

VITEBSK STATE MEDICAL UNIVERSITY
DEPARTMENT OF PROPEDEUTICS OF INTERNAL DISEASES

SPECIAL PROPEDEUTICS OF INTERNAL DISEASES

LECTURE COURSE

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The lecture course of special propedeutics of internal diseases is designed basically for students of the faculty for the training of foreign citizens through the mediation of the English language during the course of studies. The lectures can be useful to teachers of therapeutic departments of medical universities while preparing for their classes with foreign students, to senior students, post-graduates and clinical residents.

The lectures correspond to the basic educational thematic parts of the special propedeutics of internal diseases, according to Standard Educational Program of internal diseases propedeutics approved by Ministry of Public Health of Republic of Belarus in 1997 (registration number 08-14/5906) and the work program of internal diseases propedeutics for students of medical faculty approved by Vitebsk state medical university in 2003.

The reference sources of the lectures are selected with regard for the modern level of internal medicine development. We ask to send all critical remarks and wishes to the department of propedeutics of internal diseases of Vitebsk state medical university.

Diseases of respiratory system

Clinical, laboratory and instrumental methods of diagnostics

Diagnosis and management of pulmonary disorders requires a history, a physical examination, and usually chest x-rays. Laboratory examinations, such as common blood count, analysis of sputum, pulmonary function testing, arterial blood gas analysis, chemical or microbiologic tests, and other special studies (e.g. bronchoscopy) may be needed.

Subjective examination (inquiry) in diseases of respiratory system

Complaints

The basic complaints are typical for the respiratory system:

- dyspnea (character – inspiratory, expiratory, mixed; persistent, progressive, periodical);
- cough (dry, wet; character of sputum);
- bloody expectorations (hemoptysis);
- pain in the chest (localization; relationship to cough, respiratory phase, position of the patient);
- fever (character and level of body temperature).

History of the present disease gives answers about:

- beginning of diseases (acute, gradual);
- contact with infectious patient (in tuberculosis, influenza, other acute respiratory infections, AIDS)
- exposure to environmental allergens (dust mites, pet dander, or cockroach allergens in the home or allergens in the outdoor environment such as pollen and ragweed) or occupational allergens (in bronchial asthma);
- course of disease (acute, prolonged, chronic, persistent, periodical exacerbations);
- chilling and cooling (in acute bronchitis, pneumonia, chronic bronchitis);
- previous (before hospitalization of the patient) examinations and treatment (the medical preparations, their effectiveness) of present disease.

History of past life includes questions of:

- smoking history (the number of years of smoking, the intensity, passive smoking);
- occupational hazards (coal, silica, asbestos dusts; cold and wet working conditions);
- living conditions;
- allergy (polinosis, inhalant allergy- hay fever, house dust allergy, medications);
- frequent respiratory infections;

- others predisposing diseases and factors (tuberculosis, diabetes mellitus, various chronic purulent diseases, acute and chronic heart, shock, disorders of nutrition);
- family history (bronchial asthma, cystic fibrosis, α 1-antitrypsin deficiency).

Objective examination in diseases of respiratory system

Physical examination follows history taking in importance. The sequence of inspection, palpation, percussion, and auscultation should be followed when examining the lungs.

General inspection (survey) may detect typical symptoms of respiratory system diseases:

Position of patient - active, passive, forced lateral recumbent (in pneumonia, tuberculosis, exudative and dry pleurisy, pulmonary abscess or gangrene, bronchiectases), forced sitting (pneumothorax, an attack of bronchial asthma, emphysema).

Colour of skin:

- “*facies febrilis*“ is characterized by hyperemic skin, sparkling eyes and excited expression; feverish redness in acute lobar pneumonia is more pronounced on the side of the affected lung;

- cyanosis - *central cyanosis* in respiratory failure (various degrees of blueness from moderate cyanosis of the face up to diffuse cyanosis);

- *peripheral cyanosis* is associated with stasis of circulation (blueness of distal parts of extremities, prominent parts of nose, cheeks, ears and tip of tongue).

Drumstick (clubbed, Hippocratic) fingers - enlargement of the terminal digital phalanges with loss of the nail bed angle (“watch glass nails”) in prolonged suppurative processes in lungs (abscesses and gangrene), emphysema, tumours of mediastinum and lungs, bronchoectatic disease, chronic circulatory insufficiency, liver cirrhosis.

Inspection of chest

Static survey estimates the shape of the chest at quiet respiration. Pathological chest: emphysematous (barrel-like), paralytic chest, rachitic (keeled or pigeon chest), funnel, foveated, kyphoscoliotic. Asymmetric expansion of the chest is usually due to an asymmetric process affecting the lungs, such as endobronchial obstruction of a large airway, unilateral parenchymal or pleural disease, or unilateral phrenic nerve paralysis. Visible abnormalities of the thoracic cage include kyphoscoliosis and ankylosing spondylitis, either of which can alter compliance of the thorax, increase the work of breathing, and cause dyspnea.

Dynamic survey of the chest estimates the type, chest circumference, frequency, depth, symmetry and rhythm of respiration. Breathing that is

unusually rapid, labored, or associated with the use of accessory muscles of respiration generally indicates either augmented respiratory demands or an increased work of breathing.

Palpation of chest

On palpation, the symmetry of lung expansion can be assessed, generally confirming the findings observed by inspection. Chest palpation may reveal:

- *local pain* - in trauma of chest, dry pleurisy, lobar pneumonia, neuralgia, myositis;
- *resistance (rigidity) of the chest* – increased if decreased elasticity of thorax and lung tissue (pulmonary emphysema, pneumothorax, pleural effusion, elderly patients, pneumosclerosis, hypersthenics); decreased *resistance of the chest* - in children, young men, asthenics, women;
- *fremitus pectoralis (vocalis), or vocal fremitus* - increased if increased density of lung tissue (lobar pneumonia, atelectasis, pneumosclerosis), or thin chest wall (in asthenic); decreased *fremitus pectoralis* - in pulmonary emphysema, pneumothorax, pleural effusion, hypersthenics;
- *bony crepitation* – in fractured ribs;
- *subcutaneous crepitation* - in subcutaneous emphysema (due to pneumothorax);
- *pleural friction and sounds of fluid* - in dry pleurisy, effusion in pleural cavity.

Percussion of chest

The relative resonance or dullness of the tissue underlying the chest wall is assessed by *comparative percussion*. The normal (clear pulmonary) sound of underlying air-containing lung is resonant. In contrast, consolidated lung or a pleural effusion sounds dull, while emphysema or air in the pleural space results in a hyperresonant percussion note.

Topographic percussion may discover changes of lung borders:

- lowering inferior borders - if low position of the diaphragm (in asthenics), in pulmonary emphysema;
- elevation of inferior borders – if high position of the diaphragm (in hypersthenics, increased intraabdominal pressure – ascites, pregnancy); if contraction (cicatrisation) of the superior lobes of the lungs (for example, pneumonia, tbc, cancer);
- lowering superior borders – if contraction (cicatrisation) of the superior lobes of the lungs (for example, pneumonia, tbc, cancer);
- elevation of superior borders – in pulmonary emphysema;
- restriction of active respiratory mobility of the inferior border - in inflammatory infiltration or congestive plethora of the lungs, decreased

elasticity of pulmonary tissue (emphysema, pneumosclerosis), pleural effusion or adhesions.

Auscultation of chest

On *auscultation* of the lungs, the examiner listens to both the quality and intensity of the respiratory sounds and for the presence of extra, or adventitious, sounds. Normal breath sounds heard through the stethoscope at the periphery of the lung are described as *vesicular respiration*, in which inspiration is louder and longer than expiration. If sound transmission is impaired by endobronchial obstruction or by air or liquid in the pleural space, breath sounds are diminished in intensity or absent. *Harsh (coarse) vesicular respiration* is characterized by increase during both respiration phases if narrowing of the small bronchi (inflammation, edema of the mucosa, bronchospasm).

Pathological bronchial respiration well heard at both inspiration and expiration above lungs may of three types: *cavitary type* - in abscess, tubercular cavern, bronchiectasias; *infiltrative type* - in consolidation of pulmonary tissue (acute lobar pneumonia, infarction of lungs, tbc); *atelectatic type* - in compression atelectasis (for example, if exudative pleurisy of 1,5-3 liters).

The *adventitious (abnormal) sounds* that can be heard include rales, crepitation, and pleural friction rub. *Crepitation* represents the typically inspiratory sound created when alveoli open with respiration, and they are often associated with interstitial lung disease, pneumosclerosis compressive atelectasis, or filling of alveoli by liquid (in pneumonia, pulmonary congestion). *Dry rales* which are generally more prominent during expiration than inspiration, reflect the oscillation of airway walls and viscid sputum in it that occurs when there is airflow limitation, as may be produced by bronchospasm, airway edema or collapse, or intraluminal obstruction by neoplasm or secretions. *Wet (moist) rales* is the term applied to the sounds created when there is free liquid in the airway lumen; the viscous interaction between the free liquid and the moving air creates a low-pitched vibratory sound (in acute and chronic bronchitis, edema of lungs, local - in pneumonia, pulmonary abscess). The gritty sound of a *pleural friction rub* indicates inflamed pleural surfaces rubbing against each other, often during both inspiratory and expiratory phases of the respiratory cycle. *Stridor*, which occurs primarily during inspiration, represents flow through a narrowed upper airway, as occurs in an infant with croup.

Sound transmission can also be assessed by listening to whispered sounds; when these are transmitted through consolidated lung, *bronchophony* is present.

Instrumental and laboratory examination in diseases of respiratory system

X-ray (roentgenography)

X-ray (roentgenography) method, or chest radiography is often the initial diagnostic study performed to evaluate patients with respiratory symptoms, but it can also provide the initial evidence of disease in patients who are free of symptoms. Perhaps the most common example of the latter situation is the finding of one or more nodules or masses when the radiograph is performed for a reason other than evaluation of respiratory symptoms.

A number of diagnostic possibilities are often suggested by the radiographic pattern. A localized region of opacification involving the pulmonary parenchyma can be described as a nodule (usually <6 cm in diameter), a mass (usually \geq 6 cm in diameter), or an infiltrate. Diffuse disease with increased opacification is usually characterized as having an alveolar, an interstitial, or a nodular pattern. In contrast, increased radiolucency can be localized, as seen with a cyst or bulla, or generalized, as occurs with pulmonary emphysema. The chest radiograph is also particularly useful for the detection of pleural disease, especially if manifested by the presence of air or liquid in the pleural space. An abnormal appearance of the hila and/or the mediastinum can suggest a mass or enlargement of lymph nodes.

Other chest imaging methods

Bronchography is used to reveal bronchiectasis, abscesses, and caverns in the lungs and contraction of the lumen in the bronchi by a tumour.

Computed tomography (CT) is used for more accurate diagnosis of the tumours and also small indurations, cavities and caverns in the lungs, small pleural effusion.

Radionuclide scanning (scintigraphy) and angiography of the pulmonary circulation are performed for evaluation of pulmonary embolism.

Ultrasound is helpful in the detection of pleural effusion and is often used as a guide to placement of a needle for sampling of pleural liquid (i.e., for thoracentesis).

Bronchoscopy is the process of direct visualization of the tracheobronchial tree by a flexible fiberoptic bronchoscope. Bronchoscopy is able to identify endobronchial pathology, including tumors, granulomas, bronchitis, foreign bodies, and sites of bleeding. Samples from airway lesions can be taken by several methods, including washing, brushing, and biopsy.

Study of the function of external respiration (spirometry, spirometry)

The indices of lung ventilation are not constant and depend not only on the pathological conditions of the lungs or bronchi, but also on the patient's constitution, physical fitness, height, weight, sex, and age. The data obtained

during examination of the patient are therefore assessed by comparing them with the data that might be expected from a person with the given physical properties. These data are calculated by special nomograms and formulas that have been compiled from basal metabolism indices.

Diagnostic value of spirometry consists in estimation of lung ventilation. Normal spirometry is characterized by (Supplement. Table17):

$$VC = \text{predicted VC} \pm 20\% \quad (1)$$

$$FEV1 > 75\% \text{ of FVC} \quad (2)$$

VC – vital capacity, predicted VC – VC according to nomograms data, FVC – forced vital capacity, FEV1 – forced expiratory volume of the first second.

Spirometry in restrictive type of respiratory insufficiency is characterized by restriction of VC less than 70% of proper VC (in pneumonia, pneumosclerosis, accumulation of air and fluid in pleural cavity, kyphoscoliotic chest). Spirometry in obstructive type of respiratory insufficiency is characterized by restriction of FEV1 <70% of FVC (in bronchial asthma, chronic obstructive bronchitis, pulmonary emphysema). Spirometry in mixed type of respiratory insufficiency is characterized by restriction both of VC less than 70% of proper VC and of FEV1 <70% of FVC.

Pneumotachymetry and peak-fluometry are the techniques used for measuring peak velocities of air streams in forced inspiration and expiration and is intended to determine the condition of bronchial patency.

Laboratory examination of sputum

Sputum is a pathological material that is expelled from the respiratory organs during the coughing act. The study of the sputum gives information concerning the pathology of the respiratory organs and in some cases helps establish its etiology. The morning sputum taken before breakfast (after mouth rinsing) is the best material for examination. If the sputum is scarce, it should be collected during one or two days for examination for the presence of tuberculosis mycobacteria. Saprophytic flora rapidly multiplies in sputum to destroy the formed blood elements. Special calibrated bottles provided with screw caps should be used for gathering sputum.

Knowledge of the appearance and quality of the sputum specimen obtained is especially important when one is interested in Gram's staining and culture. Because sputum consists mainly of secretions from the tracheobronchial tree rather than the upper airway, the finding of alveolar macrophages and other inflammatory cells is consistent with a lower respiratory tract origin of the sample, whereas the presence of squamous epithelial cells in a "sputum" sample indicates contamination by secretions from the upper airways.

The study begins with observation of the sputum first in a transparent bottle and then in a Petri dish which is placed alternately on the black and white surface. *General properties, colour, and consistency* of the sputum are noted:

- *mucoid sputum* - colourless, liquid; blood-stained may be (in acute bronchitis; lung infarction, pulmonary congestion);

- *serous sputum* - colourless, liquid, and foamy; blood-stained may be (in pulmonary edema);

- *mucopurulent sputum* - yellow or greenish and tenacious, streaks of blood may be (in acute and chronic bronchitis, tbc, bronchiectasis, focal pneumonia);

- *purulent sputum* - semiliquid, greenish-yellow; streaks of blood, two layers and foul odour may be (in opened lung abscess);

- *bloody sputum* contains red liquid blood (if pulmonary hemorrhage in tbc, cancer, etc.);

- *rusty sputum* - semiliquid, red-brown dark (in lobar pneumonia);

- *three-layer sputum* - the upper layer is mucopurulent, the middle - serous, and the lower is pus; foul odour presents (in chronic purulent processes, gangrene).

The following elements can be seen in the sputum by an unaided eye:

- *Curschmann spirals* - small dense twisted threads (in bronchial asthma);

- *fibrin clots* - whitish and reddish branching elastic formations (in fibrinous bronchitis, pneumonia);

- *Dittrich's plugs* - lenticular formations having offensive odour on pressing (in gangrene, chronic abscess, chronic bronchitis);

- *compact lenticular greenish-yellow formations* - consists of calcified elastic fibres, cholesterol crystals and soaps containing tuberculosis mycobacteria (in tuberculosis);

- *lime grains* - lime (calcium oxide) (if decomposition of old tuberculosis foci);

- *Actinomyces druses* - yellow formations resembling coarse flour; pieces of necrotizing tissue, food remains (in pulmonary actinomycosis, decomposition of cancer).

The *medium of the sputum* is alkaline as a rule; it becomes acid in the presence of gastric juice and during decomposition; this helps differentiate between hemoptysis and hematemesis

Microscopic study of the sputum can be done with native and stained preparations. Besides processing for routine bacterial pathogens by Gram's staining and culture, sputum can be processed for a variety of other pathogens, including staining and culture for mycobacteria or fungi, culture for viruses, and staining for *P. carinii*. Diagnostic value of the study of the sputum by means of microscopy:

- *Curschmann spirals* - mucous threads consisting of central filament and spiral mantle containing leucocytes (often eosinophils) and Charcot-Leyden crystals (in bronchial asthma);
- *leucocytes* - in native preparations at large magnification (in inflammatory, especially purulent processes);
- *eosinophils* - in the native preparation by their uniform large lustrous grains; or by staining (in bronchial asthma, allergy process);
- *erythrocytes* - in decomposition of lung tissue, pneumonia, lung congestion, lung infarction;
- *epithelium* - columnar ciliated epithelium in any sputum, if large amounts - in bronchitis, bronchial asthma, etc.;
- *alveolar macrophages* - large cells (twice or thrice as great as leucocytes); heart disease cells with hemosiderin grains (large amounts in inflammatory diseases; in lung congestion);
- *malignant tumour cells* - large and disfigured cells with large (several) nuclei;
- *elastic fibres* - fine formations of two dichotomically branching filaments of the uniform thickness (in decomposition of the lung tissue in tuberculosis, cancer and abscess);
- *Charcot-Leyden crystals* - colourless octahedric of various size crystals (in decomposition of eosinophils bronchial asthma, old sputum);
- *crystals of hematoidin* - rhombic or needle-shaped brown-yellow formation (in pulmonary hemorrhage);
- *Candida albicans* - yeast-like cells and branching mycelium in native preparation (in prolonged antibiotic therapy, candidosis);
- *Actinomyces* - It separated from small yellow compact grains (drusen), Gr-stained (in pulmonary actinomycosis, decomposition of cancer);
- *bacteria* - acid-resisiting mycobacterium (in tuberculosis), Gram-positive and Gram-negative bacteria (in bronchitis, pneumonia); anaerobe (in abscess, gangrene); *Pneumocystis carinii* (AIDS or other serious immunodeficiency state).

Basic clinical syndromes of pulmonary diseases

Syndrome of focal consolidation of pulmonary tissue

The syndrome of focal consolidation of lung tissue is caused by filling of the alveoli with the inflammatory fluid and fibrin (in pneumonia), blood (in lung infarction), growing connective tissue in the lung (pneumosclerosis, carnification) in long-standing pneumonia, or developing tumour. The common complaint of the patient is dyspnea. Examination of the patient reveals thoracic lagging of the affected side during respiration; vocal fremitus is intensified in the consolidated area; the percussion sound over the consolidation site is slightly or absolutely dull; auscultation reveals bronchial

respiration, exaggerated bronchophony and (in the presence of liquid secretion in fine bronchi) resonant (consonating) rales. X-ray examination shows the focus of consolidation as an area of increased density in the lung tissue, its size and contours depending on the character and stage of the disease, and some other factors.

Syndrome of cavity in the lung

Cavity in the lung is formed in abscess or tuberculosis (cavern) or during degradation of the lung tumour. An empty large cavity is communicated with the bronchus and surrounded by a ring of inflamed tissue. Examination of the chest reveals unilateral thoracic lagging and intensified vocal fremitus. Percussion reveals dulled tympany or (if the cavity is large and peripheral) tympany with a metallic tinkling. Auscultation reveals amphoric breathing, intensified bronchophony, and often medium and large resonant vesicle rales. X-ray examination proves the presence of the cavity in the lung.

Syndrome of an atelectasis (obturator and compression atelectasis)

Atelectasis is a shrunken, airless state affecting all or part of a lung.

According to pathogenetic mechanism atelectasis may be obturator and compression.

In *obturator atelectasis*, the chief cause of acute or chronic atelectasis is intraluminal bronchial obstruction, often due to plugs of tenacious bronchial exudates, endobronchial tumors, granulomas, or foreign bodies. Other causes include bronchial strictures, distortion, or kinking.

Compression atelectasis may be due to external bronchial compression by enlarged lymph nodes, a tumor, or an aneurysm; external pulmonary compression by pleural fluid or gas (eg, due to pleural effusion or pneumothorax); and surfactant deficiency.

Atelectasis may be acute or chronic. In chronic atelectasis, the affected area is often composed of a complex mixture of airlessness, infection, bronchiectasis, destruction, and fibrosis.

Symptoms and signs depend on how rapidly the bronchus is occluded, how much of the lung is affected, and whether infection is present. Rapid occlusion with massive collapse, particularly with infection, causes pain on the affected side, sudden onset of dyspnea and cyanosis, a drop in BP, tachycardia, elevated temperature, and sometimes shock. Chest wall excursion in the area is reduced or absent. Chest percussion elicits dullness to flatness over the affected area and restriction of the respiratory mobility of the lung borders at the affected side of the chest. Slowly developing atelectasis may be asymptomatic or cause minor pulmonary symptoms. Physical and X-ray data depend on type of atelectasis (obturator or compression).

In *obturator atelectasis* survey of chest reveals decrease of affected side, unilateral thoracic lagging during respiration, and retraction of ribs at the affected side of the chest. Fremitus pectoralis is decreased. Auscultation detects decrease or absence of vesicular respiration and bronchophony. X-ray discovers elevated diaphragm; deviated mediastinum to the affected side, diminished volume of the affected lung.

In *compression atelectasis* survey of chest may reveal increased volume and flatness of intercostal spaces at the affected side of the chest, unilateral thoracic lagging during respiration. Fremitus pectoralis is increased. Auscultation over the compression atelectasis area detects bronchial respiration. If air presents in partly compressed alveoli, crepitation may be. Bronchophony may be increased. X-ray discovers shadow of the collapsed part of the lung toward the root; X-ray may discover shadows of lung tumour or fluid in pleural cavity, or air in pleural cavity (pneumothorax).

Diagnosis of atelectasis is usually made from clinical findings plus x-ray evidence of diminished lung size (indicated by retracted ribs; elevated diaphragm; deviated trachea, heart, and mediastinum to the affected side; and overdistention of the unaffected lung) and of a solid, airless area. If only a segment is affected, the shadow is triangular, with its apex toward the hilum. When small areas are affected, surrounding tissue distention causes them to appear curiously discoid, particularly in subsegmental lower lobe atelectasis. An entire lobe may be affected (lobar atelectasis). As the lobe loses air, the interlobar fissures become displaced, and the lobe becomes more densely opacified as the bronchi, blood vessels, and lymphatics are crowded together. Exact x-ray findings depend on which lobe is affected and how other structures compensate for volume loss. Posterior-anterior and lateral views aid in diagnosis.

The middle lobe syndrome is usually recognized by the characteristic x-ray findings: on posterior-anterior view, subtle obliteration of the right lateral heart border and, on lateral view, the triangular or rectangular shadow running from the posterior cardiac border to the anterior chest wall.

The cause of an obstruction should always be sought regardless of the patient's age. With a fiberoptic bronchoscope, lobar as well as segmental and subsegmental divisions can be seen. Chest CT can help clarify the mechanism of collapse; an experienced interpreter can distinguish among the causes of atelectasis: endobronchial obstruction, compression due to intrapleural fluid or air, and scars resulting from chronic inflammation.

Syndrome of thickening pleural membranes (dry pleurisy)

A characteristic symptom of dry pleurisy is pain in the chest which becomes stronger during breathing and coughing. Cough is usually dry, the patient complains of general indisposition; the temperature is subfebrile. Respiration is superficial (deep breathing intensifies friction of the pleural

membranes to cause pain). Lying on the affected side lessens the pain. Inspection of the patient can reveal unilateral thoracic lagging during respiration. Percussion fails to detect any changes except decreased mobility of the lung border on the affected side. Auscultation determines pleural friction sound over the inflamed site. X-ray picture shows limited mobility of the diaphragm because the patient spares the affected side of his chest.

Syndrome of fluid in pleural cavity

The syndrome of accumulation of pleural fluid occurs in hydrothorax (accumulation of non-inflammatory effusion, i.e. transudate, for example in cardiac failure), or in pleurisy with effusion (inflammation of the pleura). The syndrome is characterized by dyspnea due to respiratory insufficiency caused by lung compression and decreased respiratory surface, asymmetry of the chest (enlargement of the side where pleural effusion is accumulated) and unilateral thoracic lagging during respiration. Vocal fremitus is markedly weakened over the area of the pleural effusion, or it may be undeterminable; percussion reveals a dulled sound or absolute dullness; in auscultation respiration and bronchophony are markedly weakened or absent. X-ray examination reveals an area of increased density in the area of accumulation of the pleural fluid, which is usually at the bottom of the chest (often bilateral in hydrothorax). Its upper border is quite distinct. If transudate is accumulated in the pleural cavity its border is more horizontal, while in the presence of pleural effusion, the border is scant, to coincide with the Damoiseau's curve as determined by percussion.

Syndrome of air accumulation in pleural cavity

Air is accumulated in the pleural cavity when the bronchi are communicated with the pleural cavity (in subpleural tuberculosis cavern or abscess), in injury to the chest, or in artificial pneumothorax (injection of air into the pleural cavity for medical purposes in the presence of large caverns in the lungs). Asymmetry of the chest found in this syndrome is due to the enlarged side where air is accumulated; the affected side of the chest cannot take part in the respiratory act. Vocal fremitus is markedly weaker or absent altogether over the site of air accumulation; percussion reveals tympany. Breathing sounds and bronchophony are either weak or absent and are not conducted to the chest surface to be detected by auscultation. X-ray examination reveals a light pulmonary field without pulmonary pattern; a shadow of the collapsed lung can be seen toward the root.

Syndrome of increased airiness of the lungs (pulmonary emphysema)

Emphysema is defined anatomically as a permanent and destructive enlargement of airspaces distal to the terminal bronchioles without obvious fibrosis and with loss of normal architecture. Lung emphysema is

characterized by increased airiness of the lungs due to overdistended or destroyed alveoli.

The most common causes of emphysema of the lungs are obstructive bronchitis, chronic pneumonia, long-standing bronchial asthma, occupational lung diseases, etc. Lung emphysema occurs in mechanical overdistension of the lungs (in musicians playing woodwind and brass instruments) or in heavy physical exertions associated with retention of breath. Advanced age is another predisposing factor.

The patient mainly complains of dyspnea, which at the onset of the disease may only develop during exercise but later it occurs at rest. Dyspnea is usually expiratory: a healthy person expires air whereas the patient with emphysema presses it out from the chest with an effort. The intrathoracic pressure increases during expiration and the neck veins therefore swollen. In long-standing disease, the chest becomes barrel-shaped. Supraclavicular fossa are usually leveled or protrude over the clavicles. The tissues under the clavicles may protrude as well. Accessory muscles are actively involved in the respiratory act. During inspiration the rigid chest seems to rise due to contraction of the accessory muscles. A bandbox sound can be heard on percussion. Descending of the lower borders of the lungs and a limited mobility of the lower borders and the respiratory excursions of the lungs are characteristic of emphysema. Diminished vesicular respiration is heard on auscultation (the sounds are especially weakened in grave cases). In the presence of concurrent bronchitis, diffuse dry rales are heard.

The X-ray picture of the lungs is especially translucent. The lung borders are lowered, the mobility of the diaphragm is markedly limited.

Syndrome of bronchial obstruction

Syndrome of bronchial obstruction is the set of symptoms related to reduced maximal expiratory flow during forced exhalation. Bronchial obstruction may be chronic and persistent (in emphysema) or episodic (in bronchial asthma), and recurrent (chronic bronchitis).

Airflow limitation and increased airways resistance may be caused by:

- loss of elastic recoil driving passive exhalation due to emphysema,
- increased collapsibility of small airways through loss of radial traction on airways,
- increased resistance due to intrinsic narrowing of small airways (because of edema and inflammation of mucous membrane, bronchospasm, secretion of viscous sputum).

The patient mainly complains of expiratory dyspnea and cough with viscid sputum. Inspection reveals barrel (emphysematous) chest in chronic bronchial obstruction, accessory respiratory muscles force may be. Chest palpation detects decreased fremitus pectoralis, and increased rigidity of chest may be. Percussion may detect box sound (in case of emphysema) and decreased respiratory mobility of the lung borders. Harsh vesicular

respiration with prolonged expiration and dry (mostly whistling) rales are heard. Bronchophony is decreased. The X-ray picture of the lungs is increased bronchovascular pattern or/and increased translucency of lung.

Respiratory insufficiency (failure)

Definition: *Respiratory insufficiency* is the condition with abnormal gas composition of the blood, or this abnormality is compensated for by intense work of the external respiratory apparatus and higher load on the heart

The function of the external respiratory apparatus is to supply the body with oxygen and to remove carbon dioxide formed by exchange reactions. This function is realized firstly by ventilation, i.e. gas exchange between the outer and alveolar air. This ensures the required oxygen and carbon dioxide pressure in the alveoli (an important factor is intrapulmonary distribution of the inspired air). Secondly, this function is realized by diffusion of carbon dioxide and oxygen through the walls of the alveoli and lung capillaries (oxygen is supplied from the alveoli to the blood and carbon dioxide is diffused from the blood to the alveoli). Many acute and chronic diseases of the bronchi and the lungs cause respiratory insufficiency (Wintrich, 1854). The degree of morphological changes in the lungs does not always correspond to the degree of their dysfunction.

Respiratory insufficiency decreases functional abilities of the body. It should be noted that the external respiratory function is closely connected with the blood circulatory function: the heart work is intensified during external respiratory insufficiency, which is an important compensatory element of the heart function.

Among the first signs of respiratory insufficiency are inadequate changes in ventilation (rapid and deep breathing) at comparatively light loads for a healthy individual; the minute volume increases. In certain cases (bronchial asthma, lung emphysema, etc.) respiratory insufficiency is compensated by intensified work of the respiratory muscles, i.e. by the altered respiratory mechanics. In other words, in patients with pathology of the respiratory system, the external respiratory function is maintained at the required level by mobilizing compensatory mechanisms (i.e. by efforts greater than required for healthy persons), and by minimizing the respiratory reserves: the maximum lung ventilation decreases, the coefficient of oxygen consumption drops, etc.

Various mechanisms are involved gradually to compensate for progressive respiratory insufficiency depending on its degree. At the early stages of respiratory insufficiency the external respiratory function at rest is realized in normal way. The compensatory mechanisms are only actuated during exercise in a sick person. In other words, only reserves of the external respiratory apparatus are decreased at this stage. As insufficiency further

progresses, tachypnea, tachycardia, and signs of intensified work of the respiratory muscles (during both inspiration and expiration), with involvement of accessory muscles, develop during light exercise and even at rest. At the later stages of respiratory insufficiency, when the body compensatory reserves are exhausted, arterial hypoxemia and hypercapnia develop. In addition to the growing vivid arterial hypoxemia, signs of latent oxygen deficit also develop; underoxidized products (lactic acid, etc.) are accumulated in the blood and tissues.

Still at later stages, right ventricular incompetence joins pulmonary insufficiency because of the developing hypertension in the lesser circulation, which is attended by increased load on the right ventricle, and also because of dystrophic changes in the myocardium occurring as a result of its constant overload and insufficient oxygen supply. Hypertension in the vessels of the lesser circulation in diffuse affections of the lungs arises by reflex mechanisms in response to insufficient lung ventilation and alveolar hypoxia—the Euler-Liliestrand reflex (this reflex mechanism is an important adaptation means in focal lung affections; it limits blood supply to insufficiently ventilated alveoli). Further, in chronic inflammatory diseases of the lungs due to cicatricial and sclerotic changes in the lungs (and due to affections in the lung vessels) blood passage through the lesser circulation becomes even more difficult. Increased load on the myocardium of the right ventricle stimulates gradual development of its insufficiency to cause congestion in the greater circulation (*pulmonary heart*).

Classification of Respiratory Insufficiency

1. Etiology:
 - (a) Primary - due to respiratory diseases;
 - (b) Secondary - due to other pathology (chest trauma, kyphoscoliosis, intoxications, etc.).
2. Course - (a) Acute, (b) Chronic.
3. External respiration function disorders type:
 - (a) restrictive, (b) obstructive, (c) mixed.
4. Degree of respiratory insufficiency:
I (compensated), II (subcompensated), III (decompensated).
5. Stage:
 - (a) latent pulmonary, (b) pronounced pulmonary, (c) cardiopulmonary insufficiency.

Depending on the cause and mechanism of developing respiratory insufficiency, three types of disordered lung ventilation are distinguished: obstructive, restrictive and mixed (combined).

Obstructive type of respiratory insufficiency is characterized by difficult passage of air through the bronchi (because of bronchitis,

bronchospasm, contraction or compression of the trachea or large bronchi, e.g. by a tumour, etc.).

Clinical picture includes bronchial obstruction syndrome and syndrome of increased airiness of lung tissue (pulmonary emphysema). Inspection of the patient shows barrel-chest, involvement of accessory muscles, expiratory dyspnea. Chest palpation may reveal decreased fremitus pectoralis, and increased rigidity of chest may be. Percussion may detect box sound (in case of emphysema) and decreased respiratory mobility of the lung borders. Harsh vesicular respiration with prolonged expiration and dry (mostly whistling) rales are heard. Bronchophony is decreased. The X-ray picture of the lungs is increased bronchovascular pattern or/and increased translucency of lung.

Spirography shows marked decrease in the MLV and FVC, the VC being decreased insignificantly, FEV1 < 70% of FVC. Peak-fluometry detects diminished PEF (peak expiratory flow rates) < 80% of predicted PEF.

Restrictive type of respiratory insufficiency occurs in limited ability of the lungs to expand and to collapse, i.e. in pneumosclerosis, hydro- and pneumothorax, massive pleural adhesions, kyphoscoliosis, ossification of the costal cartilages, limited mobility of the ribs, etc. These conditions are in the first instance attended by a limited depth of the maximum possible inspiration. In other words, the vital capacity of the lungs decreases (together with the maximum lung ventilation), but the dynamics of the respiratory act is not affected: no obstacles to the rate of normal breathing (and whenever necessary, to significant acceleration of respiration) are imposed.

Clinical picture may include such syndromes as focal consolidation of pulmonary tissue, atelectasis, thickening of pleural membranes, accumulation of air and fluid in pleural cavity. Inspection of the patient shows asymmetric chest, decrease of respiratory mobility of the chest, inspiratory or mixed dyspnea. Diminished vesicular respiration or bronchia respiration, crepitation, pleural rub friction may be heard. Spirography shows marked decrease in the MLV and VC.

Mixed, or combined, type of respiratory insufficiency includes the signs of the two previous disorders, often with prevalence of one of them; this type of disorder occurs in long-standing diseases of the lungs and the heart.

Three degrees and three stages of respiratory insufficiency are also distinguished. The degrees of respiratory insufficiency reflect the gravity of the disease at a given moment.

-*The first degree* of respiratory insufficiency (dyspnea, in the first instance) becomes evident only at moderate or significant physical load. Cyanosis is absent. HbO₂ 80–96%; PaO₂ 100–70 mm Hg; PaCO₂ – 40–50 mm Hg. VC is normal or ≥ 70 % of predicted VC. MVL ≥ 60% of predicted MVL.

- *The second degree.* Dyspnea and cyanosis develops during light exercise in the second degree of insufficiency; the compensatory mechanisms are involved when the patient is at rest and functional diagnosis can reveal some deviations from the normal indices. HbO₂ 80–60%; PaO₂ 70–50 mm Hg; PaCO₂ 50– mm Hg. VC is ≥ 50 % of predicted VC. MVL ≥ 40 % of predicted MVL.

- *The third degree* is characterized by dyspnea at rest and cyanosis as a manifestation of arterial hypoxemia; deviations from the normal indices during functional pulmonary tests are significant. HbO₂ <60%; PaO₂ <50 mm Hg; PaCO₂ >70 mm Hg. VC is <50 % of predicted VC. MVL <40 % of predicted MVL.

Stages of respiratory insufficiency in chronic diseases of the lungs reflect the changes occurring during the progress of the disease. Stages of *latent pulmonary, pronounced pulmonary, and cardiopulmonary insufficiency* are normally differentiated.

Bronchitis

Bronchitis is inflammation of the bronchi (J20-J21, J40-J42 according to X international classification of diseases [ISD-X]). The disease stands first in the list of respiratory pathologies and occurs mostly in children and the aged.

Etiology and pathogenesis:

(1) acute respiratory viral infectious (influenza, whooping cough, measles);

(2) saprophyte bacteria (pneumococcus, streptococcus, klebsiella and others) that are present in the upper air ways.

Predisposing conditions: in supercooling, chills; mechanical and chemical factors – tobacco smoking, chronic occupational inhalation of dusts or chemicals (coal, cement, cotton, formaldehyde, acids, or acetone); chronic inflammatory diseases of upper airways (sinusitis, rhinitis, pharyngitis); residence in cities with moist climate and frequent fluctuations of the weather conditions; congestive heart insufficiency, autoimmune and allergic reactions. Predisposing conditions decrease the body's resistance to microbes (saprophytes) that are present in the upper air ways.

Pathological anatomy

The acute bronchitis begins with hyperemia and swelling of the bronchial mucosa, hypersecretion of mucus and diapedesis of leucocytes; then follows desquamation of epithelium and formation of erosions; in grave bronchitis, inflammation may involve the submucous and muscular layers of the bronchial walls and peribronchial interstitial tissues.

At the early stage of the chronic bronchitis, the mucosa is plethoric, cyanotic, and hypertrophic at some points. Mucous glands are hyperplastic. Inflammation eventually involves the submucous and muscle layers, where cicatricial tissue develops. The mucosa and cartilaginous lamina become atrophied. Bronchial walls become thin to increase the lumen and to cause bronchiectasis. The peribronchial tissue can also be involved in the process with subsequent development of interstitial inflammation and pneumosclerosis. Inter-alveolar septa become gradually atrophied and lung emphysema develops; the number of capillaries of the pulmonary artery decreases. Muscular hypertrophy of the right ventricle and also right-ventricular incompetence may join the pulmonary insufficiency.

Classification of bronchitis:

(1) *According to etiology* - bacterial, viral, mixed (viral-bacterial) bronchitis, bronchitis related to physical-chemical factors, dust bronchitis, allergic bronchitis, and congestive bronchitis.

(2) *According to pathogenesis* - primary and secondary bronchitis.

In primary bronchitis, inflammation develops as the primary process in the bronchi. Secondary bronchitis attends other diseases, such as influenza, whooping cough, measles, tuberculosis, chronic diseases of the lungs and the heart.

(3) *According to the type of inflammatory reaction* - catarrhal, mucopurulent, purulent, fibrinous, atrophic and hemorrhagic bronchitis.

(4) *Depending on the localization of inflammation* –

a) focal or diffuse bronchitis

b) according to level of bronchi - *tracheobronchitis* if inflammatory process reside only in the trachea and large bronchi, *bronchitis* - in the bronchi of the fine and medium caliber, *bronchiolitis* - in the bronchioles (occurring mostly in infants).

(5) *According to the course of the disease* - acute and chronic (recurrent) bronchitis.

(6) *Depending on the stage of disease chronic bronchitis* may be in stage of exacerbation (acute condition [acute attack] of disease) or remission (remittance).

(7) *According to the functional characteristics* bronchitis may be obstructive or non-obstructive.

(8) *According to complications:*

- noncomplicated bronchitis,

- complicated bronchitis with respiratory failure (insufficiency), focal pneumonia, hemoptysis, pneumosclerosis, pulmonary emphysema, peribronchitis, bronchiectases and cardiopulmonary insufficiency (pulmonary heart).

Acute bronchitis

Definition: Acute bronchitis - acute inflammation of the tracheobronchial tree, generally self-limited and with eventual complete healing and return of function (J20-J21 according to ISD-X).

Clinical picture

It is often preceded by symptoms of an upper respiratory infection: rhinitis, malaise, chilliness, slight fever, back and muscle pain, sore throat.

Cough is initially dry and nonproductive, but small amounts of viscid sputum are raised after a few hours or days; later, sputum may be more abundant and mucoid or mucopurulent (in bacterial infection). Burning substernal chest pain may be, it is aggravated by coughing

Dyspnea may develop secondary to airway obstruction.

The *body temperature* may be normal or subfebrile; in grave diffuse bronchitis it may rise to 38—39 °C

Tachycardia may be in severe dyspnea and in high temperature.

Percussion sounds over the lungs are usually unchanged

Auscultation reveals harsh vesicular respiration and dry buzzing and whistling rales, which often change their character and amount after cough. Moist dulled rales may be heard together with dry rales (during resolution of inflammation in the bronchi)

X-ray examination does not reveal any changes

Common blood analysis: The *leukocyte count* of the blood may rise to $9,0-11,0 \times 10^9$ in one liter, ESR slightly increases.

Sputum analysis: sputum is mucous or mucopurulent, sometimes with streaks of blood; it contains columnar epithelium and other cell elements. Fibrin clots (bronchial casts) are expectorated in acute fibrinous bronchitis.

Diagnosis is usually based on the symptoms and signs, but a chest x-ray to exclude other diseases or complications is indicated if symptoms are severe or prolonged. Arterial blood gases should be monitored when serious underlying chronic respiratory disease is present. For patients who do not respond to antibiotics or who have special clinical circumstances (e.g., immunosuppression), Gram stain and sputum culture should be performed to determine the causative organism.

Course. The patient usually recovers in two or three weeks. Although commonly mild, acute bronchitis may be serious in debilitated patients and in patients with chronic lung or heart disease. Airflow obstruction is a common consequence, and pneumonia is a critical complication. Under the effect of some aggravating factors, such as smoking or chilling, or in the absence of timely treatment, the disease may run a protracted course or become complicated with bronchopneumonia.

Chronic bronchitis

Definition: *Chronic bronchitis* (J40-J42 according to ICD-X) is chronic inflammation of the bronchi and bronchioles. *Chronic bronchitis* is defined clinically as the presence of a cough productive of sputum not attributable to other causes on most days for at least 3 months over 2 consecutive years (WHO definition).

Clinical picture

The picture of chronic bronchitis depends on the degree of bronchial involvement and on the depth of affection of the bronchial wall. The main symptoms of chronic bronchitis are cough and dyspnea.

Cough with sputum for at least 3 months over 2 consecutive years. Cough may differ in character and change depending on the season and weather, and stage of diseases

Dyspnea is mostly mixed (firstly it is only during physical exercises). In diffuse inflammation of fine bronchi, dyspnea becomes expiratory.

General symptoms may be such as weakness, rapid fatigue, and excess perspiration.

Temperature of body rises in the exacerbation of bronchitis

Inspection, palpation and percussion of the chest, and also X-ray examination do not reveal any changes in non-complicated chronic bronchitis.

In grave chronic bronchitis, when pneumosclerosis, pulmonary emphysema, and cardiopulmonary insufficiency attend the main process, *inspection* shows accessory muscles involvement in the respiratory act, neck veins swelling, and cyanosis. In this case *percussion* may reveal box sound, limited mobility of the lower border of the lung.

Auscultation detects vesicular harsh respiration, or (when emphysema develops) weakened vesicular respiration with prolonged expiration. Buzzing and whistling dry (less frequently moist) rales are also heard on auscultation.

Common blood analysis: the changes may be only in the exacerbation of bronchitis, including increased leukocyte count and accelerated ESR.

Sputum analysis: sputum is mucopurulent or purulent. Microscopy reveals a great number of leucocytes, degrading erythrocytes, and coccal flora.

X-ray examination in chronic bronchitis, complicated by pneumosclerosis or lung emphysema, reveals signs of these diseases

Bronchography may reveal deformation of the bronchi in chronic bronchitis.

Bronchoscopy gives a picture of atrophic (less frequently hypertrophic) bronchitis (with thinning or swelling of the bronchial mucosa).

Spirography detects changes if chronic bronchitis complicated by syndrome of bronchial obstruction and pulmonary emphysema: decrease of FEV₁ and of the FEV₁/FEV <70%, and decrease of PEF (peak

expiratory flow rates) <80% of predicted PEF. The FEVC₁ and the FEVC₁/FEVC fall progressively as the severity of chronic obstructive bronchitis increases. The FEVC₁ is less variable than other measurements of airway dynamics and can be predicted more accurately from age, sex, and height.

Arterial blood gas measurements detect hypoxemia and hypercapnia and determine the severity of chronic bronchitis.

Diagnosis. Chronic bronchitis is characterized by chronic productive cough for at least 3 months in each of 2 successive years for which other causes, such as infection with Mycobacterium tuberculosis, carcinoma of the lung, or chronic heart failure, have been excluded. The history and physical examination suggest the possibility of chronic bronchitis.

Chest x-rays and pulmonary function tests help establish the diagnosis. A chest x-ray helps exclude other diagnoses, such as TB and lung cancer, which can produce the same symptoms, and it provides the clearest diagnostic evidence of emphysema.

Forced expiratory spirometry quantifies airway obstruction. Airflow obstruction is an important indicator of symptomatic respiratory insufficiency and of the likelihood of blood gas abnormalities.

Course and complications. The course of chronic bronchitis varies. It may persist for many years, but the signs of the anatomical and functional changes are mildly pronounced. In other patients chronic bronchitis progresses slowly to give exacerbations on chills and during epidemic outbreaks of influenza, or under the effect of some occupational hazards. Recurrent bronchitis and peribronchitis give bronchiectases and often pneumonia. Obstruction of bronchial patency provokes the development of emphysema and cardiopulmonary insufficiency.

Pulmonary emphysema

Definition: *Emphysema* (J43 according to ISD-X) is defined anatomically as a permanent and destructive enlargement of airspaces distal to the terminal bronchioles without obvious fibrosis and with loss of normal architecture. Lung emphysema is characterized by increased airiness of the lungs due to overdistended or destroyed alveoli.

Etiology and pathogenesis. The most common causes of emphysema of the lungs are obstructive bronchitis, long-standing bronchial asthma, occupational lung diseases, etc. Lung emphysema occurs in mechanical overdistension of the lungs (in musicians playing woodwind and brass instruments) or in heavy physical exertions associated with retention of breath. Advanced age is another predisposing factor. Other risk factors: cigarette smoking, air pollution (hazardous dust, such as silica or cotton dust, chemical pollutions), α 1-antitrypsin deficiency.

Premature onset of emphysema is common among patients with homozygous α 1-antitrypsin deficiency. Elastase-antielastase imbalance may cause emphysema in smokers and in patients with chronic bronchitis who have adequate protective levels of α 1-antitrypsin. In emphysema, elastin fibers in the lung parenchyma are ruptured and frayed. This results in destruction of alveoli wall, loss of alveoli capillaries, giving obstructive disorders of lung ventilation, of gas exchange and blood circulation in lungs. Next right-ventricular incompetence may join the pulmonary insufficiency.

Pathological anatomy. The pathological changes in lung emphysema are characterized by destruction of interalveolar septa. The alveoli fuse to form bullae (bullous emphysema). The destroyed alveoli are not restored. The lungs are distended and lose elasticity.

Classification of emphysema

(1) *According to etiology* of pulmonary emphysema:

- primary (idiopathic) emphysema complicated with bronchial obstruction,
- secondary (obstructive) emphysema complicates a course of chronic obstructive bronchitis and bronchial asthma,
- involutive (senile, aging) emphysema can be included to primary emphysema because of aging distension of alveoli without reduction of vascular system of lungs.

(2) *Anatomical classification* according to the pattern of involvement of the gas-exchanging units (acini) of the lung distal to the terminal bronchiole:

- panacinar emphysema (affects all of the acinus);
- centriacinar centrilobular emphysema (begins in the respiratory bronchiole and spreads peripherally);
- distal acinar emphysema (paraseptal or subpleural emphysema).

Centrilobular emphysema is the most common form of emphysema in smokers and affects upper and posterior portions of the lungs more severely than the bases.

Distal acinar emphysema (paraseptal or subpleural emphysema) occurs subpleurally or along fibrous interlobular septa. The rest of the lung is often spared, so lung function may be well preserved despite many foci of locally severe disease. This type of emphysema, often occurring in the apices, causes spontaneous pneumothorax in young persons and may produce giant bullae.

Panacinar emphysema (at base where blood flow is and α 1-antitrypsin deficiency) involves both the central and peripheral portions of the acinus, which results, if the process is extensive, in a reduction of the alveolar-capillary gas exchange surface and loss of elastic recoil properties. When emphysema is severe, it may be difficult to distinguish between the two types, which most often coexist in the same lung.

During normal aging, airspaces enlarge and alveolar ducts increase in diameter. These changes are extremely common in lungs from persons over age 50 and may be misidentified as emphysema.

Clinical picture.

Clinical picture of emphysema includes syndrome of increased airiness of the lungs, and symptoms of complications and underlying diseases in secondary emphysema (chronic obstructive bronchitis and bronchial asthma).

The patient mainly complains of dyspnea, which at the onset of the disease may only develop during exercise but later it occurs at rest. Dyspnea increases in cold seasons, in chills, and exacerbations of bronchitis; it is especially pronounced during attacks of cough. Dyspnea is usually expiratory. The intrathoracic pressure increases during expiration and the neck veins therefore become swollen. If heart failure concurs, the veins remain swollen during inspiration as well. Inspection reveals edematous face, cyanotic mucosa, cheeks, nose and the ear lobes; the skin is grayish. The terminal phalanges are often clubbed, and the nails look like watch glass. In long-standing disease, the chest becomes barrel-shaped. Supraclavicular fossae are usually leveled or protrude over the clavicles. The tissues under the clavicles may protrude as well. Accessory muscles are actively involved in the respiratory act. During inspiration the rigid chest seems to rise due to contraction of the accessory muscles. A bandbox sound can be heard on percussion. Descending of the lower borders of the lungs and a limited mobility of the lower borders and the respiratory excursions of the lungs are characteristic of emphysema. Diminished vesicular respiration is heard on auscultation (the sounds are especially weakened in grave cases). In the presence of concurrent bronchitis, diffuse dry rales are heard.

The X-ray picture of the lungs is especially translucent. The lung borders are lowered, the mobility of the diaphragm is markedly limited.

The residual volume increases significantly in emphysema while the maximum lung ventilation and the vital capacity decrease accordingly. The FVC and FEV₁ may decrease 2.5—3 times and this intensifies the work of the respiratory apparatus (especially the respiratory muscles) and increases the oxygen demand. In order to decrease tissue hypoxia, compensatory mechanisms become actuated: cardiac rhythm is accelerated, the minute blood volume and erythrocyte counts are increased as well (compensatory erythrocytosis). Permanent intense cardiac activity in lung emphysema with insufficient oxygen supply to the heart muscle is a cause of gradually progressing myocardial dystrophy which results finally in the right-ventricular failure. The respiratory insufficiency is then supplemented by heart failure with the specific clinical symptoms. The course of bronchitis and pneumonia in such patients is grave.

Diagnosis of pulmonary emphysema is based on syndrome of increased airiness of lung tissue.

Course. Complications – pneumothorax, chronic cor pulmonale, respiratory failure. Emphysema of the lungs usually progresses slowly. The patient may die from cardiopulmonary insufficiency.

Cor pulmonale (pulmonary heart)

Definition: *Cor pulmonale* (I26-J28 according to ISD-X) is a syndrome of the right ventricular hypertrophy caused by a lung disorder that produces pulmonary artery hypertension.

Etiology and pathogenesis: Cor pulmonale is usually caused by COPD (chronic bronchitis, emphysema), extensive loss of lung tissue from surgery or trauma, etc.; pulmonary emboli; acute pneumonia, other acute respiratory infections; primary pulmonary hypertension; pulmonary veno-occlusive disease, scleroderma, diseases leading to diffuse pneumosclerosis or pneumofibrosis; kyphoscoliosis and others types of pathologic chest; obesity with alveolar hypoventilation; neuromuscular diseases involving respiratory muscles, and idiopathic alveolar hypoventilation.

Cor pulmonale does not refer to right ventricular (RV) enlargement secondary to left ventricular (LV) failure, congenital heart disease, or acquired valvular heart disease. It is usually chronic but may be acute and reversible.

Cor pulmonale is directly caused by alterations in pulmonary circulation that lead to pulmonary arterial hypertension, thereby increasing the mechanical load on RV emptying (after load). However, the most important mechanism leading to pulmonary hypertension is alveolar hypoxia, which results from localized inadequate ventilation of well-perfused alveoli or from a generalized decrease in alveolar ventilation. Alveolar hypoxia, whether acute or chronic, is a potent stimulus of pulmonary vasoconstriction, and chronic alveolar hypoxia also promotes hypertrophy of smooth muscle in the pulmonary arterioles. Hypercapnic acidosis augments the pulmonary vasoconstriction. During chronic hypoxia, pulmonary hypertension may be intensified by increased blood viscosity arising from secondary polycythemia and by increased cardiac output.

Clinical picture

Cor pulmonale should be suspected in all patients with one of the underlying causes. A history of a productive cough and dyspnea, perhaps with wheezing, is frequently elicited. Breathlessness limits the patient's ability in the minor stresses of daily living. Frequently there is a history of emergency hospital admissions because of respiratory infection, sometimes necessitating mechanical ventilation. Hypoxia due to hypoventilation is usually worse at night. Exertional dyspnea is the most common symptom of pulmonary hypertension. Some patients suffer syncope or fatigue on exertion, and substernal anginal pain is common.

Survey of the patient reveals cyanosis (warm), distended jugular veins, enlargement of abdomen (due to hepatomegaly and ascites), edema, and positive venous pulse may be.

Palpation of the heart region detects cardiac beat and epigastric pulsation of the right ventricle.

Percussion may reveal widening heart dullness to the right (emphysema can mask it).

At *auscultation* accent of II sound above pulmonary artery; systolic murmur of tricuspid insufficiency, diastolic murmur of pulmonary artery insufficiency, and gallop rhythm may be heard.

X-ray examination discovers right ventricle and proximal pulmonary artery enlargement with distal arterial attenuation, signs of emphysema.

ECG: evidence of right ventricle and right atrium hypertrophy - dextrogram, "P pulmonale" – high (>2,5 mm) acute P in II, III, AVF and right chest leads V₁₋₂; high R wave ≥ 7 mm appears in V₁₋₂, deep S wave in V₄₋₆).

Echocardiography may detect the signs of right ventricle enlargement and dysfunction, and pulmonary artery hypertension. Diagnosis of pulmonary hypertension may require right heart catheterization.

Diagnosis of pulmonary heart is based on detection of right ventricle hypertrophy and underlying lung disorders.

Conception of chronic obstructive pulmonary disease (COPD)

Chronic obstructive pulmonary disease (COPD, J44 according to ICD-10) is the name of a group of chronic and slowly progressive respiratory disorders characterized by reduced maximal expiratory flow during forced exhalation.

Definition: COPD - a disease characterized by chronic bronchitis or emphysema and airflow obstruction that is generally progressive, may be accompanied by airway hyperreactivity, and may be partially reversible.

COPD comprises emphysema and chronic bronchitis, two distinct processes, although most often present in combination. COPD may coexist with bronchial asthma, when abnormal airway reactivity is present, differentiation between these disorders can be challenging.

Clinical picture

Patients with COPD are most often tobacco smokers with a history of at least one pack per day for at least 20 years. The disease is only rarely seen in nonsmokers. Onset is typically in the fifth decade and often comes to attention as a productive cough or acute chest illness. Exertional dyspnea is usually not encountered until the sixth or seventh decade. The patient's perception of dyspnea correlates poorly with physiologic measurements, especially among older patients. A morning "smoker's cough" is frequent,

usually mucoid in character but becoming purulent during exacerbations, which in early disease are intermittent and infrequent. The frequency and severity of cough generally do not correlate with the degree of functional impairment. Wheezing may be present but does not indicate severity of illness. As COPD progresses, exacerbations become more severe and more frequent. Gas exchange disturbances, worsen and dyspnea becomes progressive. Exercise tolerance becomes progressively limited. With worsening hypoxemia, erythrocytosis and cyanosis may occur. The development of morning headache may indicate the onset of significant CO₂ retention. In advanced disease, weight loss is frequent and correlates with an adverse prognosis. When blood gas derangements are severe, cor pulmonale may manifest itself by peripheral edema and water retention.

The physical examination has poor sensitivity and variable reproducibility in COPD. Findings may be minimal or even normal in mild disease, requiring objective laboratory data for confirmation. In early disease, the only abnormal findings may be wheezes on forced expiration and a forced expiratory time prolonged beyond 6 s. With progressive disease, findings of hyperinflation become more apparent. These include an increased anteroposterior diameter of the chest, inspiratory retraction of the lower rib margins (Hoover's sign), decreased cardiac dullness, and distant heart and breath sounds. Coarse respiration and rhonchi (dry rales) may be heard, especially at the bases. To gain better mechanical advantage for their compromised respiratory muscles, patients with severe airflow obstruction may adopt a characteristic tripod sitting posture with the neck angled forward and the upper torso supported on the elbows and arms. Breathing through pursed lips prolongs expiratory time and may help reduce dynamic hyperinflation.

Cor pulmonale and right heart failure may be evidenced by dependent edema and an enlarged, tender liver. With pulmonary hypertension, a loud pulmonic component of the second heart sound may be audible, along with a right ventricular heave and a murmur of tricuspid regurgitation; these findings may be obscured by hyperinflation. If right-sided pressures are sufficiently high, neck veins may elevate instead of collapse with inspiration (Kussmaul's sign). Cyanosis is a somewhat unreliable manifestation of severe hypoxemia and is seen when severe hypoxemia and erythrocytosis are present.

X-ray examination: X-ray data may be entirely normal in mild disease. Emphysema is manifested by an increased translucency of the lungs. With hyperinflation, the chest becomes vertically elongated with low flattened diaphragms. The heart shadow is also vertical and narrow. The retrosternal airspace is increased on the lateral view, and the sternal-diaphragmatic angle exceeds 90°. In the presence of pulmonary hypertension, the pulmonary

arteries become enlarged and taper rapidly. The right heart border may become prominent and impinge on the retrosternal airspace.

Spirometry: Airflow obstruction is usually determined by forced expiratory spirometry - the recording of exhaled volume against time during a maximal expiration. Normally, a full forced expiration takes between 3 and 4 sec, but when airflow is obstructed, it takes up to 15 or even 20 sec and may be limited by breath-holding time. The normal forced expiratory volume in the first second of expiration (FEV₁) is easily measured and accurately predicted on the basis of age, sex, and height. The ratio of FEV₁ to forced vital capacity (FEV₁/FVC) normally exceeds 0,75 (75%), in bronchial obstruction FEV₁/FVC <0,7 (70%).

Bronchial Asthma

Definition: The most common definition of bronchial asthma is an allergic disease which is manifested by *paroxysmal attacks* of dyspnea.

Modern definition: *Bronchial asthma* (J45-J46 according to ICD-10) is defined as a chronic inflammatory disease of airways that is characterized by increased responsiveness of the tracheobronchial tree to a multiplicity of stimuli, and clinically by paroxysms of dyspnea, cough, and wheezing. It is manifested physiologically by a widespread narrowing of the air passages, which may be relieved spontaneously or as a result of therapy.

Etiology and pathogenesis: Bronchial asthma is a polyetiological disease. It can be provoked by external agents (exogenic allergens and irritants) and internal causes (endogenous allergens that usually depend on the infections of the airways or irritants). Non-infectious allergic (atopic), infectious-allergic and non-allergic asthma are distinguished accordingly.

Bronchospasm due to smooth muscle contraction used to be considered the major contributor to the airway obstruction. But now, inflammatory disease of the airways is known to play a critical role, particularly in chronic asthma. Even in mild asthma, there is an inflammatory response involving infiltration, particularly with activated eosinophils and lymphocytes but also with neutrophils and mast cells; epithelial cell desquamation also occurs. Many inflammatory mediators in the airway secretions of patients with asthma contribute to bronchoconstriction, mucus secretion, and microvascular leakage. Exudation, a constant component of inflammatory reactions, leads to submucosal edema, increases airway resistance, and contributes to bronchial hyperresponsiveness. Inflammatory mediators are either released or formed as a consequence of allergic reactions in the lungs; they include histamine and products of arachidonic acid metabolism (leukotrienes and thromboxane, both of which can transiently increase airway hyperresponsiveness).

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Pathological anatomy: Macroscopic study of the lungs of patients who died from an attack of asthma reveals diffuse or irregular focal emphysema. Bronchi contain thick tenacious secretion that clogs the lumen of separate small bronchi and causes atelectasis. The bronchial mucosa is markedly hyperemic and swollen. Microscopy shows desquamation of the epithelium, thickening of the basal membrane, hypertrophy of the muscular layer and eosinophilic infiltration of the bronchial wall.

Classification of bronchial asthma

(1) *According to etiology:* allergic (J45.0), non-allergic (J45.8), mixed (J45.0), unspecified bronchial asthma (J45.9).

(2) *According to degree by severity:*

I (mild intermittent) - symptoms 2 times a week, FEV1 or PEF > 80% predicted, no symptoms and normal PEF between exacerbations, PEF variability < 20%, exacerbations brief (from a few hours to a few days); intensity may vary, nighttime symptoms 2 times a month.

II (mild persistent) - symptoms > 2 times a week but not daily, FEV1 or PEF > 80% predicted, exacerbations that sometimes limit activity, PEF variability 20–30%, nighttime symptoms > 2 times a month.

III (moderate persistent) - daily symptoms, FEV1 or PEF > 60–80% predicted, daily use of inhaled short-acting β_2 -agonist, PEF variability > 30%, exacerbations that limit activity, exacerbations > 2 times a week; may last days. Nighttime symptoms > 1 time a week.

IV (severe persistent) - continual symptoms, FEV1 or PEF 60% predicted, limited physical activity, PEF variability > 30%, frequent exacerbations, frequent nighttime symptoms.

(3) *According to stage of disease:* exacerbation, instable remission, remission, stable remission.

(4) *According to complications:*

a) Pulmonary complications - pneumothorax, atelectasis, emphysema, respiratory failure, status asthmaticus (J46).

b) Extrapulmonary complications - cor pulmonale (pulmonary heart).

Clinical picture

The classical description of bronchial asthma was given in 1838 by G. I. Sokolsky. An attack of allergic asthma begins abruptly and acutely and usually quickly subsides. Attacks of dyspnea developing against the background of chronic infectious diseases of the respiratory ducts (infectious-allergic asthma) are often not severe but protracted. Signs of chronic bronchitis, pneumosclerosis, and lung emphysema can be revealed in such patients in periods clear of paroxysms.

Attacks of dyspnea in bronchial asthma are quite similar; they arise suddenly, gradually increase in strength, and last from a few minutes to several hours and even several days. A prolonged attack of asthma is called status asthmaticus.

Complaints and history: Typical complaints of patients are paroxysmal attacks of expiratory dyspnea and cough especially after previous contact with allergens or irritants.

Attacks of asthma can be provoked by various odours, such as those of flowers, hay, perfumes, petrol, carpet or pillow dusts, moulds (in damp rooms), the smell of ursoil dyes, asbestos dust; by some foods such as eggs, crabs, strawberries (food asthma), and medicinal preparations. An attack of asthma can sometimes be provoked not by the allergen itself but by memory of it or by remembrance of the conditions under which the allergen acted in the past. The patient can develop an asthmatic attack when he reappears in a certain room or a house or street, where he once had an attack, or even by remembrance of this particular room, house, street, etc. Endogenous allergens causing attacks of asthma include microbial antigens that are formed during various inflammatory processes, such as sinusitis, chronic bronchitis, chronic pneumonia, etc. Products of decomposition of microbes and tissue proteins forming due to proteolytic process at the inflammatory focus (especially in chronic infections of upper airways) can act as allergens.

Survey: During such an attack, the patient has to assume a forced position; he usually sits in bed, leans against his laps, his breath is loud, often whistling and noisy, the mouth is open, the nostrils flare out. The veins of the neck become swollen during expiration and return to norm during inspiration. At the peak of an attack, the patient begins coughing with poorly expectorated thick and tenacious sputum. The chest expands during an attack (to the size of the chest during inspiration due to acute emphysema). Accessory respiratory muscles are actively involved in the respiratory act.

Percussion of the lungs gives the bantbox sound, the lower borders of the lungs are below normal, mobility of the lower borders is sharply limited

during both inspiration and expiration. The borders of complete dullness of the heart cannot be determined because of the acute inflation of the lungs.

Auscultation reveals many whistling rales against the background of weakened vesicular respiration with a markedly prolonged expiration. The whistling rales are sometimes heard even at a distance. Tachycardia is usually observed. By the moment the attack abates the sputum thins and expectoration becomes easier: high and dry rales in the lungs determined by auscultation decrease to give way to low buzzing and often moist non-consonant rales of various calibers; the attack of dyspnea gradually abates.

X-ray examination during an attack of asthma shows high translucency of the lung fields and limited mobility of the diaphragm.

Common blood test during attacks detects moderate lymphocytosis and eosinophilia.

Sputum analysis may reveal 40 to 60 per cent of eosinophils and often Curschmann spirals (casts of the distal airways) and Charcot-Leyden crystals.

Spirometry detects FEV1 or PEF > 80% predicted, PEF variability 20–30%. The level of bronchial obstruction increases during provocative inhalation tests (allergens, irritants, histamine, acetylcholine) and decreases after β -adrenergic agonist inhalation.

Patients with uncomplicated bronchial asthma have no complaints in the periods clear of attacks. Physical, X-ray, and laboratory examinations may reveal no changes except eosinophilia of the blood at the periods clear of attacks.

Some clinical variants of bronchial asthma

Allergic (extrinsic, occupational) bronchial asthma - 2-15% of all asthmatics patients. Respiratory symptoms, and variable airflow limitation and/or bronchial hyperresponsiveness due to exposure in a particular place separate from those outside the work/or living environment. It should be considered in any case of adult-onset asthma or worsening asthma. Allergic asthma characteristics are immediate and last phase allergic reactions; indoor, outdoor allergens, seasonal variation. It may be due to chemicals, metals, dusts, pollens, insects, proteins. *Occupational bronchial asthma* is related to industrial chemicals, animal plants and proteins. Respiratory symptoms intensify when a worker returns from a weekend off or vacation. It is very common with cotton dust endotoxin in byssinosis, also in sawdust, hemp, or any factory processing raw materials.

Nonallergic (intrinsic) bronchial asthma is related to upper respiratory infection, purulent rhinitis, sinusitis, cold air, odors (tobacco smoke), perfumes, household cleaning agents, insecticides, fresh paint, air pollution, GERD (gastro-esophageal reflux disease).

Mixed bronchial asthma is combination of allergic and nonallergic bronchial asthma.

Exercise induced bronchial asthma: Contributing factors are hard exercise (>80% max heart rate for >6-8 min), cold air, low humidity (dry air), airborne particles (allergens, dust, irritants, auto exhaust, commercial pollutants like sulfur, dioxide, nitrogen dioxide, ozone). Exacerbation of exercise induced bronchial asthma may be due to respiratory infections, fatigue, emotional stress, athletic overtraining (especially running > cycling > swimming).

Aspirin induced bronchial asthma is characterized by bronchial hypersensitivity and hyperresponsiveness to acetylsalicylic acid and to most of other non-steroid anti-inflammatory drugs (NSAID). Aspirin triad (including acetylsalicylic acid sensitivity, chronic nasal polyps, asthma) is very typical.

Cough variant asthma are seen in 40% of those who present with isolated chronic nonproductive cough with normal chest x-ray. These patients need in spirometry examination to precise the level of bronchial obstruction.

Diagnosis of bronchial asthma is based on clinical picture of paroxysmal syndrome of bronchial obstruction confirmed by data of spirometry demonstrating reversible airway obstruction.

Bronchial asthma should be considered in anyone who wheezes (whistling rales); it is the likeliest diagnosis when typical paroxysmal wheezing starts in childhood or early adulthood and is interspersed with asymptomatic intervals. A family history of allergy or asthma can be elicited from most asthmatics.

The diagnosis of asthma is established by demonstrating reversible airway obstruction. *Reversibility* is traditionally defined as a 15% or greater increase in FEV₁ after two puffs of a β -adrenergic agonist. When the spirometry results are normal at presentation, the diagnosis can be made by showing heightened airway responsiveness to challenges with histamine, acetylcholine, or isocapnic hyperventilation of cold air. Once the diagnosis is confirmed, the course of the illness and the effectiveness of therapy can be followed by measuring peak expiratory flow rates (PEF) at home and/or the FEV₁ in the laboratory. Positive wheal-and-flare reactions to skin tests can be demonstrated to various allergens, but such findings do not necessarily correlate with the intrapulmonary events. Sputum and blood eosinophilia and measurement of serum IgE levels are also helpful but are not specific for asthma. Chest roentgenograms showing hyperinflation are also nondiagnostic.

Status asthmaticus

Status asthmaticus (J46) is a serious complication of bronchial asthma characterized by severe bronchial obstruction persisting for days or weeks. In unusual circumstances, acute episodes can cause death.

Fatigue and severe distress are evidenced by rapid, shallow, ineffectual respiratory movements. The patient may be unable to speak more than a few words without stopping for breath. Cyanosis becomes apparent as the attack worsens. Confusion and lethargy may indicate the onset of progressive respiratory failure with CO₂ narcosis. In such patients, less whistling rales may be heard on auscultation, because extensive mucous plugging and patient fatigue result in marked reduction of airflow and gas exchange. A *quiet-sounding chest* in a patient having an asthma attack is an alarm that the patient may have a severe respiratory problem that can quickly become life threatening.

Course of bronchial asthma

Attacks of asthma sometimes occur very rarely (once a year or even several years). Some patients develop a more severe course with frequent and grave attacks. Concurrent chronic bronchitis, pneumosclerosis, and emphysema of the lungs cause the corresponding changes detectable by routine examinations; cardiopulmonary insufficiency gradually develops. In rare cases the patient may die during an attack.

Pneumonia

Definition: Pneumonia (J10-J18 according to ICD-10) is an acute infection of lung parenchyma including alveolar spaces and interstitial tissue.

Etiology and pathogenesis:

Bacteria are the most common cause of pneumonia in adults > 30 yr. Of these, *Streptococcus pneumoniae* is the most common. Other pathogens include anaerobic bacteria, *Staphylococcus aureus*, *Haemophilus influenzae*, *Chlamydia pneumoniae*, *C. psittaci*, *C. trachomatis*, *Moraxella (Branhamella) catarrhalis*, *Legionella pneumophila*, *Klebsiella pneumoniae*, and other gram-negative bacilli. *Mycoplasma pneumoniae*, a bacteria-like organism, is particularly common in older children and young adults, typically in the spring.

Major pulmonary pathogens in infants and children are viruses: respiratory syncytial virus, parainfluenza virus, and influenza A and B viruses. These agents may also cause pneumonia in adults; however, the only common viruses in previously healthy adults are influenza A, occasionally influenza B, and rarely varicella-zoster.

Among other agents are higher bacteria including *Nocardia* and *Actinomyces*; mycobacteria, including atypical strains *Mycobacterium* strains (primarily *M. kansasii* and *M. avium-intracellulare*); fungi, including *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*, *Cryptococcus neoformans*, *Aspergillus fumigatus*, and *Pneumocystis carinii*; and rickettsiae, primarily *Coxiella burnetii* (Q fever).

The usual mechanisms of spread are inhaling droplets small enough to reach the alveoli and aspirating secretions from the upper airways. Other means include hematogenous or lymphatic dissemination and direct spread from contiguous infections. Predisposing factors include upper respiratory viral infections, alcoholism, institutionalization, cigarette smoking, heart failure, chronic obstructive airway disease, age extremes, debility, immunocompromise (as in diabetes mellitus and chronic renal failure), compromised consciousness, dysphagia, and exposure to transmissible agents.

Bronchopneumonia can develop against the background of chronic diseases of the lungs (bronchiectasis, chronic bronchitis) due to hematogenic infection in purulent inflammatory diseases (sepsis, after operations, etc.). Aged patients with long-standing and severe diseases or subjects with plethoric congestion of the lungs can develop hypostatic pneumonia. Aspiration of foreign bodies (food, vomitus, etc.) causes aspiration pneumonia. Inhalation of suffocating or irritating gases or vapours (benzene, toluene, benzine, etc.) or other toxic substances can also provoke the onset to bronchopneumonia.

It has long been established that the clinical aspects of bacterial pneumonia somewhat vary depending on the initial body's reactivity. This mainly refers to pneumonia caused by pneumococcus (*Streptococcus pneumoniae*), especially of types I and II. Sometimes the disease is hyperergic, which accounts for its special acuity, cyclic character of its course, frequent affection of the whole lobe of the lung (with involvement of the pleura) and a special character of effusion due to a markedly impaired permeability of the vessel wall (the presence of fibrin and erythrocytes in the effusion). As distinct from more frequently occurring bronchopneumonia (syn.: focal, lobular pneumonia), this pneumonia is called croupous (syn.: lobar, fibrinous pneumonia, pleuropneumonia).

Classification of pneumonias

(1) *According to etiological groups (J10-J18 ICD):* bacterial, viral, mycotic (fungal), parasitic, unspecified infectious agent.

(2) *According to clinical-epidemiological variants:*

- a) community-acquired pneumonia;
- b) nosocomial (hospital-acquired) pneumonia;
- c) atypical pneumonia (mycoplasmal, chlamidial and legionellal pneumonia);
- d) pneumonia in immunodeficiency state (in AIDS, leucosis, radio- and chemotherapy);
- e) pneumonia against a background of granulocytopenia.

(3) *According to localisation and extension of pneumonia:*

- a) one-sided (unilateral) pneumonia -
- total (subtotal) pneumonia,

- lobar (croupous) pneumonia (pleuropneumonia),
 - (poly-)segmentary pneumonia,
 - lobular pneumonia,
 - focal pneumonia (bronchopneumonia),
 - confluent pneumonia,
 - central (core) pneumonia;
- b) bilateral pneumonia (with indication of extension).

(4) *According to degree of severity:*

- mild (or abortive), moderate, severe pneumonia

6. *According to course:* acute, protracted (prolonged) pneumonia

7. *Complications of pneumonia:*

1) pulmonary complications - parapneumonic pleurisy, abscess of lung, syndrome of bronchial obstruction, acute respiratory failure;

2) extrapulmonary complications: acute cor pulmonale, infectious-toxic shock, myocarditis, toxic hepatitis, meningitis, glomerulonephritis.

Clinical picture

Typical complaints include cough with sputum production and fever, usually developing over days and sometimes accompanied by chest pain.

Physical examination may detect tachypnea and signs of consolidation of lung tissue. Inspection of the patient reveals thoracic lagging of the affected side during respiration. Vocal fremitus is intensified in the consolidated area. The percussion sound over the consolidation site is slightly or absolutely dull. Auscultation reveals bronchial respiration, exaggerated bronchophony and (in the presence of liquid secretion in fine bronchi) resonant (consonating) rales or crepitation.

X-ray examination shows the focus of consolidation as an area of increased density in the lung tissue, its size and contours depending on the character and stage of the disease, and some other factors.

Diagnosis of pneumonia

Diagnosis is based on the characteristic symptoms combined with an infiltrate or focus (foci) on chest x-ray. In the absence of the X-ray signs of pneumonia the diagnosis of pneumonia cannot be rejected in the presence of clinical symptoms.

About 30 to 50% of patients have no identifiable pathogen despite a clinical impression of bacterial pneumonia. Although the time-honored method of identifying bacterial pathogens is culturing expectorated sputum, these specimens are often misleading because normal oropharyngeal flora may contaminate them during passage through the upper airways. Special culture techniques, special stains, serologic assays, or lung biopsies are required to identify some pathogens: mycobacteria, mycoplasmas, anaerobic bacteria, chlamydiae, viruses, fungi, legionellae, rickettsiae, and parasites.

Community-acquired (out-hospital) pneumonia

Community-acquired pneumonia has traditionally been thought to present as either of two syndromes: *focal pneumonia (bronchopneumonia)* and *lobar (croupous) pneumonia (pleuropneumonia)*.

Focal pneumonia (bronchopneumonia)

Etiology: Quite varied bacterial flora would be normally found in bronchopneumonia. The wide use of antibiotics has changed the proportion of microbes that are found in pneumonia. The importance of pneumococci (*S. pneumoniae*) has preserved, but it can also be due to other bacterial pathogens, such as *H. influenzae* and mixed anaerobic and aerobic components of the oral flora. Certain viruses also produce pneumonia that is usually characterized by atypical presentations, i.e., chills, fever, shortness of breath, dry nonproductive cough, and predominance of extra pulmonary symptoms. Primary viral pneumonia can be caused by influenza virus (usually as part of a community outbreak in winter), by respiratory syncytial virus (in children and immunosuppressed individuals), by measles or varicella-zoster virus (accompanied by the characteristic rash).

Pathogenesis:

Development of bronchopneumonia is associated with the extension of the inflammatory process from the bronchi and bronchioles to the pulmonary tissue due to the transition of inflammation and infection with the mucous secretion from the inflamed bronchi into the alveoli. Infection gets inside the pulmonary tissue via the bronchi, and more frequently peribronchially, i.e. by lymph ducts and interalveolar septa. Local atelectasis that occurs in obstruction of the bronchus by a "mucopurulent plug" is important in the pathogenesis of bronchopneumonia. Obstruction of bronchial patency can be caused by a sudden bronchospasm and edema of the bronchial mucosa, inflammation (bronchitis), etc.

Pathological anatomy: The alveoli at the site of inflammation are filled with serous or mucous effusion containing large amounts of leucocytes. If bronchopneumonia is associated with influenza, microscopy shows the rupture of fine vessels. Separate lobules of the lungs are affected in bronchopneumonia, hence another name, *lobular pneumonia*. Inflammatory foci may be multiple, or they may fuse (*confluent pneumonia*). In *polysegmentary pneumonia* - the foci may be located in various parts of both lungs simultaneously (mostly in the lower parts of the lungs).

Clinical picture:

The onset of the disease is usually gradual on the background of bronchitis or the upper airways inflammation.

The most typical signs are cough, fever (usually subfebrile, remittent and irregular), and dyspnea. Pain in the chest during coughing and deep breathing may be if inflammatory foci are very closely to pleural membrane.

Palpation may detect increased vocal fremitus. Percussion sounds are dull or dulled above inflammatory foci. Respiration may be harsh or diminished vesicular, or bronchial if confluent or polysegmentary pneumonia. Adventitious sounds may be dry rales, consonating moist rales and crepitation heard over a limited part of the chest

X-ray examination of the lungs reveals foci of indistinct densities at least 1-2 cm in diameter; in confluent pneumonia – infiltration.

Sputum is mucopurulent, sometimes with streaks of blood. Sputum contains a great number of leucocytes, macrophages and columnar epithelium.

Common blood count may detect mild neutrophilic leucocytosis with shift to the left, and a moderately increased ESR

Diagnosis of focal pneumonia is based on clinical picture combined data of chest X-ray examination: focus (foci) of indistinct densities or infiltrate (in confluent pneumonia).

Course. Focal pneumonia is usually more protracted and flaccid than pleuropneumonia. Prognosis is favourable with appropriate treatment. Focal pneumonia may be complicated by abscess of the lung and bronchiectasis.

Lobar (croupous) pneumonia (pleuropneumonia)

Definition: Lobar (croupous) pneumonia (pleuropneumonia) is acute hyperergic pneumococcal inflammation of a pulmonary lobe(s) or segment(s) and their surrounding pleura.

Etiology and pathogenesis. All authors who studied the etiology of lobar pneumonia (pleuropneumonia, croupous pneumonia), discovered Frenkel pneumococci (*Streptococcus pneumoniae* of types I and II, less frequently types III and IV) in about 95 per cent of cases.

Lobar pneumonia occurs mostly after severe overcooling. The main portal of infection is bronchogenic, less frequently lymphogenic and hematogenic. Congestion in the lungs in cardiac failure, chronic and acute diseases of the upper airways, avitaminosis, overstrain and other factors promote the onset of lobar pneumonia. Lobar pneumonia is relatively frequent in patients who had pneumonia in their past history (it recurs in 30-40 per cent of cases which is another evidence of the hyperergic character of the disease).

Pneumococci usually reach the lungs by inhalation or aspiration. They lodge in bronchioles, proliferate, and initiate an inflammatory process that begins in alveolar spaces with an outpouring of protein-rich fluid. The fluid acts as culture medium for the bacteria and helps spread them to neighboring alveoli, typically resulting in lobar pneumonia.

Pathological anatomy. Four stages are distinguished in the course of acute lobar pneumonia. The stage of *congestion* is characterized by acute

hyperemia of the lung tissue, exudation, obstruction of capillary patency, and stasis of the blood. It lasts from 12 hours to 3 days. The stage of *red hepatization* continues from 1 to 3 days. The alveoli are filled with plasma rich in fibrinogen and erythrocytes: The stage of *grey hepatization* is characterized by cessation of erythrocyte diapedesis; the erythrocytes contained in the exudates decompose and their hemoglobin converts into hemosiderin. The alveoli (containing fibrin) become filled with leucocytes. The lungs become grey. The stage lasts from 2 to 6 days. The last stage is *resolution*. Fibrin is liquefied by proteolytic enzymes and exudate is gradually resorbed.

Clinical picture

Clinical data in lobar (croupous) pneumonia depend on the distribution of the process and the stage in which the patient is examined.

The onset of the disease is usually abrupt, with chills, headache, fever. The most typical complaints are cough with rusty sputum (firstly dry), continued fever (to 39-40 °C, for 9-11 days), tachypnea, pain in the affected side of the chest.

General survey shows «*facies febrilis*» with hyperemia of the cheeks, more pronounced on the affected side, cyanosis, often herpes on the lips and nose. General state of the patient may be serious.

Survey of the chest reveals lagging affected side during respiration, accelerated and superficial respiration. Vocal fremitus is slightly exaggerated over the affected lobe. At the onset of the disease, shortened percussion sound can be heard over the affected lobe, often with tympanic effect because liquid and air are simultaneously contained in the alveoli. The vesicular respiration is decreased while bronchophony is increased; the so-called initial crepitation (*crepitus indux*) is present.

The height of the disease (classified by pathologists as the *red and grey hepatization stages*) is characterized by the grave general condition. It can be explained not only by the size of the affected area of the lung which thus does not take part in respiration but also by general toxicosis. Respiration is accelerated and superficial (30-40 per min) and tachycardia (100-200 beats per min) is characteristic.

Percussion dullness is heard over the affected lobe of the lung. Bronchial respiration is revealed by auscultation; vocal fremitus and bronchophony are exaggerated.

In cases of lobar pneumonia in combination with pleurisy with effusion, and also in massive acute lobar pneumonia, in which the inflammatory exudate fills large bronchi, vocal fremitus and bronchophony may be either absent or decrease, and bronchial respiration is inaudible.

Without appropriate treatment the patient with acute lobar pneumonia would often develop *vascular failure* with a marked drop in the arterial pressure due to toxicosis. *Vascular collapse* is attended by general asthenia,

drop of temperature, increased dyspnea, cyanosis, and accelerated and small pulse. The nervous system is also affected (sleep is deranged; hallucinations and delirium are possible, especially in alcoholic patients). The heart, liver, kidneys and some other organs are also affected. Fever persists for 9-11 days if antibiotics or sulpha drugs are not given. The temperature then drops either abruptly (*crisis*) during 12—24 hours or lytically (*lysis*), during more than 2—3 days.

Resolution stage. The exudate thins, air again fills the alveoli to decrease dullness of the percussion sound, tympany increases, and bronchial breathing lessens. Crepitation is heard again (*crepitus redux*) because the alveolar walls separate as air fills them. Moist rales are heard. Exaggerated vocal fremitus, then bronchophony, and finally bronchial respiration disappear.

Common blood analysis: leucocyte count in the blood increases to $15,0\text{--}25,0 \times 10^9$ per liter; neutrophils account - for 80-90 per cent of the leucocytes; a shift to the left with the appearance of juvenile forms is sometimes observed. The number of eosinophils decreases and they can disappear completely in grave cases. Relative lymphopenia and monocytosis are observed. The ESR increases. The red blood does not change.

Sputum analysis: Sputum is tenacious during the congestion period; it is slightly crimson and contains much protein, a small number of leucocytes, erythrocytes, alveolar cells, and macrophages. In the stage of red hepatization sputum is scant and rusty; it contains fibrin and a higher number of formed elements. In the stage of grey hepatization leucocyte count in the sputum increases significantly; the sputum becomes mucopurulent. In the resolution stage, leucocytes are converted into detritus, which is found in the sputum; many macrophages are also found. Gram stain of sputum typically shows gram-positive lancet-shaped diplococci in short chains - pneumococci (*Streptococcus pneumoniae*).

X-ray changes in the lungs depend on the stage of the disease. The lung pattern is first intensified, and then dense foci develop, which later fuse. The shadow usually corresponds to the lung lobe. The lungs become normally clear in two or three weeks. Dynamics of the X-ray changes depends on the time when the therapy is begun.

Diagnosis of lobar(croupous) pneumonia is based on clinical picture combined data of chest X-ray examination: dense consolidation of whole pulmonary lobe(s) or segment(s) and their surrounding pleura (or pleural effusion).

Course and complications

The overall mortality rate is about 5-10%, and treatment has minimal effect on mortality during the first 5 days of illness. Factors that herald a relatively poor prognosis include age extremes, especially < 1 year or > 60 years; positive blood cultures; involvement of > 1 lobe; a peripheral

leucocyte count $< 15 \times 10^9 /L$; presence of associated disorders (eg, cirrhosis, heart failure, immunosuppression, agammaglobulinemia, anatomic or functional asplenia, and uremia); involvement of certain serotypes of *Streptococcus pneumoniae* (especially 3 and 8); and development of extrapulmonary complications (eg, meningitis or endocarditis).

Pulmonary complications are abscess of the lungs, and pleurisy. If pleurisy develops before resolution of pneumonia, it is called parapneumonic. If it occurs after resolution, it is referred to as metapneumonic pleurisy. If resolution of the exudate is delayed, and connective tissue grows into it, cirrhosis of the affected lobe of the lung develops (carnification). Extrapulmonary complications occur as well: sepsis, meningitis, myocarditis, endocarditis and glomerulonephritis.

Pleurisy (pleuritis)

Definition: Pleurisy (J90-J91 according to ICD-X) is an inflammation of the pleura, usually producing an exudative pleural effusion and stabbing chest pain worsened by respiration and cough.

Etiology and pathogenesis

Pleurisy may result from various pathology:

- underlying lung process (pneumonia, infarction, cancer; tuberculosis);
- extrapulmonary diseases (pancreatic pleurisy, uremia, myocardial infarction, acute rheumatic fever);
- trauma of thorax (especially rib fracture, pneumothorax);
- infections, mycotic and protozoa diseases (AIDS, sepsis, coxsackievirus B, amebiasis, coccidioidomycosis);
- allergy reactions;
- asbestos-related pleural disease (in which asbestos particles reach the pleura by traversing the conducting airways and respiratory tissues);
- drug related pleurisy (hydralazine, procainamide, isoniazid, phenytoin, and chlorpromazine);
- radiation intervention.

Serous and serofibrinous pleurisy attend tuberculosis (in 70-90 per cent of cases), and pneumonia, certain infections, and also rheumatism in 10-30 per cent of cases. The purulent process in the pleura may be caused by pneumococci, streptococci, staphylococci, and other microbes. Hemorrhagic pleurisy arises in tuberculosis of the pleura, bronchogenic cancer of the lung with involvement of the pleura, and also in injuries to the chest.

Most diseases of the pleura (pleurisy included) are secondary to disease of the lung. Pleurisy usually develops as a reaction of the pleura to pathological changes in the adjacent organs, in the lungs in the first instance, and less frequently as a symptom of a systemic disease (polyserosites of

various etiologies). Serous pleurisy often arises as an allergic reaction. Purulent pleurisy is often a complication of bronchopneumonia: inflammation may extend onto the pleura, or an inflammatory focus may turn into an abscess which opens into the pleural cavity.

Pathological anatomy

The pleura usually first becomes edematous and congested. Cellular infiltration follows, and fibrinous exudate develops on the pleural surface. The exudate may be reabsorbed or organized into fibrous tissue resulting in pleural adhesions. In some diseases (eg, epidemic pleurodynia), the pleurisy remains dry or fibrinous, with no significant exudation of fluid from the inflamed pleura. More often, pleural exudate develops from an outpouring of fluid rich in plasma proteins from damaged capillaries. Occasionally, marked fibrous or even calcific thickening of pleura (eg, asbestos pleural plaques, idiopathic pleural calcification) develops without an antecedent acute pleurisy.

Classification of pleurisy (Putov N.V., 1984)

I. According to etiology:

1. Infectious pleurisy
2. Non -infectious (aseptic) pleurisy

II. According to character of pathological process:

1. Dry (fibrinous) pleurisy
2. Pleurisy with effusion (exudative [wet] pleurisy)

III. According to character of pleural effusion:

1. Serous pleurisy
2. Serofibrinous pleurisy
3. Purulent pleurisy (pleural empyema)
4. Hemorrhagic pleurisy
5. Eosinophilic pleurisy
6. Cholesterol pleurisy
7. Chylous pleurisy

IV. According to clinical course:

1. Acute pleurisy
2. Subacute pleurisy
3. Chronic pleurisy

V. According to localisation:

1. Diffuse pleurisy
2. Encysted pleurisy
 - apical pleurisy
 - diaphragmatic pleurisy
 - parietal pleurisy
 - paramediastinal pleurisy
 - interlobular pleurisy

Clinical picture of pleurisy depends mainly on character of pathological process - dry (fibrinous) pleurisy or pleurisy with effusion (see below).

Dry (fibrinous) pleurisy

Clinical picture of dry pleurisy is characterized by syndrome of thickening pleural membranes.

A characteristic symptom of dry pleurisy is pain in the chest which becomes stronger during breathing and coughing. Cough is usually dry, the patient complains of general indisposition; the temperature is subfebrile. Respiration is superficial (deep breathing intensifies friction of the pleural membranes to cause pain). Lying on the affected side lessens the pain.

Inspection of the patient can reveal unilateral thoracic lagging during respiration. Percussion fails to detect any changes except decreased mobility of the lung border on the affected side. Auscultation determines pleural rub friction sound over the inflamed site.

X-ray picture shows limited mobility of the diaphragm because the patient spares the affected side of his chest.

