symptoms; liver cells contain dark pigment
Rotor syndrome	Similar to the Dubin-Johnson syndrome but the defect of biliary excretion of dyes is not as diffuse; high bilirubin levels in the serum, predominantly of the conjugated type; there is no dark pigment in the liver cells

Autoimmune hepatitis

Autoimmune hepatitis is an periportal hepatitis with hypergammaglobulinemia and tissue antibodies. Mostly it regresses under the immunosupressive therapy.

It is a disease resulting from the impaired immune control.

Types of autoimmune hepatitis (according to autoantibodies)

Type I

— 85 % of all autoimmune hepatites.

— Men:women = 8:1.

It is mostly observed in old people (lupiform hepatitis in young women is not referred to this type). Anhepatic clinical manifestations are rare, prognosis is good.

— Antinuclear antibodies AT-ANA.

— Antibodies to smooth muscles (actin) SMA.

Antigen S-actin observed in smooth and sceletal muscle is also present in cell membrane and cytosceleton of hepatic cells. So, revealance of SMA testifies about hepatic cell injury.

Type II

— 15 % of all autoimmune hepatites.

— 14 year old children, predominantly girls.

— systemic manifestations are often observed.

— antibodies — LKM.

It is associated with *diabetes mellitus type I*, thyroiditis, vitiligo (antigen is cytochrome P-450-D_6).

Type III

— Antibody to soluble liver antigen — SLA (soluble liver antigen).

— ANA, SMA, LKM-1 are absent.

Non-hepatic manifestations of autoimmune hepatitis

Manifestations of autoimmune hepatitis in all organ and system are determined genetically.

Fever, cutaneous vasculitis, arthralgia, arthritis, myalgia, pseudotrichinosis, lymphoadenopathy, pneumonitis, primary pulmonary hypertension, pleuritis, pericarditis, myocarditis, thyroidiris Hashimoto, glomerulonephritis, tubulointerstitial nephritis, diabetes mellius, hemolytic anemia, idiopathic thrombocytopenia.

Liver cirrhosis

It is a chronic progressive polyetiologic disease. It is characterized by the diffuse liver scarring and fibrosis. Hard fibrous nodules replace normal liver tissue, and constrictive, fibrous bands encircle the hepatocytes. Normal liver architecture and function is ruptured.

Etiology of liver cirrhosis

— Hepatitis B, C.

— Alcoholismprolonged cholestasis.
— Budd-Chiary syndrome.
— Lupiform hepatitis.
— Intoxication.
— Drugs (methotrexate).
— Metabolic impairmenrs (Wilson's disease).
— Gycogenosis type IV.
— Cryptogenic cirrhosis.

Forms of cirrhosis

— alcoholic;
— post-viral, post-necrotic;
— biliary;
— cardiac;
— hereditary;
— others.

Hepatic coma

Hepatic coma represents the final stage of the progressive liver failure. It is caused by severe intoxication of brain-hepatic encephalopathy.

Two variants of hepatic coma:

1) caused by porto-systemic shunting;
2) caused by hepatocellular insufficiency.

PATHOLOGICAL PHYSIOLOGY OF KIDNEYS

Functions of kidneys

1) excretory;
2) homeostatic;
3) control of arterial blood pressure and blood volume;
4) erythropoiesis stimulation;
5) antigen presentation;
6) control of blood coagulation;
7) hormone degradation: insulin, glucagon, gastrointestinal hormones and others.

Pathologic components of uric sedimentation

Proteinuria — protein excretion more than 150mg per day.
Hematuria — 1–2 Er in N.
Microhematuria — more than 3 Er.
Macrohematuria.
Leukocyturia — more than 5 Le.

Causes: infectious and non-infectious diseases.

Prevalence of lymphocytes testifies to the immune renal pathology, neutrophils — to inflammation, eosinophils — to allergy.

Cylindruria

Cylinders result from protein precipitation in renal tubules.

— Pure protein: hyaline, ceraceous.

— Cellular (grainy).

Diuresis impairments

N – 700–2 000 ml per day (4–6 urine output).

Polyuria — more than 2500–3000ml per day.

Oliguria — less than 500ml per day.

Anuria — less than 100–50ml per day.

Creatinine filtration rate (CFR).

GFR plasma creatinine concentration = CRF.

GRF – glomerular filtration rate.

N — 100–120ml/min

Creatinine filtration rate characterizes excretory and filtration renal functions.

Createnine is usually preset in blood of man. It is excreted only by filtration in man over 11 years old (it is not reabsorbed or secreted in tubules). It means that 100–120 ml of blood is filtred from creatinine by kidneys in 1 min, and at the same time, 100–120 ml of primary urine is formed.

Impairment of filtration and excretory renal function is characterized by low parameters of CFR.

Compounds that are also used in clearance test: exogenous inulin, hyposulphite — 100–120 ml/min, urea — 55–70 ml/min, but it is partially reabsorbed in renal tubules.

Nephritic syndrome

It is characterized by: hematuria, azotemia, variable proteinuria, oliguria, edema and hypertension.

Nephrotic syndrome

It is a clinical laboratory complex of symptoms characterized by:

— proteinuria more than 3–3,5 g per day;

— hypoalbuminemia (plasma albumin less than 30 g/l);

— disproteinemia;

— hyperlipidemia;

— edema.

Types of nephrotic syndrome

Primary (renal diseases): lupiform nephrosis, membranous glomerulonephritis, focal segmented glomerulonephritis, membranous proliferative glomerulonephritis.

Secondary (real injury is secondary): in systemic diseases (systemic lupus erythematosus, diabetes mellitus, vasculitis), infections.

Mechanisms of nephrotic syndrome

Proteinuria:

— a decrease in work of filtration barriers of glomeruli (an increase in basement membrane permeability results in glomerulus injury);

— changes in capillaries of glomerular filter;

— a decrease in tubular epithelium ability to reabsorb protein (it results from the secondary injury);

— loss of albumins, Ig, some factors of blood coagulation, erythropoietin, protein-hormone transmitters, inhibitors of blood coagulation (antithrombin III, protein C, S);

— loss of proteins with urine results in normochromic normocytic anemia;

— endocrine pathology.

Hypoalbuminemia:

— loss of albumins with urine prevail over protein synthesis;

— an increase in albumin synthesis in liver;

— compensatory decrease in albumin catabolism.

Hyperlipidemia:

— stimulation of very low-density lipoprotein synthesis;

— an increase in mevalonic acid synthesis (precursor of cholesterol synthesis);

— a decrease in activity of lipoproteinlipase in tissues results from an increase in plasma free fat acid level;

— a decrease in activity of LCAT results from a decrease in albumin level and an increase in lysolithetin level (lysolithetin is an inhibitor of LCAT);

— an increase in cholesterol and triglycerides in plasma;

— an increase in low-density lipoproteins and very low-density lipoproteins.

Mechanisms of edema in nephrotic syndrome

Proteinuria results in hypoalbuminemia (a decrease in colloid osmotic pressure) → hypovolemia (a decrease in in-vascular blood volume) → a decrease in renal blood flow. The decrease in renal blood flow results in activation of rennin synthesis → angiotensin II synthesis → increased aldosterone secretion → an increase in ADH level → an increase in water reabsorption, edema. At the same time, a decrease in renal blood flow results in a decrease in glomerular filtration, activation of aldosterone secretion causes natrium reabsorption → an increase in water reabsorption, edema.

Clinical manifestations of nephrotic syndrome

— Edema.

— Clinically minor hypogonadism results from the loss of androgens and estrogens with protein-hormone transmitters.

— The loss of 1,25 $(OH)_2D$ transmitter results in hypovitaminosis and endocrine pathology.

— An increase in blood coagulation activity results from compensatory increase in plasma proteins (in response to hypoalbuminemia). Proteins bind the inhibitors of blood coagulation and do not get in the ultrafiltrate.

Complications of nephrotic syndrome

— Increased sensitivity to infections, firstly to in-capsulated microorganisms (pneumococci), results from the loss of Ig and complement.

— An increased risk of thromboembolism (thrombosis of profound veins of low extremities results in pulmonary embolism).

— A decrease in blood coagulation is caused by the loss of antithrombin III and other inhibitors and blood coagulation controls.

Acute diffuse glomerulonephritis

It is an infection allergic disease with primary impairment of glomeruli.

Etiology:

— streptococci (beta-hemolytic streptococcus, group A, type 2);
— pneumococci- and meningococci;
— salmonella, Tr. Pallidum;
— viruses (herpes virus, inf. mononucleosis);
— malaria, plasmodium;
— toxoplasma.

Non-infectious factors: autoaggressive or cross antibodies; circulating immune complexes: antigen, immunoglobulin, Complement components; foreign proteins (vaccine, serum, cancer cell proteins).

Evidence of acute glomerulonephritis infectious origin: occurrence after the streptococci infection; revealing infectious centers in organism; revealing anti-streptococcus antibodies in blood serum.

Acute glomerulonephritis modeling (according to the cavelty model)

Signs of the acute diffuse glomerulonephritis are found out after the administration of dead culture of hemolytic streptococci and homogenized liver tissue to rats, rabbits.

Evidence of immunologic allergic character of the acute diffuse glomerulonephritis:

— it occurs in 14–18 days after the suffered streptococcus infection (it is a time of antibody formation, complexes with antigens, mediators and their action on the glomerular membrane);

— revealing nephrotoxic auto-antibodies in blood;

— revealing non-specific enabling factor (overcooling, intoxication, infection);

— revealing «antigen + antibody + Complement component» complexes on the glomerular membrane.

Acute glomerulonephritis modeling (according to the masugi model)

The infected anti-GBM antibody is rabbit immunoglobulin, which is foreign to the host and thus acts as an antigen elicting anti-Ig antibody in the rat. The rat antibodies then react with the rabbit Ig deposited in the basement membrane, leading to the further glomerular injury. This model consists of two phases:

— heterogenous phase caused by the injected anti-GBM antibody;

— autologous phase caused by the host antibody against the injected immunoglobulin.

Often the anti-GBM antibodies cross-react with other basement membranes, especially those in the lung alveoli, resulting in simultaneous lung and kidney impairments (Goodpasture syndrome).

Pathogenesis

1. Antibody formation to the streptococcus antigen.
2. Action of anti-streptococcus antibodies on streptococci (streptococcus destruction) and kidney (there are the same Ag on the renal cell membranes).
3. Protein denaturation.
4. Direct injury of the nephron structure by the streptococcus toxins resulting in additional autoantibody production.
5. Production of nephrocytotoxic autoantibodies and lymphocytes because of auto-antigen presence → in response to renal tissue injury → reactions of auto-aggression, allergy, inflammation → infiltration of kidneys by leukocytes, macrophages in capillaries and renal mesagium → IgG, complement components C_3, C_{1Q}, C_4.
6. Periodic activation of the immune aggressive process under non-specific injuring factors (overcooling, intoxication, infection, drugs, radiation).
7. Immune complexes fix on the GBM and capillaries → renal injury → diffuse glomerulonephritis.