The blood picture remains unchanged but moderate leucocytosis is observed in some cases.

Diagnosis of dry pleurisy is based on clinical picture of the syndrome of thickening pleural membranes.

Course. Dry pleurisy has a favourable course and the patient recovers completely in one or three weeks.

Pleurisy with effusion (exudative, or wet, pleurisy)

Clinical picture is characterized by syndrome of fluid accumulation in pleural cavities.

Patients usually complain of fever, pain or the feeling of heaviness in the side, and dyspnea (which develops due to respiratory insufficiency caused by compression of the lung). Cough is usually mild (or absent in some cases). Dizziness, faints, etc., sometimes occur because of the marked toxicosis.

The patient's general condition is grave, especially in purulent pleurisy, which is attended by high temperature with pronounced circadian fluctuations, chills, and signs of general toxicosis.

Inspection of the patient reveals asymmetry of the chest due to enlargement of the side where the effusion is accumulated; the affected side of the chest usually lags behind in respiratory movements.

Vocal fremitus is not transmitted at the area of fluid accumulation, and rigidity of chest is increased.

Percussion over the area of fluid accumulation produces dullness. The upper limit of dullness is usually the *S-shaped curve (Damoiseau's curve)*

whose upper point is in the posterior axillary line. The effusion thus occupies the area, which is a triangle both anteriorly and posteriorly. The Damoiseau curve is formed because exudate in pleurisy with effusion more freely accumulates in the lateral portions of the pleural cavity, mostly in the costal-diaphragmatic sinus. As distinct from effusion, which is restricted by adhesions, transudate more freely presses the lung and the Damoiseau curve is not therefore determined. In addition to the Damoiseau curve, two triangles can be determined by percussion in pleurisy with effusion. The *Garland triangle* is found on the affected side and is characterized by a dulled tympanic sound. It corresponds to the lung pressed by the effusion, and is located between the spine and the Damoiseau curve. The *Rauchfuss-Grocco triangle* is found on the healthy side and is a kind of extension of dullness determined on the affected side. The sides of the triangle are formed by the diaphragm and the spine, while the continued Damoiseau curve is the hypotenuse. The triangle is mainly due to displacement of the mediastinum to the healthy side. Mobility of the lower border of the lung on the affected side is not usually determined in pleurisy with effusion. Left-sided pleurisy with effusion is characterized by the absence of the *Traube space* (the left pleural sinus is filled with effusion and a dulled percussion sound is heard over the gastric air bubble instead of the tympany).

Respiration in the region of accumulated effusion is not auscultated, or it can be very weak. Respiration auscultated slightly above the effusion level is usually bronchial which is due to compression of the lung and displacement of air from it. Vocal fremitus and bronchophony over the effusion are not determined because the vibrating walls of the bronchi that conduct voice are separated from the chest wall by the fluid. The heart is usually displaced by the effusion toward the healthy side. Tachycardia is observed. Arterial pressure may be decreased.

X-ray examination of the chest shows a homogeneous density whose area corresponds to the area of dullness. If effusion is scarce, it accumulates in the outer sinus. Large volumes of effusion cover the entire lung to its apex and displace the mediastinum toward the intact side to lower the diaphragm. The encapsulated parietal pleurisy gives the picture of parietal density. The medial border is usually sharply outlined. Density of the interlobar pleurisy extends along the interlobar sulcus in the form of a triangle or a spindle. Diaphragmatic pleurisy is characterized either by a limited mobility of the diaphragm or its complete absence. The upper border of the effusion is convex (upward) to follow the curvature of the diaphragm.

Common blood analysis: During the initial stage of the disease the blood picture may show mild leucocytosis (marked leucocytosis is characteristic of purulent pleurisy) and sometimes eosinophilia. The ESR is increased. Tuberculosis pleurisy is characterized by lymphocytosis, while rheumatic pleurisy by neutrophilosis.

Pleurocentesis (thoracocentesis)

Pleurocentesis (thoracocentesis) is a puncture of the chest wall for extraction of pleural fluid in order to determine the properties of the exudate for accurate diagnosis.

Pleurocentesis is used: (1) to take samples of the pleural fluid for diagnostic studies, (2) to remove fluids from the pleural cavity, and, whenever necessary, to administer medicinal preparations. The chest is punctured as rule on the posterior axillary line at the point of maximum dullness, which is preliminarily determined by percussion (this is usually the 7-th or 8-th intercostal space). The puncture is made at the upper edge of the underlying rib to prevent an injury of intercostals nerves and blood vessels. The fluid obtained by pleural puncture is studied at the laboratory.

Study of the pleural fluid

The pleural fluid is studied in order (1) to determine its character (transudate, effusion, pus, blood, chylous fluid); (2) to study the cell composition of the fluid in order to obtain information concerning the character of the pathology and sometimes its diagnosis (when cancer cells are detected); (3) to reveal the causative agent of an infectious disease and to determine its sensitivity to antibiotics. Analysis of the pleural fluid includes macroscopic, physicochemical, microscopic and sometimes microbiological and biological analysis.

Transudate is characterized by clear and slightly opalescent, liquid, pale yellow appearance. Microscopy study detects many mesothelium cells, less blood cell. Transudate is not inflammatory fluid, it is typical to heart failure, and liver cirrhosis. Transudates used for *microbiological studies* are as a rule sterile but they can be infected during repeated paracenteses.

Serous effusion is characterized by clear and slightly opalescent, liquid, yellow – golden yellow appearance. Microscopy study detects abundance of leucocytes. It may be in various etiology of pleurisy.

Purulent effusion is characterized by grayish or greenish-yellow; in the presence of blood reddish or greyish-brown; thick or cream -like appearance. Microscopy - rich in neutrophils, and bacteria (Gram- stain). It is typical to suppurative infection of pleural cavity (*empyema*).

Hemorrhagic effusion is characterized by pink to dark red or even brown appearance. Microscopy study detects abundance of red blood cell; malignant cells and Micobacteria tuberculosis may be. Hemorrhagic effusion is to tuberculosis and tumours of pleura, hence it may be in various etiology of pleurisy.

Chylous (-like) effusion is like thin milk, opacity disappears in the presence of ether. Microscopy study shows fat drops (or cell detritus). Chylous (-like) effusion may be in lymphostasis, and fatty degeneration of cells (if chronic pleurisy).

Physicochemical studies of the pleural fluid can differentiate exudates and transudates. *Physicochemical studies* include determination of relative density of the fluid and protein; these are the main criteria for differentiation between the effusion and transudate. Relative density of the transudate is about 1,015 g/cm³ (1,006-1,012), and of the effusion is slightly higher, i.e. 1,018-1,022.

Protein content is lower in transudate than in the pleural fluid, i.e. not higher than 3 per cent (usually 0,5-2,5 per cent). The pleural effusion contains from 3 to 8 per cent of protein. The total protein content of transudate rarely reaches 4-5 per cent and additional tests are therefore used to differentiate it from the pleural effusion.

Rivalta's reaction: a cylinder is filled with water acidified with a few drops of acetic acid; 1 or 2 drops of the punctate are added; as effusion sinks to the bottom it leaves a cloudy trace (like cigarette smoke), while in case of transudate the reaction is negative. This reaction is used to detect the presence of seromucin in effusion. This is a mucopolysaccharide complex which is absent from transudates.

Diagnosis of pleurisy with effusion is based on syndrome of fluid in pleural cavity with typical physical (*Damoiseau's curve*) and X-ray data combined detection of exudate confirmed by *studies (physicochemical, microscopy, microbiological)* of the pleural fluid (Supplement. Table 18).

Course. The course of pleurisy with effusion depends on the etiology of the affection. Pleurisy in rheumatism would normally resolve in 2-3 weeks (with appropriate treatment). Pleurisy with effusion complicating pneumonia (metapneumonic pleurisy, usually serous) also has a comparatively mild course. A protracted course is characteristic of pleurisy with effusion of tuberculous etiology. Development of coarse adhesions interferes with resorption of the effusion (encapsulated pleurisy), while a prolonged purulent process may result in amyloidosis of the internal organs.

Resorption of effusion may be followed by some specific residual phenomena, such as sunken chest and the absence of diaphragmatic mobility on the affected side, displacement of the mediastinal organs toward the affected side, and sometimes permanent pleural friction.

Diseases of blood circulatory system

Clinical, laboratory and instrumental methods of diagnostics

The establishment of a correct and complete cardiac diagnosis often commences with the history and physical examination. Indeed the clinical examination remains the basis for the diagnosis of a wide variety of

disorders. A thorough inquiry is fundamental to the diagnosis of cardiovascular disease and cannot be replaced by routine or random noninvasive and invasive testing, which is expensive and inefficient.

Subjective examination of patients with diseases of circulatory system

Complaints

Major cardiac diseases have relatively few symptoms, including pain; dyspnea; weakness and fatigue; palpitations; light-headedness, presyncope, and syncope; and other symptoms that may be due to the cardiac disease or may accompany it. Subtle variations in these symptoms require close attention.

Pain Cardiac pain can be arbitrarily categorized as ischemic, pericardial, or atypical.

Myocardial ischemic pain is usually described as pressing, squeezing, or weightlike. The pain is usually greatest in the central precordium. Myocardial ischemic pain usually lasts only minutes. The pain is controlled by nitroglycerin, and stop of physical exertion.

Pericardial pain, which is due to inflammation involving the parietal pericardium, feels like stabbing, burning, or cutting and is made worse by coughing, swallowing, deep breathing, or lying down. It is less variable in character, position, and referral area than myocardial ischemic pain. It is diminished by leaning forward and remaining still. Pericardial pain can last for hours or days. It is not relieved by nitroglycerin. Analgesic medications and leaning forward can relieve pericardial pain.

Atypical chest pain tends to be stabbing or burning and is often quite variable in position and intensity from one episode to another. It tends to be unrelated to physical exertion and unresponsive to nitroglycerin. Its duration may be evanescent (measured in seconds) or persistent over many hours or days. Some persons with atypical chest pain have physical signs or echocardiographic evidence of mitral valve prolapse. There is no objective evidence that atypical chest pain indicates serious heart disease, except when due to disease of the great vessels or to pulmonary embolism.

Dyspnea is the perception of uncomfortable, distressful, or labored breathing. Cardiac dyspnea results from edema in bronchiolar walls and stiffening of the lung due to parenchymal or alveolar edema, which interfere with airflow. Dyspnea also results when cardiac output is inadequate for the body's metabolic demands and can occur without pulmonary edema.

Cardiac dyspnea is always worsened by exertion and partly or completely relieved by rest. Dyspnea due to elevated pulmonary venous pressure and pulmonary edema is increased in the recumbent position and decreased by sitting or standing (*orthopnea*). If orthopnea causes awakening during the night and is relieved by sitting, it is called

paroxysmal nocturnal dyspnea. Dyspnea in the presence of bronchiolar edema is associated with wheezing due to airflow obstruction; frothy and sometimes blood-tinged sputum is expectorated. A common manifestation of bronchiolar edema and stiff lungs due to heart failure is a dry cough, which must be differentiated from that occurring in 5% of patients treated with ACE inhibitors.

Cardiac dyspnea varies with physical exertion and may be associated with weakness and fatigue. In many cardiac disorders, dyspnea due to a fixed cardiac output and that due to pulmonary congestion occur simultaneously (e.g., in mitral stenosis). The onset of dyspnea in heart disease usually signifies an ominous prognosis. Dyspnea due to ischemic heart diseases may coexist with that due to another cardiac disease. Orthopnea and paroxysmal nocturnal dyspnea are unusual in pulmonary disease, except in a very advanced phase when the increased efficiency of breathing in the upright position is manifest.

Weakness and fatigue result from inadequate cardiac output for the body's metabolic needs, initially on exertion and eventually at rest. They occur in disorders that limit cardiac output and are not relieved by rest and sleep.

Palpitations are the perception of heart action by the patient. Careful inquiry into the rate and the rhythm of palpitations helps differentiate pathologic from physiologic palpitations. Palpitations due to an arrhythmia may be accompanied by weakness, dyspnea, or light-headedness.

Cardiac activity is controlled by the autonomic nervous system and is thus commonly sensed only by persons with abnormally heightened awareness of their body functions, eg, in anxiety states. It may also be sensed in healthy persons during exercise when stroke volume or heart rate increases. Palpitations can occur in disorders such as aortic regurgitation or thyrotoxicosis; the most common cause is abnormal cardiac rhythm. Palpitations accompanied by myocardial ischemia-type chest pain may be indicative of ischemic heart disease, in which decreased diastolic coronary flow and ischemia result from the tachycardia.

Serious heart disease or arrhythmias that significantly limit cardiac output may cause *light-headedness, presyncope, or syncope* (a sudden brief loss of consciousness, with loss of postural tone). When associated with palpitations (see above), any of these symptoms indicates an abrupt drop in cardiac output and denotes a serious arrhythmia or underlying organic heart disease. Exertional syncope occurs in aortic stenosis or hypertrophic cardiomyopathy, both of which limit increased cardiac output on exertion. Onset of syncope denotes a poor prognosis in patients with ischemic heart disease, myocarditis, cardiomyopathy, and known ventricular arrhythmias. Intracardiac tumors or ball-valve thrombi can intermittently obstruct blood flow within the heart, producing presyncope or syncope. Postural

hypotension and vasovagal syncope are the major benign causes of syncope. Syncope must be differentiated from epileptic seizures, although seizures due to brain hypoxia can occur in a syncopal episode.

Anamnesis (History of present disease and history of past life)

Important questions are character of onset of the disease (acute or gradual) and its first symptoms, its relation to physical exertions, emotional stress, infections and past diseases.

A history of infections (eg, streptococcal with or without rheumatic fever, viral, syphilitic, protozoan) may raise suspicion of a cardiac disorder resulting from active or temporally remote infectious agents. Endocarditis should be considered in any patient with an unexplained fever and a heart murmur. A cardiac cause should be sought for peripheral or cerebral emboli or in any stroke, which can be caused by emboli arising from a recent myocardial infarction, valvular disease (particularly mitral stenosis with atrial fibrillation), or cardiomyopathy. A history of cerebrovascular or peripheral vascular disease increases the likelihood of associated ischemic heart disease. Central cyanosis makes a congenital cardiac disorder highly likely.

Past pregnancies and labor may be accompanied by clinical manifestations of arterial hypertension, cardiac arrhythmia, and heart failure (dyspnea, edema).

A thorough family history should be taken because many cardiac disorders (eg, coronary artery disease, arterial hypertension, bicuspid aortic valve, hypertrophic cardiomyopathy, mitral valve prolapse) have a heritable basis.

Unfavourable living and working conditions (chronic exposure to cold and high humidity, nervous and psychic overstrain, occupational hazards), and bad habits (hypodynamia, overeating, smoking and alcohol abuse) may predispose to blood circulatory disorder.

Objective examination of patients with diseases of circulatory system

Physical examination follows history-taking in importance. The sequence of inspection, palpation, percussion, and auscultation should be followed when examining the heart. The physical examination begins during history-taking by observing the patient's behavior, consciousness, position, and emphasis on certain symptoms. Complete examination of all systems is essential to detect peripheral and systemic effects of heart disease and evidence of extracardiac disease that might affect the heart.

General inspection (survey)

First, the general physical appearance should be evaluated. The patient may appear tired because of a chronic low cardiac output; the respiratory rate may be rapid in cases of pulmonary venous congestion. Half-sitting position

(orthopnea), dyspnea, acrocyanosis with cool skin, often associated with clubbing of the fingers and toes, edemas of legs and loin, sometimes generalized edema with ascites (anasarca) indicate heart failure. Local edema of neck and head (“*the collar of Stokes*”) presents in exudative pericarditis or aneurysm of the aortal arch.

Non-cardiovascular details can be equally important. For example, infective endocarditis is the likely diagnosis in patients with petechiae, Osler's nodes, and Janeway lesions. The peripheral veins can be observed for abnormalities such as varicosities, arteriovenous malformations and shunts, overlying inflammation, and tenderness due to thrombophlebitis. Positive jugular venous pulse is observed in tricuspid incompetence, pronounced venous congestion in the greater circulation, in fibrillation and complete transverse heart block.

Inspection and palpation of chest

Abnormal cardiac pulsations can be visualized in case of severe right ventricular hypertrophy (cardiac beat), congenital heart disease, heart and aortic aneurysms. Properties (localization, area, height and resistance) of the apical beat can be appreciated with the fingertips.

The symptom of a *cat's purr*, i.e. low vibrating thrill, resembles purring of a cat. It is of great value in the diagnosis of heart diseases. This sign depends on the same causes that are responsible for the murmur arising in stenosed valve orifices. In order to determine the thrill, the palpating hand should be placed flat on the points where the heart is normally auscultated. Cat's purr palpated over the heart apex during diastolic contraction is characteristic of mitral stenosis, and thrills felt over the aorta during systole indicate stenosed aortic orifice.

Percussion of relative and absolute heart dullness should be performed in each patient to identify normal or abnormal position and size of the heart.

Auscultation of cardiac sounds and murmurs should be performed in each patient to identify functional and organic changes in intracardiac balloon flow. Pericardial friction rub indicates pericarditis sicca (fibrinous) and pericardial commissures and adhesions.

Vital signs

BP and pulse are measured in both arms and, in congenital heart disease or peripheral vascular disease, in both legs. It is normal to have up to a 15-mm Hg pressure difference between the right and left arms. Leg pressure is usually 20 mm Hg higher than arm pressure. If postural hypotension is suspected, BP and heart rate are measured with the patient supine, seated, and standing. If hypertension is found, a thorough examination should be performed to exclude coarctation of the aorta (suggested by weak or absent leg pulses, radial-femoral pulse delay, and lower BP in the legs than in the arms; palpable abnormal pulsation of the periscapular arterial plexus [sometimes]; and possibly a systolic murmur in

the back or upper precordium). In thyrotoxicosis and hypermetabolic states, the pulse is rapid and bounding; in myxedema, it is slow and sluggish.

Respiratory rate reflects the presence of cardiac decompensation or primary lung disease. It increases in the anxious patient and decreases in the moribund. Shallow, rapid respirations may indicate pleuritic pain.

Temperature elevation may suggest acute rheumatic fever or cardiac infection, as in endocarditis. It is very common after myocardial infarction and need not prompt a search for other causes unless it persists > 72 hours.

Major peripheral pulses in the upper and lower extremities should be examined for evidence of congenital or acquired arterial disease or systemic embolism from the heart. Care must be taken in interpreting the carotid pulse in the elderly, particularly when hypertension is present. Arteriosclerosis leads to vessel rigidity, which, with aging of the vessel wall, tends to eliminate the characteristic findings.

Instrumental investigation in diseases of blood circulatory system

The clinical examination may then be supplemented by four types of laboratory tests: (1) ECG; (2) chest roentgenogram; (3) noninvasive graphic examinations [echocardiogram, radionuclide and imaging techniques]; and occasionally (4) specialized invasive examinations, i.e., cardiac catheterization, angiocardiology, and coronary angiography.

ECG is used to detection of cardiac arrhythmias and conduction disorders, hypertrophy of heart chambers, ischemia of myocardium.

Exercise stress ECG testing: Exercise testing in a patient with typical symptoms is generally used to determine functional and ECG response to graded stress.

The ischemic ECG response during or after exercise is characterized by flat or downward-sloping ST segment depression > 0,1 millivolts (1 mm on the ECG when properly calibrated) lasting > 0,08 sec.

Phonocardiogram (PCG) is the method for recording sounds generated in the beating heart. Phonocardiography is an essential supplement to heart auscultation because it can record sounds otherwise inaudible to the human ear, such as the third and fourth heart sounds, low-frequency components of the first and the second heart sounds, and low-frequency murmurs. PCG may show specific changes in heart sounds, and the appearance of murmurs.

Chest roentgenogram

Frontal and lateral chest films should be obtained to evaluate heart size, heart shape, chamber analysis, and the nature of the lung fields, especially the vasculature.

Heart size is often unequivocally normal despite severe heart disease, especially coronary artery disease (CAD), and increased afterload (eg, in aortic stenosis). Thus, measuring heart size is mainly helpful for statistical

and serial studies of a patient. Compared with the thorax, the heart is proportionately larger in infants and young children than in adults.

Heart shape abnormalities can be difficult to interpret. Mediastinal tumors and pericardial tumors or defects are occasionally confused with abnormal chamber enlargement.

Chamber size is difficult to estimate on plain film because the chambers overlap and are covered by other structures (eg, pericardium, mediastinal fat, diaphragm). Conventional signs of specific chamber enlargement are frequently difficult to apply and are sometimes misleading. Despite these limitations, chamber size estimation can be worthwhile.

Great vessel configurations and vascular changes in the lungs are extremely important in assessing cardiac function. In cardiac diagnosis, the appearance of the lung fields is often more helpful than the appearance of the heart.

Echocardiography

Echocardiography is an ultrasound technique for diagnosing cardiovascular disorders. It is subdivided into M-mode, two-dimensional (2-D), spectral Doppler, colour Doppler, contrast, and stress echocardiography.

M-mode echocardiography is performed by directing a stationary pulsed ultrasound beam at some portion of the heart. As the beam passes through the heart, structures that border the right and left ventricles, the mitral and aortic valves, and the aorta and left atrium can be seen. Changing the direction of the ultrasound beam allows echoes from the tricuspid and pulmonic valves to be recorded.

2-D (or cross-sectional) echocardiography has become the dominant echocardiographic technique. It uses pulsed, reflected ultrasound to provide spatially correct real time images of the heart, which are recorded on videotape. Four commonly used 2-D echocardiographic views can provide multiple tomographic views of the heart and great vessels and make easy diagnosis of heart valvular diseases, congenital heart diseases, contractile dysfunction of heart in various diseases.

Spectral Doppler echocardiography uses ultrasound to record the velocity, direction, and type of blood flow in the cardiovascular system. The spectral Doppler signal is displayed on a strip chart recorder or videotape. Colour Doppler echocardiography is essentially 2-D Doppler echocardiography with flow encoded in color to show its direction (red is toward and blue is away from the transducer).

Contrast echocardiography is an M-mode or 2-D echocardiographic examination during which contrast medium is injected into the cardiovascular circulation. Almost any liquid contrast medium that is rapidly injected into the cardiovascular space acquires microbubbles in suspension, which produce a cloud of echoes within the cardiac chambers.

Stress echocardiography is performed during or after physical or pharmacologic stress.

Myocardial Perfusion Imaging

Myocardial perfusion imaging can be used for initial evaluation of certain patients with chest pain (i.e., mainly those with pain of uncertain origin) to determine the functional significance of coronary artery stenosis or collateral vessels seen on angiography and to follow up procedures such as bypass surgery, transluminal angioplasty, or thrombolysis. This imaging technique can also be used to estimate prognosis after acute MI because it can reveal the extent of the perfusion abnormality associated with the acute MI and the extent of scarring from previous infarcts. Myocardial perfusion imaging usually uses radioactive thallium (^{201}Tl), which behaves as potassium analog. After intravenous administration, ^{201}Tl rapidly leaves the vascular compartment and enters the cells in proportion to initial blood flow.

Circulatory insufficiency

Definition: Circulatory insufficiency is a pathological condition in which the cardiovascular system fails to supply the necessary amount of blood to the organs and tissues for their adequate function.

This condition arises due to affection of the heart or of the vessels alone, or it may be secondary to general disorders of the cardiovascular system. The clinic of circulatory insufficiency is usually associated with heart failure in which the function of the entire circulatory apparatus soon becomes affected.

Etiology of circulatory insufficiency

Circulatory insufficiency is a polyetiological clinical condition:

- *Infection.* The resulting fever, tachycardia, and hypoxemia and the increased metabolic demands may place a further burden on an overloaded, but compensated, myocardium of a patient with chronic heart disease.

- *Anemia.* In the presence of anemia, the oxygen needs of the metabolizing tissues can be met only by an increase in the cardiac output. Although such an increase in cardiac output can be sustained by a normal heart, a diseased, overloaded, but otherwise compensated heart may be unable to augment sufficiently the volume of blood that it delivers to the periphery.

- *Thyrotoxicosis and pregnancy.* Similar to anemia and fever, thyrotoxicosis and pregnancy are also high cardiac output states. The development or intensification of heart failure in a patient with previously compensated heart disease may actually be one of the first clinical manifestations of hyperthyroidism. Similarly, heart failure not infrequently occurs for the first time during pregnancy in women with rheumatic valvular disease, in whom cardiac compensation may return following delivery.

- *Arrhythmias*. In patients with compensated heart disease, arrhythmias are among the most frequent precipitating causes of heart failure.

- *Rheumatic, viral, and other forms of myocarditis*. Acute rheumatic fever and a variety of other inflammatory or infectious processes affecting the myocardium may precipitate heart failure in patients with or without preexisting heart disease.

- *Infective endocarditis*. The additional valvular damage, anemia, fever, and myocarditis that often occur as a consequence of infective endocarditis may, singly or in concert, frequently precipitate heart failure.

- *Physical, dietary, fluid, environmental, and emotional excesses*. The sudden augmentation of sodium intake as with a large meal, the inappropriate discontinuation of pharmaceuticals to treat heart failure, blood transfusions, physical overexertion, excessive environmental heat or humidity, and emotional crises all may precipitate heart failure in patients with heart disease who were previously compensated.

- *Arterial hypertension*. Rapid elevation of arterial pressure, as may occur in some instances of hypertension of renal origin or upon discontinuation of antihypertensive medication in patients with essential hypertension, may result in cardiac decompensation.

- *Myocardial infarction*. In patients with chronic but compensated ischemic heart disease, a fresh infarct, sometimes otherwise silent clinically, may further impair ventricular function and precipitate.

- *Pulmonary embolism*. Physically inactive patients with low cardiac output are at increased risk of developing thrombi in the veins of the lower extremities or the pelvis. Pulmonary emboli may result in further elevation of pulmonary arterial pressure, which in turn may produce or intensify ventricular failure. In the presence of pulmonary vascular congestion, such emboli also may cause pulmonary infarction.

A systematic search for these precipitating causes should be made in every patient with the new development or recent intensification of circulatory insufficiency.

Pathogenesis of circulatory insufficiency

Hemodynamic changes develop as myocardial contractility decreases and myogenic dilatation of the ventricle develops, diastolic ventricular pressure increases while systolic pressure falls because the ability of the ventricle to strain during diastole sharply diminishes. These factors result in:

- decrease of the *cardiac output* and the *minute blood volume*;

- increase of the *circulating blood volume* because the mass of the circulating blood usually increases proportionally to the degree of circulatory insufficiency. This is favored by retention of sodium chloride and water in decreased renal filtration and increased reabsorption of sodium, and the *increasing number of red blood cells* (hypoxia is attended by intensified hemopoiesis to compensate for the developing insufficiency);

- *rate of blood flow* decreases;
- *blood pressure changes* - venous and capillary pressure increases in the greater circulation; arterial pressure remains normal or diastolic pressure slightly increases and the pulse pressure decreases;
- *abnormal gas exchange* – increased oxygen absorption by the tissues; development of hypoxemia and hypercapnia.

Clinical manifestations of heart failure

Dyspnea arises in upset gas exchange and accumulation of underoxidized metabolites in the blood. It is manifested by unreasonably accelerated and intensified respiration; dyspnea develops at rest or during mild exercise. Generally cardiac dyspnea has mixed character. Development of dyspnea is also provoked by accumulation of liquid in the pleural and the abdominal cavities which interferes with the respiratory excursions of the lungs. During exercise dyspnea markedly increases; it also becomes more pronounced after meals, and in the recumbent position of the patient.

Cardiac asthma is an attack of grave dyspnea generally at the night time due to blood congestion in the lesser circulation.

Cyanosis is due to increasing content of the reduced hemoglobin in blood. The dark blood is seen through the skin to colour it bluish; the colour is especially intense at sites where the skin is thinner (lips, cheeks, ear auricles). Cyanosis in circulatory insufficiency may be due to overfilling of vessels of the lesser circulation with blood and impaired arterialization of blood (the so-called *central cyanosis*). *Peripheral cyanosis*, however, occurs more frequently. It is connected with the slowing down of the blood flow and increased oxygen utilization by the tissues. Since the slowing down of the blood flow is more pronounced in parts of the body remote from the heart, the blue colour appears in the limbs, the ears, and the tip of the nose (*acrocyanosis*). Cyanosis is expressed more if the widening of the venous network in the skin, increased volume of the circulating blood, and its increased hemoglobin content.

Edema is an important sign of circulatory insufficiency. Its development in heart diseases depends on the following factors: (1) increased hydrostatic pressure in the capillaries and slowed blood flow which promote transudation of fluids into tissues; (2) abnormal hormonal regulation of the water-salt metabolism (activation of rennin- angiotensin – aldosterone mechanism and increased secretion of antidiuretic pituitary hormone). These disorders in water-salt metabolism increase the volume of blood plasma, venous and capillary pressure, and intensify transudation of fluid in tissues; (3) during long-standing venous congestion in the great circulation, liver function decreases and the production of albumins becomes disordered to decrease oncotic pressure of blood plasma. Moreover, liver dysfunction

inhibits the decomposition of the antidiuretic hormone and aldosterone in the liver.

Cardiac edema can first be latent. Retention of fluid in the body (sometimes to 5 litres and more) does not immediately cause visible edema but provokes a rapid gain in the patient's weight and his decreased urination. Edema becomes visible in the first instance in the lower part of the body: in the lower limbs (if the patient sits or stands) and in the sacral region (if the patient keeps bed). If circulatory insufficiency is progressive, edema increases and accumulation of the fluid can be in the abdominal cavity (*ascites*), in the pleural cavity (*hydrothorax*), and in the pericardial cavity (*hydropericardium*).

Cardiovascular signs of circulatory insufficiency are closely related to dilation of the heart chambers, and relative insufficiency of atrioventricular valves: widening of the relative and absolute dullness of the heart, weak heart sounds, tachycardia, gallop rhythm sometimes, murmurs, low-wave pulse, dilation of pulmonary veins on chest X-ray.

Practically all other organs are changed in patients with circulatory insufficiency.

Congested lungs is characterized by decrease of respiratory mobility of lungs; congestive bronchitis and congestive pneumonia, and development of pneumosclerosis with cough, harsh respiration, dry or moist rales intense in the postero-inferior parts, crepitation; pulmonary hemorrhage may be.

Congested liver is detected by enlargement of liver. The patient feels heaviness or dull pain in the epigastric and right hypochondrium. Development of liver fibrosis with subsequent hepatic dysfunction and portal hypertension may be revealed by increased density of liver at palpation, slight jaundice, ascites, dilation of anterior abdominal wall veins, changes in liver biochemical tests (increase of serum bilirubin, AlAT, AsAT, and others).

Congested kidneys is characterized by decrease of the daily urine, increase of its specific gravity; small amount of protein, red blood cells, and casts may be in the urinalysis.

Gastro-intestinal signs are related to congestive gastritis and intestinal dysfunction (poor appetite, nausea, vomiting, meteorism and constipation); malnutrition (cardiac cachexia) may develop.

Dysfunction of the central nervous system is characterized by rapid fatigue, decreased work capacity and mental power, high irritability, deranged sleep, and depression.

The clinical signs and changes in various organs of the body depend on the degree and duration of circulatory insufficiency, and on the particular side of the heart that is affected (right or left).

Classification of circulatory insufficiency

1. Acute circulatory insufficiency

- 1.1. acute heart failure
 - 1.1.1. acute left ventricular (LV) failure
 - 1.1.2. acute right ventricular (RV) failure
 - 1.1.3. total heart failure
- 1.2. acute vascular insufficiency
 - 1.2.1. syncope
 - 1.2.3. collapse
 - 1.2.3. shock
- 1.3. acute cardiovascular insufficiency
- 2. Chronic circulatory insufficiency -
 - 2.1. *According to stage:*
 - H_I (latent circulatory insufficiency),
 - H_{II A} (evident compensated stage),
 - H_{II B} (decompensated stage),
 - H_{III} (dystrophic stage);
 - 2.2. *According to functional class:*
 - Class I –IV.

Strazhesko and Vasilenko (1935) provided their *classification of circulatory insufficiency*. According to this classification, the following forms of circulatory insufficiency are distinguished.

1. Acute circulatory insufficiency. It can depend on acute heart failure (either side) or failure of any of its chambers, (left or right ventricle, left atrium), or else it may be caused by acute vascular insufficiency (collapse or shock).

2. Chronic circulatory insufficiency. This can be divided into three stages.

The first stage (initial) is latent circulatory insufficiency, which is only manifested during physical exercise, while at rest the hemodynamics and functions of the organs are normal; the work capacity is decreased.

The second stage is characterized by a pronounced prolonged circulatory insufficiency, hemodynamic disorders (congestion in the lesser or greater circulation) and dysfunction of organs at rest; the work capacity of patients is markedly decreased. Two periods are distinguished at this stage: (1) the initial period, with mild hemodynamic disorders; and (2) the final period characterized by grave hemodynamic disorders.

The third stage is the terminal or dystrophic stage of circulatory insufficiency. In addition to grave hemodynamic disorders, irreversible morphological changes develop in the organs along with persistent metabolic disorders and disability.

Functional class of chronic heart failure according to NYHA (New York Heart association):

Class I - no limitation of physical activity, no symptoms with ordinary exertion;

Class II - slight limitation of physical activity, ordinary activity causes symptoms;

Class III - marked limitation of physical activity, less than ordinary activity causes symptoms, asymptomatic at rest;

Class IV - inability to carry out any physical activity without discomfort, symptoms at rest.

Clinical picture of stages of chronic circulatory insufficiency

The severity of clinical signs in heart failure depends on the stage of circulatory disorders (see classification of circulatory insufficiency).

In the *initial*, latent *stage* of circulatory insufficiency, the patient's work capacity decreases, physical exertion provokes dyspnea, palpitation, and oxygen debt increases to a greater degree than that in healthy subjects. These symptoms subside at rest.

The *second stage* of circulatory insufficiency is characterized by hemodynamic disorders. In the initial period (*stage A, or evident compensated stage*), the patient develops dyspnea during normal exercise (e.g. in walking), and his work capacity decreases markedly. Examination reveals moderate cyanosis and edema of legs. Congestion in the lungs is not pronounced: the respiratory movements of the chest and excursions of the lower lung borders are decreased; the vital capacity of the lungs is diminished. The liver is mildly enlarged. The venous pressure increases. *Stage B (decompensated stage)* is characterized by marked congestion in the greater and lesser circulation. Dyspnea develops even at rest which is intensified during slight physical exertion. Patients are fully disabled. Typical signs of heart failure (pronounced cyanosis, edema, ascites, dysfunction of various organs) are revealed.

The *third stage* is characterized by pronounced metabolic disorders caused by a prolonged circulatory insufficiency. The patient would be extremely asthenic, with irreversible morphological changes in the lungs, liver, and kidneys. The combination of metabolic disorders in circulatory insufficiency was called by Vasilenko "circulatory dystrophy".

Acute heart failure

Definition: Acute heart failure is a marked drop in the heart output and filling of the arterial system

Cardiac etiology of circulatory insufficiency is confirmed by changes in the heart proper (valve incompetence or arrhythmia, broadening of the heart borders, changes in the heart sounds and gallop rhythm).

Clinical manifestations of the acute heart failure are dyspnea, pallidness and cyanosis of the skin, cold limbs, swelling of the neck veins, changes in the heart sounds (weakness of sounds, tachy- or bradycardia, arrhythmia) and

gallop rhythm, small or thready pulse, decreased arterial pressure, rales in the lungs, enlargement of the liver, and syncopes due to brain ischemia.

Acute heart failure may depend not on the weakening of the entire myocardium but on a pronounced decrease in contractile capacity of the myocardium of one of the heart chambers: left ventricle or right ventricle.

Syndrome of acute left-ventricular heart failure

Etiology: Acute left-ventricular failure is caused by diseases in which the left ventricle is mostly affected (essential hypertension, aortic incompetence, coronary artery disease, myocardial infarction)

Pathophysiological basis of this syndrome is acute congestion in the lungs and upset gas exchange.

Clinical manifestations may be in two variants - cardiac asthma and pulmonary edema.

Cardiac asthma is attacks of severe dyspnea. Attacks of cardiac asthma can be provoked by physical exercise and nervous strain. Attacks usually occur during night sleep. This can be explained by an increased vagus tone during sleep, which causes narrowing of the coronary arteries and thus impairs nutrition of the myocardium. Blood supply to the respiratory centre decreases during sleep and its excitability diminishes. The lesser circulation becomes overfilled with blood because during a sharply decreased contractility of the left-ventricular myocardium, the right ventricle continues working intensely to pump the blood from the greater circulation to the lesser one.

Cardiac asthma is characterized by feeling of suffocation (asphyxia) and marked weakness, pallid and cyanotic skin; cold sweat appears. The patient usually takes forced position—sitting with his legs hanging down from the bed. The patient begins coughing and expectorates tenacious sputum. Moist and dry rales are heard over the lung. The heart sounds are weakened at the apex and accent over the pulmonary artery. Tachycardia and small frequent pulse are characteristic of the cardiac asthma attack.

Pulmonary edema develops if congestion in the lesser circulation progresses, the blood plasma and blood corpuscles pass from the overfilled pulmonary capillaries to the alveoli and accumulate in the respiratory ducts.

Feeling of suffocation and cough intensify more than in cardiac asthma. Respiration becomes rattling and bubbling; ample foaming sputum with traces of blood (pink or red) is expectorated. Many moist rales of various calibers are heard over the lungs (over their entire surface). Auscultation of the heart often reveals tachycardia and gallop rhythm. Pulse is markedly accelerated and thready. Edema of the lungs requires prompt and energetic measures to be taken to prevent possible death.

X-ray examination shows enlargement of left ventricle and atrium, distention of pulmonary veins (due to elevated pulmonary venous pressure),

in the stage of interstitial pulmonary edema – symptom of “peribronchial cuffing”, in the stage of alveolar pulmonary edema symptom of “bat wing”.

Syndrome of acute right-ventricular failure

Etiology: Causes of acute right-ventricular failure may be pulmonary artery embolism (into which the thrombus is carried from veins of the greater circulation or from the right chambers of the heart), tricuspid regurgitation, mitral stenosis, primary pulmonary hypertension, pulmonary artery valves stenosis.

Pathophysiological basis of this syndrome: is a pronounced venous congestion in the greater circulation.

Clinical manifestations. Complaints are fatigue, dyspnea, awareness of fullness in the neck; swelling in the abdomen, with occasional tenderness in the right upper quadrant (over the liver). Patients may feel pressure and pain in the heart. Inspection of the patient reveals cyanosis and cold sweat, pitting edema of the lowest parts of the body, neck veins swelling, ascites (in advanced stages). Abnormally large waves of the external jugular pulse, positive venous pulse, epigastric pulsation of the right-ventricle may be visible. Systolic murmur of tricuspid regurgitation along the left sternal border and right-ventricle gallop rhythm may be heard in advanced stages. Percussion and palpation detects liver enlargement and tenderness.

Chronic heart failure

Like acute heart failure, *chronic heart failure* may first depend mostly on failure of one of the heart chambers. The syndrome of *chronic left-ventricular failure* develops in many diseases attended by affections of the left ventricle (aortic incompetence, mitral failure, arterial hypertension, coronary insufficiency due to dystrophy of the left-ventricular muscle, etc.)- The syndrome is characterized by persistent blood congestion in the lesser circulation. The vital lung capacity decreases, the rate of the blood flow through the vessels of the lesser circulation is slowed, the gas exchange is upset, and dyspnea, cyanosis, and congestive bronchitis develop. Blood congestion in the lesser circulation is even more pronounced *in chronic left-atrial failure* in patients with mitral stenosis. It is manifested by dyspnea, cyanosis, cough, and hemoptysis. Prolonged venous congestion in the lesser circulation stimulates growth of connective tissue in the lungs and sclerosis of the vessels. Another, pulmonary barrier is thus produced to become an obstacle to normal passage of blood through the vessels of the lesser circulation. Pressure in the pulmonary artery elevates to increase the load on the right ventricle, which later becomes the cause of its failure.

The syndrome of chronic right-ventricular failure arises in mitral heart diseases, lung emphysema, pneumosclerosis, tricuspid incompetence, and in certain congenital heart defects. It is characterized by a marked venous congestion in the greater circulation. The patient is cyanotic, the skin

sometimes becomes icterocyanotic. The peripheral veins, especially the neck veins, become swollen, the venous pressure increases, edema and ascites develop, and the liver is enlarged.

Primary dysfunction of one of the heart chambers may eventually cause total heart failure, which is characterized by venous congestion in both the greater and lesser circulation. Moreover, chronic heart failure attended by dysfunction of the entire circulatory system arises in diseases affecting the myocardium (myocarditis, intoxication, ischemic heart disease, etc.).

Syndrome of acute vascular insufficiency

Definition: Acute vascular insufficiency is acute condition when the equilibrium between the capacity of the vessels and the volume of the circulating blood is upset.

Pathophysiological bases of this syndrome are diminished volume of blood is diminished or drop of the vascular tone. Diminished vascular tone disturbs normal distribution of blood in the body: the amount of deposited blood increases, especially in the vessels of the abdominal organs, whereas the volume of circulating blood decreases; the decreased volume of circulating blood weakens venous blood flow to the heart; the stroke volume of blood decreases and arterial and venous pressure diminish as well.

Causes:

- (1) reflex disorders in the vasomotor innervation of the injured vessels, irritation of serous membranes, myocardial infarction, embolism of the pulmonary artery, heart arrhythmias, etc;
- (2) disordered vasomotor innervation of cerebral etiology (hypercapnia, acute hypoxia, psychogenic reactions);
- (3) vascular paresis of toxic origin which occurs in many infections and toxicosis;
- (4) diminished blood volume - loss of blood, dehydration of the body.

Clinical manifestations of the acute vascular insufficiency depends on the character of etiological factors and duration of their effect, and on the particular side of circulatory mechanisms that are affected. There are three basic clinical variants of the acute vascular insufficiency: *syncope, collapse, and shock*.

Syncope

Definition: Syncope is an abrupt and transient loss of consciousness due to insufficient blood supply to the brain.

Predisposing factors are young asthenic subjects, mostly women; fatigue, excitement, fright, standing position in a non-ventilated room, decreased cardiac output, cardiac arrhythmias and conduction disorders, anemia, infectious diseases, intoxications, endocrine diseases (Addison's disease), neurologic diseases (cerebral atherosclerosis, diabetic neuropathy, syringomyelia, etc), intake of hypotensive medications (β -blockers, including

ophthalmic β -blockers, Ca blockers, clonidine), and other drugs (digitalis), that may also cause bradyarrhythmias. Sometimes exertional (effort) syncope, swallowing syncope, postural syncope, and hyperventilation syncope may be.

The most common pathophysiological basis for syncope is an acute decrease in cerebral blood flow (with resultant cerebral hypoxemia) secondary to decreased cardiac output. Syncope may be connected with upset central nervous regulation of the vascular tone, as a result of which blood is accumulated in the vessels of the abdominal cavity.

Clinical picture is characterized by abrupt and transient loss of consciousness particularly when patient suddenly changes from lying to the upright position (*orthostatic collapse*). The patient may feel a faintness, light-headedness, dizziness, confusion, or visual blurring during presyncope as the evidence of a mild to moderate reduction in cerebral blood flow. Objective examination of the patient reveals cold sweat, pallid skin, cold limbs; small or thready pulse, drop of arterial blood pressure (typically > 60/40 mm Hg). Clinical manifestations of syncope last no more than 5-10 minutes and reverse spontaneously particularly at the horizontal position of the patient.

Collapse

Definition: Collapse is a sudden loss of effective blood flow due to cardiac and/or peripheral vascular factors which may reverse spontaneously or only with medical interventions.

Causes are vasodepressor syncope, transient severe bradycardia, myocardial infarction, embolism of the pulmonary artery or cardiac arrest, infections, toxicosis; diminished blood volume (loss of blood, dehydration of the body), endocrine diseases (Addison's disease).

Pathophysiology includes decreased volume of circulating blood and reduced arterial pressure that cause ischemia of the brain and internal organs.

Clinical picture: The patient feels a faintness, light-headedness, dizziness, confusion, or visual blurring. Syncope may be at the sudden onset of the collapse particularly when patient suddenly changes from lying to the upright position. Objective examination of the patient reveals pallid skin, cold sweat, cold limbs, accelerated and superficial respiration, small and sometimes thready pulse, and drop of arterial pressure BP (typically < 60-70/40 mm Hg). Clinical manifestations of collapse may last 5-10 minutes up to hours.

Shock

Definition: Shock is the cyclic clinical syndrome in which blood flow is inadequate to sustain life because of insufficient cardiac output or insufficient perfusion of internal organs associated with arterial hypotension and oliguria.

Etiology and pathogenesis. Shock may be due to hypovolemia, vasodilation, or cardiogenic causes (poor cardiac output) or a combination. The fundamental defect in shock is reduced perfusion of vital tissues due (usually) to hypotension, so that oxygen delivery or uptake is inadequate for aerobic metabolism, resulting in a shift to anaerobic respiration with increased production and accumulation of lactic acid. When shock persists, impaired organ function is followed by irreversible cell damage and death. The degree of systemic hypotension necessary to cause shock varies and often is related to preexisting vascular disease. Thus, a modest degree of hypotension that is tolerated well by a young, relatively healthy person might result in severe cerebral, cardiac, or renal dysfunction in a patient who has significant arteriosclerosis.

Classification of shock

I. According to etiology:

- exogenous pain shock - traumatic (wound), electroconvulsive, burn shock;
- endogenous pain shock – cardiogenic, nephrogenic, abdominal shock;
- exogenous-endogenous painless shock – anaphylactic, bacter(i)emic (septic, septicemic), hemorrhagic, hypovolemic (oligemic), posttransfusion, psychogenic, toxic shock.

II. According to stage: erectile, torpid stage of shock.

III. According to degree of severity: mild, moderate, severe shock.

Clinical picture

Symptoms and signs of shock may be due to shock itself or to the underlying disease process. Clinical picture of shock depends on stage and degree of severity.

Erectile stage of shock is characterized with transient clinic of psychomotor agitation, elevation of blood stage, tachycardia, tachypnea in first minutes or hours immediately after trauma, burn, etc.

Torpid stage of shock is characterized with mentation disorders, lethargy, confusion, and somnolence are common. The hands and feet are cold, moist, and often cyanotic and pale. Capillary filling time is prolonged, and, in extreme cases, a bluish reticular pattern may appear over large areas. The pulse is weak and rapid unless heart block or terminal bradycardia is present; sometimes, only femoral or carotid pulses can be felt. Tachypnea and hyperventilation are present, but apnea may be a terminal event when the respiratory center fails due to inadequate cerebral perfusion. Blood pressure taken by cuff tends to be low (<90 mm Hg systolic) or unobtainable, but direct measurement by intra-arterial cannula often gives significantly higher values. Pulmonary complications that often coexist or develop in patients with shock must not be overlooked. This stage may last hours up to days.

Mild shock is characterized by cool extremities, diaphoresis, collapsed veins, anxiety or stupor, body temperature subnormal, systolic blood pressure - 90-100 mm Hg, diastolic blood pressure – not less than 60 mm Hg.

Moderate shock is characterized by cool extremities, diaphoresis, collapsed veins, tachycardia, tachypnea, oliguria <30 ml/hour, delayed reflexes, lethargy, systolic blood pressure - 80-90 mm Hg, diastolic blood pressure – near to 50 mm Hg.

Severe shock is characterized by cool extremities, diaphoresis, collapsed veins, hemodynamic instability, marked tachycardia, hypotension - systolic - <80 mm Hg, diastolic BP - <30 mm Hg, oliguria or anuria, mental status deterioration (coma).

Prognosis. Untreated shock is usually fatal. Even when treated, mortality from cardiogenic shock after massive myocardial infarction and from septic shock is high. Prognosis depends on the cause, preexisting or complicating illness, time between onset and diagnosis, and adequacy of therapy.

Cardiogenic shock

Definition: This is a form of shock caused by relative or absolute reduction in cardiac output due to left ventricular failure.

Causes of cardiogenic shock are myocardial ischemia or myocardial infarction, myocarditis, acute mitral or aortic regurgitation, ruptured interventricular septum, pulmonary embolism, tension pneumothorax, pericardial tamponade, atrial tumor or clot, severe tachycardia or bradycardia.

This severest clinical expression of left ventricular failure is associated with extensive damage to the left ventricular myocardium in up to 20 per cent of patients with acute myocardial infarction. Risk factors for the in-hospital development of shock include advanced age, a depressed left ventricle ejection fraction on admission, a large infarct, previous myocardial infarction and a history of diabetes mellitus. In recent years, efforts to reduce infarct size and prompt treatment appear to have reduced the incidence of cardiogenic shock from 20% to about 7%. Typically, patients who develop cardiogenic shock have severe multivessel coronary artery disease.

Clinical picture. Cardiogenic shock should be considered to be a form of severe left ventricle failure. This syndrome is characterized by marked hypotension with systolic arterial pressure of <80 mmHg and a markedly reduced cardiac output in the face of an elevated left ventricle filling. Cardiogenic shock is characterized by mental confusion, diaphoresis, and cold extremities; tachycardia (gallop rhythm may be); marked hypotension with systolic arterial pressure of <80 mm Hg, reduced urine output (oliguria or anuria), pulmonary congestion (cardiac asthma, pulmonary edema), has a mortality of > 65%. It is most often associated with massive anterior

myocardial infarction and > 50% loss of left ventricle functioning myocardium.

Clinical syndromes of arrhythmias

Bradyarrhythmias arise through abnormalities of intrinsic automatic behavior or conduction, including sinus bradycardia, sinoatrial and atrio-ventricular blocks. Tachyarrhythmias may arise by altered automaticity, reentry, or triggered automaticity, which have been identified electrophysiologically but can rarely be differentiated clinically. Most clinically significant tachyarrhythmias are probably due to reentry. Tachyarrhythmias include sinus tachycardia, extrasystoles, paroxysmal tachycardia, atrial (and ventricular) flutter and fibrillation.

Common clinical symptoms of arrhythmias

Palpitations (awareness of the heartbeat) due to an arrhythmia may be accompanied by weakness, dyspnea, or light-headedness. Atrial or ventricular extrasystoles are often described as skipped beats, whereas atrial fibrillation is identified as an irregularity. Supraventricular or ventricular tachycardia is most often perceived as being rapid and regular and of sudden onset and termination. Onset of atrial tachyarrhythmia is often followed by the need to urinate because of increased production of atrial natriuretic factor.

Hemodynamic disorders are manifested by dizziness, syncope, arterial hypotension, dyspnea, acute heart failure.

Changes of rate and regularity of cardiac rhythm are detected by pulse examination, heart auscultation, and ECG.

Clinical manifestations of complete heart block:

- bradycardia (30-40 per min), syncope, dizziness, acute heart failure, postural hypotension, and breathlessness;

- the heart sounds are dulled but a loud first sound (“*gun sound*”, or “*pistol-shot*” sound according to Strazhesko) may be heard periodically. It occurs due to coincidence of the atrial and ventricular contractions;

- *Morgagni-Adams-Stokes syndrome* (in time significant slow down of heart rate) – loss of consciousness, falls, general epileptiform convulsions, deep respiration, pale skin, the pulse is very slow or even impalpable. When the ventricular automaticity restores, the patient regains his consciousness and all other signs of the syndrome disappear. If automaticity is not restored for a time, fatal outcome is possible. Ventricular tachycardia or fibrillation, or severe bradycardias, or asystole also may cause these symptoms in the form of a Stokes-Adams attack.

Diagnosis. Whereas the history and physical examination should give a working diagnosis, the ECG remains the major diagnostic procedure.

The standard 12-lead ECG is crucial for the characterization and diagnosis of the various sustained tachycardias. However, it provides only a brief sample of cardiac rhythm, particularly when recorded by simultaneous multichannel recorders.

Ambulatory ECG monitoring is the most powerful method of capturing arrhythmic events, and its value is enhanced by keeping a diary of associated symptoms. ECG recorders are of many types, eg, those that log a continuous 24 hours (Holter 24 h) or those activated by the patient or by automatic detection of an arrhythmic episode. Solid-state recorders can eliminate the vagaries of mechanical tape transport systems. Ambulatory ECG monitoring is less useful when arrhythmias are infrequent. Patients with suspected life-threatening rhythm disturbances should be hospitalized for monitoring to avoid a fatal out-of-hospital event.

Acute rheumatic fever (Rheumatism)

Definition: Acute rheumatic fever (rheumatism, I00-I01 according to ISD-X) is a general infectious and allergic disease in which connective tissues, mainly of the cardiovascular system, are affected by inflammation; joints, serous membranes, internal organs, and the central nervous system are often involved.

This is a nonsuppurative acute inflammatory complication of group A streptococcal infection. Rheumatism is a systemic disease of connective tissue, i.e. a disease characterized by a systemic and progressive derangement of connective tissue. Rheumatism was classified as an independent disease with typical affections not only of the joints but mainly of the heart in 1835 by French physician Bouillaud and in 1836 by the Russian physician Sokolsky. Until that time rheumatism had been considered a disease of joints.

Etiology. Beta-hemolytic streptococcus of group A is believed to be the causative agent of rheumatism. This conjecture is confirmed by (1) frequent incidence of rheumatism following streptococcal infection; (2) increased antibody titers to various antigens and enzymes of the streptococcus in the blood of rheumatic patients; (3) successful prophylaxis of rheumatism by antibacterial preparations.

Pathogenesis. Pathogenesis of acute rheumatic fever is complicated and includes three important phases: (1) acute, mainly oro-pharyngeal, infection by the group A streptococcus; (2) toxic effect of streptococcal

extracellular products on the host connective tissues (; (3) an abnormal or dysfunctional immune response to one or more somatic or extracellular antigens produced by all (or perhaps only by some) group A streptococci.

At the present time, the development of the disease is described as follows. Most persons affected by streptococcus develop stable immunity. This immunity does not develop in 2-3 per cent of the affected subjects due to weakness of their defense mechanisms and they become sensitized by the streptococcus antigen. In these conditions the infection re-enters the body to cause a hyperergic response in connective tissues; clinical signs of the disease thus develop. Autoimmune processes are very important in the onset of rheumatism. The affected connective tissue acquires antigenic properties; auto-antigens (secondary antigens) cause formation of aggressive auto-antibodies. They affect not only the connective tissue that has already been affected by the primary antigen but also intact tissue to aggravate the pathology. Re-infection, cooling, and overstrain promote formation of new auto-antigens and auto-antibodies to strengthen the pathological reaction of the upset immunity and to provide conditions for the recurring progressive course of the disease.

Pathological anatomy. Four phases of derangement of connective tissue are differentiated in rheumatism: (1) mucoid swelling; (2) fibrinoid changes; (3) granulomatosis; and (4) sclerosis.

Classification of acute rheumatic fever (Minsk-2003)

1. Clinical variants:
 - acute rheumatic fever,
 - recurrent acute rheumatic fever.
2. Clinical manifestations:
 - 1) basic clinical manifestations - carditis, arthritis, chorea, rheumatic nodules, and erythema annulare (erythema marginatum);
 - 2) additional clinical manifestations – arthralgia, (poly)serositis, abdominal syndrome.
3. Degree of activity:
 - 1) minimal activity,
 - 2) moderate activity,
 - 3) maximal (high) activity.
4. Clinical outcome:
 - recovery;
 - chronic rheumatic disease of heart: without heart valvular defect; heart valvular defect.
5. Functional class of chronic heart failure according to NYHA (or degree of chronic heart insufficiency).

Clinical picture of acute rheumatic fever

Acute rheumatic fever affects children, adolescents, and young adults (between ages 4 and 20). The disease develops in 2-6 weeks after acute streptococcal pharyngeal infection (tonsillitis, pharyngitis or scarlet fever).

The typical onset of the disease is subfebrile (less frequently febrile) temperature, weakness, and sweating during 1-3 weeks. Simultaneously (or several days later) patient feels pain in the joints, palpitation and intermissions in the work of the heart, the feeling of heaviness or pain in the heart, and dyspnea.

The major manifestations of the acute rheumatic fever are *migratory polyarthritis, chorea, carditis, subcutaneous nodules, and erythema marginatum*. These can appear alone or in combination and produce many clinical patterns. Cutaneous and subcutaneous features are uncommon and almost never occur alone, usually developing in a patient who already has arthritis, chorea, or carditis.

Rheumatic carditis

The rheumatic carditis is a pancarditis involving myocarditis (~100%), and endocarditis (~60%), pericarditis (~20%).

Rheumatic myocarditis

Rheumatic myocarditis is characterized by dyspnea, the feeling of heaviness and pain in the heart, palpitation, and intermissions in the heart work.. Percussion detects enlargement of the heart. Auscultation reveals decreased heart sounds (especially the first sound); gallop rhythms develop in severe affection of the myocardium. A soft systolic murmur can be heard at the heart apex. It is associated with relative incompetence of the valve or affection of the papillary muscles. The pulse is small and soft; tachycardia and arrhythmia are frequent. Blood arterial pressure is usually decreased. A prolonged PR interval may be present on ECG as well. Circulatory insufficiency rapidly develops in grave diffuse myocarditis. Myocardial cardiosclerosis develops in benign outcome of the disease.

Rheumatic endocarditis.

Rheumatic myocarditis usually concurs with rheumatic endocarditis (*rheumocarditis*). The mitral valve is mostly affected in endocarditis. Next in incidence follows the aortic valve; the tricuspid valve is affected still less frequently.

Early endocarditis are not pronounced (symptoms of myocarditis prevail). At earlier stages of endocarditis *systolic murmurs* become coarser than in myocarditis; the murmur becomes louder after exercise; in some cases it becomes "musical". *Diastolic murmur* may be heard as well. It is probably explained by deposition of thrombotic mass on the valve cusps which produces turbulence in the blood flow as it passes from the atrium to the

ventricle. These thrombotic deposits on the valves can leave their seat and become the cause of *embolism or infarctions* in various organs (e.g. the kidneys or the spleen). If early attacks of rheumatic endocarditis are treated timely, development of the valvular heart disease may be prevented.

The introduction of echocardiography has assisted in the identification of subtle abnormalities of the mitral valve, and these may be present in an additional 20% of patients who do not have an audible heart murmur. The mitral valve is involved most frequently, followed by the aortic valve. However, isolated aortic valve disease as a consequence of acute rheumatic fever is quite rare. In patients with aortic valve disease due to rheumatic fever, the mitral valve is almost always simultaneously affected.

Rheumatic pericarditis

Rheumatic pericarditis may be dry (fibrinous) or exudative.

Rheumatic pericarditis may present with chest pain, dyspnea, fever, pericardial rub friction murmur, ECG changes, or radiologic changes or may be discovered incidentally in the course of a systemic illness. Dull or sharp precordial or substernal pain may radiate to the neck, trapezius ridge (especially the left), or shoulders. Pain varies from mild to severe and is usually aggravated by thoracic motion, cough, and respiration; it may be relieved by sitting up and leaning forward. Pericardial pain can usually be distinguished from ischemic coronary pain, which is not aggravated by thoracic motion or the recumbent position. Tachypnea and nonproductive cough may be present; fever, chills, and weakness are common.

The most important physical finding is a triphasic or a systolic and diastolic precordial friction rub. However, it is often intermittent and evanescent or may be present only in systole or, less frequently, only in diastole. Considerable pericardial fluid may muffle heart sounds, increase the area of absolute cardiac dullness, and change the size and shape of the cardiac silhouette (trapezium or triangle configuration of the heart may be).

Cardiac tamponade is rare complication of the rheumatic pericarditis. Clinical findings of the cardiac tamponade are tachycardia, together with dyspnea and orthopnea and elevated systemic and pulmonary venous pressures. Severe cardiac tamponade is nearly always accompanied by an accentuated decline in systemic systolic BP on inspiration (*pulsus paradoxus*). A decline of > 10 mm Hg is usually significant. In advanced cases, the pulse may disappear on inspiration.

Although rheumatic pericarditis can cause a serous effusion, fibrin deposits, and even pericardial calcification, it does not lead to constrictive pericarditis.

Rheumatic migratory polyarthritis

Migratory polyarthritis is present in as many as 75% cases of acute rheumatic fever. Migratory polyarthritis is characterized clinically by:

- symmetrical arthritis of large joints (ankles, wrists, knees, elbows). It usually does not affect the small joints of the hands or feet and seldom involves the hip joints;

- migrating character of pain; pain disappears in one joint and develops in others;

- extremely painful, hyperemia, hyperthermia of joints; joints become swollen, sometimes with effusion;

- polyarthritis is usually benign, all clinical findings are completely reversible.

Acute inflammation subsides in a few days, although dull pain (*arthralgia*) in the joints may persist for a long time. The difference between arthralgia (subjective joint pain) and arthritis (joint pain and swelling) must be understood.

Since salicylates and other anti-inflammatory drugs usually cause prompt resolution of joint symptoms, it is important that the clinician *not* prescribe these medications until it is determined whether the arthritis is migratory.

Sydenham's chorea

Sydenham's chorea (*Rheumatic Chorea; St. Vitus' Dance*) - a CNS disease, often of insidious onset but of finite duration, characterized by involuntary, purposeless, nonrepetitive movements and subsiding without neurologic residua.

Sydenham's chorea occurs in fewer than 10% of patients with rheumatic fever. This is due to either rheumatic vasculitis (attended by small hemorrhages or thrombosis of cerebral vessels) or inflammation of the brain and the spinal cord. Children (as a rule patients younger than 15 years) would develop encephalitis with predominant localization in the subcortical nodes (chorea minor). It is manifested by emotional lability and hyperkinesia (abnormal movements of the extremities, the trunk, and the facial muscles).

The latent period between the onset of the initiating streptococcal infection and the onset of Sydenham's chorea may be as long as several months. Many patients who appear to have only chorea may present several decades later with evidence of typical rheumatic valvular disease. There is no definitive laboratory test for establishing a diagnosis of Sydenham's chorea, and the diagnosis is one of exclusion.

Skin signs and subcutaneous nodules

Subcutaneous nodules and *erythema marginatum* are rare major manifestations of acute rheumatic fever, usually present in fewer than 10% of cases. Subcutaneous nodules are found over extensor surfaces of joints, are seen most often in patients with long-standing rheumatic heart disease, and are extremely rare in patients experiencing an initial attack. Subcutaneous

nodules are firm, painless formations varying in size from a millet grain to a bean, can be palpated, mostly on the extensor surfaces of the joints, along the course of tendons, and in the occipital region.

Erythema marginatum (*annular erythema*) is an uncommon manifestation. It is an evanescent macular eruption with rounded borders (pale-pink painless rings not elevating over the surrounding skin). The skin of the chest, neck, abdomen, and the face is affected by annular erythema.

In other cases *nodular erythema* develops: circumscribed indurated dark red foci on the skin varying in size from a pea to a plum; they are usually found on the lower limbs. If permeability of capillaries is increased, small *hemorrhages into the skin* sometimes occur.

Other clinical manifestations of acute rheumatic fever are very rare and usually completely reversible.

Lungs are affected in very rare cases. This is specific rheumatic pneumonia. Dry pleurisy or pleurisy with effusion are more common. Heart affections may be the only clinical manifestation of rheumatism.

The alimentary system is rarely affected. Acute pain in the abdomen (the abdominal syndrome) associated with rheumatic peritonitis (mostly in children) sometimes occurs. The liver is affected in certain cases (rheumatic hepatitis).

Affections of the kidneys are also common. Protein or red blood cells can be found in the urine due to affections of the renal vessels and (less frequently) developing nephritis.

Laboratory and instrumental tests in acute rheumatic fever

Common blood analysis shows moderate leucocytosis (with a shift to the left) in acute rheumatic fever; eosinophilia, mono- and lymphocytosis may further develop. ESR is always increased (to 50-70 mm/h in grave cases).

Biochemical tests include increase of C-reactive protein (CRP), α 2-globulin and γ -globulin fractions, fibrinogen. The level of mucoproteins increases and it can be revealed by a diphenylamine test (increase of seromuroid and sialic acids).

Microbiology study detects group A streptococci positive throat culture (throat swab or rapid antigen detection test).

Immunological tests discovers increased titers of group A streptococcal antibodies (anti-streptolysin O, anti-deoxyribonuclease B, anti-hyaluronidase) in blood serum.

ECG often shows atrioventricular block of the first and second degree, detected by prolonged P-R interval (~30%); extrasystoles, decreased voltage. Defective nutrition of the myocardium due to its inflammation can change the *T* wave and lower the *S-T* segment.

ECG in acute pericarditis may show abnormalities: ST segments in two or three of the standard leads become elevated but subsequently return to the baseline. Unlike in myocardial infarction, ST segments do not show reciprocal depression (except in leads aVR and V1), and there are no pathologic Q waves. Depression of the PR segment may be found. After several days or > 1 week, T waves may become flattened and then inverted throughout the ECG, T-wave inversion occurs after the ST segment has returned to baseline and thus differs from that of acute ischemia or myocardial infarction.

Phonocardiogram (PCG) show specific rheumocarditic changes in heart sounds, and the appearance of murmurs.

Echocardiography detects abnormalities of the mitral (and other) valves, effusion in pericardium.

Diagnosis criteria of rheumatic fever

There is no specific laboratory test that can establish a diagnosis of rheumatic fever. The diagnosis, therefore, is a clinical one but requires supporting evidence from the clinical microbiology and clinical immunology laboratories. Because of the variety of signs and symptoms associated with the rheumatic fever syndrome, in 1944 Jones first proposed criteria to assist the clinician in standardizing the diagnosis of rheumatic fever. The most recent modification of the *Jones criteria* (Updated Jones Criteria) was published in 1992 by a Special Writing Group of the American Heart Association.

There are five criteria termed *major* because they are most commonly found in patients with rheumatic fever: *carditis, migratory polyarthritis, Sydenham's chorea, subcutaneous nodules, and erythema marginatum*.

The *minor criteria* are nonspecific and may be present in many clinical conditions: clinical – fever, arthralgia; laboratory – elevated acute phase reactants (CRP, α 2-globulin and γ -globulin fractions, fibrinogen, seromucoid and sialic acids), and prolonged P-R intervals.

To fulfill the Jones criteria, either two major criteria, or one major criterion and two minor criteria, plus evidence of an antecedent streptococcal infection are required. The latter may be provided by recovery of the organism on positive culture of group A streptococci or by evidence of an immune response to one of the commonly measured group A streptococcal antibodies (e.g., anti-streptolysin O, anti-deoxyribonuclease B, anti-hyaluronidase). Since the accurate diagnosis of rheumatic fever has future medical and social implications, the clinician is obligated to evaluate any patient completely until the suspected diagnosis is either established or excluded.

Course of rheumatism

Active rheumatic process continues for three to six months; in some cases it may be longer. Depending on the strength of the clinical symptoms and the character of the disease course, three degrees of rheumatic activity are distinguished: (1) maximum active (acute) process with continuous relapses; (2) moderately active or subacute; and (3) rheumatism with minimal activity (flaccid or latent). If the clinical symptoms of the disease are absent and no signs of active rheumatism are revealed by laboratory testing, rheumatism is considered inactive.

Rheumatism is characterized by relapses (recurring attacks) which are provoked by infection, overcooling, and physical overstrain. The clinical symptoms of relapses resemble the primary attack of the disease, but the signs of affection of the joints or serous membranes are less pronounced. Symptoms of heart affection prevail.

Prognosis depends on the severity of the initial carditis. Patients with severe carditis during the acute episode may be left with residual heart disease that is often worsened by the rheumatic recurrences to which they are particularly susceptible. Murmurs eventually disappear in about 1/2 of patients whose acute episodes were manifested by mild carditis without major cardiac enlargement or decompensation. Healing of the rheumatic valvulitis may cause fibrous thickening and adhesion, resulting in the most serious complication of rheumatic fever, i.e., valvular stenosis and/or regurgitation. All other manifestations of the rheumatic fever subside without residual effects.

Infective (bacterial, septic) endocarditis

Definition: Infective endocarditis (I33 according to ICD-X) is a severe general infectious disease characterized by inflammation of the endocardium and ulceration of the heart valves in the presence of sepsis.

Infective endocarditis is a microbial infections of the endocardium, characterized by fever, heart murmurs, petechiae, anemia, embolic phenomena, and endocardial vegetations that may result in valvular incompetence (of aortic valves more frequently) or obstruction, and in heart failure.

Etiology. Infective endocarditis is usually caused by Streptococci, Enterococci, and less commonly by Staphylococci, Haemophilus, Candida, coliform bacilli. Predisposing factors are congenital heart defects and rheumatic valvular disease, atherosclerosis and calcification of heart valves, mitral valve prolapse, hypertrophic subaortic stenosis, and prosthetic valves. Factors weakening immunological reactions facilitate the development of the disease.

Pathogenesis. Normal endothelium is resistant to infection by most bacteria and to thrombus formation. Endothelial injury causes aberrant flow and allows direct infection by virulent organisms and the development of a platelet-fibrin thrombus that subsequently serves as a site of bacterial attachment during transient bacteremia. Microorganisms that cause endocarditis generally enter the bloodstream from mucosal surfaces, the skin, or sites of focal infection.

The pathophysiologic consequences of infective endocarditis: (1) damage to intracardiac structures; (2) embolization of vegetation fragments, leading to infection or infarction of remote tissues; (3) hematogenous infection of sites during bacteremia; (4) tissue injury due to the deposition of circulating immune complexes or immune responses to deposited bacterial antigens.

Pathological anatomy. This is characterized by the presence of ulcerous endocarditis. Ulcerated surfaces become covered with polyp-like thrombotic mass which sometimes looks like cauliflower. The valves become sclerosed and disfigured. The aortic valve is especially frequently involved. Endothelium of fine vessels is affected to cause vasculitis or thrombovasculitis: vascular permeability increases and small hemorrhages develop in the skin and mucosa.

Death usually follows heart failure, which develops from exacerbation of underlying heart disease or acute valve dysfunction; embolization of vegetations to vital organs, producing infarction; a ruptured mycotic aneurysm; renal failure.

Classification of infective endocarditis

1. According to course of disease – acute, subacute endocarditis
2. Clinical forms: acute bacterial endocarditis; subacute bacterial endocarditis, prosthetic valvular endocarditis, right-sided endocarditis.

Acute bacterial endocarditis is usually caused by *Staphylococcus aureus*, group A hemolytic streptococci, pneumococci, or gonococci and by less virulent microorganisms. It can develop on normal valves. *Subacute bacterial endocarditis* often develops on abnormal valves after asymptomatic bacteremia from infected gums or the genitourinary or gastrointestinal tract. *Prosthetic valvular endocarditis* develops in 2 to 3% of patients after valve replacement. *Right-sided endocarditis* (1-3%) - involving the tricuspid valve and less often the pulmonary valve and artery may result from intravenous use of illicit narcotic drugs or from central vascular lines.

Clinical picture

The most typical complaints are fever and dyspnea. As a rule, subfebrile fever first develops, which is followed by irregular elevation of temperature to 39 °C and more. Chills and excess sweating are characteristic of the infective endocarditis. Other complaints are weakness, weight loss,

heartbeatings, arthralgias, mialgias. Pains may be due to embolism (severe headache, heart and chest pain, abdominal, flank, lumbar pains).

Past history of the patient may reveal congenital defects and rheumatic valvular disease, myocardial infarction, heart surgery operation.

General survey of the patient shows pale skin and visible mucosa due to anemia and aortic incompetence, which is characteristic of this disease. The skin sometimes becomes yellowish-grey (“*coffee with milk*”). Small hemorrhages in the skin, mucosa of the mouth (especially the soft and hard palate), on conjunctiva, and the eyelid folds (the *Libman-Lukin symptom*) indicate affection of the joints. Positive *Konchalovsky-Rumpel-Leede sign* is another indication of this process: if the arm of the patient is compressed by a tourniquet or by a cuff of sphygmomanometer, multiple petechiae appear on the flexor surface of the elbow, and also distally of it. Brittleness of capillaries can also be established by symptom of pinching the skin. In most cases the patient's fingers become clubbed (Hippocratic fingers), while the nails are flat like a watch glass.

Auscultation of the heart reveals signs of acquired valves or congenital heart diseases in most patients. Auscultation reveals tachycardia and *organic murmurs* – diastolic murmur of aortic insufficiency, systolic murmurs of mitral and tricuspid insufficiency. Development of endocarditis is attended by the appearance of *functional murmurs* due to anemia and murmurs that are caused by changes in the affected valve. Left ventricle insufficiency is the more typical than right ventricle insufficiency (if tricuspid valves affection).

Subacute bacterial endocarditis is characterized by embolisms (caused by decomposing thrombotic deposits on the valves) in the vessels of the spleen, kidneys or brain, followed by infarction of the involved organ. Embolic lesions may be detected at inspection of the patient - *Osler`nodes* (painful nodes in the fingers, palms, toes, soles), *Roth spots* (retinae), *Janeway lesions* (thenar, hypothenar).

The spleen is enlarged due to the response of the mesenchyma to sepsis. The spleen may be painful, and left hypochondrium friction rub may be if a splenic infarction develops.

Renal lesions are revealed by hematuria and proteinuria resulted from embolic infarction of the kidney or diffuse glomerulonephritis due to immune complex deposition.

Manifestations of central nervous system involvement (in about 35% of patients) may range from transient ischemic attacks and toxic encephalopathy to brain abscess and subarachnoid hemorrhage.

Laboratory and instrumental examinations

Common blood analysis detects hypochromic anemia (caused by increased hemolysis and inhibited erythropoiesis), markedly increased ESR. Leukocyte count varies, neutrophilic leukocytosis may be. Eosinophil count decreases and there is a tendency to monocytosis.

Urinalysis shows a proteinuria, hematuria, and cylindruria.

Biochemical blood tests reveals dysproteinemia (hypoalbuminaemia, increased content of gamma-globulins), and positive thymol assay.

Positive blood culture may detect the causative agent of the endocarditis.

Echocardiography can be used to reveal vegetations on the cusps and ulceration of the aortic valves, and less frequently on the mitral and tricuspid valves.

Diagnosis of infective endocarditis is based on typical clinical picture of the disease confirmed by echocardiography data (vegetations and ulceration of heart valves) and positive blood culture.

Course. Untreated, infective endocarditis is always fatal. When treatment is given, mortality depends on the patient's age and condition, duration of infection before treatment, severity of underlying diseases, site of infection, susceptibility of the microorganism to antibiotics, and complications. Cardiac surgery that corrects acute valvular insufficiency, removes infected foreign bodies, and eliminates recalcitrant infection is associated with significantly improved survival. A poor prognosis is associated with heart failure, old age, aortic or multiple valve involvement, large vegetations, polymicrobial bacteremia, antimicrobial resistance, delay in initiating therapy, prosthetic valve infections, mycotic aneurysms, valve ring abscess, and major embolic events.

Conception of non-rheumatic myocarditis, cardiomyopathies and myocardial dystrophies

Non-rheumatic myocarditis

Definition: Non-rheumatic myocarditis (I40- I41 according to ICD-X) is inflammation of the myocardium developed most commonly as a result of an infectious process.

The disease affects both men and women at any age. Acute, subacute, and chronic myocarditis are differentiated. The disease may be local or diffuse.

Etiology and pathogenesis. Etiological factors responsible for the development of myocarditis are various bacterial and virus infections. The most common causes of myocarditis are sepsis, diphtheria, rickettsiosis, scarlet fever, and coxsackievirus B. Myocarditis may also result from a hypersensitivity to drugs or may be caused by radiation, chemicals, or physical agents.

Inflammatory changes in the myocardium caused by various infections are the result of immune reaction of the body sensitized by certain microbes. The microbe antigen or its toxin acts on the myocardium to cause formation

of tissue antigens (auto-antigens) in it. As a result, auto-antibodies are formed which account for the vast changes in the myocardium.

Pathological anatomy. Dystrophic processes in the muscle fibres are characteristic. Predominant exudative or proliferative processes are also observed in the interstitial tissue (interstitial myocarditis). The outcome of the inflammatory changes is cardiosclerosis. In an unknown number of cases, acute myocarditis progresses to chronic dilated cardiomyopathy.

Clinical picture. This includes signs of decreased contractility of the myocardium and upset cardiac rhythm. The patient complains of dyspnea on physical exertion, extreme weakness, palpitation, intermissions, dull and boring pain, or attacks of pain in the heart (like in angina pectoris). Patients with viral myocarditis often give a history of a preceding upper respiratory febrile illness or a flu like syndrome, and viral nasopharyngitis or tonsillitis may be evident clinically.

The skin is pallid, sometimes with a slight cyanotic shade. In pronounced heart failure the neck veins become swollen. The pulse is small, soft, sometimes arrhythmic and accelerated: it may however be slowed down too. Extrasystole and, less frequently, paroxysmal fibrillation develop in deranged excitation function and automaticity.

Decreased diffuse apex beat, which is displaced anteriorly, is revealed on examination of the heart. Percussion can detect displacement of the heart to the left. Auscultation reveals a markedly decreased first sound at the early systole (due to decreased rate of rise in the intraventricular pressure). The second sound is either unchanged or diminished due to hypotension. Gallop rhythm can be heard in significantly decreased myocardial contractility. Systolic murmur can often be heard over the heart apex. It arises due to relative mitral incompetence. Arterial pressure, especially systolic, decreases and the pulse pressure falls accordingly.

ECG changes in myocarditis are quite varied and transient. Sinus tachycardia, sinus arrhythmia, and extrasystole (in the form of separate or group atrial or ventricular extrasystoles) can most frequently be found on electrocardiograms. Conduction is deranged according to incomplete or complete atrioventricular block. Diffuse affections of the myocardium are shown on ECG as diminished and split *P* wave, changed *QRS* complex (decreased voltage of the waves and their splitting), decreased *S-T* interval, and presence of two phases and inversion of the decreased *T* wave.

The blood counts show moderate neutrophilic leucocytosis with shift to the left, increased ESR, and hyperglobulinemia (mainly due to α_2 - and γ -globulins). The isolation of virus from the stool, pharyngeal washings, or other body fluids and changes in specific antibody titers are helpful clinically. Endomyocardial biopsy, carried out early in the illness, may show round-cell infiltration and necrosis of adjacent myocytes.

Course. The clinical manifestations range from an asymptomatic state, with the presence of myocarditis inferred only by the finding of transient electrocardiographic ST-T-wave abnormalities, to a fulminant condition with arrhythmias, heart failure, and death. In some patients, myocarditis simulates acute myocardial infarction, with chest pain, electrocardiographic changes, and elevated serum levels of myocardial enzymes.

The course of myocarditis is usually favorable and ends with recovery. Though viral myocarditis is most often self-limited and without complications, severe involvement may recur, and it is likely that acute viral myocarditis occasionally progresses to a chronic form and to dilated cardiomyopathy. Sclerosis of the myocardium develops in some patients (myocardial cardiosclerosis).

Cardiomyopathies and myocardial dystrophies

Definition: Cardiomyopathies (I42-I43 according to ICD-X) are diseases characterized by affections of the heart muscle attended by enlargement of the heart and its insufficiency, and involved the myocardium directly, and are not the result of hypertension or congenital, valvular, coronary, arterial, or pericardial abnormalities.

Classification. In the World Health Organization classification, *specific cardiomyopathy (or myocardial dystrophies)* is used to describe heart muscle diseases associated with certain systemic or cardiac disorders; examples include hypertensive and metabolic cardiomyopathy. In many cases, however, it is not possible to arrive at a specific etiologic diagnosis, and thus it is often more desirable to classify the cardiomyopathies on the basis of differences in their pathophysiology and clinical presentation

When the cardiomyopathies are classified on an etiologic basis, two fundamental forms are recognized: (1) a primary type, consisting of heart muscle disease of unknown cause (idiopathic, familial); and (2) a secondary type, consisting of myocardial disease of known cause or associated with a disease involving other organ systems (metabolic, infections, toxic reactions, radiation, deficiency of electrolytes and nutrients, amyloidosis, hemochromatosis, neuromuscular diseases, peripartum heart disease).

The following clinical three types of cardiomyopathy would be usually differentiated: (1) congestive or dilatation; (2) hypertrophic; and (3) restrictive cardiomyopathy.

Clinical picture

Congestive cardiomyopathy is characterized by dilatation of the heart chambers with pronounced heart failure. The patients develop dyspnea during slightest physical exertion and even at rest, attacks of suffocation and cardiac pain which cannot be removed by nitroglycerin; heart palpitation and intermissions are also characteristic. As circulatory insufficiency progresses,

the liver becomes enlarged and edema and hydrops of the cavities develop. The borders of the heart are markedly displaced to the right, upwards, and to the left. The heart sounds at the apex are dulled, the second sound over the pulmonary trunk is accentuated, gallop rhythm often develops along with systolic murmur at the apex due to developing relative mitral insufficiency. The pulse is small and fast, sometimes arrhythmic. The arterial pressure is usually decreased.

ECG in congestive cardiomyopathy shows various changes in the myocardium; signs of overloading of the heart chambers and focal changes develop along with rhythm and conduction disorders.

Echocardiography reveals marked dilatation of the heart chambers and decreased contractility of the myocardium.

Hypertrophic cardiomyopathy is characterized by the primary hypertrophy of the myocardium with subsequently developing cardiac insufficiency which differs but little from congestive cardiomyopathy by its symptoms.

The special form of hypertrophic cardiomyopathy is *obstructive cardiomyopathy*, which is also known as idiopathic hypertrophic subaortic stenosis. This cardiomyopathy is characterized by asymmetric hypertrophy of the interventricular septum in the region of blood outflow from the left ventricle. The cavity of the left ventricle diminishes. A circular ridge of the hypertrophied myocardium is formed beneath the aortic valve. The ridge interferes with blood ejection into the aorta. This form of myocardial pathology is first manifested by symptoms characteristic for aortic stenosis: the patient develops headache, giddiness, faints, and heart pain (like in angina pectoris). Palpation and percussion of the heart reveals hypertrophy of the left ventricle; auscultation reveals coarse systolic murmur which is best heard at the 3rd or 4th intercostal space at the left edge of the sternum. The pulse is small and slow. Symptoms of circulatory insufficiency soon appear.

Echocardiography is most important among additional methods used to diagnose hypertrophic subaortic stenosis. It reveals asymmetrical hypertrophy of the interventricular septum, narrowing of the left ventricle and systolic deflection of the mitral valve cusp in the direction of the interventricular septum. Hypertrophic cardiomyopathy can be familial, inherited by the autosomal-dominant type.

Restrictive cardiomyopathy is associated with disordered distensibility of the myocardium due to endocardial and subendocardial fibrosis. The diastolic function of the myocardium becomes upset and heart failure (without marked hypertrophy of the myocardium or dilatation of the heart chambers) develops.

Diagnosis of non-rheumatic myocarditis, cardiomyopathies and myocardial dystrophies is based on:

- (1) typical clinical picture,

(2) confirmed by data of laboratory and instrumental study - ECG, echocardiography, biochemical tests on acute phase reactants (CRP, α 2-globulin and γ -globulin fractions, seromucoid, etc) and myocardium enzymes (LDG₁, CK-MB fraction, etc), in some cases - endomyocardial biopsy, and data of microbiological and immunological study;

(3) and on exclusion of rheumatism, essential arterial hypertension, congenital or acquired heart valves diseases, coronary, arterial, or pericardial abnormalities.

Acquired Heart Valves Diseases

Definition: Heart valves diseases are stable pathological changes in the structure of the heart that interfere with its normal function.

Congenital and acquired diseases of the heart are distinguished. The incidence of acquired heart diseases is much higher.

Congenital diseases of the heart arise due to abnormal development of the heart and the great vessels during the intrauterine growth of the fetus with preservation of the intrauterine character of circulation after birth. In defective division of the primary single-chamber arterial trunk into the pulmonary trunk and the aorta, and during formation of the heart chambers, defects in the interatrial and interventricular septa may be formed along with various abnormalities in the arrangement of the great vessels and their narrowing. Preservation of the intrauterine character of circulation after birth is the cause of patent ductus arteriosus (Botallo's duct) and patent foramen ovale. Congenital heart defects may often combine with communicated greater and lesser circulation systems and stenosis of the great vessels. Moreover, the valves (bicuspid, tricuspid, aortic, and pulmonary valves) may also have congenital defects.

Etiology of acquired heart valves diseases: rheumatic endocarditis is the main cause of acquired heart defects; on second place - infective endocarditis and atherosclerosis; more rarely - syphilis, injuries, etc.

Inflammatory processes occurring in the valve cusps often end in their sclerosis: deformation and shortening. An affected valve does not close completely to cause *valves incompetence*. The cusps of the valves may adhere to one another because of inflammation to narrow the orifice they close. This narrowing is called *stenosis*.

Classification of acquired heart valves diseases

(1) According to etiology – rheumatic (I05-I08), non-rheumatic acquired valves diseases (I34-I37): infective endocarditis, atherosclerotic, syphilitic, etc.

(2) According to pathogenesis – organic and functional heart valve disease.

(3) According to morphology and hemodynamic changes – incompetence (insufficiency, regurgitation), stenosis, combined heart valve disease (if incompetence and stenosis of the orifice simultaneously).

(4) According to localization – mitral, aortic, tricuspid, pulmonary artery, concomitant (if two and sometimes three valves simultaneously) heart valve disease.

(5) According to condition of blood circulation – compensated and decompensated (characterized by circulatory insufficiency) heart valve disease.

Diagnosis of acquired heart valves diseases is based mainly on typical auscultative data confirmed by echocardiography, and in some cases heart catheterization.

Mitral incompetence (mitral insufficiency, or mitral regurgitation)

Definition: Incompetence of the mitral (bicuspid) valve (mitral insufficiency) is incomplete closure of the atrioventricular orifice during left-ventricular systole. As a result, the blood is regurgitated from the ventricle back to the atrium. Mitral incompetence may be organic and functional.

Etiology. Organic mitral insufficiency arises as a result of rheumatic endocarditis. Connective tissue develops in the cusps of the mitral valve which then contracts to shorten the cusps and the tendons. The edges of the affected valve do not meet during systole and part of the blood is regurgitated through the slit into the left atrium from the ventricle during its contraction.

In *functional (relative) incompetence* the mitral valve is not altered but the orifice, which it has to close, is enlarged and the cusps fail to close it completely. Functional incompetence of the mitral valve may develop because of dilatation of the left ventricle (in myocarditis, myocardial dystrophy, or atherosclerosis) and weakening of the circular muscle fibres that form the ring round the atrioventricular orifice. Affection of papillary muscles may also cause functional mitral incompetence. Functional insufficiency thus depends on dysfunction of the muscles responsible for the closure of the valve.

Hemodynamics. If the mitral valve fails to close completely during systole of the left ventricle, part of the blood is regurgitated into the left atrium. Blood filling of the atrium thus increases (because of the blood from the pulmonary veins which is added to the normal blood volume). Pressure in the left atrium increases, the atrium is dilated and becomes hypertrophied.

The amount of blood that is delivered into the left ventricle from the overfilled left atrium during diastole exceeds normal and the atrium is thus overfilled and distended. The left ventricle has to perform excess work and becomes hypertrophied. Intensified work of the left ventricle compensates for

the mitral incompetence during a long time. When the contractile power of the left ventricular myocardium weakens, diastolic pressure in it increases and this in turn increases pressure in the left atrium.

Increased pressure in the left atrium increases pressure in the pulmonary veins and this in turn causes reflex contraction of the arterioles in the lesser circulation (Kitaev's reflex) due to stimulation of baroreceptors. Spasm in the arterioles increases significantly pressure in the pulmonary artery to intensify the load on the right ventricle which has to contract with a greater force in order to eject blood into the pulmonary trunk. The right ventricle can therefore also be hypertrophied during longstanding pronounced mitral incompetence.

Clinical picture

Most patients with mild or moderate mitral incompetence have no complaints for a long time and look very much like healthy subjects. As congestion in the lesser circulation develops, dyspnea, palpitation of the heart, cyanosis, and other symptoms appear.

Palpation of the heart area reveals displacement of the apex beat to the left and sometimes inferiorly. The beat becomes diffuse, intensified, and resistant, which indicates hypertrophy of the left ventricle.

Percussion reveals displacement of the heart's borders to the left and superiorly because of the enlarged left atrium and left ventricle. The configuration of the heart becomes mitral with an indistinct heart waist. The border of the heart shifts to the right in hypertrophy of the right ventricle.

Auscultation of the heart reveals decreased first sound at the heart apex because the valves never close completely in this disease. Systolic murmur can be heard at the same point, which is the main sign of mitral incompetence. It arises during systole when the stream of blood passes a narrow slit leading from the left ventricle to the left atrium. The systolic murmur is synchronous with the first sound. When the blood pressure rises in the lesser circulation, an accent of the second sound can be heard over the pulmonary trunk.

The pulse and arterial pressure do not change in compensated mitral incompetence.

Auscultation findings are confirmed and verified by *phonocardiography*. The amplitude of the first sound is decreased on a PCG taken at the heart apex; systolic murmur occupies the entire pause between the first and second heart sounds.

X-ray studies show a specific enlargement of the left atrium and the left ventricle detectable by enlargement (to the left, superiorly and posteriorly) of the heart silhouette. When blood pressure increases in the lesser circulation, the pulmonary arch dilates.

Signs of hypertrophy of the left atrium and the left ventricle can also be found on the ECG: it becomes the left type and the *P* waves become higher.

Echocardiography can visualize and quantify the mitral regurgitation blood flow.

Course. Mitral incompetence may remain compensated for a long time. But a long-standing pronounced mitral incompetence and decreased myocardial contractility of the left atrium and the left ventricle cause venous congestion in the lesser circulation. Contractility of the right ventricle can later be affected with subsequent development of congestion in the greater circulation.

Mitral stenosis (stenosis of the left atrioventricular orifice)

Definition: Mitral stenosis is an obstruction of flow from left atrium to left ventricle because of a narrowed mitral orifice.

Etiology. The left atrioventricular orifice usually narrows in a long-standing rheumatic endocarditis (stenosis ostii venosi sinistri). In very rare cases mitral stenosis may be congenital or secondary to infective endocarditis. The atrioventricular orifice narrows due to adhesion of the mitral cusps, their consolidation and thickening, and also shortening and thickening of the tendons. The valve thus becomes a diaphragm or a funnel with a slit in the middle. Cicatricial and inflammatory narrowing of the valvular ring is less important in genesis of mitral stenosis. The valve may be calcified in longstanding stenosis.

If stenosis is significant and the orifice is narrowed from the normal 4-6 cm² to 1,5cm² and less, *hemodynamics* becomes affected considerably. During diastole, blood fails to pass from the left atrium to the left ventricle and the remaining blood is added to the blood delivered from the pulmonary veins. The left ventricle thus becomes overfilled with blood, the pressure in the ventricle increases. Excess pressure is first compensated for by intensified contraction of the atrium and its hypertrophy, but the force of the left atrial muscle is insufficient to compensate permanently for the pronounced narrowing of the mitral orifice and its contractile force soon weakens; the atrium becomes dilated, and the pressure inside it rises. This in turn increases pressure in the pulmonary veins, produces a reflex spasm in the arterioles of the lesser circulation and increases pressure in the pulmonary artery. All this requires intensified work of the right ventricle, which later also becomes hypertrophied. The left ventricle in mitral stenosis receives smaller volumes of blood and is therefore less active; its size slightly decreases.

Clinical picture

When congestive changes occur in the lesser circulation, the patient complains on dyspnea and palpitation on physical exertion; he complains of pain in the heart, cough, and hemoptysis.

Inspection reveals acrocyanosis and cyanotic blush on the face. If the disease develops in childhood, the patient's physical growth often slows down and infantilism may develop ("mitral nanism"). Visual examination of

the heart region often reveals a cardiac beat consequent upon dilatation and hypertrophy of the right ventricle.

Palpation detects that apex beat is not intensified; its palpation can reveal diastolic *cat's purr* (*presystolic thrill*).

Percussion reveals the broadening of cardiac dullness to the right and superiorly due to hypertrophy of the left atrium and right ventricle. The heart becomes "mitral" in configuration.

In *auscultation* of the heart the first sound at the apex becomes loud and snapping because the left ventricle receives little blood and its contraction is fast. An adventitious sound due to the opening of the mitral valve can be heard at the apex beat. It follows the second sound of the heart. The loud first sound, second sound, and the sound of mitral valve opening give a specific "*quail rhythm*" which is characteristic of mitral stenosis. The second sound becomes accentuated over the pulmonary trunk when pressure in the lesser circulation increases.

Diastolic murmur is characteristic of mitral stenosis because the passage from the left atrium to the ventricle during diastole is narrowed. This murmur can be heard to follow the mitral valve opening sound (*protodiastolic murmur*) because the velocity of the blood flow in early diastole is higher due to the pressure difference in the atrium and the ventricle. The murmur disappears when the pressures equalize. If stenosis is not pronounced, the murmur can be heard only at the end of diastole, immediately before systole proper (*presystolic murmur*); it arises during acceleration of the blood flow at the end of ventricular diastole because of the early atrial systole. Diastolic murmur can be heard in mitral stenosis during the entire diastole. It increases before systole and joins the first snapping sound.

The pulse in mitral stenosis may be different on the left and right arms. In considerable hypertrophy of the left atrium, the left subclavian artery is compressed and the pulse on the left arm becomes smaller (*pulsus differens*). If the left ventricle is not filled completely and the stroke volume is decreased, the pulse becomes small (*pulsus parvus*). Mitral stenosis is often complicated by atrial fibrillation, and the pulse becomes arrhythmic.

Arterial pressure usually remains normal; the systolic pressure sometimes slightly decreases and diastolic pressure increases.

The PCG taken at the heart apex shows increased amplitude of the first sound, diastolic (presystolic) murmur, and the sound of the mitral valve opening.

X-ray patterns of the heart show the specific enlargement of the left atrium, which leads to disappearance of the heart waist and "mitral" configuration appears. Enlargement of the left atrium is determined in the first oblique position by the degree of displacement of the esophagus which becomes especially vivid with barium sulphate suspension. If pressure in the

lesser circulation increases, X-rays shows swelling of the pulmonary arch and hypertrophy of the right ventricle. X-ray pictures sometimes show calcification of the mitral valve. Pneumosclerosis develops during longstanding hypertension of the lesser circulation; it may also be revealed during X-ray examination.

The *ECG* of the heart with mitral stenosis shows hypertrophy of the left atrium and the right ventricle: the amplitude and duration of the *P* wave increase, especially in the first and second standard leads; the electrical axis of the heart deviates to the right, a high *R* wave appears in the right chest leads and a pronounced *S* wave in the left chest leads. Atrial fibrillation and flutter are typical arrhythmias.

Echocardiography indicates the amount of valvular calcification, the patient's suitability for valvotomy, and the size of the left atrium and thus whether the patient will benefit from cardioversion. It will also detect associated mitral regurgitation. Two-dimensional echocardiography can show the exact area of the mitral orifice.

Course. Mitral stenosis soon becomes attended by congestion in the lesser circulation which requires greater work of the right ventricle. Decreased contractility of the right ventricle and venous congestion in the greater circulation develop therefore in mitral stenosis earlier and more often than in mitral incompetence.

Dilatation of the right ventricle and weakening of its myocardium are sometimes attended by relative tricuspid insufficiency. Moreover, long-standing venous congestion in the lesser circulation in mitral stenosis causes, with time, sclerosis of the vessels and growth of connective tissue in the lungs. Another obstacle to the blood flow is thus created in the lesser circulation and this adds to the difficulties in the work of the right ventricle.

Aortic incompetence (aortic insufficiency, aortic regurgitation)

Definition: Aortic incompetence is the failure of the aortic valve to close completely during ventricular diastole; blood thus leaks back into the left ventricle.

Etiology. Aortic incompetence is usually secondary to rheumatic endocarditis, and less frequently infective (bacterial, septic) endocarditis, syphilitic affection of the aorta, or atherosclerosis. Inflammatory and sclerotic changes occurring in the base of the cusps during rheumatic endocarditis make them shrink and shorten. Atherosclerosis and syphilis can affect only the aorta (to distend it), while the valve cusps are only shortened. The cicatricial changes may extend onto the cusps to disfigure them. Parts of the valve disintegrate in ulcerous endocarditis associated with sepsis and the cusps are affected with their subsequent cicatrization and shortening.

Hemodynamics. During diastole, blood is delivered into the left ventricle not only from the left atrium but also from the aorta due to

regurgitation, which overfills and distends the left ventricle during diastole. During systole, the left ventricle has to contract with a greater force in order to expel the larger blood volume into the aorta. Intensified work of the left ventricle causes its hypertrophy, while the increased systolic volume in the aorta causes its dilatation. Aortic incompetence is characterized by a marked variation in the blood pressure in the aorta during systole and diastole. An increased volume of blood in the aorta during systole increases systolic pressure and since part of blood is returned during diastole into the ventricle, the diastolic pressure quickly drops.

Clinical picture

Subjective condition of patients with aortic incompetence may remain good for a long time because the defect is compensated for by harder work of the powerful left ventricle.

Complaints. Pain in the heart (anginal in character) may sometimes be felt; it is due to relative coronary insufficiency because of pronounced hypertrophy of the myocardium and inadequate filling of the coronary arteries under low diastolic pressure in the aorta. The patient may sometimes complain of giddiness which is the result of deranged blood supply to the brain (which is also due to low diastolic pressure). If contractility of the left-ventricular myocardium is impaired, congestion in the lesser circulation develops and the patient complains of dyspnea, tachycardia, weakness, etc.

Inspection. The skin of the patient is pallid due to insufficient filling of the arterial system during diastole. Marked variations in the pressure in the arterial system during systole and diastole account for the appearance of some signs, such as pulsation of the peripheral arteries, the carotids (*carotid shudder*), subclavian, brachial, temporal, and other arteries; rhythmical movements of the head synchronous with the pulse (*Mussel's sign*), rhythmical change in the colour of the nail bed under a slight pressure on the nail end, the so-called capillary pulse (*Quincke's pulse*), rhythmical reddening of the skin after rubbing, etc.

The apex beat is almost always enlarged and shifted to the left and inferiorly. Sometimes, along with the elevation of the apex beat, a slight depression in the neighbouring intercostal spaces can be observed. The apex beat is palpable in the sixth and sometimes seventh intercostal spaces, and in hypochondrium, anteriorly of the midclavicular line. The apex beat is diffuse, intense, and rising like a dome. This indicates significant enlargement of the left ventricle.

Percussion can find a shift to the left of the border of cardiac dullness; the heart configuration becomes "aortic" (with pronounced waist of the heart).

Auscultation reveals decreased first sound at the apex, since during left-ventricular systole the period when the valves are closed is absent. The second sound on the aorta is also weak, and if the valve is damaged

significantly, it can be inaudible. The second sound can be quite loud in atherosclerotic affection of the aorta. Diastolic murmur heard over the aorta and at the Botkin-Erb listening point is characteristic. This is a low blowing protodiastolic murmur which weakens by the end of diastole as the blood pressure in the aorta drops and the blood-flow rate decreases. The described changes in the sounds and murmurs are clearly visible on phonocardiograms. Murmurs of functional etiology can also be heard in aortic incompetence at the heart apex. If the left ventricle is markedly dilated, relative mitral incompetence develops and systolic murmur can be heard at the heart apex. Diastolic murmur (*presystolic or Austin Flint murmur*) can sometimes be heard. It arises due to an intense regurgitation of the blood that moves aside the mitral valve cusp to account for functional mitral stenosis. Doubled sound (*Traube double sound*) and doubled *Vinogradov-Duroziez murmur* can sometimes be heard over the femoral artery in this disease.

The pulse in aortic incompetence is fast, full, and high, which is due to high pulse pressure and increased volume of blood delivered into the aorta during systole. *Arterial pressure* constantly varies: the systolic pressure rises and diastolic falls, and the pulse pressure is therefore high.

PCG can detect decreased amplitude of the heart sounds and diastolic murmur above aorta.

X-ray studies show an enlarged left ventricle with a distinct waist of the heart and dilatation of the aorta; pulsation of the aorta is intense.

The *ECG* also reveals various signs of hypertrophy of the left ventricle: the electrical axis is deviated to the left, the *S* waves in the right chest leads are deep and the amplitude of the *R* wave is higher in the left chest leads; these signs often combine with signs of overstrain in the left ventricle and relative coronary insufficiency (changes in the terminal part of the ventricular complex, displacement of the *S-T* interval, and the negative *T* wave).

Echocardiograms taken from patients with aortic failure show flutter of the anterior mitral cusp during diastole caused by the thrust of the blood regurgitated from the aorta into the ventricle.

Course. Aortic incompetence can for a long time be compensated for by intensified work of the hypertrophied left ventricle. When its contractile force decreases, congestion in the lesser circulation develops. Acute weakness of the left ventricle sometimes develops and is manifested by an attack of cardiac asthma. Dilatation of the weakened left ventricle can cause relative mitral incompetence. This increases venous congestion in the lesser circulation associated with decompensated aortic incompetence and adds to the load on the right ventricle. This is mitralization of aortic incompetence, which may become the cause of venous congestion in the greater circulation.

Aortic stenosis

Definition: Aortic stenosis is a narrowing of the aortic orifice (aortic stenosis) interfered with expulsion of blood into the aorta during contraction of the left ventricle.

Etiology and pathogenesis. Aortic stenosis is usually caused by rheumatic endocarditis; less frequently it develops due to bacterial endocarditis, atherosclerosis, or it may be congenital. Stenosis results from adhered aortic valve cusps or develops due to cicatricial narrowing of the aortic orifice.

Supravalvular aortic stenosis occurs as a discrete membrane or hypoplastic constriction just above the sinuses of Valsalva (three outpouchings or bulges at the root of the aorta). Idiopathic hypertrophic subaortic stenosis is also called hypertrophic obstructive cardiomyopathy. It is due to an asymmetrically thickened septum that impinges on the anterior leaflet (rarely the posterior leaflet) of the mitral valve during systole, causing outflow obstruction.

Hemodynamics. Narrowing of the aortic outflow tract at valvular, supravalvular, or subvalvular levels causes obstruction to flow from the left ventricle into the ascending aorta and resulting in a pressure gradient across the obstruction of > 10 mm Hg. During systole, the left ventricle is not emptied completely because part of blood fails to pass the narrowed orifice into the aorta. A new normal portion of blood delivered during diastole from the left atrium is mixed with the residual volume and the ventricle becomes overfilled. The pressure inside it thus rises. This disorder is compensated for by an intensified activity of the left ventricle to cause its hypertrophy.

Clinical picture

Complaints. The typical triad of complaints is syncope, angina pectoris, and dyspnea on exertion. Aortic stenosis can remain compensated for years and would not cause any unpleasant subjective sensations (even during intense physical exertion). If obstruction of the aortic orifice is considerable, insufficient blood ejection into the arterial system upsets normal blood supply to the hypertrophied myocardium and the patient feels pain in the heart (*angina pectoris-type pain*). Disordered blood supply to the brain is manifested by giddiness, headache, and tendency to fainting. These symptoms like pain in the heart would more likely occur during physical exercise and emotional stress.

Inspection of the patient reveals a pallid skin due to insufficient blood supply to the arterial system.

Palpation finds shift of the apex beat to the left, less frequently inferiorly; it is diffuse, high, and resistant. *Systolic thrill (cat's purr)* can be palpated in the region of the heart.

Percussion reveals displacement of the left border; the heart configuration is "aortic" due to hypertrophy of the left ventricle.

Auscultation of the heart at its apex reveals diminished first sound due to overfilling of the left ventricle and prolongation of systole. The second sound is diminished over the aorta. If the aortic cusps adhere and are immobile, the second sound can be inaudible. Rough systolic murmur over the aorta is characteristic. This murmur is generated by the blood flow through the narrowed orifice. It is conducted by the blood onto the carotids and can sometimes be heard in the interscapular space.

The pulse is small, slow, and rare, since the blood slowly passes into the aorta and its volume is decreased. *Systolic arterial pressure* is usually diminished, while diastolic remains normal or increases. The pulse pressure is therefore decreased.

X-ray examination shows hypertrophied left ventricle, "aortic" configuration of the heart, and dilatation of the ascending aorta (post-stenotic); the cusps of the aortic valve are often calcified.

The ECG usually shows signs of hypertrophy of the left ventricle and sometimes of coronary insufficiency.

The phonocardiogram (PCG) shows the specific changes in the heart sounds: diminished amplitudes of the first sound at the heart apex and of the second sound over the aorta. Systolic murmur over the aorta is typical; its oscillations are recorded in the form of specific diamond-shaped figures.

Echocardiograms show decreased opening of the aortic valve during systole. Echoes from the cusps become more intense and signs of hypertrophy of the left ventricle appear.

Course. Aortic stenosis remains compensated for a long time. Circulatory insufficiency develops in diminished contractility of the left ventricle and it is manifested as in aortic incompetence.

Tricuspid incompetence (tricuspid insufficiency, or regurgitation)

Definition: Tricuspid incompetence is a retrograde flow of blood from right ventricle to right atrium due to inadequate apposition of the tricuspid valves.

Etiology and pathogenesis. Insufficiency of the tricuspid valve can be functional (relative) and organic (permanent). Organic tricuspid incompetence occurs in rare cases, mainly due to rheumatic endocarditis. Tricuspid incompetence usually combines with affections of other heart valves; as an independent disease, it occurs in exceptionally rare cases.

Relative (functional) insufficiency of the tricuspid valve occurs more often. It is due to dilatation of the right ventricle and distention of the right-atrioventricular orifice. Tricuspid incompetence often combines with mitral diseases because the right ventricle has to perform greater work due to the high pressure in the lesser circulation. This causes overstrain and distention of the right ventricle.

Hemodynamics. Due to incomplete closure of the tricuspid valve during right-ventricular systole, part of blood is regurgitated into the right atrium, where it is mixed with the normal volume of blood delivered from the venae cavae. The atrium thus becomes distended and hypertrophied. During diastole, a larger volume of blood is delivered into the right ventricle from the right atrium because the portion of blood that was regurgitated into the atrium during systole is added to the normal volume of blood delivered. This causes dilatation and hypertrophy of the right ventricle. Compensation in this disease is attained by intensified work of the right atrium and the right ventricle whose compensatory power is not great and congestion in the greater circulation therefore soon develops.

Clinical picture

Complaints. The patient complains of fatigue, cold skin, dyspnea, edema), the only specific symptom of severe tricuspid incompetence is the sensation of pulsations in the neck due to the high jugular regurgitant waves from the transmitted right ventricle pressure.

Pronounced venous congestion in the greater circulation in the presence of tricuspid incompetence causes edema, ascites, feeling of heaviness and right hypochondriac pain (due to enlargement of the liver).

General inspection. The skin becomes cyanotic, sometimes with a yellowish tint. The neck veins swell and pulsate; the positive venous pulse and pulsation of the liver are also observed. These pulsations are explained by the regurgitation of blood from the ventricle to the atrium through an incompletely closed atrioventricular orifice, owing to which pressure increases in the atrium and emptying of the neck and liver veins is made difficult. Tricuspid incompetence is characterized by extensive hepatic pulsation: the liver is displaced anteriorly and swells. This can be felt by trying to hold the liver by both hands: the pulsating liver sets the hands apart during the pulse wave.

Inspection of the heart area of the patient reveals pronounced pulsation in the region of the right ventricle. As distinct from the heart beat in mitral stenosis, this pulsation is characterized by systolic retraction and diastolic protrusion of the chest.

Systolic retraction of the chest in the region of the right ventricle is explained by pronounced diminution of its volume because much blood is delivered at that moment to the hepatic veins. Systolic retraction of the chest corresponds to the systolic swelling of the liver, and vice versa, diastolic overfilling of the right ventricle and protrusion of the chest in the ventricular region combine with diastolic diminution of the liver volume. Therefore, if the examiner places one hand on the region of the right ventricle and the other hand over the liver, he can feel specific rolling movements of the hands. The apex beat is as a rule not pronounced because the left ventricle is displaced posteriorly by the hypertrophied right ventricle.

Percussion reveals marked displacement of the heart border to the right due to hypertrophy of the right atrium and right ventricle.

Auscultation at the base of the xiphoid process reveals diminished first sound; systolic murmur can be heard at the same listening point and also at the 3rd and 4th interspaces, to the right of the sternum; this murmur increases when the patient keeps his breath at the height of inspiration. Since pressure in the lesser circulation decreases in tricuspid incompetence, the second sound over the pulmonary trunk decreases in its clearness.

The pulse does not change significantly or it becomes small and fast, because serious heart failure often occurs in tricuspid incompetence. *Arterial pressure* usually decreases. *The venous pressure* increases markedly.

X-ray signs of hypertrophy of the right heart's chambers can be detected.

Electrocardiography also shows hypertrophy of right ventricles. *Phonocardiography* records systolic murmur at the base of the xiphoid process and at the 3rd and 4th intercostal spaces, to the right of the sternum; the systolic murmur has a decreasing character. When a phonocardiogram is taken at the height of inspiration, the vibration amplitude increases.

Phlebogram of the jugular vein reveals a high positive *a* wave which is connected with the intensified activity of the hypertrophied right atrium, or the wave has the form characteristic of the positive venous pulse.

Echocardiography of the tricuspid valve is more difficult than that of the mitral or the aortic valve. Echocardiograms can reveal paradoxical movements of the interventricular septum in overloading of the right ventricle associated with tricuspid insufficiency.

Course. Tricuspid incompetence usually combines with grave circulatory insufficiency. Long-standing congestion in the greater circulation upsets the function of many organs, such as the liver, kidneys, or the gastrointestinal tract. The liver is especially affected: prolonged congestion in the liver is attended by growth of connective tissue to provoke the development of the so-called cardiac fibrosis of the liver. This, in turn, even more interferes with the normal function of the organ and causes severe metabolic disorders.

Combined and concomitant heart diseases

Acquired diseases of the heart, rheumatic in particular, often occur as *combined affections* of the valves, i.e. valve incompetence and stenosis of the orifice occur simultaneously. Moreover, *concomitant affection* of two, and sometimes three valves (mitral, aortic, and tricuspid) may occur simultaneously.

Mitral incompetence is most common. It usually concurs with stenosis of the left venous orifice. Signs of both heart diseases are then found but one

sign dominates as a rule; less frequently, signs of valvular incompetence and stenosis are equally pronounced.

Dyspnea and cyanosis are early symptoms of the mitral disease.

The heart expands to the left, superiorly, and to the right, because both ventricles and the left atrium are hypertrophied. Intensity of the first sound at the apex depends on the prevalent disease: if mitral incompetence is the leading syndrome, the first heart sound diminishes; if mitral stenosis dominates, the first sound increases and becomes squelching. Two sounds are heard at the apex: systolic due to valvular insufficiency, and diastolic due to stenosed orifice.

Pulse and arterial pressure do not change in prevalence of mitral incompetence, while if mitral or stenosis dominates, systolic arterial pressure may decrease and diastolic pressure increase; the pulse becomes small.

Combined aortic incompetence is usually secondary to rheumatic endocarditis. Both systolic and diastolic murmurs are characteristic; these sounds can be heard over the aorta. Vascular pulsation and high pulse pressure are typical of aortic incompetence; they are not so pronounced in combined aortic affection. At the same time, slow and small pulse, and low pulse pressure that are typical of aortic stenosis, are also less pronounced in combined aortic incompetence.

Detailed clinico-instrumental examination of patients with concomitant affections of several valves reveals signs typical of each particular disease. It is necessary in such cases to conclude on the gravity of each disease and the prevalence of one of them. This is especially important for prognostic conclusions and for prospective surgical treatment.

Prognosis of heart valves diseases

Mild changes in the heart valves, in the absence of marked affections of the myocardium, can remain non-manifest for a long time without impairing the work capacity of the patient. Aortic insufficiency is compensated for a long time but when decompensation develops, the patient soon dies. Mitral stenosis has a worse prognosis because the disease is compensated by a weaker left atrium. Congestion soon develops in the lesser circulation, which is followed by incompetence of the right heart chambers, and the greater circulation soon becomes affected by congestion. Repeated rheumatic attacks have an adverse effect on the course of the disease: the valvular apparatus of the heart is progressively impaired and the myocardium is affected. These disorders provoke circulatory insufficiency. Moreover, any infection, poisoning, physical or nervous overstrain, pregnancy and labour may give an impetus to the development of heart failure.

Restitution prognosis depends on the general condition and physical fitness of the patient. In the absence of symptoms of circulatory insufficiency, the patient may return to his usual occupation; in the presence

of signs of decompensation, the patient should be recommended to change his occupation. Work capacity can be preserved in a patient with heart disease provided he fulfills special recommendations for his work and rest, if he abstains from overeating, smoking, or drinking.

Conservative treatment of patients with heart diseases consists in prophylaxis and treatment of heart failure. Mitral and aortal stenoses are often corrected surgically (comissurotomy). The adhered cusps are disjoined and the atrioventricular orifice is widened. Surgical treatment of mitral and aortic incompetence consists in replacement of the destroyed valve by an artificial one.

Essential arterial hypertension

Definition: Essential (primary, idiopathic) hypertension (*morbus hypertonicus*, I10-I13 according to ICD-X) is the condition in which elevated arterial blood pressure is the leading symptom and no the definable cause of it.

Prevalence of the disease is very high: in USA and Europe nearly one-fifth of individuals has blood pressure >160/95 mm Hg, while almost one-half have pressure >140/90 mm Hg.

Etiology and pathogenesis

Etiology and pathogenesis of essential hypertension is multifactor. Development of the disease greatly depends on occupation: it occurs mostly in subjects whose occupation is associated with nervous and mental overstrain, e.g. in scientific workers, engineers, physicians, drivers, etc.

Predisposing factors of essential hypertension are age >55 years, race – black (urban), sex - postmenopausal women, smoking, alcohol intake, high serum cholesterol, glucose intolerance, weight – obesity.

Heredity is also a predisposing factor, but the exact mechanism is unclear. Environmental factors (eg, dietary Na, alcohol intake, obesity, prolonged and recurrent stress) seem to act only in genetically susceptible persons. Salt sensitivity people are genetically prone to hypertension when fed a high-salt diet) do not excrete water or Na as rapidly as those from salt-resistant, even before hypertension develops.

Humoral mechanisms of essential hypertension are renin-angiotensin-aldosterone system activity and deficiency of vasodilator substances. Insulin resistance is connected with arterial hypertension combined diabetes mellitus, obesity, and atherosclerosis. Deficiency of a vasodilator substance rather than excess of a vasoconstrictor (eg, angiotensin, norepinephrine) may cause hypertension. The kallikrein system, which produces the potent vasodilator bradykinin, is beginning to be studied. Extracts of renal medulla contain vasodilators, including a neutral lipid and a prostaglandin; absence of these

vasodilators due to renal parenchymal disease or bilateral nephrectomy would permit BP to rise.

Abnormal Na, chloride and Ca transport across the cell membrane because of generalized cell membrane defect have been described in some cases of hypertension.

Stimulation of the sympathetic nervous system and overstrain of the central nervous system, caused by prolonged and strong emotional stress and also mental overstrain, are believed to be an important cause of the disease. Some hypertensive patients have a higher-than-normal circulating plasma catecholamine level at rest, especially early in clinical development.

Disfunction of endothelium – decrease of vasodilators (nitric oxide, prostacyclin) and increase of the vasoconstrictors (endothelin) - could have a profound effect on blood pressure. The endothelium's role in hypertension is being investigated.

The pathogenic mechanisms lead to increased total peripheral vascular resistance by inducing vasoconstriction, to increased cardiac output, or to both. The mosaic theory states that multiple factors sustain elevated blood pressure even though an aberration of only one was initially responsible; eg, the interaction between the sympathetic nervous system and the renin-angiotensin-aldosterone system. Sympathetic innervation of the juxtaglomerular apparatus in the kidney releases renin; angiotensin stimulates autonomic centers in the brain to increase sympathetic discharge. Angiotensin also stimulates production of aldosterone, which leads to Na retention; excessive intracellular Na enhances the reactivity of vascular smooth muscle to sympathetic stimulation.

Hypertension leads to more hypertension. Other mechanisms become involved when hypertension due to an identifiable cause has existed for some time. Smooth muscle cell hypertrophy and hyperplasia in the arterioles resulting from prolonged hypertension reduce the caliber of the lumen, thus increasing total peripheral vascular resistance. In addition, trivial shortening of hypertrophied smooth muscle in the thickened wall of an arteriole will reduce the radius of an already narrowed lumen to a much greater extent than if the muscle and lumen were normal. This may be why the longer hypertension has existed.

Pathological anatomy.

No early pathologic changes occur in primary hypertension. Essential hypertension gradually affects permeability of vascular walls and their protein content. At late or grave forms of the disease, this causes sclerosis or necrosis of small arteries and secondary changes in the tissues of organs. Walls of large vessels are usually affected by atherosclerotic changes. The extent of vascular affection differs in various organs and various clinico-anatomical variants of the disease therefore arise, with a prevalent affection

of the vessels of the heart, brain, or kidneys (primary cirrhosis of the kidneys thus develops).

Ultimately, generalized arteriolar sclerosis develops; it is particularly apparent in the kidney (nephrosclerosis) and is characterized by medial hypertrophy and hyalinization. Nephrosclerosis is the hallmark of primary hypertension. Left ventricular hypertrophy and, eventually, dilation develops gradually. Coronary, cerebral, aortic, renal, and peripheral atherosclerosis are more common and more severe in hypertensives because hypertension accelerates atherogenesis. Hypertension is a more important risk factor for stroke than for atherosclerotic heart disease. Tiny Charcot-Bouchard aneurysms, frequently found in perforating arteries (especially in the basal ganglia) of hypertensives, may be the source of intracerebral hemorrhage.

Conception of target organ damage in arterial hypertension

The biological aggressiveness of a given level of hypertension varies among individuals. This inherent propensity to induce vascular damage can be ascertained best by examination of the eyes, heart, and kidney.

Fundoscopy changes. As described by Keith et al. in 1939, vascular changes in the fundus reflect both hypertensive retinopathy and arteriosclerotic retinopathy. The two processes induce first narrowing of the arteriolar lumen (Grade 1) and then sclerosis of the adventitia and/or thickening of the arteriolar wall, visible as arteriovenous nicking (Grade 2). Progressive hypertension induces rupture of small vessels, seen as hemorrhages and exudates (Grade 3) and eventually papilledema (Grade 4). The Grade 3 and 4 changes are clearly indicative of an accelerated-malignant form of hypertension, whereas the lesser changes have been correlated with other evidence of target organ damage.

Cardiac involvement. Hypertension places increased tension on the left ventricular myocardium, causing it to stiffen and hypertrophy, and accelerates the development of atherosclerosis within the coronary vessels. The combination of increased demand and lessened supply increases the likelihood of myocardial ischemia, leading to higher incidences of myocardial infarction, sudden death, arrhythmias, and congestive failure in hypertensives.

Abnormalities of left ventricular function. Even before left ventricular hypertrophy of the left ventricular function develops, changes in both systolic and diastolic function may be seen.

Left ventricular hypertrophy. Hypertrophy as a response to the increased afterload of an elevated systemic vascular resistance can be viewed as necessary and protective up to a certain point. Beyond that point, a variety of dysfunctions accompany LVH.

Features of coronary artery disease. As detailed elsewhere, hypertension is a major risk factor for myocardial ischemia and infarction. Beyond these multiple additional risks associated with hypertension, a higher

incidence of coronary events has been recognized when elevated diastolic blood pressures are reduced with therapy to levels below 85 to 90 mm Hg.

Renal function. Renal dysfunction, too subtle to be recognized, may be responsible for the development of most cases of essential hypertension. In patients with longstanding hypertension, a loss of concentrating ability may be manifested by nicturia, creatinine clearance falls, and the development of more significant proteinuria. As hypertension-induced nephrosclerosis proceeds, the plasma creatinine level begins to rise, and eventually renal insufficiency with uremia may develop, making hypertension a leading cause for end-stage renal disease, particularly in blacks.

Cerebral involvement. Hypertension, particularly systolic, is a major risk factor for initial and recurrent stroke and for transient ischemic attacks caused by extracranial atherosclerosis.

Clinical picture

Essential hypertension may be a long time asymptomatic until complications develop in target organ - left ventricular failure, ischemic heart (coronary artery) disease, cerebrovascular insufficiency with or without stroke, renal failure.

Complaints. During the early stage of the disease, the patient would usually complain of neurotic disorders: general weakness, impaired work capacity, inability to concentrate during work, deranged sleep, transient headache, a feeling of heaviness in the head, vertigo, noise in the ears/ These complaints are connected hypertensive encephalopathy due to severe hypertension. Some patients complain on palpitations, heart pains, episodic nasal bleeding (epistaxis). Exertional dyspnea (ascending upstairs, running) develops later.

Inspection of the patient may show a flushed face (hyperemia of face).

The main objective sign of the disease is elevated systolic pressure (over 140-160 mm Hg) and diastolic pressure (over 90 mm Hg). Arterial pressure (BP) is very variable during the early stage of the disease, but later it stabilizes.

Examination of the heart reveals signs of hypertrophy of the left ventricle: expanding apex beat, and displacement of the cardiac dullness to the left, "aortic configuration". The second sound is accentuated over the aorta. The pulse becomes firm and tense.

X-rays reveals "aortic" silhouette of the heart. The aorta is elongated, consolidated, and dilated.

EGG detects levogram, displaced S-T segment, low, negative, or two-phase T wave in the I and II -nd standard and left chest leads V4-V6.

Echocardiography finds evidence of left ventricular dysfunction and hypertrophy; aortic aneurysm may be detected.

Arterial hypertension is a major risk factor for angina pectoris and myocardial infarction. In the late period of the disease, heart failure may

develop due to fatigue of the heart muscle as a result of increased arterial pressure. Heart failure is often manifested by episodes of acute left ventricular failure (cardiac asthma or edema of the lungs); or chronic circulatory insufficiency may develop.

Fundoscopy examination. Vision may be deteriorated in grave cases. Examination of the fundus oculi reveals *hypertensive retinopathy*: degree 1 - constriction of retinal arterioles only (its general pallidness); degree 2 - constriction and sclerosis of retinal arterioles (the arteries are narrow and tortuous, the veins are mildly dilated); degree 3 - hemorrhages and exudates in addition to vascular changes (angiospastic retinitis); degree 4 (malignant hypertension) - papilledema.

Cerebrovascular disorders. High arterial pressure in the affected cerebral vessels can derange cerebral circulation. This can cause paralysis, disorders in sensitivity, and sometimes death of the patient. Cerebral circulation is deranged due to spasms of the vessels, their thrombotic obstruction, hemorrhage due to rupture of the vessel, or diapedetic discharge of erythrocytes.

Renal disorders. The affected kidneys become unable to concentrate urine (nicturia or isohyposthenuria develops). Metabolites (otherwise excreted with urine) are retained to provoke uremia. *Urinalysis* detects polyuria, diminished renal concentrating ability, proteinuria, microhematuria, and cylindruria (late manifestations). *Biochemical blood tests* find increased urea, and creatinin (due to nitrogen retention - late manifestations).

Hypertensive crisis

Definition: Hypertensive crisis is a periodically recurring transient elevations of arterial pressure accompanied by exacerbation of clinical symptoms and possible complications in target-organs

Predisposing factors. Development of such crises is preceded by psychic traumas, nervous overstrain, variations in atmospheric pressure, irregular intake of antihypertensive medications, etc.

Clinical picture. Hypertensive crisis develops with a sudden elevation of the arterial pressure that can persist from a few hours to several days. The crisis is attended by sharp headache, feeling of heat, perspiration, palpitation, giddiness, piercing pain in the heart, sometimes by deranged vision, nausea, and vomiting. In severe crisis, the patient may lose consciousness. The patient is excited, haunted by fears, or is indifferent, somnolent, and inhibited. Auscultation of the heart reveals accentuated second sound over the aorta, and also tachycardia. The pulse is accelerated but can remain unchanged or even decelerated; its tension increases. Arterial pressure increases significantly (as a rule diastolic pressure ≥ 130 mm Hg). ECG shows decreased *S-T* interval and flattening of the *T* wave. In the late stages of the disease, with organic changes in the vessels, cerebral circulation may be

deranged during crisis; myocardial infarction and acute left-ventricular failure may also develop

Complications of hypertensive crisis may be fatal up to death, such as cerebral stroke, acute myocardial infarction, acute left ventricular failure (cardiac asthma or edema of the lungs), loss of vision, dissection and rupture of the aortic aneurysm.

Classification of arterial hypertension

According to WHO (World Health Organization) Hypertension Guidelines (1999) arterial hypertension is classified:

Category	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
Stage 1 (mild)	140-159	90-99
Subgroup: Borderline	140-149	90-94
Stage 2 moderate)	160-179	100-109
Stage 3 (severe)	>180	>110
Isolated systolic hypertension	≥ 140	<90
Subgroup: Borderline	140-149	<90

Risk 1 (low risk <15%) – no risk factors , no target-organs damage;

Risk 2 (medium risk 15-20%)– 1-2 risk factors;

Risk 3 (high risk 20-30%) – 3 risk factors and/or target-organs damage (or diabetes mellitus);

Risk 4 (very high risk >30%) – associated clinical conditions (complications in target-organ).

Blood pressure should be measured several times on several occasions with the patients in sitting position using a mercury sphygmomanometer or other non-invasive device. When a patient's systolic or diastolic BPs fall into different categories, the higher category should apply.

Category of risk means the 10-year risk of cerebral stroke or acute myocardial infarction.

Risk factors are used for stratification of arterial hypertension:

- levels of systolic and diastolic blood pressure (Grades 1-3);
- men >55 years,
- women >65 years,
- smoking,
- total serum cholesterol >6,5 mmol/l,
- diabetes mellitus,
- family history of premature cardiovascular disease.

Target organ damage (TOD) is used for stratification of arterial hypertension:

- left ventricular hypertrophy (ECG, echocardiogram, or radiogram);

- renal dysfunction - proteinuria and/or elevation of plasma creatinine concentration 106-107 mmol/l (in patients with longstanding hypertension);
- ultrasound or radiological evidence of atherosclerotic plaque (carotid, iliac and femoral artery, aorta);
- retinopathy - generalized or focal narrowing of retinal arteries.

Associated clinical conditions (ACC) are used for stratification of arterial hypertension:

- cerebrovascular disease (ischemic stroke, cerebral hemorrhage, transient ischemic attack);
- heart disease (myocardial infarction, angina pectoris, coronary revascularization surgery, congestive heart failure);
- renal disease (diabetic nephropathy, renal failure - plasma creatinine concentration >177 mmol/l);
- vascular disease (dissecting aneurysm of aorta, symptomatic arterial disease of carotid, iliac and femoral artery, aorta);
- advanced hypertensive retinopathy (hemorrhages or exudates, papilledema).

In Russia and in certain some countries classification arterial hypertension according to *Myasnikov* is used now simultaneously with WHO Hypertension Guidelines. Three stages of the disease are classified; each stage is further divided into two phases, A and B.

The A phase of the first stage is latent; it is characterized by elevated arterial pressure during a psychic stress, while under normal conditions arterial pressure is normal. The B phase is transient (transitory hypertension); arterial pressure increases only occasionally and under certain conditions; objective changes are absent.

In the second stage, arterial pressure is elevated permanently and more significantly. Phase A is characterized by permanent but unstable hypertension. Subjective sensations are pronounced; hypertensive crises are possible; spasms of the cerebral and coronary arteries are likely to occur as well. Signs of hypertrophy of the left ventricle develop. Phase B is characterized by a significant and stable elevation of the arterial pressure. Hypertensive crises are frequent. Paroxysms of angina pectoris and derangement of cerebral circulation of the angiospastic character occur. Changes in the fundus oculi and pronounced signs of hypertrophy of the left ventricle can be revealed.

During the third stage, sclerotic changes in the organs and tissues are observed along with stable and marked elevation of the arterial pressure. Phase A is compensated. Arteriosclerosis of the kidneys is observed, but the renal function is not upset significantly. Cardiosclerotic changes do not provoke stable heart failure; and sclerosis of cerebral vessels is not attended by pronounced disorders in the cerebral circulation. Phase B is decompensated, with grave dysfunction of various organs and with renal

insufficiency; cerebral circulation is disordered and hypertensive retinopathy is observed. In this stage of the disease, the arterial pressure may normalize after infarction or apoplectic stroke.

Diagnosis of essential arterial hypertension

Diagnosis of essential arterial hypertension depends on repeatedly demonstrating higher-than-normal systolic and/or diastolic BP and excluding secondary causes.

At least two BP determinations should be taken on each of 3 days before a patient is diagnosed as hypertensive. More BP determinations are desirable for patients in the low hypertension range and especially for patients with markedly labile BP. Sporadic higher levels in patients who have been resting for > 5 min suggest an unusual lability of BP that may precede sustained hypertension. For example, “office” or “white coat hypertension” refers to BP that is consistently elevated in the physician's office but normal when measured at home or by ambulatory BP monitoring.

The basic or minimal evaluation recommended for patients with hypertension includes history and physical examination, common blood analysis, urinalysis, serum analysis (creatinine; K; Na; fasting glucose and cholesterol), and ECG. The more severe the hypertension and the younger the patient, the more extensive the evaluation should be. Ambulatory BP monitoring is not routinely necessary.

Course. An untreated hypertensive patient is at great risk of disabling or fatal left ventricular failure, myocardial infarction, cerebral hemorrhage or infarction, or renal failure at an early age. Hypertension is the most important risk factor predisposing to stroke. It is one of three risk factors (along with cigarette smoking and hypercholesterolemia) predisposing to coronary atherosclerosis. The higher the BP and the more severe the changes in the retina, the worse the prognosis. Effective medical control of hypertension will prevent or forestall most complications and will prolong life in patients with isolated systolic or diastolic hypertension. Coronary artery disease is the most common cause of death among treated hypertensive patients. Systolic BP is a more important predictor of fatal and nonfatal cardiovascular events than diastolic BP.

Conception of symptomatic (secondary) arterial hypertension

Definition: Symptomatic hypertension (I15 according to ICD-X) is a clinical condition in which arterial pressure rises as a symptom of some other disease, this symptom being far from the leading one.

Essential hypertension should accurately be differentiated from symptomatic hypertension. In only a small minority of patients with elevated arterial pressure can a specific cause be identified (near to 5%). Yet these patients should not be ignored for at least two reasons: (1) correction of the

cause may cure their hypertension, and (2) these secondary forms of the disease may provide insight into the etiology of essential hypertension. Nearly all the secondary forms of hypertension are related to an alteration in hormone secretion and/or renal function.

Classification of symptomatic arterial hypertension

1. Renal -
 - a. Renal parenchymal disease (chronic nephritis, polycystic disease, diabetic nephropathy, hydronephrosis);
 - b. Renovascular (renal artery stenosis, intrarenal vasculitis).
2. Endocrine -
 - a. Acromegaly;
 - b. Hypothyroidism;
 - c. Hyperthyroidism;
 - d. Hypercalcemia (hyperparathyroidism);
 - e. Adrenal:
 - (1) Cortical (Cushing's syndrome, primary aldosteronism, congenital adrenal hyperplasia, apparent mineralocorticoid excess (licorice),
 - (2) Medullary (pheochromocytoma).
3. Coarctation of the aorta.
4. Pregnancy-induced hypertension.
5. Neurological disorders -
 - a. Increased intracranial pressure (brain tumor, encephalitis, respiratory acidosis),
 - b. Acute stress, including surgery (psychogenic hyperventilation, hypoglycemia, burns, pancreatitis, sickle cell crisis, postresuscitation, postoperative).
7. Increased intravascular volume (polycythemia).
8. Alcohol and drug use.
9. Systolic hypertension -
 - a. Increased cardiac output (hyperkinetic circulation syndrome, aortic valvular insufficiency, arterio-venous fistula, patent ductus, thyrotoxicosis, beri-beri),
 - b. Atherosclerosis of aorta.

Diagnosis of symptomatic arterial hypertension is based on clinical and laboratory data confirmed the underlying disease in which arterial pressure rises as a symptom.

The basic or minimal evaluation recommended for patients with arterial hypertension revealed for the first time includes history and physical examination, analysis of Urine for protein, blood, and glucose; microscopic urinalysis; common blood analysis, hematocrit; biochemical blood tests – serum potassium and sodium, serum creatinine and/or blood urea nitrogen,

fasting glucose, cholesterol), ECG, echocardiogram, chest x-ray, fundoscopic examination, ultrasound of kidneys and adrenal gland.

Renal scintigraphy, screening tests for pheochromocytoma and other endocrine hypertension, plasma renin activity, Doppler ultrasonography, renal arteriography, aortography and other special investigations should be performed if serious indications present.

Ischemic Heart Disease (IHD, Coronary artery disease, CAD)

Definition: Ischemic heart disease (I20-I25 according to ICD-X) is a group of diseases, such as angina pectoris, myocardial infarction (MI), and coronary atherosclerosis, based on insufficient blood supply to the heart.

The disproportion between the heart's demand for blood and the actual blood supply may arise when the heart's demands increase significantly, or when the actual blood supply diminishes for some reasons.

Ischemia refers to a lack of oxygen due to inadequate perfusion, which results from an imbalance between oxygen supply and demand.

Etiology and pathogenesis. The most common *cause of myocardial ischemia* is atherosclerotic disease of epicardial coronary arteries. Most coronary artery disease is due to: (1) subintimal deposition of atheromas in the large and medium-sized arteries serving the heart; (2) less often, coronary spasm, which is usually idiopathic (with or without associated atheroma) or may be due to drugs such as cocaine; (3) rare causes include an embolus to the coronary artery and vasculitis.

The major complications of coronary artery atherosclerosis are angina pectoris, unstable angina, MI, and sudden cardiac death due to arrhythmias.

Although the precise pathogenesis of ischemic heart disease is unclear, the *risk factors* are well known:

a) *correctable risk factors* - high blood levels of low density lipoprotein cholesterol (LDL-C) and lipoprotein a, low blood levels of high density lipoprotein cholesterol (HDL-C), arterial hypertension, diabetes mellitus, and poor physical fitness (physical inactivity), smoking.

b) *incorrectable risk factors* – increasing age, male sex, familial predisposition, presence of the established coronary artery disease and/or history of prior myocardial infarction.

High blood levels of triglycerides and insulin reflecting insulin resistance may be risk factors, but the data are less clear. Ischemic heart disease risk is increased by tobacco use; diets high in fat and calories and low in phytochemicals (found in fruits and vegetables), fiber, and vitamin E and C or, at least in some persons, diets with relatively low levels of omega-3 polyunsaturated fatty acids; poor stress management; and inactivity. Several

systemic diseases (eg, hypertension, diabetes, hypothyroidism) are also associated with increased ischemic heart disease risk.

Classification of Ischemic Heart Disease

1. Acute coronary death
2. Acute myocardial infarction
3. Angina pectoris (stenocardia) -
 - a. Stable angina pectoris,
 - b. Unstable angina pectoris,
 - c. Prinzmetals variant angina pectoris.
4. Heart failure.
5. Cardiac arrhythmias.

Angina Pectoris (Stenocardia)

Definition: Angina pectoris is a clinical syndrome due to myocardial ischemia characterized by precordial discomfort or pressure, typically precipitated by exertion and relieved by rest or sublingual nitroglycerin.

Angina pectoris is a frequently occurring disease. Its main clinical symptoms are attacks of retrosternal pain due to acute but transient disorder in the coronary circulation. The disease develops mainly in people over 40, and predominantly in men. Mental workers would mostly suffer from this disease.

Etiology and pathogenesis. The most frequent cause of angina pectoris is atherosclerosis of the coronary arteries of the heart. Main causes of angina pectoris are (1) critical coronary artery obstruction due to atherosclerosis; (2) coronary spasm (idiopathic or due to cocaine); (3) rarely coronary embolism may be; 4) disease other than atherosclerosis (calcific aortic stenosis, aortic regurgitation, hyperthrophic subaortic stenosis) can cause angina directly (by increasing cardiac work) or in combination with IHD.

Much less frequently it develops in infectious and infectious-allergic vascular diseases, such as syphilitic aortitis, panarteritis, periarteritis nodosa, rheumatic vasculitis, and obliterating endarteritis. Angina pectoris often concurs with essential hypertension. Paroxysms of angina pectoris may develop due to upset nervous regulation of the coronary arteries as a reflex or in cholelithiasis, hiatus hernia, diseases of the stomach, etc. by reflex. Spasms of the coronary arteries (without their anatomical changes) can sometimes provoke angina pectoris. The spasm may develop in heavy smokers or as a result of a strong emotional stress.

Hypoxemia (ischemia) of the myocardium provokes the attack. Ischemia develops in conditions when the insufficient amount of blood is delivered to the heart muscle through the coronary arteries, and the myocardium does not receive the necessary amount of oxygen. Transient oxygen hunger causes a reversible disorder in the oxidation-reduction processes in the myocardium. Stimulation of the interoceptors of the

myocardium or the vascular adventitia by the products of upset metabolism produces a current of impulses via the centripetal pathways to the cerebral cortex to cause the specific symptom of the disease, retrosternal pain. High activation of the sympathetic-adrenal system is also very important for the onset of angina pectoris.

Pathological anatomy. No organic changes are sometimes found in those who died from an attack of angina pectoris. But in 85-90 per cent of cases signs of atherosclerosis of the coronary arteries pronounced to a different degree are discovered.

Clinical picture. The main clinical symptom of the disease is pain in the centre of the sternum (retrosternal pain). Less frequently the pain originates in the heart region. Because discomfort seldom occurs in the region of the cardiac apex, the patient who points to this precise area or describes fleeting, sharp, or hot sensations usually does not have angina.

The character of pain varies: the patient may feel constriction, compression, heaviness, burning, and sometimes sharp or stabbing pain. Pain is usually severe and the patient develops morbid fear of death. Pain radiates into the left shoulder, left arm, left side of the neck and the head, the mandible, the interscapular space, and sometimes to the upper abdomen. The characteristic radiation of pain during angina pectoris is due to hypersensitivity of the patient's skin to pain in the zones innervated by the 7th cervical and 1st-5th thoracic segments of the spinal cord (Zakharyin-Head zones). Stimuli from the heart are transmitted through these segments to the centrifugal nerves of the spinal cord (by the viscerosensory reflex).

Pain arises under certain conditions: during fast walking and other exercises (*angina pectoris of effort*), when the patient leaves a warm room and walks during cold seasons, especially if atmospheric pressure changes; under emotional stress; during sleep (*angina pectoris at rest*), after meals, in abdominal distention, and in high diaphragm. During physical exertion, the heart muscle requires more nutrition from blood. Atherosclerotic vessels cannot deliver the appropriate amount of blood and the patient has to stop exercise (walking) for a few minutes until pain subsides. Specific sign of angina pectoris is development of pain when the patient leaves a warm room and walks in the open during cold seasons. The symptom is even more pronounced if atmospheric pressure changes. Under emotional stress, the patient develops an attack of angina pectoris without any exercise. Pain may last from few seconds to 20-30 min. Quick removal of pain after taking nitroglycerin suggests angina pectoris.

Between and even during attacks of angina pectoris, signs of heart disease may be absent. The strength of attacks differs. In rare cases attacks end lethally. During an attack, the pulse is usually slow and rhythmical, but tachycardia, extrasystole, and increased arterial pressure are sometimes observed. Percussion and auscultation of the heart sometimes cannot reveal

any abnormality, provided pronounced atherosclerotic cardiosclerosis is absent. The body temperature remains normal. Usually there are no changes in the peripheral blood.

Electrocardiographs studies during attacks of angina pectoris sometimes reveal signs of disordered coronary circulation: the *S-T* segment is low; the two-phase or negative *T* wave is small in standard leads, and also in the corresponding chest leads, depending on the localization of affection in the coronary system. When the attack is abated, the electrocardiographic picture soon normalizes; ECG can sometimes reveal the described changes only during physical load.

Exercise stress ECG testing. Because the diagnosis of angina pectoris is usually primarily based on the patient's history, exercise testing in a patient with typical symptoms is generally used to determine functional and ECG response to graded stress (for exercise stress testing using radionuclide imaging; for exercise testing in asymptomatic persons to determine fitness for exercise programs). The patient exercises to a predetermined goal (e.g., 80 to 90% of maximal heart rate, which can be approximated as 220 less the age in years), unless distressing cardiovascular symptoms (dyspnea, reduced endurance, fatigue, hypotension, or chest pain) supervene. The ischemic ECG response during or after exercise is characterized by a flat or downward-sloping ST segment depression $>0,1$ millivolts (1 mm on the ECG when properly calibrated) lasting $> 0,08$ seconds.

Coronarography with contrast substances is sometimes carried out to reveal occlusion of the coronary arteries.

Diagnosis of angina pectoris is based on characteristic complaints of chest pains (or discomfort) brought on by exertion and relieved by rest and nitroglycerin. Diagnosis may be confirmed if reversible ischemic ECG changes are seen during a spontaneous attack or/and the ischemic ECG response during ECG exercise testing.

Course. The disease is chronic. Attacks can be rare, once a week or even less frequently; attacks may be absent for months or even years, or their frequency may increase and they become more severe. An attack of angina pectoris lasting more than 30-60 minutes can end in myocardial infarction. Patients with long-standing angina pectoris develop cardiosclerosis; the cardiac rhythm becomes disordered and symptoms of heart failure develop.

Clinical variants of Angina Pectoris

Stable angina

Definition: Stable angina is the episodic clinical syndrome due to transient myocardial ischemia typically caused by exertion (e.g., exercise, hurrying, or sexual activity) or emotion (e.g., stress, anger, fright, or

frustration) and relieved by rest, and which occurs predictably at a certain level of activity.

The typical patient with angina is a 50- to 60-year-old man or 65- to 75-year-old woman who seeks medical help for chest discomfort, usually described as heaviness, pressure, squeezing, smothering, or choking and only rarely as frank pain. When the patient is asked to localize the sensation, he or she will typically press on the sternum, sometimes with a clenched fist, to indicate a squeezing, central, substernal discomfort. This symptom is usually crescendo-decrescendo in nature and lasts 1 to 5 min. Angina can radiate to the left shoulder and to both arms and especially to the ulnar surfaces of the forearm and hand. It can also arise in or radiate to the back, neck, jaw, teeth, and epigastrium.

Although episodes of stable angina are typically caused by exertion (e.g., exercise, hurrying, or sexual activity) or emotion (e.g., stress, anger, fright, or frustration) and are relieved by rest, they may also occur at rest (and at night while the patient is recumbent (*angina decubitus*)). The patient may be awakened at night distressed by typical chest discomfort and dyspnea. Nocturnal angina may be due to episodic tachycardia or activities such as micturition. It can also be due to the expansion of the intrathoracic blood volume that occurs with recumbency, which causes an increase in cardiac size and myocardial oxygen demand that lead to ischemia and transient left ventricular failure.

The threshold for the development of angina pectoris varies from person to person and may vary by time of day and emotional state. Many patients report a fixed threshold for angina, which occurs predictably at a certain level of activity. In these patients coronary stenosis and myocardial oxygen supply are fixed and ischemia is precipitated by an increase in myocardial oxygen demand. In other patients the threshold for angina may vary considerably within any given day and from day to day. In such patients variations in oxygen supply, most likely due to changes in coronary vascular tone, may play an important role. A patient may report symptoms upon minor exertion in the morning (a short walk or shaving) yet by midday may be capable of much greater effort without symptoms. Angina may also be precipitated by unfamiliar tasks, a heavy meal, or exposure to cold.

Sharp, fleeting chest pain or prolonged, dull aches localized to the left submammary area are rarely due to myocardial ischemia. However, angina pectoris may be atypical in location and may not be strictly related to provoking factors. In addition, this symptom may exacerbate and remit over days, weeks, or months. Its occurrence can be seasonal, being more frequent in the winter in temperate climates. Anginal "equivalents" are symptoms of myocardial ischemia other than angina. These include dyspnea, fatigue, and faintness and are more common in the elderly.

The physical examination is often normal in the patient with stable angina. Examination during an anginal attack is useful, since ischemia can cause transient left ventricular failure with the appearance of a third and/or fourth heart sound, a dyskinetic cardiac apex, mitral regurgitation, and even pulmonary edema.

ECG recorded at rest is normal in about half the patients with stable angina pectoris, but there may be signs of an old myocardial infarction. Although repolarization abnormalities, i.e., T-wave and ST-segment changes and intraventricular conduction disturbances at rest, are suggestive of IHD, they are nonspecific, since they can also occur in pericardial, myocardial, and valvular heart disease or transiently with anxiety, changes in posture, drugs, or esophageal disease. Typical ST-segment and T-wave changes that accompany episodes of angina pectoris and disappear thereafter are more specific. The most characteristic changes include displacement of the ST segment that is similar in every way to that induced during a stress test.

Unstable angina

Definition: Unstable angina is angina characterized by a progressive increase in anginal symptoms, new onset of rest or nocturnal angina, or onset of prolonged angina. Because the characteristics of angina are usually constant for a given patient, any deterioration in the pattern of symptoms - increased intensity, decreased threshold of stimulus, longer duration, and occurrence when the patient is sedentary or waking from sleep—should be considered serious.

The following three patient groups may be said to have unstable angina pectoris: (1) patients with new onset (<2 months) angina that is severe and/or frequent (≥ 3 episodes per day); (2) patients with accelerating angina, i.e., those with chronic stable angina who develop angina that is distinctly more frequent, severe, prolonged, or precipitated by less exertion than previously; (3) those with angina at rest.

Unstable angina is precipitated by an acute increase in coronary obstruction mainly due to rupture of the fibrous plaque covering an atheroma with consequent platelet adhesion. In unstable angina, $> 1/3$ of patients studied angiographically has partially occluding thrombi in the vessel subtending the recurrent ischemic area. Other mechanisms for unstable angina have been described: (1) a nonocclusive thrombus often a platelet plugs overlying a fissured atherosclerotic plaque; (2) dynamic obstructions either spasm of an epicardial coronary artery, as in Prinzmetal's variant angina (see below), or abnormal vasoconstriction of the coronary microcirculation, as in microvascular angina; (3) severe, organic luminal narrowing; (4) arterial inflammation leading to thrombosis; and (5) increase in myocardial oxygen demands caused by conditions such as tachycardia, fever, and thyrotoxicosis in the presence of fixed, severe coronary obstruction.

Compared with stable angina, the pain of unstable angina is generally more intense, lasts longer, is brought on by less effort, occurs spontaneously at rest (angina decubitus), is progressive (crescendo) in nature, or involves any combination of these changes.

When unstable angina is accompanied by objective ECG evidence of transient myocardial ischemia (ST-segment changes and/or T-wave inversions during episodes of chest pain), it is associated with critical stenoses in one or more major epicardial coronary arteries in about 85% of cases. ECG changes are reversible during minutes up to 24 hours after episode of unstable angina pectoris.

Variants of ECG changes in unstable angina pectoris:

- *transmural or epicardial injury* - convexing elevation ST with transmission in T-wave;

- *subendocardial injury* – horizontal or concaving depression ST;

- *subendocardial ischemia* - symmetrical acute high T-wave in overlying leads (>6 mm in standard and augmented leads , >8-10 mm in chest leads);

- *transmural or epicardial ischemia* - symmetrical acute deep T-wave.

Common blood analysis is not changed. Biochemical tests on *serum cardiac markers* (myocardiospecific enzymes and proteins) are normal.

Diagnosis of unstable angina pectoris is based on a progressive increase in anginal symptoms or new onset of angina, confirmed by reversible ischemic ECG changes are seen during a spontaneous attack and absence changes in cardiospecific biochemical tests.

Prognosis. About 30% of patients with unstable angina will probably suffer a myocardial infarction within 3 months of onset; sudden death is less common. Presence of marked ECG changes with chest pain is an important marker for subsequent myocardial infarction or death.

Prinzmetal's variant angina

Definition: Prinzmetal's variant angina is usually secondary to large vessel spasm and is characterized by discomfort at rest and by ST segment elevation during the attack.

This relatively uncommon form of unstable angina is characterized by recurrent, prolonged attacks of severe ischemia, caused by episodic focal spasm of an epicardial coronary artery. Approximately three-fourths of patients with Prinzmetal's angina exhibit a mild or moderately severe fixed obstruction (with a luminal diameter 50 to 70% of normal) within 1 cm of the site of spasm. Patients with this condition are often smokers and are younger than patients with unstable angina secondary to coronary atherosclerosis. Ischemic pain usually occurs at rest, sometimes awakens the patient from sleep, and is characterized by multilead ST-segment elevation.

The diagnosis may be confirmed by detecting transient spasm occurring spontaneously or following a provocative stimulus (intracoronary acetylcholine, hyperventilation) on coronary arteriography.

While long-term survival is excellent, complications include episodes of disabling pain, myocardial infarction, serious ventricular arrhythmias, atrioventricular block, and, rarely, sudden death.

Myocardial Infarction (MI)

Definition: Myocardial infarction is formation of a necrotic focus in the heart muscle due to upset coronary circulation.

Myocardial infarction occurs mainly in people over 45; the incidence in men is higher than in women.

Etiology and pathogenesis. Causes of acute myocardial infarction:

(1) *Coronary thrombosis* - in > 90% of patients with acute myocardial infarction, an acute thrombus, often associated with plaque rupture, occludes the artery (previously partially obstructed by an atherosclerotic plaque) that supplies the damaged area;

(2) myocardial infarction is rarely caused by *arterial embolization* (eg, in mitral or aortic stenosis, infective endocarditis);

(3) *Coronary spasm* - myocardial infarction has been reported in patients with coronary spasm and otherwise normal coronary arteries.

One of the main causes of myocardial infarction (in at least 90—95 per cent cases) is atherosclerosis of the coronary arteries. In exceptionally rare cases, myocardial infarction is secondary to embolism of the coronary vessel in endocarditis or septic thrombophlebitis, in inflammatory affections of the coronary arteries such as rheumatic coronaritis, obliterating endarteritis, and nodular periarteritis. Cocaine causes intense coronary arterial spasm, and users may present with cocaine-induced angina or myocardial infarction. Autopsy studies and coronary angiography have shown that cocaine-induced coronary thrombosis may occur in normal coronary arteries or be superimposed on preexisting atheroma.

Overstrain, both physical and nervous, overeating, alcohol and nicotin poisoning can also provoke myocardial infarction.

The pathogenesis of myocardial infarction is complicated and has not been sufficiently studied. According to current views, several factors are responsible for the onset of the disease. The main of them is believed to be coronary thrombosis and stenotic coronary sclerosis. Coronary thrombosis develops due to local changes in the vascular wall which are characteristic of atherosclerosis, and also as a result of disorders in the blood coagulating system which are manifested by the decreased blood content of heparin and decreased fibrinolytic activity. In the absence of thrombosis, intense work of the heart in conditions of decreased blood supply to the myocardium (stenotic coronary sclerosis) is very important for the development of myocardial

infarction. Certain researchers believe that electrolyte imbalance in the heart muscle and accumulation of catecholamines in it and some other factors are important for the development of myocardial infarction.

Myocardial infarction is predominantly a disease of the left ventricle, but damage may extend into the right ventricle or the atria. Right ventricle infarction usually results from occlusion of the right coronary or a dominant left circumflex artery and is characterized by high right ventricle filling pressure, often with severe tricuspid regurgitation and reduced cardiac output. Some degree of right ventricle dysfunction occurs in about half of patients with an inferior-posterior infarction, producing hemodynamic abnormality in 10 to 15%. Right ventricle dysfunction should be considered in any patient with inferior-posterior infarction and elevated jugular venous pressure with hypotension or shock.

The ability of the heart to continue functioning as a pump relates directly to the extent of myocardial damage. Patients who die of cardiogenic shock usually have an infarct, or a combination of scar and new infarct, of > 50% of left ventricle mass. Anterior infarcts tend to be larger and have a worse prognosis than inferior-posterior infarcts. They are usually due to occlusion in the left coronary arterial tree, especially the anterior descending artery, whereas inferior-posterior infarcts reflect right coronary occlusion or occlusion of a dominant left circumflex artery

Pathological anatomy. When blood supply to a part of the myocardium becomes inadequate, ischemia develops, which is followed by ischemic myocardium injury and then necrosis. These three zones of myocardial damage in acute myocardial infarction may be detected histologically and by ECG: necrotic zone, ischemic myocardium injury zone, and zone of ischemia.

Inflammatory changes then develop found the necrotized area, and granular tissue grows. Necrotized mass is resorbed and replaced by cicatricial tissue. The heart muscle may rupture at the site of necrosis with hemorrhage into the pericardial cavity (*heart tamponade*). In gross myocardial infarction the scar tissue may be so thin that it can swell to give *cardiac aneurysm*. Myocardial infarction usually develops in the left ventricle. Muscle layers located beneath the endocardium are usually involved in the necrotic process (*subendocardial infarction*), but in severe cases, the entire muscle is involved (*transmural infarction*); in rare cases *subepicardial infarction* may be. Fibrinous pericarditis usually arises in such cases. Fibrin is sometimes deposited on the inner membrane of the heart at sites corresponding to myocardial necrosis (parietal thromboendocarditis). Thrombotic masses may be torn off and carried by the blood to account for embolism of the cerebral, abdominal, lung, and other vessels. According to the size of the necrotized focus, micro- and macrofocal myocardial infarctions are differentiated.

Cicatrization of uncomplicated myocardial infarction continues for one to three months. The process ends in *focal cardiosclerosis*.

Classification of myocardial infarction

(1) According to the stage MI – superacute, acute, subacute MI, reduction stage, cicatrization stage;

(2) According to the size of the necrotized focus - micro- and macrofocal MI;

(3) According to the depth of the necrotized focus – subendocardial, subepicardial, intramural, transmural MI;

(4) According to localization of the necrotized focus – anterior, posterior (diaphragmatic, posterobasal), lateral wall, apical MI of the left ventricle, anteroseptal MI, right ventricular MI, atrial MI;

(5) According to Q-wave of ECG - Q-wave and non- Q-wave MI

(6) According to clinical picture of acute MI –

a) typical forms - anginous, asthmatic, and abdominal MI;

b) atypical forms – arrhythmic, cerebral, collaptoid, edematous, peripheral with atypical localization of pain, low- or asymptomatic MI;

(7) Complications of MI: cardiogenic shock, acute left ventricular failure, myocardial rupture, arrhythmia, complete atrio-ventricular block, arterial embolism, pericarditis, ventricular aneurysm, post-MI syndrome (Dressler's syndrome).

Clinical picture. The outstanding Russian physicians Obratzov and Strazhesko were the first to describe the clinical picture of myocardial infarction in 1909; they differentiated between three typical variants of its course, namely, anginous, asthmatic, and abdominal (gastralgic) forms.

The anginous form occurs most frequently; clinically it is characterized by the pain syndrome. Pressing pain behind the sternum or in the region of the heart develops, like in angina pectoris. As a rule, pain radiates into the left shoulder and the left arm; less frequently into the right shoulder. Pain is sometimes so severe that cardiogenic shock develops which is characterized by the increasing weakness and adynamia, paleness of the skin, cold sweat, and decreased arterial pressure. As distinct from angina pectoris, pain in myocardial infarction is not removed by nitroglycerin and persists for longer time (from 30-60 minutes to several hours). Prolonged pain in myocardial infarction is termed as status anginosus.

The asthmatic form begins with an attack of cardiac asthma and lung edema. The main syndrome is either absent or weak.

The abdominal form of myocardial infarction is characterized-by pain in the abdomen, mostly in the epigastric region. The pain may be attended by nausea, vomiting, and constipation (gastralgic form of myocardial infarction).

This form of the disease occurs mostly in infarction of the posterior wall of the left ventricle.

Further observations have shown that the disease has considerably greater number of clinical signs. Myocardial infarction may sometimes begin with a sudden heart failure or collapse, various disorders in the cardiac rhythm or heart block, while the pain syndrome is either absent or is weak (painless form). This course often develops in recurrent infarction. The cerebral form of the disease is characterized by disorders in the cerebral circulation of various intensity.

Examination of the cardiovascular system reveals enlargement of cardiac dullness and low percussion sounds. The gallop rhythm can sometimes be heard. Pericardial friction is audible over a limited area, in the 3rd-4th interspaces, in transmural myocardial infarction. Pericardial friction becomes audible on the second or third day of the disease and persists for a few hours or may last one or two days. Pulse in myocardial infarction is often small, accelerated, or arrhythmical (in affection of the conduction system). Arterial pressure increases during pain attacks but then it falls.

Depending on the localization of infarction, circulation may be disordered by the left-ventricular or (less frequently) right-ventricular type. In the former case, congestive moist rales can be heard in the lungs; asphyxia resembling cardiac asthma may develop, which is then followed by edema of the lungs. In the latter case, the heart is enlarged to the right; the liver is enlarged too; the lower extremities are affected by edema.

Fever and leucocytosis develop on the second or third day of the disease. They result from reactive processes which depend on absorption of the autolysis products from the site of infarction. The larger the necrotized area, the higher is the temperature and the longer the pyretic period and leucocytosis. Elevated temperature persists for 3-5 days, sometimes 10 days and more; *ESR begins increasing and leucocytosis decreases* from the second week of the disease.

Diagnosis of myocardial infarction depends substantially on the determination of activity of some blood *serum cardiac markers* (myocardiospecific enzymes and proteins) which are released due to necrotic changes in the myocardium. *Myocardiospecific enzymes* study includes the activity of the MB-fraction of *creatine phosphokinase (CK-MB)*, the first enzyme of *lactic dehydrogenase (LDH₁)*, aminotransferase, and especially asparagines (AsAT) and (to a lesser degree) alanine (AlAT) increase by the end of the first day of the disease. The activity of CK-MB normalizes in 2-3 days, of aminotransferase in 4-5 days, and of LDH₁ in 10—14 days.

CK-MB, the myocardial component of CK, is a most specific in diagnostics of MI. It is found in blood within 6 h of myocardial necrosis. Levels are elevated for 36 to 48 h. Although small amounts of CK-MB are found in other tissues, elevations of CK with > 40% MB are diagnostic when

associated with clinical findings suggestive of MI. Routine measurement of CK-MB on admission and 6 to 8 h for the first 24 h will confirm or reject the diagnosis. Normal CK-MB for 24 h virtually rules out MI.

Myoglobin and the contractile proteins troponin-T and troponin-I are also released by infarcted myocardium. Troponin-T and troponin-I (*Cardiac-specific troponin T (cTnT) and cardiac-specific troponin I (cTnI)*) appear to be highly sensitive markers of myocardial injury and may replace conventional CK-MB analysis in early decisions in patients with chest pain and nondiagnostic ECG. Cardiac-specific troponins - troponin-T and troponin-I are found in blood within 2-4 h of myocardial necrosis. Levels are elevated for 7 days. Troponins are released in some patients with unstable angina, and activity level predicts future adverse events.

Myoglobin is released into the blood within only a few hours of the onset of acute MI. Although myoglobin is one of the first serum cardiac markers that rise above the normal range after AMI, it lacks cardiac specificity, and it is rapidly excreted in the urine, so that blood levels return to the normal range within 24 h of the onset of infarction.

ECG in myocardial infarction

Electrocardiographic examination is especially important. It establishes the presence of myocardial infarction and also some important details of the process such as localization, depth of the process, and the size of the affected area.

Three zones of myocardial damage in acute myocardial infarction can be detected by ECG: necrotic zone, ischemic myocardium injury zone, and zone of ischemia.

Myocardial necrosis is detected by pathological Q-wave:

Pathological Q-wave is characterized by width $\geq 0,04$ s (in $V_{4-6} > 0,025$ s), depth > 2 mm or $> 1/4$ R-wave (in $V_{4-6} > 15\%R$).

Ischemic myocardium injury is detected by ST-interval:

- Transmural or epicardial injury - convexing elevation ST with transmission in T-wave;

- Subendocardial injury – horizontal or concaving depression ST.

Ischemia of myocardium is detected by T-wave:

- Subendocardial ischemia – symmetrical acute high T-wave in overlying leads (> 6 mm in standard and augmented leads, $> 8-10$ mm in chest leads);

- Transmural or epicardial ischemia - symmetrical acute deep T-wave.

The *S-T* segment and *T* wave change during the first hours of the disease. The descending limb of the *R* wave transforms into the *S-T* segment without reaching the isoelectric line. The *S-T* segment rises above the isoelectric line to form a convexing arch and to coincide with the *T* wave. A monophasic curve is thus formed. These changes usually persist for 3—5 days (*acute stage of MI*).

Then the *S-T* segment gradually lowers to the isoelectric line while the *T* wave becomes negative and deep. A deep *Q* wave appears, the *R* wave becomes low or disappears at all. The *QS* wave is then formed, whose appearance is characteristic of transmural infarction. Duration of these ECG signs is 3—5 (7) days up to 1-3 weeks (*acute stage of MI*).

During *reduction stage of MI* (2-6 weeks from the onset of infarction) deep *Q* wave, *S-T* on isoelectric line and negative ischemic (symmetrical) *T* wave present.

The initial shape of ECG can be restored during *cicatrisation stage* (2- up to 6 month from the onset of infarction), or the changes (penetrating and widened *Q* wave, negative *T* wave) may remain for the rest of life.

Depending on localization of *MI*, changes in the ventricular complex are observed in the corresponding leads:

- anterior wall of left ventricle - V_{1-4} , I, aVL;
- anterior part of interventricular septum - V_{1-2} ;
- lateral wall of left ventricle - I, aVL, V_{5-6} ;
- posterior (inferior diaphragmatic) wall of left ventricle - II, III, aVF;
- posterior (superior basal) wall of left ventricle detected by high *R* wave in V_{1-2} .

Two-dimensional echocardiography is the most frequently employed imaging modality in patients with acute *MI*. Abnormalities of wall motion are almost universally present.

The radionuclide method can be helpful in diagnosing myocardial infarction. Myocardial perfusion imaging with ^{201}Tl or $^{99\text{m}}\text{Tc}$ -sestamibi, which are distributed in proportion to myocardial blood flow and concentrated by viable myocardium reveal a defect ("cold spot") in most patients during the first few hours after development of a transmural infarct. However, although perfusion scanning is extremely sensitive, it cannot distinguish acute infarcts from chronic scars and thus is not specific for the diagnosis of acute *MI*.

Characteristics of microfocal myocardial infarction

Retrosternal oppression and general weakness are the usual symptoms in microfocal myocardial infarction. Moderately high temperature usually persists for 1—2 days. Mild leucocytosis is only transient; ESR is slightly increased and the enzymatic activity is increased. The ECG changes are as follows: the *S-T* segment is below and sometimes above the isoelectric line, and the *T* wave is either negative or two-phase. These changes disappear in a few days or in a month.

Diagnosis of acute MI requires at least two of the following:

- (1) A history of ischemic-type chest pain;
- (2) Evolving ECG- changes;

(3) A rise and fall in serum cardiac markers.

Serum cardiac markers are used to support the diagnosis of acute MI:

- creatine phosphokinase (CK) - CK-MB, the myocardial component of CK, is found in blood within 6 h of myocardial necrosis. Levels are elevated for 36 to 48 h;

- cardiac-specific troponins - Troponin-T and Troponin-I are found in blood within 2-4 h of myocardial necrosis. Levels are elevated for 7 days;

- lactic dehydrogenase (first enzyme) – LDH₁ peaks at 3-4 days and remains for up to 10-14 days;

- aspartate aminotransferase (AST) increases by the end of the first day of the disease and normalizes in 4-5 days.

Serum cardiac markers should be measured in all patients with suspected MI. Levels greater twice than the upper limit of normal are confirmatory in patients with history of ischemic-type chest pain and/or ECG-changes.

Complications of myocardial infarction

Arrhythmia in some form occurs in > 90% of MI patients. Bradycardia or ventricular extrasystole may be observed early in the course of MI. Conduction disturbances can reflect damage to the sinus node, the atrioventricular node, or specialized conduction tissues. Life-threatening arrhythmias, major causes of mortality in the first 72 h, include paroxysmal tachycardia from any focus rapid enough to reduce cardiac output and lower BP, Mobitz II or second-degree or third-degree atrio-ventricular heart block, and ventricular tachycardia and ventricular fibrillation. Complete heart block with wide QRS (atrial impulses fail to reach the ventricle, ventricular rate is slow) is uncommon and usually denotes massive anterior MI. Complete atrioventricular block with narrow QRS usually indicates an inferior or posterior infarct. Asystole is uncommon except as a terminal manifestation of progressive LV failure and shock.

Atrial fibrillation and atrial flutter (which is less common than atrial fibrillation) occur in about 10% of MI patients and may reflect left ventricle failure or right atrial infarction. Paroxysmal atrial tachycardia is uncommon and usually occurs in patients who have had previous episodes.

Heart failure occurs in about 2/3 of hospitalized patients with acute MI. Left ventricle dysfunction usually predominates, with dyspnea, inspiratory rales at the lung bases, and hypoxemia. Clinical signs depend on the size of the infarction. The mortality rate varies directly with the severity of left ventricle failure.

Arterial hypotension in acute MI may be due to decreased ventricular filling or loss of contractile force secondary to massive MI.

Cardiogenic shock, characterized by hypotension, tachycardia, reduced urine output, mental confusion, diaphoresis, and cold extremities, has a

mortality of > 65%. It is most often associated with massive anterior infarction and > 50% loss of left ventricle functioning myocardium.

Myocardial rupture occurs in three forms: rupture of the papillary muscle, rupture of the interventricular septum, and external rupture. *Rupture of the papillary muscle* produces acute, severe mitral regurgitation and is characterized by the sudden appearance of a loud apical systolic murmur and thrill, usually with pulmonary edema.

Rupture of the interventricular septum, although rare, is 8 to 10 times more common than rupture of the papillary muscle. Sudden appearance of a loud systolic murmur and thrill medial to the apex along the left sternal border in the 3rd or 4th intercostal space, accompanied by hypotension with or without signs of left ventricle failure, is characteristic. Doppler echocardiography is often diagnostic.

External rupture increases in incidence with age and is more common in women. It is characterized by sudden loss of arterial pressure with momentary persistence of sinus rhythm and often by signs of cardiac tamponade. It is almost always fatal.

Ventricular aneurysm is common, especially with a large transmural infarct (most commonly anterior) and good residual myocardium. Aneurysms may develop in a few days, weeks, or months. They do not rupture but may be associated with recurrent ventricular arrhythmias and low cardiac output. Another hazard of ventricular aneurysm includes mural thrombus and systemic embolization.

An aneurysm may be suspected when paradoxical precordial movements are seen or felt, accompanied by persistent elevation of ST segments on the ECG or a characteristic bulge of the cardiac shadow on x-ray. Echocardiography helps establish the diagnosis and determine the presence of a thrombus.

Acute cardiac aneurysm is characterized by pericardial pulsation in the 3rd or 4th intercostal space, to the left of the sternum. Auscultation of the heart reveals the gallop rhythm, systolic murmur, and pericardial friction. An acute cardiac aneurysm is converted into chronic when the necrotized site turns into a scar of connective tissue, or chronic aneurysm can develop at later periods of the disease.

Signs of chronic aneurysm are pericardial pulsation, extension of the heart border to the left, systolic murmur in the region of the aneurysm, and a "stabilized" electrocardiogram on which the changes characteristic of acute period of the disease are preserved. X-ray examinations show enlargement of the heart silhouette and paradoxical pulsation. Chronic cardiac aneurysm causes heart failure which is difficult to cure.

Mural thrombosis occurs in about 20% of acute MI patients (60% of patients with large anterior infarcts). *Systemic embolism* occurs in about 10% of patients with left ventricle thrombus (best diagnosed by

echocardiography); risk is highest in the first 10 days but persists at least 3 months.

Pericarditis may cause a pericardial friction rub in about 1/3 of patients with acute transmural MI. The friction rub usually begins 24 to 96 h after MI onset. Earlier onset is unusual and suggests other diagnoses (eg, acute pericarditis), although hemorrhagic pericarditis occasionally complicates the early phase of MI. Acute tamponade is rare.

Post-MI syndrome (Dressler's syndrome) develops in a few patients several days to weeks or even months after acute MI, although the incidence appears to have declined in recent years. It is characterized by fever, pericarditis with friction rub, pericardial effusion, pleurisy, pleural effusions, pulmonary infiltrates, and joint pains. Differentiation from extension or recurrence of infarction may be difficult, but cardiac enzymes do not significantly rise. This syndrome may be recurrent.

Course of myocardial infarction

This depends on the size of the affected area, the condition of other arteries of the heart and collateral circulation, on the degree of cardiac and circulatory insufficiency, and on the presence of complications. Cardiorrhesis is among them. It occurs during the first ten days of the disease, during pronounced myomalacia leading to rapid (within a few minutes) death. Fatal outcome may be caused by ventricular fibrillation. Cardiac aneurysm can develop during the disease. An acute aneurysm occurs during the first days of transmural infarction: the increased intraventricular blood pressure causes a protrusion at the site of myomalacia of intact layers of the heart wall. The aneurysm is usually formed in the wall of the left ventricle. Cicatrization of uncomplicated myocardial infarction continues for one to three months. The process ends in focal atherosclerosis.

Conception of acute coronary syndrome

Definition: Acute coronary syndrome is a set of clinical symptoms of myocardial ischemic pain attacks (>10 minutes, nonresponsiveness to nitroglycerin) due to acute disorder of the coronary circulation permitting to suspect *unstable angina pectoris or acute myocardial infarction* with elevation ST or without elevation ST.

ECG remains the major diagnostic procedure of acute coronary syndrome. Variants of ECG patterns with acute myocardial ischemia are:

- non-infarction subendocardial ischemia - transient ST depressions;
- non-infarction transmural ischemia - transient ST elevation or paradoxical T-wave normalization, some times followed by T-waves inversions;
- non-Q-wave (non-ST elevation) infarction - ST depressions or T-inversions without Q-wave;

- Q-wave–infarction - Q-wave with hyperacute T-waves/ST-elevations followed by T-waves inversions.

Diagnosis of the “acute coronary syndrome” is permitted to use not more than 24-48 hours after the onset of clinical picture. For quick and reliable differentiation unstable angina pectoris and acute myocardial infarction the serum cardiac markers (CP-MB and/or cardiac-specific troponins - Troponin-T and Troponin-I) should be measured in all patients with acute coronary syndrome. Levels of serum cardiac markers greater twice than the upper limit of normal confirm diagnosis of acute myocardial infarction.

Diseases of digestive system

Diseases of esophagus, stomach and duodenum

Clinical examination in diseases of esophagus, stomach and duodenum

The spectrum of diseases affecting the upper gastrointestinal tract and their clinical manifestations are related to the component organ(s) involved. Thus, esophageal disorders manifest themselves mainly through their effects on swallowing; gastric and duodenum disorders are dominated by features relating to acid secretion. When no structural lesion can be identified to explain GI symptoms, the disorder is termed *functional*.

Clinical examination in diseases of esophagus

Complaints. The most typical complaints in pathology of esophagus are dysphagia, odynophagia, heartburn, chest pain, hematemesis and melena.

Dysphagia is a subjective awareness of difficulty in swallowing caused by impaired progression of matter from pharynx to stomach. This is the most frequent symptom of esophageal pathology. Dysphagia is caused by impeded transport of liquids and solids by organic lesions of the pharynx, esophagus, and adjacent organs or by functional derangements of the nervous system and musculature.

Odynophagia is a pain during swallowing. Odynophagia may occur with or without dysphagia and may be caused by mucosal destruction (eg, GERD-induced esophagitis); bacterial, viral, or mycotic infections; or tumors, chemicals, or esophageal motor disorders (eg, achalasia, diffuse esophageal spasm). The patient may describe the pain as a burning sensation or a substernal tightness typically elicited by very hot or very cold food or liquid. Pain occurs promptly with swallowing. Severe squeezing chest pain, induced by swallowing hot or cold beverages in association with dysphagia, is characteristic of esophageal motor disorders.

Heartburn is a substernal burning pain that rises in the chest and may radiate into the neck, throat, or even face. Heartburn is caused by acidification of the esophagus by GERD. It usually occurs after meals or when lying down. Heartburn may be accompanied by regurgitation of gastric contents into the mouth and subsequent “water brash”, which is hypersalivation occurring via vagal stimulation when acid irritates the lower esophagus.

Chest pain occurs in acute inflammation of the esophageal mucosa (esophagitis) and in burns. The patient usually feels pain by the course of the entire esophagus, both with and without swallowing; pain may radiate into the interscapular region.

Patients with achalasia of the cardia (cardiospasm) may have spontaneous attacks of pain, usually during night. Pain is quite severe; it radiates into the back, upwards by the esophagus, into the neck, the jaws, and continues for minutes and even hours. In the presence of hiatus hernia and gastroesophageal reflux, pain may radiate into the left side of the chest and simulate heart diseases.

Spontaneous esophageal motor disorder pain is difficult to differentiate from other esophageal symptoms and cardiac chest pain. Spontaneous esophageal chest pain may be severe and mimic angina pectoris. Definitive diagnosis is not possible unless the motor disorder can be recorded during manometry concurrent with the patient's typical pain. The presence of dysphagia with chest pain may indicate an esophageal origin.

Hematemesis and melena are signs of esophageal hemorrhage. Hemorrhage can be due to ulcer of the esophagus in GERD, injury to the esophagus by a foreign body, degradation of a tumour, bleeding of dilated esophageal veins (which occurs in congestion of blood in the portal vein system), and also bleeding of the mucosa due to small lacerations of the vessels in the esophagogastric junction in straining and vomiting (Mallory-Weiss syndrome). Hematemesis in esophageal bleeding differs from gastric hematemesis by presence of unaltered (non-digested) blood of red colour, fluid, alkaline medium reaction because absence of hydrochloric acid and pepsin (gastric juice).

Melena (tarry like feces) is a late clinical sign of the acute esophageal hemorrhage; it may be revealed in 10-12 hours up to and 2-3 days after episode of bleeding.

History. A history precisely detailing the patient's symptoms has a diagnostic accuracy of about 80%. In organic affections of the esophagus, the disease has a progressive course. Functional disorders are characterized by exacerbations connected with psychogenic factors or irritative food intake which are followed by remissions. Past life history may establish whether the patient had past burns of the esophagus, since acid or alkali burns are frequent causes of cicatricial changes in the esophagus.

The only *physical findings* in esophageal disease are (1) cervical and supraclavicular lymphadenopathy caused by metastasis, (2) swellings in the neck from large pharyngeal diverticulum, and (3) prolonged swallowing time (the time from the act of swallowing to the sound of the bolus of fluid and air entering the stomach, heard by auscultation with the stethoscope over the epigastrium; normally – 7-12 sec). Esophageal motor disorders are associated with prolonged swallowing times. Watching the patient swallow may help to evaluate patients with preesophageal dysphagia for aspiration or nasal regurgitation.

Laboratory and instrumental studies of esophagus

X-ray examination of the esophagus may show structural and motor functional disorders. In addition to the standard barium meal, video- and cinefluoroscopy aid in detecting anatomic conditions (eg, esophageal webs) and in assessing motor disorders (eg, cricopharyngeal spasm, achalasia).

Esophagoscopy can be performed diagnostically to evaluate pain or dysphagia, to identify structural abnormalities or bleeding sites, or to obtain biopsy specimens.

Esophageal biopsy may show thinning of the squamous mucosal layer and basilar cell hyperplasia, and malignant cells, even without evidence of gross esophagitis or tumour by endoscopy.

Esophageal manometry is used to evaluate patients with dysphagia, heartburn, or chest pain. It determines the pressure in the upper and lower esophageal sphincters and the effectiveness and coordination of propulsive movements and detects abnormal contractions. It is used to diagnose achalasia, diffuse spasm, scleroderma, and lower esophageal sphincter hypo- and hypertension and to evaluate esophageal function for certain therapeutic procedures (eg, antireflux surgery, pneumatic dilation for achalasia). It is performed by passing a small tube past the throat and into the esophagus.

Esophageal pH monitoring is performed either during esophageal manometry or as a prolonged study in ambulatory patients. Esophageal pH monitoring provides direct evidence of GERD.

Bernstein (acid perfusion) test is a sensitive means of determining whether acid reflux is the cause of pain, but may be falsely negative in the patient receiving treatment. This test is performed by perfusing the esophagus with alternating solutions of isotonic saline and 0,1 N hydrochloric acid through a nasogastric tube at a rate of 6 ml/min. Symptoms are promptly reproduced by acid perfusion in the esophagus and relieved by saline perfusion.

Clinical examination in diseases of stomach and duodenum

Complaints. The most typical complaints in pathology of the stomach are epigastric pain, nausea and vomiting, early satiety or increased appetite, hematemesis and melena.

Epigastric pain is the leading symptom in diseases of the stomach. Epigastric pain may be also due to diseases of the liver, pancreas, and hernia of the linea alba. Epigastric pain may develop in diseases of other abdominal organs (sometimes of organs located outside the abdomen) by the viscerovisceral reflex (acute appendicitis, myocardial infarction, affection of the diaphragmatic pleura, etc). The pain may be dull, stabbing, cutting, etc. Pain in stomach and duodenum is provoked by spasms (spastic pain), distension of the organ (distensional pain), and by its motor dysfunction.

Paroxysmal, periodical epigastric pain is due to the spasm of the pyloric muscles. The spasm of the pylorus is stimulated by the hyperacidity of gastric juice due to hyperstimulation of the vagus.

Depending on the time of paroxysmal pain (after meals), it may be *early pain* (occurring 30-40 min after meals), *late pain* (90-120 min after meals), *nocturnal pain*, and *hunger pain* (which is abated after taking food). If pain occurs after meals stimulating secretion of gastric juice (bitter, pungent, spicy or smoked foods), this indicates the leading role of stomach acid hypersecretion in its etiology. The pain then localizes in the epigastrium, radiates to the back, and is rather intense; it is abated after vomiting and taking alkali or foods that decrease acidity of gastric juice, and also after taking antysecretory and antacid preparations and after meal.

A seasonal character of pain, i.e. development of periodic pain during spring and autumn, is characteristic of the stomach and duodenal peptic ulcers, especially if the process is localized in the peripyloric region.

Permanent boring pain is usually caused by stimulation of the nerve elements in the mucous and submucous layer of the stomach; the pain is usually intensified after meals and is characteristic of exacerbation of chronic gastritis or cancer of the stomach.

Nausea is the subjective feeling of a need to vomit. *Vomiting* (emesis) is the oral expulsion of upper gastrointestinal contents resulting from contractions of gastrointestinal and thoracoabdominal wall musculature.

Vomiting can be caused by difficult evacuation of the stomach due to spasms or stenosed pylorus. Morning vomiting (on a fasting stomach) with expulsion of much mucus is characteristic of chronic gastritis, especially in alcoholics. Hyperacid vomiting in the morning indicates nocturnal hypersecretion of the stomach. Vomiting occurring 10-15 minutes after meals suggests ulcer or cancer of the cordial part of the stomach, or acute gastritis. If vomiting occurs 2-3 hours after meals (during intense digestion) it may indicate ulcer or cancer of the stomach body. In the presence of ulcer of the pylorus or duodenum, vomiting occurs 4-6 hours after meals. Expulsion of food taken a day or two before is characteristic of pyloric stenosis. Patients with peptic ulcer often vomit at the height of pain thus removing it, which is typical of the disease. The odour of the vomit is usually acid, but it can often be fetid (putrefactive processes in the stomach); the odour may be even fecal

(in the presence of a fecal fistula between the stomach and the transverse colon).