Chronic glomerulonephritis

It is a chronic renal disease. It has immune pathologic genesis (immune complex). It is characterized by the primary injury of glomeruli and involvement of the other renal structures. It is characterized by the glomerular destruction, hypertension and renal failure.

Etiology. It is an outcome of the acute glomerulonephritis in 10–20 % of cases, and it is primary chronic in 80–90 % of cases.

Pathogenesis. Pathogenesis is variable. It is a chronic autoimmune injury of GBM.

Acute renal failure

Acute renal failure is a clinical syndrome resulting in the abruptly decrease in glomerular filtration and kidney failure.

The causes of acute renal failure can be divided into three main categories:

— prerenal (functional);

— intrarenal (structural);

— postrenal (obstruction).

Etiology of pre-renal acute renal failure:

— hypotension;

— a decrease in intravascular volume depletion;

— ionic-water imbalance: cardiac failure, cirrhosis.

Etiology of acute intra-renal failure:

— post-ischemic tubular necrosis;

— toxic ischemic tubular necrosis (heavy metals, ethylene glycol, insecticides, poison mushrooms, carbon tetrachloride).

Etiology of post-renal acute renal failure

— Intra-renal factors: salt dropout in real tubules.

— Extra-renal factors: large stones or blood clots in ureters, bladder obstruction, urethra obstruction.

Pathogenesis

Tubular necrosis. The leading mechanisms: intubular obstruction by necrotic cells, backward glomerular filtrate flow through the tubular epithelium ruptures.

Stages:

1) initial, shock stage: prevalence of the main disease signs, oliguria, a decrease in arterial blood pressure, tachycardia, pallor. Absence of azotemia;

2) oliguria, anuria: oliguria, anuria, low density urine, proteinuria, hematuria, metabolic acidosis, hyperhydration, hyperpotassemia, hypocalcemia, anemia, hypertension, azotemia, clinical signs of uremia;

3) polyuria: polyuria, low density urine, dehydration, hypocalcemia, decrease in azotemia level;

4) regeneration.

Chronic renal failure

It is a clinical syndrome resulting from irreversible progressive nephron destruction and a decrease in number of functioning nephrons.

Etiology of chronic renal failure

— Metabolic disorders: diabetes mellitus.

— Renal vascular disorders: nephrosclerosis, hypertension.

— Immunologic disorders: glomerulonephritis.

— Congenital disorders: polycystic disease.

— Acute renal failure.

— Infections: pyelonephritis.

— Unknown cause.

Pathogenesis

1. Hypertrophy of safe nephrons with the consequent their hyper-functional insufficiency.

2. Impairments of homeostasis.

Stages

Stage 1 — latent:

1) Phase 1A — normal creatinine level in blood plasma and normal volume of glomerular filtration; a decrease in functional kidney reserve.

2) Phase 2B — createnine level is on the higher norm level. Glomerular filtration is reduced to 50 % of normal, a decrease in concentrative renal ability.

Stage 2 — hyperazotemia:

- concentration in blood serum: createnine — 0,13 mmol/l and higher, urea — 11 mmol/l and higher;
- glomerular filtration:

— phase IIA: GF is reduced to 40–20 % of normal;

— phase IIB: GF is reduced to 19–10 % of normal.

Stage 3 — uremic:

— GF is reduced to 5–10 % of normal;

— high hyperazotemia;

— clinical signs of uremia.

Uremia

Uremia is an increase in urea ad other nitrogens (azotemia). The non-protein nitrogens include urea, uric acid, createnine and other compounds.

It is a clinical syndrome of progressing renal failure characterized by various metabolic and functional impairments.

Uremia is observed on the 2nd and 3rd stage of chronic renal failure.

Clinical manifestations of chronic renal failure and uremia

1. Fatigue, sleeplessness, a decrease in appetite, nausea, vomiting, itches.
2. Impairments of central and peripheral NS functions.
3. Convulsions, consciousness inhibition.
4. Peripheral sensor neuropathy.
5. Gastrointestinal tract pathology: uremic gastritis, colitis (excretion of nitrogens through mucous membranes), an increased risk of gastrointestinal bleedings.
6. Hypertension, uremic myocarditis and pericarditis, arrhythmia, an increased risk of myocardial infarction.
7. Anemia caused by a decreased erythropoietin secretion.
8. Uremic pneumonia, plevritis, Kussmaul's respiration.
9. Osteomalacia caused by the vitamin D and phosphate retention by the kidney.
10. Glucose intolerance, resistance to insulin, hyperlipiemia, an increase in testosterone and estrogen blood level.
11. An increase in nitrogen blood level, urea, creatinine.

Uremic toxins

— urea and its metabolic products, aminoethanamidine, dimethylamine;

— parathyroid hormone. High level if parathyroid hormone is observed in

chronic renal failure → accumulation of calcium in cells → dissociation of oxidation and phosphorylation, ATP deficiency, impairments of energy supply;

— inadequate microelement concentration in blood, intercticium and cells (Mg^{2+}, Zn^{2+}, Cu^{2+}, Cr^{2+}).

Nephrolitiasis

The main pathogenic chain is a uric acid stone formations in the urinary system.

— It is observed in 1–3 % of population

— It occurs after the inflammatory diseases in 30–40 % of cases

— It is observed in 20–50-year-old man

Its occurrence is promoted by:

— the present-day conditions (physical inactivity results in calcium phosphate metabolism impairments), nutrition character (presence of proteins in food);

— the predisposing factors (age, sex, race, profession, climate, geographic conditions, housing conditions, genetic factors);

— factors of local character (infections of urinary system, pH of urine, urine relative density, anatomic and pathologic changes in the upper urinary tract resulting in the obstruct urine outflow, metabolic and vascular impairments in organism and kidney).

Mineralogical classification of stones: calcium stones, uric acid stones, protein stones (cystinuria), struvite stones.

PATHOLOGICAL PHYSIOLOGY OF THE ENDOCRINE SYSTEM

Endocrine system is a set of anatomically and histologically differentiated structures producing hormones.

Hormones are synthesized in:

1) endocrine glands (hypophysis, epiphysis, thyroid gland, parathyroid glands, sex glands);

2) set of cells or single cells (neurosecreting cells of hypothalamus, pancreas islet cells, Gastrointestinal tract, interstitial cells of kidneys, endocrine cells of lungs, epithelial cells of thymus).

Now the principle of feedback forms a basis of endocrine system self-management (K. Hoskinnz has united ideas of feedback and pituitary-thyroid axes in the «thyrostate» concept. Some loops of eedback are allocated:

1) «a long loop of feedback» (an increase in a hormone level produced by peripheral gland — a decrease in tropic hormone level produced by anterior pituitary or releasing factors produced by hypothalamus);

2) «a short loop of feedback» (an increase in tropic hormone level — a decrease in releasing factor level);

3) «an ultra-short loop» (an increase of tropic hormone or releasing factor level decreases its own production).

Hormones are organic alarm molecules with unconducting actions, which are recognized by receptors, influence on gene expression, enzyme activity in target cells on the distance from a place of production.

Hormone is an endogenous regulator, which operates through interaction with the specific receptors and changes the physiological functions and morphological structures (according to I. A. Pankov). Hormones operate only those cells (target cells), which have the specific receptors to a hormone. Variants of control: endocrine, paracrine, autocrine.

The main principle of endocrine pathology: principle of feedback and principle of permissive effect.

The mechanism of endocrine pathology

Impairments of endocrine gland function results from:

1) direct damage of gland tissue;
2) impairments of endocrine gland influence on each other;
3) hereditary causes;
4) control impairments.

Principles of classification

— According to origin: primary, secondary, thirdly.
— According to a level of hormone production: hypofunctional, hyperfunctional.
— According to the volume of injury: partial, subtotal, total.

Hypofunctional conditions

Glandular:

1) genetic defect of hormone synthesis (hereditary forms of hypothyroiditis, Diabetes mellitus type II;
2) deficiency of hormone components (hypothyroiditis in iodium deficiency);
3) intoxications (influence of food factors and application of medical substances, e. g. 1 kg of turnip by anti-thyroid action comes nearer to S tablet of mercazole);
4) destruction or information block of hormone producing cells (it results in impairment of hormone transport into the blood):

— non-hormone producing tumors (chromophobic adenomas of pituitary — hypopituitarism);
— gland metastases, infiltration by leukemia blasts;
— infection, inflammation (tuberculosis of adrenal glands, Addison's disease);
— autoimmune processes (autoimmune hypoparathyroiditis);
— trauma;
— acute impairments of blood circulation (Waterhouse-Friderichsen syndrome — acute adrenal failure in bilateral thromboembolic apoplexy of adrenal gland cortex).

Extraglandular

1) the suppression of a prohormone transition into a hormone (hormone synthesis is not impaired, but there is a decrease in hormone activity);

2) presence of circulating hormone antagonists (antibodies to hormone, other hormones, drugs, metabolits).

Hyperfunctional conditions

Glandular:

1) non-controllable hyperproduction of hormones (tumor);

2) metabolic block resulting in excess of intermediate product (but not only in lack of hormones);

3) hyperplasia and hyperfunction of endocrine gland;

4) presence of stimulator antibodies.

Extraglandular:

1) ectopic excessive production of hormones;

2) jiatrogenic excess of hormones;

3) presence of antibodies to hormone receptor (immidiators);

4) tissue hypersensitivity to hormones;

5) a decrease in hormone binding in blood and an increase in hormone degradation.

Characteristics of hormones

According to chemical structure: amines, steroids, peptides, eicosanoids (prostaglandins and prostacyclines).

Typical forms of posterior pituitary pathology

Diabetes insipidus. It results from a lack of ADH (antidiuretic hormone). It is characterized by an inability to concentrate urine, despite of the normal osmotic gradient in kidneys.

Etiology

1) central diabetes insipidus (a decrease in ADH secretion);

2) nephrogenic diabetes insipidus (hyposensitivity of ADH receptors in kidneys) or an increased ADH inactivation in tissues).

Clinical manifestations:

1) polyuria (3–15 l per day), sometimes 20–30 l, nicturia;

2) polydipsia (3–15, 30 l per day), it results from the thirst center neuron activation in hypothalamus owing to plasma hyperosmium and cellular hypohydration;

3) low relative density of urine (less than 1005): ADH insufficiency results in a decrease of reabsorption of liquids in a distal renal tubules. That why a plenty of non-concentrated urine is excreted;

4) plasma hyperosmolarity results from an increased tubular filtration, hemoconcentration, polyuria;

5) hypersodiumemia due to activation of aldosterone production.