Gastroparesis can produce nausea within minutes of food consumption but, in severe cases, leads to vomiting of meal residue ingested hours or days previously. Blood in the vomitus raises suspicion of an ulcer or malignancy; feculent emesis is noted with distal intestinal or colonic obstruction. Bilious vomiting excludes gastric obstruction, whereas emesis of undigested food is consistent with a pharyngoesophageal process such as diverticulum or achalasia. Relief of abdominal pain by emesis characterizes stomach and duodenum peptic ulcers and small bowel obstruction, but vomiting has no effect on pancreatitis or cholecystitis pain. Pronounced weight loss raises concern about malignancy or obstruction.

Increased appetite is a symptom connected with the stomach acid hypersecretion in peptic ulcers, gastritis and functional dyspepsia. This symptom may be also in diabetes mellitus, thyrotoxicosis, etc. That is why patients with increased appetite are necessary in thorough examination.

Early satiety is the symptom connected a distress of an accommodation of the stomach in reply to reception of nutrition. In this case an accommodation means ability of proximal department of the stomach to be relaxed after reception of nutrition because of constantly increasing pressure of contents on its walls. This symptom is typical to patients with functional dyspepsia. Early satiety accompanied absence or decrease of appetite may be connected also with low stomach secretion (gastric hypo- and anacidity) in chronic gastritis, cancer of stomach, various toxic conditions, active inflammatory pathology, decompensated insufficiency of vital organs (heart, liver, kidney), central nervous system pathology.

Hematemesis is a very important symptom of stomach and duodenum hemorrhage. It may be manifested by vomiting of blood (hematemesis) or by black tarry stools (*melena*). Gastric hemorrhage is usually manifested by the presence of blood in the vomitus if volume of bleeding more than 50-100 ml.

The appearance of the vomitus depends on the time during which the blood is present in the stomach. If the blood was in the stomach for a long time, the blood reacts with hydrochloric acid of the gastric juice to form hematin hydrochloride, and the vomitus looks like *coffee grounds*. If hemorrhage is profuse (damage to a large vessel) the vomitus contains much scarlet (unaltered) blood and clots, and has acid medium reaction.

Hematemesis occurs in peptic ulcer, cancer, and polyps, in erosive gastritis, rarely in sarcoma, tuberculosis and syphilis of the stomach, and in varicosity of the esophageal veins.

Melena (tarry like feces) is a late and not obligatory sign of gastroduodenal hemorrhage. It may be revealed in 10-12 hours up to and 2-3 days after episode of bleeding if loss of blood more than 250-300 ml.

History. A thorough clinical history is essential in directing the clinician's attention to appropriate diagnostic considerations in the patient with gastroduodenal symptoms. Pain of abrupt onset more often reflects serious illness requiring urgent intervention, while a history of chronic discomfort is most often related to an indolent disorder. Dyspepsia, an ill-defined upper abdominal discomfort, is especially common and is often accompanied by varying degrees of nausea, bloating, and distention. Dyspepsia may be associated with peptic ulceration, but non-ulcer dyspepsia is more common. A change in the pattern or character of pain may signify disease progression. Pain occurring shortly after the meal may signify functional dyspepsia or gastritis; pain 30 to 90 min later is typical of peptic disease. Conversely, factors that relieve the symptom are also helpful. For example, eating or antacid use typically relieves pain in peptic ulcer disease or gastritis.

The patient should be asked about his nutrition. It is important to establish if meals are regular because taking food at random is an important factor in the etiology of gastric diseases. Food quality is as important as its amount taken during one meal. Conditions of rest and work, and possible occupational hazards should be established. Abuse of alcohol and smoking are important factors in the etiology of gastric diseases. The patient should be asked about his nutrition. It is important to establish if meals are regular because taking food at random is an important factor in the etiology of gastric diseases. Food quality is as important as its amount taken during one meal. Mastication of food matters as well. Conditions of rest and work, and possible occupational hazards should be established. Abuse of alcohol and smoking are important factors in the etiology of gastric diseases.

Physical examination in gastroduodenal diseases

Inspection may disclose signs of nutritional deficiencies. Examination of the abdomen for an abnormal contour may reveal signs of a mass. *Auscultation* may elicit a succussion splash in patients with symptoms of stenosis of pylorus, gastroparesis, and gastric hypersecretion. Careful *palpation* of the abdomen is especially important in detecting tenderness, distention and masses.

Laboratory and instrumental in diseases of stomach and duodenum

Upper gastrointestinal endoscopy (gastroduodenoscopy) is used to establish the site of upper GI (gastrointestinal) bleeding; to visually define and biopsy abnormalities seen on upper GI series (gastritis, gastric and duodenal ulcers, filling defects, mass lesions); to follow up treated gastric ulcers; and to evaluate stomach and duodenum for infection *Helicobacter pylori*.

Now *X-ray examination* is a complementary (to endoscopy) method in assessing motor disorders and evacuation of stomach and duodenum.

CT (computer tomography) is useful in the diagnosis of a tumour.

Study of gastric secretion

Study of gastric secretion is important part of complex diagnosis of the gastric mucosa function. The most reliable data on the gastric secretion can be obtained by *studying gastric juice* and *intragastric pH-metry*.

Study of gastric juice

Adequate probing implies obtaining pure gastric juice and studying gastric secretion for long periods of time, during various periods of the secretory cycle.

The study usually begins with evacuation of gastric juice from a fasting stomach. Gastric intubation with thin gastric tube is used to obtain a sample of gastric contents for analysis. Four 15-minute samples of the juice are taken from the fasting stomach. This is the so-called *basal secretion*, though the term does not exactly define the essence of the process, because it is very difficult to decide whether the obtained juice is spontaneous secretion or secretion induced by the swallowing movements, or the tube itself (see Supplement, table 14).

After the last (fourth) portion of the basal secretion is obtained (in 60 min), the patient is given a stimulating agent (*test meal*), which may be given either through the gastric tube or parenterally (pentagastrin, histamine, insulin). Pentagastrin (synthetic) and histamine are very effective; these are physiological stimulants of gastric secretion. Histamine is contraindicated in organic cardiovascular diseases, allergic diseases, high arterial pressure, pheochromocytoma, and after recent (2-3 weeks ago) gastro-intestinal hemorrhage. The dose of histamine is calculated according to the patient's weight (0,008 mg/kg of body weight). This stimulation of gastric secretion is *submaximal*. There exists a maximum dose of *histamine (maximal stimulation)*: a further increase of the dose does not intensify secretion of the stomach (0,024 mg of histamine phosphate/kg of body weight). If the maximum dose of histamine is given (Kay's test), the patient should first be given an antihistamine preparation.

After administration of histamine or pentagastrin (0,006 mg/kg of body weight, gastric juice is collected for an hour, at 15-minute intervals for estimation of *stimulation secretion*.

Acidity of gastric juice is determined by titrating it with a 0,1 N sodium hydroxide solution in the presence of indicators. Acidity is expressed in milliliters of 0,1 N NaOH solution which are used to neutralize 100 ml of the juice. In this case 1 milliliter of 0,1 N NaOH solution equals to 1 titrating unit. It has become usual now to express acidity in milligrams of HCl or milli-equivalents (MEq).

Thus the *normal content of hydrochloric acid in the fasting stomach* of a healthy subject was considered to be maximum 10-20 titrating units (t.u.),

or the acid might be absent at all. Normal acidity of basal secretion is 20-40 titrating units for free HCl and 40-60 for total acidity. Normal acidity after submaximal stimulation is 60-85 titrating units for free HCl and 90-100 for total acidity. Normal acidity after submaximal stimulation) is 60-85 titrating units for free HCl and 90-100 for total acidity. Normal acidity after maximal stimulation is 90-110 titrating units for free HCl and 100-120 for total acidity.

The excess of free HCl in gastric juice in basal and/or stimulation secretion is called *hyperchlorhydria*. This symptom is typical to peptic ulcers and chronic gastritis B. The low level or absence of free HCl in gastric juice in basal and stimulating secretion simultaneously is called respectively *hypochlorhydria* or *achlorhydria*. This symptom is typical to atrophic gastritis and cancer of stomach. The absence of free HCl in gastric juice after giving the maximum dose of histamine or pentagastrin is called refractory *achlorhydria*. This symptom may suggest atrophic process in gastric mucosa.

Acidity (concentration of the acid) does not characterize completely the acid-secreting function of the stomach. *A more detailed information can be obtained by determining the hourly secretion of the stomach.* To that end, acid concentration in the gastric juice should be multiplied by the hourly secretion of the stomach and divided by 100 (if acid concentration is expressed in mg/100 ml) or by 1000 (if the concentration is given in mEq/l).

Acidity in titration units can be expressed as concentration of the acid in mg/100 ml by multiplying the acidity index by 3,65, because the weight equivalent of the titration unit is 3,65 mg HCl or 0,1 mEq HCl in 100 ml of gastric juice. For example, acidity of 60 t.u. can be expressed as $(3,65 \times 60)$ mg/100 ml or 60 mEq/l, or 60 mmol/l HCl.

Continuous hourly basal secretion of HCl is called *basal acid output (BAO)*. Hourly stimulation (histamine 0,024 mg/ kg or pentagastrin 0,006 mg/kg) secretion of HCl is called *maximal (or peak) acid output (MAO or PAO)*. Samples are titrated with sodium hydroxide to calculate BAO and stimulated MAO secretory rates. In norm BAO equals 8-14 mmol/l of common HCl or 6,5-12 mmol/l of free HCl; MAO equals 18-26 mmol/l of common HCl or 16-24 mmol/l of free HCl.

Microscopic studies of gastric juice. Native preparations are made from a settled or centrifuged precipitate. Gastric juice precipitate of healthy subjects contains mostly cells of the mouth (squamous epithelium and leucocytes). The presence of food remains (muscle fibres, fat, fatty acids, subcutaneous fat) indicates evacuation dysfunction of the stomach. Acid stagnant juice contains sarcinae (saprophytes). If acidity is absent, lactic bacilli are present in the juice. Erythrocytes in small quantities are diagnostically unimportant because their presence may be due to an injury caused by probing or strain during vomiting. Ample erythrocytes suggest the presence of ulcer, tumour, or erosive gastritis.

Intragastric pH-metry

The basic condition of intragastric pH-metry is complete emptying of a stomach before research. The research APFS (acid-production function of stomach) is usual provided at the morning on empty stomach. In presence of the motor (evacuation) dysfunction of stomach, contents of it are removed with the help of a gastric tube before the research.

pH-probe prepared for research is introduced through a mouth or nasopharyngeal meatus into a stomach of the patient up to conditional labels allowing to judge about a place of the probe. For correct interpreting of the data the control of a position of a probe is extremely important. Control of installation of a probe can be determined with the help ultrasonic or X-ray inspection. In dependence from the aims of research the pH-probe can be fixed in a stomach or at duodenum both and esophagus. The pH-metry probe has two electrodes: the upper electrode C (corpus) - for body of the stomach (acid-production part of the stomach); the lower electrode A (antrum) – for antrum part of the stomach (alkalinising part of the stomach).

The first stage of pH-metry is a state of APFS in *basal secretion* (see Supplement, table 15); the research lasts 30 up to 45 minutes. It is necessary to note, that in basal condition a secretory device of stomach is in a state of functional rest, and about 15 % of parietal cells “work”.

For definition of functional activity of the secretory device of a stomach stimulators of gastric secretion would be applied. The most widespread stimulators of a stomach secretion are histamine and pentagastrin. Their submaximal and maximal doses stimulate 45 % and 90 % of parietal cells accordingly. *Stimulation secretion* can be estimated within 45 minutes up to 1 hour.

In stimulation phase of the stomach secretion *the alkaline test* is performed, and time of recovery pH in body of a stomach can be estimated. Duration of the test – 15 minutes.

Assessment of values of the alkaline test in a stimulated phase:

- less than 5 minutes – sharp increase of production of hydrochloric acid at stimulation;
- from 5 about 10 minutes – increased production of hydrochloric acid at stimulation;
- from 10 about 15 minutes – normal intensity of acid-production at stimulation;
- more than 15 minutes – diminished production of a hydrochloric acid at stimulation.

As it is visible from the submitted data, the assessment of parameters of intragastric pH represents a complex enough (multiple enough) problem. In this connection in last models of acidometers the received data are interpretative with the help of the computer.

Syndrome of dysphagia

Definition: Dysphagia (R13 according to ICD-X) is a difficult passage of food from pharynx via the esophagus to stomach.

Classification:

- (1) According to cause -
 - a. Functional (motor) dysphagia,
 - b. Organic (obstructive) dysphagia
- (2) According to localization -
 - a. Preesophageal (oropharyngeal) dysphagia,
 - b. Esophageal dysphagia.
- (3) According to course of dysphagia -
 - a. Intermittent dysphagia,
 - b. Progressive dysphagia.

Dysphagia can be due to *organic or functional* narrowing of the esophagus. *Organic dysphagia* develops gradually and progresses in cancer, and cicatricial stenosis of the esophagus. Solid food first passes with difficulty, then the patient feels difficulty in swallowing soft, and then liquid food. When cancer tumour disintegrates, patency of the esophagus may be restored almost completely. Dysphagia develops immediately in the presence of a foreign body or if the esophagus is burnt. Dysphagia may also develop due to compression from outside by an aortic aneurysm or mediastinal tumour.

Functional esophagus is explained by muscular spasms caused by reflex disorders in innervation of the esophageal muscles, or by neurosis. As distinct from organic dysphagia, functional dysphagia more often occurs in paroxysms when food passes the esophagus. Sometimes solid food passes more readily than liquid.

Preesophageal (oropharyngeal) dysphagia is a difficulty emptying bolus material from the oral pharynx into the esophagus.

Preesophageal dysphagia occurs with abnormal function proximal to the esophagus, most often in patients with neurologic or muscular disorders that affect skeletal muscles (eg, dermatomyositis, myasthenia gravis, muscular dystrophy, Parkinson's disease, amyotrophic lateral sclerosis, bulbar poliomyelitis, other central nervous lesions). The patient frequently presents with nasal regurgitation or tracheal aspiration followed by coughing.

Esophageal dysphagia is a difficulty passing food down the esophagus, possibly caused by obstructive or motor disorders.

Esophageal dysphagia is sometimes associated with obstructive disorders (eg, cancer, benign peptic stricture, lower esophageal ring). Obstructive disorders usually produce dysphagia for solids alone by mechanically reducing the esophageal lumen. Meat and bread are often singled out as the major offenders, but some patients cannot tolerate any

solids, only liquids. Patients who complain of dysphagia in the lower esophagus are usually correct in terms of origin, whereas patients who complain of dysphagia in the upper esophagus are often incorrect. Dysphagia can be *intermittent* (eg, from lower esophageal ring), *progress* rapidly over weeks to months (eg, from esophageal cancer), or *progress* over years (eg, from peptic stricture). In cases of peptic stricture, dysphagia is preceded by a prominent history of gastroesophageal reflux disease (GERD).

Esophageal dysphagia is sometimes associated with motor disorders (eg, achalasia, symptomatic diffuse esophageal spasm, scleroderma). Motor disorders involve dysfunction of the smooth muscle of the esophagus. They produce dysphagia for both solids and liquids by impairing esophageal peristalsis and lower esophageal sphincter function, thus interrupting the smooth esophageal transport of a bolus. The presence of dysphagia for both liquids and solids accurately distinguishes motor from obstructive causes.

Diagnosis of dysphagia is based on clinical picture confirmed by data of X-ray examination and esophagoscopy.

Dysphagia caused by obstructive disorders has extrinsic and intrinsic causes. Extrinsic obstruction results when tumors or adjacent organs compress the esophagus, which may occur with an enlarged left atrium, aortic aneurysm, aberrant subclavian artery, substernal thyroid gland, bony exostosis, or extrinsic tumors - most commonly lung. Diagnosis is usually made on x-ray, and prognosis depends on the cause. Intrinsic obstruction is usually caused by esophageal cancer. Mechanical obstruction may also be caused by esophageal involvement by lymphoma, leiomyosarcoma, or (very rarely) metastatic cancer.

Dysphagia should not be confused with globus sensation (*globus hystericus*), a feeling of having a lump in the throat, which is unrelated to swallowing and occurs without impaired transport. Often noted in association with anxiety or grief, globus sensation is mainly emotional in origin.

Gastroesophageal reflux disease (GERD)

Definition: GERD (K21 according to ICD-X) is a chronic disease caused by periodic reflux of gastric contents into the esophagus, resulting in to development of reflux - esophagitis or without it, accompanying with heartburn arising more of 1 time weekly within 6 months, and characteristic extraesophageal symptoms.

Etiology and pathogenesis: GERD is a multifactor disease concerned – (1) failure of inferior esophageal sphincter; (2) reflux of stomach and duodenal contents in an esophagus; (3) decrease of esophageal clearance and of stomach emptying; (4) decrease of mucous esophagus resistance, weakening of antireflux barrier of inferior esophageal sphincter.

It is important affection of anatomic structures that prevent gastroesophageal reflux (the lower esophageal sphincter, the crura of the diaphragm, and the phrenoesophageal ligament) due to increased intrabdominal pressure, overfilling stomach after abundant drink and meal, relaxation of the lower esophageal sphincter by some toxic substances and medicines.

Predisposing factors include a stress, obesity, pregnancy, forced position of a body with an inclination forward, smoking, alcohol, hiatus hernia, some medicines (nitrates, non-steroid anti-inflammatory, anticholinergic, beta-blockers, sedative, etc.)

Clinical picture. The most prominent symptom is heartburn, with or without regurgitation of gastric contents into the mouth. Burning sensation presents behind a sternum, more often arising after meal, at inclinations of a trunk forward or in a horizontal position.

Complications of GERD include esophagitis, esophageal stricture, esophageal ulcer, and Barrett's metaplasia. Esophagitis may cause odynophagia and even hemorrhage, which can be massive. Periodic retrosternal pains arising during meal (odynophagia) or exactly after of meal which can irradiate in interscapular range, the left half of chest, neck, mandible.

Peptic stricture causes a gradually progressive dysphagia for solid foods. Peptic esophageal ulcers cause the same type of pain as gastric or duodenal ulcers but are usually localized to the xiphoid or high substernal region. They heal slowly, tend to recur, and usually leave a stricture on healing.

Hiccup may be mainly if GERD accompanied irritation of phrenic nerve (by hiatus hernia, solid food, etc). This is a repeated involuntary spasm of the diaphragm, followed by sudden reflectory closure of the glottis, which checks the inflow of air and produces the characteristic sound.

Extraesophageal symptoms of GERD

Pulmonary symptoms are due to gastroesophageal and following esophagotracheobronchial reflux in horizontal position of the patient. Pulmonary symptoms of GERD include cough intensified after reception of nutrition and in a horizontal position, and dyspnea arising at night and badly stopped by reception of bronchodilators. These symptoms are frequent if GERD attended bronchial asthma and chronic bronchitis.

Otolaryngologic symptoms are due to gastroesophageal and following esophagopharyngolaryngeal reflux in horizontal position of the patient. These symptoms include laryngospasm, dull voice, intensive strain of neck muscles, and recurring otitis.

Oral symptoms are due to gastroesophageal and following esophagopharyngooral reflux mainly in horizontal position of the patient. These symptoms include burning sensations of the tongue, acid taste in the

mouth, hypersalivation, halitosis (unpleasant odor from the mouth), erosions on tongue in places of contact to dens, generalized caries of teeth.

Stomach symptoms are periodic pains in the epigastrium intensified through 30 - 60 minutes after meal, sense of gravity and overflow in epigastrium after meal, nausea, vomiting. These symptoms develop because functional dyspepsia or concomitant diseases of the stomach.

Cardiological symptoms are reflectory because heart and esophagus corresponded to the tender Zakharyin and Head's zones of innervation. These are pains in the chest, reminding attacks of angina pectoris, disorders of cardiac rhythm (extrasystole, blockades of His bundle branches).

Complications of GERD are esophagitis, esophageal stricture, esophageal ulcer, Barrett's metaplasia, esophageal hemorrhage.

Laboratory and instrumental examinations in GERD

Esophagoscopy and esophageal biopsy are the diagnostic method of the failure of inferior esophageal and pyloric sphincters, reflux – esophagitis and hemorrhage. Esophageal biopsy may show thinning of the squamous mucosal layer and basilar cell hyperplasia, even without evidence of gross esophagitis by endoscopy.

GERD includes endoscopy negative and endoscopy positive variants of diseases. According to degree of manifestation of reflux - esophagitis the endoscopy positive GERD divides on 4 degrees after classification of Savari-Miller:

- reflux esophagitis of I degree - esophagitis and single erosia less than 10 % of the distal part esophagus mucosa;

- reflux - esophagitis of II degree - erosias become confluent, esophagitis is up to 50 % of the distal part esophagus mucosa;

- reflux - esophagitis of III degree - are marked the circular confluent erosias occupying practically all mucosal surface the distal part of the esophagus;

- reflux - esophagitis of IV degrees - it is characterized by formation of peptic ulcers and strictures of an esophagus, and also development of intestinal metaplasias of the esophagus mucosa (*Barrett's esophagus*).

X-rays taken with the patient in Trendelenburg's position may show reflux of barium from the stomach into the esophagus. Abdominal compression may be used, but x-ray maneuvers usually are not sensitive indicators of GERD. X-rays after a barium swallow readily show esophageal ulcers and peptic strictures but are only rarely diagnostic in patients with hemorrhage caused by esophagitis.

Esophageal pH monitoring provides direct evidence of GERD. The «gold standard» of GERD diagnosis is the diurnal pH-metry of epyesophagus which allows to estimate pH within 24 hours. The pathological reflux

considers, if esophageal pH is lesser than 4 during more than 5 minutes not less than 50 times for a day

Esophageal manometry determines pressure at the lower esophageal sphincter.

In the *Bernstein test*, symptoms of GERD are promptly reproduced by acid perfusion in the esophagus and relieved by saline perfusion.

A positive biopsy or a positive Bernstein test correlates best with esophageal symptoms of reflux regardless of endoscopic or x-ray findings. Endoscopic biopsy is also the only test that consistently detects the columnar mucosal changes of Barrett's metaplasia.

Diagnosis of GERD is supported by detailed history, confirmed with positive data of the laboratory -instrumental examination (esophagoscopy, X-rays with the patient in Trendelenburg's position, esophageal pH monitoring, esophageal manometry, and positive Bernstein acid perfusion test).

Course. Many patients with GERD remain asymptomatic or self-treated and do not seek attention until severe complications occur. Persistent dysphagia suggests development of a peptic stricture. Most patients with peptic stricture have a history of several years of heartburn preceding dysphagia. However, in one-third of patients, dysphagia is the presenting symptom. Rapidly progressive dysphagia and weight loss may indicate the development of adenocarcinoma in Barrett's esophagus. Bleeding occurs due to mucosal erosions or Barrett's ulcer. Severe reflux may reach the pharynx and mouth and result in laryngitis, morning hoarseness, and pulmonary aspiration. Recurrent pulmonary aspiration can cause aspiration pneumonia, pulmonary fibrosis, or chronic bronchial asthma.

Functional dyspepsia (FD)

Definition: Functional dyspepsia (K30 according to ICD-X) is a discomfort often described as 1 or more of these symptoms (postprandial fullness, early satiation, or epigastric pain or burning) localized to the upper abdomen that has no specific cause on diagnostic evaluation.

Pathogenesis of functional dyspepsia concerns (1) disorders of a motility of a stomach and a duodenum, (2) disorders of rhythm peristalsis and evacuation functions of stomach; (3) distress of an accommodation of a stomach in reply to reception of nutrition; (4) hypersensibility of the stomach receptor to a distention (so-called visceral hypersensitivity).

Clinical picture of functional dyspepsia is characterized by early satiety, abdominal distention, and fullness is often described in addition to epigastric or substernal burning discomfort or pain. Eating may worsen or relieve symptoms. Other associated symptoms may include anorexia and

nausea. Dysphoric states (eg, anxiety, depression) may often occur, particularly among patients with more refractory symptoms.

Diagnostic criteria for functional dyspepsia (Rome III, 2006) must include -

1. One or more of:
 - a. Bother some postprandial fullness;
 - b. Early satiation;
 - c. Epigastric pain;
 - d. Epigastric burning;

AND

2. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms

These criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis

Classification of functional dyspepsia

According to Rome II criteria (1999):

- ulcer-like FD (ulcer-like epigastric pain);
- dyskinetic FD (epigastric fullness, early satiety, abdominal distention, nausea);

- nonspecific (mixed) variant of FD.

According to Rome III criteria (2006):

- postprandial distress syndrome;
- epigastric pain syndrome.

Clinical picture of the postprandial distress syndrome (Rome III, 2006) corresponds to the dyskinetic variant of FD (Rome II, 1999). Clinical picture of the epigastric pain syndrome (Rome III, 2006) corresponds to the ulcer-like variant of FD (Rome II, 1999).

Diagnostic criteria for postprandial distress syndrome must include one or both of the following:

1. Bother some postprandial fullness, occurring after ordinary sized meals, at least several times per week;
2. Early satiation that prevents finishing a regular meal, at least several times per week;

These criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Supportive criteria;

1. Upper abdominal bloating or postprandial nausea or excessive belching can be present;
2. EPS (epigastric pain syndrome) may coexist.

Diagnostic criteria for epigastric pain syndrome must include one or both of the following:

1. Pain or burning at epigastrium of at least moderate severity at least once per week;

2. The pains intermittent;
3. Not generalized or localized to other abdominal or chest regions;
4. Not relieved by defecation or passage of gas;
5. Not fulfilling criteria for gallbladder and sphincter of Oddi disorders.

These criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Supportive criteria:

1. The pain with out a retrosternal component;
2. The pain is commonly induced or relieved by ingestion of a meal but may occur while fasting;
3. Postprandial distress syndrome may coexist.

Diagnosis of functional dyspepsia is supported by the following points:

1. The patient constants signs of dyspepsia (a pain or sensation of the discomfort, localized in epigastrium on midline in upper abdomen) for the last 3 months with symptoms onset at least 6 months before diagnosis are marked.

2. The inspection of the patient including upper gastrointestinal endoscopy excludes organic diseases that are capable to explain signs.

3. The signs of dyspepsia are not relived after defecation or are not connected to changes of frequency and character of defecation, i.e. there are no symptoms of an irritable bowel syndrome.

Diagnostic methods of the functional dyspepsia usually include:

- (1) esophagogastroduodenoscopy (to exclude esophagitis, gastritis, peptic ulcer or cancer of stomach);

- (2) abdominal ultrasound (to exclude pathology of pancreas, biliary tract and liver);

- (3) clinical and biochemical analysis of blood, specifically, erythrocytes and leucocytes count, ESR, alkaline phosphatase (AP), γ -glutamyl transpeptidase (GGTP), aspartate aminotransferase (AsAT) and alanine aminotransferase (AlAT), urea, and creatinine), common analysis of feces and analysis of feces on occult blood;

- (4) Under the indications it were used the X-ray inspection of a stomach, electrogastrography and scintigraphy of the stomach, (assisting to establish presence of gastroparesis), diurnal monitoring of intraesophageal pH, ECG.

Course. Removal of the symptom is not always sufficient. Patients who achieve some psychologic adaptation from their symptoms may develop other kinds of gastrointestinal symptoms when the functional dyspepsia symptoms resolve, or the FD symptoms may recur. The adaptations derived from chronic illness may require that the illness is accepted and that treatment is oriented toward improving function despite continued symptoms.

Changes in the clinical state may require more extensive evaluation if new problems arise or if symptoms persist and become more disabling;

however, for most patients with functional dyspepsia, continued observation, support, and reassurance, with minimal diagnostic studies, suffice.

Gastritis

Definition: Gastritis (K29 according to ICD-X) is an inflammation of the gastric mucous membrane.

The term gastritis should be reserved for histological documented inflammation of the gastric mucosa. Gastritis is not the mucosal erythema seen during endoscopy and is not interchangeable with "functional dyspepsia". Prevalence of gastritis is near 40-50% of adults.

The etiologic factors leading to gastritis are broad and heterogeneous.

Classification of gastritis

I. Acute gastritis -

- A. Acute H. pylori infection;
- B. Other acute infectious gastritis.
 - 1. Bacterial (other than H. pylori);
 - 2. Helicobacter helmanni;
 - 3. Phlegmonous;
 - 4. Mycobacterial;
 - 5. Syphilitic;
 - 6. Viral;
 - 7. Parasitic;
 - 8. Fungal.

II. Chronic Gastritis -

- A. Type A: Autoimmune, body-predominant (~5-7% of cases);
- B. Type B: H. pylori-related, antral predominant (~85-90% of cases);
- C. Indeterminant.

III. Uncommon Forms of Gastritis -

- A. Lymphocytic;
- B. Eosinophilic;
- C. Crohn's disease;
- D. Sarcoidosis
- E. Isolated granulomatous gastritis.

Gastritis has been classified according to a course (acute vs. chronic), morphological features, anatomic localization, and proposed pathogenic mechanism. It can also be classified according to the site of involvement within the stomach (ie, cardia, corpus, antrum). Gastritis can be further classified histologically as acute or chronic based on the inflammatory cell type.

Acute gastritis is characterized by polymorphonuclear cell infiltration of the mucosa of the antrum and corpus. *Chronic gastritis* implies some degree of atrophy (with loss of functional capacity of the mucosa) or

metaplasia. It predominantly involves the antrum, with subsequent loss of G (gastrin) cells and decreased gastrin secretion, or the corpus, with loss of oxyntic glands, leading to reduced acid, pepsin, and intrinsic factor.

Chronic gastritis

Definition: Chronic gastritis is a chronic inflammatory disease of the stomach accompanying with restructuring of its mucosa down to an atrophy with inflammatory reaction of a stroma and disorders of secretory, motor and other functions of a stomach.

Etiology: There are two most common clinical-etiological variants of the chronic gastritis: chronic gastritis A is autoimmune, body-predominant (~5-7% of cases); and chronic gastritis B is a *Helicobacter pylori*-related, antral predominant (~85-90% of cases).

Pathology anatomy.

Superficial gastritis: The predominant infiltrating inflammatory cells in this condition are lymphocytes and plasma cells mixed with neutrophils; inflammation is superficial and may involve the antrum, corpus, or both. It is usually not accompanied by atrophy or metaplasia. Prevalence increases with age. Most patients harbor the organism with only minimal histological changes and no discernible clinical symptomatology.

Atrophic gastritis: Atrophy of gastric glands may follow various injuries, especially gastritis, most often secondary to long-standing antral (type B) gastritis. Some patients with gastric atrophy manifest autoantibodies to parietal cells, usually in association with corpus (type A) gastritis and pernicious anemia (see below).

Atrophy may occur without specific symptoms. Endoscopically, the mucosa may appear normal until atrophy is advanced, when the submucosal vascular tree may be visible. As atrophy becomes complete, acid and pepsin secretion diminish and intrinsic factor may be lost, resulting in vitamin B12 malabsorption.

Metaplasia: Mucous gland metaplasia (pseudopyloric metaplasia) occurs in the setting of severe atrophy of the gastric glands, which are progressively replaced by mucous glands (antral mucosa), especially along the lesser curve. Intestinal metaplasia begins in the antrum and may extend to the corpus. Intestinal metaplasia is associated with stomach cancer.

Clinical picture. The clinical pattern of a chronic gastritis is characterized by three basic groups of the symptoms - pain, dyspeptic and asthenoneurotic syndromes which depend on increased or diminished secretory function of the stomach.

The signs of chronic gastritis are difficult to describe because the course and symptomatology of the disease are quite variable. Some patients do not complain of anything during remissions; the disease may also develop for a long time without any manifestations and it is therefore difficult to establish the time of its onset.

The main syndrome of chronic gastritis is gastric dyspepsia manifested by postprandial fullness, early satiation, nausea, vomiting (emesis), regurgitation - acid regurgitation in stomach hypersecretion; putrefactive belching in stenosed pylorus and stomach hyposecretion); bitter belching if duodeno-gastral reflux presents; deranged (poor or increased, or perverted) appetite. It may combine with intestinal dyspepsia characterized by meteorism, rumbling sounds in the abdomen, constipation, and diarrhea.

The patient with chronic gastritis can also feel pressure and distention in the epigastrium, and sometimes epigastric pain and burning. These symptoms are connected with distention of the stomach by ingested food and the attending pathological sensitivity of mucosal interoceptors. Pain is dull and boring, but sometimes becomes severe.

The general condition of patients with chronic gastritis varies. Some patients do not lose weight, remain active, while others lose weight, become flaccid and slow, their appetite is poor. A pronounced decrease in gastric secretion may be attended by diarrhea which causes even greater wasting and impairs absorption of proteins, vitamins, and iron. Anemia develops along with signs of polyhypovitaminosis and albumin deficiency.

Examination of the abdomen sometimes reveals inflation. Palpation of the epigastrium is painless in most of cases.

The acid secretion may remain normal or it may decrease. Free hydrochloric acid may be absent from the gastric juice (*achlorhydria*). In neglected cases secretion of pepsin is upset as well (condition of *achylia*).

Gastroscopy can give valuable diagnostic information; it must be combined with sighting biopsy from not less than three points of the stomach (cardia, body, antrum). Histological study of biopsy material detects the morphological variant of gastritis and reveals *H. pylori* infection.

X-ray is but of little use in the diagnosis of chronic gastritis.

Chronic gastritis A may be for a long time without any manifestations. *Chronic gastritis A* is characterized by autoimmune, body-predominant affection of the gastric mucosa and gradual development gastric atrophy, achlorhydria and achylia. Clinical picture includes mainly the syndrome of gastric dyspepsia - postprandial fullness, early satiation, nausea, putrefactive belching, poor appetite. Loss of weight may be. Vitamin B₁₂ -deficiency anemia may develop in 15-20 years because of absence of intrinsic factors (gastromucoprotein).

Chronic gastritis B is a *Helicobacter pylori*-related with antral predominant affection of the gastric mucosa. It is characterized by tendency to hyperchlorhydria in early stages, and in late stage hypochlorhydria may if diffuse gastric atrophy develops. Clinical picture includes epigastric pain and burning, acid regurgitation and increased appetite due to gastric hypersecretion. Diagnosis of chronic gastritis B is supported by the detection of *Helicobacter pylori* in specimens of gastric biopsy or by other techniques.

Chronic gastritis should be differentiated from peptic ulcer and functional gastric dyspepsia in the presence of hyperchlorhydria and functional achylia.

Diagnosis of chronic gastritis is supported by:

(1) Endoscopy and gastric biopsy -

(2) Diagnostic tests to detect *Helicobacter pylori* for chronic gastritis B diagnosis – biopsy, rapid urease test, urea breath tests use ¹³C- or ¹⁴C-labeled urea, stool antigen test, antibody testing.

(3) Diagnostic tests for chronic gastritis A diagnosis - serum cobalamin (vitamin B₁₂) levels, antibody testing (antiparietal antibodies in the serum).

Supplemental methods:

- study of gastric juice, pH-metry,
- X-ray and ultrasound (gastric emptying),
- eleltrogastrography,
- serum levels of the pepsinogen.

Course. Chronic gastritis may progress for a long time without any clinical manifestation. Complications of chronic gastritis may be peptic ulcers, hemorrhagic erosias (mainly in chronic gastritis B), nutritional problems – loss of weight, hypovitaminosis, iron- and vitamin B₁₂ – deficiency anemia (mainly in chronic gastritis A), gastric mucosa dysplasia and gastric mucosal tumours (late complications).

Peptic ulcers of stomach and duodenum (Peptic ulcer disease)

Definition: Peptic ulcer (K25-K27) is a general chronic and relapsing disease characterized by seasonal exacerbations with ulceration of the stomach wall or the duodenum.

An *ulcer* is defined as disruption of the mucosal integrity of the stomach and/or duodenum leading to a local defect or excavation due to active inflammation. Prevalence of peptic ulcer is near 10-12% of adults in Europe and USA.

Etiology. *Helicobacter pylori* (HP) is the main etiology agent in approximately 95% of duodenal ulcers and in 70% of stomach ulcers. Non steroidal anti inflammatory medication (NSAD), steroids, stress, burns, hyperparathyroidism may cause peptic ulcers.

The predisposing factors are heredity (blood type 0, elevated pepsinogen levels, indicating maximal acid secretory ability of the stomach) and environmental factors, among which nutrition is the leading one. Irregular nutrition, with prevalence of easily assimilable carbohydrates in the diet, excess ingestion of poorly assimilated and long digested foods cause hypersecretion of the stomach. In the presence of the main factors, the predisposing factors cause ulceration with time. Alcohol and nicotine have also an adverse effect on the gastric mucosa.

Pathogenesis. Although the traditional theories regarding the pathogenesis of peptic ulcers focus on acid hypersecretion, this finding is not universal, and it is now known that hypersecretion is not the primary mechanism by which most ulceration occurs. Certain factors, namely *H. pylori* and NSAIDs, disrupt the normal mucosal defense and repair, making the mucosa more susceptible to the attack of acid.

Classification of peptic ulcer

(1) According to localization:

a) Gastric ulcer (ulcer of stomach) - cardial, subcardial, corporeal gastric ulcer; ulcer of lesser curvature, ulcer of greater curvature; antral, prepyloric, pyloric ulcer.

b) Duodenal ulcer - duodena bulb ulcer, postbulbar ulcer.

(2) According to stage of disease -
exacerbation, remission (incomplete, complete).

(3) Complications of peptic ulcer - gastric (duodenal) bleeding, perforated ulcer, penetrating ulcer, malignant ulcer, pyloric cicatrical stenosis.

Clinical picture

Compalints. Symptoms depend on ulcer location and patient age; many patients, particularly the elderly, have few or even no symptoms. Only about half of patients present with the characteristic pattern of symptoms.

Pain is the most common symptom; it is often localized to the epigastrium and relieved by food or antacids. The pain is described as burning, gnawing, or hunger. It has been noticed that gastric ulcer is manifested by pain in the epigastrium above the navel, while in duodenal ulcer pain is felt in the epigastrium to the right of the median line; ulcer of the cardia is characterized by pain in the vicinity of the xiphoid process. The «early» pain is typical of gastric ulcer. «Late» pain, nocturnal or hunger pain are characteristic of peripyloric and duodenal ulcer. Irradiation of pain may be at the right hypochondrium (in duodenal ulcer), left side of chest, behind the sternum, the left shoulder blade, and into the thoracic part of the vertebra column.

Symptoms of *gastric ulcer* often do not follow a consistent pattern (eg, eating sometimes exacerbates rather than relieves pain). This is especially true for pyloric channel ulcers, which are often associated with symptoms of obstruction (eg, bloating, nausea, vomiting) caused by edema and scarring.

In *duodenal ulcer*, pain tends to be consistent. Pain is absent when the patient awakens but appears in midmorning; it is relieved by food but recurs 2 to 3 h after a meal. Pain that awakens a patient at night is common and is highly suggestive of duodenal ulcer.

Vomiting occurs in 70-75 per cent of patients. It arises without preliminary nausea, at the height of pain, and relieves it. The vomitus is acid

to taste and smell. Secretion of the gastric juice in a fasting stomach is often attended by vomiting as well.

Heartburn is encountered in 60-85 per cent of patients. It occurs not only during exacerbations but can also precede exacerbation for several years; it can be periodic or seasonal. The mechanism of heartburn is associated with motor dysfunction of the esophagus (in addition to the acid factor of the gastric contents, which was formerly believed to be decisive).

Eructation, regurgitation, and salivation are frequent symptoms. Appetite is often increased. Regular connection between meals and development of pain is the cause of a morbid fear of eating (*citophobia*).

The intestinal symptoms of peptic ulcer disease are constipations, which are closely connected with the character of nutrition and bed-rest during exacerbations, and are mainly connected with reflex dyskinesia of the small and large intestine.

History of disease and past life shows the seasonal character of pain (spring and autumn), irregular food intake, smoking, physical and emotional stresses, and familial predisposition to the disease.

Physical examination. Wasting is characteristic of exacerbations. The skin and mucosa are pallid after hemorrhage. The tongue is usually clean.

The configuration of the abdomen is normal. In the presence of pyloric stenosis peristaltic and antiperistaltic movements of the epigastrium can be seen. Brown pigmentation develops on the abdomen after prolonged application of warmth. During exacerbations, the epigastric region is tender to surface palpation; if the peritoneum is involved (positive *Mendel's test*) the muscles are strained. Late splashing sound to the right of the median line (*Vasilenko's symptom*) indicates gastric evacuatory dysfunction or increased secretion between meals.

Common blood analysis may detect anemia after hemorrhage.

Positive test on occult blood in feces may be too after hemorrhage.

Gastroduodenoscopy is a powerful tool for the diagnosis and management of peptic ulcer disease. An alternative diagnostic study is *double-contrast barium x-ray*. Although endoscopy and x-ray have similar sensitivities for detecting ulcer, endoscopy is becoming the diagnostic modality of choice. Endoscopy more reliably detects esophagitis and esophageal ulcers as well as ulcers located on the posterior wall of the stomach and at sites of surgical anastomosis. Conversely, some 10% of duodenal bulb and postbulbar ulcers may be missed endoscopically, sometimes leading to follow-up with a barium study if the clinical suspicion is high. Endoscopy also allows for biopsy or cytologic brushing of gastric and esophageal lesions to distinguish between simple ulceration and ulcerating stomach cancer. Endoscopy can also be used to definitively diagnose *H. pylori* infection.

Gastric secretory function. If the ulcer is found in the stomach, hydrochloric acid and pepsin of the gastric juice vary within normal limits. In duodenal ulcer all these indices significantly exceed normal values. Hypersecretion of the gastric juice is determined in this case by hypersensitivity of the vagus, intensified adrenal function, and increased quantity and hypersensitivity of the parietal cells. Study of the basal secretion of a fasting stomach is very important for the diagnosis of duodenal ulcer.

Diagnosis of peptic ulcer is supported by (1) endoscopy and biopsy; (2) Diagnostic tests to detect *Helicobacter pylori* (see above Gastritis).

Supplemental methods are study of gastric juice, gastric pH-metry, double-contrast barium x-ray.

Complications of peptic ulcer

Hemorrhage is the most common complication of peptic ulcer disease. Symptoms include hematemesis (vomiting of fresh blood or “coffee ground” material); passage of bloody or black tarry stools (hematochezia and melena, respectively); and weakness, orthostatic syncope, thirst, and sweating caused by blood loss.

Penetration (confined perforation): A peptic ulcer may penetrate the wall of the stomach or duodenum and enter the adjacent confined space (lesser sac) or organ (eg, pancreas, liver). Adhesions prevent leakage into the free peritoneal cavity. Pain may be intense, persistent, referred to sites other than the abdomen (usually the back when caused by penetration of a posterior duodenal ulcer into the pancreas), and modified by body position. X-ray evaluation with contrast study or CT is usually needed to confirm the diagnosis.

Free perforation usually presents as an acute abdomen. Ulcers that perforate the peritoneal cavity are usually located in the anterior wall of the duodenum or, less commonly, in the stomach. The patient experiences sudden, intense, steady epigastric pain that spreads rapidly throughout the abdomen, often becoming prominent in the right lower quadrant and at times referred to one or both shoulders. The patient usually lies still because even deep breathing can worsen the pain. Palpation of the abdomen is painful, rebound tenderness is prominent, abdominal muscles are rigid (boardlike), symptoms of peritoneum irritation present (positive *Schetkin-Blumberg* and *Mendel's tests*); and bowel sounds are diminished or absent. Symptoms may be less striking in the elderly, the moribund, and those receiving corticosteroids or immunosuppressants.

Diagnosis is confirmed if an upright or a lateral decubitus x-ray of the abdomen shows free air under the diaphragm or in the peritoneal cavity, but the diagnosis is not excluded if no air is seen.

Pain and abdominal rigidity may partially subside, and the patient's condition appears to improve several hours after onset. However, peritonitis with a temperature elevation may develop, and the patient's condition

seriously deteriorates. Shock may ensue, heralded by increased pulse rate and decreased BP and urine output.

Gastric outlet obstruction (pyloric stenosis): This may be caused by scarring, spasm, or inflammation associated with an ulcer. Symptoms include recurrent large volume vomiting, occurring more frequently at the end of the day and often as late as 6 h after the last meal. Persistent bloating or fullness after eating, loss of appetite also suggest gastric outlet obstruction. Prolonged vomiting may cause weight loss, dehydration, and alkalosis.

If the patient's history suggests obstruction, physical examination, gastric aspiration, or x-rays may provide objective evidence of retention. A succussion splash heard > 6 h after a meal or aspiration of fluid or food residue > 200 mL after an overnight fast suggests gastric retention. If gastric aspiration shows marked retention, the stomach should be emptied and endoscopy or x-rays performed to determine the site, cause, and degree of obstruction.

Stomach cancer: *H. pylori* is associated with intestinal-type adenocarcinoma of the gastric body and antrum but not cancer of the gastric cardia. Infected persons are three to six times more likely to develop stomach cancer. Gastric lymphomas and mucosa-associated lymphoid tissue (MALT) lymphomas have also been linked to this infection.

Course. Peptic ulcer is chronic and relapsing disease characterized by seasonal exacerbations with ulceration. Remission periods last from several months to many years. Exacerbations continue for 4-6 weeks. Cicatrization of the ulcer is completed in 6-8 weeks. Remission may occur without treatment. Seasonal exacerbations are more characteristic of duodenal ulcer. Unless complicated by hemorrhage or perforation, peptic ulcer is never fatal.

Conception of acid-dependending- and HP -(Helicobacter Pylori) - associated diseases

Acid-dependending diseases are closely connected in pathogenesis with a gastric hypersecretion (hyperchlorhydria) or acid regurgitation, such as:

- gastroesophageal reflux disease (GERD),
- functional dyspepsia (epigastric pain syndrome);
- chronic gastritis type B,
- peptic ulcers of stomach and duodenum.

HP -(Helicobacter Pylori) - associated diseases are etiologically related to *Helicobacter Pylori* infection of stomach and duodenal mucosa, such as:

- chronic gastritis type B,
- peptic ulcers of stomach and duodenum,
- mucosa-associated lymphoid tissue (MALT) lymphoma,
- gastric adenocarcinoma.

Symptomatology and diagnostics of intestinal diseases

Clinical examination in diseases of small and large intestines

Complaints and history

Clinical manifestations of intestinal diseases depend on the affected department of small or large colon, character of functional disorders and pathological process.

Patients with pathology of small intestines (jejunum, Ileum) complain typically on a pain, diarrhea, and weight loss.

Patients with pathology of large intestines (colon) complain typically on a diarrhea or constipation, pain, and blood in stool.

Patients with anorectal pathology complain typically on pain, pruritus in perineum, urgency, hematochezia (feces with unchanged blood), and tenesmus.

Character of the intestinal pain. The general signs by which intestinal pain may be differentiated from others are:

(1) absence of regular dependence of pain on food taking; the only exception is inflammation in the transverse colon (transversitis) due to reflex peristaltic contractions of the transverse colon when food enters the stomach;

(2) close association of pain with defecation: pain occurs before, during, and (rarely) after defecation;

(3) pains relief after defecation or passage of gas.

Intestinal pain is mostly caused by spasms (spasmodic contraction of smooth muscles; hence *spastic pain*), or by distension of the intestine by gases (*boring pain*). Both mechanisms often become involved. Pain arising due to intestinal distension by gases, and associated with tension and irritation of the mesentery, differs from spastic pain (1) by the absence of periodicity; it is long-standing and gradually lessens in prolonged inflation; and (2) by exact localization. In intestinal obstruction (complete or partial) colicky pain is combined with almost permanent pain in the abdomen.

Pain preceding defecation is associated with the disease of the descending colon or sigmoid colon. Pain during defecation is characteristic of hemorrhoids, anal fissures, and cancer

Rectal colic, or tenesmus, is characterized by frequent and painful urges to defecate and is associated with spasmodic contractions of the intestine and the sphincter ani. Only clots of mucus are sometimes expressed instead of actual defecation. Tenesmus occurs in dysentery and other inflammatory or ulcerous diseases, and in cancer of the rectum.

Typical localization of intestinal pain depends on the affected department of small or large colon: paraumbilical region and left hypochondrium - in pathology of jejunum, right ileum region – the terminal part of ileum and cecum, right flank – ascending colon; right hypochondrium – hepatic curvature of transverse colon; epigastrium and mesogastrium -

transverse colon; left hypochondrium – hepatic curvature of transverse colon; left flank - descending colon; left ileum region – sigmoid colon; hypogastrum, perineum and sacral region – rectum.

Constipation is a common complaint and may reflect an obstructing process but is more often due to impaired motility; though often functional in nature, drugs (e.g., anticholinergics), neurologic processes (e.g., Hirschsprung's disease), or smooth-muscle diseases (e.g., scleroderma) may cause decreased motility. The history and physical examination may provide evidence of a more generalized disorder such as hypothyroidism or depression. Pain associated with constipation may suggest an anal or perianal process with stool retention. The history may clarify that "constipation" actually reflects more an unrealized expectation of regularity than significant pathology. In contrast, progressively worsening constipation and weight loss in an adult with previously regular habits suggests the possible presence of an underlying obstructing process, particularly malignancy.

Diarrhea refers to an increased frequency of movements, though some patients often use the term to describe loose or watery stools. If diarrhea is described, the daily average number of stools, their consistency, their pattern, and the presence of blood should be defined. The occurrence of nocturnal or true bloody diarrhea almost always reflects structural rather than functional bowel disease. A pungent stool odor or the presence of undigested meat in the movement is suggestive of pancreatic insufficiency. An alteration in color can be seen in cholestasis or steatorrhea (light-colored) or hemorrhage (melanic to maroon or bright red). Mucus in the movement is usually a sign of a functional bowel syndrome, while pus suggests infectious or inflammatory disease.

Less common but more dramatic are the *symptoms of acute gastrointestinal bleeding*, including hematemesis, melena, and hematochezia, which usually lead to prompt seeking of medical attention but should always be enquired after by the clinician.

Physical examination

Inspection may disclose signs of nutritional deficiencies (loss of weight, anemia, and hypovitaminosis).

Examination of the abdomen for an abnormal contour or inspection of the perianal region may reveal signs of a mass (tumor, inflammatory infiltrate or retained hard feces in obstipation) or a draining fistula (Crohn's disease, paraproctitis).

Auscultation may elicit the absence of bowel sounds or an alteration in pitch that can lead to recognition of an evolving ileus or an obstructing process. A bruit (rumbling sound) may be noted when symptoms of ischemic bowel disease are present.

Careful *palpation* of the abdomen is especially important in detecting tenderness and masses, which can lead to the recognition of Crohn's disease, periappendiceal abscess, and many other disorders. Elicitation of rebound tenderness, either direct or referred, after abrupt removal of the examining hand provides an important clue to localized or more generalized peritonitis, which may suggest abdominal emergencies, such as a perforated intestine, intraabdominal abscess, or bowel infarction.

In addition to the examination of the abdomen, a *digital rectal examination* is also essential. In the patient with complaints of stool incontinence, the integrity of the sphincter can be assessed. Masses intrinsic to the rectum as well as abnormalities in the pelvis or the pouch of Douglas may only be detected by this examination.

Laboratory and instrumental examination

Endoscopy

Rectosigmoidoscopy (RRS) is a direct visualization of the mucosa in the rectum and the sigmoid colon. Rectosigmoidoscopy can be used to inspect the mucosa of the rectum and sigmoid colon to the depth of 35 cm. Rectosigmoidoscopy is used to evaluate symptoms referable to the sigmoid colon, rectum or anus (eg, bright rectal bleeding, discharge, protrusions, pain). Normal mucosa is smooth, moist, and moderately red. In acute inflammation the mucosa is edematous, opaque, and covered with mucus. Hemorrhage, erosions, ulcers, hemorrhoids, and fissures of the anus can also be seen. Rectosigmoidoscopy helps early diagnosis of cancer tumours in the rectum and the lower portion of the sigmoid colon. The instrument is provided with a special device for sighting biopsy for morphological studies. Finger examination of the rectum is only possible at depths of 6 to 8 cm.

Colonoscopy is a more complete endoscopy of the large intestine performed with a colonoscope (endofibroscope), whose length is 86-186 cm. Because of high flexibility, it can be introduced through the anus to reach any portion of the large intestine and often the terminal ileum, resulting in more accurate diagnosis of inflammatory bowel disease and mass lesions. In addition to visual examination, the instrument can be used to take specimens of the intestinal mucosa for establishing a diagnosis. Colonic polyps can almost always be removed at the time of their initial identification.

Endoscopic tools are not useful in assessing intestinal motility, which may be assessed more accurately by barium studies.

X-ray study of intestines

Enterography is X-ray studies used to determine the morphological and functional properties of the *small intestine*. Contrast substance (100 g of barium sulphate in an equal quantity of water) is used for the purpose. The patient takes the barium meal and 2.5 hours later the suspension enters the cecum. Earlier or delayed entrance of the suspension from the small intestine

to the cecum indicates its upset motor function. The relief of the mucosa in the small intestine has a feather-like pattern, which becomes disfigured in its inflammatory affections (Crohn's disease). Shallow horizontal ridges between accumulations of liquid and gas in the intestinal loops can sometimes be seen in hypersecretory disorders. Small protrusions and diverticula occur sometimes along the course of the small intestine. Tumours of the small intestine have no specific X-ray signs.

Irrigoscopy is X-ray study of the *large intestine* after administering the contrast suspension by enema (per rectum).

If barium is given per os, it reaches the cecum in 2,5-4 hours. The ascending portion of the intestine is filled in 3—6 hours. The transverse colon is filled with barium in 12 hours. In 24 hours the large intestine can be seen along its entire course. This roentgenological study of the large intestine gives information on its motor function, length, position, shape, tone, and haustration.

Giving a contrast substance per rectum (200 g of barium sulphate suspension in 1,5 liters of water) ensures a more detailed information on possible constrictions, and adhesions in the large intestine and also the relief of its mucosa.

CT (computer tomography), though more expensive, is often more effective in the evaluation of the lower abdomen, where inflammatory masses in patients with Crohn's disease or complications of diverticular disease may be accurately imaged. CT "virtual colonoscopy", a nonendoscopic method of visualizing the colon, is developing rapidly.

MRI (magnetic resonance image) may give exquisitely accurate information on the anatomic extent of invasive rectal cancers and blood flow in patients with vascular disorders.

Radionuclide scans can be used to localize a site of bleeding in the gastrointestinal tract. *Radiolabeled technetium* can detect a source of bleeding.

Coprology studies

Coprology studies means analysis of feces. Feces of a healthy subject consist of about equal volumes of undigested food remains, secretions of the alimentary organs and microbes (mainly dead ones). This is an important item in the study of patients with diseases of the alimentary system.

General clinical analysis of feces (*coprocytogram*) helps assess assimilation of food, discover disorders in the biliary secretion, latent hemorrhage, inflammation, the presence of parasites, etc. Coprology includes macroscopy, microscopy, and simple chemical analysis. Microbiological studies of feces are necessary in cases suspected for infectious diseases of the intestine.

Feces are collected in a dry clean container and studied as soon as possible (not later than 8-12 hours after defecation, provided the specimen is kept in the cold). Feces should be examined for the presence of protozoa immediately after defecation. When feces are examined for the degree of food assimilation, the patient is given a common diet (or a special diet for more detailed studies) several days before the study.

Macroscopy study of feces

Macroscopy study of feces includes assessment of the amount of daily excretion, the colour of feces, their consistency, shape, and odour, presence of undigested food remains, mucus, blood, pus, and parasites.

The normal *daily excretion* (with varied nutrition) is 100-200 g. Increased amount (>200 g) of feces (*polyfecalia*) may be in ample vegetable diet, poor assimilation of food (in diseases of the pancreas), and intensified peristalsis. Diminished amount (<100 g) of feces may be observed in proteinous diet, in constipations and hunger.

Shape of feces depends mainly on their consistency. Normal feces resemble sausage and are usually soft. In constipation feces are hard, while in spastic colitis they resemble feces of sheep ("small nuts"). The consistency of feces depends largely on absorption of water in the intestine. Feces are pasty when rich in fat (in steatorrhea).

Normal *colour of feces* is brown due to the presence of bilirubin derivatives (stercobilin and mesobilifuscin). In constipation, and also during antibiotic therapy, bilirubin is not reduced and feces are golden-yellow. In cases with upset bile excretory function, feces are greyish-white, clayish, or sandy (*acholic feces*). In the absence of acholia, fatty feces are grey as well (amyloidosis of the intestine, or sprue), but they darken on exposure to light and give a positive reaction to stercobilin. Black colour of feces can be due to hemorrhage in the upper portions of the gastro-intestinal tract (formation of sulphur compounds of iron), due to ingested black currants, coffee, carbolen, preparations of bismuth, iron, etc.

Normal odour of feces is specific, slightly fecal. The *odour of feces changes* with intensification of fermentation (acid odour of organic acids) or putrefaction (putrid dyspepsia), especially in degradation of tumour of the large intestine.

Remains of undigested food are easier detectable in fecal emulsion in a Petri dish placed against a dark background. Remains of vegetable foods are usually found. In the insufficiency of gastric and pancreatic digestion, or in the absence of teeth, feces usually contain otherwise readily digested food (*lientery*). Connective tissue remains undigested (in the form of whitish fibrous structures) in gastric achylia. Ample fat in stools (*steatorrhoea*) is characterized by the appearance of a solidified fat coat on the fecal surface.

The pathological components of stools, such as mucus, blood, and pus can be seen by an unaided eye if they originate in the large intestine. If these

components join feces in the small intestine, mucus is mixed with feces, while leucocytes and erythrocytes are decomposed.

Clots or bands of *mucus* found on the surface of feces indicate inflammatory changes in the large intestine. In membranous colitis, mucus is excreted in the form of dense bands which are sometimes mistaken by the patients for helminthes.

Appearance of *blood in feces* is a serious symptom. Dysentery and ulcerative colitis are characterized by secretion of bloodstained mucus. In hemorrhoid bleeding, unaltered blood is seen on the surface of stools.

Pus is liberated with feces in ulcerative affections of the large intestine (dysentery, tuberculosis, degrading tumour), or in rupture of a paraproctal abscess.

Feces may contain stones (gallstones, coprolites, pancreatic calculus).

Ascarides, acanthocephala, and members of platyhelminths can be found in stools.

Microscopy study of feces

Microscopy of feces is done to reveal remains of food cells, mucus, eggs of helminthes, and protozoa. Most components of feces can be found in a native preparation which is prepared from fecal emulsion in a small quantity of water. The preparation is then covered with a glass and viewed in the dark field with small and great magnification.

Detritus is the main component of feces. This is material whose particles (minutest particles of food, decomposed cells and microbes) are difficult to differentiate. Among food remains, only muscle fibres and connective tissue can be identified.

Muscle fibres are yellow cylinders with a transverse striated pattern which remains unchanged after cooking of meat but which disappears under the action of digestive enzymes. Feces of a healthy individual on a meat diet contain separate fibres which have lost their striated pattern. Many muscular fibres can be found in feces (*creatorrhea*) if the transport speed of the intestinal contents through the bowels is accelerated. The presence of fibres with preserved striated pattern indicates enzymatic insufficiency of digestive glands.

Connective tissue in feces indicates inadequate gastric digestion. It appears as semitranslucent fibres with indistinct contours.

Starch and vegetable cellular tissue can be identified among remains of carbohydrate food. Plant cells are easily identifiable by thick coats, and vegetable tissue by thick intercellular partitions. The amount of cellular tissue depends on the character of food and the time of its passage through the large intestine, where it is partly destroyed by microbes. In order to reveal starch, a drop of Lugol's solution is added to the fecal emulsion. Starch grains are stained blue or violet. Starch is a readily assimilable product and normal feces contain it in very small quantity or do not contain at all. Increased

starch content of the feces (*amylorrhoea*) is usually associated with diseases of the small intestine: starch remains unsplit due to accelerated peristalsis.

Neutral fat and products of its decomposition (crystals of *fatty acids*, *soaps*) are found both in native preparations and preparations stained with Sudan III. From 90 to 98 per cent of neutral fat is assimilated by normal digestion. The remaining fat is excreted mainly as soaps. A great amount of fat is found in feces (*steatorrhoea*) in the absence of sufficient lipase. If bile is present in deficient quantity, fatty acids are found in feces. The following microscopic elements are originated from intestinal wall: leucocytes, erythrocytes, macrophages, cells of intestinal epithelium and of malignant tumours.

Leucocytes occur in normal feces only as single cells, and their large accumulations (mainly with mucus and erythrocytes) are found in ulcerative affections of the large intestine (dysentery, tuberculosis, ulcerative colitis, cancer). Neutrophils prevail among leucocytes. Eosinophils are found in amoebic dysentery and some helminthiases.

Erythrocytes occur in feces of patients with ulcerative affections of the large intestine, fissures of the anus, and hemorrhoids. If the lesion stands higher in the intestine, erythrocytes decompose before they reach the colon and the presence of blood in feces should be determined by chemical analysis.

Macrophages occur in feces in the presence of inflammation especially in bacterial dysentery. Macrophages are larger than leucocytes. The cytoplasm contains many inclusions, products of phagocytosis.

Single cells of *intestinal columnar epithelium* can occur in normal feces. Their large accumulations, which are usually found in mucus, suggest colitis. They are often disfigured by digestion and impregnation with soaps.

Cells of malignant tumours can be found only in the presence of newgrowths at the distal end of the large intestine.

An important object of microscopic studies is the detection of *protozoa* and *helminthes*. If ova are numerous they are found in native preparations. If their quantity is scarce, their concentration should be increased as follows by precipitation of the feces emulsion. Ova are precipitated by centrifuging. Acanthocephala ova are detected in the material scraped from the perianal folds using a spatula or a cotton wool tampon wetted with glycerin.

Protozoa should be better revealed in freshly defecated material. The staining techniques are difficult. Cysts of protozoa are well differentiated by staining with Lugol's solution. Amoeba, lamblia, and balantidia are important pathogenic factors.

Chemical study of feces

The *medium* of feces is determined by litmus paper. If feces are hard, the paper should be moistened. Normally feces react weakly alkaline or neutral. This reaction depends on the vital activity of the intestinal flora,

which is either fermentative or putrid. If carbohydrate assimilation is insufficient the fermentative flora is activated and feces become acid (fermentative dyspepsia). If proteins are poorly assimilated (gastric or pancreatic achylia), and also in the presence of inflammation in the large intestine with exudation of protein, putrid flora becomes more active (putrid dyspepsia): feces become markedly alkaline due to formation of ammonia.

Stercobilin is detected by test with solution of mercury dichloride. If feces are decoloured, it is important to find out whether secretion of bile into the intestine has stopped or only decreased. This can be determined by the test for *stercobilin*.

The presence of *blood* in feces is of great diagnostic importance since it indicates ulcer or newgrowth of the gastro-intestinal tract. The colour of feces changes only in profuse hemorrhage. Scant blood or its latent presence can be determined by chemical analysis. In order to identify hemorrhage as a gastro-intestinal one, it is necessary to rule out other possible sources of bleeding, e.g. nose, gums, esophagus, hemorrhoids, etc. and also foods containing blood, e.g. meat and fish which should be excluded from the diet three days before the analysis.

Methods used for the purpose of the *occult blood* detection are based on the property of hemoglobin to catalyse oxidation-reduction reactions. Pairs of oxidants and reductants are so selected that reactions between them only occur in the presence of hemoglobin (catalyst). Hydrogen peroxide is an oxidant and benzidine a reductant in the *Gregersen test*. Benzidine changes its colour on oxidation in the presence of blood. The Gregersen reagent is placed in drops on the smear. (The reagent is prepared extemporarily by mixing equal quantities of a 1 per cent benzidine solution and 50 per cent acetic acid in hydrogen peroxide.) In the presence of blood, a green or blue colour develops, whose brightness and the speed of development depend on the amount of the blood present (the higher the blood content, the brighter the colour and the sooner it appears).

Weber's guaiac test is less sensitive than the benzidine one. It only becomes positive in the presence of profuse hemorrhage.

Coprology syndromes

Coprology studies can show a set of laboratory syndromes typical to the particular pathology of digestive apparatus.

Gastric coprology syndrome is characterized by presence of undigested muscles fibres (creatorrhoea), connective tissue, and vegetable fibres (cellulose). This syndrome is typical to stomach and duodenum secretory insufficiency (in chronic gastritis type A, diffuse atrophic gastritis and duodenitis, gastrectomy).

Pancreatic coprology syndrome is characterized by profuse discharge of liquid excrements, *polyfecalia*, yellow-grey colour, ointment-like consistency of feces, presence of neutral fat (*steatorrhea*), *creatorrhea*, and

starch grains (*amylorrhoea*). This syndrome may be revealed in pancreatic secretory insufficiency (chronic pancreatitis, cystic fibrosis of pancreas, tumour of the body of pancreas).

Bile deficiency coprology syndrome is characterized by grey colour of feces, presence of fatty acids, and *stercobilin* negative test. This is typical to pathology of the liver and biliary tract (in cholecystitis, cholangitis, and hepatitis).

Enterol coprology syndrome is characterized by the feces of yellow loose consistency, presence in feces of leucocytes, epithelial cells, fatty acids crystals, soluble proteins. This syndrome may be revealed in small intestines inflammation (enteritis), deficiency of intestinal enzymes (lactase deficiency), gluten enteropathy, sprue, etc.

Iliocecal coprology syndrome is characterized by the liquid foamy stool with acid smell, presence of mucus, indigested cellulose, *amylorrhoea*, iodophil flora. This is typical to inflammation and pathological digestion of carbohydrate and cellulosa in ileum and cecum (enterocolitis, fermentative dyspepsia).

Colitis coprology syndrome is characterized by bolus-like feces, or scybalous ("sheep's") stool with mucus, presence of leucocytes, blood, epithelial cells. This is typical to inflammation of large intestines.

Basic clinical syndromes of intestinal diseases

Syndrome of slow evacuation of intestinal contents (Constipation)

Definition: Constipation (obstipation, K59.0 according to ICD-X) is a difficult or infrequent passage of feces (no more than 3 times a week), hardness of stool, or a feeling of incomplete evacuation.

Causes of constipation:

- colonic obstruction – neoplasm, stricture, ischemic, diverticular, inflammatory, megacolon;
- anal sphincter spasm - anal fissure, painful hemorrhoid;
- medications - aluminum hydroxide, bismuth and iron salts, cholestyramine, anticholinergics, opioids, β - blockers, Ca^{2+} -blockers, antidepressants tranquilizers and sedatives;
- irritable bowel syndrome;
- disorders of rectal evacuation - pelvic floor dysfunction, descending perineum syndrome, rectal mucosal prolapse;
- endocrinopathies - hypothyroidism, hypercalcemia;
- pregnancy;
- psychiatric disorders (depressive disorders);
- neurologic diseases - parkinsonism, multiple sclerosis, spinal cord injury;

- generalized muscle disease - progressive systemic sclerosis.

Classification of constipation

1. According to pathogenesis –
 - a) dysfunctional - spastic and atonic constipations;
 - b) organic constipation.
2. According to course - acute (acute onset) and chronic constipation.

Organic and functional constipation is differentiated. *Organic constipation* is usually associated with mechanical obstruction, such as narrowing of the intestinal lumen due to a tumour, scar, adhesion, and also abnormalities in the intestine (megacolon, dolichosigmoid, megasigmoid, diverticulosis).

Functional constipation is subdivided into: (1) alimentary constipation; it occurs due to ingestion of easily assimilable foods, which leave small residue and normally stimulate peristalsis of the intestine by irritating its nervous receptors; (2) neurogenic constipation due to dysfunction of the intramural nervous apparatus or vagus nerve; these are the so-called dyskinetic constipation, caused by the reflex action on the intestinal motor function of another affected organ (cholecystitis, adnexitis, prostatitis, etc.), or by organic affections of the central nervous system (tumours of the brain, encephalitis, posterior spinal sclerosis); (3) constipation associated with inflammatory affections, mainly of the large intestine (dysentery); (4) toxic constipation occurring in exogenous poisoning with lead, morphine, or cocaine; (5) constipation of endocrine etiology, occurring in thyroid or pituitary hypofunction; (6) constipation caused by lack of physical exercise; (7) constipation caused by flaccidity of the prelum (abdominal wall).

Acute constipation occurs when a change in bowel habits produces infrequent stools or hard stools that are difficult to pass. A sudden change suggests an organic cause: (1) mechanical bowel obstruction must be considered in patients complaining of constipation for only hours or a few days; (2) adynamic ileus often accompanies acute intra-abdominal disease (e.g., localized peritonitis, diverticulitis) and may complicate various traumatic conditions (e.g., head injuries, spinal fractures) or may follow general anesthesia; (3) acute onset of constipation in bedridden patients (particularly the elderly) is also common.

A detailed drug history should be obtained because acute constipation can be caused by many drugs, including those that act within the lumen (aluminum hydroxide, bismuth salts, iron salts, cholestyramine), anticholinergics, opioids, ganglionic blockers, and many tranquilizers and sedatives.

Chronic constipation is a state when a change of bowel habit persists for weeks or occurs intermittently with increasing frequency or severity. Colonic tumors and other causes of partial obstruction should be suspected.

A reduced stool size suggests an obstructive lesion in the distal colon. Local anorectal conditions (e.g., anal fissures) that cause pain or bleeding should be sought.

The common functional causes of chronic constipation intercept normal bowel movements because the storage, transport, and evacuation mechanisms of the colon are deranged. The cause is sometimes a systemic disorder (e.g., debilitating infections, hypothyroidism, hypercalcemia, uremia, porphyria), but is more often a local neurogenic disorder (eg, irritable bowel syndrome, megacolon). Certain neurologic disorders (eg, Parkinson's disease, cerebral thrombosis, tumor, spinal cord injury) are important extraintestinal causes. Psychogenic factors are most common. Chronic constipation is particularly common in the elderly because of age-related decreases in intrinsic colonic reflexes, low-fiber diets, lack of exercise, and use of constipating medications.

Clinical picture

The most typical symptoms of constipation:

- straining, hard stools or scybala (hard, inspissated stool);
- non-productive calls (“want to but can not”, *tenesmus*);
- infrequent stools, or incomplete evacuation;
- ≤ 3 bowel movements (defecations) per week;
- daily stool weight ≤ 35 g/day.

Loose stools are rarely present without use of laxatives. Fecal impaction, which may cause or develop from constipation, is particularly common in the bedridden elderly and after barium has been given by mouth or enema. The patient has rectal pain and tenesmus and makes repeated but futile attempts to defecate. The patient may have cramps and may pass watery mucus or fecal material around the impacted mass, mimicking diarrhea. Rectal examination discloses a firm, sometimes rocklike, but often rubbery, putty-like mass.

Constipation is blamed for many complaints (abdominal pain, nausea, fatigue, anorexia) that are usually symptoms of an underlying problem (irritable bowel syndrome, depression, etc.). Depression may be associated with failure to defecate daily.

Examination of abdomen may reveal palpatory tenderness, some times palpated mass due to neoplasm or solid impact feces. Constipation is accompanied usually by meteorism. Auscultation of abdomen may detect diminished rate and loudness or absence of intestinal peristalsis sounds.

Local anorectal conditions (eg, anal fissures, hemorrhoids) that can cause also pain or bleeding should be sought by local inspection, digital rectal examination, anoscopy and anorectal manometry.

X-ray series with barium sulphate suspensions show prolonged whole gut or colonic transit. X-ray (barium enema, barium passage) and endoscopy

(rectosigmoidoscopy, colonoscopy) can reveal organic causes of constipation. Stool examination for occult blood is obligate.

Diagnosis of constipation is based on typical complaints and history; data of endoscopy (rectosigmoidoscopy, colonoscopy) and/or x-ray (barium enema, barium passage), anorectal examinations (digital rectal examination is necessarily) and stool examination for occult blood.

Syndrome of accelerated evacuation of intestinal contents (Diarrhea)

Definition: Diarrhea (A09; K59.1 according to ICD-X) is a passage of abnormally liquid or unformed stools at an increased frequency (≥ 3 times a day) and or increased weight (≥ 200 g/day).

Diarrhea occurs usually when stool weight is > 300 g/day, unless this weight is normal (e.g., in persons whose diet is rich in vegetable fiber). Diarrhea results mainly from excess fecal water (i.e., 60 to 90% of stool weight is water).

Etiology and pathogenesis of diarrhea

Diarrhea has infectious, drug-induced, food-related, postsurgical, inflammatory, transit-related, and psychologic causes. These many causes produce diarrhea by four distinct mechanisms: increased osmotic load, increased secretion, inflammation, and decreased absorption time.

Osmotic diarrhea occurs when unabsorbable, water-soluble solutes remain in the bowel, where they retain water. Osmotic diarrhea occurs with sugar intolerance, including lactose intolerance caused by lactase deficiency, and with the use of poorly absorbed salts (Mg sulfate, Na phosphates) as laxatives or antacids. Ingestion of large amounts of the hexitols (eg, sorbitol, mannitol), which are used as sugar substitutes, causes osmotic diarrhea as a result of their slow absorption and stimulation of rapid small-bowel motility ("dietetic food" or "chewing gum" diarrhea). Even eating too much of some foods, such as certain fruits, can produce osmotic diarrhea.

Secretory diarrhea occurs when the small and large bowel secrete more electrolytes and water than they absorb. Secretagogues include bacterial toxins (e.g., in cholera), enteropathogenic viruses, bile acids (e.g., after ileal resection), unabsorbed dietary fat (eg, in steatorrhea), some drugs (e.g., anthraquinone cathartics, castor oil, prostaglandins), and peptide hormones (e.g., vasoactive intestinal peptide produced by pancreatic tumors). Microscopic colitis (collagenous or lymphocytic colitis) causes 5% of secretory diarrhea. It is 10 times more common in women, generally affecting persons > 60 years.

Exudative diarrhea occurs with several mucosal diseases (eg, regional enteritis, ulcerative colitis, tuberculosis, lymphoma, cancer) that cause mucosal inflammation, ulceration, or tumefaction. The resultant outpouring of plasma, serum proteins, blood, and mucus increases fecal bulk and fluid

content. Involvement of the rectal mucosa may cause urgency and increased stool frequency because the inflamed rectum is more sensitive to distention.

Decreased absorption time diarrhea occurs when intestinal content is not in contact with an adequate absorptive surface of the GI tract for a long enough time so that too much water remains in the feces. Factors that decrease contact time include small- or large-bowel resection, gastric resection, pyloroplasty, vagotomy, surgical bypass of intestinal segments, and drugs (e.g., Mg-containing antacids, laxatives) or humoral agents (e.g., prostaglandins, serotonin) that speed transit by stimulating intestinal smooth muscle.

Malabsorption (see below) produces diarrhea by osmotic or secretory mechanisms. The mechanism may be osmotic if the unabsorbed material is abundant, water-soluble, and of low molecular weight. Lipids are not osmotic, but some (fatty acids, bile acids) act as secretagogues and produce secretory diarrhea. In generalized malabsorption (eg, nontropical sprue), fat malabsorption causes colonic secretion, and carbohydrate malabsorption causes osmotic diarrhea. Malabsorption-related diarrhea may also develop when the intestinal transport is prolonged and fecal bacteria proliferate in the small bowel.

Classification of diarrhea:

1. According to course - *acute* if <2 weeks, *persistent* if 2 to 4 weeks, and *chronic* if >4 weeks in duration.
2. According to etiology - infectious, drug-induced, food-related, postsurgical, inflammatory, transit-related, and psychologic causes.
3. According to pathogenesis – osmotic, secretory, exudative, decreased absorption time, malabsorption-related diarrhea.
4. Clinical variants – enteral, colitis, gastric, pancreatic diarrhea.

Clinical picture

The main symptoms of diarrhea are increased frequency, fluid content, or increased volume of fecal discharge (usually >300 ml per a day).

Associated symptoms - abdominal pain, nausea, vomiting flatulence, and weight loss may occur, although the diarrhea is often without other symptoms. Rectal urgency or tenesmus may be if diarrhea connected with pathology of the sigmoid colon and rectum. Symptoms are often prolonged.

Physical examination may show changes in general state of patient in case of acute severe or prolonged diarrhea (loss of body mass; dry skin and visible mucosa, diminished turgor of skin due to dehydration). Examination of abdomen may detect meteorism and palpatory tenderness. Auscultation reveals increased rate of intestinal peristalsis sounds.

Digital rectal examination is important in case of rectal urgency or tenesmus. Patients with prolonged or severe diarrhea should undergo proctoscopic examination and (at sigmoidoscopy) biopsy of the rectal mucosa for histologic examination (infectious, ulcerative, or collagenous

colitis). X-ray series with barium sulphate suspensions show increased frequency and timing of bowel peristalsis.

Micro- and macroscopic stool examination may be helpful. The consistency, volume, and presence of blood (apparent or occult), mucus, pus, or excess fat in the stool should be noted.

Macroscopy study of stool may show changed consistency, volume, of feces, blood in the stool or change in color, evidence of steatorrhea (fatty stools with a foul odor), mucus, pus, etc. Microscopy may confirm the presence of leucocytes (indicating ulceration or bacterial invasion), unabsorbed fat, meat fibers, or parasitic infestation (eg, amebiasis, giardiasis). Stool pH, normally $> 6,0$, is decreased by bacterial fermentation of unabsorbed carbohydrate (*fermentative dyspepsia*) and protein in the colon. Alkalinization of the stool can reveal the pink color of phenolphthalein, a commonly abused laxative or in *putrid dyspepsia*. With large volume, stool electrolytes can be measured to determine if diarrhea is osmotic or secretory.

Studies of stool may show the signs of coprology syndromes according to the particular affected organ or department of digestive system. Generally, in diseases of the small bowel, stools are voluminous and watery or fatty. In colonic diseases, stools are frequent, sometimes small in volume, and possibly accompanied by blood, mucus, pus, and abdominal discomfort. In diseases of the rectal mucosa, the rectum may be more sensitive to distention, and diarrhea may be characterized by frequent, small stools.

Stool culture, examination feces to parasites and helminthes ova may reveal etiology of diarrhea.

Diagnosis of diarrhea is based on (1) typical complaints and history, (2) data of coprology examination, (3) endoscopy (RRS, colonoscopy); and (4) stool culture, examination for occult blood, helminthes, parasites.

Clinical variants of diarrhea

Enterol diarrhea is characterized by stool frequency up to 4-6/day, profuse discharge with remains of undigested food; steatorrhea may be; paraumbilical pains – often. This is typical for diarrhea related to affection of small bowels.

Colitic diarrhea is characterized by stool frequency up to 10-15/day, scanty excrements with admixtures of mucus and blood, bolus-like feces ("sheep's" stool). It is often accompanied by pains along the rectum. Colitic diarrhea is related to affections of large bowels.

Gastric diarrhea is characterized by stool frequency up to 4-6/day, fluid excrements with remains of undigested food and mucus, putrefactive odour. Melena may be due to gastric hemorrhage. Epigastric pains may be often. This variant of diarrhea may be in incase of stomach achlorhydria and achylia (chronic gastritis A, diffuse atrophic gastritis), diffuse tumour of stomach, after stomach surgery.

Pancreatic diarrhea is characterized by stool frequency up to 4-6/day, polyfecalia, liquid or semi-liquid stool of yellow-grey colour, steatorrhea, putrefactive odour. It is often accompanied by belting pains in abdomen, meteorism, weight loss. This variant of diarrhea is caused by pancreatic secretory insufficiency (in chronic pancreatitis, cystic fibrosis of pancreas, tumour of the body of pancreas).

Complications of diarrhea may be dehydration, electrolyte loss (Na, K, Mg, Cl), metabolic acidosis (due to loss of HCO₃). Vascular collapse may develop rapidly in patients who are very young or old, are debilitated, or have severe diarrhea (e.g., those with cholera). Electrolyte loss after prolonged diarrhea may cause convulsions.

Syndrome of the fermentative dyspepsia

Definition: Fermentative dyspepsia is a set of clinical symptoms due to predominance of fermentative flora of the intestine

Causes of fermentative dyspepsia are deranged digestion of carbohydrates (carbohydrates intolerance, lactase deficiency), excess intake of sweet fruits and vegetables, inflammatory pathology of intestines (enterocolitis).

Cinical picture is characterized by diarrhea 2-3 stools per a day, meteorism (abdominal bloating) and flatulence. It is often accompanied by pains in paraumbilical region and right lower abdomen. Feces are semiliquid, foamy, with acid smell.

Coprology study detects numerous gas bubbles in feces, acid reaction of feces; microscopy shows indigested cellulose, numerous starch grains (amylorrhoea), and iodophilic microbes.

Diagnosis is based on typical complaints and history, and data of coprology studies (acid reaction, indigested cellulose, amylorrhoea, and iodophilic microbes).

Syndrome of the putrid dyspepsia

Definition: Putrid dyspepsia is a set of clinical symptoms due to predominance of putrefactive flora of the intestine.

Causes of putrid dyspepsia are secretory hypofunction of the stomach, chronic gastritis, accelerated intestinal transport, excess intake of protein food.

Clinical picture is characterized by diarrhea 2 - 3 stools per a day, meteorism and flatulence. It is often accompanied by pains in paraumbilical region and epigastrium. Feces are liquid dark excrements with clots of undigested food and foul putrid smell. Evidence of steatorrhea may be (yellow-grey colour, ointment-like consistency of feces)

Coprology study shows visible remains of undigested food, and alkaline reaction. Microscopy detects much fats (*steatorrhea*), muscular

fibres with vivid transverse and longitudinal striation (*creatorrhea*). The iodophilic flora is absent.

Diagnosis is based on typical complaints and history, and data of coprology studies (alkaline reaction, creatorrhea, steatorrhea).

Syndrome of inadequate absorption (maldigestion and malabsorption)

Definition: Syndrome of inadequate absorption (K90.0 - K90.9 according to ICD-X) is a symptom complex resulting from impaired absorption of nutrients from the small bowel.

The mechanism may be direct impairment of absorption (*malabsorption*) or abnormalities of digestion (*maldigestion*) that lead to impaired absorption. Malabsorption may occur for many nutrients or for specific carbohydrates, fats, or micronutrients (for example, calcium, iron, cobalamin, folic acid, etc).

Classification of the inadequate absorption (according to cause)

1. Defective intraluminal hydrolysis – pancreatic insufficiency, stomach acid hypersecretion (inactivate pancreatic enzymes), bile acid insufficiency (in liver and biliary tract diseases).

2. Small intestines diseases: (a) Intestinal wall diseases - Cronh's disease, enteritis, amyloidosis; (b) primary mucosal cell pathology – gluten enteropathy, sprue, lactase deficiency.

3. Inadequate absorption surface – short bowel syndrome, ileum resection, jejunocolic fistula.

4. Lymphatic obstruction – lymphoma, tuberculosis, Whipple's diseases, intestinal lymphangiectasia.

5. Bacterial overgrowth – small intestinal diverticuli, bacterial overgrowth syndrome, enterocolic fistula, scleroderma.

6. Miscellaneous – parasites, drugs, mesenteric vascular insufficiency, vasculitis, diabetes mellitus, thyrototoxicosis.

Clinical picture and laboratory findings:

Gradual wasting, symptoms of metabolic disorders of all types (protein, fat, vitamin, water-salt), progressive atrophy of subcutaneous fat and muscles, dystrophic changes of the skin, nails hairs and in the internal organs with their subsequent dysfunction, and also constant diarrhea with steatorrhea, creatorrhea, and amyloorrhea are characteristic.

Hypoproteinemia develops (mostly at the expense of reduction of the serum albumin level); hypocholesterolemia, hypocalcemia, and moderate hypoglycemia occur. Hypoproteinemic edema develops in the presence of hypoproteinemia below 40-50 g/l. The characteristic symptoms of polyhypovitaminosis are osteoporosis (pains in bones, pathologic fractures), anemia (hypochromic anemia in predominant malabsorption of iron, and hyperchromic anemia in upset absorption of vitamin B12), trophic changes in

the skin, nails, progressive atrophy of the muscles, signs of polyglandular insufficiency, weakness, and (in severe cases) acidosis and cachexia.

Coprologic studies reveal increased content of undigested food in the feces and also increased excretion of the products of enzymic decomposition of food.

Endoscopy and enterobiopsy reveals atrophic changes in the mucosa of the proximal parts of the small intestine.

Since the walls of the small intestine absorb great amounts of various substances, different methods are used to study their absorption. These are tests with folic acid, galactose, D-xylose absorption test, etc. Caseine, albumin, oleic acid, methionine, glycine, vitamin B₁₂, folic acid, and other substances labelled with radioactive isotopes may be used. The method is based on the determination of concentration of labelled substances and the time of their appearance in the blood, their excretion with the urine or feces, and assessment of residual radioactivity of faecal masses that is indicative of the amount of unabsorbed substances. Determination of the absorbed nutrients is based on the study of the chemical composition of food and stools during a certain period of time.

Diagnosis is based on typical clinical picture confirmed by the findings of laboratory examinations (hypoproteinemia, hypocholesterolemia, hypoglycemia, and other disorders due to malabsorption).

Course of the disease depends on the underlying condition and prospects for its cure. The prognosis is unfavourable in severe cases.

Diseases of intestines

Irritable bowel syndrome (IBS)

Definition: Irritable bowel syndrome (K58 according to ICD-X) is a functional bowel disorder in which abdominal pain or discomfort associated with defecation or a change in bowel habit, and with features of disordered defecation in the absence of detectable structural abnormalities.

Cause of IBS is unknown. No anatomic cause can be found. Predisposing factors are emotional factors, individual sensitiveness to food intake and drugs, anxiety disorders, panic disorders and depressive disorders.

Emotional factors, diet, drugs, or hormones may precipitate or aggravate heightened gastrointestinal motility. Some patients have anxiety disorders, particularly panic disorder; major depressive disorder; and somatization disorder. However, stress and emotional conflict do not always coincide with symptom onset and recurrence. Some patients with IBS appear to have a learned aberrant illness behavior; i.e., they tend to express emotional conflict as a gastrointestinal complaint, usually abdominal pain. The physician evaluating patients with IBS, particularly those with refractory

symptoms, should investigate for unresolved psychologic problems, including the possibility of sexual or physical abuse.

Clinical picture: IBS tends to begin in the second and third decades of life, causing bouts of symptoms that recur at irregular periods. Onset in late adult life is rare. Symptoms usually occur in the awake patient and rarely rouse the sleeping patient. Symptoms can be triggered by stress or the ingestion of food. Features of IBS are pain relieved by defecation, an alternating pattern of bowel habits, abdominal distention, mucus in the stool, and sensation of incomplete evacuation after defecation. In general, the character and location of pain, precipitating factors, and defecatory pattern are distinct for each patient.

Variations or deviations from the usual symptoms may suggest intercurrent organic disease and should be thoroughly investigated. Patients with IBS may also have extraintestinal symptoms (eg, fibromyalgia, headaches, dyspareunia, temporomandibular joint syndrome).

Two major clinical types of IBS have been described. In *constipation-predominant IBS*, constipation is common, but bowel habits vary. Most patients have pain over at least one area of the colon, associated with periodic constipation alternating with a more normal stool frequency. Stool often contains clear or white mucus. The pain is either colicky, coming in bouts, or a continuous dull ache; it may be relieved by a bowel movement. Eating commonly triggers symptoms. Bloating, flatulence, nausea, dyspepsia, and pyrosis can also occur.

Diarrhea-predominant IBS is characterized by precipitous diarrhea that occurs immediately on rising or during or immediately after eating. Nocturnal diarrhea is unusual. Pain, bloating, and rectal urgency are common, and incontinence may occur. Painless diarrhea is not typical and should lead the physician to consider other diagnostic possibilities (eg, malabsorption, osmotic diarrhea).

Clinical criteria of IBS (Rome III, 2006):

- Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months -

Associated with 2 or more of the following -

1. Improvement with defecation;
2. Onset associated with a change in frequency of stool;
3. Onset associated with a change in form (appearance) of stool.

These criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Classification of IBS by predominant stool pattern:

1. IBS with constipation (IBS-C);
2. IBS with diarrhea (IBS-D);
3. Mixed IBS (IBS-M);

4. Unsubtyped IBS — insufficient abnormality of stool consistency to meet criteria for IBS-C, D, or M.

Diagnosis of IBS is based on (1) presence of clinical criteria of IBS; (2) excluding infection, inflammatory and neoplastic diseases of intestines by the data of laboratory and instrumental methods (sigmoidoscopy, colonoscopy, X-ray - barium enema, anoscopy, stool examination for occult blood, helminthes ova, protozoa, stool culture).

Diagnosis of IBS should never preclude suspicion of intercurrent disease. Changes in symptoms may signal another disease process. For example, a change in the location, type, or intensity of pain; a change in bowel habits; constipation and diarrhea or vice versa; and new symptoms or complaints (eg, nocturnal diarrhea) may be clinically significant. Other symptoms that require investigation include fresh blood in the stool, weight loss, very severe abdominal pain or unusual abdominal distention, steatorrhea or noticeably foul-smelling stools, fever or chills, persistent vomiting, hematemesis, symptoms that wake the patient from sleep (eg, pain, the urge to defecate), or a steady progressive worsening of symptoms. Patients > 40 years are more likely than younger patients to have an intercurrent organic illness.

Course of IBS is benign with recurrent symptoms over a long period of time (years).

Cronh's disease (Regional Enteritis; Granulomatous Ileitis or Ileocolitis)

Definition: Cronh's disease (K50 according to ICD-X) is a nonspecific chronic transmural inflammatory disease that most commonly affects with ulceration of the distal ileum and colon but may occur in any part of the gastrointestinal tract.

Cause of Cronh's disease is unknown. Predisposing factors are genetic predisposition and unregulated intestinal immune response to an environmental, dietary, or infectious agent. However, no inciting antigen has been identified. Cigarette smoking seems to contribute to the development or exacerbation of Crohn's disease.