Syndrome of inadequate antidikretic hormone secretion

It results from a release of non-osmotic stimulated ADH:

1) posterior pituitary (trauma, tumor);

2) ectopic (in lymphogranulomatosis — LGM, lung carcinoma).

Clinical manifestations:

— oligouria results from an increased liquid reabsorption in distal renal tubules;

— an increase in body weight (without edema due to a decrease in sodium level in intersticium);

— hyposodiumemia — the main sign of the syndrome;

— psychoneurologic impairments: apathy, inertia, sometimes convulsions. It is also called water intoxication.

Typical forms of anterior pituitary impairments

Hypopituitarism is a lack of content or effect of one or several anterior pituitary hormones.

Total. 1. Total hypopituitarism — Simmond's disease.

Total hypopituitarism — panhypopituitarism (panhypopituitarism). Causes — trauma, infection, hypo-and atrophy of the anterior pituitary. Clinically: a rapid loss of weight 3–6 kg per month (in some cases up to 20–25 kg), premature aging, disorders of the exchange-trophic.

Panhypopituitarism — Sheehan's syndrome — it is based on the substantial and not timely reimbursed blood loss during childbirth → vasospasm PDG.

Partial. Pituitary dwarfism.

Pituitary hypogonadism

a) In male — evnuhoidizm — tall, narrow shoulders and a relatively wide pelvis, undeveloped skeleton, immature gonads and secondary sex characteristics, behavioral traits are not peculiar to males.

b) In females — pitiutary infantilism — the subtile body constitution without female characters: undeveloped mammary glands, menstrual irregularities, inability to conceive, the various disorders of pregnancy.

Neuroendocrine obesity

Inadequate synthesis of fat mobilizing lipotropin by anterior pituitary in defeat of the pituitary or hypothalamus. Fat deposition in the abdomen, back, proximal parts of extremities, the relative «thinness» of distal parts of extremeties — the forearms and shins.

Adiposogenital dystrophy (Frohlich's syndrome). It is observed in ongenital abnormalities of hypothalamus and pituitary gland. Hypothalamus and pituitary gland are impaired by various infections and non-infectious factors in embryonal and post-embryonal period. It is manifested by two main syndromes: obesity and hypogonadism.

Hyperpituitarism. It is an excess of content or effects of a pituitary hormone (hormones).

1) Giantism, acromealy (an increase in STH production).

2) Early maturation, etc., impairments in sex shere.

3) Syndrome of long-lasting lactation (galactorrhea + amenorrhea).

4) Melanotropin hypersecretion (intermediate pituitary — partial pituitary pathology).

The main effects of growth hormone

Somatotropic hormone «growth hormone». It is found out by A. Long in 1921. It was received in pure state in 35 years. STH secretion is stimulated by growth hormone-releasing factor, also thyroid hormone releasing factor, beta-endorphine, dopamine, serotonin. STH secretion is inhibited by growth hormone, adrenaline, non-esterificated fat acids.

Metabolic action of STH consists of its own effects and effects mediated by somatomedin.

Somatomedin (IGF). IGF is a tissue autocrine and paracrine STH mediator. The most known effects are caused by somatomedin C (IGF-I) and somatomedin A (IGF-II). Somatomedins act by the way of a decrease in adenilatecyclase activity in cells.

IGF-I is a mediator of the main growth and metabolic effects. It is synthesized by hepatic macrophages, placenta, kidneys, bones, muscles and pituitary. It inhibits growth hormone-releasing factors and feedback loops in the system of central hormone control. IGF-1 level is increased in obesity and it results in a decrease of STH production.

IGF-II. It acts as a growth factor on fetus tissues. STH is not found out in intrauterine period of development. The growth effect of IGF-II decreases during the 1st year of life, but it is important for the dental germ forming.

Biologic effects of the somatotropic hormone somatomedin system

It influences the metabolism of other hormones.

Slow *«growth»* effects. They are mediated by somatomedins. According to A. Guyton the STH-somatomedin system stimulates the growth of «all what can grow».

1. Chondrogenesis.
2. Osteogenesis.
3. Hyperplasy and hypertrophy of soft tissues.
4. Lymphoproliferative action.
5. Immune modulating action.
6. Erythropoiesis stimulation.
7. Anabolic action (an increase in protein synthesis from aminoacids).

Fast *«growth»* effects.

Somatotropic hormone is a diabetogenic hormone because of the contra insulin action:

1) it decreases the glucose utilization by cell;

2) it decreases lipid synthesis in adipocytes;

3) it increases lipogenesis.

Giantism

It results from STH hyperproduction or a decrease in somatomedin production.

Etiology

1. Somatotropinoma — eosinophilic pituitary adenoma, sometimes it can results from ectopic somatotropins: in GIT, bronchi, pancreas, parapharyngeal area — 96 %.

2. Hyperproduction of growth hormone-releasing factor.

3. Non-tumor hyperplasy of somatotropins.

Other causes: tissue hypersensitivity to STH, excess of somatomedin C.

Congenital and early STH excess results in an increased growth of bones length wise. Giantic growth: female more than 190 sm, male more than 200 cm. Supergiantic growth more than 2,5 m (245,7 cm, Mozambique), at last — Fedor Machov (285 cm, 182 kg, 25 years old, Vitebsk).

Genetic model of pituitary giantism in dog-breeding — irish wolf-hound and bulldog.

1. An increase in skeleton and muscle growth does not result in physical force increase in giants, because of the weight of skeleton is big. So, it results in muscle weakness, a decrease in energic metabolism due to STH inhibition of hexokinase, insulin production deficiency (Diabetes mellitus — 25 %).

2. An increase in size of internal organs — splanchomegaly. Organomegaly (visceromegaly) increases the intra-abdominal pressure, that results in hernia formation.

3. A decrease in immune system function.

4. Hypogenitalism (hypogonadism) – insufficiency of gonadotropins.

It can be hemigiantism (one part of the body grows very intensive).

Acromegaly

Firstly, this disease was described by P. Marie in 1886. Acromegaly (across — extreme, megas — big). It is a neuroendorine disease and it is characterized by pathologically increased growth activity (it results from STH hypersecretion, which occurs after metepuiphyseal cartilaginous ossification (in male — 21–23 years, in female — 23–25 years). Such acromegaly manifests in 40–45 years (such type of pathology is not associated with giantism).

If somatotropinoma producing STH after pubertal period or pregnancy. These patients suppose to refuse abortion. Pregnancy is a very rare case in women with acromegaly.

Etiology of acromegaly and giantism is the same.

All patients with acromegaly look like each other:

1) Acromegaly is characterized by an increase in size of feet, hands (because of the periosteal growth), hyperplasy of nose, ears, tongue (glossomegalia), an

increase in size of larynx (the voice becomes deep), diastema occurs (diastema is a presence of interdental space due to IGF-1, the relative size of tooth is decreased).

2) An increase in musculature tissue occurs due to connective tissue overgrowth (but not because of the muscular tissue hypertrophy).

3) An increase in size of lower parts of extremities (hands, feet).

4) Hardened features, bone prominences are contured, an increase in size of nose, lips, mouth is opened, periorbital hypertrophy of soft tissues. Also kyphoscoliosis, skin is pigmented, wet, worm, hypertrichosis is observed.

5) Visceromegaly is observed, but organ growth is not correlate with the growth rate. It may result in heart failure, pulmonary and hepatic failure).

6) A decrease in libido, potency, dysmenorrheal.

7) An increase in T_3 conversion into T_4 – signs of thyroid hyperfunction (in 3–7 % of patients — hyperthyroidism, IGF-1 causes thyroid gland hypertrophy).

8) Neurologic symptomatology (headache, hydrocephaly, rhinorrhea).

Stages of clinical picture: preacromegalic, hypertrophic, tumoral, cahexia.

Also partial forms of acromegaly are described (increased growth of single organs — heart, head).

Diseases of growth hormone deficiency

— Dwarfism.

— A reduction of growth potential may occur in children.

— Alteration in metabolic functioning, including insulin resistance and abnormal lipid profile, may occur in children and adults.

Clinical manifestations

— In children, GH deficiency results in proportional short stature (below the 3rd percentile for their age). Affected children have decreased muscle mass and increased subcutaneous fat stores. They are typically bright mentally.

— Short stature different from predicted based on familial patterns may be observed if a reduction in growth potential occurs.

— Delayed onset of puberty may accompany GH deficiency, especially if abnormalities in the gonadotropins occur concomitantly.

— Adult-onset GH deficiency may result in nonspecific changes in functioning, including alterations in physical and mental well-being, cardiac function and metabolic parameters.

— Adults with GH deficiency may experience lower levels of energy and libido.

Glucocorticoids

Glucocorticoids are steroid hormones released from the cortex (outer layer) of the adrenal gland that affect many aspects of metabolism, especially glucose metabolism. In humans, the main glucocorticoid is cortisol. The glucocorticoids also affect many other systems of the body, including the cardiovascular and immune systems. Glucocorticoids are released in a diurnal (daily) manner, peaking in the early morning hours.

Pathological physiology of hypercorticism

1. Primary hypercorticism — primary hyperplasy and hyperfunction of adrenal gland cortex.

2. Secondary hypercorticism — excess production of adrenal cortex hormone stimulators by hypothalamus–pituitary-adrenal gland system.

3. Jiatrogenic hypercorticism.

They are differ by ACTH blood level.

Diseases of excess glucocorticoids

— Cushing's syndrome refers to any condition of high glucocorticoids and includes glucocorticoid excess caused by therapeutic administration of corticosteroids.

— Cushing's disease refers to high glucocorticoids caused specifically by malfunction of the anterior pituitary resulting in excess ACTH.

Clinical manifestations

Altered fat metabolism leads to fat pads on the back (subclavian buffalo hump), moon face, protruding abdomen with thin extremities, and stretch marks on breasts, thighs, and abdominal surface. Muscle weakness from protein breakdown.

— Hypertension as a result of increased catecholamine responsiveness.

— Weight gain resulting from strong appetite stimulation. Because of effects on hepatic gluconeogenesis, a reversible form of diabetes mellitus may result.

— Inhibition of immune and inflammatory reactions, leading to poor wound healing.

— Extreme emotional swings (lability), sometimes causing psychosis and occasionally resulting in suicide.

— Masculinization of women and children as a result of adrenal androgen stimulation if ACTH levels are high.

— Bronzing of the skin if ACTH levels are high.

Syndrome of ectopic adrenocorticotropic hormone hyperproduction

It is mostly observed in men (opudoma). The specific features of this pathology are: hyperpigmentation of the skin (due to ACTH hypersecretion), hyperaldosteronism, hyperandrogenism, obesity is mostly absent.

Jiatrogenic hypercorticism

It is observed in prolonged glucocorticosteroid treatment (in autoimmune and immune pathologic diseases. It may not occur in shirt-term treatment of extreme conditions.

Abstinence syndrome in acute glucocorticoid abolution

It occurs in acute glucocorticoid abolution in patients with prolonged glucocorticosteroid treatment. It is characterized by the severe impairments: a decrease in blood pressure level, severe muscular adynamics, hypoglucemic crisis, diarrhea, hypohydration, coma → death.

Mechanism. Endogenous glucocorticoid production is inhibited in prolonged administration of exogenous glucocorticoids (big doses) to the patients according to the feedback mechanism. It may results in the cessation of glucocorticoids. Adrenal failure may occur in case of acute abolition of intake of exogenous glucocorticoids → death.

Waterhouse-friderichsen syndrome

It is an acute adrenal cortex and medulla failure.

Etiology

1. DIC-syndrome (the cause of thrombosis, infarction is an activation of endothelium thrombogenic properties by circulating cytokines).
2. Generalized infections with bacteremia and viremia (in meningococcal sepsis, streptococcal and meningococcal infections).
3. Abstinence syndrome.
4. Decompensation of metabolic processes in patients with chronic adrenal failure.
5. Non-infectious factors: trauma, stress, surgical operations, trauma in childbirth.

Macrosomia (an increase in the body weight and growth of newborn), hirsutism.

Clinical manifestations: hypotension, hypoglucemia, thrombo-hemorrhagic syndrome and symptoms of the main disease.

The disease is associated with HLA $A_{1,}$ $B_{8,}$ $DR_{3,}$ DR_4 (the increased risk in heterozygots DR_3 / DR_4).

In present days, autoimmune adrenaline is the main cause of chronic adrenal failure. Also this disease is called «idiopathic Addison's disease». The target for antibodies is a key enzyme ***steroidigenase*** — 21-hydrolase, which promotes cortisol synthesis and also reaction of progesterone transfer into the 11-deoxycorticosteron in glomerular zone (aldosterone synthesis). First of all, glomerular zone of adrenal glands is involved in process. It results in a decrease in aldosterone level, and an increase in plasma rennin activity. Then, fascicular zone is destructed: it results in a cessation of cortisol secretion, and an increase in ACTH secretion.

Clinical manifestations: fatigue, skin and mucosa hyperpigmentation, arterial hypotension, polyuria, hypoglucemia, malabsorption.

Morphologically it is characterized by a decrease in adrenal gland size, atrophy of cortex, intact medulla. Cortex is fully infiltrated by lymphocytes.

Hyperaldosteronism

Primary hyperaldosteronism (Conn syndrome)

1) adrenal adenoma;
2) adrenal cortex adenoma.

Pathogenesis. Arterial hypertension is the main sign of primary aldosteronism. The hypersecretion of mineralocorticoids enhances sodium reabsorption by the renal tubules, thereby increasing body sodium. Hypertension is caused not only by the retention of sodium and consequent volume expansion,

but also by increased peripheral vascular resistance. Hypokalemia reflects aldosterone induced loss of potassium in the distal renal tubule. All the listed above may result in hypertrophy and heart dilation.

Renal tubules are not sensitive to aldosterone action in long-term hypertension. This results in an increase in sodium and water excretion. So, these patients may not have edema. A high decrease in potassium and proton results in fatigue, polyuria especially at night time, hypokalemic nephropathy. Also, redistributive alkolisis occurs due to an increase in proton level in cell → a decrease in Calcium plasma level results in tetania.

A decrease in glucose tolerance due to a potassium inflow associated with glucose utilization by cells.

Low rennin activity is observed in primary aldosteronism.

Secondary aldosteronism. It occurs due to kidney pathology, liver cirrhosis, in various hypovolemias.

Opposite to primary, it is characterized by a high rennin level, edema (sometimes systemic).

Hypoaldosteronism

1. Defect of mineralocorticoid receptors — pseudoaldosteronism.
2. Insufficiency of rennin-angiotensin system.
3. Renal canaliculous acidosis.
4. Iatrogenic overdosage of the abolition of mineralocorticoids.

Adrenogenital syndrome

It is caused by adrenal gland dysfunction (excessive secretion of androgens) and manifested by the signs of virilization.

I. ***Congenital:***

1) It is characterized by the deficiency of enzymes, which are necessary for corticosteroid synthesis: 21-hydroxylase, beta-hydroxylase.

2) In pregnant women: complications in pregnancy, drugs.

II ***Aquired.*** Malignant or benign hormone-active tumor of adrenal cortex (reticular zone).

Clinical forms of adrenogenital syndrome

— Simple verilizing form.

— Solt loser form (verilizm + hypotensive syndrome).

— Hypertonic (verilism + hypertensive syndrome).

Synthesis of mineralo- and glucocorticoids is impaired, adrenal androgen synthesis is increased, ACTH level increases.

Excess of ACTH additionally stimulates reticular zone, it increases androgen production and causes hyperplasia (reticular and fascicular zone). Sometimes organ looks like cerebral cortex.

It manifested by masculinization of female infant. It is apparent at birth and may include ambiguous genitalia with an enlarged clitoris, fused labia, and malformation of the urogenital area. The degree of abnormality is variable.

Male fetuses are usually normal at birth or have slightly enlarged genitalia.

Clinically it is manifested by hyperandrogenism, mineralocorticoid level increase, hypoaldosteronism.

Pathological physiology of thymus

Thymus is a central lymphoid organ of immune system. Embryologically, the thymus derives from the 3rd pair of pharyngeal pouches, with an inconstant contribution from the 4th pair. The organ is irregularly pyramidal, with its base located inferiorly and its two lobes fused in the middle. It is covered with fibrous capsule. It weights in birth about 15 g. It continues to grow until puberty, and then may weight 50 g. I. Gammar described thymus involution. The most intensive thymus atrophy is observed in 25–40 years. It is programmed genetically. Ageing immunodeficiency occurs due to thymus involution (atrophy).

Thymic hormones

1. Thymopoietin — blockage of neuromuscular transmission, a decrease in autoimmune process intensity, early stages of T-lymphocyte differentiation.
2. Thymulin — stimulates end point stages of T-lymphocyte production.
3. Thymosin alpha 1, alpha 5, alpha 7 — it influences the late stages of lymphocyte differentiation.
4. Thymic hormone factor — T-lymphocyte activator.
5. Thymic factor X — stimulator of lymphocytosis, it increases Delayed type Hypersensetivity.
6. Thymosterin — it promotes growth, lymphocyte content, hyperglucemic effect.
7. Homeostatic thymic hormone — synergist of STH, antagonist of GTH, ACTH, TTH.

Thymus pathology

I. *Thymic hyperplasia*

1. Congenital (secondary immune deficiency):

— hypercorticism;
— irradiation;
— cytostatics;
— starvation.

II. Hyperplastic processes

— tumors;
— hyperplasia of parenchyma and lymphoid follicules.

Thymic follicular hyperplasia may also be found in other diseases in which autoimmunity played role: Graves disease, Addison's disease, systemic lupus erythematous, scleroderma and rheumatoid arthritis.

Parathyroid gland function pathology

Causes of primary hypoparathyroiditis:

— congenital gland absence;

— surgical removal of damaged gland;
— injury by physical, chemical, biological factors;
— mmune aytoaggression;
— impairment of blood circulation / innervation.

Hereditary hypoparathyroiditis is a very rare disease. It is associated with malformations. It is presented in DiGeorge syndrome. It is caused by 22 chromosome pair deletion.

Hypoparathyroidism is also associated with family poly glandular syndrome (autoimmune pathology of parathyroid, thyroid gland, sex glands).

Effects of parathhormone

1. It increases Ca (Mg) reabsorption in GIT.
2. A decrease in Ca^{2+} and Mg^{2+} clearance in kidneys (due to increased effectivity of Ca^{2+} and Mg^{2+} reabsorption in distal nephron tubules).
3. It increases phosphate excretion with urine.
4. It stimulates cardiac contractions.
5. It activates osteoclasts, osteolysis and Ca^{2+} release from bones. Osteolysis prevails in high hormone level, osteogenesis in low hormone level.
6. It promotes contrainsulin action.
7. It stimulates secondary hydroxylation of vitD in kidneys, it transfers parathhormone in active hormone (calcitriole).

Physiologic antagonist of parathhormone is calcitonin. It is found out in 1962 by D. Kopp.

Acquired hypoparathyroiditis:

— iatrogenic;
— autoimmune;
— amyloidosis, hemohromatosis, hemosiderosis of parathyroid glands, chronic alcoholism (because of severe decrease in serum Mg level). In case of high Mg deficiency there is an impairment of cAMP-dependent processes of parathyroid hormone secretion. Clinical manifestations remind blue devils.

Mg influences parathyroid hormone similar to Ca. If Mg deficiency is not high, parathyroid hormone will be synthesized. But if Mg deficiency is high, cAMP-dependent process and parathyrocrine signal transmission in target-cells will be impaired.

Clinical manifestations:

— cataract;
— increase in neuron-muscular excitability;
— neuron-psychic frustration, tetanus, convulsions;
— hypocalcemia, hyperphosphatemia;
— respiration impairments;
— urination impairments;
— bile-intestinal impairments.

Hyperparathyroiditis

Primary hypeparathyroiditis. It is characterized by parathyroid gland hyperfunction and formation of gegantocellular overgrowth (osteoblastoclustoma localizing in Houship's lacuna). So regeneration of bone goes behind osteolysis and fibrous tissue formation.

Cysts with mucoid and brown fluid are formed in bones (on X-ray they look like bubbles).

Insufficient mineralization of bone results in bone deformation and pathologic fractures.

Clinical Manifestations:

— muscular hypotonicity;
— hypertension;
— ulcers of stomach and duodenum;
— hypercalcemia, increase in alkaline phosphate activity;
— hypercalciuria;
— metastatic nephrocalcinosis and other;
— parathyroid gland adeoma, carcinoma,hyperplasia;
— pain in muscles, bones, stomach;
— it also can results in acute renal failure, heart failure, pulmonary edema.

Hypercalcemic crisis is possible. It results in uremic hypocalcemic coma and high mortality rate.

Crisis in case of icreased hypercalcemia, hypecaciuria and renal resistance to ADH results in severe dehydration (polyuria, vomiting, the decrease in temperature).

Secondary hyperparathyroidism

It results from the increased function and parathyroid cell proliferation because of:

— vitamin D deficiency;
— chronic renal failure;
— lack of Ca;
— agravity parathyroid gland dysfunction.