Pathological anatomy. The earliest mucosal lesion of Crohn's disease is crypt injury in the form of inflammation (cryptitis) and crypt abscesses, which progress to tiny focal aphthoid ulcers, usually located over nodules of lymphoid tissue. Transmural spread of inflammation leads to lymphedema and bowel wall thickening, which may eventually result in extensive fibrosis. Development of patchy mucosal ulcers and longitudinal and transverse ulcers with intervening mucosal edema frequently creates a characteristic “cobblestoned” appearance. Granulomas can occur in lymph nodes, peritoneum, the liver, and all layers of the bowel wall and are occasionally seen at laparotomy or laparoscopy as miliary nodules.

Segments of diseased bowel are characteristically sharply demarcated from adjacent normal bowel (“skip areas”)—thus the name regional enteritis. Of all cases of Crohn's disease, about 35% involve the ileum (ileitis); about 45% involve the ileum and colon (ileocolitis), with a predilection for the right side of the colon; and about 20% involve the colon alone (granulomatous colitis). Occasionally, the entire small bowel is involved (jejunoileitis), and rarely, the stomach, duodenum, or esophagus. The perianal region is also affected in 1/4 to 1/3 of cases.

Clinical picture

The disease occurs about equally in both sexes. Most cases begin in patients < 30 year, with the peak incidence in those aged 14 to 24 years.

Chronic diarrhea with abdominal pain, fever, anorexia, weight loss, and a right lower quadrant pain or fullness are the most common presenting features. However, many patients are first seen with an acute abdomen that simulates acute appendicitis or intestinal obstruction. About 1/3 of patients have a history of perianal disease, especially fissures and fistulas, which are sometimes the most prominent or even initial complaint.

General survey shows malnutrition. Abdominal and perianal fistulas may find by local inspection. Abdominal examination reveals painful abdominal masses in right lower abdominal quadrant; meteorism may be.

The most common patterns of Crohn's disease pathology are (1) inflammation characterized by right lower quadrant abdominal pain and tenderness; (2) recurrent partial obstruction caused by intestinal stenosis and leading to severe colic, abdominal distention, constipation, and vomiting; (3) diffuse jejunoileitis, with inflammation and obstruction resulting in malnutrition and chronic debility; and (4) abdominal fistulas and abscesses, usually late developments, often causing fever, painful abdominal masses, and generalized wasting.

Complication. Intestinal obstruction; development of enteroenteric, enterovesical, retroperitoneal, or enterocutaneous fistulas; and abscess formation are common complications of inflammation. Intestinal bleeding, perforation, and small-bowel cancer develop rarely.

Extraintestinal manifestations of Crohn's disease are categorized as:

(1) Complications that usually parallel the activity of the intestinal disease and possibly represent acute immunologic or microbiologic concomitants of the bowel inflammation: peripheral arthritis, episcleritis, aphthous stomatitis, erythema nodosum, and pyoderma gangrenosum. These manifestations may be reported by > 1/3 of patients hospitalized with inflammatory bowel disease;

(2) Disorders associated with inflammatory bowel disease but running an independent course: ankylosing spondylitis, sacroiliitis, uveitis, and primary sclerosing cholangitis.

(3) Complications that relate directly to disrupted bowel physiology:

- kidney stones from disorders of uric acid metabolism, impaired urinary dilution and alkalization, and excessive dietary oxalate absorption;
- urinary tract infections, especially with fistulization into the urinary tract; and hydronephrosis and hydroureter from ureteral compression by retroperitoneal extension of the intestinal inflammatory process;
- other bowel-related complications include malabsorption, especially in the face of extensive ileal resection or bacterial overgrowth from chronic small-bowel obstruction or fistulization;
- gallstones, related to impaired ileal reabsorption of bile salts;
- amyloidosis, secondary to long-standing inflammatory and suppurative disease.
- thromboembolic complications may occur, usually with severe disease activity, as a result of hypercoagulability associated with altered levels of clotting factors and platelet abnormalities.

Laboratory findings are nonspecific and may include anemia, leukocytosis, hypoalbuminemia, and increased levels of acute-phase reactants reflected in elevated ESR, C-reactive protein, or seromucoid. Elevated alkaline phosphatase and g-glutamyl transpeptidase accompanying colonic disease often reflect primary sclerosing cholangitis.

Definitive diagnosis is usually made by *X-ray*. Barium enema X-ray may show reflux of barium into the terminal ileum with irregularity, nodularity, stiffness, wall thickening, and a narrowed lumen. A small-bowel series with spot X-rays of the terminal ileum usually most clearly shows the nature and extent of the lesion. Air double-contrast barium enema and enterography may show superficial aphthous and linear ulcers. In advanced cases, the “string sign” may be seen with marked ileal strictures and separation of bowel loops.

In questionable cases, *colonoscopy and biopsy* may help confirm the diagnosis of Crohn's colitis and allow direct visualization and biopsy of the terminal ileum. Colonoscopy finds usually linear, serpiginous, white-based ulcers surrounded by colonic mucosa (“cobblestoned pavement”) which is relatively normal.

Upper gastrointestinal endoscopy may identify gastroduodenal involvement in Crohn's disease patients with upper gastrointestinal symptoms.

Diagnosis of Crohn's disease is based on (1) typical clinical picture (right lower quadrant abdominal painful mass, perianal fistulas or abscesses), and (2) X-ray findings (terminal ileitis with superficial aphthous and transmural linear ulcers, segmentary intestinal affection with a narrowed lumen), (3) confirmed by data of endoscopy (linear transmural ulcers, sign of “cobblestoned pavement”) and biopsy.

Crohn's disease should be suspected in a patient with the inflammatory or obstructive symptoms described above and in a patient without prominent

gastrointestinal symptoms but with perianal fistulas or abscesses or with otherwise unexplained arthritis, erythema nodosum, fever, anemia.

Course. Although spontaneous remission or medical therapy may result in a prolonged asymptomatic interval, established Crohn's disease is rarely cured but instead is characterized by intermittent exacerbations. In the absence of surgical intervention, the disease never extends into new areas of small bowel beyond its initial distribution at first diagnosis. GI cancer, including cancer of the colon and small bowel, is the leading cause of Crohn's disease-related death. Approximately 70% of Crohn's disease patients ultimately require surgery. Furthermore, Crohn's disease is likely to recur even after resection of all clinically apparent disease.

Non-specific ulcerative colitis

Definition: Non-specific ulcerative colitis (K51 according to ICD-X) is a chronic, inflammatory, and ulcerative disease arising primary in the colonic mucosa of rectosigmoid, characterized most often by bloody diarrhea.

Cause of ulcerative colitis is unknown. Evidence suggests that a genetic predisposition leads to an unregulated intestinal immune response to an environmental, dietary, or infectious agent. However, no inciting antigen has been identified. The evidence for a specific microbial etiology for ulcerative colitis is even less convincing than for Crohn's disease, and the familial tendency is less pronounced. Unlike in Crohn's disease, current cigarette smoking appears to decrease risk.

Pathological anatomy. Pathologic changes begin with degeneration of the reticulin fibers beneath the mucosal epithelium, occlusion of the subepithelial capillaries, and progressive infiltration of the lamina propria with plasma cells, eosinophils, lymphocytes, mast cells, and macrophages. Crypt abscesses, epithelial necrosis, and superficial mucosal ulceration ultimately develop. The disease usually begins in the rectosigmoid and may extend proximally, eventually involving the entire colon, or it may involve most of the large bowel at once. Ulcerative proctitis, which is localized to the rectum, is a very common and more benign form of ulcerative colitis. It is often refractory to treatment and undergoes late proximal spread in about 20 to 30% of cases.

Clinical picture. Like Crohn's disease, ulcerative colitis may afflict people at any age, but the age-onset curve shows a bimodal distribution, with a major peak at ages 15 to 30 and a second smaller peak at ages 50 to 70.

The most typical complaint is bloody diarrhea. Malaise, fever, anorexia, weight loss may be in case of extensive active ulcerative colitis.

Bloody diarrhea of varied intensity and duration is interspersed with asymptomatic intervals. Usually an attack begins insidiously, with increased urgency to defecate, mild lower abdominal cramps, and blood and mucus in the stools. However, an attack may be acute and fulminant, with sudden

violent diarrhea, high fever, signs of peritonitis, and profound toxemia. Some cases develop following a documented infection (eg, amebiasis, bacillary dysentery).

When ulceration is confined to the rectosigmoid, the stool may be normal or hard and dry, but rectal discharges of mucus loaded with red and white blood cells accompany or occur between bowel movements. If ulceration extends proximally, stools become looser and the patient may have > 10 bowel movements/day, often with severe cramps and distressing rectal tenesmus, without respite at night. The stools may be watery, may contain mucus, and frequently consist almost entirely of blood and pus.

Complications. Toxic megacolon (or toxic dilation) exists when the diameter of the transverse colon exceeds 6 cm. The severely ill patient has a fever to 40° C, leukocytosis, abdominal pain, and rebound tenderness, signs of peritonitis, and profound toxemia. This condition usually occurs spontaneously in the course of especially severe colitis, but some cases may be precipitated by overzealous use of narcotic or anticholinergic antidiarrheal drugs. With prompt, effective treatment, the mortality rate can be held at < 4% but may be > 40% if perforation occurs.

Other complications of severe non-specific ulcerative colitis are massive hemorrhage, perforation, or sepsis and toxemia.

The incidence of *colon cancer* is increased when the entire colon is involved and the disease lasts for > 10 yr, independent of disease activity. After 10 year, the cancer risk in extensive colitis appears to be about 0,5 to 1%/year. Although cancer incidence is highest in cases of universal ulcerative colitis, the risk is significantly increased with any extent of ulcerative colitis above the sigmoid.

Extracolonic manifestations of non-ulcerative colitis include problems of (joints arthritis, ankylosing spondylitis, sacroiliitis); ophthalmologic complications (anterior uveitis and episcleritis); skin complications (erythema nodosum, pyoderma gangrenosum); diseases of liver (autoimmune hepatitis, primary sclerosing cholangitis, cirrhosis of liver). These conditions may precede the colitis by many years and tend to occur more commonly in persons with the *HLA-B27 antigen*.

Laboratory and instrumental examinations

Common blood count: anemia, leukocytosis, hypoalbuminemia, and elevated ESR may be present with extensive active ulcerative colitis.

Rectosigmoidoscopy (RRS) provides a direct, immediate indication of disease activity. In early cases, the mucous membrane is finely granular and friable, with loss of the normal vascular pattern and often with scattered hemorrhagic areas; minimal trauma (friability) causes bleeding in multiple pinpoint spots. The mucosa soon breaks down into a red, spongy surface dotted with many tiny blood- and pus-oozing ulcers. As the mucosa becomes progressively involved, the inflammation and hemorrhage extend into the

bowel muscle. Large mucosal ulcers with copious purulent exudate characterize severe disease. Islands of relatively normal or hyperplastic inflammatory mucosa (*pseudopolyps*) project above areas of ulcerated mucosa.

Colonoscopy with biopsy is mandatory to evaluate the nature of a stricture. Biopsy may also help distinguish ulcerative colitis from Crohn's disease if the inflammation is highly focal or if a granuloma is seen.

X-ray examination. Barium enema, like colonoscopy, is not usually necessary before treatment and may be hazardous in active stages because of risk of perforation. Later in the course of disease, however, the entire colon should be evaluated to determine the extent of involvement. Total colonoscopy is the most sensitive and widely used method, although barium enema can be informative. Barium studies show loss of haustration, mucosal edema, minute serrations, or gross ulcerations in severe cases. A shortened, rigid colon with an atrophic or pseudopolypoid mucosa is often seen after several years' duration.

Diagnosis of non-ulcerative colitis is based on the history and stool examination that should always be confirmed by rectosigmoidoscopy.

Course. Usually, ulcerative colitis is chronic with repeated exacerbations and remissions. A rapidly progressive initial attack becomes fulminant in nearly 10% of patients, with complications of massive hemorrhage, perforation, or sepsis and toxemia. Complete recovery after a single attack may occur in another 10%. Patients with localized ulcerative proctitis have the best prognosis. Nearly 1/3 of patients with extensive ulcerative colitis require surgery. Total proctocolectomy is curative: Life expectancy and quality of life are restored to normal, and the risk of colon cancer is eliminated.

Diseases of liver and bile ducts

Clinical and laboratory examination in the liver and bile ducts diseases

In most instances, a diagnosis of liver and bile ducts diseases can be made accurately by a careful history, physical examination, and application of laboratory tests and instrumental examinations.

Subjective examination (inquiry) in diseases of liver and bile ducts

Complaints

The symptoms of hepatobiliary disease include *constitutional (systemic) symptoms* such as fatigue, weakness, nausea, poor appetite, and malaise and

the more *liver-specific symptoms* of jaundice, dark urine, light stools, itching, abdominal pain, and bloating.

Fatigue is the most common and most characteristic symptom of liver disease. It is variously described as lethargy, weakness, listlessness, malaise, increased need for sleep, lack of stamina, and poor energy. The fatigue of liver disease typically arises after activity or exercise and is rarely present or severe in the morning after adequate rest (afternoon versus morning fatigue). Fatigue in liver disease is often intermittent and variable in severity from hour to hour and day to day. In some patients, it may not be clear whether fatigue is due to the liver disease or to other problems such as stress, anxiety, sleep disturbance, or a concurrent illness.

Nausea occurs with more severe liver disease and may accompany fatigue or be provoked by odors of food or eating fatty foods. *Vomiting* can occur but is rarely persistent or prominent. *Poor appetite* with weight loss occurs commonly in acute liver diseases but is rare in chronic disease, except when cirrhosis is present and advanced. Diarrhea is uncommon in liver disease, except with severe jaundice, in which case lack of bile acids reaching the intestine can lead to *steatorrhea*.

Right upper quadrant discomfort or ache ("liver pain") occurs in many liver diseases and is usually marked by tenderness over the liver area. The pain arises from stretching or irritation of Glisson's capsule, which surrounds the liver and is rich in nerve endings. *Severe pain* is most typical of gall bladder disease, liver abscess, but is an occasional accompaniment of acute hepatitis.

Itching occurs with acute liver disease, appearing early in obstructive jaundice (from biliary obstruction or drug-induced cholestasis) and somewhat later in hepatocellular disease (acute hepatitis). Itching also occurs in chronic liver diseases, typically the cholestatic forms such as primary biliary cirrhosis and sclerosing cholangitis where it is often the presenting symptom, occurring before the onset of jaundice.

Jaundice is the hallmark symptom of liver disease and perhaps the most reliable marker of severity. Patients usually report darkening of the urine before they notice scleral icterus. Jaundice is rarely detectable with a bilirubin level less than 43 $\mu\text{mol/L}$. With severe cholestasis there will also be lightening of the color of the stools and steatorrhea. Jaundice without dark urine usually indicates indirect (unconjugated) hyperbilirubinemia and is typical of hemolytic anemia and the genetic disorders of bilirubin conjugation, the common and benign form being Gilbert's syndrome.

History of the present disease

The clinical history should focus on the symptoms of liver disease - their nature, pattern of onset, and progression and on potential risk factors for liver disease. Acute onset of the disease is more typical in gallbladder diseases; it is accompanied usually by severe pain in right hypochondrium,

fever and jaundice. Gradual onset of the disease with prevalence of the constitutional (systemic) symptoms is observed usually in chronic liver diseases.

Life history of patients can reveal major risk factors for hepatobiliary diseases. It may be details of alcohol use, medications (including herbal compounds, birth control pills, and over-the-counter medications), past infectious diseases (viral hepatitis, lambliosis, typhoid fever, malaria, syphilis), exposure to jaundiced or other high-risk persons, injection drug use, recent surgery, remote or recent transfusion with blood and blood products, accidental exposure to blood or needlestick, personal habits (fat, meat and mushrooms food intake), occupation, and familial history of liver disease (Wilson's disease; hemochromatosis and α_1 -antitrypsin deficiency) and diseases of the gall bladder (cholelithiasis).

Objective examination in diseases of liver and bile ducts

Survey. General and local survey in liver diseases shows typically jaundice (icterus), scratches, xanthomatosis, spider angiomas (liver teleangiectasia), liver palms (palmar erythema), raspberry tongue, ascites, dilated venous network on the anterior abdominal wall.

Icterus (jaundice) is best appreciated by inspecting the sclera under natural light. In fair-skinned individuals, a yellow color of the skin may be obvious. In dark-skinned individuals, the mucous membranes below the tongue can demonstrate jaundice. Jaundice is rarely detectable if the serum bilirubin level is $<43 \mu\text{mol/L}$ but may remain detectable below this level during recovery from jaundice (because of protein and tissue binding of conjugated bilirubin).

Spider angiomata and *palmar erythema* occur in both acute and chronic liver disease and may be especially prominent in persons with cirrhosis, but they can occur in normal individuals and are frequently present during pregnancy. Spider angiomata are superficial, tortuous arterioles and, unlike simple telangiectasias, typically fill from the center outwards. Spider angiomata occur only on the arms, face, and upper torso; they can be pulsatile and may be difficult to detect in dark-skinned individuals.

Several skin disorders and changes occur commonly in liver disease. Hyperpigmentation is typical of advanced chronic cholestatic diseases such as primary biliary cirrhosis and sclerosing cholangitis. In these same conditions, xanthelasma and tendon xanthomata occur as a result of retention and high serum levels of lipids and cholesterol. A slate-gray pigmentation to the skin also occurs with hemochromatosis if iron levels are high for a prolonged period. Vasculitis with palpable purpura, especially on the lower extremities, is typical of cryoglobulinemia of chronic virus (B, C) hepatitis.

Signs of advanced liver disease include muscle-wasting, ascites, edema, dilated abdominal veins, hepatic fetor (odour), asterixis, mental

confusion, stupor, and coma. *Fetor hepaticus* refers to the slightly sweet, ammoniacal odour that is common in patients with liver failure, particularly if there is portal-venous shunting of blood around the liver. *Asterixis* ("liver flap," "flapping tremor") is a nonrhythmic asymmetric lapse in voluntary sustained position of the extremities, head, and trunk. It is best demonstrated by having the patient extend the arms and dorsiflex the hands.

Peripheral edema can occur with or without ascites. Other signs of advanced liver disease include umbilical hernia from ascites, prominent veins over the abdomen, and *caput medusa*, which consists of collateral veins seen radiating from the umbilicus and resulting from the recannulation of the umbilical vein.

Percussion determines the borders, size, and position of the liver and the spleen. Ascites is best appreciated by attempts to detect shifting dullness by careful percussion.

Surface palpation may find tenderness at the right upper abdomen in liver diseases. Localized pain at the projection of gallbladder (near the inferior edge of the right costal arch 5-7 cm from anterior midline) is typical to gallbladder diseases. Expressed tenderness is detected by palpation in cases of acute cholecystitis, biliary (hepatic) colic due to cholelithiasis, liver abscess, but is an occasional accompaniment of acute hepatitis.

Palpation by the Obraztsov and Strazhesko method can detect enlarged liver, lien, and gallbladder.

Hepatomegaly is not a very reliable sign of liver disease, because of the variability of the size and shape of the liver and the physical impediments to assessing liver size by percussion and palpation. Marked hepatomegaly is typical of cirrhosis, venoocclusive disease, right ventricle heart failure, metastatic or primary cancers of the liver, and alcoholic hepatitis. Careful assessment of the liver edge may also demonstrate unusual firmness, irregularity of the surface, or frank nodules. Perhaps the most reliable physical finding in examining the liver is hepatic tenderness. Discomfort on touching or pressing on the liver should be carefully sought with percussive comparison of the right and left upper quadrants.

Splenomegaly occurs in many medical conditions but can be a significant physical finding in liver disease (chronic hepatitis and liver cirrhosis).

Auscultation can find peritoneal friction rub at the right hypochondrium in pericholecystitis and perihepatitis.

Laboratory and instrumental examinations in hepatobiliary diseases

Functional study of the liver

Pigmentary metabolism

Concentration of bilirubin and its reduction products in the blood, feces, and urine demonstrate the pigment function of the liver. Deranged

pigment metabolism indicates disordered functional condition of hepatocytes and helps differentiate between various types of jaundice.

Bilirubin is formed in the reticulo-endothelial cells of the bone marrow, lymph nodes, and mainly in the spleen and the stellar reticuloendotheliocytes of the liver. The liver participates in bilirubin metabolism to perform the following functions: (1) formation of bilirubin in stellar reticuloendothelial cells; (2) capture of unbound (unconjugated) bilirubin from blood; (3) formation of bilirubin compounds (conjugation) with glucuronic acid; (4) secretion of bilirubin glucuronide (bound bilirubin, conjugated bilirubin) into bile.

Hyperbilirubinemia results from increased bilirubin production, decreased liver uptake or conjugation, or decreased biliary excretion. Increased bilirubin production (eg, from hemolysis) or decreased liver uptake or conjugation (e.g., Gilbert's disease) causes unconjugated (or free) bilirubin in serum to increase. Decreased bile formation and excretion (cholestasis) elevates conjugated bilirubin in serum, and the latter appears in urine.

Total bilirubin is normally < 20 mmol/L. *Unconjugated hyperbilirubinemia* presents when the unconjugated fraction is $> 15\%$ of total bilirubin. Unconjugated hyperbilirubinemia is typical in prehepatic (hemolytic) jaundice and to decreased liver uptake or conjugation in Gilbert's disease, chronic hepatitis and some other liver diseases. *Conjugated hyperbilirubinemia* is typical in posthepatic (mechanic, obstructive) jaundice and in liver diseases with cholestasis (cholestatic hepatitis, biliary cirrhosis). Both unconjugated and conjugated hyperbilirubinemia present in hepatic jaundice.

Urine bilirubin is normally absent. A positive test for urine bilirubin confirms that any raised plasma levels are from conjugated hyperbilirubinemia.

Urobilinogen (urobilin) is normally present in trace amounts in the urine. This intestinal metabolite of bilirubin becomes elevated from hemolysis (excess pigment formation) or from mildly impaired liver uptake and excretion (i.e., when the enterohepatic circulation of this pigment exceeds the liver's capacity to clear and excrete it). Urobilinuria is an early and very sensitive sign of liver dysfunction. Failure of bilirubin excretion into the small intestine reduces urobilinogen formation so that the urine may test falsely low or absent.

The greater portion of bilirubin is reduced in the intestine to *stercobilinogen*. Its main portion is excreted with feces in which it is converted into stercobilin to give feces its normal colour (upon exposure to air and light). In hemolytic jaundice, increased production of stercobilin intensifies its excretion with urine. In obstructive jaundice, when bile is not supplied to the intestine, stercobilin is absent in feces and the urine is free from urobilin.

Protein metabolism

Amino acids, polypeptides of food, and products of breakdown of tissue proteins are delivered into the liver with blood where they are catabolized, detoxicated, and the unused breakdown products are removed. Some amino acids are deaminated and reaminated. The released ammonia is converted by the liver into less toxic urea. Amino acids (both produced by the liver and carried from outside) are used by the liver to build proteins of its own tissue and also blood proteins: albumin, globulins, (alpha, beta, and to a certain extent gamma globulins), fibrinogen, prothrombin, heparin, and certain enzymes. Hepatocytes also make specific proteins: α_1 -antitrypsin (absent in α_1 -antitrypsin deficiency), ceruloplasmin (reduced in Wilson's disease), and transferrin and ferritin (saturated with iron and greatly increased, respectively, in hemochromatosis).

The disorder in the protein-synthesizing function of the liver is revealed by studying the proteins of the blood plasma or serum. This dysfunction has its effect not only on the total protein content but also on the ratio of its different fractions, which is more important diagnostically: the upset protein ratio (*dysproteinemia*) is characteristic of most liver pathologies.

Normal *total plasma protein* content is 65-85 g/L. *Hypoproteinemia* (total plasma protein less than 65 g/L) is typical to severe hepato-cellular failure.

Serum albumin is the main determinant of plasma oncotic pressure, transports numerous substances (e.g., unconjugated bilirubin). Normal serum albumin fraction is 55-70%. Its serum concentration is determined by the relative rates of its synthesis and degradation or loss, by its distribution between the intra- and extravascular beds, and by the plasma volume. In adults, the liver normally synthesizes 10 to 15 g (0,2 mmol) of albumin daily, which represents about 3% of the total body pool. Its biologic half-life is about 20 days; thus, serum levels do not reflect hepatocellular function in acute liver disease. Serum albumin (and its synthesis) is decreased (*hypoalbuminemia*) in chronic liver disease (e.g., cirrhosis, ascites), largely because of the increased volume of distribution. Alcoholism, chronic inflammation, and protein malnutrition depress albumin synthesis. Hypoalbuminemia can result from excess albumin loss from the kidney (nephrotic syndrome), gut (protein-losing gastroenteropathies), and skin (burns).

The albumin-globulin ratio (normally 1,2-2,0) most frequently decreases in liver diseases. This occurs mainly due to the decrease in the albumin content (their upset synthesis). In patients with acute inflammation of the liver (acute hepatitis) the content of α_2 -globulins in the blood plasma increases, while in chronic hepatitis the γ -globulin content increases probably due to accumulation of antibodies which move during electrophoresis with

gamma globulins. The total serum protein content often increases as well. The total protein content decreases sharply (at the expense of albumins) in patients with liver cirrhosis; the content of gamma globulins, however, increases markedly.

Prothrombin (factor II of blood coagulation) is synthesized in the liver with participation of vitamin K. Normal serum prothrombin index is 80-105%. The cause of hypoprothrombinemia is either upset synthesis of prothrombin by the hepatocytes or vitamin K deficiency (vitamin K is fat-soluble and is delivered to the liver from the intestine). In the presence of obstructive jaundice, when absorption of vitamin K is deranged due to the obstructed delivery of bile acid to the intestine, the synthesis of prothrombin in the liver decreases and the blood prothrombin content decreases as well.

Fibrinogen is synthesized in the liver and its content of plasma therefore decreases significantly if the liver is seriously affected. This affects blood coagulation. The normal fibrinogen content of plasma is 2-4 g/l. Hypoprothrombinemia and hypofibrinogenemia are manifested by hemorrhagic syndrome.

The *thymol turbidity test* is based on determination of turbidity of a colloidal thymol reagent caused by adding 1/60 volume of serum. The test is positive mostly in the increased blood serum beta-lipoprotein content. It is always positive in virus hepatitis and diffuse affections of the liver. It is negative in obstructive jaundice. In the presence of significant excess of globulins, and especially of fibrinogen, *thymol-gel test* becomes positive (the serum converts into gel from the addition of formaldehyde).

Amino acids, urea, residual nitrogen and ammonia are the products of protein decomposition which have a certain diagnostic importance. The total blood content of amino acids increases only in severe affections of the liver with impairment of its deaminating and urea-forming functions (otherwise rather stable). The condition for the increase in residual nitrogen of blood is a simultaneous renal dysfunction. Increased residual nitrogen occurring in renal insufficiency alone differs from that occurring in hepatorenal insufficiency by the main component of residual nitrogen. This is urea in renal insufficiency and amino acids in hepatorenal dysfunction.

The blood ammonia content increases when the liver is unable to detoxicate ammonia delivered from the intestine (by synthesizing urea). Accumulation of ammonia in the blood produces a toxic effect on the central nervous system. Hyperammoniaemia is therefore a forerunner of hepatic coma.

Fat metabolism

The liver performs the decisive role in the synthesis and splitting of fats, phospholipids, and cholesterol, in esterification and liberation of cholesterol, and in maintaining constant cholesterol content of blood. Blood lipids change their concentration in liver affections.

Normal *serum cholesterol* content is 3,9-5,2 mmol/l. The cholesterol concentration decreases in patients with severe forms of acute chronic hepatitis and cirrhosis of the liver. Cholesterol increases in obstructive jaundices and in liver cholestasis (cholestatic hepatitis, biliary cirrhosis. The activity of alkaline phosphatase usually increases simultaneously.

The blood phospholipid content in the presence of liver pathology changes mainly in the same way as the content of cholesterol. The blood content of lipoprotein fractions is also affected by liver diseases.

Liver enzymes

The liver cells contain numerous enzymes regulating metabolic processes in the liver. Affection of hepatocytes causes an increased excretion into the blood of some enzymes, while the synthesis of other enzymes decreases. Changes in activity of enzymes in the blood serum, which are a sensitive and quick response to liver affections, are widely used for diagnostic purposes. Some of these enzymes are produced not only by the liver but also by some other organs. But changes occurring in some enzymes during liver pathology are so constant that their determination becomes of great practical value.

Serum enzyme tests can be grouped into three categories: (1) enzymes whose elevation in serum reflects damage to hepatocytes; (2) enzymes whose elevation in serum reflects cholestasis; and (3) enzyme tests that do not fit precisely into either pattern.

Enzymes that reflect damage to hepatocytes. The aminotransferases (transaminases) are sensitive indicators of liver cell injury and are most helpful in recognizing acute hepatocellular diseases such as hepatitis. They include the *aspartate aminotransferase (AsAT, or AST)* and the *alanine aminotransferase (AlAT, or ALT)*. AAT is found in the liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, and erythrocytes in decreasing order of concentration. ALT is found primarily in the liver. The aminotransferases are normally present in the serum in low concentrations. Normal blood serum concentrations of ALT is 0,1-0,45 mmol/l (5-40 U/L), AST - 0,1-0,68 mmol/l (8-55 U/L). These enzymes are released into the blood in greater amounts when there is damage to the liver cell membrane resulting in increased permeability.

The pattern of the aminotransferase elevation can be helpful diagnostically. In most acute hepatocellular disorders, the ALT is higher than or equal to the AST. An AST/ALT ratio $>2:1$ is suggestive while a ratio $>3:1$ is highly suggestive of alcoholic liver disease. The AST in alcoholic liver disease is rarely >300 U/L and the ALT is often normal.

Affection of hepatocytes also may be reflected by elevation of such blood serum enzymes such as *lactic dehydrogenase – fifth fraction (LDG₅)*, *aldolase (fructose 1,6-phosphate aldolase)*, and sometimes γ -glutamyl transpeptidase (GGT).

Enzymes that reflect cholestasis. The activities of three enzymes - *alkaline phosphatase (AP)*, *5'-nucleotidase*, and *gamma glutamyl transpeptidase (GGT)* - are usually elevated in cholestasis. Alkaline phosphatase and 5'-nucleotidase are found in or near the bile canalicular membrane of hepatocytes, while GGT is located in the endoplasmic reticulum and in bile duct epithelial cells. Reflecting its more diffuse localization in the liver, GGT elevation in serum is less specific for cholestasis than are elevations of alkaline phosphatase or 5'-nucleotidase. The increase in the activity of these enzymes is especially pronounced in obstructive jaundice, due to malignant tumour, and also in intrahepatic cholestasis, and biliary cirrhosis. In patients with the affected liver parenchyma, the activity of this enzyme increases moderately. GGT may increase in patients with alcohol diseases of the liver.

Serum cholinesterase (pseudocholinesterase) splits acetylcholine and other choline esters. It is formed in the cells of the liver parenchyma. Its determination is of great prognostic importance: the lower the activity of pseudocholinesterase in hepatitis, the more severe is the course of the disease.

Certain blood *microelements* are important diagnostically. The most informative are *iron* and *copper*. Both elements are contained in the serum as metal proteids, i.e. compounds with proteins, in which they are present in microgram quantities. These metals are also present in the liver, which serves as a depot for them. *Iron* is deposited in the liver as *ferritin*, an iron-protein complex that is a reserve of iron used for the synthesis of hemoglobin in the bone marrow. Another iron compound is *hemosiderin*, the product of hemoglobin decomposition, which is accumulated in the liver in increased hemolysis and also in some liver diseases. *Transferrin* (the transport protein) which carries iron from the liver to the bone marrow is also synthesized in the liver. Iron that is not bound in hemoglobin is also determined in the blood serum for diagnostic purposes: its content increases significantly (2—3 times) in acute hepatitis; in chronic hepatitis and cirrhosis the increase is less significant, while it does not change (or even decreases) in obstructive jaundice.

Copper is contained in the blood as an oxidative enzyme *ceruloplasmin*; it is also contained in the liver as a copper-containing protein hepatocuprein. The blood serum copper content slightly increases in hepatitis, and the increase is pronounced in obstructive jaundice. The iron to copper ratio is always decreased in obstructive jaundice and is mostly increased in parenchymatous affections of the liver.

Study of duodenal contents

Duodenal contents are studied for determining the bile composition. This is necessary to diagnose affections of the gall bladder and bile ducts, and

also to estimate the function of the pancreas. Duodenal contents are obtained by technique of the duodenal intubation by the special duodenal tube with oval bulb.

Duodenal multifractional intubation

The procedure is carried out on a fasting stomach. The normal duodenal contents discharged from the tube (*the first phase* of examination, *choledochus-phase or bile A*) is golden-yellow, slightly viscous, clear, and opalescing (Supplement. Table 16). If it contains gastric juice, it becomes turbid from precipitating bile acids and cholesterol. This is a mixture of bile, pancreatic and intestinal secretion. Their proportion in the mixture is unknown and the diagnostic value of this fluid is therefore low. Bile A is collected for 10-20 minutes. An agent stimulating contraction (*cholekinetic breakfast*) of the gall bladder is then given through the tube. This is usually a warm solution of magnesium sulphate (25-50 ml of 25-33 per cent solution). Less frequently this is vegetable oil, egg yolk, 10 per cent sodium chloride solution, 30-40 ml of a 40 per cent glucose solution or 40 per cent sorbitol solution, and also hormones (cholecystokinin or pituitrin) which are given subcutaneously.

Following the administration of the stimulant into the duodenum, the Oddi sphincter contracts and excretion of bile is discontinued. This is the *second phase (phase of closed Oddi's sphincter)*. Normally it continues 4—6 minutes following the administration of magnesium sulphate and about 10 minutes after administration of olive oil. The phase is elongated if the tone of the Oddi sphincter is increased and shortened in its hypotonia.

Next follows the *third phase*, the excretion of golden-yellow contents of the bile duct and the neck of the gall bladder (*bile A1 of bile duct and neck of gall bladder*). Normal duration of this phase is 3-4 minutes; normal volume of bile A1 – 3-4 ml; normal rate of bile A1 excretion is near to 1ml/min.

The fourth phase of bile B is evacuation of the gall bladder, which is attended by discharge of thicker dark-yellow, brown or olive bile. It is greenish when congested or if the gall bladder is inflamed. Portion B is the bile of the gall bladder, whose secretion is associated with positive Meltzer-Lyon reflex: contraction of the gall bladder concurrent with relaxation of the bladder sphincter and Oddi sphincter. Bladder bile (B bile) is a kind of concentrated liver bile. The wall of the gall bladder has selective absorbability: the sodium ion and water are absorbed especially actively. As a result, the content of bile acids and their salts increases 5—8 times, and that of bilirubin and cholesterol 10 times compared with their content in the hepatic bile (*bile C*). Epithelium of the gall bladder secretes mucus whose concentration in B bile is from 1 to 4 per cent. In accordance with the capacity of the gall bladder, the amount of secreted B bile is 30-60 ml during 20—30 minutes; normal rate of bile excretion is near to 2 ml/min. Increased

rate ($\geq 2,5$ ml/min) of bile B excretion is detected in hyperkinetic dyskinesia of gall bladder; diminished rate ($\leq 1,5$ ml/min) of bile B excretion is detected in hypokinetic dyskinesia of gall bladder.

The bladder reflex may sometimes be absent in healthy subjects after administration of magnesium sulphate, but it usually appears in repeated examinations, or after giving vegetable oil, pituitrin, or atropine (subcutaneously). The appearance of the reflex after giving pro-came or atropine indicates spasm of the sphincter and the absence of organic obstacles. Persistent absence of the bladder reflex is observed in cholelithiasis, cirrhosis of the gall bladder, obstruction of the bile duct with a stone or an inflammatory process in its mucosa, in contractile dysfunction of the gall bladder, etc. Excretion of very thick dark bile or ample amounts of bile indicates its congestion in dyskinesia of the bile ducts. Intensification of colour alone indicates hemolysis (excess secretion of bilirubin).

After B bile excretion discontinues, *bile C (hepatic bile)* is delivered from the tube. This is the *fifth phase* of the examination. The golden-yellow C bile is considered to be hepatic though it also contains admixtures of duodenal juice.). Usually duration of this phase is 30-40 minutes; normal rate of bile C excretion is near to 1ml/min. Diminished rate of bile C excretion may be revealed in liver disease.

Microscopy of duodenal contents

Microscopy of duodenal contents should be carried out immediately after collection of each portion. Leucocytes are decomposed more slowly but their breakdown is still very rapid. If the sample of bile cannot be examined immediately corrosive sublimate or 10 per cent formaldehyde should be added (with warming up). But these reagents distort the cells and kill lamblia.

Until recently, the *presence of leucocytes in bile* was given great diagnostic importance. Their presence in B bile was considered as a diagnostic sign of cholecystitis, and in C bile of cholangitis. At present, many investigators believe that accumulations of round cells in bile are actually altered and rounded nuclei of intestinal epithelium. Their combination with bilirubin depends probably not on the place of their origin but on the thickness of mucous coat that protects them. Diagnostic importance can therefore only be given to the presence of leucocytes in bile after their identification (by peroxidase staining).

Epithelium can be quite informative provided it is well preserved and its properties can be indicative of the site of its origin: fine prisms originate from the bile ducts, elongated columnar cells with oblong nuclei originate from bile passages; large cells with a large round nucleus and vacuolized cytoplasm are attributed to the mucosa of the gall bladder; large epithelial cells with a round nucleus, accounting for the expanded lower third of the cell, and with a thickened cuticle, belong to the duodenum. The cells can easily be identified in the native preparation by phase-contrast microscopy.

The presence of *tumour cells* in bile is of great diagnostic importance. Microscopy of native preparations only in rare cases can reveal them. Histological study of consolidated duodenal precipitate is more informative.

Discovery of *cholesterol crystals* and brown grains of *calcium bilirubinate* are of importance. They can be found in small quantities in healthy subjects but large amounts suggest cholelithiasis.

Discovery of *parasites* in bile is of great significance. *Lambia intestinctlis* occur frequently; the eggs of liver fluke or Chinese fluke, eggs of duodenal wryhead and also larvae of intestinal *Strongyloides stercoralis* are found less frequently.

Chemical study of duodenal contents

Some chemical constituents of bile are determined. These are bilirubin, cholesterol, bile acids, and protein. It is not the total *bilirubin* of bile that is important, but rather bilirubin proportion in C and B bile, which characterizes the concentration capacity of the gall bladder. The normal bilirubin content in B bile is 3,4-6,8 mmol/l and of C bile, 0,17-0,34 mmol/l. Decreasing concentration of bilirubin in the gall bladder can depend on bile dilution with inflammatory exudation.

Cholesterol is determined as in the blood. A bile contains about 0,5 mmol/l, B bile about 2,6-23,4 mmol/l, and C bile 2-2,6 mmol/l of cholesterol. Protein is absent from the normal bile. Its presence (proteinchoelia) indicates inflammation.

Bile adds (cholates) are metabolites of cholesterol. Decreasing the cholate to cholesterol ratio below 10 in bile (the *cholatocholesterol coefficient*) indicates predisposition to formation of bile stones.

Instrumental methods of diagnosis

X-ray study

The usefulness of *plain X-ray of the abdomen* is limited to identifying calcifications in the liver or gallbladder, opaque gallstones, and air in the biliary tract. Hepatic or splenic enlargement and ascites may be detected.

Oral cholecystography is based on a per oral administration of iodine-containing contrast substance after a light early supper. The substance is absorbed in the intestine, trapped by the liver, and secreted with bile to enter the gall bladder, where iodine is gradually accumulated. Next morning, the patient with a fasting stomach is given an X-ray examination of the gall bladder. A distinct shadow of the gall bladder can be seen 10—15 hours following the intake of the contrast substance; this indicates normal concentration function of the gall bladder. In the presence of stones the shadow is non-uniform and areas of rarified density can be seen, their number and size corresponding to the number and size of the stones. If the shadow of the bladder is free from stones, the next stage of examination is begun: a cholecystokinetic (usually 10 ml of raw egg yellow) is given to the

patient. The preparation provokes contraction and evacuation of the gall bladder. Series of pictures taken at regular intervals are used to assess the motor function of the gall bladder (by the time of its evacuation and the size of the maximum contracted gall bladder).

IV (intravenous) cholangiography is used to study the intra- and extrahepatic bile ducts (e.g. in patients with removed gall bladder) and also the gall bladder in patients in whom the shadow of the bladder is not determined by cholecystography.

Endoscopic retrograde cholangiopancreatography (ERCP) combines (1) endoscopy for identifying and cannulating the ampulla of Vater in the second portion of the duodenum and (2) radiology after injection of a contrast agent into the biliary and pancreatic ducts. This technique places a side-viewing endoscope in the descending duodenum, identifies and cannulates the papilla of Vater, and then injects a contrast agent to visualize the pancreatic duct and the biliary duct systems. It has revolutionized the diagnosis and management of pancreaticobiliary disease. ERCP is especially valuable in assessing the biliary tract in cases of persistent jaundice. In jaundice and cholestasis, ultrasound to assess duct size should precede ERCP.

Splenoportography is the method by which the splenic vein and portal vein with its intrahepatic branches can be determined with contrast substances and with serial radiography. Splenoportography gives a distinct picture of branching veins. Their section and the pattern of branching can be used to judge about ultra- and extrahepatic causes of portal hypertension, the development of collateral circulation, the character of extension and the degree of pathology of the liver (cirrhosis, primary and metastatic tumours, cysts).

The presence of portal hypertension can be established indirectly by *contrast X-ray study of the esophagus* (using barium meal). It reveals varicosity of the esophageal veins.

Computed tomography (CT) is sensitive to variations in density of differing hepatic lesions. The addition of an intravenous contrast agent helps differentiate more subtle differences between soft tissues and define the vascular system and the biliary tract. CT is especially useful for visualizing space-occupying lesions (e.g., metastases) in the liver and masses in the pancreas. CT can detect fatty liver and the increased hepatic density associated with iron overload.

Other imaging methods

Ultrasonography (US, echography) can be used to assess the condition of the liver tissue, to detect cysts (almost in 90 per cent of cases), abscesses and tumours of the liver (almost in 80 per cent of cases). Ultrasound helps to perform sighting biopsy of the liver and to differentiate between cirrhosis, hepatitis, and fatty degeneration, and to assess the extent of liver affection. This method can be used to reveal liver affections in a comparatively early

stage of the process. Ultrasound is used to study the v. porta hepatis, e.g. to detect dilated and twisted portal vein in portal hypertension. Examination of the spleen establishes its position, reveals possible enlargement (which may be an indirect sign of liver cirrhosis), and determines the structure of this organ.

US is especially useful to diagnose diseases of the gall bladder. Position of the gall bladder, the presence of stones in it, and the condition of its walls can be assessed. US can be used to study the common bile duct and sometimes to establish the cause of its obstruction (stones, tumour). Echography is used to diagnose obstruction of the gall bladder by a stone, dropsy or empyema of the gall bladder which arise in such obstructions, and also cancer of the gall bladder, which occurs not infrequently.

Magnetic resonance imaging (MRI, MRT) is an exciting, although expensive, technology that may prove advantageous for identification of tumors and hepatic blood flow. Blood vessels are easily identified without contrast agents. MRI is comparable to CT for detecting mass lesions and can visualize perihepatic vessels and the biliary system.

Radioisotope hepatography is performed with rose bengal labelled with ^{131}I . The liver function is then examined by a radiometric apparatus whose scintillation. Transmitters are fixed over the heart region (to determine stain withdrawal from the blood; blood clearance), over the right lobe of the liver (to determine stain accumulation and withdrawal), and the central part of the abdomen (to control stain discharge via the bile passages to the intestine). Radiohepatography can thus assess blood circulation in the liver, the absorption-excretion function of the liver, and patency of the bile ducts.

In liver pathology, the rate and the degree of absorption and discharge of rose bengal decreases. If polyhedral cells are affected, the absorption process is especially affected. The secretory function of the liver is predominantly affected in inflammation and especially in impaired patency of the bile ducts.

Radionuclide scanning involves hepatic extraction of an injected radiopharmaceutical from the blood, most commonly technetium 99m ($^{99\text{m}}\text{Tc}$). Liver-spleen scanning uses $^{99\text{m}}\text{Tc}$ -sulfur colloid, which is apidly extracted from the blood by reticuloendothelial cells. Normally, radioactivity is uniformly distributed. In a space-occupying lesion > 4 cm (eg, cyst, abscess, metastasis, hepatic tumor), the replaced liver cells produce a cold spot. Generalized liver disease (e.g., cirrhosis, hepatitis) causes a heterogenous decrease in liver uptake and increased uptake by the spleen and bone marrow. In hepatic vein obstruction, there is decreased visualization of the liver except for the caudate lobe because of its special drainage into the inferior vena cava.

Cholescintigraphy. For scanning the hepatobiliary excretory system, cholescintigraphy uses $^{99\text{m}}\text{Tc}$ -iminodiacetic acid derivatives. These radiopharmaceuticals are organic anions, which the liver avidly clears from

plasma into bile much like bilirubin. A minimum 2-hours fast is necessary. A normal scan shows rapid, uniform liver uptake; prompt excretion into the bile ducts; and a visible gallbladder and duodenum by 1 h. In acute cholecystitis (with cystic duct obstruction), the gallbladder is not visible by 1 hour. Acute acalculous cholecystitis can similarly be detected. After cholecystectomy, this biliary scan can quantitate biliary drainage and assist in defining sphincter of Oddi dysfunction.

Liver puncture biopsy (percutaneous, laparoscopy) remains the gold standard in the evaluation of patients with liver disease, particularly in patients with chronic liver diseases. In selected instances, liver biopsy is necessary for diagnosis but is more often useful in assessing the severity (grade) and stage of liver damage, in predicting prognosis, and in monitoring response to treatment.

Study of gallbladder motility

Oral cholecystogram or ultrasound with cholekinetic test:

- normal gallbladder emptying is more than 40-50% to 70% of fasting gallbladder volume in 30 minutes up to 1 hour after cholekinetic breakfast;
- *gallbladder hypokinesia* – emptying volume < 40-50% of fasting gallbladder volume after cholekinetic breakfast;
- *gallbladder hyperkinesia* - emptying volume > 70% of fasting gallbladder volume after cholekinetic breakfast.

Cholescintigraphy with infusion of cholecystokinin is the “gold standard” of the study of gallbladder motility. The criterion of the normal gallbladder emptying is more than 60%-70% of fasting volume in 30 minutes since beginning cholecystokinin infusion.

Basic clinical syndromes of the hepatobiliary pathology

Syndrome of biliary dyspepsia

Definition: Biliary dyspepsia is a set of clinical symptoms due to disordered biliary tract functions and/or biliary reflux (from duodenum to upper parts of digestive tract).

Causes of biliary dyspepsia are not only of diseases of the hepatobiliary system (cholecystitis, cholelithiasis, fatty liver, hepatitis, hepatobiliary parasitism, and others) but also of other parts of the digestive system (duodenitis, gastritis, pancreatitis, etc.).

Predisposing factors are intake of fat food, inactive mode of life (hypodynamia), rare meals.

Clinical picture includes steady pain in the epigastrium and right upper quadrant of abdomen, bitter taste in the mouth, decreased appetite, eructation, nausea, vomiting, distension of the abdomen and rumbling, constipations or diarrhea.

Laboratory and instrumental examinations are necessary for discovering underlying diseases in biliary dyspepsia:

- tests of liver biochemistries and pancreatic enzymes;
- ultrasonography of the liver, gall bladder and biliary tract, pancreas;
- duodenal intubation and microscopy of bile;
- gastroduodenal endoscopy;
- CCK-cholescintigraphy or ultrasonography assessment of gall bladder emptying.

Jaundice

Definition: Jaundice is an icteric colouration of the skin and mucosa by the increased content of bilirubin in the tissues and blood.

Causes of jaundice include many diseases of the liver, bile ducts, blood, and also diseases of other organs and systems, to which bilirubin metabolic disorders are secondary. Accurate diagnosis of various types of jaundice is possible with special laboratory studies.

Classification of jaundice according to causes:

- (1) *prehepatic (hemolytic) jaundice* – due to excessive decomposition of erythrocytes and increased secretion of bilirubin;
- (2) *hepatic (parenchymatous, hepatocellular) jaundice* - due to impaired capture of unbound bilirubin by the liver cells and its inadequate combination with glucuronic acid;
- (3) *posthepatic (obstructive, mechanic) jaundice* – due to obstacles to excretion of bilirubin with bile into the intestine and reabsorption of bound bilirubin in the blood.

Clinical picture of jaundice:

Jaundice can develop very quickly, within 1-2 days, to become very intensive, or it can develop gradually and be not pronounced (subicteric). Patients themselves (or their relatives) notice yellow colour in their skin. They consult a doctor for this reason. Jaundice can develop with severe itching of the skin, skin hemorrhages and hemorrhages of the nose and the gastro-intestinal tract.

Jaundice is attended (often preceded) by changes in the colour of the urine, which becomes dark-yellow or brown; feces can be very light or even colourless, or on the contrary, dark-brown. Accurate diagnosis of various types of jaundice is possible with special laboratory studies.

Prehepatic (hemolytic) jaundice develops as a result of excessive destruction of erythrocytes in the cells of the reticuloendothelial system (spleen, liver, bone marrow). The amount of unbound bilirubin formed from hemoglobin is so great that it exceeds the excretory liver capacity to account for its accumulation in the blood and development of jaundice. Prehepatic (hemolytic) jaundice is the main symptom of hemolytic anemia. It can also be a symptom of other diseases, such as B₁₂-(folic)-deficiency anemia, malaria, bacterial endocarditis, etc.

The skin of a patient with hemolytic jaundice is lemon-yellow. Skin itching is absent. The amount of unbound bilirubin in the blood is moderately increased. Bilirubin is absent from the urine but the urine is still coloured rather intensely by the markedly increased (5-10 times) stercobilinogen and (partly) urobilinogen. Feces are intense dark due to the presence of considerable amount of stercobilinogen.

Hepatic (parenchymatous, hepatocellular) jaundice develops due to the damage of the parenchyma cells (hepatocytes). The content of free and bound bilirubin in the blood serum thus increases 4-10 times. Bound bilirubin appears in the urine (bilirubin glucuronide is water soluble and easily passes via the capillary membranes as distinct from free bilirubin). Excretion of stercobilinogen with feces also decreases because the amount of bilirubin excreted by the liver into the intestine decreases, but feces are rarely completely discoloured.

Common diseases in hepatic jaundice are hepatitis, cirrhosis, cancer of the liver, infection (virus hepatitis, leptospirosis) and toxic affections of the liver (poisoning with mushrooms, phosphorus, arsenic and other chemical substances, medicinal preparations included).

The skin of patients with this jaundice is typically yellow with a reddish tint. Skin itching is less frequent than in obstructive jaundice because the synthesis of bile acids by the affected liver cells is upset. Symptoms of pronounced hepatic insufficiency may develop in severe course of the disease.

Posthepatic (obstructive, mechanical) jaundice develops due to partial or complete obstruction of the common bile duct. This occurs mostly due to compression of the duct from the outside, by a growing tumour (usually cancer of the head of the pancreas, cancer of the major duodenal papilla, etc.), or due to obstruction by a stone.

Skin and mucosa of patients with obstructive jaundice are yellow. Later, as bilirubin is oxidized to biliverdin, the skin and mucosa turn green and dark-olive. The bound bilirubin content in the blood may be as high as 250-340 mmol/l, and more. In protracted jaundice associated with liver dysfunction, free bilirubin content increases as well. Bound bilirubin can be found in the urine to give it brown colour and bright-yellow foaming. In complete obstruction of the bile ducts, feces become colourless (*acholic*); their colour is clayish and grey-white; stercobilin is absent from feces.

Bound bilirubin and also bile acids produced by the hepatocytes in ample quantity (*cholemia*) are delivered to the blood in this type of jaundice. Some symptoms associated with toxicosis develop: pronounced skin itching, which intensifies by night, and bradycardia (bile acids increase the tone of the vagus nerve by reflex). The nervous system is also affected: the patient develops rapid fatigue, general weakness, adynamia, irritability, headache, and insomnia. If it is impossible to remove the cause of impatency of the

common bile duct (stones or a tumour) the liver is gradually affected to add symptoms of hepatic insufficiency.

Laboratory tests are necessary to confirm a syndrome of jaundice:

- total and bound serum bilirubin;
- bile pigments of urine (bilirubin, urobilinogen);
- stercobilinogen of feces.

Portal hypertension

Definition: Portal hypertension is a syndrome of increased pressure in the portal venous system.

Causes: Portal hypertension results from increased portal flow or, in most cases, increased resistance to flow. According to etiology three variants of portal hypertension are distinguished – (1) *prehepatic portal hypertension* – due to affection of the portal vein and its prehepatic branches, such as portal or splenic vein thrombosis, increased portal flow, arteriovenous fistula, massive splenomegaly in primary hematologic disease (leucosis, lymphoma, etc.); (2) *hepatic portal hypertension* – due to affection of intrahepatic portal vein branches in liver cirrhosis, hepatitis, congenital hepatic fibrosis, etc.; (3) *posthepatic portal hypertension* – due to affection of hepatic veins or inferior vena cava, such as hepatic vein thrombosis (Budd-Chiari syndrome), obstruction of inferior vena cava, cardiac causes (e.g., constrictive pericarditis, restrictive cardiomyopathy).

Clinical picture of portal hypertension includes symptoms due to portocaval anastomoses dilation, ascites, and enlargement of spleen (*splenomegaly*).

The most important is acute variceal bleeding - usually from the distal esophagus and fundus of stomach, more rarely rectal hemorrhage. “Caput medusae” is a symptom of varicose veins radiated from the umbilicus.

Ascites is an accumulation of free fluid in the abdominal cavity. Massive ascites may cause nonspecific abdominal discomfort and dyspnea, but lesser amounts are usually asymptomatic. Ascites is diagnosed by detecting shifting dullness on abdominal percussion, although ultrasound or CT can detect much smaller amounts of fluid. In advanced cases, the belly is taut, the umbilicus is flat or everted, and a fluid wave (symptom of fluctuation) can be elicited.

Usually, however, portal hypertension is inferred by the presence of hepatosplenomegaly and portal-systemic encephalopathy (see below) in a patient with chronic liver disease.

Diagnosis methods:

– ultrasonography, Doppler ultrasound - reveals dilated intra-abdominal collaterals, and Doppler ultrasound can determine portal vein patency and flow;

- GI endoscopy detects esophagogastric varices and may also identify a high bleeding risk;
- splenoportography is a contrast techniques to reveal obstruction of the portal vein.

Hepatic (portal-systemic) encephalopathy

Definition: Hepatic (portal-systemic) encephalopathy is a neuropsychiatric syndrome caused by liver disease and usually associated with portal-systemic shunting of venous blood.

Causes. Portal-systemic encephalopathy may occur in acute hepatitis caused by viruses, drugs, or toxins, but it more commonly occurs in cirrhosis or other chronic disorders when extensive portal-systemic collaterals have developed as a result of portal hypertension. The syndrome also follows portacaval shunt or similar portal-systemic anastomoses.

Predisposing factors are gastrointestinal bleeding; infection; electrolyte imbalance, especially hypokalemia; alcoholic debauches) or iatrogenic causes (tranquilizers, sedatives, analgesics, diuretics).

Pathogenesis. The liver metabolizes and detoxifies digestive products brought from the intestine by the portal vein. In liver disease, these products escape into the systemic circulation if portal blood bypasses parenchymal cells or if the function of these cells is severely impaired. The resulting toxic effect on the brain produces the clinical syndrome. Ammonia, a product of protein digestion, plays an important role, but biogenic amines, short chain fatty acids, and other enteric products may also be responsible or may act with ammonia.

Clinical picture. Personality changes (e.g., inappropriate behavior, altered mood, impaired judgment) are common early manifestations that may antedate apparent change in consciousness. Usually, impaired consciousness occurs. Initially, subtle sleep pattern changes or sluggish movement and speech may be present. Drowsiness, confusion, stupor, and frank coma indicate increasingly advanced encephalopathy. A typical musty sweet odor of the breath, called *fetor hepaticus*, often occurs. A peculiar, characteristic flapping tremor (*asterixis*) is elicited when the patient holds his arms outstretched with wrists dorsiflexed; as coma progresses, this sign disappears and hyperreflexia and the Babinski response may occur.

Diagnosis is based on clinical picture. There is no correlation with liver function tests. An EEG (electro encephalography) usually shows diffuse slow-wave activity, even in mild cases, and may be useful in questionable early encephalopathy.

Syndrome of hypersplenism

Definition: Hypersplenism is a considerable enlargement of the spleen, characterized by anemia, leucopenia, thrombocytopenia and hemorrhagic complications.

Pathogenesis. Splenomegaly in hepatobiliary diseases is a result of increased splenic vein pressure and hypertrophy of reticulohistiocytic tissue. Considerable enlargement of the spleen is usually attended by its hyperfunction (*hypersplenism*), including inhibition of the hemopoiesis in the bone marrow, intensified destruction of the blood cells in the spleen, and antierythrocytic, antileucocytic, and antithrombocytic auto-antibodies production in the spleen.

Syndrome of hepatic insufficiency

Definition: Hepatic insufficiency (K72 according ICD-X) - clinical syndrome of disorders in important functions of liver due to the marked dystrophy and destruction of the hepatocytes.

Causes of hepatic insufficiency are acute and chronic hepatitis, liver cirrhosis, tumours of liver, poisoning with hepatotropic chemical substances (phosphorus compounds, arsenic, large doses of alcohol) or vegetable poisons (inedible mushrooms).

Hepatic insufficiency is explained by various complicated metabolic disorders in the liver, upset bile secretory and excretory function, and impaired detoxicating function of the liver. Portal hypertension aggravates this situation. Portocaval collaterals develop in cases when the blood flow from the portal vein into the liver is obstructed in any affection of this organ. Large amounts of blood containing toxic substances absorbable in the large intestine pass through the collaterals into the greater circulation system to bypass the liver. The body is poisoned by the non-detoxicated products of intestinal (bacterial) protein decomposition, final products of metabolism, and especially ammonia. The electrolyte metabolism becomes upset, and in severe cases, hypokalaemia and alkalosis develop.

Hepatic insufficiency may be aggravated and coma may be provoked by alcohol, barbiturates, some analgesics (morphine, promedol), protein-rich diet, by profuse hemorrhage from the digestive tract, by large doses of diuretics, instantaneous withdrawal of large amounts of ascitic fluid, severe diarrhea, and the attending grave infectious diseases.

Classification of hepatic insufficiency:

1. According to course – acute and chronic hepatic insufficiency.
2. Stages of hepatic insufficiency – (1) early compensated stage ; (2) pronounced decompensated; (3) terminal dystrophic stage that ends in a hepatic coma and death.

Clinical picture: The clinical symptoms are absent during the early stage of hepatic insufficiency.

During the second stage, clinical signs of hepatic insufficiency develop. Patient complains about non-motivated fatigue, poor appetite, increased weakness, frequent dyspepsia, poor tolerance of fat food, meteorism, rumbling and pain in the abdomen, changed stools.

Loss of weight, hypoproteinaemic edema and ascites develop due to deranged albumin synthesis in the liver. Hemorrhagic diathesis (skin hemorrhages, nasal bleeding, hemorrhage in the intestinal tract) may be because upset synthesis of some blood coagulating factors (fibrinogen, prothrombin, proconvertin) and also decreased blood platelet content (due to hypersplenism that attends many chronic diseases of the liver). Jaundice with accumulation of free (indirect) and bound (direct) bilirubin in the blood are frequent in hepatic insufficiency. Inadequate inactivation of estrogens by the chronically affected liver provokes endocrine disorders (gynaecomastia in men, menstrual disorders in women) and such skin symptoms as palmar erythema, and spiders angioma.

The third, final stage of hepatic insufficiency is characterized by even deeper metabolic disorders and dystrophic changes, which are pronounced not only in the liver but also in other organs. Patients with chronic liver diseases develop cachexia. They also suffer from nervous and psychic disorders which are precursors of coma: decreased mental ability, slow thinking, slight euphoria, sometimes depression, and apathy. The patient becomes easily irritable, his moods are quickly changed, and sleep is deranged. Specific tremor (slow and fast) of the upper and lower limbs is characteristic. The precoma period may last from a few hours to several days and even weeks.

The clinical picture of hepatic coma is characterized first by excitation and then by general inhibition (stupor) and progressive derangement of consciousness (sopor), to its complete loss (coma). The reflexes are decreased, but hyperreflexia and pathological reflexes (sucking and grasping) develop. Motor anxiety, clonic convulsions due to hypokaliaemia, muscular twitching, and tremor of the extremities (arrhythmical and rhythmical twitching of the fingers and toes) are characteristic. Kussmaul respiration (less frequently Cheyne-Stokes respiration) develops. Incontinence of feces and urine ensues. The patient's breath (and also urine and sweat) smells "sweety hepatic" (*fetor hepaticus*). Inspection of the patient often reveals bleeding gums, nasal and skin haemorrhage. Jaundice is intensified. The liver may remain enlarged or its size may decrease.

Laboratory tests show anemia, thrombocytopenia, increased ESR. The bilirubin level increases. Characteristic is the decreased content of substances produced by the liver: albumin, cholesterol, fibrinogen, prothrombin. The content of residual nitrogen and ammonia in the blood serum increases to indicate secondary affections of the kidneys (*the hepatorenal syndrome*). Hyponatraemia, hypokaliaemia, and metabolic acidosis develop.-

Biochemical syndromes of liver pathology

Hepatocellular insufficiency is a decreased concentration in the blood of substances synthesized by hepatocytes:

- serum albumins;
- cholesterol;
- prothrombin, proconvertin, fibrinogen;
- serum cholinesterase (pseudocholinesterase).

Cholestasis is an increased concentration in blood of substances excreted in bile by hepatocytes:

- cholesterol;
- bile acids;
- bound bilirubin;
- alkaline phosphatase (AP);
- γ -glutamyl transpeptidase (GGT);
- copper.

Cytolysis is an increased concentration in blood of cytoplasmatic enzymes of hepatocytes:

- aspartate aminotransferases (AsAT, AST);
- alanine aminotransferase (AlAT, ALT);
- lactic dehydrogenase – fifth fraction (LDG5);
- γ -glutamyl transpeptidase (GGT).

Mesenchymal inflammation is an increased content of various globulin fractions produced by reticulohistiocytary cells of liver:

- globulins, (alpha, beta, gamma globulins);
- thymol turbidity test;
- ESR.

Biliary dysfunction (dysfunction of gallbladder and sphincter of Oddi)

Definition: Biliary dysfunction (K82.8 according to ICD-X) defines the motor disorders of the gall bladder and the sphincter of Oddi (SO) without note of the potential etiologic factors for the difficulty to differentiate purely functional alterations from subtle structural changes.

Etiology is unknown. The potential role on the *pathogenesis* - of psychosocial conditions and genetic factors, and relation with other gastrointestinal functional disorders particularly with IBS (irritation bowel syndrome) and functional (stomach) dyspepsia.

Classification of biliary dysfunction (Rome III, 2006)

E. Functional gallbladder (GB) and sphincter of Oddi (SO) disorders;

E1. Functional gallbladder disorder;

E2. Functional biliary sphincter of Oddi disorder;

E3. Functional pancreatic sphincter of Oddi disorder.

Clinical diagnostic criteria for functional GB and SO disorders must include episodes of pain located in the epigastrium and/or right upper

quadrant and all of the following: (1) episodes lasting 30 minutes or longer; (2) recurrent symptoms occurring at different intervals (not daily); (3) the pain builds up to a steady level; (4) the pain is moderate to severe enough to interrupt the patient's daily activities or lead to an emergency department visit; (5) the pains not relieved by bowel movements, by postural change, by antacids; (6) exclusion of other structural disease that would explain the symptoms.

Supportive criteria of the biliary dysfunction are the following (1 or more): (1) pain is associated with nausea and vomiting; (2) pain radiates to the back and/or right infrascapular region; (3) pain awakens from sleep in the middle of the night.

Diagnosis of biliary dysfunction is based on:

- (1) typical complaints and history;
- 2) exclusion of other structural and inflammatory diseases that would explain the symptoms by means of
 - liver functional tests and pancreatic enzymes;
 - transabdominal ultrasound;
 - GI endoscopy;
 - duodenal intubation and analysis of bile;
 - endoscopic retrograde cholangiopancreatography (ERCP);
 - Oddi sphincter manometry.

Gall bladder and SO dysfunctions can cause significant clinical symptoms but do not explain many instances of biliopancreatic type of pain. In the diagnostic workup, invasive investigations should be performed only in the presence of compelling clinical evidence and after non-invasive testing has yielded negative findings. Gall bladder dysfunction is suspected when laboratory, ultrasonographic, and microscopic bile examination have excluded the presence of gallstones and other structural abnormalities.

The finding of decreased gall bladder emptying at cholecystokinincholescintigraphy) is the only objective characteristic of gall bladder dysfunction.

The diagnosis of SO dysfunction is supported by elevated serum aminotransferases (AlAT, AsAT), alkaline phosphatase (AP), or conjugated bilirubin, and/or pancreatic enzymes (amylase/lipase). Acute recurrent pancreatitis can also indicate pancreatic SO dysfunction.

Symptomatic manifestation of SO dysfunction may be accompanied by features of biliary obstruction (biliary-type SO dysfunction) or significant elevation of pancreatic enzymes and pancreatitis (pancreatic-type SO dysfunction). Biliary-type SO dysfunction occurs more frequently in postcholecystectomy patients. Pancreatic-type SO dysfunction is less well classified into types. When non-invasive investigations and endoscopic retrograde cholangiopancreatography show no structural abnormality, manometry of both biliary and pancreatic sphincter may be considered.

Course of biliary dysfunction is benign with recurrent symptoms over a long period of time (years). Gall bladder dysfunction may predispose to cholelithiasis and cholecystitis. SO dysfunction may be complicated by acute recurrent pancreatitis and episodes of biliary obstruction.

Cholecystitis

Definition: Cholecystitis (K81 according to ICD-X) is an inflammation of the gall bladder wall.

Etiology and pathogenesis. Various infections, autolytic affections of the gall bladder mucosa associated with regurgitation of pancreatic juice into the gall bladder, and helminthic invasions are important factors provoking cholecystitis. The etiological role of infection in development of cholecystitis is confirmed by bacteriological studies of microbial flora of B bile obtained during operation or by duodenal probing. Infection may enter the gall bladder by enterogenic (from the intestine), hematogenic (from remote foci of infection such as affected tonsils, carious teeth, etc.) and lymphogenic routes.

Bile congestion in the gall bladder predisposes to cholecystitis. The disease can be provoked by gall stones, biliary dysfunction (under the effect of various psychoemotional factors, endocrine disorders, dysfunction of the vegetative nervous system, numerous nerve reflexes of the pathologically changed organs of the digestive system, etc.), anatomical properties of the gall bladder and bile ducts, ptosis of the internal organs, pregnancy, inactive mode of life, rare meals, habitual constipation, etc. Acute and chronic cholecystites are differentiated.

Classification.

1. *According to cause* – calculous, acalculous cholecystitis;
2. *According to etiology* – bacterial, protozoa and helminth invasions;
3. *According to course* – acute, chronic cholecystitis (phase – exacerbation, remission);
4. *Clinical variants* of cholecystitis -
 - (a) typical hepatic colic, (b) atypical pain, (3) biliary dyspepsia, (4) latency cholecystitis;
5. *According to gallbladder motility* –hypokinetic, hyperkinetic types of gallbladder dysfunction;
6. *Complications* of cholecystitis –
 - cholangitis, pancreatitis, hepatitis;
 - autonomic nervous dysfunction;
 - reflex angina pectoris, myocardiodystrophy.

Clinical picture

Complaints. In case of *biliary (hepatic) colic* the patient complains of severe steady pain at the right upper quadrant and epigastrium, often radiating to the right scapula, right shoulder and neck which usually develops

in 1-3 hours after taking abundant (especially fat and roasted) food. Nausea and vomiting are usual in biliary colic.

Dyspeptic signs are also present: bitter and metallic taste in the mouth, eructation, nausea, abdominal flatulence, and alternation of diarrhea with constipation. The disease is sometimes not attended by pain except that the patient feels heaviness in the epigastrium or right hypochondrium, and dyspepsia develops. High body temperature may be in acute cholecystitis and exacerbation of chronic cholecystitis, usually subfebrile).

Physical examination. Moderate obesity is sometimes observed. Examination of the abdomen can reveal its flatulence (either uniform or predominantly in the upper portion).

Surface palpation of the abdomen reveals sensitivity and sometimes pronounced tenderness in the region of gall bladder projection. Muscular resistance of the abdominal wall is usually absent. De Mussy-Georgievsky, Ortner's, Obraztsov-Murphy, and Vasilenko's symptoms are positive. Vasilenko's symptom is a sharp pain in the region of the gall bladder when it is tapped over at the height of inspiration. Obraztsov-Murphy symptom is a sharp pain in the right hypochondrium when the examiner's hands press the gall bladder at the height of inspiration. Ortner's symptom is a pain during tapping over the right costal arch by the edge of the hand). The de Mussy-Georgievsky symptom is a tenderness at the point of the phrenic nerve, between the heads of the sternocleidomastoid muscle) can often be positive. Zones of skin hyperaesthesia (Zakharyin-Head symptom) can be found below the inferior angle of the right scapula and in the region of the 9th-11th interspaces.

The liver is usually of normal size but in the presence of complications, such as hepatitis or cholangitis, the liver may be slightly enlarged with firm and tender (to palpation) edge. The gall bladder is impalpable.

Laboratory and instrumental data. The blood changes (in acute cholecystitis and during exacerbation of chronic cholecystitis) are characterized by moderate leucocytosis and mildly increased ESR.

Signs of inflammation (mucus, leucocytes, desquamated epithelium) can be found in B bile. If inflammation involves bile ducts (cholangitis), C bile contains the same signs of inflammation. The vesical reflex (B bile) is sometimes impossible to obtain even by repeated probing. This indicates disordered contractility of the gall bladder which is typical of chronic cholecystitis. Bacteriological studies of B bile reveal the character of microbial flora.

Abdominal ultrasound demonstrates sonographic Murphy's sign, gallbladder wall thickening, or pericholecystic fluid in acute cholecystitis and in exacerbation of chronic cholecystitis. After taking a stimulating meal (cholekynetic test) the gall bladder contracts insufficiently.

Cholecystography shows changes in the configuration of the gall bladder and the absence of its distinct contours. This indicates upset concentrating capacity of the gall-bladder mucosa.

Diagnosis of cholecystitis is supported by (1) typical clinic and history, (2) transabdominal ultrasound; (3) multifractional duodenal intubation and bile analysis (increased leucocytes, acid reaction, mucus; bacterial culture, lamblia, helminthes, microcrystals of cholesterol, calcium bilirubinatis, phosphates, carbonates).

Course. The course of chronic cholecystitis is characterized by alternation of exacerbations and remissions. The disease can be exacerbated by abuse of fatty or fried foods, smoked meat and fish, condiments, alcoholic drink, etc., by acute intestinal infections, and other factors. The process continues for many years and even decades. Cholecystitis is often complicated by inflammation of the bile ducts (cholangitis) or of the pancreas (pancreatitis).

Cholelithiasis

Definition: Cholelithiasis (K80 according to ICD-X) is a metabolic diseases characterized by formation of stones in the gall bladder or, less frequently, in the bile ducts.

Etiology and pathophysiology. The disease is underlain by general metabolic disorders which provoke formation of stone, such as upset cholesterol metabolism with hypercholesterolemia attended by the supersaturation of cholesterol in bile, decrease of cholate (bile acids) level in the bile. Excess bilirubin in bile is the cause of gall stone in hemolytic anemia.

Bile congestion in the gall bladder (in pregnancy, ptosis of the internal organs, persistent constipations, hypodynamia, and rare meals) provides conditions for stone formation because it promotes concentration of bile and stimulates an increase (10-12 times) in cholesterol concentration in the bile, while gradual absorption of bile acids decreases their content in the bile. Moreover, bile congestion can provide favourable conditions for development of infection. The importance of the infectious factor consists in that protein-rich exudate of inflamed gall bladder upsets the normal colloidal and chemical composition of bile to precipitate bilirubin, cholesterol and calcium, and to cause formation of mixed stones typical for infectious diseases of the gall bladder.

Hereditary predisposition is also very important. Stones often occur in several generations of the one family (especially among women). Excessive food rich in fats and calories causes hypercholesterolemia and stimulates formation of gall stones.

Classification of cholelithiasis according to a stage of disease -
(1) Physical and chemical changes in bile;

- (2) Microscopic stones (sludge);
- (3) Cholelithiasis without cholecystitis;
- (4) Calculous cholecystitis.

Clinical picture.

Clinical variants of the disease include typical hepatic colic, atypical pain, biliary dyspepsia, and latency cholelithiasis.

Pain attacks in the right hypochondrium (the so-called *biliary, or gallstone, or hepatic colic*) are the most characteristic symptom of cholelithiasis. Pain is caused by spastic contractions of the gall bladder and the ducts which develop as a result of a sudden distension of the gall bladder and increased pressure inside it due to a mechanical obstruction to bile outflow. A gall-bladder colic can be provoked by physical or nervous strain, jolting motion, ingestion of much fat, etc.

Gallstone colic develops suddenly. In contrast to other types of colic, biliary colic typically is constant, with pain progressively rising to a plateau and falling gradually, lasting up to several hours and even days. The pain is first diffuse and is felt in the entire right hypochondrium. Later it localizes in the region of the gall bladder or in the epigastrium. The pain can specifically radiate upwards, to the right posteriorly, to the right shoulder, neck, the jaw, and into the right subscapular region. Pain can radiate also into the heart to provoke an attack of angina pectoris.

If the colic is long-standing, jaundice may develop at the end due to a spasm of the common bile duct. The jaundice usually is not intense and is only transient (2 to 3 days).

Gallstone colic is usually attended by nausea and recurrent vomiting. The reflex mechanism explains the fever which often attends the pain attack. The fever ends with the attack. If fever persists, it indicates its connection with inflammatory complication of cholelithiasis.

The patient may sometimes be obese, with xanthomatous plaques (cholesterol deposits) on the upper eyelids (less frequently on the other parts of the skin). The abdomen is distended; surface palpation reveals tension of the anterior abdominal wall, especially in the region of the right hypochondrium, and also excessive tenderness of this region. As pain is abated, the muscular tension subsides, and the tender edge of the liver can then be palpated. The gall bladder can sometimes be palpated as an oval or pear-shaped elastic body.

Tender points and sites of hyperesthesia can be determined on the body according to innervation zones of Zakharyin and Head in cholecystitis and cholelithiasis: (1) the region of the gall bladder (its projection on the skin), (2) epigastrium, (3) pancreato-biliary-cystic point. (4) shoulder zone, (5) point of the scapular angle. (6) paravertebral points to the right of the 8-th to 1-th thoracic vertebra, (7) phrenic nerve site (tender to pressure in the region

between the anterior heads of the right sternocleidomastoid muscle (phrenic symptom, or de Mussy-Georgievski symptom).

Laboratory and instrumental data. Some laboratory and instrumental studies reveal signs of cholelithiasis in the full absence of its symptoms. Blood test shows an increased cholesterol content. Duodenal probing (carried out in remission) can sometimes reveal fine stones (microliths) and a large quantity of cholesterol crystals.

The most important diagnostic techniques in cholelithiasis are echography studies and contrast roentgenography (cholecysto- or cholangiography). Real-time ultrasonography is the method of choice for diagnosing possible gallbladder calculi. Sensitivity (probability of a positive test when disease is present) is 98%; specificity (probability of a negative test when the disease is absent) is 95%.

Diagnosis of cholelithiasis is supported by the data of abdominal ultrasound or contrast roentgenography (cholecysto- or cholangiography).

Course. Most patients remain asymptomatic for long periods, frequently (near 50%) for life. Non-complicated cholelithiasis can manifest itself by only one attack of gall-stone colic. The attacks however are usually recurrent. Long-standing cholelithiasis is usually attended by infection. The symptomatic disease is then aggravated by symptoms of calculous cholecystitis.

Possible complications of the disease are posthepatic (mechanic) jaundice, gallbladder hydropsy, perihepatitis, peritonitis, hepatic abscesses, cholangitis, pancreatitis, hepatitis, autonomic nervous dysfunction, reflex angina pectoris, myocardiodystrophy.

Cholangitis

Definition: Cholangitis (K 83 according to ICD-X) is an inflammation of the intrahepatic and extrahepatic bile ducts.

Classification:

1. According to cause – primary, secondary cholangitis (in cholelithiasis, biliary ducts obstruction in case of pancreatitis, tumours of pancreas and bile ducts);
2. According to etiology - bacterial, protozoa and helminthes invasions, autoimmune cholangitis;
3. According to character of inflammation – suppurative, nonsuppurative, autoimmune sclerosing cholangitis;
4. According to course – acute, chronic (with remissions, permanent) cholangitis;
5. Clinical variants of chronic cholangitis – recurrent, septic, latency cholangitis;

6. Complications - posthepatic (mechanic) jaundice, sepsis (bacteremia), hepatic abscesses, cholangiocarcinoma, secondary cholestatic (biliary) hepatitis and liver cirrhosis.

Clinical and laboratory data. Clinical picture shows usually *Charcot's triad* - pain in right hypochondrium, jaundice, intermittent fever. Liver tests indicating obstruction of bile ducts (elevated serum bilirubin and alkaline phosphatase) usually accompany the symptoms. In septic cholangitis and in exacerbations of chronic recurrent there are neutrophilic leucocytosis, increase of ESR, and anemia.

ERCP, percutaneous transhepatic or intravenous cholangiography, CT, ultrasound may detect choledocholithiasis, ductal dilation and strictures of bile ducts.

Hepatobiliary parasitism

Invasion of the biliary tract by adult helminths or their ova may produce a chronic, recurrent pyogenic cholangitis with or without multiple hepatic abscesses, ductal stones, or biliary obstruction.

This condition is relatively rare but does occur in inhabitants of Europe, and especially of Western Siberia, Far East and elsewhere in Southeast Asia/

The organisms most commonly involved are trematodes, including *Clonorchis sinensis*, *Opisthorchis viverrini* or *O. felineus*, and *Fasciola hepatica*. The biliary tract also may be involved by intraductal migration of adult *Ascaris lumbricoides* from the duodenum or by intrabiliary rupture of hydatid cysts of the liver produced by *Echinococcus granulosus*.

The diagnosis is made by

- cholangiography;
- finding eggs in the feces or duodenal contents;
- *Echinococcus granulosus* is confirmed by
 - (a) CT and ultrasound detect single and daughter cysts in liver;
 - (b) Casoni skin test (test with echinococcus antigen),
 - (c) serologic tests - detection of antibodies to the echinococcal antigen.

Chronic Hepatitis

Definition: Chronic hepatitis (K73 according to ICD-X) represents a series of liver disorders of varying causes and severity in which hepatic inflammation and necrosis continue for at least 6 months.

Etiology. The following etiological variants of chronic hepatitis are distinguished: (1) infectious and parasitogenic (virus of hepatitis B,C,D, herpes, AIDS, brucellosis, tuberculosis, syphilis and others); (2) toxic hepatitis caused by industrial, medicamentous, domestic and food chronic poisoning (alcohol, chloroform, isoniazid, aminazine, lead compounds, etc);

(3) toxico-allergic hepatitis (medicamentous hepatitis, hepatitis associated with collagenosis); (4) metabolic hepatitis (protein-vitamin deficiency, fat dystrophy, amyloidosis); (5) hereditary predisposition (α 1-antitrypsin deficiency, Wilson's disease); (6) autoimmune hepatitis; (7) cholestatic hepatitis; (7) idiopathic, or cryptogenic, hepatitis.

Pathogenesis. The mechanism of chronicity is uncertain, but a direct cytopathic effect of the virus appears to be only minor, especially with HBV infection; instead, liver injury is largely caused by an immune-mediated host reaction to the infection. The pathogenesis varies with the drug and may reflect an altered immune response, cytotoxic intermediate metabolites, or genetically determined metabolic defects. Many cases are idiopathic. A high proportion of these cases have prominent immune features; this is considered a specific variant of the disorder (autoimmune hepatitis).

Pathological anatomy. Mild cases may have only minor hepatocellular necrosis and inflammatory cell infiltration, usually in portal regions, with normal acinar architecture and little or no fibrosis. The inflammatory and cicatricial processes are more distinct in the liver affected by active hepatitis. Inflammatory infiltration extends from the periportal zones inside the liver lobules whose outlines are indistinct. Hepatocytes are extensively necrotized and have dystrophic changes; fibrosis is found in the liver. The size of the liver increases, its surfaces are coarse and necrotized zones can be seen as red amorphous spots.

In most instances, the specific cause cannot be discerned, although cases caused by HBV can be distinguished by the presence of ground-glass hepatocytes and special stains for HBV components. Autoimmune cases usually have a more pronounced infiltration by lymphocytes and plasma cells. Cholestatic hepatitis is also characterized by marked affection of bile ducts {cholangitis and cholangiolitis) and signs of cholestasis.

Classification of Chronic Hepatitis

1. *According to cause* (common etiological variants):
 - chronic viral hepatitis B,C,D;
 - autoimmune hepatitis;
 - drug-associated chronic hepatitis;
 - cryptogenic chronic hepatitis (unknown etiology).
2. *According to grade* (hystological assessment of necroinflammatory activity):
 - portal inflammation (minimal [mild] activity);
 - periportal necrosis (moderate activity);
 - bridging necrosis (severe activity).
3. *According to stage* (is based on the degree of fibrosis):
 - 0 = no fibrosis; 1 = mild fibrosis; 2 = moderate fibrosis; 3 = severe fibrosis, including bridging fibrosis; 4 = cirrhosis.
4. *Clinical variants*

- chronic persistent (benign) hepatitis;
- chronic active (aggressive) hepatitis;
- chronic autoimmune hepatitis;
- chronic cholestatic hepatitis.

Clinical picture. Chronic hepatitis is characterized by (1) - biliary dyspepsia; (2) jaundice (it may be absent in some cases); (3) moderate enlargement and induration of the liver and the spleen (hepato- and splenomegaly); (4) asthenoneurotic syndrome - nonspecific malaise, anorexia, and fatigue are common, sometimes with low-grade fever; (5) dysfunction of the liver as determined by laboratory tests (various degree of one or several biochemical syndromes - cytolysis, cholestasis, mesenchymal inflammation, hepatocellular insufficiency). But the clinical picture and also the course of each clinicomorphological form of hepatitis have their special features.

Chronic benign hepatitis is characterized by obliterated clinical picture. The patients complain of heaviness or dull pain in the right hypochondrium, decreased appetite, bitter taste in the mouth, nausea and eructation. Jaundice is usually absent or it is moderate. Objective studies reveal a mildly enlarged liver with a smooth surface and a moderately firm edge, which is slightly tender to palpation. Enlargement of the spleen is not marked. Laboratory biochemical tests (bilirubin, prothrombin, activity of the enzymes) are either normal or only slightly changed.

Chronic active (aggressive) hepatitis is characterized by complaints and objective symptoms: weakness, loss of weight, fever, pain in the right hypochondrium, loss of appetite, nausea, regurgitation, meteorism, skin itching, jaundice, and frequent nasal bleeding. The liver is enlarged, firm, with a sharp edge. The spleen is enlarged. Laboratory tests often reveal anemia, leucopenia, thrombocytopenia (a sign of hypersplenism), and increased ESR. Functional tests are changed considerably: they show hyperbilirubinemia, hyperproteinemia, hypergammaglobulinemia, positive protein-sedimentation tests, increased activity of transaminase, aldolase, and alkaline phosphatase; decreased activity of cholinesterase. The serum iron content is significantly increased while the prothrombin index is sharply decreased.

In the *autoimmune chronic hepatitis*, multisystemic or "immune" manifestations often occur, especially in young women. These can affect virtually any body system and include acne, amenorrhea, arthralgia, ulcerative colitis, pulmonary fibrosis, thyroiditis, nephritis, and hemolytic anemia.

Chronic cholestatic hepatitis is mainly characterized by the cholestatic syndrome: jaundice (subhepatic), severe skin itching, hyperbilirubinaemia, alkaline phosphatase in the blood, and high cholesterol of blood. Persistent subfebrile temperature and regular increase in ESR are also not infrequent.

Diagnosis of chronic hepatitis is based on clinical and laboratory features are helpful, but liver biopsy is essential for definitive diagnosis.

Course. Prognosis is highly variable. With drug etiology, disease may regress completely when offending agent is withdrawn. Cases associated with HBV or HCV tend to progress slowly and are usually relatively resistant to therapy. Autoimmune cases generally improve substantially with treatment. With adequate therapy, patients usually live several years or decades, but hepatocellular failure, cirrhosis, or both eventually develop in many cases.

Liver Cirrhosis

Definition. Cirrhosis of the liver (K74 according to ICD-X) is a chronic progressive disease characterized by increasing hepatic insufficiency in connection with dystrophy of the liver cells and diffuse disorganization of normal hepatic structure by regenerative nodules that are surrounded by fibrotic tissue.

Etiology of the cirrhosis is similar to chronic hepatitis. It may develop due to: (1) infection (virus hepatitis B,C,D); (2) alcoholism and other toxic-allergic factors (drug-associated - aminazine, chloroform, some antibiotics, sulpha preparations, etc; carbon tetrachloride, compounds of phosphorus or arsenic, in food poisoning - inedible mushrooms, seeds of heliotrope); (3) autoimmune process; (4) cholestasis (obturation of intra- and extrahepatic bile ducts and their inflammation); (5) metabolic disorders - hemochromatosis, Wilson's disease, α 1-antitrypsin deficiency, galactosemia, and congenital tyrosinosis, diabetes mellitus, malnutrition; (6) circulatory diseases – chronic right ventricle insufficiency, chronic venous outflow obstruction (e.g., Budd-Chiari syndrome); (7) of unknown etiology, termed *cryptogenic*.

Pathogenesis. The etiological factor does not always determine the way of development of liver cirrhosis. One and the same factor can cause various morphological variants of cirrhosis; at the same time various etiological factors can cause similar morphological changes. The liver may be injured acutely and severely (as in submassive necrosis with hepatitis), moderately over months or years (as in biliary tract obstruction and chronic active hepatitis), or modestly but continuously (as in alcohol abuse). Cytokines and hepatic growth factors (e.g., epidermal growth factor) are presumably responsible for the response to injury: fibrosis plus regenerating nodules.

During the repair process, new vessels form within the fibrous sheath that surrounds the surviving nodules of liver cells; these “bridges” connect the hepatic artery and portal vein to the hepatic venules, restoring the intrahepatic circulatory pathway. Such interconnecting vessels receive blood from the sinusoids and provide relatively low-volume, high-pressure drainage that is less efficient than normal and results in increased portal vein pressure

(portal hypertension). Disordered blood flow to the nodules and compression of hepatic venules by regenerating nodules also contribute to portal hypertension.

Histopathologic classification of liver cirrhosis:

- *Micronodular cirrhosis* is characterized by uniformly small nodules (< 3 mm in diameter) and regular bands of connective tissue. Typically, nodules lack portal organization; terminal (central) hepatic venules or portal tracts are difficult to identify.

- *Macronodular cirrhosis* is characterized by nodules that vary in size (3 mm to 5 cm in diameter) and contain some normal lobular structure (portal tracts, terminal hepatic venules). Broad fibrous bands of varying thickness surround the large nodules. Collapse of the normal liver architecture is suggested by the concentration of portal tracts within the fibrous scars.

- *Mixed cirrhosis* (incomplete septal cirrhosis) combines elements of micronodular and macronodular cirrhosis. Regeneration in micronodular cirrhosis can result in macronodular or mixed cirrhosis. Conversion from micronodular to macronodular cirrhosis takes > 2 years.

- *Biliary cirrhosis* begins with injury or prolonged obstruction of either the intrahepatic or extrahepatic biliary system, associated with impaired biliary excretion, destruction of hepatic parenchyma, and progressive fibrosis.

Clinical picture.

Clinical manifestations of liver cirrhosis depend on the degree of affection of the liver cells and the associated hepatic dysfunction and portal hypertension, on the stage of the disease (compensated or decompensated), and also on the activity of the process. The following syndromes of the disease are most characteristic of the majority of patients with various forms of liver cirrhosis: hepato- and splenomegaly, portal hypertension with variceal bleeding and ascites, portal-systemic encephalopathy, hypersplenism, hepatic insufficiency, hepatic jaundice.

Complaints. Many patients with cirrhosis are asymptomatic for years. Others complain on generalized weakness, anorexia, weight loss, malaise, and insomnia. Fever is usually irregular and sometimes of the undulant type. Marked fever is characteristic of the active period and infectious cirrhosis.

Pain may be in the region of the liver and in the epigastrium, or diffuse pain in the whole abdomen. It is usually dull and boring, intensifying after meals especially after fatty food, ample drinking and physical exercise. Pain is usually associated with enlargement of the liver and distension of the capsule, or with necrotic foci located near the capsule, with perihepatic symptoms, and also concurrent inflammatory affections of the bile ducts.

Dyspepsia in the form of decreased appetite to complete anorexia, the feeling of heaviness in the epigastrium after meals, nausea, vomiting, meteorism and dyspeptic stools (diarrhea especially after fatty meals, rarely -

constipation) depend mainly on deranged secretion of bile and hence defective digestion.

Physical examination. Cachexia is especially characteristic of cirrhosis patients with portal hypertension. In long-standing disease the subcutaneous fat disappears along with atrophy of muscles, especially of the upper shoulder girdle. The appearance of such patients is quite specific: the face is very thin with grey or subicteric skin; the lips and the tongue are bright-red; the cheek bone region is affected by erythema; the extremities are thin and the abdomen is large (due to ascites, enlarged liver and spleen); the subcutaneous veins of the abdominal wall are dilated (*caput medusae*), the legs are edematous. Malnutrition is usually associated with disordered digestion and assimilation of food, and impaired synthesis of proteins in the affected liver.

The intensity of jaundice varies from light subicteric to marked jaundice (depending on the degree of obstruction of the bile ducts). Jaundice is usually characterized by partial decolouration of feces and by the presence of bile in the duodenal contents. Jaundice is often attended by skin itching. Jaundice associated with biliary cirrhosis resembles obstructive jaundice; severe skin itching and xanthelasmas are observed. In biliary cirrhosis the skin acquires a greenish tint which depends on oxidation of bilirubin to biliverdin. Moreover, brown pigmentation of the skin may also be observed. It depends on accumulation of melanin.

A hemorrhagic syndrome is observed in near of 50 per cent of patients with liver cirrhosis. Profuse bleeding from varicose veins of the esophagus and the stomach can often be early signs of portal cirrhosis. Gastro-intestinal hemorrhage (blood vomiting and *melena*) is caused by the rupture of varicose nodes in the lower third of the esophagus or, less frequently, in the stomach. A direct cause of varicose hemorrhage is physical strain or local affection of the mucosa (e.g. by coarse food). Nasal, gum, uterine and skin hemorrhages may develop in marked decompensation. They depend on the decreased coagulability of blood due to liver dysfunction and thrombocytopenia in the syndrome of hypersplenism.

“Minor” clinical signs of cirrhosis can also be revealed during examination of the patient and may suggest chronic liver disease. These signs are as follows: (1) *spider angiomas* (skin teleangiectasia may develop years before marked symptoms of the disease develop; < 10 may be normal); their number increases and the colour intensifies during exacerbation of the disease; (2) erythema of the palms (*palmar erythema*); (3) red lustrous lips, scarlet mucosa of the mouth, scarlet (lacquered) tongue; (4) gynecomastia (increased mammary glands) and other female sex characters developing in men (decreasing growth of hair on the face, chest, abdomen, and the head; , axillary hair loss, testicular atrophy); (5) xanthomatous plaques on the skin (observed in patients with biliary cirrhosis of the liver); (6) *Hippocratic (drumstick, clubbed,) fingers* with hyperemic skin at the nail beds and “*watch*

glass” nails. Other clinical signs may be in chronic liver disease, particularly in alcoholics, but none is specific: muscle wasting, *Dupuytren's contractures* (fibrosis of palmar aponeurosis), parotid gland enlargement, and peripheral neuropathy.

Inspection of the abdominal skin can reveal dilation of the veins that can be seen through the thinned skin of the abdominal wall (*caput medusae*). Collateral venous system can be seen on the chest as well. Hemorrhoidal veins are often dilated.

Ascites is the most characteristic sign of the portal hypertension. Ascites may develop slowly, and the abdomen grows to huge size; the patient develops dyspnea. Edema may develop; hydrothorax may also occur in some cases.

A palpable, firm liver with a blunt edge is typical in cirrhosis, but at times the liver is small and difficult to palpate. Regenerating nodules are only occasionally palpable. The enlargement can be insignificant, only determinable by percussion, or considerable when the liver occupies the entire left part of the abdominal cavity. The surface of the liver is sometimes irregular, and the lower edge sharp. Enlargement of the spleen is often attended by its increased activity (hypersplenism).

Laboratory data. Common blood analysis in active cirrhosis is characterized by anemia, leucopenia, thrombocytopenia, and increased ESR. Anemia can be due to hypersplenism and gastro-intestinal hemorrhage, hepatocellular insufficiency, and often increased hemolysis, which is accompanied by reticulocytosis of the peripheral blood.

Biochemical blood analysis shows dysfunction of the liver as determined by laboratory tests - various degree of one or several biochemical syndromes - cytolysis, cholestasis, mesenchymal inflammation, hepatocellular insufficiency (see above).

The blood serum bilirubin content becomes considerable only in the final stage of the disease. At the same time, the affection of the excretory function of the cirrhotic liver can be assessed by the presence of the conjugated fraction of bilirubin (*bound bilirubin*). Its content increases in normal and increased total bilirubin. The *free bilirubin* content increases in the blood serum as a result of upset conjugation of bilirubin in the liver cell and hemolysis.

The presence of much urobilin in the urine indicates liver insufficiency. The amount of urobilin in the urine and stercobilin in the feces decreases in the presence of pronounced jaundice when a small amount of bilirubin enters the intestine. Bilirubin is found in the urine of patients with jaundice.

Hepatocellular insufficiency is manifested by characteristic changes in the protein tests: decreased concentration of serum albumins and hypergammaglobulinemia, decreased levels of prothrombin, lipids and cholesterol,

decreased activity of pseudocholinesterase. Mesenchymal inflammation syndrome involves an increase in the α_2 - and γ -globulins, while jaundice causes an increase in β -globulins. The blood level of lipids and cholesterol also increases considerably in the presence of biliary cirrhosis. Activity of alkaline phosphatase (AP) and γ -glutamyl transpeptidase (GGTP) also increase in cholestasis syndrome. Transaminase (AlAT, AsAT) activity increases in cytolysis syndrome at the exacerbation of liver cirrhosis. The decreased prothrombin content (which is synthesized by the liver cells), decreased platelet count are important in haemorrhagic syndromes.

Instrumental examination. Isotopic scintiscans with technetium-99m sulfur colloid show irregular liver uptake and increased uptake in the spleen and bone marrow. Ultrasound may reveal textural abnormalities suggestive of cirrhosis, confirm hepatosplenomegaly, and detect features of portal hypertension: enlargement or obstruction of the portal or splenic veins and the presence of esophageal varices. Doppler ultrasound can demonstrate portal blood flow. CT better evaluates liver size and texture and, for hemochromatosis, density. Endoscopy is best for diagnosing esophageal varices.

Laparoscopy and especially biopsy (laparoscopic or transcutaneous) of the liver help reveal intravital morphological signs of each variant of liver cirrhosis.

Diagnosis of the liver cirrhosis is based on: (1) clinical picture of the most characteristic syndromes, such as hepato- and splenomegaly, portal hypertension, portal-systemic encephalopathy, hepatic insufficiency; (2) various degree of one or several biochemical syndromes, such as cytolysis, cholestasis, mesenchymal inflammation, hepatocellular insufficiency; (3) data of biopsy (laparoscopic or transcutaneous).

Complications of the liver cirrhosis include hepatic coma, gastroesophageal varices bleeding, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome (acute renal failure), and hepatocellular carcinoma.

Course. The course of the disease is usually progressive. The overall term of the disease is usually 3 to 5 years; in rare cases the disease may last 10 years and even longer (usually in biliary cirrhosis of the liver).

Complaints of patients with *compensated liver cirrhosis* are not serious. The disease is often revealed accidentally during examination (enlarged liver and spleen). Remissions may be long (measured by years) *Decompensated active cirrhosis* is characterized by marked symptoms of the disease and rapid progressive course.

The terminal period of the disease is characterized by gastro-intestinal hemorrhage and progressive signs of functional insufficiency of the liver, with finally developing coma. These are two most frequent direct causes of death of patients with liver cirrhosis. Profuse hemorrhage (if it does not cause

death) can cause anemia with subsequent impairment of the function of the liver cells and accelerated development of hepatic coma.

Diseases of kidneys and urinary paths

Clinical, laboratory and instrumental methods of diagnostics

Subjective examination (inquiry)

Complaints. Complaints of patients in kidneys and urinary tract diseases may include both renal and extrarenal complaints.

Renal complaints are pains in the lumbar region, hypogastria, and external genitalia, disordered urination (*dysuria*), and edema.

Kidney pain usually is felt in the flank or back between the 12th rib and the iliac crest, the costovertebral angle formed by the 12th rib and the lumbar spine, with occasional radiation to the epigastrium (in acute glomerulonephritis, pyelonephritis, acute ureteral obstruction, tumors, in heart decompensation ("congestive kidney").

Renal colic is periodical severe unilateral pain over the lumbar area, in the flank and hypochondria, with radiation into the iliac area and often into the upper thigh, testicle, or labium. The pain is intermittent but does not completely remit between waves of colic. Renal colic relieved by hot application, hot bath and spasmolytic medications. Inflammation or acute distention of the renal pelvis or ureter in nephrolithiasis, and «movable kidney» are the most common causes of renal colic.

Bladder pain is most commonly caused by bacterial cystitis; it is usually suprapubic and referred to the distal urethra during urination.

Prostate pain due to prostatitis may be felt as a vague discomfort or fullness in the perineal or rectal area, but prostatic disease is generally painless.

Dysuria is deranged excretion of urine, including changes in the daily volume of excreted urine, rhythm and character of urination, and changes in properties of urine. Normally, adults void about 4 to 6 times/day, mostly in the daytime, totaling 700 to 2000 ml/day. Causes of dysuria are infectious and other inflammatory processes in kidneys and urinary tract, nephrolithiasis, neoplasm, hereditary diseases (polycystic disease, hereditary nephropathy), nephrosclerosis, traumas, neurology and genitalia disorders, cardiovascular disorders, toxic, allergy.

Dysuric symptoms include pain in urination, *stranguria* (a difficult and painful urination), *pollakiuria* (frequent micturition >7-8 times a day); changes in the daily volume of excreted urine - *polyuria* (> 2500 ml/day), *oliguria* (< 500 ml/day, or 24ml/h), *anuria* (< 100 ml/day); *nycturia* (*nocturia*) if the volume of urine excreted during night often exceeds the amount of

daily urine; *ischuria* when the urine is retained in the bladder and the patient is unable to evacuate (in compression or other affection of the spinal cord, and in loss of consciousness); *enuresis*, or bed-wetting (involuntary urination at the night sleep delayed neuromuscular maturation of the lower urinary tract or organic disease; e.g., infection or distal urethral stenosis, or neurogenic bladder); *urinary incontinence* is an uncontrollable loss of urine; and *abnormal color or appearance of urine* – *hematuria*, *pyuria*, excretion of food pigments (usually red urine) or drugs, *pyuria*, cloudy or milky uria (phosphate salts in an alkaline urine), *bricky uria* (urates salts).

Extrarenal (general) complaints are due intoxication or systemic complications of underlying disease such as renal arterial hypertension - headache, dizziness, deranged vision; left ventricle insufficiency - pain in the heart, dyspnea; uremia – itching, weakness, absence of appetite, nausea, vomiting; inflammation - elevated body temperature.

History of the present disease contains information about previous infections (tonsillitis, scarlet fever, otitis, and acute respiratory diseases), diseases of the kidneys and the urinary ducts (acute nephritis, pyelitis, cystitis, nephrolithiasis). Chilling and cooling may cause of inflammatory diseases of kidneys and urinary tract diseases.

Life history of patient. Special attention should be given to the factors that might provoke the present disease or have effect on its further course, such as poor home or working conditions, genital infection, tuberculosis, diabetes mellitus, various chronic purulent diseases, nephropathy of pregnancy, diffuse diseases of connective tissue, prolonged or in large doses intake of medicine (aminoglycosides, amidopyrin, phenacetin, barbiturates, etc.) or of some poisons (bismuth, silver, sulphur and phosphorous preparations).

Objective examination

Survey. It shows edema, “*facies nephritica*”, pale skin, scratches on the skin and coated dry tongue, unpleasant odour of ammonia.

Edema usually represents excessive extracellular water and Na due to abnormal renal excretion, but it may also be caused by heart or liver disease. Edematous skin in chronic nephritis is pallid due to the spasm of skin arterioles, and anemia which attends this disease. Edema associated with kidney disease is sometimes noted first as facial puffiness rather than swelling in dependent or lower parts of the body.

Facies nephritica is the sign of renal edema characterized by the pallid, swollen face with edematous eyelids and narrowed eye-slits.

Scratches on the skin, coated dry tongue, unpleasant odour of ammonia from the mouth and skin of the patient (*factor uremicus*) are the signs of chronic renal insufficiency (uremia).

Inspection of the abdomen and the loin does not usually reveal any noticeable changes. It is possible to notice swelling on the affected side of the

loin in paranephritis. Especially large tumour of the kidney may be manifested by protrusion of the abdominal wall. Overfilling bladder can be protruded over the pubic bone in thin persons in, for example, due to retention of urine in adenoma or cancer of the prostate.

Percussion. Percussion of the superior border of filled urinary bladder gives a dull sound at the suprapubic region.

Pasternatsky's symptom is positive if the patient feels pain during the tapping in the lumbar regions. This symptom is positive in nephrolithiasis, paranephritis, inflammation of the pelvis, and also in myositis and radiculitis. This decreases the diagnostic value of Pasternatsky's symptom.

Palpation. Palpation of kidneys by Obratzsov and Strazhesko method at vertical and horizontal position should assess the shape, size, surface (smooth or tuberos), tenderness, mobility, and consistency of the kidneys. Hence kidneys are not palpated in the norm with the exception of inferior pole of the right kidney at the vertical position of asthenic patients. Palpation of kidneys becomes possible in enlarged volume of kidneys or at their ptosis.

Palpation of the urinary bladder in absence of its pathology and its overflow yields a negative result. If it contains much urine, especially in persons with thin abdominal wall, the urinary bladder can be palpated over the pubic bone as an elastic fluctuating formation. If the bladder is markedly distended, its superior border reaches the umbilicus.

Pressure in ureteric points in norm routinely painless becomes sharply responsive in pyelonephritis, paranephritis, nephrolithiasis, tumor and tuberculosis of kidneys.

Auscultation in diagnostics of kidneys disease is used for recognition of pathology of renal arteria. Systolic murmurs of renal artery stenosis can be auscultated in the costovertebral angles and on anterior abdominal wall in points placed 5 sm above umbilicus and near 4-5 sm aside.

Laboratory and instrumental examinations

Urinalysis

The study of urine is important for establishing a diagnosis of and concluding on the course of the pathology (Supplement. Table 9). Urinalysis includes evaluation of physical and chemical properties of urine, and microscopic examination of sediment. Urine samples taken after night sleep are usually studied.

Physical properties of urine

The normal *daily amount of urine* (daily diuresis) excreted by an adult varies from 1000 to 2000 ml, the ratio of the urine evacuated during day to the nocturnal diuresis being 3:1 or 4:1. The daily amount of below 500 ml (*oligouria*) and over 2000 ml (*polyuria*) can be considered pathological under certain conditions.

The *color* of normal urine depends on its concentration and varies from straw-yellow to the colour of amber. The most marked changes in the urine colour depend on the presence of greenish-brown bilirubin, large quantity of erythrocytes (appearance of *meat wastes*), reddish-brown urobilin, and medicines (acetylsalicylic acid and amidopyrine give pink colour to the urine; methylene blue colors it blue).

Normal urine is clear. *Cloudiness* may be due to salts, cell elements, mucus, fats, and bacteria.

The *smell* of urine is specific and not pungent. When decomposed by bacteria in- or outside the bladder, urine smells of ammonia. In the presence of ketone bodies (in grave forms of diabetes mellitus), urine smells "fruity" (the odour of decomposing apples).

The *specific gravity* of the normal urine varies from 1,008 to 1,028. Determination of the specific gravity of the urine is of great clinical importance because it gives information on the concentration of substances dissolved in it (urea, uric acid, salts) and characterizes the concentrating and diluting capacity of the kidneys. Specific gravity depends not only on the amount of particles dissolved but mainly on their molecular weight. *Hyperstenuria* means increase of specific gravity of the urine more than 1,028, may be due to glucosuria (in diabetes mellitus), proteinuria, salts, in oliguric stage of acute renal failure. The specific gravity of the urine may exceed 1,030-1,040 in the presence of high quantity of glucose (glucosuria), because the concentration of 10 g/l increases gravity of the urine by 0,004. *Hypostenuria* is a decrease of specific of the urine less than 1,012, may be due to reduction of renal concentration function, for example, in chronic renal diseases, and in polyuric stage of acute renal failure. *Isostenuria* is monotonous specific gravity of urine ($<\pm 0,005$) to due to reduction of renal concentration function. *Isohypostenura* means a combination of isostenuria and hypostenuria.

Chemical analysis of urine

Reaction of the urine. The kidneys are important for maintaining acid-base equilibrium in the body. Urinary pH varies from 5,0 to 9,0. The mean pH value of the urine in healthy subjects (with normal nutrition) is about 6.0 (slightly acid). Acidity of urine can increase in diabetes mellitus, renal insufficiency, tuberculosis of the kidneys, acidosis, and hypokaliemic alkalosis. Urine reacts alkaline in vomiting and chronic infections of the urinary tracts due to bacterial-ammoniac fermentation.

Study of protein in urine. Normal urine does not practically contain protein. The small quantity of plasma proteins (to 150 mg/day), that is present in the urine, cannot be determined by qualitative tests used in practical medicine. The appearance of protein in the urine in concentrations determinable by qualitative methods is called *proteinuria*. It can be of renal and extrarenal origin.

Organic renal proteinuria occurs in kidney affections due to increased permeability of glomeruli which is underlined by vascular inflammation or structural disorganization of the basal membrane. Glomerular permeability is upset by the "molecular sieve" mechanism, i.e. low-molecular proteins are lost in the first instance. This proteinuria is called *selective*. As the process progresses, high-molecular proteins are also lost (*non-selective proteinuria*). Selectivity of proteinuria is an important diagnostic and prognostic sign.

Functional renal proteinuria is connected with the permeability of membranes in the renal filter in the presence of strong stimulation, slowing of the blood flow in the glomeruli, etc. Functional proteinuria includes emotional, athletic (effort), cold, and orthostatic (a condition characterized by the appearance of protein in the urine when the patient is in the erect posture; hence the name). In cases with *extrarenal proteinuria*, proteins enter the urine from the urinary and genitalia ducts (admixture of inflammatory exudates); extra-renal proteinuria does not exceed 1 g/l.

Measurements of a daily protein excretion are useful for diagnosis and follow-up, especially in constant proteinuria. A 24-hour measurement of total protein excretion (normal, < 150 mg/day) may be done. Heavy proteinuria (>2 g/day) is found in patients with glomerulopathy producing the nephrotic syndrome

Study of glucose in urine. The urine of a healthy person contains very small quantity of glucose (0,03-0,15 g/l) which cannot be detected by common qualitative tests. Glucose in the urine (*glucosuria*) can be both physiological and pathological. In the presence of normal renal function, glucosuria occurs only in increased concentration of glucose in the blood (*hyperglycemia*). The so-called renal glucose threshold (glucose concentration in the blood) does not usually exceed 9,9 mmol/l; higher concentration of sugar indicates glycosuria.

Physiological glucosuria can be observed in persons whose diet is rich in carbohydrates (*alimentary glucosuria*), following emotional stress, and administration of some medicines (caffeine, corticosteroids). Less frequent is *renal glucosuria* associated with disturbed resorption of glucose in the tubules: glucosuria develops in the presence of normal amount of glucose in the blood. As a primary disease, glucosuria occurs in the form of renal diabetes. Secondary renal glucosuria occurs in chronic nephritis, nephrotic syndrome, and in glycogen-storage disease. Pathological glucosuria occurs most frequently in diabetes mellitus, less frequently in thyrotoxicosis, in pituitary insufficiency (Itsenko-Cushing syndrome), and in liver cirrhosis.

In order to assess correctly glucosuria (especially in patients with diabetes mellitus), it is necessary to calculate the daily loss of glucose with urine.

Study of ketone (acetone) bodies. The presence of ketone bodies (acetone, acetoacetic and β -oxybutyric acid) in the urine is called *ketonuria*. Ke-

tonuria offers clues to the causes of metabolic acidosis. Ketonuria is usually observed in severe diabetes mellitus but it can also develop due to carbohydrate deficit (in grave toxicosis, long standing gastrointestinal disorders, alcohol intoxication, starvation, etc.); it may develop postoperatively. *Lange test* is most commonly used for the detection of ketone bodies in the urine.

Study of bile pigments. Determination of bilirubin. Normal urine is practically free from bilirubin. Increased amounts of bilirubin in the urine at which common qualitative bilirubin tests become positive (*bilirubinuria*) occur in hepatic and subhepatic jaundice at which the concentration of bound bilirubin (bilirubin glucuronide) in the blood increases.

Determination of urobilinoids. Urobilinoids are urobilin (urobilinogens, urobilins) and stercobilin (stercobilinogens, stercobilins). Urobilin and stercobilin bodies are not determined separately. Excretion of large amounts of urobilinoids in the urine is called *urobilinuria* which occurs in diseases of the hepatic (hepatitis, cirrhosis) and in prehepatic jaundice (hemolytic anemia).

Microscopy of urine sediment

A urine specimen is stirred thoroughly and its 10 ml are transferred into a centrifugal test tube. After centrifuging, the supernatant is decanted while the precipitate transferred onto an object glass for microscopy. The precipitate is first examined at small and then at large magnification to study the *formed elements (cells and cylinders), and salts.*

Erythrocytes (red blood cells) can be altered and unaltered. *Unaltered erythrocytes* contain hemoglobin and appear as greenish-yellow discs. *Altered erythrocytes* are free from hemoglobin and are colourless one- or two-contour rings. These erythrocytes occur in the urine of low specific gravity; erythrocytes shrink in the urine of specific gravity. The urine of a healthy person can have single erythrocytes.

Erythrocytes may be liberated either from the kidneys or from the urinary tract. The presence of erythrocytes in the urine is called *hematuria*. Hematuria that can only be established by microscopy is called *microhematuria*, while hematuria revealed by unaided eyes is called *macrohematuria*. It is important practically to decide whether hematuria is of glomerular or non-glomerular origin. In *non-glomerular hematuria* the blood pass into the urine from the urinary tract due to the presence of stones in the kidney pelvis, urinary bladder or ureters, and because of tuberculosis or malignant newgrowths of the urinary bladder. In the presence of *glomerular hematuria*, the urine usually contains much protein. Proteinoerythrocytic dissociation (i.e. hematuria with insignificant proteinuria) usually suggests hematuria associated with pathology of the urinary tract. An intermittent character of hematuria (with strongly varying intensity) is another evidence of non-glomerular hematuria.

A *three-glass test* is used for differential diagnosis of hematuria. The patient urinates into three vessels. If the blood originates in the urinary tract

(urethra), the highest amount of blood is present in the first portion of the urine; if bleeding occurs in the urinary bladder, hematuria is the highest in the last portion. If the source of hemorrhage is located in other parts of the urinary system, all three portions of the urine contain equal quantity of erythrocytes.

Leucocytes are found in the urine as small granular rounded cells. They swell in the urine of low specific gravity. Leucocytes in the urine of a healthy person are usually neutrophils and their amount is insignificant (to 1-2 in the microscope's vision field). Increased quantity of leucocytes in the urine (*leucocyturia*) indicates inflammation in the kidneys or urinary tract (urethritis, prostatitis, cystitis, and pyelonephritis). *Thompson's test* is used for differential diagnosis of leucocyturia. The first portion of an early morning urine specimen is collected in the first glass, the main bulk of the urine in the second glass, and only the residue in the third glass. If prevailing quantity of leucocytes is found in the first portion, it indicates the presence of urethritis and prostatitis. If the main quantity of leucocytes is found in the third portion, this suggests the disease of the urinary bladder. Uniform distribution of leucocytes in all portions of the urine may suggest affection of the kidneys.

Microscopy can reveal cells of *squamous, transitional, and renal epithelium*). Squamous epithelium cells are rounded or polygonal; they are large, colourless, and contain a small nucleus; they enter the urine from the external genitalia and the urethra; their diagnostic importance is low. Cells of transitional epithelium line the mucosa of the urinary tract; their configuration is quite varied; they are smaller than squamous epithelium cells; the nucleus is rounded. The presence of large amount of transitional epithelium in the urine indicates inflammatory process in the kidney pelvis or the bladder. Cells of renal (cubical) epithelium of tubules are rounded or polyhedral; they are small (slightly larger than leucocytes) and have a large, eccentrically located nucleus; their granularity is coarse. They are often found in hyaline cylinders. The presence of renal epithelium in the urine is a specific sign of acute and chronic affections of the kidneys, and also of fever, toxicosis, and infectious diseases.

Casts (cylinders) are proteinous or cell formations of tubular origin; they have cylindrical configuration and variable size. *Hyaline casts* are proteinous formations of indistinct contour with smooth and slightly granular surface; they are found in acute and chronic nephritis, nephrotic syndrome, and also in physiological transient albuminuria. Hyaline casts can be found in the urine of practically healthy people when the pH of the urine decreases sharply along with increasing specific gravity of the urine, which is characteristic of dehydration. It is believed that hyaline casts are formed by glycoprotein secreted in the tubules; but there are no reliable data that would confirm this conjecture. *Granular casts* have distinct contours; they consist of dense granular mass formed by degraded cells of renal epithelium. Their

presence indicates dystrophic processes in the tubules. *Waxy casts* have distinct contours and a homogeneous yellow structure. Their presence is characteristic of chronic diseases of the kidneys. The urine can also contain epithelial, erythrocytary, hemoglobin and leukocyte casts, and cylindrical formations of amorphous salts, which are diagnostically unimportant.

"*Non-organized sediment*" of the urine consists of salts that precipitate as crystals and amorphous substances. Their character depends on the colloidal composition of the urine, its pH, and other properties. Acid urine contains uric acid (yellow rhomboid-type crystals), urates (yellowish-brown amorphous salt), oxalic lime, or oxalates (colourless octahedral crystals that may also occur in alkaline urine). Alkaline urine contains ammonium urate, calcium carbonate, triple phosphates, amorphous phosphates, and neutral calcium phosphate. The sediment is diagnostically insignificant but pathological urine can contain crystals of cystine, tyrosine, and leucine. The presence of tyrosine and leucine is especially characteristic of subacute dystrophy of the liver and of phosphorus poisoning. The presence of lipoids in the urine is characteristic of nephrotic syndrome. In a polarizing microscope, lipoids give a dual reflection and appear as lustrous crosses.

Bacterioscopic and bacteriological study of urine. Urine cultures are used to establish the infectious nature of a disease of the urinary system. Sterile glassware should be used for the purpose. Whenever necessary, the urine is studied by bacterioscopy for the presence of tuberculosis mycobacteria. A smear is prepared from the urinary sediment with Ziehl-Nielsen staining. The urine is studied bacteriologically to determine qualitative and quantitative composition of its microbial flora. *Bacteriuria* is characterized by $> 10^5$ colony-forming units (CFU)/ml. In the presence of *bacteriuria*, it is very important to determine its degree and microorganism sensitivity to various antibiotics.

Quantitative determination of the formed elements of urine

Addis-Kakovsky test. The test is used for quantitative determination of the formed elements in the urinary sediment. Urine collected during ten hours is stirred thoroughly, its amount is measured and a 12-minute aliquot (1/50th of the full volume) is placed in a graduated centrifugal test tube. The quantity of cells counted in one microlitre is multiplied by 60 000 to find the quantity of the formed cells of the urine excreted during the day. The normal counts are $1,0 \times 10^6$ /day for erythrocytes, $2,0 \times 10^6$ / day for leucocytes, and $20,0 \times 10^4$ /day for casts.

Nechiporenko's method is now widely used to count erythrocytes and leucocytes in 1 ml of urine. The main advantage of this method is that an average sample of first morning urine is taken for analysis and the presence of pus from the genitalia is thus excluded. The normal counts are $1,0 \times 10^6$ /l for erythrocytes, $2,0 \times 10^6$ /l for leucocytes, and $20,0 \times 10^3$ /l for hyaline casts.

Assessment of the renal function by specific gravity and amount of the urine excreted

Zimnitsky's test. The main advantage of this method is that the renal function is tested without interfering with the normal life of the patient. The patient collects his urine at 3-hour intervals (8 portions during 24 hours). The volume of each portion and specific gravity of the urine are determined. The volumes of daily and night urine are compared and a conclusion is derived concerning daily and nocturnal diuresis. Fluctuations in specific gravity of the urine during the course of the day and its maximum value are thus determined. Normally the daily diuresis exceeds the nocturnal one 4:1 or 3:1; volumes of urine portions can vary from 50 to 250 ml, and their specific gravity from 1,005 to 1,028. Nocturnal diuresis (*nycturia*) prevails in renal insufficiency to indicate longer work of the kidneys because of their impaired functional capacity. If renal insufficiency is pronounced, decreased specific gravity becomes permanent (*hyposthenuria*). Combination of polyuria with low specific gravity of the urine and nycturia is a specific sign of renal dysfunction.

Assessment of the glomerular filtration and renal reabsorption function

Assay of Rehberg is the test for studying the glomerular filtration by endogenous creatinine. The renal clearance of this substance is actually equal to glomerular filtration. Renal clearance means the volume of blood or plasma could be freed of specified constituent in a specified time (usually one minute) by excretion of the constituent into the urine through the kidneys. Blood is taken from the vein of the patient on a fasting stomach and creatinine concentration is determined. Urine is collected during 2 hours. Diuresis is measured thoroughly and creatinine content determined. Next, using the formulae, the glomerular filtration and reabsorption percentage are calculated. The normal assay of Rehberg: glomerular filtration rate (GRF) - 65-120ml/min, renal reabsorption of water – 98,5-99,0%.

Renal insufficiency arises in cases where the mass of the active parenchyma is 20 per cent (and lower) of the normal weight. The determination of the mass of the active nephrons is thus important to assess the renal function. The measure of active nephrons is the glomerular filtration rate. As renal failure develops, glomerular filtration decreases gradually to attain as low values as 5-2-1 ml/min. Tubular reabsorption changes less markedly to decrease in cases of pronounced insufficiency to 80-60 per cent.

Diagnostic value of examination of blood and blood serum in kidneys and urinary tract diseases

Biochemical blood tests. *Serum creatinine* can be used as the most important index of renal function because creatinine production and excretion are reasonably constant in the absence of muscle disease. Serum concentration of creatinine varies inversely with the GFR and therefore is a useful in-

dex of the GFR if production (related to muscle mass and age) and metabolism (increased in uremia) are considered. The serum creatinine concentration in patient with normal GFR varies 0,088-0,176 mmol/l.

It is possible to reveal and assess the degree of renal insufficiency by increase of blood concentration of (1) nitrogen substances - *creatinine, urea, urea acid, indican, residual nitrogen*; (2) and minerals - *potassium, sodium, calcium, magnesium and phosphates*.

Common blood analysis. Anemia (particularly normochromic from a lack of erythropoietin) may be a clue to renal failure, but many other causes (e.g., neoplasia, systemic inflammatory diseases) must be excluded. Polycythemia may occur in renal cell carcinoma or polycystic disease, but more common causes should be considered first.

Instrumental method of diagnosis

Plain x-ray of the abdomen can demonstrate the size and location of the kidneys.

Intravenous urography (IVU; excretory urography) is often used to visualize the kidney and lower urinary tract. The patient is given intravenously a contrast substance that is readily excreted by the kidneys (25-40 ml of a 30-50 per cent solution of iodine benzoic acid derivative). The iodine provides radiopacity, while the benzoic acid is rapidly filtered by the kidney. Then a series of pictures are taken by which determined are the size, position and functional capacity of the kidneys (by the readiness with which they excrete the contrast substance), the size and configuration of the pelves, position of the ureters, and the presence of concrements (stones). The best urograms are obtained in patients with a normal GFR who do not actively diuresis during contrast agent administration.

Retrograde pyelography is performed in cases when findings of the excretory pyelography are not reliable or not sufficiently informative to establish correct diagnosis of pelvic affection. Additionally, retrograde evaluation may be indicated to assess the degree, type, cause, and length of ureteral obstruction or when the patient is allergic to IV radiocontrast. It is also useful for detailed examination of the pelvicalyceal collecting system, ureters, and urinary bladder.

Renal angiography is used to diagnose disordered blood supply to the kidneys due to upset circulation in the renal artery (stenosis, atherosclerotic plaque, etc.). A special contrast substance is injected into the aorta (through the femoral artery using a special tube) at the level of branching of the renal arteries.

Ultrasonography (US) is a noninvasive, relatively innocuous technique, is advantageous in that visualization does not depend on function of kidney. US is the preferred diagnostic method in a uremic patient when uptake of contrast agent or isotope is impaired. US is widely used in nephrology

to determine the size and position of the kidneys, the condition of the renal tissue, to reveal cysts, tumours of the parenchyma, stones in the pelvis, etc.

Radioisotope renography (diodrast or hippuran labelled ^{131}I) is used to study the general secretory function of the kidneys by the rate of blood clearance of the labelled preparation and accumulation of the preparation in the urinary bladder (to show the general urodynamics in the upper urinary tract).

Radionuclide scanning (^{203}Hg labelled neohydrin) studies accumulation of the labelled radioactive preparation. The renal function is assessed by the intensity of accumulation of the labelled preparation. The presence of focal accumulation defects indicates tumours, cysts, tuberculous affections of the kidneys, and other destructive processes. The shape and size of the kidneys can be determined from a scanogram.

Computed tomography (CT) and *magnetic resonance imaging (MRI, MRT)* are most useful in evaluating the character and extent of renal masses or determining the cause of a retroperitoneal mass distorting the normal urinary tract (e.g., an enlarged abdominal lymph node). In addition, MRI defines vascular and perirenal structures, permitting diagnosis of thrombosis, aneurysm, arteriovenous fistula, and neoplastic extension. MRI with contrast provides information about GFR and tubular function.

Renal puncture biopsy (percutaneous, open) is performed to establish a histological diagnosis, help estimate prognosis and the potential reversibility or progression of the renal lesion, estimate the value of therapeutic modalities, and determine the natural history of renal diseases. The only absolute contraindication to biopsy is uncontrollable bleeding.

Basic clinical syndromes of kidneys and urinary paths diseases

Urinary syndrome

Definition: *Urinary syndrome* includes symptoms of dysuria and pathological properties of urine.

Causes of urinary syndrome may be infectious and other inflammatory processes in kidneys and urinary tract, nephrolithiasis, neoplasm, hereditary diseases (polycystic disease, hereditary nephropathy), nephrosclerosis, traumas, neurology and genitalia disorders, cardiovascular disorders, toxic, allergy.

Clinical picture is characterized by dysuric symptoms, including disorders in the daily volume of excreted urine, rhythm and character of urination, such as pain in urination, pollakiuria (frequent micturition), polyuria (>2500 ml/day), oliguria (<500 ml/day, or 24ml/h), anuria (< 100 ml/day), nycturia.

Urinalysis shows changes of physical and chemical properties of the urine: specific gravity of urine (*isosthenuria*, *hyposthenuria*, *hypersthenuria*), reaction of urine – increased acidity, alkaline; *proteinuria* (renal and extra-

renal, selective and non-selective), *glucosuria* (physiological, pathological - renal, extrarenal); and pathological changes of urinary sediment - *hematuria* (micro- and macrohematuria), leucocyturia, epithelium - transitional and renal, casts (cylinderuria - hyaline, waxy, granular), crystalluria (urate, oxalate, phosphate, etc.), bacteriuria - if microscopy $>1,0 \times 10^5$ /ml, and/or positive urine culture.

Renal edema

Definition: Renal edema is a syndrome of general disorder of water-salt metabolism specific to most kidney diseases and can easily be differentiated from edema of other origin, e.g. cardiac edema.

Causes of renal edema arise in various kidney diseases due to (1) diffuse increased permeability of the capillary wall, (2) colloidal-osmotic (hypoproteinemic) mechanism of edema, (3) hypernatremia, (4) acute anuria.

Clinical features of renal edema: (1) affection of loose connective tissue (the eyelids, the face) rather than of the lower extremities; (2) pale skin above edema; (3) more expressed at morning hours; (4) renal edema can develop and resolve quickly; (5) in pronounced cases anasarca, enlarged liver, and fluid in serous cavities (ascites, hydrothorax) may be; (6) the enlargement of the liver is usually proportional to enlargement of the other organs.

Renal edema can also be confirmed by the McClure-Aldrich test: 0,2 ml of isotonic sodium chloride solution is injected into the skin on the median surface of a forearm and the time of disappearance of the resulting weal is noted. In a healthy subject, the weal is resolved within one hour. In "readiness for renal edema" the weal is resolved significantly faster.

Nephrotic syndrome

Definition: Nephrotic syndrome (N04 according to ICD-X) is a predictable set of symptoms that results from a severe, prolonged increase in glomerular permeability for protein. The main feature is heavy proteinuria (> 2 g/day), but hypoalbuminemia (<30 g/l), generalized edema, lipiduria, and lipemia are also common.

Causes. Nephrotic syndrome occurs in chronic glomerulonephritis, amyloidosis, malaria, sepsis, tuberculosis, systemic diseases of connective tissue (lupus erithematosus, etc.), diabetes mellitus, and certain other diseases. Less frequently the cause of the nephrotic syndrome cannot be established immediately, but in most cases a detailed analysis of anamnestic data and a thorough examination of the patient reveal chronic glomerulonephritis.

Pathogenesis of the nephritic syndrome includes disorders of fat and protein metabolism, with subsequent derangement of trophics and capillary permeability in the glomeruli. Proteinuria is thought to occur through functional derangement of two mechanisms: the size-selective barrier leaks large

protein molecules, and the charge-selective barrier fails to retain lower mol weight proteins.

Clinical and laboratory features

The main, and often the only complaint of patients is persistent edema. An early sign of nephritic syndrome is frothy urine due to protein. Other features include anorexia, malaise, puffy eyelids, retinal sheen, abdominal pain, and wasting of muscles. Focal edema may present as difficulty breathing (pleural effusion or laryngeal edema), substernal chest pain (pericardial effusion), scrotal swelling, swollen knees (hydrarthrosis), and swollen abdomen (ascites); abdominal pain may be due to edema of the mesentery.

Edema is especially pronounced on the face which becomes swollen and pallid, the eyelids are only a narrow slit, and the patient opens his eyes in the morning with difficulty. The legs, the loin, the skin of the abdomen and the hands are also affected by edema. Parallel white lines in fingernail beds may be due to subungual edema.

Most often, the edema is mobile (e.g., detected in the eyelids in the morning and in the ankles after ambulation). Edema may mask muscle wasting. Fluid is accumulated also in the internal organs and the serous cavities. Anasarca with ascites and pleural effusions may occur.

As the edema progresses, diuresis usually decreases and the patient often eliminates only 250-400 ml of urine a day. Oliguria or acute renal failure may develop because of hypovolemia and diminished renal perfusion. In typical cases the arterial pressure remains unchanged or even decrease.

Urinalysis is characterized by hyperstenuria (1,030-1,040) and heavy proteinuria (from 2-3 g/l to 10-20 g/l and more). Microscopy of the urinary sediment shows great quantity of hyaline, granular and waxy casts, cholesterol crystals and cells of renal epithelium.

Biochemical blood tests detect hypoproteinemia, especially hypoalbuminemia (<30g/l). The content of α_2 -globulins, and also γ -globulins, slightly increases. The constant symptoms are pronounced hyperlipidaemia, increased blood serum concentration of cholesterol (to 13-15 mmol/l, i.e. or 3 times as great), phospholipids, and triglycerides. Lipid levels > 10 times normal are associated with severe hypoalbuminemia due to increased lipid production and decreased elimination.

Coagulopathies are common, perhaps because of the urinary loss of coagulation factors IX and XII and thrombolytic factors (urokinase and antithrombin III) and increased serum levels of factor VIII, fibrinogen, and platelets. The blood clearing function of the kidneys is not substantially affected in the nephrotic syndrome, and azotemia does not develop for a long time.

Diagnosis of the nephrotic syndrome is based on edema, pronounced proteinuria, hypoproteinemia (mainly due to hypoalbuminemia), hyperlipidemia (hypercholesterolemia). Severe proteinuria is essential to the diagno-

sis. Biopsy of the kidneys supplies valuable information concerning the nature of the nephrotic syndrome in chronic renal diseases.

Complications. The biochemical consequences of severe proteinuria are the main clinical problem. Prolonged nephritic syndrome may result in nutritional deficiencies, including protein malnutrition resembling kwashiorkor, brittle hair and nails, alopecia, stunted growth, demineralization of bone, glucosuria, hyperaminoaciduria of various types, K⁺ depletion, myopathy, decreased total Ca, tetany, and hypometabolism. Spontaneous peritonitis may occur, and opportunistic infections are prevalent. The high incidence of infection is thought to be due to the urinary loss of immunoglobulins. Coagulation disorders, with decreased fibrinolytic activity and episodic hypovolemia, are a serious thrombotic risk (notably, renal vein thrombosis). Hypertension with cardiac and cerebral complications is most likely in patients with diabetes or collagen vascular disease.

Renal arterial hypertension

Definition. Renal arterial hypertension is a symptomatic hypertension caused by the affection of the kidneys or renal vessels and upset renal mechanism of arterial pressure regulation.

The renal hypertension syndrome can be of primary significance in the clinical picture of the disease and can be decisive for its course and outcome.

Causes. Many diseases of the kidneys, in the first instance acute and chronic glomerulonephritis, pyelonephritis, nephrosclerosis and various affections of the renal blood vessels are attended by elevated arterial pressure. This is underlain by the important role that the kidneys play in the regulation of arterial pressure due to increased renin secretion. However, < 5% of adult hypertension is due to kidneys and renovascular problems.

Clinical features of the renal arterial hypertension are (1) high persistent level of blood pressure (especially high diastolic BP and low pulse pressure); (2) rare hypertensive crisis; (3) renal hypertension often tends to an especially rapid and malignant course accompanied by progressive of such target-organs as left ventricle, cerebral circulation, retina; (4) evident hypertrophy and dilatation of the left ventricle, complicated often by acute left ventricular failure with attacks of cardiac asthma and pulmonary edema; (5) angina pectoris and myocardial infarction often occurs; (6) changes in the fundus oculi (renal retinopathy) and deranged vision; (7) disorders in cerebral circulation with paralysis, deranged sensitivity; (8) pronounced urinary syndrome (often previous to high BP); (9) serious changes in functional test of kidneys; (10) urinary and kidneys disorders in past history often previous to high BP.

Diagnosis of the renal arterial hypertension is supported by typical clinical features and laboratory-instrumental findings that confirm pathology of kidneys and renovascular problems.

Screening tests required for diagnosis of the renal arterial hypertension are urinalysis, Nechiporenko's test, Zimnitsky's test, blood serum urea and creatinine, assay of Rehberg, ultrasonography of kidneys and urinary paths.

Special tests required for diagnosis of the underlying disease may be intravenous urography, radioisotope renography, radionuclide scanning, CT, MRT, renal angiography, renal puncture biopsy.

Complications of the renal arterial hypertension may be acute left ventricular failure, angina pectoris, renal retinopathy, deranged vision. Finally, disorders in cerebral circulation with paralysis, dysfunction of the pelvic organs, and also myocardial infarction can develop as a result of renal arterial hypertension.

Acute renal failure

Definition: Acute renal failure (N17 according to ICD-X) is toxicosis of the body caused by rapid (days to weeks), steadily decreasing renal dysfunction (azotemia) with oliguria.

Causes of the acute renal failure may be acute pathology of kidneys or renal vessels, shock and the accompanying systemic circulatory disorders, a grave infectious disease, a poisoning (compounds of mercury and lead, carbon tetrachloride, barbiturates); transfusion of incompatible blood, profuse hemolysis, urinary obstruction.

Pathogenesis. Mechanisms that appear responsible for glomerular hypofiltration include a marked decrease in renal blood flow, reduced glomerular permeability, tubular obstruction from. It has been established that products of protein decomposition are accumulated in the blood of patients with renal failure. These are nitrogenous substances, such as urea, uric acid, creatinine, and other guanidines. The content of indican, phenol and other aromatic substances that are formed in the intestine and pass into the blood through the intestinal wall (normally, these substances are eliminated from the blood by the kidneys) increases. Various compounds of sulphur, phosphorus, magnesium, and other substances are accumulated; the ionic equilibrium is upset. Acidosis develops as a result of the accumulation of acid products and disordered production by the kidneys of ammonia that neutralizes the acids. Acute renal failure is attended by a grave affection of the liver and metabolic disorders.

Classification of the acute renal failure

1. According to cause:

- (a) prerenal (in shock and the systemic circulatory disorders),
- (b) renal (in acute pathology of kidneys or renal vessels),
- (c) postrenal (in urinary obstruction);

2. According to stage:

- (1) initial stage (from several hours - to 6-7 day),
- (2) oligoanuric stage,
- (3) polyuric stage,

(4) recovery stage (normalization of diuresis; from 3 to 12 months).

Clinical picture. Acute renal failure varies slightly, depending on the character of the main disease. The most important clinical features are rapidly development of oliguria (or anuria), azotemia (increased blood urea and creatinine), proteinuria, cylindruria, and erythrocyturia.

Four clinical stages of acute renal failure are distinguished:

1-t *initial stage* lasting from several hours to 6-7 days; its clinical picture is characterized by the main symptoms of the disease (traumatic or transfusion shock, severe infectious disease, poisoning, etc.).

2-d *oligoanuric stage* characterized by changes in diuresis (to complete anuria), uremic toxicosis, edema and water-electrolyte disorders (increased R. Vomiting, mental confusion, dyspnea, deranged respiration and upset heart activity (heart incompetence, pulmonary edema), arterial hypertension may be observed. Proteinuria, cylindruria, and erythrocyturia are revealed on examination. The oligoanuric stage can end with death of the patient or his recovery.

In the latter case, diuresis suddenly or gradually increases (the 3-d *polyuric stage*). Polyuria characterized by excretion of large amounts of Na, K, Mg, and other solutes may result. Self-limited hypokalemia, hyponatremia, hypernatremia, hypomagnesemia, or marked contraction of extracellular fluid volume with peripheral vascular collapse can occur. The specific gravity of the urine is low, the concentration of residual products of protein metabolism in the blood decreases, water-electrolyte balance is restored and the pathological changes in the urine disappear.

The 4-th stage, *recovery*, begins with normalization of diuresis; it lasts from 3 to 12 months.

Diagnosis of acute renal failure is based on a progressive daily rise in serum creatinine accompanied by oligouria or anuria.

Characteristic laboratory findings are progressive azotemia, acidosis, hyperkalemia, and hyponatremia. Ultrasonography or CT is helpful because a normal or enlarged kidney favors reversibility, whereas small size suggests chronic renal insufficiency. Ultrasonography can show urinary obstruction. Renal arteriography or venography may be indicated if vascular causes are suggested clinically.

Prognosis. Acute renal failure and its immediate complications (e.g., hypervolemia, metabolic acidosis, hyperkalemia, uremia, bleeding diathesis) are treatable, but the survival rate remains about 60% despite more aggressive nutritional and dialytic therapy. Further improvement seems unlikely because of commonly associated sepsis, pulmonary failure, major wounds, burns, surgical complications, and consumption coagulopathy.

Chronic renal failure

Definition: Chronic renal failure (N18 according to ICD-X) is the clinical condition resulting from chronic derangement and insufficiency of renal excretory and regulatory function (uremia).

Causes of the chronic renal failure are any major cause of renal dysfunction - chronic renal diseases (chronic glomerulonephritis, pyelonephritis), diabetes mellitus, amyloidosis, affections of the renal vessels, arterial hypertension, tumours of the kidneys, hereditary nephropathies.

Pathogenesis. Development of the chronic renal failure is determined by the progressive affection of the kidney parenchyma. The first signs of renal failure in patients with chronic renal diseases only appear when the functioning parenchyma diminishes to at least one fourth of its normal size. The functional effects of the can be categorized as diminished renal reserve, renal insufficiency (failure), and uremia (azotemia). Plasma concentrations of creatinine and urea (which are highly dependent on glomerular filtration) begin a nonlinear rise as the GFR diminishes. Changes in creatinine and urea concentrations are minimal early on; when the GFR falls below 6-10 ml/min, levels increase rapidly and are usually associated with systemic manifestations (uremia). For substances that are excreted mainly through distal nephron secretion (e.g., K), adaptation usually produces a normal plasma concentration until advanced failure occurs.

Classification of the chronic renal failure according to stage

- (1) latency chronic renal failure,
- (2) intermittent chronic renal failure,
- (3) progressive (pronounced) chronic renal failure,
- (4) terminal chronic renal failure.

Clinical picture of the chronic renal failure depends on the stage.

Latent stage of chronic renal failure has no pronounced clinical symptoms. Nycturia may be noted, principally due to a failure to concentrate the urine during the night. Latency chronic renal failure can only be revealed by special tests for concentrating capacity and by Zimnitsky test. The patient's urine is usually of low specific gravity (below 1,017). Variations in specific gravity are only insignificant (*isohyposthenuria*). The clearance tests reveal moderate decrease of reabsorption in the renal tubules and in glomerular filtration. Mild renal dysfunction can be revealed by radioisotope nephrography. Insignificantly increased residual nitrogen and creatinine may be detected.

Intermittent chronic renal failure is characterized by episodes of marked azotemia. A patient with mild to moderate renal insufficiency may have only vague symptoms despite elevated creatinine and urea; nocturia is noted, principally due to a failure to concentrate the urine during the night. Lassitude, fatigue, and decreased mental acuity often are the first manifesta-

tions of this stage. In the absence of azotemia the laboratory data are such as in the latent stage.

Progressive (pronounced) chronic renal failure is characterized by persistent marked azotemia. Progressive renal failure is attended by nycturia. The concentration and dilution tests reveal significant disorders in the concentrating capacity of the kidneys, pronounced isohyposthenuria (the specific gravity of all urine specimens varies from 1,009 to 1,011. More pronounced disorders in reabsorption and glomerular filtration are determined by the clearance tests and nephrography. Laboratory studies reveal increased concentration in the blood of various products of protein decomposition: urea (3,23-8,46 mmol/l in norm and 10-15 and more times higher in renal failure), creatinine (0,088-0,176 mmol/l in norm and 1-1,3 mmol/l in renal failure), indican (0,68-5,44 /miol/l in norm).

Terminal stage of the chronic renal failure is characterized by pronounced clinical picture of uremia and electrolyte disorders.

Urea crystals (as a white powder) can sometimes be seen on the patient's skin. This is especially noticeable at the orifices of the sweat glands (at the base of hairs). Strong itching develops and the patient scratches his skin. The skin may appear pallid and yellow-brown; occasionally, urea from sweat may crystallize on the skin as uremic frost.

Decomposition of the urea (excreted by the mucosa of the air ways and the mouth) to ammonia by the bacteria accounts for the specific *uremic breath*. In serious cases, the smell of uremic breath can be felt by the physician as he approaches the patient's bed.

The nitrogenous substances, and in the first instance urea, are liberated by the gastric mucosa and decomposed to form ammonia salts. These salts irritate the mucosa of the stomach and the intestine to stimulate nausea, vomiting (*uremic gastritis*), and diarrhea (*uremic colitis*). Irritation of the respiratory mucosa causes laryngitis, tracheitis, and bronchitis. Severe stomatogingivitis develops. The mucosa becomes affected by ulcers and necrosis. Poisons accumulated in the blood are also liberated by the serous membranes. *Uremic pericarditis* is especially characteristic. It can be revealed by auscultation the heart using a stethoscope: the specific coarse pericardial friction can be heard.

Memory and sleep become deranged due to general poisoning; weakness, dull headache, somnolence, apathy and deranged vision are characteristic. Examination of the fundus oculi reveals narrowed arteries and dilated veins, edema of the papilla of the optic nerve, and whitish local foci (retinopathy). Development of retinopathy is explained by trophic disturbances due to the vascular spasm of the fundus oculi vessels and uremic toxicosis which intensifies these changes. The pupils are usually narrowed.

Metabolic disorders are pronounced: the patient develops cachexia; the liver and bone marrow functions are affected by dystrophy; toxic *uremic*

anemia develops which is usually attended by leucocytosis and thrombocytopenia. The tendency to hemorrhages develops due to a decreased blood platelet count, disorders in the blood coagulating system and increased capillary permeability (as a result of toxicosis). Hemorrhages of the gastrointestinal tract, urinary tract, uterus, and the nose may develop. Skin hemorrhages also occur. The body temperature slightly decreases.

Plasma Na concentrations may be normal or reduced. The serum K is normal or only moderately elevated (<6 mmol/l). Abnormalities of Ca, phosphorus, parathyroid hormone (PTH), vitamin D metabolism, and renal osteodystrophy can occur; hypocalcemia and hyperphosphatemia are found regularly.

Usually, moderate acidosis and anemia are characteristic. The anemia of the chronic renal failure is normochromic. It is usually caused by deficient erythropoietin production due to a reduction of functional renal mass. Other causes include deficiencies of iron, folate, and cyanocobalamin.

Later, toxicosis increases, the patient's consciousness becomes dimmed, and *uremic coma* develops. Periods of stupor alternate with periods of excitation, hallucinations, and noisy slow breathing with very deep inspirations (Kussmaul's breathing); respiration with alternating periods of hyperpnoea and apnea (Cheyne-Stokes respiration) occurs less frequently. At the terminal stage the patient is in a deep coma; muscular cramps occur at times and the patient dies.

Diagnosis of the chronic renal failure is based on progressive azotemia (increased blood creatinine and urea), accompanied by decreased renal filtration and reabsorption, and isohyposthenuria (low specific gravity).

The definitive diagnostic tool is renal biopsy, but it is not recommended when ultrasonography indicates that the kidneys are small and fibrotic.

Prognosis depends on the nature of the underlying disorder and superimposed complications. The latter may cause acute reductions in renal function that are reversible with therapy. Controlling hyperglycemia in diabetic nephropathy and hypertension substantially reduces deterioration of the chronic renal failure. Protein restriction probably has a modest benefit.

Factors aggravating or producing chronic renal failure (e.g., Na and water depletion, nephrotoxins, heart failure, infection, hypercalcemia, obstruction) must be treated specifically. However, progression of underlying chronic renal disease generally does not respond to specific treatment. If uremia results from a progressive and untreatable disorder, conservative management is palliative until dialysis or transplantation is required.

Acute glomerulonephritis

Definition: Acute glomerulonephritis (acute nephritic syndrome, post-infectious glomerulonephritis, N00-01 according to ICD-X) is acute diffuse

inflammation in the glomeruli associated with hematuria, casts in urine sediment, proteinuria, and, often, hypertension, edema, and azotemia.

Etiology acute infectious diseases, such as tonsillitis, scarlet fever, acute respiratory diseases, pneumonia, and otitis - especially hemolytic streptococcus of group A, more rare - pneumococci or staphylococci, and other infections. Predisposition condition may be overcooling, especially in damp weather.

Pathogenesis. Acute glomerulonephritis typically arises not during an infectious disease but only following a period of time, usually 2-3 weeks later. Thus, the onset of acute nephritis usually coincides with the period when antibodies to streptococcus are produced. The antigen-antibody complexes are fixed in the endothelial and epithelial cells of the renal glomeruli and also in the basal membrane of the glomerular capillaries to cause their injury. Both kidneys are always involved in acute diffuse glomerulonephritis and all glomeruli are equally affected.

Clinical picture

The disease is most common in children and in young adults, but 5% of patients are >50 years. A latency period of 1 to 6 weeks (average, 2 week) occurs between the infection and the onset of acute glomerulonephritis.

The clinical picture of acute glomerulonephritis is quite specific and is determined by the main three syndromes: edema, arterial hypertension, and changes in the urine (hematuria and proteinuria).

Complaints. The patients would usually complain of edema, which arise first on the face, under the eyes, and then extend onto the entire body and the extremities. Headache and heaviness in the head are frequent symptoms. Vision can be deranged due to spasm of the retinal vessels and hemorrhages into the retina. Many patients complain of general fatigue and reduced work capacity.

In the presence of a pronounced edema and massive pleural effusion, and when the heart muscle is overloaded due to markedly increased arterial pressure, patients with acute nephritis suffer from severe dyspnea, sometimes with attacks of asphyxia (like in cardiac asthma).

The patient with acute nephritis would often complain of dull lumbar pain. The gravity of the disease depends on the degree of oliguria. Complete anuria occurs in some cases. If hematuria is marked, the urine looks like "meat waste water".

Physical findings. Inspection of the patient reveals his specific appearance: pallid skin, edematous face, swollen eyelids, and edema of the trunk. Some patients assume the forced semireclining or sitting position because of pronounced dyspnea due to acute left ventricle failure or exudative pericarditis.

Percussion of the chest in the presence of generalized edema reveals free fluid in the pleural cavity (transudate) and congestion in the lung root re-

gion (dulled tympany). Normal or harsh respiration is heard by auscultation. In the presence of pronounced congestion, dry and moist congestive rales are heard.

Acute nephritis is characterized by a tense arterial pulse which is sometimes slow. Systolic pressure increases to 200-220 mm Hg, but in some cases it is not so high. Diastolic pressure increases to 100-160 mm Hg almost in all cases. The apex beat is somewhat shifted to the left and increased due to myocardial hypertrophy which soon develops in the presence of arterial hypertension. The left border of the heart extends beyond the corresponding midclavicular line. Auscultation of the heart reveals bradycardia. The first sound is sometimes decreased at the heart apex. If the heart muscle is much overloaded, the gallop rhythm is heard. The second sound is usually accentuated over the aorta due to increased arterial pressure.

Laboratory and instrumental data.

During development of edema, diuresis usually decreases to oliguria. Urinalysis is characterized by proteinuria and hematuria. If hematuria is pronounced, urine can be reddish-brown (the colour of "meat wastes"). Microscopy of the urinary sediment usually reveals the presence of casts (mainly hyaline casts) and cells of renal epithelium.

Nitrogenous substances (creatinine, urea) can only accumulate in the blood in serious cases attended by anuria. The clearance tests (Rebergh assay) reveal more or less considerable reduction of glomerular filtration.

The infectious-allergic character of acute glomerulonephritis is confirmed by immunological shifts: the content of α_2 - and γ -globulins in the blood increases during the acute period. The antibody titer against the causal infectious agent usually rises within 1 to 2 weeks. The increase in antibodies to streptococcal antigenic products can be measured: antistreptolysin-O (ASO), and antihyaluronidase and antideoxyribonuclease.a. Cryoglobulinemia usually persists for several months, whereas circulating immune complexes are detectable for only a few weeks.

X-ray studies of the chest confirm the presence of pleural effusion and congestion in the lung roots. Dilatation and hypertrophy of the left ventricle are clearly determined (the heart apex is rounded).

Electrocardiography reveals signs of hypertrophy and overload of the left-ventricular myocardium. The amplitude of ECG waves decreases in pronounced edema of the trunk.

Ultrasonography may help differentiate acute disease (usually normal or slightly enlarged kidneys) from an exacerbation of chronic disease (small kidneys).

Complications of the acute glomerulonephritis may be acute left ventricle failure, disorders of cerebral circulation, renal eclampsy, acute renal failure, nephritic syndrome.

The gravest and even dramatic complication of is *renal eclampsy* which occurs in 4-10 per cent of patients (mostly in children and women). The pathogenesis of eclampsy is largely underlain by increased intracranial pressure, edema of the cerebral tissue and cerebral angiospasm. Eclampsy in all these conditions usually arises in pronounced edema and increased arterial pressure. Attacks of the disease are provoked by salted food and excess liquid.

The onset of an eclampsia attack is heralded by increasing arterial pressure and a severe headache. The first signs of approaching eclampsy are often unusual somnolence and flaccidity. These are followed by severe headache, vomiting, temporary blindness (amaurosis), aphasia, transient paralysis, mental confusion, and a rapid rise in the arterial pressure. Convulsions develop unexpectedly, sometimes after uttering a cry, or after a noisy deep inhalation. The convulsions are first strong tonic spasms, which are followed (in 0,5-1,5 minutes) by strong clonic contractions. Less frequently only twitching of some muscles is observed. The face becomes cyanotic, the neck veins swell, the eyes turn aside or roll up, the tongue is bitten, and foam emerges from the mouth. The pupils are dilated and do not respond to light; the eyeballs are firm. The pulse is tense, slow, the arterial pressure increases. The body temperature rises in frequent attacks. Involuntary defecation and urination often occur.

Attacks of renal eclampsy usually last for a few minutes, rarely for longer time. Eclampsy occurs in some cases as a series of two or three attacks which follow one another. The patient then calms down to stupor, deep sopor or coma; consciousness is then regained. After recovery from the state of stupor the patient sometimes remains in amaurosis (blindness of the central origin) and aphasia (mutism). During a convulsive attack, the patient may be heavily contused or his ribs may be fractured. Attacks of eclampsy usually leave no consequence.

Diagnosis of the acute glomerulonephritis is based on main three syndromes: edema, arterial hypertension, and is supported by changes in the urine (hematuria, proteinuria, casts). A history of sore throat, impetigo, or culture-proven streptococcal infection 1 to 6 wk before onset of the syndrome and an elevated serum titer of antistreptococcal antibodies aid in diagnosis.

Prognosis. Mild and indistinct forms of glomerulonephritis, like acute forms of this disease with classical clinical symptoms, give rise to chronic glomerulonephritis, unless the appropriate therapy is given. Cases were reported where patients died from cerebral circulatory disorders or lung edema; true, such cases are rare.

Chronic glomerulonephritis

Definition: Chronic glomerulonephritis (chronic nephritic syndrome, N03 according to ICD-X) is a syndrome caused by several diseases of differ-

ent etiologies, characterized pathologically by diffuse inflammation and sclerosis of glomeruli and clinically by proteinuria, cylindruria, hematuria, usually hypertension, and insidious loss of renal function over years.

Etiology is diverse and includes postinfectious, diffuse diseases of connective tissue, bacterial endocarditis, idiopathic. It is often secondary to the acute form of this disease if the patient is not timely and properly treated.

Pathogenesis. Antibodies to altered proteins of the renal tissue are probably formed in patients with the disease, in addition to formation of antibodies to streptococcus and others antigens. Deposits of immunoglobulins detected by fluorescence microscopy are present in glomeruli. This maintains the inflammatory process in the kidneys and is the cause of chronic progressive course of the disease.

Clinical picture

The disease remains asymptomatic for years and is thus undetected in many patients. Two periods can be easily distinguished in the course of the disease: the first period, when the nitrogen secretory function of the kidneys is impaired only insignificantly (*the stage of renal compensation*), and the second period, during which this function is affected substantially (*the stage of renal decompensation*).

Clinical manifestations of the stage of renal compensation vary according to guiding syndrome. The most typical clinical forms of the chronic glomerulonephritis are *nephrotic, hypertensive, isolated urinary syndrome, mixed, and latent*. Clinical picture of the *nephrotic form* of chronic glomerulonephritis corresponds to nephritic syndrome, characterized by edema, the urinary syndrome, and a comparatively rapid course. *Hypertensive form* is comparatively benign and is characterized by the hypertensive syndrome and insignificant changes in the urine. The *form of the isolated urinary syndrome* is discovered only by persistent mild or moderate proteinuria and hematuria, accompanied by cylindruria (hyaline, erythrocyte casts) and isohypostenuria. The *mixed form* is characterized by edema, changes in the urine, and arterial hypertension. This form of glomerulonephritis is the gravest and comparatively rapid: a pronounced renal failure develops in 2-3 years. Finally, there is the *latent form* of the disease, which is not manifested by edema or pronounced hypertension; the changes in the urine are only insignificant; renal failure develops at late terms, often only in 10-15 years

Symptoms of the second, or final, *stage of renal decompensation* develop gradually due to the progressive nephrosclerosis. The concentration capacity of the kidneys gradually decreases along with the decrease in the specific gravity of the urine. Nocturnal diuresis increases by the compensatory mechanism as well: it is two thirds-one half of the daily diuresis (nycturia). As the concentration capacity of the kidneys is affected to a greater extent, the specific gravity of the urine becomes low and its variations between 1,009 and 1,011 during the course of the day (and under the effect of dry

food) are insignificant (isohyposthenuria). The content of nitrogenous slags in the blood of patients (urea, creatinine, indican) increases during this period.

Symptoms of uremia develop: weakness becomes more considerable, the patient complains of lassitude, headache, nausea, skin itching, unpleasant ammonium breath, and impaired vision. Not long before death, the patients develop uremic coma.

Complications of the chronic glomerulonephritis may be neprosclerosis, uremia(chronic renal failure), left ventricular incompetence (cardiac asthma, pulmonary edema), retinopathy and cerebrovascular disorders, anemia.

Diagnosis. The disease may be discovered during a routine medical examination when the patient is asymptomatic and renal function is normal except for *proteinuria and (possibly) hematuria*. Before renal function is significantly impaired, biopsy may help.

Course. Chronic nephritis usually lasts from 2-3 to 10-15 years. The first period of the disease (renal compensation) is long; the second period (decompensation) is shorter. During the course of the disease, there occur more or less prolonged periods of exacerbation, which are usually provoked by cooling or infections; exacerbations are followed by remissions. As a rule, the patient dies of renal failure.

Pyelonephritis

Definition: Pyelonephritis (N10-11 according to ICD-X) is bacterial infection of the kidney pelvis and its parenchyma, than can produce atrophy and calyceal deformity with overlying parenchymal scarring.

Etiology and pathogenesis. Pyelonephritis arises as a result of (a) ascending infection from intestines and urogenitalia region (conventionally pathogenic flora, intestinal Escherichia; less frequently enterococcus, Proteus, or others); (b) hematogenous infection (tonsillitis, sepsis, osteomyelitis, typhoid fever).

Difficult urine outflow from the kidney (stone in the ureter, twisting of the ureter) stimulates development of pyelonephritis. Nephrolithiasis facilitates fixation of the infection in the pelvis and its spreading onto the renal tissue. Neurogenic bladder dysfunction may be associated with urinary tract infections in spinal cord injury, tabes dorsalis, multiple sclerosis, diabetes, and other diseases.

Pyelonephritis is uncommon in men with a normal urinary tract. In 30 to 50% of women with a normal urinary tract, pyelonephritis occurs by the ascending route despite the dynamics of urine flow and the interference of the vesicoureteral junction. Cystitis alone or anatomic defects may produce reflux. This tendency is greatly enhanced when peristalsis is inhibited (e.g., during pregnancy, by obstruction, by endotoxins of gram-negative bacteria).

Hematogenous pyelonephritis occurs most often in debilitated patients who are either chronically ill or receiving immunosuppressive therapy. Metastatic staphylococcal or candidal infections of the kidney may follow bacteremia or fungemia, spreading from distant foci of infection in the bone, skin, vasculature, or elsewhere

The process is often unilateral. If both kidneys are involved, the extent of affection may differ.

Classification of pyelonephritis:

1. According to cause –
-primary pyelonephritis,
-secondary pyelonephritis (due to urogenitalia infection, nephrolithiasis, obstructive uropathy, congenital and acquired urinary abnormalities);
2. According to course – acute, chronic pyelonephritis;
3. According to localization – unilateral, bilateral pyelonephritis;
4. According to stage (of the chronic pyelonephritis) – exacerbation, remission.

Clinical picture

Acute pyelonephritis: Typical onset is rapid and characterized by chills, fever, lumbar and/or flank pain, nausea, and vomiting. Symptoms of lower urinary tract infection (e.g., frequency, dysuria) occur concomitantly in about 1/3 of patients. If abdominal rigidity is absent or slight, a tender, enlarged kidney may sometimes be palpable. Costovertebral tenderness and positive Pasternatsky's symptom are generally present on the infected side. A tender, enlarged kidney may sometimes be palpable

Chronic pyelonephritis: Symptoms of the exacerbation may be similarly to the clinical picture of acute pyelonephritis. But symptoms and signs in chronic pyelonephritis (e.g., fever, lumbar or abdominal pain) are often vague and inconsistent.

Clinical forms (of the chronic pyelonephritis) according to leading syndrome may be *hypertensive, nephrotic, septic, hematuric, anemic, latency*.

Clinical picture of the *nephrotic form* of chronic pyelonephritis corresponds to nephritic syndrome, characterized by edema, the urinary syndrome, and a comparatively rapid course. *Hypertensive form* is comparatively benign and is characterized by the hypertensive syndrome and insignificant changes in the urine. The *septic form* is characterized by high fever, bacteremia and leucocytosis. The *hematuric form* is detected by persistent macro- or micro-hematuria. The *anemic form* is characterized by anemia due to decrease of erythropoietin production and hematuria. The *latent form* of the disease, which is not manifested by edema or pronounced hypertension; the changes in the urine are only insignificant.

Laboratory and instrumental findings.

Urinalysis shows bacteriuria and leucocyturia (especially the presence of active leucocytes known as Sternheimer-Malbin cells in the urinary sedi-

ment). Proteinuria, hematuria and cylinderuria may present. Urine pH may be alkaline because of urea-splitting organisms.

Bacteriological study of the urine is of great significance: (cultivation of the urine on a nutrient media, and determination of bacterial sensitivity to antibiotics). It should be remembered that urine specimens from women should only be taken by catheterization of the bladder.

Intravenous or retrograde pyelography can reveal deformation of the renal pelves and urinary obstruction.

Complications of pyelonephritis are abscess of kidney, paranephritis, bacteremia (sepsis), nephrotic syndrome, arterial hypertension, nephrosclerosis, acute and chronic renal failure. Death of patients is in most cases caused by uremia.

Diagnosis of pyelonephritis is based on presence of bacteriuria and leucocyturia. In complicated cases the diagnosis is supported by deformation of the renal pelves and urinary obstruction according to intravenous or retrograde pyelography. Renal biopsy can support the diagnosis.

Diseases of blood

Clinical, laboratory and instrumental methods of diagnostics

Subjective examination (inquiry)

Complaints. Some general complaints, such as weakness, fatigue, sweating, vertigo, syncope, exertion dyspnea, palpitation, and loss of work capacity are typical in anemia, and in acute and profuse hemorrhage (e.g. internal, gastro-intestinal).

Elevated body temperature may be subfebrile in hemolytic and vitamin B₁₂-deficiency anemia due to pyrogenic effect of the erythrocyte decomposition products, and in other types of anemia due to compensatory intensification of basal metabolism. Moderate and high fever often occurs in acute and chronic leucosis, and lymphogranulomatosis due to intense decomposition of leucocytes with great quantity of pyrogenic purine bases are released. Elevated temperature may be the result of necrotic-ulcerous processes and concurrent secondary infections, especially in acute and chronic leucoses, myelodysplastic syndrome, agranulocytosis.

Skin itching may be the first symptom of lymphogranulomatosis, which develops long before the other symptoms of the disease appear. Skin itching is also characteristic of erythremia and chronic lymphoid leucosis.

Poor appetite and loss of weight may be in many blood diseases. Wasting is especially pronounced (cachexia) in chronic leucosis and malignant lymphoma.

Perverted taste (pica chlorotica) and *olfaction changes* are typical in iron deficiency anemia. The patient readily eats chalk, clay, earth, coal. The patient finds pleasure smelling ether, petrol, and other substances with unpleasant odour.

Burning sensation in the tip and edges of the tongue is a characteristic of vitamin B₁₂ deficiency anemia.

Increased bleeding and hemorrhagic eruptions present in hemorrhagic diathesis, myelodysplastic syndrome and leucosis. Hemorrhagic eruptions on the skin and mucosa and bleeding from the nose, gums, gastro-intestinal tract, lungs, kidneys, and the uterus develop spontaneously or due to insignificant causes (pressure, mild contusion).

Pain. Pain in the bones, especially in flat bones, is a characteristic of diseases with intense bone marrow hyperplasia (e.g. acute leucosis, chronic myeloleucosis, erythremia). Pain in the throat during swallowing because of developing necrotic and ulcerous tonsillitis may be in acute leucosis and agranulocytosis.

Dull pain (or feeling of heaviness and distension) in the left hypochondrium may be if the spleen is enlarged and its capsule is overdilated in chronic myeloid leucosis, liver cirrhosis, cardiac decompensation and thrombosis of the splenic vein. Sharp pain develops in perisplenitis. It is intensified during deep breathing and coughing. But the most severe pain develops in massive infarction of the spleen and spleen rupture. If enlargement of the spleen (*splenomegaly*) is significant, it may be ruptured by a slight injury.

Heaviness and pain in the right hypochondrium may be in considerable enlargement of the liver (*hepatomegaly*) due to myeloid or lymphoid chronic leucosis. Right hypochondriac pain of the colic type is characteristic of hemolytic anemia. It may be caused by pigmented (bilirubin) stones in the gallbladder and bile ducts that are formed due to pronounced hyperbilirubinemia and hypersecretion of the bile pigment.

History of the present disease contains information about period preceding the onset of the present disease and also the causes of the disease. It is necessary to establish the time of the appearance of the symptoms, to study thoroughly the dynamics of the disease, to establish if the patient had his blood examined in the past, and the results of these studies. It is also necessary to find out if the patient was treated for the present disease and the results of this treatment.

Life history of patient. Special attention should be given to the factors that might provoke the present disease or have effect on its further course.

Probable causes of anemia may be inadequate nutrition and vitamin deficit; acute and chronic industrial poisoning with mercury salts, lead, phosphorus and other noxious substances; diseases of many organs that can be complicated obvious or latent hemorrhages (e.g. tumours or ulcers of the gastrointestinal tract, bronchiectasis, pulmonary tuberculosis, etc.); atrophic ga-

stritis and removal of the stomach or even its partial resection due to impairment of assimilation of iron and vitamin B₁₂ assimilation; chronic diseases of the liver and kidneys attended by their insufficiency; prolonged uncontrolled intake of medicinal preparations (nonsteroidal anti-inflammatory drugs, chloramphenicol, sulpha drugs, cytostatics, etc.). Chronic diseases of the liver are often accompanied by the hemorrhagic syndrome due to upset production of some coagulating factors, such as prothrombin and fibrinogen. Exposure to radiation often becomes the cause of affection of the hemopoiesis.

Some diseases of the blood system such as hemolytic anemia and hemophilia can be hereditary. It is therefore necessary to inquire the patient about his relatives, paying special attention to the presence in them of signs of anemia or increased tendency to hemorrhages.

Objective examination

General survey. Many diseases of the blood system such as progressive anemia, and leucosis are characterized by a very grave general condition and loss of consciousness at their terminal stages.

The skin and mucosa should be inspected at diffused daylight. Paleness of the skin and visible mucosa is a characteristic of anemia. The tint of the skin colour differs in various types of anemia. The skin of young patients with iron deficiency anemia (*juvenile chlorosis*) is "alabaster" pallid, sometimes with a greenish hue. The skin of patients with vitamin B₁₂ deficiency is slightly yellowish and waxy. The yellow hue of the skin and visible mucosa are more pronounced in hemolytic anemia. A mild yellow hue can be easier revealed on the sclera. Paleness may be easier revealed by inspecting the conjunctiva of the upper and lower eyelids

Pallid skin does not always indicate anemia and can also be due to special anatomic properties of the skin (deep vascularization), spasm of the peripheral vessels (collapse, nephritis), and some other factors. Moreover, pallor of the skin can also be masked by its hyperpigmentation (due to exposure to the sun). A more informative sign is a pallor of the mucosa.

In chronic leucosis the skin becomes grey. In erythremia patients have "plethoric" cherry-red skin, the colour being especially marked on the face, the neck, and the hands.

Hemorrhagic spots of various size and shape develop on the skin and mucosa of patients with hemorrhagic diathesis. Collections of blood in the skin are called *purpura* and may be subdivided on the basis of the site of bleeding in the skin. Small pinpoint hemorrhages into the dermis due to the leakage of red cells through capillaries are called *petechiae* and are characteristic of platelet disorders in particular, severe thrombocytopenia. Larger subcutaneous collections of blood due to leakage of blood from small arterioles and venules are called *ecchymoses* (common bruises) or, if somewhat deeper and palpable, *hematomas*. They are also common in patients with platelet de-

fects and result from minor trauma. Dilated capillaries, or *telangiectasia*, may cause bleeding without any hemostatic defect. In addition, the loss of connective tissue support for capillaries and small veins that accompanies aging increases the fragility of superficial vessels, such as those on the dorsum of the hand, leading to extravasation of blood into subcutaneous tissues - *senile purpura*.

Hemorrhagic lesions are first red but as hemoglobin converts into biliverdin, bilirubin or its other coloured products of oxidation, the colour changes to cherry-blue, green, and yellow. In contrast to inflammatory rash and telangiectasia, hemorrhagic spots do not disappear when they are pressed upon.

The skin is dry and sometimes scaling in patients with iron deficiency anemia. Hairs become brittle and their ends break.

Palpation of flat bones or epiphyses of tubular bones (and also tapping over them) is painful in the presence of marked hyperplasia of the bone marrow (in acute leucosis).

Survey of oral cavity. Pronounced atrophy of the tongue papillae is a characteristic of vitamin B₁₂ deficiency anemia: the tongue surface becomes smooth, as if varnished (*Hunter's glossitis*). Intense caries of the teeth and inflammation of the mucosa round dental necks (*alveolar pyorrhea*) often occur in patients with iron deficiency anemia. Necrotic ulcerous tonsillitis and stomatitis are frequent symptoms of acute leucosis.

Examination of lymph nodes. Considerable enlargement of the regional lymph nodes is discovered by local swelling on the neck, above the clavicles, in the armpits and the groin. Less frequently swelling of other location can be revealed by inspection of patients with certain forms of leucosis.

Palpation of the *lymph nodes* is however more informative. The physician must eventually decide whether the palpable lymph node is a normal finding or one that requires further study, up to and including biopsy. Soft, flat, submandibular nodes (<1 cm) are often palpable in healthy children and young adults, and healthy adults may have palpable inguinal nodes of up to 2 cm, which are considered normal. Lymph nodes may be enlarged not only in diseases of the blood system but also in some other diseases, such as infectious diseases, tuberculosis, cancer metastases, systemic inflammatory diseases of connective tissue, local inflammatory process, etc.

Enlargement of lymph nodes is most pronounced in lymphoid leucosis, lymphogranulomatosis, and lymphosarcoma. These diseases are characterized by regular and multiple affection of the lymph nodes. The lymph nodes of only one group are first affected, but later other groups become involved too (both surface and deep nodes of the mediastinum and the abdominal cavity). Enlarged lymph nodes in leucosis and malignant lymphomas are painless, they never fuse with the skin, do not suppurate or form fistulae, as distinct from affections of other etiology (e.g. in tuberculosis). The nodes are pasty

and elastic in lymphoid leucosis. Lymph nodes are firm and fuse into conglomerates, sometimes as large as 15-20 cm in diameter in lymphogranulomatosis, and especially in lymphosarcoma.

Examination of spleen. The left part of the abdomen is distended in considerable enlargement of the spleen (e.g. in chronic myeloid leucosis), which can also be confirmed by percussion and palpation.

A normal spleen is impalpable. It can only be palpated in rare cases of extreme ptosis, and more frequently in enlargement of the organ. The spleen is enlarged in many diseases of the hemopoietic system (hemolytic anemia, thrombocytopenic purpura, acute and chronic leucosis), but also some acute and chronic infectious diseases (typhus, viral hepatitis, sepsis, malaria, etc.), in liver cirrhosis, thrombosis or compression of the splenic vein.

A considerable enlargement of the spleen is called *splenomegaly*. The greatest enlargement of the spleen is observed at the terminal stage of chronic myeloid leucosis: it often occupies the entire left part of the abdomen, while its lower pole is found in the small pelvis.

Considerable splenomegaly may be attended by perisplenitis. In perisplenitis the spleen becomes sensitive to palpation, with irregular edges, unsmooth surface, and limited mobility. Peritoneal friction sound can be heard in perisplenitis in the region overlying the spleen.

Not only the spleen but also the liver sometimes becomes enlarged (*hepatosplenomegaly*) in leucosis and hemolytic anemia.

Laboratory and instrumental examination

Conception of hemopoiesis

Hemopoiesis is the process by which the formed elements of the blood are produced. The process is regulated through a series of steps beginning with the pluripotent hematopoietic stem cell. Stem cells are capable of producing red cells, all classes of granulocytes, monocytes, platelets, and the cells of the immune system.

The hemopoietic scheme is now described as follows.

The first class of polypotent precursor cells is represented by the stem cell. The stem cells are self-sustaining, characterized by rapid proliferation and differentiation.

The *second class* of partly determined polypotent precursor cells is represented by precursors of lymphopoiesis and hemopoiesis; their self-sustaining power is limited; the cells are found in the bone marrow.

The *third class* of unipotent precursor-cells includes colony-forming cells {precursors of granulocytes and monocytes), erythropoietin-sensitive cells, precursors of B-lymphocytes and T-lymphocytes precursors.

The fourth class includes morphologically identifiable proliferating cells.

The *fifth class* includes maturing cells and the *sixth class* mature cells with a limited life cycle. The cells of the sixth class are mainly delivered to the peripheral blood.

General blood analysis (Complete blood count)

Hemoglobin. Concentration of hemoglobin in healthy people varies from 120-140 g/l in women and from 130-170 g/l in men (Supplement. Table 1).

Erythrocyte count (RBC count). Normal erythrocyte counts in women are $3,5-4,5 \times 10^{12}/l$ and in men - $4,0-5,5 \times 10^{12}/l$ of blood.

Anemia is a pathological condition characterized by decreased number of erythrocytes and/or hemoglobin content in a blood unit volume due to their general deficiency.

Colour index is a conventional value derived from the ratio of hemoglobin to the number of erythrocytes. This value is found by dividing a tripled quantity of hemoglobin in grams by the first three figures expressing the quantity of erythrocytes. Normally this value approaches 1 (*normochromia* 0,85 - 1,1). If it is less than 0,85 (*hypochromia*), the erythrocyte saturation of hemoglobin is insufficient; if the value exceeds 1,1 (*hyperchromia*), the volume of erythrocytes is higher than normal.

Normally one erythrocyte contains 33 ng of hemoglobin. To that end hemoglobin content in one liter is determined and the found quantity divided by the number of erythrocytes in the same volume.

Erythrocytes are studied in the blood smears. Normal erythrocytes in the smear are rounded, their diameter is varying. The size of erythrocytes often changes in anemia of various nature. Excessive variation in the size of erythrocytes is called *anisocytosis*. Prevalence of smaller erythrocytes (*microcytosis*) occurs in iron deficiency anemia. *Macrocytosis* develops in hemopoietic dysfunction of the liver. *Megalocytes* (large, oval hyperchromic erythrocytes formed during maturation of megaloblasts) appear in the blood of patients with vitamin B₁₂ deficiency (vitamin B₁₂-deficiency anemia). In pathological conditions of erythrocyte maturation, along with anisocytosis, the change in the shape of erythrocytes (*poikilocytosis*) is also observed; in addition to round erythrocytes, blood contains also erythrocytes of oval, pear-shaped and other configurations.

If erythrocytes are undersaturated with hemoglobin (colour index less than 0,85) they are poorly stained to become *hypochromic*; in vitamin B₁₂ deficiency they are coloured intensely, i.e. *hyperchromic* (colour index higher than 1,1).

A mature erythrocyte is oxyphilic, i.e. coloured pink. An immature erythrocyte is *polychromatophilic*. In supravital staining these erythrocytes appear as *reticulocytes* (see below). Normal blood contains polychromatophilic erythrocytes in meagre quantity: single cells per 1000 erythrocytes. Since they are less noticeable than reticulocytes, the latter are counted to as-

sess the number of juvenile polychromatophilic cells. The importance of this count is that the number of reticulocytes in the blood is a measure of the activity of the bone marrow. Normally this number is 2-10 per 1000 erythrocytes. Erythropoiesis is activated in blood loss and hemolysis, and the number of reticulocytes in normal bone marrow and peripheral blood increases. The absence of this increase indicates decreased function of the bone marrow, and conversely reticulocytosis in the absence of anemia indicates latent but well compensated loss of blood. High reticulocytosis is observed in effective treatment of vitamin B₁₂ deficiency anemia.

In erythropoietic hypofunction of the bone marrow, more immature nuclear (but still containing nuclei) elements of the red blood, i.e. *normoblasts* and *erythroblasts*, are delivered into the blood from the bone marrow. During maturation of erythrocytes in pathological conditions, nuclear remnants, known as *Jolly bodies*, may be preserved. These are round chromatin formations 1—2 /mi in size, stained cherry-red. Red *Cabot rings* (thread-like rings or convolutions) may also remain. They are believed to be the remnants of the nuclear envelopes, and occur mostly in vitamin B₁₂ deficiency anemia.

Basophilic granulation of erythrocytes is also the result of their abnormal maturation. Basophil-granular erythrocytes occur in B₁₂ deficiency anemia and some intoxications, especially in lead poisoning.

Reticulocytes are stained with brilliant cresyl blue in unfixed smears of fresh blood in which erythrocytes are still alive. Mature erythrocytes are stained green. Against this background, reticulocytes (depending on their maturity) have blue granules, filaments, or other formations that may resemble a crown, a ball, or a network. Reticulocyte count - in norm 0,2–1,0%.

Erythrocyte sedimentation rate (ESR, COЭ rus.). Erythrocytes do not clog together in the stream of blood because they are all negatively charged. If a blood specimen is placed in a vertical vessel and an anticoagulating agent is added to it, erythrocytes gradually settle by gravity. Then they agglomerate into heavier groups which precipitate at a faster rate. Agglomeration is promoted by some protein components of the plasma (globulins, fibrinogen) and by mucopolysaccharides. Therefore, the processes which increase their accumulation in the blood are attended by acceleration of erythrocyte sedimentation. This condition occurs in most inflammatory processes, infections, malignant tumours, and tissue decomposition. In certain diseases erythrocyte sedimentation is not accelerated in their initial stage (acute viral hepatitis, typhoid fever); in other pathological conditions erythrocyte sedimentation rate is slowed (heart failure).

Erythrocyte sedimentation rate is not an independent diagnostic symptom; it only indicates the activity of the process. Changes in the erythrocyte sedimentation rate do not always agree with other signs of activity. For example, ESR lags behind the rate of temperature elevation and leucocytosis in appendicitis or myocardial infarction; its normalization is also slower than

normalization of the mentioned symptoms. The normal ESR does not rule out the presence of disease which would be usually attended by an increased erythrocyte sedimentation rate. But it should be remembered that ESR does not increase in healthy people.

The *Panchenkov method of ESR determination* is widely used in the Belarus. A Panchenkov capillary graduated in 1 mm (100 divisions) is used for the purpose. The number of millimetres of a settled plasma column is noted in 60 minutes. The normal rate for men is 2-10 mm/h and for women 2-15 mm/h.

Thrombocyte count (platelet count). Their normal number is $150,0-400,0 \times 10^9 / l$ of blood. If the number of thrombocytes decreases significantly (*thrombocytopenia*), a tendency to hemorrhages develops. The critical figure at which hemorrhage occurs is believed to be $30,0 \times 10^9 / l$. Thrombocytopenia occurs in affection of the bone marrow by infectious causative agents, some medicinal preparations, ionizing radiation, and in auto-immune processes. *Thrombocytosis* occurs after hemorrhage, in polycythemia, and malignant tumours.

Leucocyte count (WBC count)

Blood for counting leucocytes is diluted either in a special mixer or a test tube. A 3-5 per cent solution of acetic acid destroying erythrocytes is mixed with a small amount of a suitable aniline dye to stain leucocyte nuclei. The counting chamber is filled as for counting erythrocytes. It is convenient to count leucocytes in 100 greater (undivided) squares. The normal leucocyte count are $4,0-9,0 \times 10^9 / l$ of blood.

The total quantity of leucocytes alone is of great diagnostic significance, because it characterizes the condition of the hemopoietic system and its response to harmful effects. The increased number of leucocytes (*leucocytosis*) is the result of activation of leucopoiesis. The decreased number of leucocytes (*leucopenia*) may be in affection of the bone marrow by infectious causative agents, some medicinal preparations, ionizing radiation, and in auto-immune processes.

The *leucocyte formula (leukogram, differential blood count)* is counted in stained smears. Romanovsky-Giemsa staining method is commonly used. The stain is a mixture of weakly acid (eosin) and weakly alkaline (azure II) stains. Depending on the reaction of the medium, the cells and their parts differently accept the stain: acid (*basophilic*) substances are coloured blue by azure, while alkaline (*oxyphilic*) substances are coloured red by eosin. Neutral substances accept both dyes and turn violet. Azure II, which is generally blue, contains a small quantity of azure I. In some cells the cytoplasm contains grains which selectively accept red azure I. The grains are called azurophilic.

Leucocyte formula is the percentage of separate forms of blood leucocytes. Leucocytes quickly respond to various environmental factors and

changes inside the body. Shifts in their counts are very important diagnostically. But individual variations in leucocyte composition are quite significant and it is therefore necessary to compare individual findings not with the average values, but with a certain range within which these variations are normal.

When assessing the composition of leucocytes, it is necessary to bear in mind that changes in percentage ratios can give an incorrect picture of the shifts occurring in the blood. For example, an increase in the absolute amount of a given type of cells in the blood decreases the percentage of all other cell elements. The picture is reverse with decreasing absolute amount of this given type of blood cells. A correct conclusion can be derived not from relative (percentage) but absolute values.

Neutrophils are the most changeable group of leucocytes. Their number increases in many infections, intoxication, and tissue decomposition. Normal neutrophil count includes 1-6% stab (band) and 45-70% segmented neutrophils.

Neutrophilia (neutrophilosis) is characterized not only by the increased total number of neutrophils but also by the appearance in the blood of immature forms: the quantity of *stab neutrophils* increases; *juvenile neutrophils* (absent in norm) and even *myelocytes* appear. This rejuvenation of the neutrophil composition is called *the blood shift to the left*, because the figures grow on the left side of the laboratory blank where leucocyte counts are normally recorded. *Regenerative and degenerative shifts* are distinguished. In the regenerative shift to the left the mentioned changes are observed, while in the degenerative shift to the left, the number of stab neutrophils only increases along with the degenerative changes in neutrophils in the absence of leucocytosis (vacuolization of cytoplasm, nuclear pyknosis, etc.). The regenerative shift indicates active protective response of the body, while the degenerative one indicates the absence of this response. The protective role of neutrophils consists in phagocytosis, bactericidal action, and production of proteolytic enzymes promoting resolution of necrotized tissue and healing of wounds. The regenerative shift to the left occurs most frequently in the presence of an inflammatory or necrotic focus. An especially marked shift to the left (to promyelocytes and even myeloblasts in the presence of significant leucocytosis) is called *leucemoid reaction*.