Thirdly hyperparathyroiditis. It is associated with parathyroid gland adenoma secreting parathyroid hormone.

In thirdly hyperparathyroiditis parathyroid hormone production doesn't depend on Ca and P level. It is autonomic.

In secondary hyperparasthyroiditis parathyroid hormone production depends on Ca and P level.

Thyroid gland pathology

Thyroid hormone

Thyroid hormone is an amine hormone synthesized and released from the thyroid gland. It is made when one or two iodine molecules are joined to a large glycoprotein called thyroglobulin, which is synthesized in the thyroid gland and

contains the amino acid tyrosine. These iodine-containing complexes are called iodotyrosines. Two iodotyrosines then combine to form two types of circulating TH, called T_3 and T_4. T_3 and T_4 differ in the total number of iodine molecules they contain (three for T_3 and four for T_4). Most (90 %) of the TH released into the bloodstream is T_4, but T_3 is physiologically more potent. In passage through the liver and kidney, most T_4 is converted to T_3. T_3 and T_4 are carried to their target cells in the blood bound to a plasma protein, but enter the cell as free hormone. T_3 and T_4 collectively are referred to as TH.

Effects of thyroid hormone

Target cells for TH include almost all cells of the body. The primary effect of TH is to stimulate the metabolic rate of all target cells by increasing the metabolism of protein, fat, and carbohydrate. TH also appears to stimulate the rate of the sodium-potassium pump in its target cells. Both functions serve to increase utilization of energy by the cells, thereby increasing BMR, burning calories, and increasing heat production by each cell.

Thyroid hormone also increases the sensitivity of target cells to catecholamines, thus increasing heart rate and causing heightened emotional responsiveness. TH increases the rate of depolarization of skeletal muscle, which increases the speed of skeletal muscle contractions, often leading to a fine tremor. TH is essential for normal growth and development of all cells of the body and is required for the function of growth hormone.

Factors controlling thyroid hormone secretion

The stimulus for the secretion of TH is thyroid-stimulating hormone (TSH), released into the bloodstream from the anterior pituitary. The stimulus for the release of TSH is thyroid-releasing hormone (TRH), secreted from the hypothalamus into the portal bloodstream. Thyroid hormone appears to act in a negative feedback manner on the hypothalamus, to decrease the further release of TRH, and on the pituitary, to decrease the release of TSH. TSH may also act on the hypothalamus to decrease further release of TRH.

Factors Controlling Thyroid-Releasing Hormone Secretion

The stimuli responsible for increasing TRH secretion include exposure of the body to cold temperature, physical and perhaps psychological stress, and low levels of TH. When the secretion of TRH is stimulated by cold temperature, the result is an increase in TH, which increases BMR, thereby increasing body heat and reducing the demand for a further increase in TRH (Fig. 9–3). This is an example of negative feedback.

Hyperthyroiditis

***Causes of hyperthyroiditis*:**

— Goiter producing thyroid gland hormones.

— Thyroiditis.

— Toxic adenoma of thyroid gland.
— Ectopic tumors from thyroid tissue producing thyroid hormones.
— Administration of iodium.

Hyperthyroidism

Hyperthyroidism is excessive levels of circulating TH. This disorder can result from dysfunction of the thyroid gland, pituitary, or hypothalamus. Increased TH caused by malfunction of the thyroid gland is accompanied by decreased TSH and TRF, as a result of the negative feedback on their release by TH. Hyperthyroidism caused by malfunction of the pituitary results in high TH and high TSH. TRF is low because of negative feedback from TH and TSH. Hyperthyroidism caused by malfunction of the hypothalamus shows high TH accompanied by excess TSH and TRH.

Diseases of hyperthyroidism

Graves' disease, the most common cause of hyperthyroidism, is an autoimmune disorder usually characterized by production of autoantibodies that mimic the action of TSH on the thyroid gland. These IgG autoantibodies, termed thyroid-stimulating immunoglobulins, turn on the production of TH, but are not inhibited by rising levels. TSH and TRH levels are low because they are inhibited by high TH. The cause of Graves' disease is unknown; however, there appears to be a genetic predisposition to autoimmune disease. Women in their 20s and 30s are most often diagnosed, although the disease may start during 10 years.

Nodular goiter is an increase in the size of the thyroid gland caused by increased demand for thyroid hormone. Increased demand for thyroid hormone occurs during periods of growth or excess metabolic demand such as puberty or pregnancy. In these cases, increased TH is caused by metabolically driven activation of the hypothalamus, and therefore is accompanied by increased TRH and TSH. When the demand for thyroid hormone is lessened, the thyroid gland usually returns to its previous size. Occasionally, irreversible changes may have occurred and the gland does not regress. The enlarged thyroid may continue to produce excess TH. If the individual remains hyperthyroid, the condition is referred to as a toxic nodular goiter. Pituitary adenomas of TSH-producing cells or hypothalamic diseases rarely occur.

Clinical manifestations

- Increased heart rate.
- Increased muscle tone, tremors, irritability, increased sensitivity to catecholamines.
- Increased basal metabolic rate and heat production, intolerance to heat, excess sweating.
- Weight loss, increased hunger.
- A staring appearance.

- Exophthalmos (bulging of the eyes) may develop.
- Increased number of bowel movements.
- Goiter (usually), which is an increase in the size of the thyroid gland.
- Changes in skin and hair condition may occur.
- Reproductive irregularities.

Diagnostic tools

- A good history and physical examination will help diagnose hyperthyroidism.
- Blood tests measuring levels of TH (both T_3 and T_4), TSH, and TRH will allow diagnosis of the condition and localization of the problem at the level of the CNS or the thyroid gland.
- Decreased serum lipids may accompany hyperthyroidism.
- Decreased sensitivity to insulin, which may result in hyperglycemia.

Complications

— Arrhythmias are common in patients with hyperthyroidism and may be the presenting symptom of the disorder. Any person complaining of arrhythmia should be evaluated for thyroid disorder.

— A life-threatening complication of hyperthyroidism is thyrotoxic crisis (thyroid storm), which may develop spontaneously in patients with hyperthyroidism undergoing therapy or during surgery on the thyroid gland, or may occur in undiagnosed patients with hyperthyroidism. The result is a large burst of TH release that causes tachycardia, agitation, tremors, hyperthermia and, if untreated, death.

Hypothyroidism

Hypothyroidism results from decreased levels of circulating thyroid hormone. Hypothyroidism is characterized by myxedema, the non-pitting, boggy edema that develops around the eyes, feet, and hands and infiltrates other tissues as well. Hypothyroidism may result from malfunction of the thyroid gland, the pituitary, or the hypothalamus. If it results from thyroid gland malfunction, low TH levels are accompanied by high TSH and high TRH because of the lack of negative feedback on the pituitary and hypothalamus by TH. If hypothyroidism results from pituitary malfunction, low levels of TH are caused by low TSH. TRH from the hypothalamus is high because there is no negative feedback on its release by TSH or TH. Hypothyroidism caused by hypothalamic malfunction results in low TH, low TSH, and low TRH. Medically-induced hypothyroidism may follow previous thyroid therapy or surgery, radioiodine therapy, or drugs such as cytokines, amiodarone, and lithium.

Diseases of hypothyroidism

— Hashimoto's disease, also called autoimmune thyroiditis, results from autoantibody destruction of thyroid gland tissue. This results in decreased TH, with increased TSH and TRH levels caused by minimal negative feedback. The

cause of autoimmune thyroiditis is unknown, but there appears to be a genetic tendency to develop the disease.

— Endemic goiter is hypothyroidism caused by a dietary deficiency of iodide. A goiter is an enlargement of the thyroid gland. Goiter occurs with a deficiency of iodide because the thyroid cells become overactive and hypertrophic (larger) in an attempt to sequester all possible iodide from the bloodstream. Low TH levels are accompanied by high TSH and TRH because negative feedback is minimal.

— Thyroid carcinoma may cause hypothyroidism or hyperthyroidism. Treatment of this rare cancer may include thyroidectomy, TSH suppression drugs, or radioactive iodine therapy to destroy thyroid tissue. All of these treatments may result in hypothyroidism. Exposure to radiation, especially during childhood, is a cause of thyroid cancer. Iodine deficiency may also increase the risk of developing thyroid cancer because it stimulates thyroid cell proliferation and hyperplasia.

Clinical manifestations

— Sluggishness, slow thinking, and clumsy, slow movements.

— Decreased heart rate, enlarged heart (myxedemic heart), and decreased cardiac output.

— Bogginess and edema of the skin, especially under the eyes and in the ankles.

— Intolerance to cold temperatures.

— Decreased metabolic rate, decreased caloric requirements, decreased appetite and nutrient absorption across the gut.

— Constipation.

— Change in reproductive function.

— Dry, flaky skin and brittle, thin body and head hair.

Diagnostic tools

- A good history and physical examination will help diagnose hypothyroidism.
- Blood tests measuring levels of TH (both T_3 and T_4), TSH, and TRH will allow diagnosis of the condition and localization of the problem at the level of the central nervous system or the thyroid gland.

Complications

- Myxedema coma is a life-threatening situation characterized by exacerbation (worsening) of all symptoms of hypothyroidism, including hypothermia without shivering, hypotension, hypoglycemia, hypoventilation, and a decrease in consciousness resulting in coma.
- Death can occur without TH replacement and stabilization of symptoms.
- There are also risks associated with the treatment of thyroid deficiency. These risks include hormone over-replacement, anxiety, muscle wasting, osteoporosis and atrial fibrillation.

Treatment

— Treatment always includes replacement of thyroid hormone with synthetic thyroxine.

— For endemic goiter, iodide replacement may relieve symptoms.

— If the cause of hypothyroidism is related to a central nervous system tumor, it may be treated with chemotherapy, radiation, or surgery.

Hormones of the adrenal cortex

- Aldosterone.
- Glucocorticoids (primarily cortisol).
- Androgens (primarily testosterone).
- Estrogens.

Sex gland function impairment

Gonadotropins

The gonadotropins include 2 anterior pituitary hormones: FSH and LH. Target tissues of FSH and LH are the ovary in women and the testis in men.

Effects of the gonadotropins

In response to FSH and LH in women, the ovary secretes the steroid hormones estrogen and progesterone. Estrogen feeds back on the hypothalamus and anterior pituitary in a complicated manner, with a negative effect on increasing the release of FSH and a positive effect on the release of LH, ultimately resulting in ovulation (the rupture of an ovarian follicle). With ovulation, the egg, also called the ovum, is released (Chapter 20) and becomes available for fertilization by a sperm. Progesterone appears to feed back on the anterior pituitary to limit secretion of FSH and LH.