The number of neutrophils decreases (*absolute neutropenia*) in the presence of the inhibiting action of toxins of some microbes (e.g. causative agents of typhoid fever or sepsis) and viruses, ionizing radiation, and some medicinal preparations. In grave toxicosis, granularity of neutrophils becomes even more pronounced, the granules become larger and coloured; this granulation is called toxicogenic.

Lymphocytes. Lymphocyte count is 18-40% in norm. The absolute number of lymphocytes increases less frequently. *Lymphocytosis* occurs during recovery in acute infectious diseases, infectious mononucleosis, infec-

tious lymphocytosis, lymphoid leucosis, rubella, brucellosis, and thyrotoxicosis. More frequently lymphocytosis is only relative, associated with a decreased number of neutrophils (*like* relative *lymphopenia* in the presence of increased number of neutrophils). Absolute lymphopenia occurs in radiation sickness and systemic affections of the lymphatic system: lymphogranulomatosis and lymphosarcoma.

Indistinct spots are sometimes revealed in blood smears; they are stained like the nuclear substance of leucocytes. These are *Botkin-Gumprecht shadows*, the remains of nuclear chromatin characterizing brittleness of leucocytes due to which they decompose (leucocytolysis).

Eosinophils are present in the blood in relatively small quantity (1-5% in norm) but their number increases (*eosinophilia*), and sometimes significantly, in allergic processes (serum sickness or bronchial asthma), in helminthiasis, and itching dermatosis. Eosinophilia in allergic processes is associated with the role played by eosinophils in removal of toxic substances produced in these reactions. Decreased number of eosinophils (*eosinopenia*), to their complete absence, occurs in sepsis, severe forms of tuberculosis, typhus, and poisoning.

Basophils are carriers of important mediators of tissue metabolism. Their number (0-1% in norm) increases in sensitization of patients and decreases markedly during decomposition caused by the repeated administration of the allergen. Combined increase of the number of basophils and eosinophils (*basophil –eosinophil association*) may be in chronic myeloid leucosis.

Monocyte count is 4-9% in norm. Increased number of monocytes (*monocytosis*) indicates development of the immune processes. *Monocytosis* occurs in some chronic diseases (e.g. tuberculosis, malaria, visceral leishmaniasis, syphilis) and in infectious mononucleosis. *Monocytopenia* sometimes occurs in severe septic (hypertoxic) forms of typhoid fever and other infections.

In rare cases, apart from the mentioned cells, normal blood contains *plasma cells*. Their number increases in pathology. The cells have an eccentrically arranged dense nucleus (often a wheel-like structure) and a markedly basophilic vacuolized cytoplasm. Their number increases in plasmacytoma (myeloma), certain infectious diseases, wound sepsis, hypernephroma, myeloma, etc.

Examination of hemopoietic organs

The morphological composition of the blood does not always show the changes occurring in the hemopoietic organs. For example, the cell composition of blood remains almost unaltered in aleukemic form of leucosis despite significant changes in the bone marrow.

M. Arinkin (1928) proposed *sternal puncture* for intravital study of the bone marrow. Owing to the simplicity and safety of the procedure, it is used

for the study of almost all patients with diseases of the hemopoietic system. After fixation and staining (Romanovsky-Giemsa), not less than 500 elements containing nuclei are counted in the smear. A *myelogram* is then derived. The marrow specimen can show upset maturation of the cells: increased number of juvenile forms or prevalence of primary undifferentiated elements, upset proportion between the red and white cells, changes in the total number of cells, presence of the pathological forms, etc. Apart from the sternum, other bones (e.g. iliac bone) can also be used for taking the bone marrow.

More accurate information on the composition of the bone marrow is given by *trepanobiopsy*. A special needle (troacar) is passed into the iliac crest to cut out a column consisting of the bone-marrow tissue, which is then used for making histological preparations. The structure of the bone-marrow remains unchanged in the preparations while the absence of blood makes it possible to evaluate its cells composition and to reveal focal and diffuse changes in it.

Enlarged lymph nodes are often punctured. It makes it possible to establish the character of changes in the cell composition and to verify the diagnosis of some systemic diseases of the lymph apparatus (lymphoid leucosis, lymphogranulomatosis, lymphosarcomatosis), to reveal metastases of tumours, etc. More accurate data can be obtained with *biopsy of the lymph node*. The puncture is made without anesthesia, by a simple injection needle attached to a 10-ml syringe. The obtained material is used to prepare smears. The spleen is punctured by the same method. The patient is asked to keep breath at the inspiration height to prevent possible injury of the spleen during respiratory movements.

Combined study of cell composition of the bone marrow, spleen and lymph nodes reveals the relations between these organs of the hemopoietic system and the presence of extramedullar hemopoiesis which develops in some affections of the bone marrow.

Evaluation of hemolysis

Evaluation of hemolysis becomes necessary mainly in anemia of the hemolytic character. Erythrocytes undergo constant decomposition in physiological conditions (hemolysis). Pathological hemolysis is detected by (1) increase concentration of unbound bilirubin in blood and excretion of stercobilin with feces and urine; (2) diminished osmotic stability of erythrocytes; (3) and relatively by reticulocytosis.

Another sign suggesting hemolysis is the *degree of osmotic stability (osmotic fragility, or resistance)* of erythrocytes. Congenital microspherocytic hemolytic anemia is characterized by decreased osmotic stability of erythrocytes. This anemia is diagnosed by mixing blood specimens with sodium chloride solutions whose concentration increases in 0,02 per cent gradient from 0,2 to 0,7 per cent (1 ml of each solution). The minimum resistance is

determined by the test tube where the concentration of sodium chloride is the highest and the pink colour becomes appreciable. The maximum resistance is determined by the test tube where the concentration of sodium chloride is the lowest and in which there is no sediment. Normally hemolysis begins at sodium chloride concentrations from 0,42 to 0,46 per cent and terminates at 0,30 to 0,36 per cent. In hemolytic anemia hemolysis begins at 0,54-0,70 per cent and ends at 0,40-0,44 per cent concentration of sodium chloride.

The third sign of hemolysis (also only relative) is *reticulocytosis*. Increased decomposition of erythrocytes stimulates erythropoiesis. The number of reticulocytes increases although the increase is not always proportional to the degree of hemolysis.

Study of hemostasis

Hemostasis is an arrest of bleeding from an injured blood vessel. It requires the combined activity of vascular, platelet, and plasma factors counterbalanced by regulatory mechanisms to limit the accumulation of platelets and fibrin in the area of injury. Hemostatic abnormalities can lead to excessive bleeding or thrombosis (Supplement. Table 6).

Classical tests of hemostasis

There are many tests that can reveal predisposition to bleeding or thrombus formation and to find their causes. The classical tests are used to determine (1) blood coagulation time; 2) platelet (thrombocyte) count; (3) bleeding time; (4) retraction of blood clot; and (5) permeability of capillaries.

Coagulation time characterizes coagulability of blood in general without accounting for separate phases of the coagulation process. In physiological conditions, the blood coagulates in 5-10 minutes (Lee and White method). Coagulation time increases in increased anticoagulation activity of blood or decreased concentration of procoagulants and shortens in the presence of the tendency to thrombus formation. The longest coagulation time (to several hours) is observed in hemophilia A. It does not change in certain hemorrhagic diatheses.

Platelet count correlates well with the propensity to bleed. The normal platelet count is $150,0-400,0 \times 10^9/l$ of blood. As long as the count is $>100,0 \times 10^9/l$, patients are usually not symptomatic and the bleeding time remains normal. Platelet counts of $50,0-100,0 \times 10^9/l$, cause mild prolongation of the bleeding time; bleeding occurs only from severe trauma or other stress. Patients with platelet counts $<50,0 \times 10^9/l$, have easy bruising, manifested by skin purpura after minor trauma and bleeding after mucous membrane surgery. Patients with a platelet count $<20,0 \times 10^9/l$, have an appreciable incidence of spontaneous bleeding, usually have petechiae, and may have intracranial or other spontaneous internal bleeding.

Bleeding time screens for overall adequacy of formation of hemostatic plugs independent of blood coagulation reactions. The normal bleeding time

(by Duke's method) is 2-4 minutes. Since discontinuation of bleeding is associated with formation of a white thrombus, the test results depend on the number of thrombocytes and the ability of the vascular wall to contract, which is promoted by liberation of the vasoconstricting factor, serotonin, by thrombocytes. The bleeding time in thrombocytopenia is considerably prolonged.

Clot retraction also depends on the number and activity of thrombocytes since it occurs under the effect of retractozyme liberated by the blood platelets. A specimen of venous blood (3-5 ml) is placed in a graduated centrifuge test tube and placed in a thermostat at a temperature of 37 °C. The serum separated in 24 hours is removed and its volume is divided by the volume of the blood specimen to calculate the retraction index which is normally 0,3-0,5.

Capillary permeability tests. Konchalovsky-Rumpel-Leede sign. A tourniquet is applied to the forearm and changes occurring in the skin are assessed. If petechiae appear on the skin below the tourniquet, the test is positive. Application of a sphygmomanometer cuff and the appearance of more than 1 petechiae on the skin area of 1 cm² at a pressure of about 100 mm Hg is interpreted in the same way.

Cupping glass test. Air is evacuated from a cup applied to the skin (rarefaction of about 200 mm Hg) for two minutes. If the test is positive, petechiae develop on the skin under the cup. The number of petechiae shows the degree of affection of the vascular wall.

Pinch test, A hemorrhagic spot appears at the site of a pinch, which gradually increases in size and becomes more intense.

Conventional tests of hemostasis

Conventional tests of hemostasis are subdivided:

- *tests of hemostatic plugs (thrombus) formation* are (1) platelet (thrombocyte) count, (2) platelet aggregation evaluates adequacy of platelet responsiveness to physiologic stimuli activating platelets, (3) bleeding time;

- *tests of fibrin formation* are (1) activated partial thromboplastin time (APTT), (2) prothrombin time (PT) , (3) thrombin time, (4) fibrinogen, (5) prothrombin, (6) time of plasma recalcification, (7) international normalized ratio (INR)

- *tests of fibrin stability and fibrinolytic activity* are (1) plasminogen activity, (2) α 2-antiplasmin, (3) plasma D-dimer.

Basic clinical syndromes of the blood diseases

Syndrome of anemia

Definition: Anemia is a pathological syndrome characterized by decreased number of erythrocytes and/or hemoglobin content in a blood unit volume due to their general deficiency.

Anemia should be differentiated from hydremia (abnormally watery blood) in which the erythrocyte and hemoglobin are deficient as well, but not at the expense of their absolute reduction but due to dilution of blood in renal, cardiac and other edema.

Etiology and pathogenesis. Anemia results from one or more of three basic causes: blood loss, deficient erythropoiesis (erythrocyte production), and excessive hemolysis (erythrocyte destruction).

Anemia is often characterized not only by quantitative changes in the red blood composition, but also qualitative changes in the structure of erythrocytes and hemoglobin molecules. These changes are important for the transport function of blood and tissue respiration, and can be the cause of additional pathological changes in the body. For example, a congenital defect of erythrocytes in some hereditary hemolytic anemia may (due to their intense hemolysis) cause hemosiderosis of the internal organs, formation of pigment stones in the gall bladder, etc.

Anemia causes oxygen hunger of organs and tissues (hypoxia) and their dystrophy. Unoxidized products of metabolism (lactic acid, in the first instance) accumulate in the body due to hypoxia. The alkaline reserve of blood decreases. In grave cases, a tendency to acidosis develops which causes further dystrophy of tissues. Severe anemia attended by marked disorders in tissue metabolism is incompatible with life.

Anemia of any origin is accompanied by some compensatory processes, which partly remove or lessen its consequences: (1) blood circulation is intensified, i.e. stroke and minute volumes increase, tachycardia develops, and the rate of blood flow increases; (2) blood distribution is altered, blood depots in the liver, spleen, and muscles are activated, and the blood supply to the peripheral tissues becomes limited at the expense of the increased blood supply to the vital organs; (3) oxygen utilization in tissues is intensified and the role of anaerobic processes in tissue respiration increases (anaerobic respiration with glutathione); (4) the erythropoietic function of bone marrow is stimulated.

Classification of anemia

I. According to causes:

1. Posthemorrhagic anemia - due to loss of blood (acute and chronic);
2. Anemia due to disordered hemopoiesis:
 - iron-, vitamin B₁₂ - , folic acid *deficiency anemia*,
 - hypo- and aplastic anemia* due to inhibition of the bone marrow by toxosis, radiation, metastasis, hemablastoses, myelodysplastic syndrome;
 - sideroachrestic* (iron refractory) anemia;

3. *Hemolytic anemia* - due to excessive hemolysis (congenital and acquired).

II. According to hemoglobin saturation of erythrocytes (by the colour index):

-*normochromic anemia* (colour index 0,85-1,05);

-*hypochromic anemia* (colour index less than 0,85) – iron-deficiency and chronic (less acute) posthemorrhagic anemia;

- *hyperchromic anemia* (more than 1,1) -vitamin B₁₂-, folic acid deficiency anemia.

III. According to regenerative capacity of the bone marrow:

-regenerative anemia;

-hyporegenerative anemia;

-aregenerative, or aplastic anemia.

IV. According to degree of anemia:

- mild anemia (hemoglobin 110-80 g/l),

- moderate anemia (hemoglobin 80-60 g/l),

- severe anemia (hemoglobin <60 g/l).

Common clinical and laboratory features in all types of anemia:

-paleness of skin and mucous membranes,

-weakness, vertigo (dizziness), headache, tinnitus, spots before the eyes, fatigability, drowsiness, irritability, and even strange behavior,

-breathlessness (dyspnea), tachycardia (particularly with physical exertion), arterial hypotension; finally, heart failure or shock can result.

- amenorrhea, loss of libido in women can occur;

- gastrointestinal complaints, and sometimes jaundice and splenomegaly can occur;

- hemoglobin - female <120,0 g/l, male<140,0 g/l;

- RBC (erythrocyte) - female <3,8×10¹²/l, male <4,0×10¹²/l;

- leukocytopenia, thrombocytopenia may be in severe anemia.

Symptoms associated with chronic anemia depend on the age of the patient and the adequacy of blood supply to critical organs. Mild anemia is most often recognized by abnormal screening laboratory tests.

Laboratory tests in anemia

Complete blood count shows erythrocytopenia and changes of the size, shape and coloration of erythrocytes, hemoglobinopenia, and in severe anemia leukocytopenia, thrombocytopenia can occur. Hemoglobin saturation of erythrocytes is estimated by the colour index.

Reticulocyte count increases more than 1,2% in hemolytic anemia and in acute and severe bleeding. A normal reticulocyte count and reticulocytopenia in anemia indicates failure of the bone marrow to respond appropriately.

Bone marrow aspiration and biopsy provide direct observation of erythroid activity and maturation of the erythrocyte precursors; abnormal maturity (dyspoiesis) of the cells; and semiquantitation of the amount, distribution, and cellular pattern of iron content.

Sideropenic syndrome

Definition: Sideropenic syndrome is a clinical and laboratory condition of iron-deficiency.

Causes of sideropenic syndrome include iron deficiency in food, pregnancy, lactation, gastrointestinal tract pathology, occult bleeding.

Clinical signs of iron-deficiency:

- perverted taste (*pica* to egg, dirt, paint, etc.) and olfaction changes (pleasure smelling ether, petrol, and other substances with unpleasant odour);
- cheilosis* (angular stomatitis) - fissures at the corners of the mouth;
- atrophic glossitis means that the papillae of the tongue are leveled;
- koilonychia* is a spooning of the fingernails in severe cases of iron-deficiency. The nails become flat, sometimes spoon-like, opaque, marked by transverse folds;
- rarely sideropenic dysphagia (described by Plummer and Vinson) associated with a postcricoid esophageal web.

Laboratory tests.

Serum iron (Fe) and Fe-binding capacity should both be tested because their relationship is important. Various tests exist; the range of normal values relates to the test used. In general, normal serum Fe is 13 to 27 mmol/l for men and 11 to 25 mmol/l for women; total Fe-binding capacity is 45 to 81 mmol/l. Serum Fe concentration is low in Fe deficiency and chronic disease and elevated in hemolytic states and Fe-overload syndromes. The Fe-binding capacity (or transferrin) is increased in Fe deficiency but reduced in anemia of chronic disease.

Serum ferritin, which is measured by radioimmunoassay, is an Fe-storage glycoprotein that exists as a tissue-specific isoferritin. The range of normal in most laboratories is 30 to 300 mcg/l. Serum ferritin concentrations closely correlate with total body Fe stores; thus, low concentrations (< 12 mcg/l) occur only in Fe deficiency and elevated concentrations in Fe overload. Low serum ferritin concentrations always identify Fe deficiency, but they may be falsely elevated because of hepatocellular injury or the presence of an acute-phase response.

General blood count shows hypochromic and microcytic anemia.

Bone marrow biopsy. Normally 40 to 60% of developing erythroblasts – called *sideroblasts* - will have visible ferritin granules. This represents iron in excess of that needed for hemoglobin synthesis. In sideropenia there will be few or no sideroblasts.

Sideroachrestic syndrome

Definition: Sideroachrestic syndrome (Fe-utilization anemia, D64 according to ICD-X) is caused by inadequate or abnormal utilization of intracellular iron for hemoglobin synthesis, despite adequate or increased amounts of iron.

Etiology and pathogenesis. Causes are hereditary, hemoglobinopathies (thalassemia), toxic (lead, alcohol, etc.), tumours, viral and bacterial infections.

Anemia develops due to abnormal utilization of intracellular Fe for hemoglobin synthesis, despite adequate or increased amounts of Fe within the mitochondria of the developing erythrocyte precursors. This defect includes hemoglobinopathies, primarily of the thalassemic type (congenital hemolytic state), and sideroblastic or myelodysplastic anemia.

Chronic iron (Fe) overload is characterized by increased focal or generalized deposition within the tissues (*hemosiderosis*).

Clinical features. In addition to the manifestations of refractory (to treatment) anemia, symptoms of myelodysplastic syndrome (see below) and hemosiderosis may present. Hemosiderosis manifests clinically by dark grey skin, diabetes mellitus, hepatosplenomegaly, myocardiodistrophy.

Laboratory features. Anemia is commonly microcytic and hypochromic. An important clue to defective heme synthesis in the peripheral blood is the presence of polychromatophilic, stippled, targeted erythrocytes (i.e., *siderocytes*).

Other laboratory features include increased serum Fe and serum ferritin concentrations.

The anemia is characterized by ineffective erythropoiesis, which is defined clinically as anemia, and a relative or absolute reticulocytopenia in the presence of erythroid hyperplasia. Fe-staining reveals the pathognomonic morphologic feature of Fe-engorged paranuclear mitochondria in the developing erythrocytes (*ringed sideroblasts*).

Diagnosis of the sideroachrestic syndrome (Fe-utilization anemia) is supported by (a) refractory microcytic and hypochromic anemia, reticulopenia; (b) increased serum iron and serum ferritin concentrations.

Syndrome of funicular myelosis

Definition: Syndrome of funicular myelosis represents neurology manifestations due to the predominant affection of the lateral spinal columns because of vitamin B₁₂ (cobalamin)-deficiency.

Funicular myelosis begin pathologically with demyelization, followed by axonal degeneration and eventual neuronal death; the final stage, of course, is irreversible.

Neurologic involvement may be present even in the absence of B₁₂-deficiency anemia. This is particularly true in patients >60 years. The peri-

peripheral nerves are most commonly involved, followed by the spinal cord. The neurologic symptoms occasionally precede the hematologic abnormalities (or occur in their absence, particularly if folic acid has been taken).

Clinical signs of funicular myelosis are:

- numbness (skin anesthesia) and paresthesia in the extremities (the earliest neurological manifestations);
- sphincter disturbances (function of the urinary bladder and the rectum can also be affected);
- the gait is often affected in grave cases: spastic paresis develops (incomplete spastic paralysis of the lower extremities);
- reflexes may be diminished or increased, the knee reflex disappears;
- Romberg and Babinski signs may be positive, and position and vibration senses are usually diminished;
- disturbances of mentation will vary from mild irritability and forgetfulness to severe dementia or frank psychosis.

Neurologic manifestations may occur in a patient with normal erythrocyte indexes.

Serum vitamin B₁₂ assay is the most commonly used method for establishing B₁₂-deficiency. Levels <110 pmol/l reliably indicate vitamin B₁₂-deficiency.

Myelodysplastic syndrome

Definition. Myelodysplastic syndrome (D46 according to ICD-X) is a clonal proliferative disorder in which a normal or hypercellular bone marrow associated with ineffective and abnormal myelopoiesis.

This is a group of hematologic disorders characterized by cytopenias associated with a dysmorphic (or abnormal appearing) and usually cellular bone marrow, and consequent ineffective blood cell production.

Etiology and pathogenesis. Causes of this syndrome include radiation, intoxication (benzene), immunosuppressive treatment, chemotherapy, chronic (viral) infection. Myelodysplastic syndrome is a clonal hematopoietic stem cell disorder leading to impaired cell proliferation and differentiation.

Clinical features. Previous chemotherapy or radiation exposure is an important historic fact. The most characteristic symptoms are caused by refractory anemia, hemorrhagic diathesis, necrotization of tissues, and secondary infection (e.g. in agranulocytosis – sepsis, pneumonia). The physical examination is remarkable for signs of anemia; about 20% of patients have splenomegaly.

Laboratory features. Anemia is commonly a prominent feature of myelodysplasia. Anemia is present in the majority of cases, either alone or as part of bi- or pancytopenia; isolated neutropenia or thrombocytopenia is more unusual. The anemia is normochromic-normocytic and associated with de-

creased erythroid activity in the bone marrow, megaloblastoid and dysplastic changes, and sometimes increased numbers of ringed sideroblasts.

Myelodysplastic syndromes represent progressive bone marrow failure but with an insufficient proportion of blast cells (< 30%) for definite diagnosis of acute myeloblastic leucosis.

Myelodysplastic syndromes should be considered in any patient with unexplained refractory anemia and confirmed by a normal or hypercellular bone marrow with the associated morphologic features of dysmyelopoiesis.

Prognosis. Most patients die as a result of complications of pancytopenia (sepsis, pneumonia, hemorrhage). 40 to 60% of cases evolve into acute myeloid leucosis.

Anemia

Clinical features of basic variants of anemia

Acute posthemorrhagic anemia

Definition. Acute posthemorrhagic anemia (D62 according to ICD-X) is an anemia caused by rapid massive hemorrhage.

Etiology and pathogenesis. Anemia may result from massive hemorrhage associated with spontaneous or traumatic rupture or incision of a large blood vessel, erosion of an artery by lesions (e.g., peptic ulcer, neoplasm), or failure of normal hemostasis.

Immediate effects depend on the duration and volume of hemorrhage. Sudden loss of 1/3 of blood volume may be fatal, but as much as 2/3 may be lost slowly over 24 h without such risk. Symptoms are caused by a sudden decrease in blood volume and by subsequent hemodilution with a decrease in the O₂-carrying capacity of the blood.

Clinical features. In cases with external hemorrhage, the physician can often locate the source of bleeding at first sight (e.g. in injury). Faintness, dizziness, thirst, sweating, weak and rapid pulse, and rapid respiration (at first deep, then shallow) may occur. Orthostatic hypotension is common. BP may at first rise slightly because of reflex arteriolar constriction, then gradually fall. If blood loss >40% of total blood volume, hemorrhagic shock develops. If bleeding continues, BP may fall and death may ensue.

Laboratory features. During and immediately after hemorrhage, the erythrocyte count and hemoglobin may be deceptively high because of vasoconstriction. Within a few hours, tissue fluid enters the circulation, resulting in hemodilution and a drop in the erythrocyte count and hemoglobin proportional to the severity of bleeding.

The resultant anemia is normochromic. Polymorphonuclear granulocytosis and a rise in platelet count may occur within the first few hours. Several days after the bleeding event, regeneration (i.e., reticulocytosis) is evident:

Blood smears may disclose polychromatophilia. If hemorrhage was massive and acute, occasional normoblasts and immature leucocytes may be seen.

Diagnosis of the acute posthemorrhagic anemia is supported by (a) history or clinical signs of recent bleeding; (b) normochromic anemia and reticulocytosis according to laboratory data.

Iron deficiency anemia

Definition: Iron deficiency anemia (D50 according to ICD-X) is anemia due to the deficit of iron which is necessary for the production of hemoglobin in erythrocytes.

Etiology and pathogenesis. The most frequent cause is chronic occult bleeding, usually from the gastrointestinal tract (peptic ulcer, hemorrhoids, tumour). In premenopausal women, menstrual loss may be the cause, but other mechanisms must be considered (pregnancy, lactation). Other bases for anemia may be decreased iron absorption after gastrectomy, upper small-bowel malabsorption syndromes, helminths. Anemia may be due to iron deficiency in food or increased growth requirements in adolescents.

In the absence of adequate iron supply to the body or its utilization from the store, the synthesis of hemoglobin, myoglobin, and iron-containing enzymes of various cells involved in the oxidation processes is upset. This impairs nutrition of tissues and accounts for the development of many symptoms of the disease. The clinical picture of iron deficiency anemia is explained by insufficient oxygen transport to tissues due to anemia on the one hand, and by disordered cell respiration on the other.

Clinical features. In addition to the usual manifestations of anemia, symptoms of the sideropenic (iron deficiency) syndrome are specific (see above).

Laboratory features. Hypochromic and microcytic anemia is typical. Study of the blood reveals decreased erythrocyte and even more decreased hemoglobin content of the blood. The colour index is less than 0,85; in grave cases it is 0,6-0,5, and even lower. Microscopy of blood reveals pallid erythrocytes (hypochromia), anisocytosis, and poikilocytosis. The average diameter of erythrocytes is less than normal (microcytosis). The number of reticulocytes is small. Anemia is usually attended by thrombocytopenia, sometimes relative monocytosis, lymphocytosis, and eosinopenia.

The iron content of the serum is decreased (1,5-2,5 times and more). Low serum ferritin concentrations always identify Fe deficiency. The serum Fe-binding capacity increases.

Diagnosis of the iron deficiency anemia is supported by (a) symptoms of the sideropenic syndrome; (b) hypochromic and microcytic anemia (c) decreased serum iron and serum ferritin, and increased serum Fe-binding capacity.

Vitamin B₁₂- (folic acid) deficiency anemia

Definition: This is megaloblast macrocytic anemia (D51-52 according to ICD-X) resulted from defective DNA synthesis in erythroid bone marrow precursors due to Vitamin B₁₂- (folic acid) deficiency.

Etiology and pathogenesis. Vitamin B₁₂ deficiency that may result from one of several factors: (a) absence of intrinsic factor secretion (gastro-mucoprotein) – in atrophic gastritis, chronic gastritis A, after gastrectomy and vast resection of the stomach; (b) disordered intestinal absorption - in small-intestine disorders (celiac disease, sprue, malignancy, helminthosis (tape-worm); (c) inadequate utilization – in liver, kidney, malignancy diseases; (d) inadequate diet – in vegetarianism, chronic alcoholism; (e) increased requirement - hyperthyroidism, pregnancy, infancy.

Causes of the folate deficiency include (a) disordered intestinal absorption – malabsorption syndromes (especially celiac disease, sprue), drugs (phenytoin, primidone, barbiturates), blind loop syndrome; (b) inadequate utilization – folic acid antagonists (methotrexate, triamterene, diamidine compounds, trimethoprim), enzyme deficiency (congenital, acquired), vitamin B₁₂ deficiency, alcoholism, scurvy; (c) increased requirement - Pregnancy, lactation, infancy, malignancy; (d) inadequate diet - diet lacking fresh, slightly cooked food; chronic alcoholism.

In conditions associated with vitamin B₁₂ and folate deficiency, the synthesis of DNA is disordered; this in turn causes disorders in cell division; the cells become large and qualitatively inadequate. Erythroblasts are affected most severely: large cells of embryonal hemopoiesis, megaloblasts, are found in the bone marrow instead of erythroblasts. Most megaloblasts are decomposed in the bone marrow before they reach the stage of a nucleated cell. Only a small quantity of megaloblasts is differentiated to anuclear cells (megalocytes) and enter the blood vessels. Megalocytes are larger and more saturated with hemoglobin than erythrocytes and differ from them by morphological and functional inadequacy. Megalocytes have no such high oxygen-transport capacity as the erythrocytes and are quickly decomposed.

Degenerative changes in the nervous system (funicular myelosis) are referred to vitamin B₁₂ deficiency. Degenerative changes in the cerebral white matter and peripheral nerves, involving axons and myelin sheaths, usually precede degenerative changes in the posterior columns and corticospinal tract. The cortical neurons may also degenerate, but neuronal changes are minor compared with those in myelinated tracts.

Clinical features. The patient with florid cobalamin deficiency is pale, with slightly icteric skin and eyes. Elevated bilirubin levels are related to high erythroid cell turnover in the bone marrow.

Considerable weight loss is common. Various gastrointestinal manifestations may be present, including anorexia, intermittent constipation and diarrhea, and poorly localized abdominal pain. Hunter's glossitis, usually de-

scribed as burning of the tongue, may be an early symptom. The mouth mucosa and the posterior wall of the throat are also atrophied. The tip and edges of the tongue, and also the mouth mucosa can be ulcerated. Splenomegaly and hepatomegaly may occasionally occur

Syndrome of funicular myelosis (see above) present in vitamin B₁₂ deficiency (*pernicious anemia*). Neurologic involvement may be present even in the absence of anemia. This is particularly true in patients > 60 years. The neurologic symptoms occasionally precede the hematologic abnormalities (or occur in their absence, particularly if folic acid has been taken). In the early stages, peripheral loss of position and vibratory sensation in the extremities are accompanied by mild to moderate weakness and reflex loss. In later stages, spasticity, Babinski's responses, more severe loss of proprioceptive and vibratory sensation in the lower extremities, and ataxia emerge. Tactile, pain, and temperature sensations are uncommonly impaired. The upper extremities are involved later and less consistently than the lower. Some patients also have irritability and mild depression. Paranoia (*megaloblastic madness*), delirium, confusion, spastic ataxia, and at times postural hypotension may occur in advanced cases.

Folate deficiency is indistinguishable from B₁₂ deficiency in regard to peripheral blood and bone marrow findings, but neurologic lesions (as seen in B₁₂ deficiency) do not occur.

Laboratory features. The anemia is macrocytic and hyperchromic (colour index >1,2). The smear shows macroovalocytosis, anisocytosis, and poikilocytosis. Jolly bodies (residual fragments of the nucleus) are common. Unless the patient has been treated, reticulocytopenia is present. Hypersegmentation of the granulocytes is one of the earliest findings; neutropenia develops later. Thrombocytopenia is present in severe cases

Bone marrow shows erythroid hyperplasia and megaloblastic changes. Serum indirect bilirubin may be elevated because of ineffective erythropoiesis and shortened survival of the defective erythrocytes.

Serum vitamin B₁₂ assay is the most commonly used method for establishing vitamin B₁₂ deficiency as the cause of megaloblastosis. Levels <110 pmol/l reliably indicate vitamin B₁₂-deficiency.

Serum folic acid levels < 4 ng/ml (< 9 nmol/l) suggest a folate deficiency.

Autoantibodies to gastric parietal cells can be identified in 80 to 90% of patients with pernicious anemia (vitamin B₁₂ deficiency anemia). More important for diagnosis are antibodies to intrinsic factor, which can be found in the sera of most patients with pernicious anemia.

Achlorhydria is present in most patients with pernicious anemia. Gastric analysis demonstrates a small volume of gastric secretions (*achylia gastrica*) with a pH>6,5; achlorhydria is confirmed if the pH rises to between 6,8 and 7,2 after giving histamine.

Diagnosis of the vitamin B₁₂- (folic acid) deficiency anemia is supported by (a) macrocytic anemia (colour index 1,2-1,5), (b) megaloblastic erythropoiesis according to bone marrow analysis.

Hemolytic anemia

Definition. Hemolytic anemia (D55-59 according to ICD-X) is a group of anemias caused by excessive hemolysis.

Etiology and pathogenesis. Causes are hereditary enzymo-, erythrocyto- and hemoglobinopathy (thalassemia, hereditary spherocytosis and ovalocytosis; sickle cell diseases), autoimmune, toxic (lead, alcohol, etc.), tumours, viral infections.

The essential feature of hemolytic anemia is a shortened erythrocyte life span; hemolytic anemia results when bone marrow production can no longer compensate for the shortened erythrocyte survival.

Most hemolysis is extravascular, i.e, it occurs in phagocytic cells of the spleen, liver, and bone marrow. Hemolysis may result (1) from intrinsic abnormalities of erythrocyte contents (Hb or enzymes) or membrane (permeability, structure, or lipid content), or (2) from problems extrinsic to the erythrocyte (serum antibodies, trauma in the circulation, or infectious agents). The spleen is usually involved; it reduces erythrocyte survival by destroying mildly abnormal erythrocytes or warm antibody-coated cells. If the spleen is enlarged, there may be trapping (sequestration) of erythrocytes.

Intravascular hemolysis is uncommon; it results in hemoglobinuria when the Hb released into plasma exceeds the Hb-binding capacity of plasma-binding proteins (e.g., haptoglobin).

Clinical and laboratory features. Systemic manifestations resemble those of other anemias. Hemolysis may be acute, chronic, or episodic. Hemolytic crisis (acute, severe hemolysis) is uncommon; it may be accompanied by chills, fever, pain in the back and abdomen, prostration, and shock. In severe cases, hemolysis increases (jaundice, splenomegaly, and, in certain types of hemolysis, hemoglobinuria and hemosiderinuria), and erythropoiesis increases (reticulocytosis, hyperactive bone marrow).

Syndrome of hemolytic jaundice, spleno- and hepatomegaly are the most typical in chronic hemolytic anemia. In chronic hemolysis, anemia may be exacerbated by aplastic crisis (temporary failure of erythropoiesis); this is usually related to an infection, often parvovirus.

Diagnosis is based on laboratory signs of the pathological hemolysis detected by (a) increase concentration of unbound bilirubin in blood and excretion of stercobilin with feces and urine; (b) diminished osmotic stability of erythrocytes; (c) reticulocytosis, (d) positive Coombs' test (used to reveal anti-erythrocytic antibodies) in autoimmune hemolytic anemia.

Aplastic (hypoplastic) anemia

Definition: Aplastic (hypoplastic) anemia (D60-62 according to ICD-X) is an anemia resulting from a loss of erythrocyte precursors, either from a defect in stem cell pool or an injury to the microenvironment that supports the marrow.

Etiology and pathogenesis. About 1/2 of the cases of true aplastic anemia (most common in adolescents and young adults) are idiopathic. Recognized causes are chemicals (e.g., benzene, inorganic arsenic), radiation, drugs (e.g., antineoplastics, antibiotics, NSAIDs, anticonvulsants), autoimmune diseases (e.g., systemic lupus erythematosus), infections (e.g., viral hepatitis, AIDS, infectious mononucleosis), cancer metastasis in bone marrow, hemoblastosis, myelodysplastic syndromes.

Bone marrow failure results from severe damage to the hematopoietic cell compartment. In aplastic anemia, replacement of the bone marrow by fat is apparent in the morphology of the biopsy specimen.

Clinical features. History of the disease shows that aplastic anemia can appear with seeming abruptness or have a more insidious onset. Bleeding is the most common early symptom; a complaint of days to weeks of easy bruising, oozing from the gums, nose bleeds, heavy menstrual flow, and sometimes petechiae will have been noticed. With thrombocytopenia, massive hemorrhage is unusual, but small amounts of bleeding in the central nervous system can result in catastrophic intracranial or retinal hemorrhage. History of drug use, chemical exposure, and preceding viral illnesses must often be elicited with repeated questioning. Life-threatening infections are common. In agranulocytosis, where necrotic tonsillitis and stomatitis, pharyngitis, anorectal infection, or frank sepsis occur early.

A striking feature of aplastic anemia is the restriction of symptoms to the hematologic system, and patients often feel and look remarkably well despite drastically reduced blood counts.

Laboratory features. Anemia is normochromic-normocytic. Pancytopenia (anemia in combination with leucopenia) is typical. Leucocyte count $<1,5 \times 10^9/l$ is common, the reduction occurring chiefly in the granulocytes (agranulocytosis). Reticulocytes are decreased (*reticulocytopenia*) or absent, even with coexistent hemolysis.

The bone marrow is acellular characterized by replacement of the bone marrow by fat tissue. In hypoplastic anemia the myelogram detects decrease of erythroid or myeloid precursors in bone marrow. Serum iron is elevated.

Diagnosis of aplastic anemia is usually based on the combination of pancytopenia with a fatty, empty bone marrow.

Hemorrhagic diathesis

Definition. Hemorrhagic diathesis (D65-69 according to ICD-X) is the syndrome characterized by the tendency to bleeding and repeated hemorrhages.

Etiology. Some types of hemorrhagic diathesis are hereditary (hemophilia) but many of them can be caused by external factors. Avitaminosis (deficit of vitamins C and P) is an especially predisposing factor. Some infections (long-standing sepsis, louse-born typhus, virus hemorrhagic fevers, icterohemorrhagic leptospirosis), allergic conditions, some diseases of the liver, kidneys, and of the blood system can also provoke the onset of hemorrhagic diathesis.

Classification according to pathogenesis:

- (1) hemorrhagic diathesis due to disordered capillary permeability (hemorrhagic vasculitis, vitamin C deficiency, some infectious diseases, trophic disorders, etc.)
- (2) hemorrhagic diathesis due to disorders in the blood coagulation and anticoagulation system:
 - a) disorders of plasma factors (hemophilias A, B, C)
 - b) disorders of thrombocytes (thrombocytopenia)
 - c) hemorrhagic diathesis caused by disseminated intravascular coagulation.

Clinical picture. The general clinico-morphological symptoms of hemorrhagic diathesis are hemorrhages into various organs and tissues, external and internal hemorrhages (from the gastro-intestinal tract, lungs, uterus, kidneys, etc.) and secondary anemia. Hemorrhage may occur spontaneously and may be caused by injuries; injury can be quite insignificant, which otherwise would never provoke bleeding in a normal individual.

The most common sign is the skin and mucous membranes hemorrhages (*purpura*), including *petechia* - small circumscribed punctate foci of extravasation, and *ecchymoses* - larger confluent areas of extravasation. The disease is complicated by dysfunction of the hemorrhage-affected organs, by hemiparesis in disordered cerebral circulation, regional paralysis and paresis in compression of large nervous trunks by hematomas, hemarthroses in repeated hemorrhages into the joints, etc.

Laboratory tests. The most important screening tests of the primary hemostatic system are (1) bleeding time (a sensitive measure of platelet function), and (2) thrombocyte count. Patients with normal thrombocyte count need in advanced study of hemostasis (see above - *Study of hemostasis*).

Clinical features of basic variants of hemorrhagic diathesis

A. Disorders of plasma factors of coagulation

The most common diseases are hemophilias A, B, C, vitamin K deficiency.

Hemophilia A (factor VIII deficiency), which affects about 80% of hemophiliacs, and hemophilia B (factor IX deficiency) have identical clinical manifestations, screening test abnormalities, and X-linked genetic transmission. Hemophilia may result from gene mutations: point mutations involving a single nucleotide, deletions of all or parts of the gene, and mutations affecting gene regulation.

History in hemophilias A, B reveals familial predisposition - autosomal or X-linked recessive genetic transmission. Because factor VIII and factor IX genes are located on the X chromosome, hemophilia affects males almost exclusively. Daughters of hemophiliacs will be obligatory carriers, but sons will be normal.

Vitamin K deficiency may be due to inadequate diet, syndrome of malabsorption, liver diseases, certain drugs, including anticonvulsants, anticoagulants, certain antibiotics (particularly cephalosporins), salicylates, and megadoses of vitamin A or E.

Character of hemorrhage is a deep tissue hemorrhages (hemarthroses, hematomas in muscles, retroperitoneum). Onset of bleeding is delayed (hours or days) after trauma. Hemophilia A, B manifests in the age <18 years, male sex.

Minor trauma can result in extensive tissue hemorrhages and hemarthroses, which, if improperly managed, can result in crippling musculoskeletal deformities. Bleeding into the base of the tongue, causing airway compression, may be life threatening and requires prompt, vigorous replacement therapy. Even a trivial blow to the head has a risk of intracranial bleeding. Such patients may also bleed excessively after surgery or dental extraction

Laboratory features: Coagulation time is >15 min. Bleeding time is normal (3-5 min).

Decreased plasma factors VIII (antihemophilic globulin), IX, and XI are in hemophilia. In vitamin K deficiency prothrombin index decreases less than 40%, the prothrombin time (PT) and the activated partial thromboplastin time (PTT) are usually prolonged.

B. Disorders of platelets (thrombocytes)

The diseases are thrombocytopenic purpura (Werlhof's disease), thrombocytopathies.

Platelet disorders may cause defective formation of hemostatic plugs and bleeding because of decreased platelet numbers (thrombocytopenia) or because of decreased function despite adequate platelet numbers (platelet dysfunction).

Idiopathic thrombocytopenic purpura usually results from development of an antibody directed against a structural platelet antigen (an autoantibody). Viral antigen is thought to trigger synthesis of antibody that may react with viral antigen associated with the platelet surface.

History reveals family predisposition with autosomal dominant genetic transmission; viral infection. Some medications (quinidine, quinine, sulfa preparations, oral antidiabetic drugs, gold salts, and rifampin less commonly) induce thrombocytopenia in sensitive patients. The history may elicit symptoms suggestive of underlying immunologic disease (e.g., arthralgia, Raynaud's phenomenon, unexplained fever); a blood transfusion within 10 days, liver diseases, and significant alcohol consumption.

Character of hemorrhage. The onset of bleeding is immediate after trauma. Severe thrombocytopenia results in a typical pattern of bleeding: multiple *petechiae* in the skin, often most evident on the lower legs; scattered small *ecchymoses* at sites of minor trauma; *mucosal bleeding* (epistaxis, bleeding in the gastrointestinal and genitourinary tracts, vaginal bleeding); and excessive bleeding after surgery. Heavy gastrointestinal bleeding and bleeding into the central nervous system may be life threatening. However, thrombocytopenia does not cause massive bleeding into tissues (e.g., deep visceral hematomas or hemarthroses), which is characteristic of bleeding secondary to coagulation disorders (e.g., hemophilia). Tests of capillary permeability (tourniquet test, pinch test) are positive

Laboratory features: Bleeding time is >15-20 min, thrombocyte count $<50,0 \times 10^9/l$.

C. Disorders of vascular hemostasis

The diseases are hemorrhagic vasculitis (Henoch-Schölein purpura), Rendu-Osler-Weber disease (hereditary hemorrhagic teleangiaectasia), vitamin C deficiency (*scurvy*).

History in hemorrhagic vasculitis reveals previous acute respiratory viral infection, supercooling, autoimmune and allergy disease. A drug may be the inciting agent. Deposition of IgA-containing immune complexes with consequent activation of complement is thought to represent the pathogenetic mechanism for the vasculitis.

Vitamin C deficiency may be due improper diet, in gastrointestinal diseases. Pregnancy, lactation, and thyrotoxicosis increase vitamin C requirements; acute and chronic inflammatory diseases, surgery, and burns can significantly increase requirements. Vitamin C (ascorbic acid) is essential for collagen formation and helps maintain the integrity of substances of mesenchymal origin, such as connective tissue, osteoid tissue, and dentin.

Character of hemorrhage. Hemorrhagic vasculitis begins with the sudden appearance of a purpuric skin rash that typically involves the extensor surfaces of the feet, legs, and arms and a strip across the buttocks. Purpuric skin rash at the extensor surfaces, gastrointestinal bleeding and hematuria are typical. Onset of bleeding is delayed (hours or days) after allergy, supercooling, viral respiratory infection.

The purpuric lesions may start as small areas of urticaria that become indurated and palpable. Crops of new lesions may appear over days to several

weeks. Most patients also have fever and polyarthralgia with associated periarticular tenderness and swelling of the ankles, knees, hips, wrists, and elbows. Many patients develop edema of the hands and feet. GI findings are common and include colicky abdominal pain, abdominal tenderness, and melena. Stool may test positive for occult blood. From 25 to 50% of patients develop hematuria and proteinuria. The disease usually remits after about 4 weeks but often recurs at least once after a disease-free interval of several weeks. In most patients, the disorder subsides without serious complications; however, some patients develop chronic renal failure. Capillary permeability tests (Konchalovsky-Rumpel-Leede, pinch tests) are positive.

Signs of scurvy are multiple splinter hemorrhages near the distal ends of the nail, bleeding of gums, bulbar conjunctival hemorrhage, oliguria, edema of the lower extremities, arthritis. The gums become swollen, purple, spongy, and friable; they bleed readily in extreme deficiency. Secondary infection, gangrene, and loosening of teeth eventually occur.

Laboratory features: In vascular bleeding disorders, tests of hemostasis are usually normal. Biochemical tests detect increase of γ -globulins and CRP in hemorrhagic vasculitis.

The diagnosis is made from the clinical findings.

Leucosis

Definition. Leucosis (C91-95 according to ICD-X) is the malignant neoplasm of the hemopoietic cells with the primary locus of the tumour in the bone marrow.

Leukemia is the release of tumour (leucosis) cells into the blood ($>50,0-100,0 \times 10^9/l$).

Etiology and pathogenesis. Etiology of leucosis in humans is uncertain. Human T-cell lymphotropic virus type I, an RNA retrovirus, is associated with some T-cell leucosises and lymphomas. Exposure to ionizing radiation and certain chemicals (e.g., benzene, some antineoplastic drugs) is associated with an increased risk of leucosis. Some genetic defects (e.g., Down syndrome) also predispose to leukemia.

Transformation to malignancy (through two or more steps) occurs in a single cell, with subsequent proliferation and clonal expansion. Usually, transformation occurs at the pluripotent stem cell level, but sometimes it may involve a committed stem cell with capacity for more limited differentiation. In general, leucosis cells divide with longer cell cycles and smaller growth fractions than normal bone marrow cells, but they accumulate because of slowed apoptosis (programmed cell death).

Clinical and laboratory features of leukemia are caused by suppression of normal blood cell formation and organ infiltration. Inhibitory factors produced by leucosis cells or replacement of marrow space may suppress normal hematopoiesis, with ensuing anemia, thrombocytopenia, and granulocy-

topenia. Organ infiltration results in enlargement of the liver, spleen, and lymph nodes, with occasional kidney and gonadal involvement. Meningeal infiltration results in clinical features associated with increasing intracranial pressure (e.g., cranial nerve paralysis).

Classification.

I. According to hemopoietic abnormalities:

1. Acute leucosis – acute lymphoblastic leucosis, acute myeloblastic leucosis;
2. Chronic leucosis - chronic myeloid leucosis, -chronic lymphoid leucosis, -chronic erythromyelosis, -erythremia, etc.

II. According to stage:

- initial (latency) stage,
- exacerbation (pronounced clinical and hematological symptoms),
- stage of clinical and hematological remission,
- terminal stage,
- recovery.

III. According to quantity of pathological cells in the peripheral blood

- leukemic form - significant increase ($>50,0-100,0 \times 10^9 / l$);
- subleukemic form – moderate increase ($9,0-50,0 \times 10^9 / l$);
- aleukemic form - normal or decreased quantity of white blood elements ($<9,0 \times 10^9 / l$).

Hemopoietic abnormalities in leucosises: (a) in acute leucosis - hemopoiesis is transformed at the expense of low differentiated blast cells or precursor cells of the 3rd and even 2nd series (see above Conception of hemopoiesis); (b) in chronic leucosis - hemopoiesis is transformed at the expense of more mature cells of differentiated hemopoiesis.

Common clinical syndromes in leucosis

Hemorrhagic syndrome – skin, nasal, oral hemorrhages, gastrointestinal bleeding, hemoptysis, metrorrhagia, hematuria due to thrombocytopenia

Necrotic syndrome– necrotic stomatitis, tonsillitis, and dermatitis due to thrombocytopenia due to agranulocytosis.

Septic syndrome – high persistent fever, septic foci (abscess, flegmonas, suppurative inflammation), severe bacterial infections (pneumonia, meningitis, pyelonephritis) due to agranulocytosis.

Anemic syndrome – hypo-aplastic anemia due to suppression of normal blood cell formation or replacement bone marrow by leucosis cells.

Spleno- and hepatomegaly syndrome - due to organ infiltration by leucosis cells.

System lymphadenopathy syndrome – symmetrical enlargement 2 and more groups of lymphatic nodes, painless, elastic, and movable due to infiltration by leucosis cells.

Laboratory findings in leucosis

Acute leucosis is characterized by (1) presence of blast cells and “hiatus leucaemicus” (absence of premature differentiating cells) in leucocyte formula, (2) anemia, (3) thrombocytopenia, (4) prevalence of blast cells (>40-60%) in myelogram (bone marrow analysis).

Chronic leucosis is characterized by (1) presence of blast cells and premature cells of differentiated hemopoiesis in leucocyte formula, (2) (2) anemia, (3) thrombocytopenia, (4) infiltration of the bone marrow by pathologic premature differentiating cells of hemopoiesis (lymphoid or myeloid metaplasia of bone marrow).

Primary diagnosis of leucosis based on (1) typical clinical picture and (2) typical changes of the complete blood count.

Concluding diagnosis of leucosis is confirmed by the bone marrow biopsy and analysis (*myelogram*).

Basic variants of leucosis

Acute leucosis

Definition. Acute leucosis is a usually rapidly progressing disease characterized by replacement of normal bone marrow by blast cells of a clone arising from malignant transformation of a hematopoietic stem cell and leukemia. Lympho- and myeloblastic forms of the disease are common.

Clinical picture. Acute leucosis occurs at any age, but men and women from 20 to 30 are mostly affected.

The presenting symptoms are usually nonspecific (e.g., fatigue, fever, malaise, weight loss) and reflect the failure of normal hematopoiesis and acute septic affections. The cause of fever is often not found, although granulocytopenia may lead to an obvious and often severe bacterial infection. Pain in the throat is often one of the first complaints: swallowing becomes painful because of necrotic ulceration of the throat and fauces. For this reason the disease is often mistaken for necrotic tonsillitis and only further observation of the patient and the study of the bone marrow and blood help the physician establish a correct diagnosis

Bleeding is usually manifested by petechiae, easy bruisability with mucous membrane hemorrhage (e.g., epistaxis), or menstrual irregularity. Hematuria and gastrointestinal bleeding are uncommon. Initial central nervous system involvement (causing headaches, vomiting, and irritability) is uncommon. Bone and joint pain sometimes occur, especially in acute lymphoblastic leucosis.

Inspection of the patient usually reveals grave condition from the very onset of the disease. In the terminal period the condition is particularly grave: the patient is passive, answers the doctor's questions with difficulty, or is unconscious. The skin is pallid, sometimes with yellowish or greyish hue, and moist; its turgor is decreased. Traces of subcutaneous and in tracutaneous hemorrhages can be seen. The tourniquet and the pinch tests are positive;

hemorrhage is considerable at points of injections. Necrosis and bed-sores are possible. Necrosis of the mucosa, especially of the mouth and throat, is especially pronounced. Ulcerous and necrotic tonsillitis, gingivitis, and stomatitis are quite characteristic of the disease. Necrotized surfaces are covered with a poorly removable grey or yellowish coat. When removed, it reveals bleeding ulcers. The breath of the patient is putrefactive. Palpation reveals enlargement of separate groups of the lymph nodes, spleen, and the liver. The heart borders are broadened; tachycardia, systolic murmur at the heart apex (due to dystrophic processes in the heart muscle), and anemia are revealed. Pericarditis and pleuritis are possible. Each hematological form of leucosis is characterized (though not necessarily) by some special clinical features.

Laboratory findings and diagnosis

General blood count. The blood of patients contains increased number of white blood cells: to $100,0 \times 10^9/l$ and even $200,0 \times 10^9/l$ (in rare cases even this figure may be exceeded). Subleukemic forms of the disease can occur. Leucopenia can develop in some cases at the early stage of acute leucosis. Leucopenia is then succeeded by leucocytosis.

The most specific hematological sign of the disease is the presence of blast cells in the peripheral blood. Blast cells are usually found in the blood smear unless the leucocyte count is markedly decreased. The immature forms may amount to as high as 95 and even 99 per cent in leucocyte formula. Only the youngest and the most mature cells can be revealed in the blood of most patients with acute leucosis, while intermediate forms are absent (*hiatus leukemicus*). Eosinophils and basophils are absent; other cell forms are decreased significantly not only relatively but also absolute.

Anemia and thrombocytopenia are very common (75 to 90%). Coagulability of blood and the bleeding time are abnormal in most cases; ESR sharply increases.

Myelogram (bone marrow study). Although the diagnosis can usually be made from the blood smear, bone marrow examination should always be performed. The bone marrow punctate contains 80-90 per cent of leukaemic blast cells, which displace all other cell elements.

All blast cells are similar morphologically but special cytochemical reactions can be used to differentiate between them. The blasts of acute lymphoblastic leucosis should be distinguished from those of acute myeloblastic leucosis by histochemical studies, cytogenetics, immunophenotyping, and molecular biology studies.

Course. The course of the disease without treatment is progressive. But modern therapy can prolong the patients' life to 3-5 and more years; in some cases complete recover may be achieved.

Chronic lymphoid leucosis

Definition. Chronic lymphoid leucosis is a clonal expansion of mature-appearing lymphocytes involving lymph nodes and other lymphoid tissues

with progressive infiltration of bone marrow and presence in the peripheral blood.

The hematological basis is mainly B-lymphocytes (morphologically mature but functionally inadequate). Chronic lymphoid leucosis is characterized by systemic hyperplasia of the lymphoid apparatus, lymphoid metaplasia of the spleen, bone marrow, and other organs.

The cause is unknown, but some cases are familial, suggesting a genetic factor.

Clinical picture. Chronic lymphoid leucosis usually occurs in the middle-aged and aged individuals (from 35 to 70), mostly in men.

Onset is usually insidious, and chronic lymphoid leucosis is often initially diagnosed from incidental blood tests or during evaluation of asymptomatic lymphadenopathy.

The initial complaints are general weakness, subfebrile temperature, indisposition, and rapid fatigue. Initial findings include generalized lymphadenopathy and minimal-to-moderate hepatomegaly and splenomegaly. Depending on a particular enlarged lymph node group and the organ affected by lymphoid infiltration, additional symptoms develop: dyspepsia, diarrhea (in affection of the gastro-intestinal tract), dyspnea and attacks of asphyxia (in compression of the trachea and bronchi by the bifurcation lymph nodes), erythema, dryness and itching of the skin (in *leukemic lymphodermia*), etc.

Enlarged lymph nodes can often be revealed during inspection of the patient. Lymph nodes of one or several groups are often enlarged; later all other lymph nodes become also involved. The tonsils can be enlarged too. Skin infiltration is attended by its consolidation, reddening, dryness and scaling. At the terminal stage, the patients are extremely thin (*cachexia*). Lymphoid metaplasia of the bone marrow may cause hemorrhagic symptoms (due to thrombocytopenia) and anemia. Leukemic infiltration can cause radicular pain and exophthalmos. A predisposition to bacterial, viral, and fungal infection occurs in late disease because of hypogammaglobulinemia and granulocytopenia.

Palpation reveals the enlargement of the lymph nodes and their properties. The lymph nodes are elastic-pasty; they do not fuse with the skin or with one another, and are painless in most cases. Even markedly enlarged, the lymph nodes never ulcerate or suppurate (as distinct from tuberculosis affection of the nodes). The liver and the spleen are enlarged and consolidated. Infarctions of the spleen can occur; its palpation then becomes tender, and auscultation detects peritoneum rub friction in the left hypochondrium.

Laboratory findings and diagnosis

General blood count. Leucocyte counts in the leukemic form of the disease are as high as $300,0 \times 10^9/l$, and more. Lymphocytes make 80-95 per cent of the leucocyte formula, they are mostly mature. The structure of their nucleus and cytoplasm are weak: the cells are very soft and are easily de-

stroyed when preparing a smear; specific *Botkin-Gumprecht shadows* are formed. The relative quantity of neutrophils is much decreased (to 20 - 4 per cent). The blood picture is less specific in subleukemic and aleukemic forms of the disease, where lymphocytosis is usually less pronounced. Anemia and thrombocytopenia (mainly of the auto-immune genesis) join at the terminal period.

Myelogram. Study of the bone marrow reveals its lymphoid metaplasia: great quantity of lymphoid cells is found (> 30% to 50% and even 90 % in especially grave cases). The number of cell elements of the granulocytic and erythroid precursors is decreased.

Course. The disease progresses in cycles or gradually. The average life expectancy of patients is near 10 years. The patients die of secondary infections, usually pneumonia (which is promoted by inhibition of humoral immunity), of hemorrhagic complications, and cachexia.

Chronic myeloid leucosis

Definition. Chronic myeloid leucosis is a clonal myeloproliferation caused by malignant transformation of a pluripotent stem cell and characterized by striking overproduction of granulocytes primarily in the bone marrow but also in extramedullary sites (spleen, liver).

The cause is unknown, but the effect of large dose radiation was demonstrated in the study of the atomic bomb survivors.

Clinical picture. Chronic myeloid leucosis may occur in either sex and at any age but its incidence at the age of 20-45 is higher.

Patients are often asymptomatic early on; the disease may be diagnosed during an incidental complete blood count. In other patients, insidious onset of nonspecific symptoms (e.g., fatigue, weakness, anorexia, weight loss, fever, night sweats, a sense of abdominal fullness) may prompt evaluation. Initially, pallor, bleeding, and easy bruisability and lymphadenopathy are unusual, but moderate or occasionally extreme splenomegaly is common (60 to 70% of cases). With disease progression, splenomegaly may increase, and pallor and bleeding occur.

A common symptom is the feeling of heaviness in the left part of the abdomen which depends on the pronounced enlargement of the spleen. Pain may be due to a considerable distension of the spleen capsule. Splenic infarction is manifested by piercing pain which intensifies during breathing. Pain in the bones is not infrequent. It is due to hyperplasia of the myeloid tissue. Myeloid infiltration in various internal organs can be the cause of some additional symptoms, such as dyspeptic signs in affections of the gastrointestinal tract, coughing in the presence of infiltrations in the lungs and the pleura, neurological changes due to affection of the brain, the spinal cord, nerve radices, etc.

The terminal stage is characterized by pronounced cachexia and considerable enlargement of the abdomen due to markedly enlarged liver and

spleen. The skin is pallid, with a yellowish or greyish hue; it is flaccid and moist. The legs are affected by edema. Gingivitis and necrosis of the mouth mucosa are possible. Palpation reveals moderate enlargement of the lymph nodes of various groups. The liver and especially the spleen are markedly enlarged. The liver and the spleen are firm. In the presence of infarctions of the spleen it is tender to palpation. Peritoneal friction sound can be heard over the spleen by auscultation. Applying pressure to the bones and tapping over them are painful.

Laboratory findings and diagnosis

General blood count. In the asymptomatic patient, the leucocyte count is usually $<50,0 \times 10^9/l$. In the symptomatic patient, the leucocyte count is usually about $200,0 \times 10^9/l$, but may reach $600,0 \times 10^9/l$. The platelet count is normal or moderately increased, and the hemoglobin is usually >100 g/l. During the accelerated phase of disease progression, anemia and thrombocytopenia develop. ESR usually increases to 30-70 mm/h.

On blood smears there are all stages of granulocyte differentiation which make 95%-97% of all white blood elements. The absolute eosinophil and basophil concentrations can be strikingly increased (*basophil-eosinophil association*), but the absolute lymphocyte and monocyte concentrations may be normal

Myelogram. The bone marrow is hypercellular on aspirate and biopsy. Cells of the myeloid series prevail (especially juvenile forms: promyelocytes, myelocytes, and myeloblasts). Characteristic also is the increase in the number of basophilic and eosinophilic promyelocytes and myelocytes. Leukocyte alkaline phosphatase is characteristically low in myeloid cells. The content of the erythroid precursors markedly decreases in the bone marrow (especially when the disease approaches its terminal stage). In the bone marrow, myelofibrosis may develop and sideroblasts may be seen on microscopy. Megakaryocyte count slightly increases in the first half of the disease.

Karyotype. The Philadelphia chromosome (Ph) in the myeloid precursors can be demonstrated in almost all patients (95%) by chromosomal analysis.

Diagnosis of chronic myeloid leucosis is based on associated splenomegaly, leukocytosis with immature granulocytes and absolute eosinophilia and basophilia, and presence of the Ph chromosome. Myelogram

shows the myeloid series prevalence (especially juvenile forms: promyelocytes, myelocytes, and myeloblasts).

Course. The course of the disease is progressive, sometimes with transient spontaneous remissions. Before modern methods of treatment of the disease were introduced into clinical practice, the average life expectancy of patients was 2,5-3 years (sometimes to 10 years). Today the life of patients is prolonged more significantly. Patients die of cachexia, anemization incompatible with life, hemorrhagic complications, or from infection.

Diseases of endocrine system and metabolism

Clinical, laboratory and instrumental methods of diagnostics

Subjective examination (inquiry)

Complaints. Endocrine system has multiple effects on various body functions, and the patient's complaints are therefore varied. The patient may complain of increased excitability, interrupted and superficial sleep, impaired memory, irritability, hyperhidrosis, changes of body weight, chills, heart palpitation, noise in the ears, blood rush to the head, skin itching, increased thirst, and considerable wasting. When inquiring the patient, the physician can reveal some features of his nervous and psychic character that may suggest some endocrine diseases: e.g., fussiness, rapid movements, hasty speech, apathy, and flaccidity suggest hyperthyroidism, while tiredness, weakness, difficulty concentrating and poor memory, feeling cold, impaired hearing - hypothyroidism.

Anamnesis. It is important to establish the direct cause of the disease. Strong emotions, fear, and psychic traumas are the predisposing factors for thyrotoxic goitre. Endocrine diseases often develop during sexual maturation, after childbirth, and during menopause.

The hereditary factor is also important in endocrine diseases, e.g. in diabetes mellitus. The endocrine function can be affected by some other diseases. Tuberculosis of the adrenal glands, for example, is the cause of their hypofunction (Addison's disease).

Conditions that predispose to metabolic disease include gross underweight, gross overweight, recent weight loss, alcoholism, malabsorption, hyperthyroidism, protracted fever, sepsis, fad diets, drug usage, and psychiatric disorders. Hypertension, diabetes, and coronary artery disease are associated with obesity. The gastrointestinal system can be injured by malnutrition and alcoholism.

Objective examination

General survey

Inspection of the patient is a valuable diagnostic procedure. Sometimes the diagnosis becomes clear at first sight. The patient's appearance and some special features of his behavior are quite characteristic in diffuse thyrotoxic goitre, myxedema, acromegaly, nanism (dwarfism), Itsenko-Cushing syndrome, upset fat metabolism, etc.

Endocrine diseases, especially affections of the thyroid and pituitary glands, can alter the expression of *the patient's face*. Patients with thyroid hyperfunction have large, wide open, protruded eyes; wrinkling is rare, the eyes are lustrous, and the patient's face has the expression of horror or fear. The face of patients with thyroid hypofunction (myxedema) is round, without wrinkles, with motionless eyes; the general expression is dullness and apathy. The acromegalic face is characterized by protruding superciliary arches, abnormally large nose, lips, tongue and the chin; the abnormally large lower jaw has widely set teeth (diastema).

Neck. Inspection of the anterior surface of the neck can reveal the size of the thyroid gland (its enlargement).

Height. Gigantism (over 195 cm) is mostly the result of anterior pituitary hyperfunction (acromegalic gigantism) or hypofunction of the sex glands (hypogonadal gigantism). Dwarfism (the height below 135 cm) can be due to hypofunction of the anterior pituitary lobe with preservation of childish proportions of the body, underdevelopment of the sex organs and the absence of the secondary sex characters. The same symptoms can be observed in marked thyroid hypofunction with signs of myxedema and mental retardation (to idiotism).

Skin. Pallid face with a yellowish tint is characteristic of myxedema (hypothyroidism). Dry and scaling skin is characteristic of thyroid and parathyroid hypofunction; the skin is dry and cold in hypothyroidism. Edema of the skin is characteristic of hypothyroidism due to its impregnation with mucinous substance. Nails are brittle in hypothyroidism and hypoparathyroidism. The skin is smooth and moist in patients with hyperthyroidism.

The Itsenko-Cushing syndrome (anterior pituitary hyperfunction) is characterized by atrophy of the skin on the femur and the abdomen (red-violet striae), and hyperemic face. The mucosa and skin are bronze (especially skin folds, the palms) in patients with Addison's disease (adrenal hypofunction). Thickening of the skin associated with hypertrophy of its papillar layer is found in acromegaly. Scratching of the skin and furunculosis, cholesterol deposition in the skin of the eyelids is often observed in diabetes mellitus.

The effects of malnutrition on the skin can include rashes, petechial hemorrhages, ecchymoses, pigmentation, edema, and dryness.

Hair. Changes in hair are important diagnostic signs in endocrine diseases. A female pattern of hair growth in men is typical of eunuchoidism, while male-type pilosis in women occurs in acromegaly and Itsenko-Cushing syndrome; falling of hair from the eyelids, brows, mustaches, and the head is characteristic of myxedema.

Subcutaneous fat. Uniform distribution of fat over the entire body is characteristic of thyrogenic obesity, while deposition of fat mostly in the pelvic region (lower abdomen, buttocks, thighs) occurs in pituitary and pubertal obesity. Excess fat on the face and trunk is a sign of the Itsenko Gushing syndrome. Excess wasting is observed in some forms of diabetes mellitus and thyrotoxic goitre. Cachexia is a sign of Simmonds's disease which is due to the affection of the pituitary gland (pituitary cachexia).

Bones. Eunuchoidism is characterized by a delayed growth of the epiphyseal ends of long tubular bones. Acromegaly is marked by abnormal thickening of the enlarged bones of the skeleton. Bones and joints are diseased in metabolic diseases (rickets, osteomalacia, osteoporosis, and scurvy).

Muscles. The hormone of the parathyroid glands is produced in deficient quantity and the blood calcium content is thus decreased. As a result, patients develop tonic convulsions (mostly of the flexor muscles). The patient's hand is flexed to give the specific appearance of the "obstetrician hand". When the facial muscles are affected by convulsions, the face acquires the expression of a forced smile. The muscles are developed in excess in acromegaly.

Palpation of the thyroid gland. In addition to the examination of the thyroid itself, the physical examination should include a search for signs of abnormal thyroid function and the extrathyroidal features of *ophthalmopathy* and *dermopathy* (see below). Examination of the neck begins by inspecting the seated patient from the front and side, and noting any surgical scars, obvious masses, or distended veins. Tentative palpation by mild tips of the three bent fingers of the right arm assesses the density of the organ, the character of its surface, and the presence of nodes. Tentative palpation of the thyroid gland is repeated during swallowing movements of the patient. By asking the patient to swallow, thyroid consistency can be better appreciated as the gland moves beneath the examiner's fingers.

Then special palpation follows. The examiner places four flexed fingers of both hands deep beyond the posterior edges of the sternocleidomastoid muscle, and the thumbs beyond the anterior edges of this muscle. The patient is now asked to make swallowing movements: the thyroid together with the larynx moves between the examiner's thumbs. This method is used to reveal even insignificant enlargement of the thyroid gland that cannot be detected by common palpation. Mobility of the gland during swallowing, the presence or absence of pulsation, and tenderness of the

thyroid can also be determined by this method. Palpation of one lateral lobe of the gland can be facilitated by pressing the thyroid cartilage on the opposite side. The thyroid isthmus is palpated by the sliding movements of the examining fingers in the direction of the sternal manubrium. The lower portion of the thyroid, which is concealed behind the sternal manubrium, may be affected by nodes. In order to palpate them (for outlining their borders and assessing their consistency), the patient is asked to make swallowing movements, while the examiner's fingers palpate the thyroid in the suprasternal notch. The size, location, and consistency of any nodules should also be depicted. The thyroid examination is not complete without assessment for lymphadenopathy in the supraclavicular and cervical regions of the neck.

Percussion can reveal a *retrosternal struma* (goitre). Large retrosternal goiters can cause venous distention over the neck and difficulty breathing, especially when the arms are raised (Pemberton's sign).

Auscultation. Sounds and murmurs can be heard over the enlarged thyroid in patients with thyrotoxicosis. These are explained by accelerated flow of blood and its intensified supply to the thyroid gland.

Anthropometric measurements

Generally, height and weight are measured as part of the physical examination. Other anthropometric measurements include skin fold thickness and midarm circumference. Height and weight are critical to an estimation of desirable weight and body proportions. *Body mass index (BMI)* $\text{weight(kg)/height (m}^2\text{)}$ is a guide to desirable body composition. Values > 30 = obese; 25 to 30 = overweight; 20 to 25 = normal; 18,5 to 20 = thin; and $< 18,5$ = undernourished. Values < 12 are incompatible with life. The generally accepted normal BMI range corresponds to the range of desirable weights in Table 1.

Table 1
Classification of nutritional status by BMI (body mass index)

Nutritional status	Body mass index (weight [kg]/ height [m] ²)	Change from desirable weight (%)
Undernourished		
Grade 2	< 16	> -30
Grade 1	16 to 18,5	-30 to -15
Thin	18,5 to 19,9	-15 to -10
Normal	20 to 25	-10 to +10
Fat	25,1 to 30	+11 to +32
Obese		
Grade 1	>30,0 to 34,9	+32 to +55
Grade 2	35 to 40	+55 to +77
Grade 3	> 40	> +77

Triceps skin fold (TSF) provides an estimate of fat stores. Using specialized calipers and a tape measure, anthropometry estimates body fat from the thickness of the skin-fold of the posterior mid-upper arm. About 50% of the average person's adipose tissue is beneath the skin. The skin fold, which consists of a double layer of skin and subcutaneous fat, is measured with a special skin fold caliper at several sites. Subscapular, lower thoracic, iliac, and abdominal sites can be used, but the deltoid triceps is used most often because it is easily accessible and usually is free of edema. The TSF varies from 0,5 to 2,5 cm (average, 1,2 cm) in healthy adult males and from 1,2 to 3,4 cm (average, 2,0 cm) in healthy adult females. A patient whose TSF < of the norm is considered to have depleted body fat stores; one whose TSF is 100% above the norm is considered obese.

Mid upper arm muscle circumference (MUAMC) is used to estimate lean body muscle mass. It is derived from the TSF and the midarm circumference, which is measured at the same site as the TSF, with the patient's right arm in a relaxed position. The average midarm circumference (MC) is about 32 ± 5 cm for males and 28 ± 6 cm for females. Mid upper arm muscle circumference is calculated according to formula:

$$\text{MUAMC (cm)} = \text{MC} - (\pi \times \text{TSF})$$

Normal mid upper arm muscle circumference is in average is 25,5 cm in male and 23,0 cm in female. Body muscle mass depletion presents if mid upper arm muscle circumference <15,0 cm in male and <14,0 cm in female.

The use of anthropometry is limited by the requirement for specialized calipers, the experience of the observer, and potential confounding effects of edema or dehydration.

Laboratory and instrumental studies

Tests of the thyroid function

Laboratory testing of thyroid function includes immunassay, radioimmunassay, and radioassay methods of the thyroid hormones.

Thyroid hormones. Thyroxine (*tetraiodothyronine*, T_4) contains four iodine atoms. Deiodination leads to production of the potent hormone, *triiodothyronine* (T_3), or the inactive hormone, reverse T_3 .

Regulation of thyroid hormone synthesis is a classic example of an endocrine feedback loop. Hypothalamic TRH (*thyrotropin-releasing hormone*) stimulates pituitary production of TSH (*thyroid-stimulating hormone*), which, in turn, stimulates thyroid hormone synthesis and secretion. Thyroid hormones feed back negatively to inhibit TRH and TSH production .

Serum T_3 and T_4 are increased in hyperthyroidism and decrease in hypothyroidism.

Serum thyroid-stimulating hormone (TSH). Measuring serum TSH is the best way to determine thyroid dysfunction. Normal test results essentially

rule out hyperthyroidism or hypothyroidism, except in hyperthyroidism secondary to a TSH-secreting pituitary adenoma or pituitary resistance to thyroid hormone and in some patients with central hypothyroidism due to disease in the hypothalamus and/or pituitary gland.

Serum thyrotropin-releasing hormone (TRH) is measured before and after an intravenous injection of 500 mg synthetic TRH. Normally, there is a rapid rise in TSH levels of 5 to 25 mU/ml, reaching a peak in 30 min and returning to normal by 120 min. The rise is exaggerated in primary hypothyroidism. Patients with hypothyroidism secondary to a pituitary deficiency have an absent or impaired TSH response to TRH. In hyperthyroidism, TSH release remains suppressed, even in response to injected TRH, because of the inhibitory effects of the elevated free T₄ and free T₃ on the pituitary thyrotropic cells.

Thyroid autoantibodies. Autoantibodies to thyroid peroxidase and, less commonly, to thyroglobulin are present in almost all patients with autoimmune (Hashimoto's) thyroiditis, and thyroid peroxidase autoantibodies are usually detected in patients with diffuse toxic goiter (Graves' disease).

Thyroglobulin. The thyroid gland is the only source of this iodinated high molecular weight glycoprotein, which is readily detectable in normal patients and is usually elevated in patients with nontoxic and toxic goiter.

Radioactive iodine uptake (absorption). Normal accumulation of ¹³¹I in the thyroid gland during two hours is 7-12 %, and during 24 hours - 20-29 %. In patients with hyperthyroidism, these figures are 9,5-72% and 11-89 %, respectively, while in patients with hypothyroidism 1-2 and 2-5 %, respectively.

Ultrasound is commonly used to visualization of the thyroid gland. It determines the shape, size, location of the thyroid gland, and reveals diffuse and focal (nodules, cysts) abnormalities in the thyroid gland.

According to ultrasound measurements, normal volume of the thyroid gland in adults: male - up to 24 cm³, female - up to 18 sm³.

Scanning with radioiodine or technetium-99 determines the shape, size, and location of the thyroid gland and reveals "warm" and "cold" nodes in the thyroid tissue, and to determine metastases of tumours.

X-ray can reveal retrosternal goitre, deposition of calcium in the thyroid, and displacement and compression of the trachea and esophagus by the thyroid gland.

X-rays are used to detect the enlarged sella turcica in patients with pituitary adenoma. These are indirect evidence of pituitary affection (usually by tumour).

CT and MRT can be used in diagnosis of retrosternal goiter, pituitary adenoma and cerebral abnormalities.

Fine-needle aspiration biopsy can determine histopathologic features of the goiter, thyroiditis, and nodules of the thyroid gland.

Tests of the carbohydrate metabolism

Plasma (serum) glucose. Fasting plasma glucose levels of $>6,7$ mmol/l and plasma glucose levels 2 hours after a 75g oral glucose $>11,1$ mmol/l be considered diagnostic for diabetes mellitus.

Glucose tolerance test. If *hyperglycemia* (increased concentration of the blood plasma glucose) appears to exceed normal in repeated, the diagnosis of diabetes mellitus can be considered proved. After determining blood sugar on a fasting stomach, the patient is given to drink 75,0 g of glucose in 200 ml of water. Blood specimens are then taken in 2 hours. The blood sugar in a healthy individual increases but not over 7,8 mmol/l in 2 hour after intake of 75,0 g of glucose. Impaired glucose tolerance (IGT) is defined as plasma glucose levels between 7,8 and 11,1 with IGT are at substantial risk for developing type 2 of diabetes mellitus and cardiovascular disease in the future, though they may not meet the criteria for diabetes mellitus.

Glucosuria. In the presence of normal renal function, glucosuria occurs only in increased concentration of glucose in the blood (*hyperglycemia*). The so-called renal glucose threshold (glucose concentration in the blood) does not usually exceed 9,9 mmol/l; higher concentration of sugar indicates glycosuria.

Ketonuria. Ketonuria may be observed in severe diabetes mellitus but it can also develop due to carbohydrate deficit (in grave toxicosis, long standing gastrointestinal disorders, alcohol intoxication, starvation, etc.).

Glycosylated hemoglobin (Hb A1c) - is the stable product of nonenzymatic glycosylation (to estimate plasma glucose control during the preceding 1 to 3 months). There is a strong correlation between elevations in the plasma glucose and the HbA1c.

Laboratory tests used to evaluate nutritional status

Complete blood count, including hematocrit, hemoglobin, erythrocyte count, leucocyte, lymphocytes, and leucocyte formula.

Plasma proteins, including albumin, globulin, and transferrin.

Plasma indices of protein catabolism, including plasma nitrogen, residual nitrogen, creatinine, uric acid.

Plasma lipids, including total cholesterol, triglycerides, LDL (low-density lipoprotein) cholesterol, and HDL (high-density lipoprotein) cholesterol.

Plasma electrolytes: Na^+ , K^+ , Cl^- , HCO_3^- , Mg^{2+} , Ca^{2+} , HPO_4^{2-} .

Vitamins and vitamin-dependent substances: vitamin A, vitamin E, $25(\text{OH})\text{D}_3$, vitamin K, vitamin C, folate, and vitamin B_{12} in plasma; thiamine, riboflavin, and N-methylnicotinamide in urine.

Minerals: iron, zinc, copper, and manganese in plasma; sodium, zinc, copper, manganese, and phosphorus in urine.

Urinary nitrogen substances, including urinary nitrogen, urea, creatinine, uric acid, hydroxyproline.

Skin tests for antigens (to assess cell-mediated immunity).

Goiter (goitre, struma)

Definition. Goiter (E01, E04 according to ICD-X) refers to an enlarged thyroid gland or congenital anomaly of its position

Causes. Iodine deficiency remains the most common cause of goiter worldwide. Biosynthetic defects, iodine deficiency, autoimmune disease, and nodular diseases can each lead to goiter, though by different mechanisms. Biosynthetic defects and iodine deficiency are associated with reduced efficiency of thyroid hormone synthesis, leading to increased TSH, which stimulates thyroid growth as a compensatory mechanism to overcome the block in hormone synthesis. Recurrent cycles of stimulation and involution may result in nontoxic nodular goiters. Graves' disease and Hashimoto's thyroiditis are also associated with goiter.

Euthyroid goiter is the most common cause of thyroid enlargement and is more frequently noted at puberty, during pregnancy, and at menopause. Numerous other causes include intrinsic thyroid hormone production defects and, in iodine-deficient countries, the ingestion of food goitrogens, which contain antithyroid substances that inhibit hormone synthesis. Many drugs, including aminosalicylic acid and lithium, and even iodine in large doses, may decrease the synthesis of thyroid hormone.

Classification of goiter

1. *Cause* – endemic, sporadic, congenital, juvenile goiter; pregnancy, autoimmune, thyroiditis, thyroid tumours, etc.

2. *Structure* – diffuse, nodular, multinodular, diffuse-nodular (mixed) goiter.

3. *Thyroid function* – euthyroid (nontoxic, simple), hypothyroid, toxic (hypothyroid) goiter.

4. *Localization* – aberrant, substernal (retrosternal), thoracic, intratracheal, lingual, sublingualis, retroesophageal (-tracheal) goiter.

5. *Degree of the thyroid gland hyperplasia* (according to WHO, 1994):

0 – absence of a goiter;

1 – the invisible goiter, but the goiter is defined as a lateral lobe with a volume greater than the thumb of the individual being examined;

2 – the visible and palpable goiter;

3 – the goiter is visible from a distance.

Hyperthyroidism (thyrotoxicosis)

Definition. Hyperthyroidism (thyrotoxicosis, E05 according to ICD-X) is the clinical syndrome, characterized by hypermetabolism and elevated serum levels of free thyroid hormones.

Etiology and pathogenesis. Hyperthyroidism may be the result of increased synthesis and secretion of thyroid hormones (T_4 and T_3) from the thyroid gland, caused by thyroid gland stimulators in the blood or autonomous thyroid hyperfunction. It can also be caused by excessive release of thyroid hormone from the thyroid gland into the peripheral circulation without increased synthesis of the hormones. This is commonly caused by destructive changes in the thyroid secondary to the various causes of thyroiditis. The last major cause of hyperthyroidism is the conscious or accidental ingestion of excess quantities of thyroid hormone, termed thyrotoxicosis factitia.

Inappropriate TSH secretion is determined in TSH-secreting anterior pituitary tumor or in patients with pituitary resistance to thyroid hormone. Chorionic gonadotropin-secreting tumors and pregnancy are conditions involved elevated serum levels of human chorionic gonadotropin, which is a weak thyroid stimulator.

Hyperthyroidism causes catabolic changes in various tissues and organs and disturbs various types of metabolism: protein-carbohydrate, fat, mineral, water metabolism, etc. Upset function of the sympathico-adrenal system is also a very important factor which accounts for many symptoms of the disease.

Etiological classification of hyperthyroidism

I. Primary hyperthyroidism - due to disorders of the thyroid gland:

- Graves' disease (diffuse toxic goiter),
- toxic solitary or multinodular goiter (Plummer's disease),
- metastatic thyroid cancer,
- drugs: iodine excess (Jod-Basedow phenomenon), amiodarone, lithium;
- subacute thyroiditis,
- other causes of thyroid parenchyma destruction: radiation, infarction of adenoma,
- ingestion of excess thyroid hormone (thyrotoxicosis factitia) or thyroid tissue.

II. Secondary hyperthyroidism – due to disorders of the pituitary gland or other extrathyroid hormone dysfunction:

- TSH-secreting pituitary adenoma,
- chorionic gonadotropin-secreting tumors,
- gestational thyrotoxicosis.

Clinical picture

Most common complaints are increased psychic excitability, non-motivated anxiety, deranged sleep, hyperhidrosis, tremor of the fingers or in the entire body, frequent defecation, wasting, fatigue and muscular weakness.

Inspection of the patient immediately reveals the special features in his behavior: hyperactivity, irritability fussiness, hasty speech; sometimes the patient drops the subject quite unexpectedly and starts discussing another subject.

Despite preserved or even increased appetite, the patient may lose much of his weight (to cachexia). The patient's skin is smooth, warm and moist to the touch. Some patients develop diffuse pigmentation of the skin which however does not colour the mucosa. The pigment is sometimes deposited selectively in the skin of the eyelids. The hair of the head becomes thin and soft. The characteristic signs are heat intolerance and sweating, subfebrile fever, tremor.

During inspection special attention should be paid to the size of the thyroid gland and symmetry of its enlargement. If the thyroid gland is enlarged significantly, the patient's breathing becomes stridorous. Inspection of the patient should be followed by palpation of the thyroid gland (see above).

Ocular signs are noted in patients with hyperthyroidism include stare, lid lag, lid retraction, and mild degrees of conjunctival injection. These eye signs are largely due to excessive adrenergic stimulation and usually remit with successful treatment. A common symptom of thyrotoxicosis is bilateral dilation of the eye slits which gives an expression of astonishment to the patient's face. Another frequent manifestation is *Graefe's sign*: white strip of sclera between the edge of the eyelid and the upper margin of the cornea which appears as the eyeball moves downward. Among other symptoms are *Stellwag's sign* (infrequent blinking), *Kocher's sign* (exposure of the sclera between the lower edge of the upper eyelid and the upper edge of the iris when the eyes are fixed on an upwardly moving object). The eyelids can swell, and weakness of convergence can be observed; the eyeball can move aside when attention is fixed on a slowly approaching object (*Moebius' sign*). This symptom is associated with upset function of the oculomotor muscles.

Circulatory system. Tachycardia is one of the most frequent symptoms of the disease. Pulse rate varies within the range of 90 to 120 and in grave cases to 150 beats per minute. Systolic and minute volumes, the mass of the circulating blood and the rate of the blood flow increase, systolic pressure grows, diastolic pressure falls, and the pulse pressure increases. Auscultation of the heart reveals a snapping first sound and systolic murmur at the apex and over the pulmonary artery which are due to increased blood flow rate and low tone of the papillary muscles. A most frequent and serious complication is atrial fibrillation (tachysystolic form) due to the toxic effect of the thyroid

hormones on the myocardium. Circulatory insufficiency can also develop. ECG studies reveal slightly increased amplitude of all waves (especially of the *T* wave), sinus tachycardia, extrasystole, and atrial fibrillation. X-rays examination reveals a slightly enlarged left ventricle of the heart.

Digestive system. The appetite increases. The increased motor function of the intestine accounts for diarrhea. Hepatic dysfunction can have various effects: from slight disorders (that can only be revealed by functional tests) to cirrhosis.

Nervous system. The clinical symptoms of disorders in the higher nervous activity are excitability, increased reactivity, general motor restlessness, fidgetiness, and fine tremor of the fingers of the stretched arms (*Marie's signs*).

Endocrine system. A pronounced clinical picture of the disease is attended by a marked hypofunction of the sex glands (*amenorrhea*). Gynecomastia and sexual impotence may be in female patients. Hypofunction of the adrenal cortex (*hypoadrenocorticism*) manifests by brown pigmentation of the skin and arterial hypotension. Diabetes mellitus can join the process.

Thyroid storm (thyrotoxic crisis) is characterized by the abrupt onset of more florid symptoms of hyperthyroidism, with some exacerbated symptoms and atypical signs. Included are fever; marked weakness and muscle wasting; extreme restlessness with wide emotional swings; confusion, psychosis, or even coma; and hepatomegaly with mild jaundice. The patient may present with cardiovascular collapse and shock. Thyroid storm results from untreated or inadequately treated hyperthyroidism and may be precipitated by infection, trauma, a surgical procedure, embolism, diabetic acidosis, or toxemia of pregnancy or labor. Thyroid storm is a life-threatening emergency requiring prompt and specific treatment.

Complete blood count reveals hypochromic anemia, leucopenia, and lymphocytosis. *Biochemical tests* of blood can reveal hypocholesterolemia and hyperglycemia.

Basal metabolism increases by 50% and sometimes by 100 %. Tests with ¹³¹I show accelerated and increased absorption of radioactive iodine by the thyroid gland, increased levels of blood plasma thyroid hormones (*T*₄ and *T*₃).

Laboratory criteria of hyperthyroidism are increased plasma levels of *T*₄ and *T*₃, radioactive iodine uptake.

Decreased serum thyroid-stimulating hormone (TSH) is typical in primary hyperthyroidism. Increased serum thyroid-stimulating hormone (TSH) may be in secondary hyperthyroidism (in TSH-secreting pituitary adenoma).

Diffuse toxic goitre (Basedov's, or Grave's disease)

Definition. Diffuse toxic goitre (Basedov's, or Grave's disease; E05.0 according to ICD-X) is the disease of the thyroid gland characterized by hyperthyroidism and one or more of the following: goiter, exophthalmos, and pretibial myxedema.

Graves' disease is the most common cause of hyperthyroidism, is an autoimmune disease, and has a chronic course with remissions and relapses.

Etiology and pathogenesis. The etiology of Graves' disease is an antibody against the thyroid TSH receptor, which results in continuous stimulation of the gland to synthesize and secrete excess quantities of T₄ and T₃. The extrathyroidal manifestations of Graves' disease, ophthalmopathy and dermopathy, are due to immunologically mediated activation of fibroblasts in the extraocular muscles and skin, with accumulation of glycosaminoglycans, leading to the trapping of water and edema.

Psychic trauma, infection (tonsillitis, rheumatism, etc.), dysfunction of other endocrine glands (pituitary) are important for the development of the disease. Familial factors are also important: toxic goitre can often be found in close relatives.

Pathological anatomy. The thyroid gland is enlarged. Microscopy shows intense blood filling in the thyroid gland and reconstruction of follicular epithelium into columnar or polymorphous epithelium. Sometimes the affected thyroid gland differs only insignificantly from the normal one by the character of its epithelium and follicles; the follicles may only have cyst-like dilatations and contain little colloidal substance. Lymphocytes are accumulated, and lymphoid follicles are formed.

Clinical picture. The disease most commonly occurs in women between the ages of 30 and 50; the incidence in men is 5-10 times lower.

The clinical picture includes syndrome of hyperthyroidism (see above) and one or more of the following: goiter, ophthalmopathy (*exophthalmos*), and *pretibial myxedema*. The signs of ophthalmopathy (*exophthalmos*) and dermopathy are specific for Graves' disease.

Infiltrative ophthalmopathy is characterized by orbital pain, lacrimation, irritation, photophobia, increased retro-orbital tissue, exophthalmos, and lymphocytic infiltration of the extraocular muscles which can produce ocular muscle weakness frequently leading to double vision. In grave exophthalmos, keratitis and ulcers of the cornea can also develop, and the patient's power of vision can thus be endangered.

Infiltrative dermopathy, also called *pretibial myxedema* (a confusing term, because myxedema suggests hypothyroidism), is characterized by nonpitting infiltration by proteinaceous ground substance, usually in the pretibial area. It rarely occurs in the absence of Graves' ophthalmopathy (in <5% of Graves' disease). The lesion is often pruritic and erythematous in

its early stages and subsequently becomes brawny. Like ophthalmopathy, infiltrative dermopathy may appear years before or after hyperthyroidism.

Most patients with Graves' disease have circulating antithyroid peroxidase antibodies and fewer have antithyroglobulin antibodies.

The diagnosis is based (1) detailed clinical history and physical examination, (2) increased plasma levels of T₃, T₄, and decreased serum thyroid-stimulating hormone (TSH), (3) antibody against the thyroid TSH receptor.

Course. Clinical features generally worsen without treatment; mortality was 10 to 30% before the introduction of satisfactory therapy. Some patients with mild Graves' disease experience spontaneous relapses and remissions. About 15% of patients who enter remission after treatment with antithyroid drugs develop hypothyroidism 10 to 15 years later as a result of the destructive autoimmune process.

The main complications in thyrotoxicosis are affections of the internal organs, e.g. the heart or the liver, severe degree of opthalmopathy, and also psychoses, hypoadrenocorticism, and thyrotoxic crisis.

Hypothyroidism (myxedema)

Definition. Hypothyroidism (myxedema; E02 - E03 according to ICD-X) is the pathological clinical syndrome associated with thyroid hypofunction and characterized by clinical response to thyroid hormone deficiency.