In men, FSH stimulates cells of the testis to initiate and support spermatogenesis (production of sperm). The cells of the testis predominantly affected by FSH in the male are *Sertoli cells*. *Sertoli cells* make up the inner lining of the seminiferous tubules, the site of spermatogenesis, and are important in providing nutrients to the developing sperm. A hormone produced by *Sertoli cells*, inhibin, influences the production of testosterone by acting directly on the pituitary gland to decrease the release of FSH.

LH also is released from the anterior pituitary in men. LH causes interstitial cells of the testes to produce and secrete testosterone. Estrogen and testosterone are also synthesized by the adrenal gland, in men and women, in response to stimulation by ACTH.

Factors controlling gonadotropin release

The gonadotropins are released from the pituitary in response to GnRH from the hypothalamus. It appears that one hypothalamic hormone controls the release of both of the pituitary gonadotropins. An increase in GnRH synthesis and release causes the onset of puberty.

Factors controlling gonadotropin-releasing hormone

Before puberty, circulating GnRH is very low. With maturation of the hypothalamus and perhaps attainment of a certain body mass, GnRH increases and initiates puberty. After sexual maturation has been established, the circulating level of GnRH is controlled in a negative feedback manner by estrogen and testosterone. Stress, starvation, and fear may affect the release of GnRH at any time, influencing the release of estrogen and progesterone in females and testosterone in males, and altering reproductive function.

Estrogens

Estrogens are steroid hormones that affect their target tissues by altering the rate of DNA replication, DNA transcription, or RNA translation. Although the effects of estrogens are most apparent in females, males also produce and are affected by estrogens. There are 3 main types of estrogens in humans: estrone, estradiol and estriol.

Effects of estrogens include the following:

- Development in utero of female internal and external sex organs.
- Female distribution of body fat.
- Pigmentation of the nipples.
- Stimulation of breast development during pregnancy.
- Stimulation of growth of the endometrial lining of the uterus each month to prepare for implantation of the embryo.
- Maintenance of pregnancy.
- Stimulation of lactation.
- Stimulation of bone formation throughout life in males and females.
- *Gonadotropin deficiency* limiting bone resorption (breakdown) by direct action on bone or by limiting bone response to parathyroid hormone in males and females.
- Affecting liver protein production of lipoproteins (stimulates HDL, decreases LDL), coagulation factors, and carrier molecules for steroid hormones and thyroxine in males and females.
- Acting to reduce the risk of coronary artery disease, most likely as a result of increasing HDL, in males and females.
- Stimulating the kidneys to retain sodium in males and females.
- Influencing brain neural signaling in males and females, affecting behavior and mood.
- Estrogen excess in men can cause gynecomastia (breast enlargement).

Progesterone

Progesterone, like estrogen, is a steroid hormone. In women, progesterone is synthesized by thecal cells of the developing follicle, and later the corpus luteum, in response to stimulation by LH and, to a lesser extent, FSH.

Effects of progesterone include the following:

- Progesterone is released from an ovarian follicle after the follicle has ruptured during ovulation. It causes the endometrial lining of the uterus to become secretory in anticipation of fertilization of the ovum and embryo implantation, with the result that blood vessels in the endometrium begin to branch and glands begin secreting a thin glycogen-rich fluid. The ruptured follicle becomes the corpus luteum, which continues progesterone secretion.
- If the ovum is fertilized and the embryo implants in the uterus, the corpus luteum and later the placenta maintain the pregnancy by secreting progesterone. If progesterone decreases, the pregnancy terminates.
- If pregnancy does not occur, the corpus luteum degenerates over the next 14 days, progesterone levels decline, and menstruation (sloughing off of the uterine lining) occurs.
- Progesterone works with estrogen and prolactin to stimulate breast development during puberty and pregnancy.
- Progesterone relaxes smooth muscles, including the uterus and the vascular smooth muscle of the arterioles.
- Progesterone appears to be protective against some cancers.

Testosterone

Testosterone, also a steroid hormone, is the most abundant of the powerful androgen hormones. Testosterone synthesis occurs in specialized cells of the testes called *Leydig cells*, and in the adrenal gland in women.

Effects of testosterone include the following:

- Development in utero of male internal and external sex organs.
- Maintenance of sperm production throughout a man's lifetime.
- Stimulation and maintenance of male distribution of muscle.
- Stimulation of bone formation throughout life in males and females.
- Stimulation of red blood cell formation in males and females.
- Stimulation of anabolism (buildup) of proteins in males and females.
- Involvement in brain neural signaling, affecting behavior and mood, in males and females.
- Testosterone excess in women can cause clitoral enlargement, voice deepening, and beard development.

Prolactin

Prolactin is a protein hormone released from the anterior pituitary.

Effects of prolactin

When a girl reaches puberty, prolactin acts in concert with estrogen, progesterone, and GH to promote breast tissue development. Each of these hormones increases dramatically during pregnancy, resulting in further

stimulation of breast development. After the birth of an infant, prolactin acts on the breast to stimulate lactation (milk production), allowing the infant to breastfeed. In postpartum women, the posterior hypothalamic hormone oxytocin works in concert with prolactin and is required for successful breastfeeding.

In non-pregnant women, high prolactin levels inhibit the release of two other anterior pituitary hormones: FSH and LH. Because FSH and LH are essential for ovulation and pregnancy, high prolactin in women who breastfeed full-time may offer some protection against another pregnancy occurring.

The role of prolactin in men has not been identified, although recent evidence suggests that, in men and women, prolactin may affect the immune system, possibly by modulating the release of certain cytokines.

Factors controlling prolactin release

The secretion of prolactin from the anterior pituitary is controlled by release of a prolactin-inhibitory hormone (PIH) from the hypothalamus, recently identified as the catecholamine dopamine. A decrease in the release of dopamine stimulates prolactin release. There may also be a prolactin-stimulating hormone released from the hypothalamus, although it is yet to be identified.

Stimulation for increased prolactin during pregnancy appears to be an estrogen-dependent decrease in the hypothalamic release of PIH. The suckling of the mother's nipple during breastfeeding by the infant stimulates prolactin release after pregnancyвЂ”stimulation of the nipple by suckling appears to cause increased prolactin by decreasing the hypothalamic release of PIH.

The major hypothalamic and anterior pituitary hormones and their target organ effects

Gonadotropin deficiency is a decrease in circulating levels of FSH and LH. Gonadotropin deficiency is usually caused by pressure exerted on the gonodotropin-producing cells by a pituitary tumor of another hormone-producing cell type. Oversecretion of the target gland hormones estrogen, progesterone, or testosterone can also act in a negative feedback manner to cause gonadotropin deficiency. Prolactin is known to inhibit pituitary secretion of the gonadotropins, and prolactin-secreting tumors can cause gonadotropin deficiency. Finally, the hypothalamus may decrease its secretion of gonadotropin-releasing hormones under periods of physical stress, obesity, starvation, or emotional trauma.

Clinical manifestations

— Amenorrhea (lack of menstrual periods), vaginal, uterine, and breast atrophy in women.

— Testicular atrophy and reduction in beard growth in men.

— Patients with hypogonadotropic hypogonadism manifest decreased testosterone levels and interruption of spermatogenesis.

Diagnostic tools

Blood tests measuring the levels of estrogen, testosterone, and the gonadotropins will allow diagnosis of the condition and localization of the problem at the level of the CNS or the ovary or testicle.

Treatment

— Surgery if a tumor is present.
— Gonadotropin, estrogen, or testosterone replacement may be considered.
— Stress reduction, weight gain, or weight loss.

Hypoprolactemia

Hypoprolactemia is a decrease in circulating levels of prolactin. Hypoprolactemia may occur as a result of hypothalamic dysfunction leading to increased release of prolactin-inhibiting hormone. It may also occur because of dysfunction of the prolactin-secreting cells of the pituitary. Dysfunction of pituitary cells may be caused by increased pressure from a pituitary tumor of another cell type. More commonly, hypoprolactemia is diagnosed after an episode of pituitary ischemia and necrosis.

Diseases of hypoprolactemia

Sheehan's syndrome is a condition of hypopituitarism resulting from an intrapartum or postpartum hemorrhage (during or after delivery of an infant). With a significant loss of blood volume during the birth process, blood flow to the anterior pituitary may be reduced. Complicating the problem further is that during pregnancy the anterior pituitary grows and becomes very active metabolically. This is especially true for cells that produce prolactin, TSH, and GH. The result is a very high oxygen demand. In addition, anterior pituitary blood flow is venous blood coming from the hypothalamus through the hypothalamic-pituitary portal system, and is therefore relatively deoxygenated. Thus, the anterior pituitary is particularly susceptible to ischemic damage with a birth hemorrhage. Sheehan's syndrome may manifest after delivery of the infant when the woman experiences an inability to breastfeed. Other pituitary hormones may also be deficient.

Clinical manifestations

- Inability to breastfeed in women.
- In Sheehan's syndrome, other symptoms will depend on which hormone-producing cells were affected by the ischemia.

Diagnostic tools

- Blood tests measuring decreased levels of prolactin will allow diagnosis of the condition.
- Treatment.
- Treatment is related to needs of the individual and may involve hormone replacement therapy.

Hyperprolactemia

Hyperprolactemia is an increase in circulating levels of prolactin. Hyperprolactemia may be caused by a decrease in secretion of prolactin-inhibiting hormone by the hypothalamus, or as a result of a prolactin-secreting tumor of the pituitary (prolactinoma). Certain phenothiazine drugs, used to treat psychosis, sometimes cause hyperprolactemia, probably by affecting the hypothalamus. It may also occur with pregnancy and during hypothyroidism.

Clinical manifestations

- Infertility, hypogonadism, anovulation, and amenorrhea in women as a result of prolactin-mediated decreases in LH or FSH secretion by the pituitary. This may result in osteopenia.
- Galactorrhea (lactation not associated with childbirth or nursing) may develop.
- No clinical signs are apparent in men.

Diagnostic tools

- Blood tests measuring the increased level of prolactin will allow diagnosis of the condition.
- Imaging of the sella turcica may provide evidence of tumor.

Treatment

- A prolactin-secreting tumor may be surgically resected.
- If the condition is drug related and the patient is concerned about her reproductive status, further use of the drug should be evaluated.
- Dopamine agonists (cabergoline and bromocriptine) to inhibit prolactin secretion may be prescribed.

PATHOLOGICAL PHYSIOLOGY OF NERVOUS SYSTEM

Nervous system features

The brain is sensitive to hypoxia and hypoglucemia: in 5–7 min — lose of consciousness, in 3–5 min — reversible changes, in 6 min — irreversible changes.

Presence of blood-brain barrier, multiple neuron contact, hierarchy system, NS plasticity (an ability to consolidate changes). It provides the NS development, an ability of new association formation, study and others.