Etiology and pathogenesis. Factors causing the onset of primary hypothyroidism are hypoplasia or aplasia of the thyroid gland, iodine deficiency in the body, subtotal thyroidectomy, overdosage of ¹³¹I (which is given in hyperthyroidism) or overtreatment with propylthiouracil, methimazole, and iodide; acute (in the past) or chronic thyroiditis. Hyposecretion of T₄ and T₃ upsets normal metabolism and causes changes in tissues, organs, and systems of the body.

Etiological classification

I. Primary hypothyroidism - due to disorders of the thyroid gland:

- Autoimmune hypothyroidism: Hashimoto's thyroiditis, atrophic thyroiditis;
- Iatrogenic: ¹³¹I treatment, thyroidectomy, external irradiation of neck;
- Drugs: iodine excess (including iodine-containing contrast media and amiodarone), lithium, antithyroid drugs, p-aminosalicylic acid, interferon- α ;
- Congenital hypothyroidism: absent or ectopic thyroid gland, dysmorphogenesis, Iodine deficiency;
- Infiltrative disorders: amyloidosis, sarcoidosis, hemochromatosis, scleroderma, cystinosis, Riedel's thyroiditis;

II. Secondary hypothyroidism - due to disorders of the pituitary gland:

Hypopituitarism: tumors, pituitary surgery or irradiation, infiltrative disorders, Sheehan's syndrome, trauma, genetic forms of pituitary hormone deficiencies;

Isolated TSH deficiency or inactivity;

III. Tertiary hypothyroidism - due to disorders of the hypothalamus: Hypothalamic disease: tumors, trauma, infiltrative disorders, idiopathic.

Pathological anatomy. Morphological changes in the thyroid gland are marked hypoplasia, aplasia, or atrophy. Hyperplastic changes occur in the thyroid gland in hypothyroidism caused by disordered synthesis of the hormones associated with the defective enzyme systems.

Clinical picture of hypothyroidism

The symptoms and signs of primary hypothyroidism are generally in striking contrast to those of hyperthyroidism and may be quite subtle and insidious in onset.

The main *complaints* are apathy, lack of interest in the surroundings, difficulty concentrating and poor memory, decreased work capacity, tiredness, weakness, somnolence, feeling cold, weight gain with poor appetite, impaired hearing.

Inspection. The patient's appearance is quite specific: the eye slits are narrow, the face is puffy, the edematous neck, the skin is pallid with a yellowish hue, sometimes with blush on the cheek bones. The skin is rough to the touch, thick, dry, cold, and scaling. The skin is thickened due to accumulation in it of mucopolysaccharides which give the impression of edema (*myxedema*). As distinct from edema, pressure on the skin does not leave depressions. Hair on the head is rare; it falls off from the brows. Movements are slow and speech is monotonous. Hoarse voice is typical.

Central and peripheral nervous systems. The mentioned complaints are associated with changes -in the function of the central nervous system. Psychosis may develop in long-standing hypothyroidism. Disorders in the peripheral nervous system are manifested by strong severe radicular pain in the extremities, paraesthesia, cramps, and shaky gait. Delayed tendon reflex relaxation is typical.

Cardiovascular system. Bradycardia develops; the minute blood volume decreases and the blood flow rate is slow. The heart sounds are dulled. Fluid containing much protein and mucinous substances is often accumulated in the pericardium; it can be accumulated also in the pleural and abdominal cavity. Systolic pressure falls while diastolic pressure remains normal. ECG shows low voltage, especially in *P* and *T* waves. Heart failure develops in rare cases.

Castro-intestinal tract. Hypo- and achlorhydria often develops. The intestinal motor function is decreased, constipation and meteorism develop.

Endocrine system. A pronounced clinical picture of the disease is attended by a disordered function of the sex glands (*menorrhagia, later oligomenorrhoea or amenorrhoea*).

Metabolism. Weight gain is modest and is largely the result of decreased metabolism of food and fluid retention. Protein synthesis is decreased. Blood cholesterol is usually increased. Moderate hypoglycemia is observed. Electrolyte level remains unchanged in most cases. Blood calcium sometimes decreases, and ESR increases. Anemia is often present, usually normocytic-normochromic, but it may be hypochromic owing to menorrhagia, and sometimes macrocytic because of associated pernicious anemia or decreased absorption of folic acid.

Reduction of basal metabolism to 50 per cent and also of the protein-bound iodine is of great diagnostic significance. Absorption of ^{131}I in the thyroid gland is low. Myxedema coma may develop in grave cases.

Myxedema coma is a life-threatening complication of hypothyroidism. Its characteristics include a background of long-standing hypothyroidism, coma with extreme hypothermia (temperatures $34, 0 - 32, 0^\circ \text{C}$, reflexes, seizures, CO_2 retention, and respiratory depression. Severe hypothermia may be missed unless special low-reading thermometers are used. Rapid diagnosis based on clinical judgment, history, and physical examination is imperative because early death is likely. Precipitating factors include exposure to cold, illness, infection, trauma, and drugs that suppress the central nervous system..

Laboratory criteria of diagnosis

Primary hypothyroidism is diagnosed by (1) increased serum thyroid-stimulating hormone (TSH). (2) decreased plasma levels of T_3 , T_4 , radioactive iodine uptake, (3) normal serum thyroid-stimulating hormone releasing factor (TSH -RF).

Secondary hypothyroidism is diagnosed by (1) increased serum thyroid-stimulating hormone releasing factor (TSH -RF); (2) decreased plasma levels of T_3 , T_4 , serum thyrotropin-releasing hormone (TRH), radioactive iodine uptake;

Tertiary hypothyroidism is diagnosed by decreased plasma levels of T_3 , T_4 , serum thyroid-stimulating hormone (TSH), serum thyrotropin-releasing hormone (TRH), radioactive iodine uptake.

Diabetes mellitus (DM)

Definition: Diabetes mellitus (E10-E14 according to ICD-X) is a syndrome of metabolic disorders characterized by hyperglycemia resulting from absolute or relative impairment in insulin secretion and/or insulin action.

Etiology and pathogenesis. Organic or functional affection of β - cells of the pancreas islets is the main factor in the pathogenesis of diabetes mellitus. This affection accounts for insufficient synthesis of insulin. Primary

insufficiency of these cells can arise after infection, psychic trauma, removal of the pancreas, destruction by a tumour, sclerosis of the pancreatic vessels, in pancreatitis, regular overeating, or insufficient intake of substances required for the normal function of the insular apparatus.

Familial predisposition (genetically determined functional insufficiency of beta cells) is a background against which the diabetogenic effect of the named factors is realized. About 80% of patients with *type I DM* (*insulin-dependent DM [IDDM]*, or *juvenile-onset diabetes*) have specific HLA phenotypes associated with detectable serum islet cell cytoplasmic antibodies and islet cell surface antibodies (antibodies to glutamic acid decarboxylase and to insulin are found in a similar proportion of cases). In these patients, type I DM results from a genetically susceptible, immune-mediated, selective destruction of > 90% of their insulin-secreting β -cells. The clinical onset of type I DM may occur in some patient's years after the insidious onset of the underlying autoimmune process.

Type II DM (non-insulin-dependent DM [NIDDM]) has a strong genetic component. Although the major genes that predispose to this disorder have yet to be identified, it is clear that the disease is polygenic and multifactor. The concordance of type II DM in identical twins is between 70 and 90%. Individuals with a parent with type II DM have an increased risk of diabetes; if both parents have type II DM, the risk in offspring may reach 40%. Type II DM is a heterogeneous group of disorders in which hyperglycemia results from both an impaired insulin secretory response to glucose and decreased insulin effectiveness in stimulating glucose uptake by skeletal muscle and in restraining hepatic glucose production (insulin resistance). The resulting hyperinsulinemia may lead to other common conditions, such as obesity (abdominal), hypertension, hyperlipidemia, and coronary artery disease (*syndrome of insulin resistance*).

Secondary insufficiency of β -cells can be due to endocrine dysfunction: pituitary, adrenal and thyroid hyper function. Somatotropic and thyrotropic hormones, corticotropin, glucocorticoids and glucagon have diabetogenic properties and are called *contra-insulin hormones*. The pathogenesis of diabetes mellitus also depends on the presence of excess insulin inhibitor, i.e. enzyme insulinase (which is produced in the liver and is activated in the anterior pituitary hyperfunction) and also insulin antagonists and antibodies to insulin contained in the blood of patients.

Etiological classification of Diabetes Mellitus (DM) (adapted from American Diabetes Association, 2000):

- I. Type 1 diabetes (β -cell destruction, usually leading to absolute insulin deficiency):
 - A. Immune-mediated;
 - B. Idiopathic;

II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance);

III. Other specific types of diabetes:

A. Genetic defects of b-cell function characterized by mutations,

B. Genetic defects in insulin action;

C. Diseases of the exocrine pancreas (pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy);

D. Endocrinopathies (acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma);

E. Drug- or chemical-induced (nicotinic acid, glucocorticoids, thyroid hormone, b-adrenergic agonists, thiazides, α -interferon, protease inhibitors, β -blockers);

F. Infections (congenital rubella, cytomegalovirus, coxsackie);

G. Uncommon forms of immune-mediated diabetes (anti-insulin receptor antibodies);

H. Other genetic syndromes sometimes associated with diabetes (Down's syndrome, Klinefelter's syndrome, myotonic dystrophy, porphyria).

IV. Gestational diabetes mellitus (GDM).

Risk classes of DM -

Impaired glucose tolerance (previous or potential – obesity, familial predisposition, others).

Metabolic disorders in DM

In patients with DM absolute or relative impairment of insulin is caused the set of metabolic disorders:

- hyperglycemia and hyperglucosuria,
- inhibited synthesis of protein and neoglucogenesis;
- disorders of fat metabolism;
- ketoacidosis - accumulation in the blood of acetone bodies and ketones (β -hydroxybutyric acid, acetoacetic acid, acetone);
- polyuria, loss of sodium and partially of potassium;
- vascular changes (retinopathy, nephropathy) and atherosclerosis;
- neuropathy.

Upset protein metabolism is manifested by formation of trophic ulcers and slow healing of wounds. Disorders of fat metabolism clinically manifest by wasting of the patient, fat infiltration of the liver, and in severe cases ketoacidosis develops. Diabetic coma, a fatal complication of diabetes mellitus, can develop in this disorder of fat metabolism.

Polyuria, loss of sodium and partially of potassium are signs of upset water-salt metabolism in diabetes mellitus. The pathogenesis of polyuria is

associated with glycosuria which elevates osmotic pressure in the tubules to decrease reabsorption of water. Reabsorption of sodium in the kidneys is also decreased.

A long-standing and incompletely compensated diabetes mellitus results in vascular changes (retinopathy, nephropathy, or Kimmelstiel-Wilson syndrome) and atherosclerosis. Pronounced fluctuations in the blood sugar cause spastic atonia of the vessels, which, in turn, affects the structure of their walls, accelerates the destruction of elastic fibres, and promotes sclerosis and calcinosis. Insulin deficit inhibits phosphorylation of vitamin B₆ which often causes neuropathic complications of diabetes mellitus.

Clinical picture of DM

Clinical picture of diabetes mellitus includes (1) *syndrome of hyperglycemia* (polydipsia, increased appetite, polyuria, hyperglycemia, glycosuria, wasting, weakness, and skin itching), (2) acute complications (diabetic ketoacidosis, diabetic comas – hyperglycemic ketoacidosis coma, hypoglycemic coma), (3) late complications (retinopathy, diabetic nephropathy, polyneuropathy, autonomic neuropathy, diabetic angiopathy, foot ulcers and gangrene, infections).

Complaints. The symptoms of diabetes mellitus are excessive thirst (polydipsia), increased appetite, polyuria, wasting, weakness, decreased work capacity, and skin itching, especially in the perinea region.

Inspection of the patient reveals *rubeosis* (reddening of the face, the cheeks, supraciliary arches, and the chin due to dilated cutaneous vessels) and *xanthosis* (yellowish decolouration of the palms and soles associated with upset conversion of carotin into vitamin A in the liver and accumulation of carotin in the skin). The patient's skin is dry, rough, easily scaling, covered with traces of scratching (due to skin itching). Furuncles, exematous and ulcerous lesions can also be found. At points of insulin injection, there are zones where fat is absent (*insulin lipodystrophy*).

Muscles and bones. Muscular atrophy and osteoporosis are observed in decompensated diabetes mellitus.

Circulatory system. Atherosclerosis of various arteries with the corresponding clinical symptoms, angina pectoris, gangrene of the feet, etc. is not infrequent.

Respiratory organs. Diabetes mellitus often concurs with bronchitis, pneumonia, and pulmonary tuberculosis.

Digestive system. Mouth mucosa and the tongue are dry. Parodontosis and pyorrhea frequently occur. Appetite is very good and sometimes voracious (*bulimia*). Study of the gastric juice reveals the presence of hypo- or achlorhydria. Fat dystrophy of the liver and its cirrhosis develop in some patients with long-standing decompensated diabetes mellitus.

Diabetic nephropathy. Arteriolosclerosis of the kidneys and intracapillary glomerulosclerosis (Kimmelstiel-Wilson syndrome) may occur.

They are manifested by hypertension, retinopathy, and albuminuria. Pyelonephritis is not infrequent. Diabetic nephropathy is usually asymptomatic until end-stage renal disease develops, but it can cause the nephrotic syndrome.

Retinopathy. Retinopathy in diabetes mellitus is manifested by the presence of exudate in the retina, hemorrhages, and pigment abnormality-in the yellow spot. Retinopathy can progress to macular edema or proliferative retinopathy with retinal detachment or hemorrhage, which can cause blindness. Cataracts often occur.

Changes in the nervous system. Polyneuropathy is frequent. Headache, deranged sleep, and decreased work capacity are the symptoms of affection of the central nervous system. Autonomic neuropathy occurs primarily in diabetics with polyneuropathy and can cause postural hypotension, disordered sweating, impaired bladder function, delayed gastric emptying, esophageal dysfunction, constipation or diarrhea, and nocturnal diarrhea.

Laboratory diagnosis

The main laboratory methods used to diagnose diabetes mellitus and assess its gravity are based on determination of *glycemia* (concentration of glucosa in the blood) on a fasting stomach and glucose tolerance tests, and determination of *glucosuria and ketonuria* (glucose and ketone bodies in the urine).

An oral glucose tolerance test (OGTT) may be helpful in diagnosing type II diabetes mellitus in patients whose fasting glucose is higher 6,7 mmol/l and in those with a clinical condition that might be related to undiagnosed diabetes melitus (e.g., polyneuropathy, retinopathy). Patients with clear signs of diabetes mellitus do not require glucose tolerance testing. The results of glucose tolerance test depend on various factors: fasting, pathological processes in the liver parenchyma, injuries, infections, acute disorders in cerebral circulation, and strong emotions.

Laboratory criteria of DM are fasting hyperglycemia $>6,7$ mmol/l or 2 hours after a 75-g oral glucose $>11,1$ mmol/l.

Criteria of impaired glucose tolerance (IGT) are 2 hours after a 75-g oral glucose $>7,8$ and $< 11,1$ mmol/l. Individuals with IGT are at substantial risk for developing type 2 DM and cardiovascular disease in the future, though they may not meet the criteria for diabetes mellitus.

Glucosuria is an indirect sign of hyperglycemia. The presence of glucose in the urine in the absence of hyperglycemia cannot be used as an evidence of diabetes mellitus either, since glucosuria can be due to decreased sugar permeability of the kidneys (renal threshold). In the presence of kidney pathology (nephrosclerosis), glucosuria may be absent even when the blood sugar is abnormally high.

Determination of acetone and acetoacetic acid (ketone bodies) is obligatory. It should however be remembered that *ketonuria (acetonuria)* can occur also in healthy individuals during fasting and in toxemia of pregnancy.

Glycosylated hemoglobin (Hb A1c) is used to estimate plasma glucose control during the preceding 1 to 3 months. The normal Hb A1c level is about 6%; in poorly controlled diabetics, the level ranges from 9 to 12%. Hb A1c is not a specific test for diagnosing diabetes; however, elevated Hb A1c often indicates existing diabetes.

Diagnosis of DM is based on (1) fasting glycemia $>6,7$ mmol/l or 2 hours after a 75-g oral glucose $>11,1$ mmol/l; (2) a random plasma glucose concentration $>11,1$ mmol/l accompanied by classic symptoms of diabetes mellitus (polyuria, polydipsia, weight loss).

Course. The onset of the disease may be acute or gradual. The first signs of diabetes mellitus may be persistent itching and furunculosis. The following three stages are distinguished in its course: prediabetes, masked diabetes, and true diabetes mellitus. Prediabetes cannot be diagnosed by the existing methods. This can be defined as hereditary predisposition, obesity, and cases where newborns (both dead and alive) weigh over 4,5 kg. Masked diabetes mellitus can be detected by the glucose tolerance test. True diabetes mellitus is diagnosed by clinical and laboratory findings.

Patients without adequate glycemic control and treatment can die due to complications (diabetic comas, serious infections, gangrene of foot, kidney insufficiency, disorders of blood circulation).

Diabetic (hyperglycemic ketoacidosis) coma

Definition: This is a coma because of metabolic acidosis from the accumulation of ketone bodies due to severely depressed insulin levels.

This is a grave and sometimes fatal complication of diabetes mellitus.

Causes. Diabetic ketoacidosis is seen primarily in individuals with type 1 DM. It occurs if diabetes mellitus is treated improperly or if the disease is complicated by acute infections, injuries, or nervous stress. The proximate causes are (1) inadequate insulin administration, lapse in insulin treatment; (2) infection (pneumonia/urinary tract infection/gastroenteritis/sepsis); (3) infarction (cerebral, coronary, mesenteric, peripheral); (4) drugs (cocaine, glucocorticosteroids) that makes usual insulin treatment inadequate.

Pathogenesis. Diabetic ketoacidosis results from grossly deficient insulin availability, causing a transition from glucose to lipid oxidation and metabolism. The abnormal ketogenesis results from the loss of insulin's normal modulating effect on free fatty acid (FFA) released from adipose tissue and on hepatic FFA oxidation and ketogenesis.

In diabetic ketoacidosis, the marked hyperglycemia causes osmotic diuresis; excessive urinary losses of water, Na, and K; and volume contraction with acidosis resulting from increases in hepatic ketone body synthesis and release. The major ketone bodies, acetoacetic acid and β -

hydroxybutyric acid, are strong organic acids; the hyperketonemia induces a metabolic acidosis and respiratory compensation, and the marked increases in urinary excretion of acetoacetic acid and β -hydroxybutyric acid obligate additional losses of Na and K. Acetone derived from the spontaneous decarboxylation of acetoacetic acid accumulates in plasma and is slowly disposed of by respiration; it is a central nervous system anesthetic. The pathogenesis of diabetic coma is associated with acidosis mainly on account of accumulation of ketone bodies and their toxic effect on the central nervous system.

Clinical picture. Toxic symptoms develop gradually in most cases and the onset of coma is preceded by its precursors (*precomatose state*). Excessive thirst develops along with polyuria, epigastric pain, dyspepsia (nausea, vomiting), headache, and loss of appetite. The patient's breathe smells of acetone (odour of rotten apples).

Precomatose state is followed by the first phase of coma which is characterized (in addition to the mentioned symptoms which are gradually intensified) by a strong nervous excitement: insomnia, restlessness, clonic convulsions, and Kussmaul's respiration. The excitement is followed by a marked inhibition, the second phase of diabetic coma: the patient develops dizziness, shows no interest in surroundings, and finally loses consciousness.

When in a deep coma, the patient is motionless, the face may be pink or pallid, the skin dry, the muscle tone and tendon reflexes are decreased, pathological reflexes sometimes develop, the eyeball tone decreases, the eyeballs are soft to the touch, the pupils are narrow. Signs of dehydration are usually present. Kussmaul's respiration is heard at a considerable distance. The pulse is low and fast; the arterial pressure falls. Hypothermia, oliguria, and sometimes anuria develop.

But gradual development of diabetic coma and distinct stages of this process are not always observed, and the terminal phase of diabetic coma may come suddenly, without precursors.

Laboratory findings. Laboratory data support the diagnosis: (1) hyperglycemia from 22,0 to 55,0 mmol/l; (2) ketonuria and glucosuria.

The number of ketone bodies increases along with increased content of non-protein (residual) nitrogen; the chloride content decreases. Leucocytosis in coma can be as high as $50,0 \times 10^9/l$ of blood with a neutrophilic shift to the left. Ketone bodies and considerable amounts of sugar are found in the urine.

Hypoglycemic coma

Definition: This is a coma due to abnormally low plasma glucose level that leads to symptoms of sympathetic nervous system stimulation and of central nervous system dysfunction.

Causes. Hypoglycemia occurs most commonly as a result of treating patients with diabetes mellitus: (1) overdosage of insulin or other

hypoglycemic medications (sulfonylureas), alcohol; more rarely - salicylates, propranolol, quinine (2) diet lacks carbohydrates in DM patients.

Endogenous hypoglycemia may be in a number of other disorders, including islet cell adenoma or carcinoma (insulinoma), large mesenchymal tumors, end-stage organ (liver, kidney) failure, alcoholism, endocrine deficiencies, postprandial reactive hypoglycemic conditions, and inherited metabolic disorders.

Pathogenesis. The brain depends on plasma glucose as its major metabolic fuel under most conditions. Centers within the central nervous system (CNS) monitor plasma glucose levels and react to a deficiency of glucosa by rapidly increasing adrenergic nervous system activity, resulting in epinephrine and glucagon release. If profound CNS glucose deficiency develops, higher brain center activity decreases to reduce brain energy requirements. If the hypoglycemia in unconscious patients is not treated rapidly, seizures and irreversible neurologic deficits or death may follow.

Clinical picture. Hypoglycaemic coma arises in patients treated with insulin for diabetes mellitus, if their diet lacks carbohydrates or as a result of insulin over-dosage. Hypoglycemic coma develops rapidly, sometimes within a few minutes. Coma is preceded by a sudden feeling of hunger, weakness, sweating, tremor in the entire body, psychic and motor excitement. Precomatose state characteristics are tachycardia, palpitations, nausea, vomiting (unusual), visual disturbances, mental dullness, amnesia, tingling (paresthesia) of the mouth and fingers (paresthesia). Precomatose state lasts typically few minutes.

Comatose state is characterized by pallor and moist skin, increased muscular tone and tendon reflexes, and convulsions; the pupils are dilated, the eyeballs remain firm. The blood glucosa is low; glucosa and acetone are absent from the urine. The patient quickly responds to treatment: after an intravenous infusion of a hypertonic solution of glucose, the patient quickly regains consciousness.

Laboratory data support the diagnosis are hypoglycemia $<2,5-2,8$ mmol/l and absence of glucose in urine.

Treatment of hypoglycemia

Oral ingestion of glucose or saccharose is usually adequate to relieve acute adrenergic symptoms and early CNS symptoms. Patients treated with insulin or a sulfonylurea are advised to drink a glass of fruit juice or water with 3 table spoons of table sugar added and to teach family members to give such treatment if they suddenly exhibit confusion or inappropriate behavior. A glass of milk also works well. Insulin-treated patients are advised to carry sugar lumps, candy, or glucose tablets at all times. In patients treated with a sulfonylurea, especially the long-acting ones such as chlorpropamide, hypoglycemia may recur over many hours or even days if oral intake is

inadequate. When oral glucose is not available or adequate, IV (intravenous) glucose or glucagon may be used (see below).

IV injection of 50 or 100 ml of 40-50% glucose followed by a continuous infusion of 10% glucose (20% or 30% glucose may be needed) may be needed for severe symptoms or when a patient cannot take oral glucose. Blood glucose levels are monitored within a few minutes after the start of the 10% glucose infusion and frequently thereafter with a glucose analyzer, and the rate of infusion is adjusted to maintain a normal plasma glucose level.

Obesity

Definition. Obesity (adiposis; E65-E66 according to ICD-X) is excessive deposition of fat in subcutaneous and other tissues, which is associated with metabolic disorders.

The prevalence of obesity in the USA and Europe is high and rising higher. In the past decade, the overall prevalence rose from 25 to 33%, an increase of 1/3. Prevalence is 35% among women and 31% among men, and it more than doubles between the ages of 20 and 55.

Etiology. Overeating is the main etiological factor. Hypodynamia, hereditary and constitutional predisposition are also important. Pregnancy lactation, and menopause are among other factors responsible for obesity in women.

Obesity can be regarded as an independent disease in cases with an excessive caloric intake (alimentary obesity). Obesity can also be a symptom of endocrine diseases (thyroid or pituitary dysfunction) or diseases of the central nervous system (infection, injury, tumour).

Weight gain can be produced by medications such as steroid hormones and psychoactive drugs - antidepressants (tricyclics, tetracyclics, monoamine oxidase inhibitors), benzodiazepines, lithium, and antipsychotic drugs.

Psychologic factors may be important determinants of obesity in deviant eating patterns. *Binge eating disorder* is characterized by the consumption of large amounts of food in a short time with a subjective sense of loss of control during the binge and distress after. *The night-eating syndrome* consists of morning anorexia, evening hyperphagia, and insomnia. It occurs in about 10% of persons seeking treatment for obesity.

Pathogenesis. The main pathogenic mechanism of obesity is dysfunction of the central nervous mechanisms, i.e. the cerebral cortex and hypothalamic centres (the ventromedial and ventrolateral nuclei of the hypothalamus) that regulate fat and carbohydrate metabolism. The result of these disorders is upset equilibrium between the caloric intake and the amount of energy spent by a living body.

An increase in fat cells and adipose tissue mass during infancy and childhood—and for some severely obese persons, even during adulthood—

predisposes to obesity. This increase can result in five times as many fat cells in obese persons as in persons of normal weight. Dieting reduces only fat cell size, not fat cell number.

The vast majority of obese people have increased leptin levels but do not have mutations of either leptin or its receptor. Leptin is a hormone synthesized by fatty tissue and regulates feeling of satiety. They appear, therefore, to have a form of functional "leptin resistance." Data suggesting that some individuals produce less leptin per unit fat mass than others or have a form of relative leptin deficiency that predisposes to obesity are at present contradictory and unsettled.

The role of the endocrine factors and also changes in the local tissue metabolism with increased deposition of fat should also be considered in various types of obesity. Changes in insulin content in obese individuals are of special practical interest: at the early stage of obesity, these patients have hyperinsulinism, which is followed by hypoinsulinemia on account of exhaustion of the insular apparatus in long-standing obesity. Hypoinsulinemia impairs tolerance to carbohydrates which occurs in most obese persons, and often causes diabetes mellitus. Obesity can thus be regarded as prediabetes.

Pathological anatomy. Fat deposition is more pronounced in subcutaneous tissue, omentum, around the kidneys, and in the mediastinum. In the epicardium, fat is mainly deposited at the apex of the heart and around its right chambers. Fat can grow into the depth of the heart to separate muscle fibres, which thus grow thinner. The liver is enlarged at the expense of fatty (adipose) infiltration, which also affects the pancreas. Fat loosens the pancreatic parenchyma and causes atrophy of pancreatic islets.

Classification of obesity.

I. Causes

1. Primary obesity - alimentary obesity;
2. Secondary obesity:
 - (a) cerebral (hypothalamic) obesity - due to affection of the central nervous system,
 - (b) endocrine obesity- dysfunction of the pituitary, thyroid and adrenal glands, or the ovaries

II. Body mass index: I degree – 30-34,9, II – 35-40, III >40 kg/m² .

III. Distribution of fat tissue:

- diffuse obesity, android (male) obesity (waist/hip $>1,0$), gynoid (female) obesity (waist/hip $<0,8$), local obesity (lipomatosis).

Clinical picture

The clinical picture of obesity is quite varied, depending on the degree of the condition, length of a pathological process, and the presence of changes in other organs and systems.

Complaints. Individuals with the first and second degree of obesity do not complain of their disease. They attend the doctor only for aesthetic consideration. Patients with obesity of the third and fourth degree complain of dyspnea (which develops first under considerable load and later during light exercise), fatigue, impaired memory, hyperhidrosis, flaccidity, constipation, and menstrual disorders.

General inspection of the patient alone is enough to establish the diagnosis of obesity. The colour of the skin may be normal; the skin can also be pallid or hyperemic. White, red, or violet stripes (*striae*) can be seen on the skin of the abdomen and the thighs. Sometimes the skin sags together with the subcutaneous fat to resemble an apron. Because of hyperhidrosis, obese patients often have skin diseases, such as eczema, pyoderma, and furunculosis (pyoderma). Edema of inferior extremities may be.

The triceps skin fold (TSF) is >2,5 cm in males and >3,5 cm in females. There is a type of obesity in which fat is deposited in tender tumour-like growths (lipomatosis).

Some special distributions of body fat are important in the diagnosis of certain disorders, for example, the «buffalo hump» of hyperadrenocorticism and the peculiar accumulation of fluid in hypothyroidism.

Recognizing the significance of body fat distribution, particularly of the visceral fat depot, has measurably advanced the understanding of obesity. Clinically, this distribution is assessed by the waist/hip ratio, with high-risk upper body obesity defined as a ratio of > 1,0 for men and > 0,8 for women. Risk, however, is directly proportional to the size of the ratio, the greater mortality and morbidity of men is a function of their greater waist/hip ratio.

Joints and bones. Obesity may lead to orthopedic disturbances of weight-bearing and non-weight-bearing joints and bones - osteoporosis, osteoarthritis, and osteochondrosis. Obesity is associated with increased risk of gout and podagric arthritis.

Respiratory system. The diaphragm is high and for this reason obese patients often develop bronchitis and pneumonia. Prominent among obese patients is *sleep apnea*, a seriously underdiagnosed disorder, characterized by moments during sleep when breathing ceases, as often as hundreds of times a night. In the *obesity-hypoventilation syndrome (Pickwickian syndrome)*, impairment of breathing leads to hypercapnia, a reduced effect of CO₂ in stimulating respiration, hypoxia, *cor pulmonale*, and a risk of premature death.

Circulatory system. Long-standing and pronounced obesity provokes changes in the cardiovascular system. Arterial hypertension, coronary and cerebral atherosclerosis are frequent. These pathological changes and also mechanical factors (accumulation of fat in the mediastinum, decreased respiratory excursions, high diaphragm) interfere with normal work of the

heart and cause myocardiodystrophy, left ventricle hypertrophy, and chronic circulatory insufficiency.

Digestive system. Patients with obesity have increased appetite. They develop tendency to constipation and meteorism. Fat liver and steatohepatitis, cholelithiasis, cholecystitis, cholangitis, and acute pancreatitis occur in obese patients more frequently than in normosthenic individuals.

Kidney. Patients with obesity have increased risk of nephrolithiasis and urinary tract infections.

Endocrine system. Hyperinsulinemia and insulin resistance are pervasive features of obesity, increasing with weight gain and diminishing with weight loss. Obesity is a major risk factor for diabetes, and as many as 80% of patients with type 2 diabetes mellitus are obese.

Reproductive system. Disorders that affect the reproductive axis are associated with obesity in both men and women. Male hypogonadism and gynecomastia are associated with increased adipose tissue, often distributed in a pattern more typical of females. Obesity is associated with menstrual abnormalities and polycystic ovarian syndrome in women.

Cancer. Obesity in males is associated with higher mortality from cancer of the colon, rectum, and prostate; obesity in females is associated with higher mortality from cancer of the gallbladder, bile ducts, breasts, endometrium, cervix, and ovaries.

Laboratory findings include impaired glucose tolerance test, hyperglycemia, hyperurcemia, increase of serum lipids (cholesterol, fat acids, pre- β - and β - lipoproteins).

Diagnosis of obesity is based on BMI > 30 kg/m². For practical purposes, the eyeball test is sufficient: If a person looks fat, the person is fat.

Cachexia

Definition. Cachexia (emaciation, protein-energy malnutrition, PEM, protein-calorie malnutrition, PCM; E40-E46 according to ICD-X) is a deficiency syndrome caused by the inadequate intake of macronutrients (proteins, lipids, carbohydrates).

Etiology of protein-energy malnutrition

I. Starvation:

A. Decreased diet intake - social and economic (poverty, chronic alcoholism), psychiatric (anorexia nervosa, severe depression), neurodegenerative dementias of aging, anorexia associated with AIDS, disseminated cancer, renal failure; abdominal pain triggered by food intake (pancreatitis, intestinal ischemia)

B. Decreased assimilation of the diet - impaired transit of diet (benign or malignant esophageal, gastric, or intestinal obstruction); impaired digestion of diet (pancreatic insufficiency, stomach surgery); intestinal malabsorption of dietary constituents, e.g., celiac disease.

II. Stress (hypermetabolism with gluconeogenesis):

- A. Acute trauma, e.g., accident, burns, major surgery;
- B. Acute sepsis;
- C. Acute or chronic inflammation: pancreatitis, collagen diseases, chronic infectious disease (tuberculosis, AIDS opportunistic infections);
- D. Endocrine: hyperthyroidism, I type DM.

III. Mixed mechanisms:

- A. Futile metabolic cycles and anorexia (AIDS, disseminated cancer);
- B. Increased energy demands, e.g., chronic obstructive pulmonary disease;
- C. Abnormal metabolism and decreased biliary digestion (chronic liver disease);
- D. Protein-losing enteropathy and chronic inflammation, e.g., Crohn's disease, ulcerative colitis.

Risk of cachexia presents if:

(1) unintentional loss of >10% of usual body weight in the preceding 3 months,

(2) body weight <90% of ideal for height according to table data, or body mass index (BMI) <18,5;

(3) alcohol intake of > 185,0 g of ethanol per day;

(3) no oral intake for > 10 days;

(4) protracted nutrient losses due to malabsorption syndromes, short-bowel syndromes, fistulas, diabetes, renal dialysis, draining abscesses, or wounds;

(5) increased metabolic needs due to extensive burns, infection, trauma, protracted fever, or hyperthyroidism;

(6) intake of drugs with antinutrient or catabolic properties, e.g., appetite depressants, corticosteroids, immunosuppressants, antitumor drugs.

Pathophysiology. The *dry form*, *marasmus*, results from near starvation with deficiency of protein and nonprotein nutrients. The marasmic patient consumes very little food and is very thin from loss of muscle and body fat.

The *wet form* is called *kwashiorkor*. The protein deficiency is usually more marked than the energy deficiency, and edema results.

If unchecked by appropriate therapy, the process of progressive malnutrition in such patients is associated with decreased cardiac and renal function, fluid retention, intestinal mucosal atrophy, loss of intracellular minerals (zinc, magnesium, and phosphorus), diminished cell-mediated immune functions, increased risk of infection, and eventual death.

Pathological anatomy. The body mobilizes its own tissues as a source of energy, which results in the destruction of visceral organs and muscle and in extreme shrinkage of adipose tissue. Loss of fat and muscle results in increased extracellular water, low tissue tension, and inelastic skin. Loss of organ weight is greatest in the liver and intestine, moderate in the heart and kidneys, and least in the nervous system.

Classification of malnutrition

1. Levels of severity

- (1) body weight <90% of ideal for height, or body mass index (BMI) <18,5 represents risk of malnutrition,
- (2) body weight <85% of ideal constitutes *malnutrition*,
- (3) body weight <70% of ideal represents *severe malnutrition*, and
- (4) body weight <60% of ideal is usually incompatible with survival.

2. Clinical-pathophysiological variants:

- Marasmus (dry form);
- Kwashiorkor (wet form),
- Combined form (marasmic kwashiorkor).

Clinical picture

The patient complaints and history

The patient feels weak. Work capacity is diminished because of muscle destruction and, eventually, is worsened by cardiorespiratory failure. The clinical nutritional history should include diet and weight change, socioeconomic conditions, and symptoms unique to each clinical setting.

Social and economic conditions that may lead to poverty include inadequate income, homelessness, and activities that restrict real income and promote involuntary diet restriction, such as drug abuse or chronic alcoholism.

Anorexia, or loss of appetite, is a feature of psychiatric disorders, such as anorexia nervosa and neurodegenerative dementia in the elderly. Many self-selected, inadequate diets may promote malnutrition. During binge drinking, chronic alcoholics typically substitute more than half their daily food calories with excessive amounts of ethanol, the metabolism of which consumes energy and promotes unbalanced metabolism of fat and carbohydrates. Strict vegetarianism may lead to selective deficiencies of specific nutrients such as vitamin B₁₂ and iron.

Digestive diseases are major causes of malnutrition, both in the inpatient and outpatient settings. The malnourished patient with digestive disease may present with symptoms of: (1) dysphagia or recurrent vomiting due to benign or malignant esophageal or gastrointestinal obstruction; (2) chronic diarrhea due to abnormal pancreatic or biliary digestion, intestinal mucosal malabsorption, or protein-losing enteropathy; or (3) recurrent abdominal pain exacerbated by eating, as occurs in patients with chronic pancreatitis, inflammatory bowel disease, or intestinal ischemia.

Protein-energy malnutrition (PEM) is prevalent in patients with multiple chronic illnesses that are associated with anorexia, recurrent stress, and abnormal nutrient metabolism. PEM is comorbid with chronic recurrent pancreatitis, renal failure, chronic liver disease, chronic obstructive pulmonary disease, disseminated cancer, and chronic infections such as AIDS and tuberculosis.

Physical examination

Anthropometry. Measurements of unclothed weight and height are essential for establishing the severity of malnutrition (*see above*) in all patients but may be confounded by the effects of fluid overload as a result of edema and ascites. These data for weight (in kg) and height (in cm) are compared with normal values provided in tables for men and women. These values can be adjusted by $\pm 10\%$ to account for variability in body build. Body weight $< 85\%$ of ideal constitutes malnutrition. Values of BMI $< 18,5 \text{ kg/m}^2$ – undernourished, values $< 12 \text{ kg/m}^2$ are incompatible with life.

Using specialized calipers and a tape measure, anthropometry estimates body fat from the thickness of the skin-fold of the posterior mid-upper arm (TSF, triceps skin fold). The TSF $< 0,5 \text{ cm}$ in adult males and $< 1,2 \text{ cm}$ in adult females are characteristic of the protein-energy malnutrition. Body muscle mass depletion in malnutrition presents if mid upper arm muscle circumference $< 15,0 \text{ cm}$ in male and $< 14,0 \text{ cm}$ in female.

Inspection. Emaciation is most obvious in areas where prominent fat depots normally exist. Muscle mass shrinks and bones protrude. The skin becomes thin, dry, inelastic, pale, and cold. The hair is dry and sparse and falls out easily.

A variety of nutritional deficiencies can be identified by examination of the patient's general appearance, including skin, hair, nails, mucus membranes, and neurologic system. Initially, a pinch of the posterior upper arm may reveal loss of subcutaneous fat in the malnourished patient. Hollowing of the temporal muscles, wasting of upper arms and thigh muscles, easily plucked hair, and peripheral edema are all consistent with protein deficiency. Examination of the skin may reveal the papular keratitis ("goose bump rash") of vitamin A deficiency, perifollicular hemorrhages of vitamin C deficiency, ecchymoses of vitamin K deficiency, the "flaky paint" lower extremity rash of zinc deficiency, hyperpigmentation of skin-exposed areas from niacin (vitamin H) deficiency, seborrhea of essential fatty acid deficiency, spooning of nails in iron deficiency, and transverse nail pigmentation in protein deficiency. The eye examination yields conjunctival pallor of anemia, pericorneal and corneal opacities of severe vitamin A deficiency ("Bitot spots"), and nystagmus and isolated ocular muscle paresis of thiamine (vitamin B₁) deficiency. The oral examination may reveal angular stomatitis and cheilosis of either riboflavin or niacin deficiency; glossitis with smooth and red tongue of riboflavin, niacin, vitamin B₁₂, or pyridoxine (vitamin B₆) deficiency; and hypertrophied bleeding gums of vitamin C deficiency.

Most body systems are affected. Achlorhydria and diarrhea are common. Heart size and cardiac output are reduced; the pulse slows and blood pressure falls. Respiratory rate and vital capacity decrease. The main endocrine disturbance is gonadal atrophy with loss of libido in men and

women and amenorrhea in women. The patient feels weak. Work capacity is diminished because of muscle destruction and, eventually, is worsened by cardiorespiratory failure. Reduction in body temperature frequently contributes to death. Cell-mediated immunity is compromised, and wound healing is impaired, threatening-life infections (pneumonia, diarrhea, sepsis, etc.) are typical.

Intellect remains clear, but apathy and irritability are common. Examination of the neurologic system, particularly in the setting of chronic alcohol abuse, may detect memory loss with confabulation, a wide-based gait, and past pointing, which, together with ophthalmoplegia and peripheral neuropathy, constitute the Wernicke-Korsakoff syndrome of thiamine deficiency. Other neurologic causes of dementia include pellagra due to niacin and/or tryptophan deficiency. Additional causes of peripheral neuropathy include deficiencies of pyridoxine or vitamin E; loss of distal vibratory and position sense is characteristic of the subacute combined degeneration of vitamin B₁₂ deficiency.

Clinical variants of malnutrition

Marasmus (dry form) refers to generalized starvation with loss of body fat and protein.

Kwashiorkor (wet form) refers to selective protein malnutrition with edema and fatty liver.

Combined form (marasmic kwashiorkor) are more commonly seen in the context of a wide variety of acute and chronic illnesses that lead to depletion of body fat, muscle wasting, multiple signs of micronutrient deficiencies, decubitus ulcers, and life-threatening infections.

Laboratory findings

Protein-energy malnutrition may cause a slight depression of plasma albumin and a decrease in the urinary excretion of urea. Blood glucose falls and is maintained at a lower normal level.

In marasmus and kwashiorkor, electrolytes, especially potassium and magnesium, are depleted; levels of some enzymes and circulating lipids are low, and blood urea decreases.

Kwashiorkor is characterized by low plasma levels of albumin (10 to 25 g/L), transferrin, essential amino acids, β -lipoprotein, and glucose. Plasma cortisol and growth hormone levels are high, but insulin secretion and insulin-like growth factor are depressed.

Anemia is usually due to iron deficiency. Macrocytic anemia due to vitamin B₁₂ and folate deficiency may be. Total lymphocyte count is often $<1,0 \times 10^9/L$ and may be accompanied by anergy to common skin test antigens.

Diagnosis of protein-energy malnutrition is based on (1) body weight <85% of ideal mass and BMI<18,5 kg/m²; and (2) clinical and laboratory signs of macronutrients deficiency.

Course. In adults, untreated protein-energy malnutrition can result in morbidity and some mortality, but mortality data are scarce. Except when organ failure occurs, treatment is uniformly successful.

Acute allergic diseases

Conception of allergy (hypersensitivity)

Definition: *Allergy (hypersensitivity)* refers to pathologic processes that result from immunologically specific interactions between antigens (exogenous or endogenous) and humoral antibodies or sensitized lymphocytes.

This definition excludes those disorders in which demonstrated antibodies have no known pathophysiologic significance (e.g., the antibody to heart tissue that follows heart surgery or myocardial infarction), even though their presence may have diagnostic value.

Gell and Coombs classification of allergy

Type I is reactions in which antigens (allergens) combine with specific IgE antibodies that are bound to membrane receptors on tissue mast cells and blood basophils.

Type II is cytotoxic reactions resulting when antibody reacts with antigenic components of a cell or tissue elements or with antigen or hapten that is coupled to a cell or tissue.

Type III is immune complex (IC) reactions resulting from deposition of soluble circulating antigen-antibody ICs in vessels or tissue.

Type IV is cellular, cell-mediated, delayed, or tuberculin-type hypersensitivity reactions caused by sensitized T-lymphocytes after contact with a specific antigen.

Conception of acute allergosis

Definition: Acute allergosis (acute allergy) is disorders with type I hypersensitivity reactions including the atopic diseases (allergic rhinitis, allergic conjunctivitis, atopic dermatitis, and allergic [extrinsic] asthma) and some cases of urticaria and gastrointestinal food reactions and systemic anaphylaxis.

The term *atopic allergy (atopy)* implies a familial tendency to manifest such conditions as bronchial asthma, rhinitis, urticaria, and eczematous dermatitis (atopic dermatitis) alone or in combination.

Pathogenesis of the acute allergy includes three stages:

- *immunological stage* - sensitization of the body during the first intake of the antigen and production of antibodies;

- *pathochemical stage* - rapid release of potent vasoactive and inflammatory mediators generated by IgE-dependent activation of mast cells can elicit common but sequential target cell effects leading to acute and sustained inflammatory responses;
- *pathophysiological stage* - the mediators produce vasodilatation, increased capillary permeability, glandular hypersecretion, smooth muscle spasm, and tissue infiltration with eosinophils and other inflammatory cells.

Diagnosis of acute allergosis

History: Review of the symptoms, their relation to the environment and to seasonal and situational variations, their clinical course, and the family history of similar problems should yield sufficient information to classify the disease as atopic. The history is more valuable than tests in determining whether a patient is allergic, and the patient should not be subjected to extensive skin testing unless reasonable clinical evidence of atopy exists. Age of onset may be an important clue (e.g., childhood asthma is more likely to be allergy-related than is asthma beginning after age 30). Also indicative are seasonal symptoms (e.g., correlating with specific pollen seasons) or symptoms that appear after exposure to animals, hay, or dust, or that develop in specific environments (e.g., at home). The effects of contributory factors (e.g., tobacco smoke and other pollutants, cold air, exercise, alcohol, certain drugs, and life stresses) should be evaluated.

Nonspecific tests: Eosinophils in the blood and secretions are often associated with atopic disease, particularly asthma and atopic dermatitis. *IgE* levels are elevated and will rise during exacerbations and fall during remissions in atopic dermatitis. Although usually elevated, *IgE* levels are not diagnostically useful in atopic asthma and allergic rhinitis.

Specific tests: Specific tests are used to confirm sensitivity to a particular allergen or allergens. Skin tests are the most convenient way to confirm specific sensitivity. They should be selective and based on clues provided by the history. Test solutions are made from extracts of inhaled, ingested, or injected materials (e.g., wind-borne tree, grass, and weed pollens; house dust mites; animal danders and sera; insect venoms; foods; and penicillin and its derivatives).

For the *prick (puncture) test*, which is usually performed first, a drop of a dilute allergenic extract is placed on the skin, which is then pricked or punctured through the extract, usually by “tenting” up the skin with the tip of a stylet or needle held at a 20° angle until the tip pops loose.

For the *intradermal test*, just enough dilute sterile extract is injected (using a 0,5- or 1-ml syringe and a short-bevel needle) to produce a 1- or 2-mm bleb. Each set of skin tests should include the diluent alone as a negative control and histamine (10 mg/ml of the base for the prick test or 0,1 mg/ml for the intradermal test) as a positive control. A skin test is considered posi-

tive if it produces a wheal and flare reaction in 15 min with a wheal diameter at least 5 mm larger than the control.

The prick (scratch) skin test is usually sufficient for detecting sensitivity to most allergens. The more sensitive intradermal test can then be used to test suspected inhaled allergens that have produced negative or equivocal prick tests. For foods, prick tests alone are diagnostic. Intradermal tests to food are likely to produce positive reactions of no clinical significance, as determined by double-blind, oral symptom-provoking challenge tests.

A *radioallergosorbent test (RAST)* may be performed when direct skin testing is impossible because of generalized dermatitis, extreme dermographia, or the patient's inability to cooperate or to stop using antihistamines. A RAST detects the presence of allergen-specific serum IgE.

WBC (leucocytes) histamine release, an in vitro test, detects allergen-specific IgE on sensitized basophils by measuring allergen-induced histamine release from the patient's WBCs.

Provocative challenge tests may be performed when a positive skin test raises a question about the role of the particular allergen in the production of symptoms. *Bronchial challenge* is sometimes used when the clinical significance of a positive skin test is unclear or when skin test reagents are unavailable to show that symptoms are related to materials to which a patient is exposed (e.g., in occupation-related asthma). *Oral provocative challenges* must be used when regularly occurring symptoms are suspected of being food-related because positive skin tests are not necessarily clinically significant.

Tests of unproven effectiveness: No evidence supports the use of cutaneous or sublingual provocation testing in allergy diagnosis.

Disorders of vasoactive mediators: Urticaria and angioedema

Definition: Disorders of vasoactive mediators derived from mast cells and other sources (even though an IgE-mediated or other immunologic mechanism may not be involved) as cutaneous manifestations of localized non-pitting edema. A similar process may occur at mucosal surfaces of the upper respiratory or gastrointestinal tract.

Urticaria (L50 according to ICD-X) is local wheals and erythema in the superficial dermis.

Angioedema (Quincke's edema, T78.3 according to ICD-X) is a deeper swelling due to edematous areas in the deep dermis and subcutaneous tissue and may also involve mucous membranes.

Etiology. Acute urticaria and angioedema can be due to drug allergy, insect stings or bites, desensitization injections, or ingestion of certain foods (particularly eggs, shellfish, or nuts), viral infections (hepatitis, infectious mononucleosis, rubella), psychogenic stimuli, physical stimuli such as cold,

heat, solar rays, exercise, and mechanical irritation. Urticaria may be the first or only visible sign of cutaneous vasculitis.

Some acute reactions are unexplained, even when recurrent. If acute angioedema is recurrent, progressive, painful rather than pruritic, and not associated with urticaria, a hereditary enzyme deficiency should be considered.

Chronic urticaria and angioedema lasting > 6 wk are more difficult to explain, and only in exceptional cases can a specific cause be found. Occasionally, chronic ingestion of an unsuspected drug or chemical is responsible; e.g., from penicillin in milk; from the use of nonprescription drugs; or from preservatives or other food additives. Chronic underlying disease (systemic lupus erythematosus, polycythemia vera, thyroid diseases, lymphoma, or infection) should be ruled out.

Classification of urticaria and angioedema (according to etiology and pathogenesis)

1. IgE-dependent urticaria and angioedema:
 - (a) Specific antigen sensitivity (pollens, foods, drugs, fungi, molds, Hymenoptera venom, helminths);
 - (b) Physical: dermatographism, cold, solar, cholinergic, vibratory, exercise-related;
2. Complement-mediated urticaria and angioedema:
 - (a) Hereditary angioedema;
 - (b). Acquired angioedema;
 - (c) Necrotizing vasculitis;
 - (d) Serum sickness;
 - (e) Reactions to blood products.
3. Nonimmunologic urticaria and angioedema:
 - (a) Direct mast cell-releasing agents: opiates, antibiotics, curare, D-tubocurarine, radiocontrast media;
 - (b) Agents that alter arachidonic acid metabolism: aspirin and nonsteroidal anti-inflammatory agents, azo dyes, and benzoates;
4. Idiopathic urticaria and angioedema.

Clinical picture

Urticaria is characterized by (1) pruritus (generally the first symptom), (2) the appearance of wheals that may remain small (1 to 5 mm) or enlarged, (3) the larger ones tend to be clear in the center and may be noticed first as large rings of erythema and edema., (4) crops of hives appear and subside;(5) a lesion may remain in one site for several hours, then disappear, only to reappear elsewhere; (6) if a lesion persists > 24 hours the possibility of vasculitis should be considered.

Angioedema (Quincke's edema) is characterized by (1) swelling of loose subcutaneous tissue and mucous membranes, (2) edema develops acutely, a few seconds or minutes following the intake of the allergen (usually without any precursors); (3) localization of edema - lip, cheek, eye, dor-

sum of hands or feet, but it can also develop in any organ (edema of throat, stomach, genitalia, etc.); (4) the edema persists from a few minutes to several hours; (4) the size of the swollen area varies, but it rarely exceeds the size of the palm

The most common sites for urticaria are the extremities and face, with angioedema often being periorbital and in the lips. Although self-limited in duration, angioedema of the upper respiratory tract may be life-threatening due to laryngeal obstruction, while gastrointestinal involvement may present with abdominal colic, with or without nausea and vomiting, and may precipitate unnecessary surgical intervention. No residual discoloration occurs with either urticaria or angioedema unless there is an underlying process leading to superimposed extravasation of erythrocytes.

Diagnosis of urticaria and angioedema is based on (1) clinical picture; (2) the cause of acute urticaria or acute angioedema is usually obvious by a detailed history.

Diagnostic tests (see above) are seldom required because of the self-limited, nonrecurrent nature of these reactions. In chronic urticaria, an underlying chronic disease should be ruled out by a detailed history and physical examination and routine screening tests. Eosinophilia is uncommon in urticaria. Other tests (e.g., stool examination for ova and parasites, serum complement, antinuclear antibody, and sinus or dental x-rays) are not helpful without additional clinical indications.

Acute anaphylaxis (Anaphylactic shock)

Definition: *Anaphylactic shock* (T78.0, T78.2, T80.5, T88.6 according to ICD-X) is a symptom complex of acute grave general allergic reactions of immediate type, characterized mainly by the initial stimulation and subsequent inhibition of the function of the central nervous system, bronchospasm, and a marked arterial hypotension.

Anaphylaxis is an acute, often explosive, IgE-mediated systemic reaction that occurs in a previously sensitized person who receives the sensitizing antigen. In atopy (hereditary allergy characterized by congenital presence of antibodies to certain allergens), an anaphylactic shock may develop during the first contact with this substance.

The terms “anaphylaxis” and “anaphylactic shock” are differed from term “anaphylactoid reaction”.

Anaphylactoid reactions are clinically similar to anaphylaxis, but may occur after the first injection of certain drugs (polymyxin, opioids, aspirin and other NSAIDs) and contrast media. They have a dose-related, toxic-idiosyncratic mechanism rather than an immunologically mediated one.

Etiology of acute anaphylaxis are usually parenteral administration of medicinal preparations (antibiotics, such as penicillin and others, procaine, vitamin B₁, sulpha drugs, vaccines, blood products, extracts of pollen of some

plants, etc.), heterologous proteins in the form of hormones (insulin, vasopressin, parathormone), enzymes (trypsin, chymotrypsin, penicillinase, streptokinase), and insect stings. It is important to note that an anaphylactic shock may develop after administration of small doses of the preparation which was given earlier in larger doses, e.g. in intracutaneous injection of only a few units of penicillin (in diagnostic test for allergy).

Pathophysiology. Histamine, leukotrienes, and other mediators are generated or released when the antigen reacts with IgE on basophils and mast cells. These mediators cause the smooth muscle contraction (responsible for wheezing and gastrointestinal symptoms) and vascular dilation that characterize anaphylaxis. Vasodilatation and escape of plasma into the tissues causes urticaria and angioedema and results in a decrease in effective plasma volume, which is the major cause of shock. Fluid escapes into the lung alveoli and may produce pulmonary edema. Obstructive angioedema of the upper airway may also occur. Arrhythmias and cardiogenic shock may develop if the reaction is prolonged.

Clinical picture. Anaphylactic shock develops rapidly, in a few seconds or minutes (to 30 minutes), following the intake of the allergen. Symptoms vary, and rarely does any one patient develop all the symptoms. Typically, in 1 to 15 min (but rarely after as long as 2 h), the patient feels uneasy, becomes agitated and flushed, and complains of vertigo, headache, fear, cold sweat, palpitations, anxiety, pressure in the chest, paresthesias, pruritus, throbbing in the ears, coughing, sneezing, and difficulty breathing owing to laryngeal edema or bronchospasm.

In some cases, skin itching develops simultaneously. Some patients develop allergic urticaria, allergic edema, tachycardia, abdominal pain, vomiting, diarrhea, and often convulsions. The further picture varies: rapidly developing edema of the throat and asphyxia, progressive arterial hypotension, edema and hemorrhages into the internal organs (which are especially dangerous if they affect the brain). In grave cases, the patient soon loses consciousness.

Shock may develop within another 1 or 2 min, and the patient may convulse, become incontinent, become unresponsive, and die. Often convulsions are unfavourable prognostic sign. Primary cardiovascular collapse can occur without respiratory symptoms. Recurrent episodes of anaphylaxis in the same person are usually characterized by the same symptoms.

The shock may occur immediately. A routine systemic examination of the patient is impossible and urgent measures should be taken to recover the patient from the shock.

Clinical diagnosis of an anaphylactic shock depends largely (1) on an accurate history revealing the onset of the appropriate symptoms and the sign within seconds-minutes after the responsible material is encountered; (2) the

rapid response of the patient to the administration of the medicine required in anaphylaxis.

The prognosis is serious in all cases: the patient may die within the first minutes or hours of asphyxia, cardiovascular insufficiency, or irreversible affections of the vitally important organs. The latter may develop and become the cause of death at later terms (in several days). After the patient has been drawn from the critical state, he should be given a thorough medical observation and examination by laboratory and instrumental methods. This enables the physician to diagnose the affection of this or that organ at the early stage of the process.

Treatment. Early recognition of an anaphylactic reaction is mandatory, since death occurs within minutes to hours after the first symptoms.

Immediate treatment with epinephrine is imperative. Mild symptoms such as pruritus and urticaria can be controlled by administration of 0,2 to 0,5 ml of 0,1% epinephrine (adrenaline) subcutaneously, with repeated doses as required at 20-min intervals for a severe reaction. If the antigenic material was injected into an extremity, the rate of absorption may be reduced by prompt application of a tourniquet proximal to the reaction site, administration of 0,2 ml of 0,1% epinephrine into the site, and removal without compression of an insect stinger, if present. An intravenous infusion should be initiated to provide a route for administration of 2,0 ml 0,1% epinephrine diluted 1:10, at 5- to 10-min intervals, volume expanders such as normal saline (0,9% sodium chloride solution), and vasopressor agents such as dopamine if intractable hypotension occurs. Replacement of intravascular volume due to postcapillary venular leakage may require several liters of saline. Epinephrine provides both α - and β -adrenergic effects, resulting in vasoconstriction, bronchial smooth-muscle relaxation, and attenuation of enhanced venular permeability.

When epinephrine fails to control the anaphylactic reaction, hypoxia due to airway obstruction or related to a cardiac arrhythmia, or both, must be considered. Oxygen via a nasal catheter or intermittent positive-pressure breathing of oxygen with 0,5 ml isoproterenol diluted 1:200 in saline may be helpful, but either endotracheal intubation or a tracheostomy is mandatory for oxygen delivery if progressive hypoxia develops.

Ancillary agents such as the antihistamine diphenhydramine (dime-drol), 50 to 100 mg intramuscularly or intravenously, and aminophylline, 0,25 to 0,5 g intravenously, are appropriate for urticaria-angioedema and bronchospasm, respectively. Intravenous glucocorticoids (8-12 mg dexamethasone, 75 mg prednisolone) are not effective for the acute event but may alleviate later recurrence of bronchospasm, hypotension, or urticaria. Furthermore, in a syndrome termed *idiopathic anaphylaxis* with recurrent angioedema of the upper airways, glucocorticoid administration may be beneficial by reducing the frequency of attacks and/or the severity of episodes.

Prophylaxis. A thoroughly collected allergic anamnesis is very important. The patient should be asked to what preparations he might have allergic response, or if he has atopy or hereditary predisposition to allergic reactions. If this information is available, the physician should exclude those preparations to which the patient has the allergic reaction. A knowledge of cross-reactivity among agents is critical since, for example, cephalosporins share a common β -lactam ring with the penicillins. Beta blockers are relatively contraindicated in persons at risk for anaphylactic reactions, especially those sensitive to Hymenoptera venom or those undergoing immunotherapy for respiratory system allergy.

A skin test should be performed before the administration of certain materials that are likely to elicit anaphylactic reactions, such as allergenic extracts, or when the nature of the past adverse reaction is unknown. A scratch test should precede an intradermal test in very sensitive patients. Skin testing for antibiotics should be performed only on patients with a positive clinical history consistent with an IgE-mediated reaction and in imminent need of the antibiotic in question.

Any room, where patients are given injections of medicinal preparations, should be equipped with all necessary means to recover patients from possible anaphylactic shock.

Symptomatology and diagnosis of HIV and AIDS

Definition

Human immunodeficiency virus (HIV) infection (B20-B24 according to ICD-X) is an infection caused by one of two related retroviruses (HIV-1 and HIV-2) resulting in a wide range of clinical manifestations varying from asymptomatic carrier states to severely debilitating and fatal disorders related to defective cell-mediated immunity.

AIDS (acquired immunodeficiency syndrome) is a disorder of cell-mediated immunity characterized by opportunistic infections, malignancies, neurologic dysfunction, and a variety of other syndromes. AIDS is the most severe manifestation of a spectrum of HIV-related conditions.

Etiology

The etiologic agent of AIDS is HIV, which belongs to the family of human retroviruses (Retroviridae) and the subfamily of lentiviruses. The four recognized human retroviruses belong to two distinct groups: the human T lymphotropic viruses (HTLV) I and HTLV-II, which are transforming retroviruses; and the human immunodeficiency viruses, HIV-1 and HIV-2, which are cytopathic viruses. The most common cause of HIV disease throughout the world is HIV-1. HIV-1 comprises several subtypes with different geo-

graphic distributions. HIV-1 causes most cases of AIDS in the Western Hemisphere, Europe, Asia, and Central, South, and East Africa; HIV-2 is the principal agent of AIDS in West Africa and appears less virulent than HIV-1. In certain areas of West Africa, both organisms are prevalent.

Transmission of HIV

HIV transmission requires contact with body fluids containing infected cells or plasma. HIV is transmitted by (1) both homosexual and heterosexual contact; (2) by blood and blood products; and (3) by infected mothers to infants either intrapartum, perinatally, or via breast milk.

There is no evidence that HIV is transmitted by casual contact or that the virus can be spread by insects, such as by a mosquito bite. Risk of HIV transmission from infected medical personnel who observe good techniques to uninfected patients is very small but is less clear.

Pathogenesis of HIV infection

HIV (like all retroviruses) contains an enzyme called reverse transcriptase that converts viral RNA into a proviral DNA copy that becomes integrated into the host cell DNA. These integrated proviruses are duplicated by normal cellular genes each time the cell divides. The proviral HIV DNA is both transcribed to RNA and translated to proteins to produce hundreds of copies of the infectious virus.

HIV infects a major subset of T-lymphocytes defined phenotypically by the CD4 transmembrane glycoprotein and functionally as helper/inducer cells. HIV also infects nonlymphoid cells, such as macrophages, microglial cells, and various endothelial and epithelial cells. As a result of HIV infection, the numbers and functions of T-cells, B-cells, natural killer cells, and monocytes-macrophages are disturbed. Despite abnormalities of cells other than CD4⁺ lymphocytes, much of the immunologic dysfunction in AIDS appears to be explained by loss of the helper function of these lymphocytes, which is critical to cell-mediated immunity.

The best predictors of onset of the serious opportunistic infections that define AIDS are the total number of circulating CD4⁺ lymphocytes (*CD4 count*) and the level of HIV RNA in plasma (*viral load*). The CD4 count is the percentage of lymphocytes that bear the CD4 marker. Normal counts are about 750 ± 250 cells/ml ($0,75 \pm 0,25 \times 10^9/l$), but levels are usually reduced by about 40 to 50% early in HIV infection. Vulnerability to opportunistic infections increases markedly when CD4 lymphocyte levels are $< 200/ml$.

Suppressor/cytotoxic CD8⁺ lymphocytes appear to be functionally normal and increased in number in HIV infection, which may contribute further to immunosuppression and results in reduction of the *CD4:CD8 ratio* (normally $\gg 2:1$) to < 1 . Because other viral infections (e.g., cytomegalovirus, Epstein-Barr virus, influenza, hepatitis B) may produce transient reductions in the CD4:CD8 ratio, decreased ratios are not specific.

Humoral immunity is also affected. Hyperplasia of B-(antibody-producing) lymphocytes in lymph nodes causes lymphadenopathy and increased secretion of antibodies, leading to hyperglobulinemia. Production of antibodies to previously encountered antigens persists; however, response to new antigens is defective and sometimes absent. Thus, total antibody levels (especially IgG and IgA) may be elevated and titers of antibodies to specific agents (e.g., cytomegalovirus) unusually high, but response to immunizations increasingly declines as CD4 counts decline.

The immunologic abnormalities in AIDS include anergy (demonstrated by lack of delayed hypersensitivity responses to intradermal injection of common antigens; e.g., tetanus, mumps, *Candida albicans*), poor T-cell proliferative responses to mitogens and antigens, polyclonal hypergammaglobulinemia, elevated plasma immune complex levels, diminished antibody responses to both recall and new antigens, decreased natural killer function.

Opportunistic infections (*Toxoplasma gondii*, *Pneumocystis carinii* and *Mycobacterium avium*, etc.) are referred to microorganisms that usually being harmless but can become pathogenic when host's resistance to infections is impaired. Patterns of specific opportunistic infections vary geographically, among risk groups, and as a result of medical interventions. In the USA and Europe, > 90% of AIDS patients with Kaposi's sarcoma are homosexual or bisexual men, probably because they are co-infected with human herpesvirus 8, a newly identified viral cofactor (with HIV) for Kaposi's sarcoma. Toxoplasmosis and tuberculosis are more common in tropical areas where the prevalence of latent infections with *Toxoplasma gondii* and *Mycobacterium tuberculosis* in the general population is high.

Clinical picture of HIV infection

HIV causes a broad spectrum of clinical problems, which may mimic other diseases. HIV disease includes four stages.

Stages of HIV:

(1) *Antibody-negative carrier state.* Immediately after infection and for a prolonged period (more than several months in a small number of persons), there is a brief antibody-negative carrier state. During this time, the virus reproduces rapidly until the immune system begins to react and/or targets are exhausted. HIV RNA or HIV p24 (capsid) antigen is detectable in plasma, even when no antibody to HIV is detectable.

(2) *Acute retroviral syndrome or primary HIV infection* develops within 1 to 4 weeks after infection. Patients have fever, malaise, rash, arthralgias, and generalized lymphadenopathy, usually lasting 3 to 14 days, followed within days to 3 months by seroconversion for antibody to HIV. Acute retroviral syndrome is frequently misdiagnosed as a febrile upper respiratory illness ("flu") or mononucleosis.

(3) *Asymptomatic (clinical latency) stage.* Subsequently, these acute manifestations disappear (although lymphadenopathy usually persists) and

patients become antibody-positive, asymptomatic HIV carriers. Some of these patients develop mild, remittent symptoms and signs that do not meet the definition of AIDS (e.g., thrush, zoster, diarrhea, fatigue, fevers). Leucopenia is common and anemia and immune-mediated thrombocytopenia may also occur.

(4) *Symptomatic disease.*

Symptoms of HIV disease can appear at any time during the course of HIV infection. Many patients first become aware of their HIV infection when diagnosed with a life-threatening opportunistic infection or malignancy without having experienced preceding chronic symptoms. AIDS was initially defined by the development of serious opportunistic infections and/or certain secondary cancers, such as Kaposi's sarcoma and non-Hodgkin's lymphoma, known to be associated with defective cell-mediated immunity.

Generally speaking, the spectrum of illness that one observes changes as the CD4+ T-cell count declines (Table 2).

Table 2

Classification system for HIV Infection and expanded AIDS surveillance case definition (according to Centers for Disease Control and Prevention's, 1993)

CD4+ T Cell Categories	Clinical Categories		
	A Asymptomatic Acute (Primary) HIV	B Symptomatic, Not A or C Conditions	C AIDS-Indicator Conditions
>500/ml	A1	B1	C1
200-499/ml	A2	B2	C2
<200/ml	A3	B3	C3

The more severe and life-threatening complications of HIV infection occur in patients with CD4+ T cells counts <200/uL. A diagnosis of AIDS is made in anyone with HIV infection and a CD4+ T cell count <200/ml ($0,2 \times 10^9/l$) and in anyone with HIV infection who develops one of the HIV-associated diseases considered to be indicative of a severe defect in cell-mediated immunity (category C, Table). Approximately 80% of deaths among AIDS patients are as a direct result of an infection other than HIV, with bacterial infections heading the list. While the causative agents of the secondary infections are characteristically opportunistic organisms such as *Pneumocystis carinii*, atypical mycobacteria, CMV, and other organisms that do not ordinarily cause disease in the absence of a compromised immune system, they also include common bacterial and mycobacterial pathogens.

Clinical Categories of HIV Infection

Category A: Consists of one or more of the conditions listed below in an adolescent or adult (>13 years) with documented HIV infection. Conditions listed in categories B and C must not have occurred.

- Asymptomatic HIV infection;
- Persistent generalized lymphadenopathy;
- Acute (primary) HIV infection with accompanying illness or history of acute HIV infection.

Category B - criteria:

- (1) The conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity;
- (2) the conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection.

- Bacillary angiomatosis;
- Candidiasis, oropharyngeal (thrush);
- Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy;
- Cervical dysplasia (moderate or severe)/cervical carcinoma in situ;
- Constitutional symptoms, such as fever (38.5 C) or diarrhea lasting >1 month;
- Hairy leukoplakia, oral;
- Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome;
- Idiopathic thrombocytopenic purpura;
- Listeriosis;
- Pelvic inflammatory disease, particularly if complicated by tuboovarian abscess;
- Peripheral neuropathy.

Category C:

- Candidiasis of bronchi, trachea, or lungs, esophageal;
- Cervical cancer, invasive;
- Coccidioidomycosis, disseminated or extrapulmonary;
- Cryptococcosis, extrapulmonary;
- Cryptosporidiosis, chronic intestinal (>1 month's duration);
- Cytomegalovirus disease (other than liver, spleen, or nodes), cytomegalovirus retinitis (with loss of vision);
- Encephalopathy, HIV-related;
- Herpes simplex: chronic ulcer(s) (>1 month's duration); or bronchitis, pneumonia, or esophagitis;
- Histoplasmosis, disseminated or extrapulmonary;
- Isosporiasis, chronic intestinal (>1 month's duration);
- Kaposi's sarcoma;
- Lymphoma, Burkitt's (or equivalent term); Lymphoma, primary, of brain;

Lymphoma, primary, of brain;
Mycobacterium avium complex or *M. kansasii*, disseminated or extrapulmonary;
Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary);
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary;
Pneumocystis carinii pneumonia;
Pneumonia, recurrenta;
Progressive multifocal leukoencephalopathy;
Salmonella septicemia, recurrent;
Toxoplasmosis of brain;
Wasting syndrome due to HIV.

Clinical manifestations of HIV symptomatic disease

AIDS of digestive system

Oral symptoms include:

- oral candidiasis (thrush) is among the earliest and most common manifestations of HIV,
- oral hairy leukoplakia (Epstein-Barr virus),
- ulcers (aphthous), herpes simplex,
- periodontal disease (leading to bleeding, swelling of gums, loss of teeth),
- both Kaposi's sarcoma and lymphomas of the oral cavity.

GI symptoms include:

- abdominal pain, nausea and vomiting, diarrhea, weight loss and wasting commonly afflict advanced AIDS patients;
- various opportunistic infections and tumors - esophagus (herpes simplex, cytomegalovirus, Candida), stomach (Kaposi's sarcoma and lymphoma), bowel (*Salmonella*, *Clostridium difficile*, cytomegalovirus, herpes simplex virus), and biliary tract (*cryptosporidium* and cytomegalovirus);
- over 95% of HIV-infected individuals have evidence of infection with hepatitis B virus (HBV); 5-40% of patients are co-infected with hepatitis C virus (HCV); and co-infection with hepatitis D, E, and/or G viruses is common.;
- drug-associated pancreatitis or hepatitis may complicate therapy;
- diarrhea for which no cause can be found may persist for long periods or recur intermittently, even in patients without severe immunosuppression or other symptoms.

AIDS of respiratory system

Acute bronchitis and sinusitis are prevalent during all stages of HIV infection. Sinusitis presents as fever, nasal congestion, and headache.

The two most common causes of pneumonia are bacteria infections and *Pneumocystis carinii* infection. Pneumococcal infection may be the earliest serious infection to occur in patients with HIV disease. This can present as pneumonia, sinusitis, and/or bacteremia. Patients with HIV infection have

a sixfold increase in the incidence of pneumococcal pneumonia and a 100-fold increase in the incidence of pneumococcal bacteremia.

Patients with *Pneumocystis carinii pneumonia (PCP)* generally present with fever and a cough that is usually nonproductive or productive of only scant amounts of white sputum. They may complain of a characteristic retrosternal chest pain that is worse on inspiration and is described as sharp or burning. HIV-associated PCP may have an indolent course characterized by weeks of vague symptoms and should be included in the differential diagnosis of fever, pulmonary complaints, or unexplained weight loss in any patient with HIV infection and <200 CD4+ T cells/ml. The most common finding on chest x-ray is either a normal film, if the disease is suspected early, or a faint bilateral interstitial infiltrate. A mild leucocytosis is common, although this may not be obvious in patients with prior neutropenia. Arterial blood gases may indicate hypoxemia. A definitive diagnosis of PCP requires demonstration of the trophozoite or cyst form of the organism in samples obtained from induced sputum, bronchoalveolar lavage, transbronchial biopsy, or open lung biopsy. PCR has been used to detect specific DNA sequences for *P. carinii* in clinical specimens where histologic examinations have failed to make a diagnosis.

Tuberculosis (TB), which is frequently the first manifestation of HIV infection, where TB is heavily endemic. Atypical presentations (infrequent cavitation, lower-lobe infiltrates, miliary disease, and lymphadenopathy), anergy to tuberculin skin tests, and confusion or coexistence with other opportunists may make the diagnosis difficult.

The lung is also a common site for opportunistic infections caused by fungi such as *Cryptococcus neoformans*, *Histoplasma neoformans*, *Coccidioides immitis*, and *Aspergillus* sp.

Both Kaposi's sarcoma and B-cell lymphomas may involve mediastinal nodes and the lung.

Diagnosis tests are X-ray, analysis of sputum and rinsed waters of bronchi, bronchoscopy, open biopsy of lungs.

AIDS-manifestations of other systems

Neurologic symptoms: Neurologic symptoms are common and may be the first manifestation of AIDS. Symptoms may be due to direct effects of HIV, opportunistic (*Toxoplasma*, *Cryptococcal*, *histoplasmal*, and *tuberculous*) infections, neoplasms, or vascular complications. They include acute aseptic meningitis; peripheral neuropathies of several types; encephalopathy with seizures; focal motor, sensory, or gait deficits; and cognitive dysfunction progressing to dementia.

Dermatologic symptoms: Skin manifestations of HIV infection complicate every stage from the rash and genital ulcers of primary infection to widespread Kaposi's sarcoma in AIDS. Among the more common nonneoplastic problems are seborrheic dermatitis, eosinophilic pustular folliculitis,

and opportunistic infections. Zoster, which is common throughout the course of infection, is often the first manifestation.

Cardiovascular complications of AIDS include marantic (thrombotic) or bacterial endocarditis (especially in intravenous drug abusers) or a cardiomyopathy with congestive heart failure.

Renal insufficiency or nephrotic syndrome uncommonly complicates AIDS, but may be a source of severe disability.

Hematologic symptoms: Disorders of the hematopoietic system including lymphadenopathy, anemia, leucopenia, and/or thrombocytopenia are common throughout the course of HIV infection and may be the direct result of HIV, manifestations of secondary infections and neoplasms, or side effects of therapy.

Neoplastic diseases. The neoplastic diseases clearly seen with an increased frequency in patients with HIV infection are Kaposi's sarcoma and non-Hodgkin's lymphoma. In addition, there also appears to be an increased incidence of Hodgkin's disease; multiple myeloma; leukemia; melanoma; and cervical, brain, testicular, oral, and anal cancers.

Symptoms in women: The presentation and course of HIV infection in women resembles that in men overall with the exception of chronic refractory vaginal candidiasis and increased risk of cervical intraepithelial neoplasia. Pelvic inflammatory disease may be atypical, more aggressive, and resistant to treatment in HIV-infected women. HIV testing for women with recurrent, aggressive, or unusually resistant STDs or vaginal candidiasis is recommended.

Laboratory diagnosis of HIV infection

Tests for detection of HIV:

- Immune complex-dissociated p24 antigen capture assay (measurement of levels of HIV-1 core protein);
- Tests for detecting antibody to HIV include ELISA, which can detect antibodies to HIV proteins. ELISA is both highly sensitive and specific, but some false-positive ELISA tests occur. When reactive, ELISA should be repeated on the same sample. If it is positive a second time, a test that is more specific should be performed, e.g., the Western blot;
- Western blot, which is an immunoelectrophoretic procedure for identifying antibodies to specific viral proteins separated by their molecular weight;
- HIV RNA by PCR (the reverse-transcription polymerase chain reaction (RT-PCR), which amplifies viral nucleic acids, or the branched DNA (bDNA), which amplifies signal, are sensitive and accurate over a wide range of viral concentrations (up to 1,000,000 copies/ml of plasma). The lower limits of detection are about 400 copies/ml for RT-PCR and 5000 copies/ml for bDNA.

Additional laboratory tests:

- decrease of CD4+lymphocytes count (in the norm - 750 ± 250 cells/ml or $0,75 \pm 0,25 \times 10^9/l$),
- decrease of CD4+/CD8+lymphocytes $<1,0$ (normally $\gg 2:1$),
- decrease of total lymphocyte count (lymphopenia) $<0,5-1,0 \times 10^9/l$,
- erythrocytopenia, leucopenia, thrombocytopenia;
- decrease of natural T-killer cells, and level of interferon in the blood,
- increased concentrations of blood plasma immunoglobulins and plasma immune complexes.

Diagnosis criteria of AIDS

1. Presence of the most typical sets of symptoms:
 - (1.1) Chronic diarrhea (not less than 2 months);
 - (1.2) Inexplicable weight reduction (10 % and more);
 - (1.3) Long inexplicable fever;
 - (1.4) Pneumonia of an obscure etiology, steady against routine therapy;
 - (1.5) Lymphadenopathy
 - (1.6) Lymphopenia;
 - (1.7) Opportunistic infections;
 - (1.8) Tumors (Kaposi's sarcoma and cerebral lymphoma).
2. Detection of antibodies to HIV.
3. Detection of HIV- virus in blood and others biological substances.

Prognosis

Active virus replication and progressive immunologic impairment occur throughout the course of HIV infection in most patients. With the exception of long-term nonprogressors, HIV disease in untreated patients inexorably progresses even during the clinically latent stage.

An HIV-infected person's risk of developing AIDS or dying can be estimated by combining CD4+ lymphocyte counts (see Table 2 above) and levels of plasma RNA. Reduction of plasma RNA levels by antiretroviral therapy reduces the risk of complications and death and often increases CD4+ lymphocyte counts.

Opportunistic infections have remained the immediate cause of death for nearly all AIDS patients. Better drug treatment of these infections and, to a lesser extent, of Kaposi's sarcoma has improved outcomes as well.

The introduction of combination antiretroviral drug therapy has dramatically prolonged the survival for patients with AIDS over periods of 2 to 3 years, but the duration of benefit is variable and as yet incompletely defined. New antiretroviral drugs used in potent combinations and monitored by plasma viral (RNA) levels promise to extend the survival of patients at all stages of HIV infection.

Supplement

Standards of laboratory tests

Table 1

Peripheral blood tests

Test	SI units ¹
Hemoglobin: male	130,0 - 160,0 g/l
female	120,0 - 140,0 g/l
Erythrocytes: male	4,0 - 5,0×10 ¹² / l
female	3,9 - 4,7×10 ¹² / l
Colour index	0,85 - 1,05
Reticulocytes %	0,2 - 1,2%
Average content of hemoglobin in 1 erythrocyte	24 - 34 pg
Thrombocytes (platelets)	180,0 - 320,0×10 ⁹ / l
Leucocytes	4,0 - 9,0×10 ⁹ / l
Neutrophils:	
-stab (bond) neutrophils	1 - 6 % 0,040 - 0,300×10 ⁹ / l
- segmental (segmentonuclear) neutrophils	47 - 72 % 2,000 - 5,500×10 ⁹ / l
Eosinophils	0,5 - 5 % 0,020 - 0,300×10 ⁹ / l
Basophils	0 - 1 % 0 - 0,065×10 ⁹ / l
Lymphocytes	19 - 37 % 1,200 - 3,000×10 ⁹ / l
Monocytes	3 - 11 % 0,090 - 0,600 ×10 ⁹ / l
Erythrocyte sedimentation rate (ESR): male	2 - 10 mm/h
female	2 - 15 mm/h
Hematocrit (packed cell volume, PCV) male	40-48%
female	36-42%

¹ SI units - international system of units

Table 2

Blood serum tests

Test	SI units
Bilirubin - total - indirect	8,5 - 20,5 $\mu\text{mol/l}$ < 16,5 $\mu\text{mol/l}$
Serum iron: male female	10,0-30,0 $\mu\text{mol/l}$ 9,0 - 29,0 $\mu\text{mol/l}$
Serum Fe-binding capacity	50-84 $\mu\text{mol/l}$
Serum ferritin	30-300 $\mu\text{g/l}$
Glucose	
1) plasma	4,2 - 6,1 mmol/l
2) capillary blood	3,88 – 6,7 mmol/l
3) glucose tolerance test (capillary blood) fasting in 120 minutes	up to 6,7 mmol/l up to 7,8 mmol/l
4) glycated (glycosylated) hemoglobin	4,5-6,1 molar %
Total cholesterol	3,9 - 5,2 mmol/l
High-density lipoproteins	0,9-1,9 mmol/l
Low-density lipoproteins	<2,2 mmol/l
Atherogenic coefficient	up to 3,0 unit
Triglycerides	0,40 – 2,1 mmol/l
Total protein	65 – 85 g/l
Protein fractions: albumin	56-66%
globulins	34-44%
α_1 - globulins	2,5-5%
α_2 - globulins	5-9%
β - globulins	8-12%
γ -globulins	12,8-19%
Seromuroid	0,13-0,2 unit
Haptoglobin	0,9- 4 g/l
Thymol (turbidity) test	up to 5 unit
Rheumatoid factor	up to 8 IU ¹ /l
Antistreptolysine-O	up to 250 IU/l
C-reactive protein	0-6,0 mg/l
Circulating immune complexes	0-56 unit
Sialic acids	125-200 unit
Ceruloplasmin	1,5-2,3 g/l

¹ IU - international unit

Table 3

Rest (nonprotein) nitrogen and its some components in blood serum

Test	SI units
Creatinine	0,044 - 0,120 mmol/l
Urea	4,2 - 8,3 mmol/l
Uric acid: male female	0,14 - 0,4 mmol/l 0,24 - 0,50 mmol/l
Glomerular filtration	80-120 ml/min
Glomerular reabsorbtion	97-99%

Table 4

Blood serum ionogram

Test	SI units
Sodium (Na ⁺ ; 22,989)	130 - 157 mmol/l
Potassium (K ⁺ ; 39,102)	3,4 - 6,3 mmol/l
Calcium (Ca ⁺⁺ ; 40,08)	2,2 - 2,75 mmol/l
Magnesium (Mg ⁺⁺ ; 24,312)	0,75 - 1,4 mmol/l
Chloride (Cl ⁻ ; 35,453)	95 - 110 mmol/l

Table 5

Blood serum enzymes

Enzyme	Normal activity
Aspartate aminotransferase (AsAT)	0,1-0,45 mmol/l (5-40 IU/l)
Alanine aminotransferase (AlAT)	0,1-0,68 mmol/l (8-55 IU/l)
Creatine phosphokinase (CK)	24-170 U/l CK-BB – absent, CK-MB <4-6%, CK-MM >94-96%
Lactate dehydrogenase (LDG)	0,8- 4,0 mmol/l (up to 460 IU/l) LDG ₁ – 19-29%, LDG ₂ – 23-37%, LDG ₃ – 17-25%, LDG _{4,5} – 8-18%
γ- Glutamyl transpeptidase (γ-GGT): male female	up to 35 IU/l up to 50 IU/l
Alkaline phosphatase (AP)	up to 120 IU/l
α- Amylase	12-32 mg/ml/h (<96 unit/l)

Table 6

Coagulation tests (coagulogram)

Test	Normal	Hypo-coagulation	Hyper-coagulation
Bleeding time (by Duke's method)	2-4 minutes	↑	↓
Coagulation time (Lee and White method)	5-10 minutes	↑	↓
Platelet count	150,0-400,0×10 ⁹ /l	↓	↑
Clot retraction index	0,3-0,5	↑	↓
Activated partial thromboplastin time (APTT)	30-42 seconds	↑	↓
Prothrombin time (PT)	11-15 seconds	↑	↓
International normalized ratio (INR)	1,0-1,4	↑	↓
Prothrombin index	80-100%	↓	↑
Thrombin time	12-16 seconds	↓	↑
Fibrinogen	1,8-4,0 g/l	↓	↑
Time of plasma recalcification	80-140 seconds	↑	↓
Plasminogen activity	75-140%	↑	↓
α ₂ -Antiplasmin	80-120%	↓	↑
D-D-dimer	<0,5 mcg/ml	-	↑

Table 9

Urinalysis

Tests	Normal value
Specific gravity	1008 – 1026
Colour	straw-yellow
Transparency	complete (transparent urine)
Reaction of the urine , pH	neutral, slightly acid, slightly alkaline (4,5 – 8,0)
Protein	absent or traces (25 -75 mg /day)
Glucose	absent (up to 0,02%)
Acetone	absent
Urobilin	absent τ
Bilirubin	absent
Plane epithelium	up to 5 in area of vision
Renal epithelium	absent
Leucocytes	up to 5 in area of vision
Erythrocytes	up to 5 in area of vision
Casts (cylinders)	absent
Mucus	insignificant amount
Bacteria	insignificant amount (up to 50000 B 1 ml)
Non-organized sediment	-oxalates – in any medium reaction; -in acid reaction - crystals of uric acid, urates; -in alkaline reaction – amorphous phos- phate, ammonium urate, triple phosphates

Table 10

Nechiporenko's urine sediment analysis

Index	Normal value
Leucocytes	up to $4,0 \times 10^6 / l$
Erythrocytes	up to $1,0 \times 10^6 / l$
Casts (cylinders)	up to $250,0 \times 10^3 / l$

Table 11

Addis- Kakovsky's urine sediment analysis

Index	Normal value
Leucocytes	up to $1,0 \times 10^6$ / day
Erythrocytes	up to $2,0 \times 10^6$ / day
Casts (cylinders)	up to $20,0 \times 10^4$ /day

Table 12

Zimnitsky's analysis of urine

Index	Normal value
Diurnal (24-hours) diuresis	1000-2000 ml (65 - 75% of water input)
Daily diuresis	3/4 of diurnal diuresis
Specific gravity	1008 – 1024
Fluctuation of the specific gravity	$\leq 0,008$

Table 13

Coprology studies (feces analysis)

Characterystics	Normal value
Amount of diurnal excretion	100 – 250 g
Consistency	formed (soft or solid)
Shape	cylindric
Colour	brown
Reaction	neutral or slightly alkaline
Blood	absent
Muscular fibres	only separate digested fibres (without striated pattern)
Connective tissue	absent
Fatty acids	absent
Vegetable cellulose: - digestible - indigestible	single cells or groups in various number (depends on the character of food)
Starch	absent
Iodinophil flora	absent
Mucus, epithelium	absent
Leucocytes	single

Table 14

Normal parameters of gastric secretion

Gastric secretion	Fasting stomach	Basal secretion	Stimulated after Leporsky (7% cabbage decoction)	Histamine stimulated (submaximal) secretion (0,008 mg/kg)	Histamine stimulated (maximum) secretion (0,024 mg/kg) or pentagastrin (0,006 mg/kg)
Total acidity (titration units)	До 40	40-60	40-60	80-100	100-120
Free HCl (titration units)	До 20	20-40	20-40	60-85	90-110
Output of total HCL (millequiv/l or mmol/l)	До 2	1,5-5,5	1,5-6	8-14	18-26
Output of free HCL (millequiv/l or mmol/l)	До 1	1-4	1-4,5	6,5-12	16-24
Pepsin concentration after Tugolukov (mg/l)	До 200	200-400	200-450	500-650	500-750
Pepsin output after Tugolukov (mg/l)	До 10	10-40	10-50	50-90	90-160
Volume of gastric juice (ml)	До 50	50-100	50-110	100-140	180-220

Table 15

Intragastric pH-metry

pH of body of stomach		Acid-production function of stomach	
Basal secretion	Stimulation secretion		
<1,5	<1,2	hyperacid state	
1,6-2,0	1,3-1,7	normaacid state	
2,1-6,0	1,7-3,0	hypoacid state	
6,0	>3,0	anacid state	
pH of antral part of stomach		Alkalinising function of antral part of stomach	
>6,0	>5,0		compensated alkalinisation
3,5-5,9	4,9-2,0		Subcompensated alkalinisation
<3,5	<2,0		Decompensated alkalinisation

Table 16

Multifractional duodenal intubation

Phase of study	Colour of bile	Volume of bile (ml)	Duration of phase (min)	Rate of bile excretion
I – choledochus-phase (bile A)	golden-yellow	15-30	15-30	1 ml/min
II – phase of closed Oddi's sphincter	-	-	4-6 (<10)	-
III – phase of bile A ₁ (of bile duct and neck of gall bladder; latency period of gall bladder reflex)	golden-yellow	3-4	3-4	1 ml/min
IV – phase of bile B (of gall bladder)	dark-yellow, brown or olive	30-50	15-25	2 ml/min
V – phase of bile C (hepatic bile)	golden-yellow	-	up to 30	1 ml/min

Table 17

**Functional indexes of external respiration
according to data of spirometry**

Index	Normal value
Vital capacity (VC, %)	> 80% of proper VC
Maximal voluntary ventilation (MVV, %)	85 – 75% of proper MVV
Forced expiratory vital capacity (FEVC, liters)	> 75% VC
Forced expiratory volume after 1 second (FEV ₁ ,%)	85 – 75% of proper FEV ₁
Tiffeneau index (FEV ₁ / FEVC)	>75%

Table 18

Differentiations between exudate and transudate

Characteristics	Transudate	Exudate
Specific gravity	<1,015 kg/l	>1,018 kg/l
Protein, g/l	<20	>30
Rivalta's reaction	negative	positive
Leucocyte (in area of vision)	up to 15	>15

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