Etiology of nervous system frustrations

Exogenous factors: physical, biological (neurotropic viruses: rhabdovirus, polymyelitis, herpes virus; microbes: infectious agents of syphilis, leprae; microbe toxin: botulinous toxin and other; phytatoxins), chemical (spirits, phosphorganic substances, drugs), psychosocial.

Endogenous factors

Primary. Hereditary impairments of genetic sructure, structural functional impairments of tissue (organ, system): CNS blood circulation impairments, CNS inflammation process, endocrine pathology, hypervitaminosis, ageing).

Secondary (after the action of CNS primary injuring factor) - endogenization of process:

— metabolic changes, ionic imbalance in neuron;
— impairment of secretion and reception of neuromediators;
— acquired neuron alteration;
— change in transneuronal interaction;
— trophic neuron changes;
— formation of pathologically increased excitability generator, pathologic determinants, pathologic systems.

There are two types of NS pathologic changes:

Primary pathologic changes. This is a morphologic functional impairment, disintegration of physiologic systems resaults from direct pathologic agent action — «break down».

According to I. P. Pavlov «break down» is a cause and condition of pathogenic process development expectionless by endogenous mechanisms of impaired nervous tissue.

Secondary pathologic changes — occurrence of new pathologic integrations from primary and secondary changed NS formations:

- on the level of transneuron associations (pathologic increased excitability generator);
- on the level of cell-cell associations (pathologic system).

Outcomes of pathologic processes in nervouse system:

- hyperactivation or neuron destruction;
- chronization of pathologic processes;
- recovery.

Clinical recovery (liquidation of pathological process). Safety of latent structural functional changes in terms of tracer reactions of last pathologic process.

Regeneration of signs of perished pathologic process on the background of tracer reactions in new specific pathogenic action is called «acute stroke phenomenon».

Mechanisms of nervouse system pathology development

Neuron. *T*he neuron, also called a nerve cell, is the functional unit of the nervous system and is a highly specialized cell. Neural maturation occurs before or soon after birth. Once mature, the neuron does not undergo cellular

reproduction and cannot be replaced. Each neuron functions to receive incoming stimuli from, and to send outgoing stimuli to, other nerves, muscles, or glands. Neurons pass and receive signals through changes in the flow of electrically charged ions back and forth across their cell membranes.

Parts of neuron. Most neurons have four parts: the dendrite, an afferent end that receives incoming signals; the cell body, a central area containing the nucleus; the axon, a long extension on which the signal passes; and the axon terminals, which branch off of the axon and deliver the signal to other cells.

Dendrite. A dendrite is a neural extension from the cell body. The dendrite is the part of the neuron that receives stimulation from other nerves. Each neuron may have many dendritic branches. Excitation of a neuron typically begins at the dendrite. The dendrite passes its excitation on to the adjacent segment, the cell body.

Cell body. The cell body contains the typical organelles of a human cell. The nucleus, which contains the genetic information of the neuron, orchestrates the production of the proteins, enzymes, and neurotransmitters required by the nerve for its proper function. The cell body delivers these substances as needed to the rest of the neuron. Although neural excitation typically begins with excitation of the dendrites, a cell body sometimes may be stimulated directly by incoming stimuli from other neurons and by chemical and electrical stimuli. The cell body delivers the electrical signal to the next segment, the axon.

Axon. Projecting from the cell body is the axon, the beginning of which is called the initial segment or trigger zone. The axon is a long fiber on which passes the electrical signal initiated in the dendrites and cell body. The axon transmits the original signal to another neuron or to a muscle or gland. Branching off the main stem of the axon may be multiple collateral fibers. Collateral fibers convey information to many other interconnected nerve cells, increasing the influence of the neuron throughout theNS. Down the length of the axon, contractile proteins and microtubules transport substances produced in the cell body.

The axon is also called a nerve fiber; many nerve fibers traveling together in a bundle are called a nerve.

In some nerves, the axons are covered by an insulating, lipid sheath, called myelin. Myelin is produced when support cells wrap their plasma membranes around an axon. In the peripheral NS, the support cells are the Schwann cells. In the central nervous system, myelin is produced by a specialized type of cell, the oligodendrocytes. Myelin increases the velocity with which an electrical signal is transmitted down an axon, as described later.

Axon terminals. At the end of each main axon stem and collateral, the branching becomes extensive. These final divisions of the axon are called axon terminals. It is through axon terminals that an electrical signal is passed to the dendrites or the cell body of a 2nd neuron. In the peripheral NS, the signal also may pass to a muscle or glandular cell.

Categories of neurons. Neurons that carry information from the periphery to the CNS are called sensory or afferent neurons. These neurons are the only type of nerve cell that do not have dendrites, but possess receptors on their distal ends that sense physical or chemical stimuli. Neurons that carry information out of the CNS to various target organs (muscle cells, other nerves or glands) are called motor or efferent neurons. A 3rd group of neurons passes messages between afferent and efferent neurons. These neurons are called interneurons. Almost 99 % of all neurons in the body are interneurons, and all interneurons are in the CNS.

Mechanisms of neuron damage

Specific mechanisms:

— neuromediator synthesis impairment;
— axon transport impairment (neuromediators, enzymes, trophogens);
— impairment of depot, secretion and interaction of mediator with receptors;
— impairment of mediator destruction.

Non-specific mechanisms:

— impairment of energy supply;
— impairment of ionic balance;
— impairment of protein synthesis;
— impairment of neuron membrane;
— impairment of incell homeostasis;
— impairment of endogenous amplifying systems: acetylcholinesterase/cAMP; phospholipase C/inosite-TP and diacylglicerin (these system actions results in multiple amplyfyong of incoming signal and increasing of its effects on neuron exit);
— dendrite pathology;
— apoptosis.

Pathogenesis of dominant interactions in central nervouse system

Dominant (according to A. A. Uchtimsky) — prevailing CNS center or physiologic system of nervous control (in this moment):

- providing activity of such system in the moment because of associated inhibition of other systems;
- express principle of intersystem relations in CNS.

Pathology of dominant interactions is expressed by:

- insufficiency of dominant;
- excess increase of dominant.

Generator of athologic increased excitability. It is a composition of hyperactive neuron generating non-controlled impulses run and manifesting self-supporting activity.

Conditions of generator of pathologically increased excitability formation: primary insufficiency of braking control, neuron hyperactivity.

It is a typical pathological process on tthe leve of transneuron interaction. Pathologic role: intial part of pathologic determiant foration.

Pathologic determinant is an endogenous mechanism of pathologic process development. It is a key self-forming and controlling part of pathologic system.

It is a typical pathological process of the system level. It is a most resistive part of pathologic system. It can be primary and secondary.

Pathologc system according to G. N. Krydganowski is forming in conditions of injury. It is a new integration in CNS. It has negative role.

The main biologic sign — neuropathologic syndrome: disadaptative direct pathogenic role.

Features:

- ability to consolidate through positive feedback;
- it is not controlled by feedback principle (inhibition of one system may provoke activatin of another, resistance to treatment).

Typical pathologic processes in nervouse system

1) impairment of NS influence intensty on tissues and target-organs: pathologic decrease — denervaton syndrome, spinal shock; pathologic increase — deafferentation;

2) impairment of response approximation: inadequate NS response to irritant parameters; inadequate NS response to organism requirements;

3) impairment of NS activity type: sensation impairments, locomotion impairments, trophic impairments;

4) higher NS impairments;

5) impairment of vegetative NS control.

Denervation syndrome is a complex of changes in post-synaptic neurons, organs and tissues after their disassociation with NS results from mechanical, physical, chemical action impairing excitability transmission in nerve fibers and synapses.

Signs of deervation syndrome in muscular tissue:

- oxyparhy to physiologic active substances;
- fibrile convulsions of denervated muscle.

Effect is associated with absence end-plate of muscular fiber and appearance of new acetylcholine receptors on the whole its span.

Deafferntation is a stop of afferent impulse transmission from the periphery to the center resulting from integrality of sensetive afferent nervous fiber impairment.

Consequences:

- lose of sensetivity and trophic impairments in the irritant zone;
- increase in neuron excitability and barking mechanism impairment;
- the group of neuron can get an ability of generator.

Spinal shock

Spinal shock involves immediate loss of all reflexes from 2 segments above and below the site of cord injury. Lost reflexes include those controlling posture, bladder and bowel function, blood pressure, and maintenance of body temperature. Spinal shock appears to occur from the sudden loss of all of the tonic discharge normally carried in neurons descending from the brain, which acts to maintain the function of the reflexes. Spinal shock typically lasts 7 to 21 days, but may last longer. As spinal shock regresses, hyper-reflexia may occur, characterized by muscle spasticity and reflex bladder and bowel emptying.

Brain death

Brain death is irreversible loss of cerebral hemisphere, brainstem, and cerebellum function. Consciousness is lost, as is maintenance of respiration, cardiovascular, and temperature control function. There is no sleep-wake cycle, no pain response, and no reflexes. The EEG is flat in an individual with brain death.

Establishing brain death has several legal implications. A patient cannot be legally discontinued from life support without prior living will instructions unless brain death is established. Organ donation is allowed only when brain death is established. Unfortunately, a donated organ is more likely to be healthy when taken from an individual before brain death occurs.

Typical forms of sensation disorders

Abnormal perception of stimulus intensity (dysesthesia) abnormal perception of stimulus pattern, number, and localization:

- hyperesthesia;
- hypoesthesia;
- anesthesia;
- hypalgesiaparesthesia;
- hyperpathia;
- polyesthesia;
- synesthesia;
- allodynia.

Hyperesthesia — exaggerated perception of sensations in response to mild stimuli (e. g. hyperalgesia).

Allodynia — an ordinarily nonpainful stimulus, once perceived, is experienced as painful.

*Hyperpathi*a — a broad term, encompasses all the phenomena described by hyperesthesia, allodynia, and hyperalgesia.

Polyesthesia — an abnormal sensation of touch in which a single stimulus is felt at 2 or more places.

Synesthesia: a sensation in one area from a stimulus applied to another part; a subjective sensation of a sense other than the one being stimulated (hearing sound may also produce the sensation of smell).

***Three levels of sensation disorders*:**

1) disorders of reception:

— changes in threshold parameters, surface density and number of receptors;

2) damage of the sensory pathways:

— polyneuropathy during metabolic disorders (diabetes), intoxication or inflammatory reactions;

3) disorders of the central analyzers of sensation (postcentral gyrus of the parietal cortex):

— complex sensational deficits, such as stereognosis.

Stereognosis — the ability to identify common objects by palpation, recognizing their shape, texture, and size.

Types of locomotor dysfunction:

- muscle weakness;
- movement disorders;
- ataxia, imbalance, other disturbances in the initiation or coordination of movement.

Typical manifestations of the pyramidal upper motor neuron lesions:

- central weakness (spasticity);
- hyperreflexia;
- clonus;
- pathologic segmental reflexes;
- synkinesis.

Weakness (or palsy) is a reduction in normal power of one or more muscles. Weakness is commonly described by severity and distribution. Paralysis and the suffix «-plegia» indicate weakness that is so severe that it is complete or nearly complete. «Paresis» refers to weakness that is mild. The prefix «hemi-» refers to one half of the body. For example, hemiplegia means paralysis of one side of a body. Prefix «para-» ferers to both legs or both hands, and «quadric-» to all 4 limbs. Tone is the resistance of a muscle to passive stretch.

Spasticity is an increased tone that is velocity dependent, has a sudden release after reaching a maximum (the «clasp-knife» phenomenon), and predominantly affects antigravity muscles (i. e., upper limb flexors more than extensors and lower limb extensors more than flexors).

Clonus is spasmodic alteration of muscular contractions between antagonistic muscle groups caused by a hyperactive stretch reflex.

Pathologic segmenatry reflexes are those observed in children in early postnatal period, such as Babinski's reflex. Babinski's reflex is a dorsification of the great toe when the sole of the foot is stimulated.

Synkinesis is an involuntary movement produced in association with a voluntary one.

Typical manifestations of the lower motor neuron lesions:

- muscle weakness of the flaccid type;
- areflexia;
- muscles atrophy;
- fasciculations (isolated small twitches);
- changes in excitability of the muscle fibers.

Typical disorders observed during damage to the extrapyramidal system:

• muscle dystonia;

• movement disorders:

— hypokinetic type;

— hyperkinetic type.

Muscle dystonia is a prolonged muscle tonic contraction that may cause twisting and progress to abnormal posture.

Movement disorders

Movement disorders are neurologic syndromes in which abnormal movements (or dyskinesias) occur due to a disturbance of fluency and speed of voluntary movement or the presence of unintended extra movements.

Hypokinetic movement disorders. These syndromes are manifested as bradykinesia, with a masked expressionless facial appearance, loss of associated limb movements during walking, and rigid turning.

Hyperkinetic movement disorders. Abnormal involuntary movements are divided into those that are rhythmical and those that are irregular. Those that are rhythmical are termed tremors.

The types of hyperkinetic movement disorders are shown in the table 12.

Table 12 — Types of hyperkinetic movement disorders

Rhythmical	Irregular
Tremors: — rest tremor; — postural tremor; — intention tremor	Athetosis
	Chorea
	Tics
	Myoclonus

Athetosis: slow, irregular, twisting, snakelike movements that occur in the upper extremities, esp. hands and fingers.

Chorea: rapid, jerky, semipurposive movement, movement usually of the extremities.

Tics: stereotyped, rapid, recurring, motor movements or vocalization that are nonrhythmic, seemingly involuntary, and sudden in onset (e. g., eye-blinking, couph, etc.).

Myoclonus: sudden, brief jerks or spasms, usually involving the limbs.

Neurosis is a class of functional mental disorders involving distress but neither delusions nor hallucinations, whereby behavior is not outside socially acceptable norms.

As an illness, neurosis represents a variety of mental disorders in which emotional distress or unconscious conflict is expressed through various physical, physiological, and mental disturbances, which may include physical symptoms (e. g., hysteria). The definitive symptom is anxieties. Neurotic tendencies are common and may manifest themselves as depression, acute or chronic anxiety, obsessive-compulsive tendencies, specific phobias, such as social phobia, arachnophobia or any number of other phobias, and even personality disorders, such as borderline personality disorder or obsessive-compulsive personality disorder. It has perhaps been most simply defined as a «poor ability to adapt to one's environment, an inability to change one's life patterns, and the inability to develop a richer, more complex, more satisfying personality». Neurosis should not be mistaken for psychosis, which refers to loss of touch with reality, or neuroticism, a fundamental personality trait according to psychological theory.

According to psychoanalytic theory, neuroses may be rooted in ego defense mechanisms, but the 2 concepts are not synonymous. Defense mechanisms are a normal way of developing and maintaining a consistent sense of self (i. e., an ego), while only those thought and behavior patterns that produce difficulties in living should be termed «neuroses».

Pain

Pain that is classified on the basis of its presumed underlying pathophysiology is broadlycategorized as nociceptive or neuropathic pain.

Nociceptive pain is caused by the ongoing activation of A- and C-nociceptors in response to a noxious stimulus (e. g., injury, disease, inflammation). Pain arising from visceral organs is called visceral pain, whereas that arising from tissues such as skin, muscle, joint capsules, and bone is called somatic pain. Somatic pain may be further categorized as superficial (cutaneous) or deep somatic pain.

In contrast to neuropathic pain, the NS associated with nociceptive pain is functioning properly. Generally, there is a close correspondence between pain perception and stimulus intensity, and the pain is indicative of real or potential tissue damage. Differences in how stimuli are processed across tissue types contribute to the pain's varying characteristics.

The examples and characteristics of nociceptive pain are shown in the table 13.

Table 13 — Examples and characteristics of nociceptive pain

	Superficial somatic pain	Deep somatic pain	Visceral pain
Nociceptor location	Skin, subcutaneous tissue and mucous membrane	Deep somatic pain. Muscles, tendors, joints, fascial, bones	Visceral organs
Potential stimuli	External mechanical, chemical or thermal events. Dermatologic disorders	Overuse stain, mechanical injury, cramping, ischemoia, inflammation	organ distension, muscle spasm, tration, ischemia, inflammation
Localization	Well localized	Localized or diffuse and radiating	Well or poorly localized
Quality	Sharp, pricking or burning sensation	Usually dull or aching, cramping	Deep aching or sharp stabbing pain, which is often referred to cutaneous sites
Associated symptoms and signs	Cutaneous tenderness, hyperalgesia, hyperesthesia, allodynia	Tenderness, reflex muscle spasm, and sympathetic hyperactivity	Malaise, nausea, vomiting, sweating, tenderness, reflex muscle spasm
Clinical examples	Sunburn, chemical or thermal burns, cuts and conusions of the skin	Arthritis, pain, tendonitis, myofascial pain	Colic, appendicitis, pancreatitis, peptic ulcer disease, bladder, distension

Although pain classes are not diagnoses, categorizing pain helps guide treatment. Multiple systems for classifying pain exist. These include multidimensional classification systems, such as the IASP classification of chronic pain, and a variety of systems based on a single dimension of the pain experience. Of the latter systems, those based on pain duration (i. e. acute vs. chronic pain) and underlying pathophysiology (i. e., nociceptive vs. neuropathic pain) are used most often.

We explores the distinction between acute and chronic pain. It also reviews elements of a mixed pain classification system in which pain is categorized as acute pain, cancer pain or CNCP.

Neuropathic pain is caused by aberrant signal processing in the peripheral or central NS. In other words, neuropathic pain reflects NS injury or impairment. Common causes of neuropathic pain include trauma, inflammation, metabolic diseases (e. g., diabetes), infections (e. g., herpes zoster), tumors, toxins, and primarym neurological diseases.Neuropathic pain can be broadly categorized as peripheral or central in origin. Painful peripheral mononeuropathy and polyneuropathy, deafferentation pain, sympathetically maintained pain, and central pain are subdivisions of these categories. Neuropathic pain is sometimes called «pathologic» pain because it serves no purpose. A chronic pain state may occur when pathophysiologic changes become independent of the inciting event.

Pain types and features

Acute pain. Pain usually concordant with degree of tissue damage, which remits with resolution of the injury. Reflects activation of nociceptors and/or sensitized central neurons. Often associated with ANS and other protective reflex responses (e. g., muscle spasm, «splinting»).

Chronic pain. Low levels of identified underlying pathology that do not explain the presence and/or extent of the pain.

Perpetuated by factors remote from the cause. Continuous or intermittent with or without acute exacerbations.

Symptoms of ANS hyperactivity less common. Irritability, social withdrawal, depressed mood and vegetative symptoms (e. g., changes in sleep, appetite, libido), disruption of work, and social relationships.

Cancer pain. Strong relationship between tissue pathology and levels of pain. Limited time frame that permits aggressive pain management. Rarely involves medical-legal or disability issues.

Chronic noncancer pain. Weak relationship between tissue pathology and pain levels. Prolonged, potentially life-long, pain. May involve medical, legal, disability issues/conflicts, work or relationship problems, physical deconditioning, psychological symptoms.

May progress to CPS weak relationship between tissue pathology and pain levels. Prolonged, potentially life-long, pain.

May involve medical, legal, disability issues/conflicts, work or relationship problems, physical deconditioning, psychological symptoms. May progress to CPS.

Complex partial seizure. Preoccupation with somatic functioning. Lifestyle centered on seeking immediate Pain relief, with excessive, nonproductive, and often harmful use of health care services. Repeated attempts to obtain pain-related financial compensation (e. g., Social Security, Veterans' benefits). Numerous symptoms and signs of psychosocial dysfunction that the patient attributes to the pain (e. g., anger, depression, anxiety, substance abuse, disrupted work or personal relationships).

Systems of excitability and recipient of pain signal.

The main processes of physiologic nociception:

1) transduction — injury transformation into the nerve end electric activity;

2) transmission — transmission of impulse in CNS;

3) modulation — change of nociceptive information by antinociceptive influences;

4) perception — subjective emotional feeling forming under the action of CNS genetically determinated features and muscular irritations from periphery.

Pathologic algic system. It is a new pathologic integration forming from primary and secondary achanged formations of pain system under the influence of pathologically increased excitability generator.

It has peripheral, spinal, central levels of organisation. It is a pathological base of pain syndrome.

Endogenous anti-nociceptive system

It controls the pain signal transmission and analyze pain signal (modulation). It is characterized by the constant activity level. That forms sensation threshold (adaptive role).

Mechanisms of anti-nociceptive system:

— neurogenic;

— humoral.

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CONTENTS

Учебное издание

Ермакова Ольга Андреевна
Угольник Татьяна Станиславовна

ЧАСТНАЯ ПАТОФИЗИОЛОГИЯ
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В двух частях

Часть 2

Редактор *О. В. Кухарева*
Компьютерная верстка *А. М. Елисеева*

Подписано в печать 24.01.2012.
Формат 60×84$^{1}/_{16}$. Бумага офсетная 65 г/м^{2}. Гарнитура «Таймс».
Усл. печ. л. 6,51. Уч.-изд. л. 7,12. Тираж 50 экз. Заказ № 29.

Издатель и полиграфическое исполнение
Учреждение образования
«Гомельский государственный медицинский университет»
ЛИ № 02330/0549419 от 08.04.2009.
Ул. Ланге, 5, 246000, Гомель.